ORIGINAL ARTICLE

# Atacicept in primary IgA nephropathy: efficacy, biomarker modulation, and safety - a systematic review and meta-analysis

Abdulrahman Alkhamis[1], Khalid Aldawsari[2], Abdulrahman Aljaafar[3], Hammad Altemani[4], Turki Alhazmi[3], Naif Abdullah Alrommani[5]*, Mohammad Allumaylim[6], Musaad Alsulaim[6], Sami Alsweed[1], Jaber Abdullah Alshahrani[7]

## ABSTRACT

**Background:** IgA nephropathy (IgAN) is a leading cause of chronic kidney disease and kidney failure worldwide, with limited disease-specific therapies available. Atacicept, a dual inhibitor of B cell activating factor and a proliferation inducing ligand, targets key immunological pathways involved in disease pathogenesis. This systematic review and meta-analysis evaluated the efficacy and safety of atacicept in patients with IgAN.

**Methodology:** A systematic search of PubMed, Google Scholar, ScienceDirect, Cochrane Library, and ClinicalTrials.gov was conducted from inception to March 2026. Randomized, double blind, placebo-controlled trials in adults with biopsy confirmed IgA nephropathy were included. Data were pooled using a random effects model. Continuous outcomes were analyzed as mean differences (MD) and dichotomous outcomes as risk ratios (RRs), each with 95% confidence intervals. Heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were performed by atacicept dose (25 mg, 75 mg, and 150 mg).

**Results:** In adults with primary IgAN, three randomized controlled trials (560 participants total) evaluated atacicept against placebo. Atacicept significantly reduced urine protein to creatinine ratio (UPCR) at week 24 (MD −29.92%; $p < 0.0001$) and week 36 (MD −38.61%; $p < 0.0001$), with no heterogeneity. Estimated glomerular filtration rate (eGFR) improved significantly at week 36 (MD +8.59 ml/minute/1.73 $m^2$; $p = 0.002$). Galactose-deficient IgA1 and total immunoglobulin levels were significantly suppressed. The overall adverse event profile was comparable to placebo across all safety endpoints.

**Conclusion:** Atacicept was associated with improvements in proteinuria, eGFR, and immunological biomarkers compared with placebo, while demonstrating a safety profile comparable to placebo. Because proteinuria and eGFR are surrogate renal endpoints, these findings should be interpreted as evidence of short-term biological activity rather than established long-term renal benefit. Larger, long-term trials evaluating clinically meaningful renal outcomes are needed to define the role of atacicept in clinical practice.

**Keywords:** IgA nephropathy, atacicept, proteinuria, BAFF/APRIL inhibition, meta-analysis.

## Introduction

IgA nephropathy (IgAN), the most prevalent type of primary glomerulonephritis worldwide, is a significant contributor to end stage renal failure and chronic kidney disease [1]. IgA containing immune complexes are deposited in the glomerular mesangium, causing glomerular inflammation, increasing renal damage, and declining kidney function. According to epidemiological research, 20%-40% of individuals develop kidney failure within 20 years after diagnosis, and IgAN is thought to be

**Correspondence to:** Naif Abdullah Alrommani
*College of Medicine, Sulaiman Alrajhi University, Saudi Arabia.
**Email:** naif3764@gmail.com
Full list of author information is available at the end of the article.
**Received:** 13 October 2026 | **Accepted:** 19 October 2026

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responsible for a significant percentage of biopsy proven glomerular disorders, especially in Asian populations [2]. Hematuria, proteinuria, and different degrees of renal impairment are clinical manifestations of the disease that reflect the diverse characteristics of its course.

A multi-hit theory that includes the overproduction of aberrantly glycosylated IgA1 molecules, development of autoantibodies against these molecules, and accumulation of immune complexes in the kidney explains the pathophysiology of IgAN [3]. These immune complexes trigger complement cascades and inflammatory pathways, leading to progressive glomerular injury. The main focus of current treatment approaches is supportive care, which includes blood pressure management and renin angiotensin system blockage to reduce proteinuria [4]. In the very rare patient with a rapidly progressive course and necrotic and crescentic lesions affecting most glomeruli, we only have case series that have yielded conflicting results, namely, some groups advocate immunosuppression with cyclophosphamide and steroids analogous to vasculitis associated RPGN, whereas in other series, the renal outcome was dismal with and without immunosuppression [5].

For the majority of patients with IgAN who do not present with rapidly progressive disease, management centers on optimized supportive care, including renin angiotensin system blockade, blood pressure control, and, more recently, sodium glucose cotransporter 2 (SGLT2) inhibitors, all of which slow but do not halt progression to kidney failure in patients with persistent proteinuria [6,7]. The 2021 KDIGO guideline update emphasized that a substantial proportion of patients remain at high risk of progression despite maximally tolerated supportive therapy, defined by proteinuria persisting above 0.75-1 g/day, underscoring an unmet need for disease-modifying therapies that act on the underlying immunopathogenesis of IgAN rather than on hemodynamic or metabolic consequences alone [8]. This treatment gap has driven interest in therapies targeting the mucosal immune dysregulation considered central to IgAN pathogenesis, including agents directed at B cell and plasma cell survival pathways such as B-cell activating factor (BAFF) and APRIL inhibitors, of which atacicept is among the most clinically advanced [9].

Atacicept is a recombinant fusion protein that simultaneously suppresses BAFF and a proliferation inducing ligand (APRIL), both of which are critical drivers of B-cell survival, plasma cell differentiation, and immunoglobulin class switching. By inhibiting BAFF and APRIL, atacicept targets a key upstream step in the pathogenesis of IgAN: the APRIL-driven mucosal overproduction of aberrantly glycosylated IgA1. Its primary therapeutic mechanism in IgAN is thus the reduction of circulating GdIgA1 and total IgA, the pathogenic immunoglobulins responsible for immune complex formation and mesangial deposition [10]. Notably, atacicept also reduces circulating IgG and IgM; however, these reductions represent off target immunosuppressive effects rather than therapeutic goals and are a recognized safety concern contributing to hypogammaglobulinemia and increased infection susceptibility with prolonged use. The degree of IgG and IgM depletion appears dose dependent, raising questions about the therapeutic window between clinically meaningful IgA/GdIgA1 reduction and potentially harmful systemic immunosuppression. Early phase clinical trials have demonstrated that atacicept reduces circulating GdIgA1 and proteinuria, but the consistency and magnitude of these effects across dose levels, as well as the full safety profile with extended exposure, remain incompletely characterized.

Accordingly, this systematic review and meta-analysis was conducted to evaluate the efficacy and safety of atacicept in patients with biopsy confirmed primary IgAN. The research question is framed as follows: in adult patients with primary IgAN and significant proteinuria (population), does atacicept at any evaluated dose (intervention) compared with placebo (comparator) produce meaningful reductions in proteinuria as measured by urinary protein to creatinine ratio (UPCR) and estimated glomerular filtration rate (eGFR) decline, with associated changes in GdIgA1 and immunoglobulin levels, and an acceptable safety profile (overall and drug related treatment emergent adverse events). The primary efficacy outcome was the percentage change from baseline in UPCR at weeks 24 and 36. Secondary outcomes included change in eGFR at week 36, change in circulating GdIgA1, and changes in IgA and IgG levels as measures of immunomodulatory effect and safety.

## Methods

### *Protocol and reporting standards*

This systematic review and meta-analysis was performed in accordance with AMSTAR 2 tool [11] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12] to ensure methodological transparency and reporting quality. According to the TITAN Guidelines 2025, which regulate transparent AI implementation in academic publications, AI support was limited to linguistic improvement during manuscript development and had no role in study design, data collection, analysis, or result interpretation [13].

### *Data sources and search strategy*

A systematic literature search was conducted using PubMed, Google Scholar, Science Direct, the Cochrane Library (CENTRAL), and ClinicalTrials.gov from database inception through March 2026 to identify randomized controlled trials evaluating the safety and clinical efficacy of atacicept (a dual BAFF/APRIL inhibitor) in adult patients with primary IgA nephropathy. The search strategy employed a combination of MeSH terms and keywords, including "atacicept," "TACI Fc," "B cell activating factor (BAFF)," "A proliferation inducing ligand (APRIL)," "dual BAFF/APRIL inhibitor," and "IgA nephropathy". Detailed search strings for each database are provided in the Supplementary Appendix. Eligibility was limited to peer reviewed articles published in the English language. In addition, the reference lists of all included trials and relevant systematic reviews were manually screened to capture any additional eligible studies that may have been missed during the initial electronic search.

### *Study selection*

All retrieved records were downloaded into EndNote reference management software (Version X7.5, Clarivate Analytics) for deduplication and organization. The study selection process was conducted independently by two reviewers in two distinct phases, an initial screening of titles and abstracts to identify potentially relevant citations, followed by an extensive full-text assessment of the remaining articles to determine final eligibility. Any disagreements between reviewers regarding study inclusion were resolved through mutual discussion or by consulting a third reviewer. Trials were eligible for inclusion if they were randomized, double blind, placebo-controlled trials (RCTs) involving adult patients (≥18 years of age) with biopsy confirmed primary IgA nephropathy and persistent proteinuria, defined as a 24-hour UPCR ≥ 0.75 mg/mg or ≥1.0 g/d, despite receiving a stable, maximally tolerated dose of renin angiotensin system (RAS) inhibitors for at least 12 weeks. To ensure a comparable baseline of renal function across the synthesis, included studies were restricted to those with an initial eGFR ≥ 30 ml/min/1.73 m². Studies were excluded if they involved secondary causes of IgA nephropathy (e.g., liver cirrhosis or IgA vasculitis), rapidly progressive glomerulonephritis, or the concomitant use of other systemic immunosuppressants. Furthermore, non-randomized trials, observational cohorts, animal models, case reports, and narrative reviews were excluded from the analysis.

### *Data extraction*

For each eligible trial, two reviewers working independently utilized a standardized collection form to retrieve all pertinent data. The information extracted included general study descriptors (first author, year, phase, and location) as well as participant level characteristics such as average age, sex, and ethnicity. We also documented disease-specific baseline values, specifically the interval from the diagnostic biopsy, initial eGFR, and 24-hour UPCR. Regarding the treatment protocols, details on the subcutaneous atacicept dosage (25, 75, or 150 mg) and the duration of the blinded period were recorded. The primary efficacy measure was the percentage change in the 24-hour UPCR at weeks 24 and 36. Secondary endpoints comprised reductions in serum galactose-deficient IgA1 (Gd-IgA1), renal function preservation (eGFR stability), immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM). Safety data, including the incidence of treatment emergent adverse events (TEAEs), drug-related TEAEs, serious adverse events, TEAEs leading to study drug discontinuation and infections, were also gathered. Discrepancies between reviewers were settled through mutual discussion, and the primary study authors were contacted if further clarification or missing data points were necessary.

### *Quality assessment*

Methodological quality was appraised independently by two researchers using the Cochrane Risk of Bias 2.0 (RoB 2) framework for randomized trials [14]. The domains assessed were randomization methods, adherence to planned interventions, completeness of outcome data, accuracy of outcome measurement, and reporting selectivity. The trials were allocated to having low risk of bias, some concerns, or high risk of bias. Any conflicting judgments were settled by consensus or a third author.

### *Data synthesis and statistical analysis*

Statistical synthesis was executed using Review Manager software (RevMan, Version 5.4; The Cochrane Collaboration). For continuous outcomes, such as the percentage change in UPCR and Gd IgA1, results were pooled as mean differences (MD) and SD. Dichotomous variables, including the incidence of safety events, were reported as risk ratios (RRs). All outcomes were presented with corresponding 95% confidence intervals (CIs). A random effects model was employed for all primary analyses to account for anticipated clinical and methodological variation across trial phases and dosages. Two trials contributed more than one atacicept dose arm ([15]: 25 mg and 75 mg; [16]: 25 mg, 75 mg, and 150 mg). In the primary analyses, each dose arm was entered as a separate comparison against the placebo group of the same trial, which allowed dose-specific subgroup analyses but meant that the shared placebo participants contributed to more than one comparison. To avoid a unit-of-analysis error from double counting these participants, a sensitivity analysis was performed for the efficacy outcomes (UPCR at weeks 24 and 36, eGFR at week 36, and Gd-IgA1 at week 36) in which the placebo group of each multi-arm trial was divided approximately equally among its dose arms, with the placebo mean and SD left unchanged, as recommended by the Cochrane Handbook [17]. Statistical heterogeneity was evaluated using the Cochran's Q test ($X^2$) and the $I^2$ statistic, where $I^2 > 50\%$ was predefined as indicating significant heterogeneity [18]. To investigate the stability of our findings, sensitivity analyses were performed for outcomes demonstrating high heterogeneity. Subgroup analyses were conducted based on the subcutaneous dose of atacicept (25 mg, 75 mg, and 150 mg). Formal assessment for publication bias through funnel plots or Egger's regression was not carried out because the analysis included only three randomized trials, making these tests statistically unreliable. A two-tailed $p < 0.05$ was considered the threshold for statistical significance.

#### *GRADE assessment*

The certainty of the body of evidence for each outcome was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [19]. Evidence from randomized controlled trials started at high certainty and was rated down by one or two levels across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Risk of bias was informed by the RoB 2 assessment. Inconsistency was judged from the I2 statistic and the overlap of CIs, with I2 above 50% prompting consideration of a downgrade. Indirectness was assessed from the applicability of the population, intervention, comparator, and outcomes to the review question and accounted for the fact that proteinuria, eGFR, and the immunological markers are surrogate

measures rather than patient important kidney failure endpoints. Imprecision was based on the width of the CI, whether it crossed the threshold of no effect, the number of events, and the optimal information size. Publication bias was appraised qualitatively, because the inclusion of only three trials precluded funnel plot or regression based testing. Two reviewers applied GRADE independently and resolved disagreements by discussion.

## Results

### *Study selection and characteristics*

A total of 1,916 records were identified through database and registry searches. After removal of 113 duplicates, 1,803 records were screened, of which 1,781 were excluded via title and abstract screening. Twenty two full-text articles were assessed for eligibility, and nineteen were excluded (reviews, non-original studies, not meeting PICO criteria, or secondary analyses). Ultimately, three RCTs [20,21,16] were included in the meta-analysis (Figure 1).

The included trials comprised 560 participants and were all randomized, double blind, placebo controlled studies evaluating atacicept in adults with biopsy proven IgA nephropathy and persistent proteinuria despite standard therapy. Sample sizes ranged from 16 to 428 participants. Atacicept was administered at doses of 25 mg, 75 mg, and 150 mg once weekly. Baseline characteristics were comparable between atacicept and placebo groups across studies. Mean age ranged from approximately 38 to 46 years, with a predominance of male participants. Baseline proteinuria, renal function (eGFR), and immunological markers were similar between groups. Most patients were receiving renin–angiotensin system inhibitors, with additional use of SGLT2 inhibitors reported in more recent trials. Detailed study and baseline characteristics are presented in Tables 1 and 2.

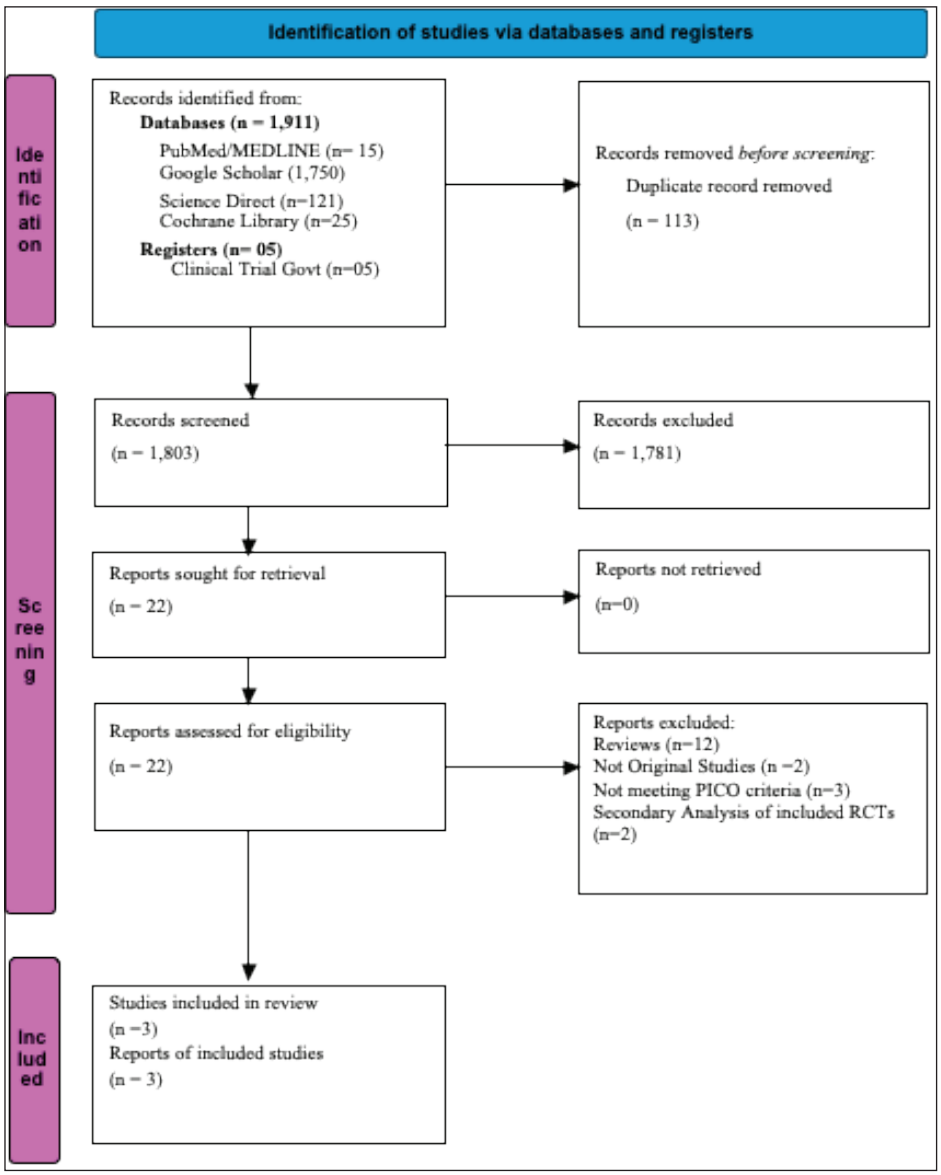



*Figure 1. PRISMA flow chart*

### *Risk of bias assessment*

The risk of bias across the included RCTs was assessed using the Cochrane Risk of Bias tool. Overall, all three studies were judged to be at low risk of bias across all domains. Random sequence generation and allocation concealment were adequately performed in all trials using centralized or appropriate randomization methods. Blinding of participants, personnel, and outcome assessors was consistently maintained, as all studies were double blind and placebo controlled, with outcomes primarily based on objective laboratory measures, thereby minimizing performance and detection bias. Incomplete outcome data and selective reporting were assessed as low risk in all studies, with no evidence of attrition bias or selective outcome reporting. Additionally, no other significant sources of bias were identified. The risk of bias is presented in Figure 2A and 2B and detailed in Supplementary Table 2.

### *Renal efficacy outcomes*

#### *UPCR at week 24*

A meta-analysis of six study arms (400 participants) demonstrated a statistically significant reduction in UPCR with atacicept compared to placebo at week 24 (MD = –29.92, 95% CI: –39.77 to –20.07; $p < 0.0001$), with no heterogeneity across studies ($I^2 = 0\%$) (Figure 3).

#### *UPCR at week 36*

At week 36, the pooled estimate across four study arms (368 participants) showed a similar magnitude of reduction (MD = –38.61, 95% CI: –48.39 to –28.84; $p < 0.0001$), with no heterogeneity observed ($I^2 = 0\%$), demonstrating a consistent reduction in this surrogate renal endpoint across studies at the 36-week assessment (Figure 4).

#### *eGFR at week 36*

At week 36, atacicept was associated with a statistically significant increase in eGFR compared with placebo (MD = 8.59, 95% CI: 3.15–14.02; $p = 0.002$). As eGFR at this follow-up duration represents a surrogate renal endpoint, these findings should not be interpreted as evidence of long-term renal protection (Figure 5).

In the sensitivity analysis in which the shared placebo groups of the multiarm trials were divided among their dose arms, the renal efficacy estimates were essentially unchanged and remained statistically significant: UPCR at week 24 (MD = –30.53, 95% CI: –41.61 to –19.45; $p < 0.0001$; $I^2 = 0\%$), UPCR at week 36 (MD = –38.81, 95% CI: –49.95 to –27.67; $p < 0.0001$; $I^2 = 0\%$), and eGFR at week 36 (MD = 8.61, 95% CI: 2.06 to 15.15; $p = 0.010$; $I^2 = 0\%$).

### *Immunological biomarker outcomes*

#### *Gd-IgA1 at week 36*

Across six study arms (379 participants), atacicept was associated with a significant reduction in Gd-IgA1 levels compared to placebo, with a pooled mean difference of –49.37 (95% CI: –65.62 to –33.12; $p < 0.0001$) (Figure 6). Substantial heterogeneity was observed ($I^2$

***Table 1.*** *Study characteristics.*

| Study | Clinical trial no. | Study design | Patient category | Total sample | Sample size | | Dosage | Primary outcome |
|---|---|---|---|---|---|---|---|---|
| | | | | | Atacicept | Placebo | | |
| Barratt et al. [20] | NCT02808429 | randomized, double blind, placebo-controlled phase 2 study | 18 years or older, with IgAN and persistent proteinuria despite being on a stable dose of ACEi and/or ARBs. | 16 | 6 | 5 | 25 mg once weekly | The safety and tolerability of atacicept patients with IgAN and persistent proteinuria |
| | | | | | 5 | | 75 mg once weekly | |
| Lafayette et al. [21] | NCT04716231 | randomized, international, multicenter, double-blind, placebo controlled, phase 2b trial | Aged 18 years had biopsy proven IgAN within 10 years before screening | 116 | 16 | 34 | 25 mg once weekly | Change from baseline in 24-hour UPCR at week 24 |
| | | | | | 33 | | 75 mg once weekly | |
| | | | | | 33 | | 150 mg once weekly | |
| Lafayette et al. [16] | NCT04716231 | Double blind, randomized, placebo-controlled phase 3 trial | Adults 18 years of age or older with IgA nephropathy confirmed by biopsy. | 428 | 214 | 214 | 150 mg once weekly | Change from baseline at week 36 in the urinary protein to-creatinine ratio |

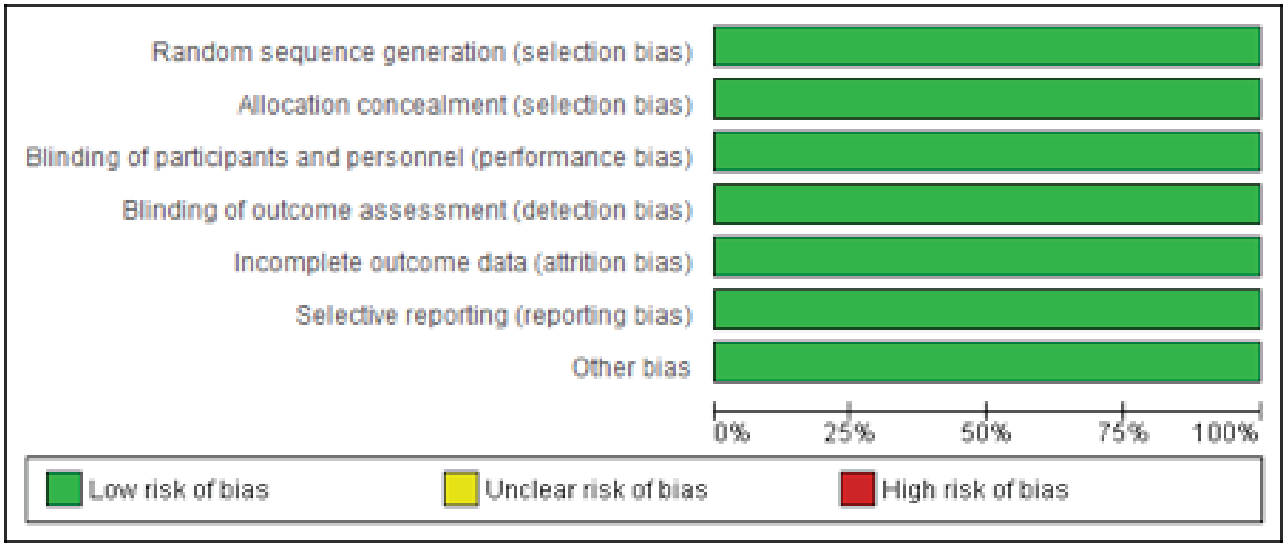



***Figure 2A.*** *Risk of bias graph.*

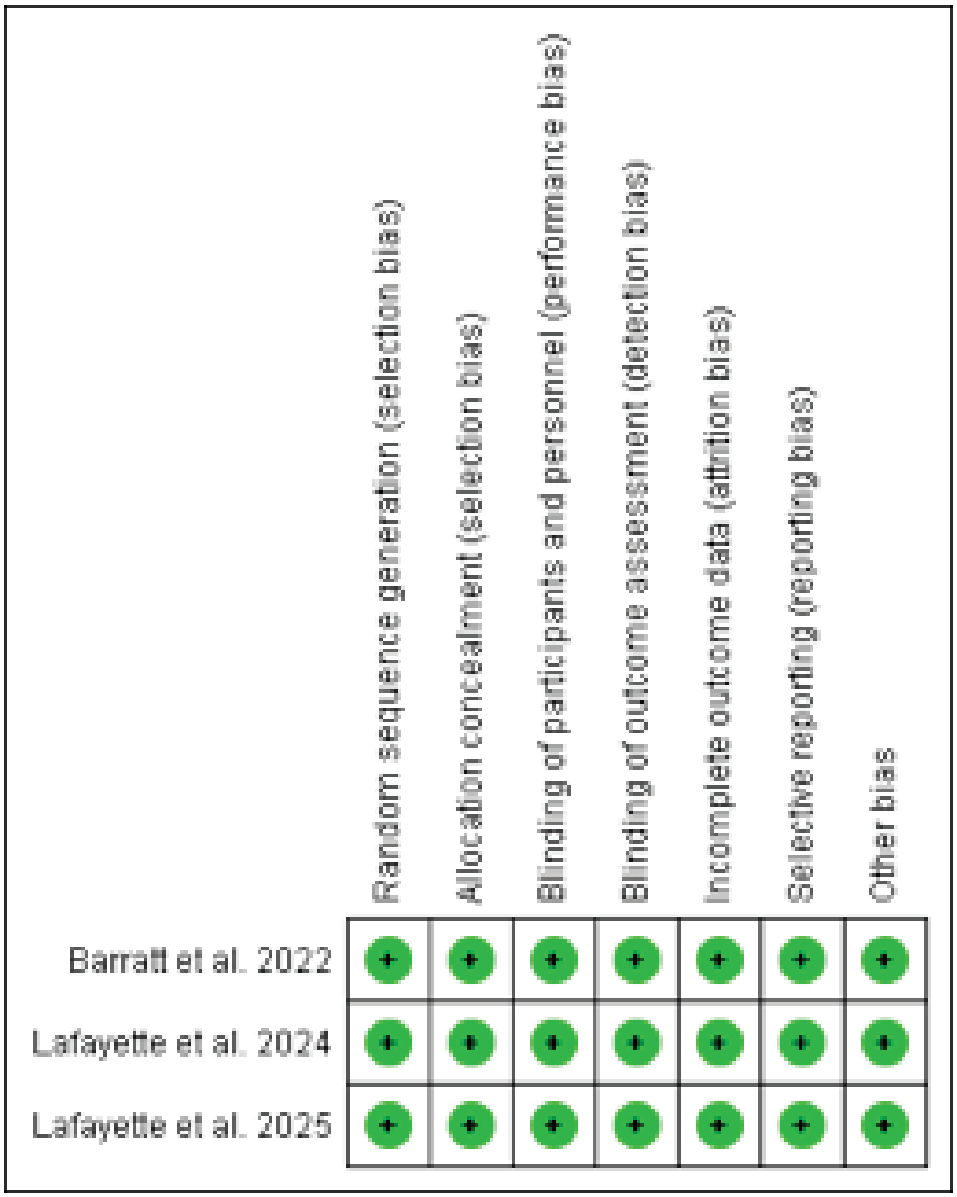



***Figure 2B.*** *Risk of bias summary.*

***Table 2.*** *Baseline characteristics.*

| Variable | Barratt et al. [17] | | | Lafayette et al. [18] | | | | Lafayette et al. [19] | |
|---|---|---|---|---|---|---|---|---|---|
| | Atacicept | | Placebo | Atacicept | | | Placebo | Atacicept | Placebo |
| | 25 mg (n = 06) | 75 mg (n = 05) | (n = 05) | 25 mg (n = 16) | 75 mg (n = 33) | 150 mg (33) | (n = 34) | 150 mg (n = 106) | (n = 97) |
| Age, year, mean(SD) | 41 ± 16.9 | 43 ± 8.9 | 46 ± 3.1 | 40 (15) | 41 (13) | 38 (11) | 39 (13) | 40.1 ± 11.1 | 40.9 ± 11.6 |
| Sex — no. (%) | | | | | | | | | |
| Male | 1 (17) | 3 (60) | 4 (80) | 9 (56) | 19 (58) | 22 (67) | 19 (56) | 57 (54) | 58 (60) |
| Female | 5 (83) | 2 (40) | 1 (20) | 7 (44) | 14 (42) | 11 (33) | 15 (44) | 49 (46) | 39 (40) |
| Time from biopsy to screening, yr | 1.80 (0.12,2.96) | 0.97 (0.33,2.52) | 0.50 (0.31,1.05) | 1.7 (1.6) | 3.4 (2.8) | 3.3 (3.4) | 2.1 (2.4) | 2.5 ± 2.6 | 2.5 ± 2.4 |
| Urine protein excretion, g/24 hours, | 2.1 (1.9,2.9) | 1.7 (1.6,2.3) | 3.2 (2.3,3.3) | 2.3 (1.0) | 2.1 (1.0) | 2.3 (1.2) | 2.0 (0.9) | 2.2 ± 1.0 | 2.3 ± 1.4 |
| Urinary proteintocreatinine ratio | 1.8 (0.8,2.2) | 1.4 (1.3,1.7) | 1.6 (1.5,1.6) | 1.6 (0.8) | 1.7 (0.9) | 1.7 (1.0) | 1.6 (0.8) | 1.7 ± 0.9 | 1.8 ± 1.2 |
| Urinary albumintocreatinine ratio | - | - | - | 1.2 (0.7) | 1.3 (0.7) | 1.4 (0.8) | 1.2 (0.7) | 1.3 ± 0.7 | 1.3 ± 0.9 |
| Estimated glomerular filtration rate — ml/minute/1.73 m2 | 57 (53,85) | 55 (52,92) | 49 (48,54) | 71 (29) | 64 (25) | 56 (23) | 66 (32) | 65.3 ± 27.7 | 64.9 ± 29.0 |
| Galactosedeficient IgA1 — µg/L | 6258 ± 3211 | 6052 ± 2773 | 7690 ± 3642 | 6292(4572) | 5813(3573) | 5646(2697) | 6340(3697) | 5248.2 ± 4192.5 | 4671.8 ± 2411.7 |
| IgA — mg/dl | 3.58 ± 1.22 | 3.02 ± 0.85 | 3.97 ± 1.72 | 315 (143) | 313 (131) | 320 (100) | 337 (154) | 336.7 ± 119.1 | 332.5 ± 109.8 |
| IgG — mg/dl | 9.45 ± 1.82 | 10.89 ± 1.10 | 10.51 ± 2.63 | 1018(217) | 1159(289) | 1059(206) | 1153(305) | 1165.9 ± 278.7 | 1150.1 ± 277.0 |
| IgM — mg/dl | 0.90 ± 0.55 | 1.09 ± 0.30 | 1.29 ± 0.51 | 98 (44) | 121 (100) | 94 (56) | 102 (50) | 111.8 ± 57.1 | 99.1 ± 54.8 |
| Stable use of SGLT2 inhibitor — no. (%) | - | - | - | 3 (19) | 3 (9) | 4 (12) | 6 (18) | 59 (56) | 49(51) |
| Use of RAS inhibitor — no. (%) | - | - | - | - | - | - | - | 105 (99) | 97 (100) |
| Unspecified RASi | | | | | | | | | |
| ACEi only | 3 (50) | 1 (20) | 3 (60) | 10 (63) | 6 (18) | 6 (18) | 11 (32) | - | - |
| ARB only | 3 (50) | 4 (80) | 2 (40) | 4 (25) | 21 (64) | 23 (70) | 19 (56) | - | - |
| ACEi + ARB | 6 (100) | 5 (100) | 5 (100) | 1 (6) | 3 (9) | 3 (9) | 2 (6) | - | - |

= 94%), though the effect persisted across all leave one out sensitivity analyses (Supplementary Figure S1). The reduction was also unchanged when the shared placebo groups of the multi-arm trials were divided among their dose arms (MD = –49.21, 95% CI: –66.73 to –31.68; $p <$ 0.0001; $I^2 = 92\%$).

### *IgG at week 36*

Total IgG levels were significantly reduced in the atacicept group compared to placebo (MD = –24.30, 95% CI: –40.75 to –7.86; $p = 0.004$) across six study arms (385 participants) (Supplementary Figure S2). Although substantial variability was present ($I^2 = 97\%$), sensitivity analyses indicated that the effect remained statistically significant in all leave one out analyses (Supplementary Figure S3).

### *IgA at week 36*

A significant reduction in total IgA was observed with atacicept compared to placebo (MD = –45.71, 95% CI: –62.95 to –28.48; $p < 0.0001$) across six study arms (385 participants) (Supplementary Figure S4). Substantial heterogeneity was observed ($I^2 = 96\%$), and the effect remained statistically significant in all leave one out analyses (Supplementary Figure S5).

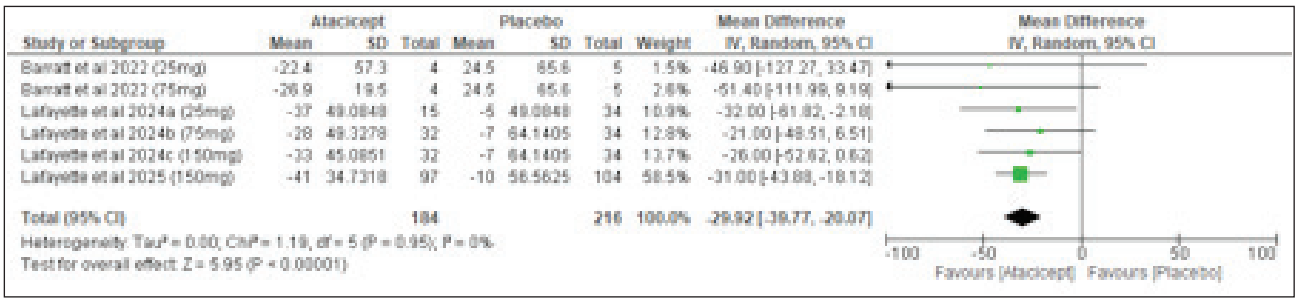



***Figure 3.*** *Forest plot of percentage change from baseline in 24 hours urinary protein-to-creatinine ratio (UPCR) at week 24.*

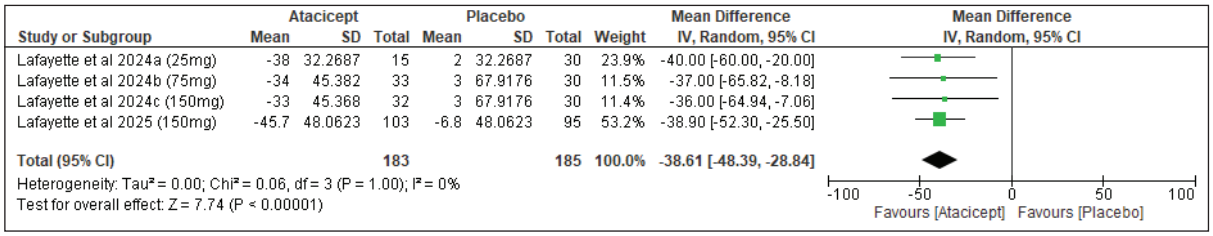



***Figure 4.*** *Forest plot of percentage change from baseline in 24 hours urinary protein-to-creatinine ratio (UPCR) at week 36.*

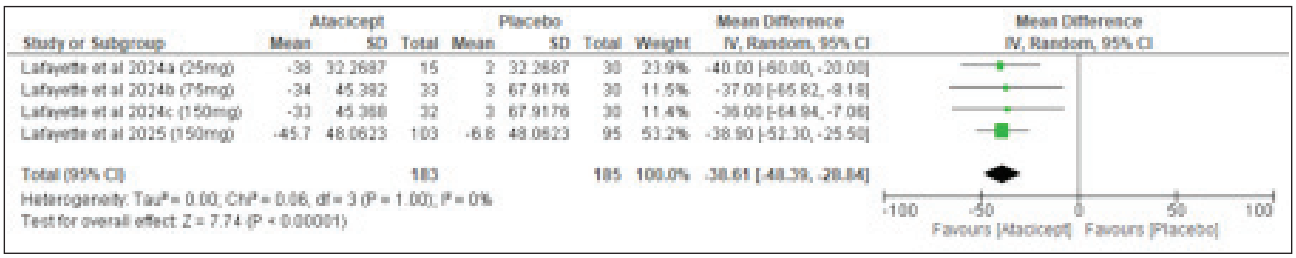



***Figure 5.*** *Forest plot of percentage change from baseline in estimated glomerular filtration rate (eGFR) at week 36.*

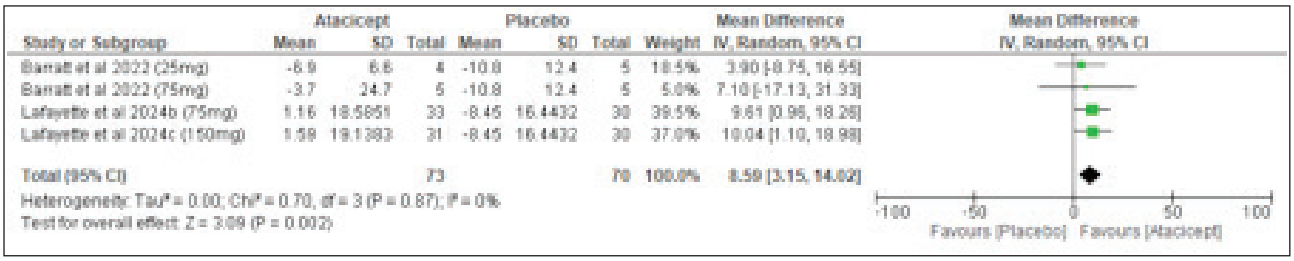



***Figure 6.*** *Forest plot of percentage change from baseline in galactose-deficient IgA1 (Gd-IgA1) at week 36.*

### *IgM at week 36*

For IgM, atacicept was associated with a significant reduction compared to placebo (MD = –62.26, 95% CI: –74.79 to –49.73; $p < 0.0001$) across six study arms (385 participants) (Supplementary Figure S6). High heterogeneity was observed ($I^2 = 86\%$); however, the reduction remained consistent across all sensitivity analyses (Supplementary Figure S7).

## *Safety outcomes*

The overall incidence of TEAEs was comparable between the atacicept and placebo groups, with no statistically significant difference detected (RR = 1.00, 95% CI: 0.87 to 1.14; $p = 0.97$) and low heterogeneity across studies ($I^2 = 25\%$) (Supplementary Figure S8). Similarly, drug-related TEAEs did not differ significantly between groups (RR = 1.32, 95% CI: 0.96 to 1.80; $p = 0.09$; $I^2 = 0\%$) (Supplementary Figure S9), nor did rates of discontinuation due to TEAEs (RR = 0.49, 95% CI: 0.17 to 1.43; $p = 0.19$; $I^2 = 0\%$) (Supplementary Figure S10).

Serious TEAEs were infrequent in both arms, and the difference between groups did not reach statistical significance (RR = 0.40, 95% CI: 0.14 to 1.11; $p = 0.08$; $I^2 = 15\%$) (Supplementary Figure S11). Infection rates were numerically higher in the atacicept group but similarly did not differ significantly from placebo (RR = 1.21, 95% CI: 0.96 to 1.52; $p = 0.10$; $I^2 = 0\%$) (Supplementary

Figure S12). Across all safety outcomes, between-study heterogeneity was low to absent, supporting the consistency of these findings.

### *Subgroup analyses by dosage*

Subgroup analyses stratified by dosage (25 mg, 75 mg, and 150 mg) suggested that the relationship between dose and treatment effect varied depending on the outcome. For renal and proteinuric outcomes, effects were consistent across all dose levels without evidence of a dose–response relationship. UPCR reductions were statistically significant across all subgroups at both week 24 and week 36, with between subgroup differences remaining non-significant at both timepoints (week 24: $Chi^2 = 0.16$, $p = 0.92$; week 36: $Chi^2 = 0.03$, $p = 0.98$). For eGFR at week 36, improvements were numerically greater at higher doses, but between subgroup differences did not reach significance ($Chi^2 = 0.66$, $p = 0.72$), and the 25 mg subgroup did not achieve a statistically significant eGFR increment.

Immunological outcomes at week 36 showed dose-dependent effects across all markers examined. Reductions in Gd-IgA1, IgG, IgA, and IgM increased progressively with dose, with between subgroup differences reaching significance for all four markers ($p < 0.0001$ for Gd-IgA1, IgA, and IgG; $p = 0.010$ for IgM). The 25 mg subgroup did not achieve a significant IgG reduction, whereas reductions were statistically significant at 75 mg and 150 mg, with the 150 mg subgroup showing the largest effects across all immunological parameters. These findings suggested that the relationship between dose and immunological suppression may differ from that observed for proteinuric outcomes.

With respect to safety, the tolerability profile of atacicept was broadly consistent across dosing levels, with no evidence of dose-dependent differences in any adverse event category. TEAE incidences were comparable between atacicept and placebo across all subgroups, and although drug-related TEAEs were modestly more frequent with atacicept overall, this did not vary significantly by dose ($Chi^2 = 0.85$, $p = 0.65$). Serious TEAEs, discontinuations, and infection rates were each statistically comparable between arms across all dosing subgroups, with between subgroup heterogeneity tests remaining non-significant throughout. Detailed results are provided in Supplementary Figures 13(A)–13(L).

### *Certainty of evidence*

The certainty of evidence for all outcomes is summarized in Table 3. For the renal efficacy outcomes, the certainty was moderate for the percentage change in UPCR at week 24 and week 36, each rated down once for indirectness because proteinuria is a surrogate for patient important kidney failure endpoints. The certainty for eGFR at week 36 was low, rated down for the same indirectness and additionally for imprecision, as the pooled estimate was derived from only 143 participants and did not meet the optimal information size. For the immunological biomarkers, Gd-IgA1, IgG, IgA, and IgM at week 36 were each graded as low certainty, rated down for serious inconsistency, with I2 ranging from 86% to 97%, and for indirectness, since these markers are mechanistic surrogates rather than direct measures of renal outcome. For the safety outcomes, the certainty was moderate for overall TEAEs, drug-related TEAEs, and infections, each rated down once for imprecision because the CI crossed the threshold of no effect. The certainty for serious TEAEs and for discontinuation due to TEAEs was low, rated down two levels for very serious imprecision arising from few events and wide CIs. No outcome was rated down for risk of bias, as all three trials were judged at low risk across the RoB 2 domains; however, all included trials were industry sponsored and the small number of studies prevented formal testing for publication bias. The ratings and their justifications were compiled in a Summary of Findings table (Supplementary Table 3).

## Discussion

This meta-analysis demonstrated that atacicept was associated with significant reductions in proteinuria and favorable immunological modulation in patients with IgAN. Proteinuria, quantified as the UPCR, was significantly reduced at both weeks 24 and 36, and improvements in eGFR together with reductions in the principal pathogenic biomarkersGd-IgA1 and circulating immunoglobulins were observed. Because UPCR and eGFR are surrogate renal endpoints, these findings should be interpreted as evidence of short-term biological and clinical activity rather than established long-term renal benefit.

To appropriately interpret the clinical significance of the antiproteinuric effect observed with atacicept, its magnitude must be considered in relation to that of other recently evaluated targeted therapies. In the PROTECT trial, sparsentan, a dual endothelin-1, and angiotensin receptor antagonist, achieved a mean UPCR reduction of approximately 49% versus 15% with irbesartan at 36 weeks, supporting its superiority over optimized RAS blockade alone [22]. In the NefIgArd trial, targeted-release budesonide produced a placebo subtracted proteinuria reduction of approximately 27% at 9 months, at the cost of corticosteroid related adverse events [9]. The APPLAUSE-IgAN trial evaluating the proximal complement factor B inhibitor iptacopan demonstrated a 38% reduction in proteinuria relative to placebo at 9 months [23]. The antiproteinuric effect of atacicept across the included trials appears numerically comparable to or exceeding these benchmarks, although direct comparison is confounded by differences in background therapy, trial populations, dosing regimens, and follow-up duration.

The role of SGLT2 inhibitors as background supportive therapy in IgAN has also been established following positive results from dedicated trials [24]. Importantly, SGLT2 inhibitors exert nephroprotective effects predominantly through hemodynamic and metabolic mechanisms rather than through modulation of the GdIgA1-autoantibody axis [25]. The mechanisms of action of atacicept and SGLT2 inhibitors are non-overlapping, raising the biologically plausible hypothesis that their combination may produce additive or complementary renoprotection. Formal evaluation of such combinations in adequately powered trials is

warranted in the future. Furthermore, the TESTING, STOP-IgAN, and NEFIGAN trials have established proteinuria reduction as a validated surrogate endpoint in IgAN clinical trials, providing the methodological justification for using UPCR as the primary efficacy outcome in the present synthesis [26–28].

Taken together, the available evidence suggests that atacicept is associated with substantial reductions in proteinuria compared with placebo, alongside favorable immunological effects. However, because these findings are based on surrogate renal endpoints evaluated over relatively short follow up periods, the extent to which they translate into durable preservation of kidney function or reductions in kidney failure remains uncertain [29]. Whether atacicept should be positioned as a first line adjunct to optimized supportive care, a second-line option following SGLT2 inhibition, or as part of combination immunotherapy requires confirmation in future head to head and long term outcome trials.

Mechanistically, the antiproteinuric and eGFR effects of atacicept are attributable to its inhibition of BAFF and APRIL, which curtails B-cell activation and plasma cell differentiation in IgAN. This reduces synthesis of GdIgA1 and related autoantibodies, limiting immune complex formation and mesangial deposition [30]. Reduced downstream complement activation and glomerular inflammation in turn help preserve podocyte function and the integrity of the filtration barrier, providing a plausible biological basis for both the observed reduction in proteinuria and the stabilization or improvement of eGFR at week 36 [31,32]. However, because both UPCR and eGFR are surrogate renal endpoints assessed over a relatively short follow up period, these findings should be interpreted as evidence of biological activity rather than confirmed long term preservation of kidney function.

Atacicept had a strong effect on key pathogenic biomarkers in terms of immunological outcomes. There were large drops in GdIgA1, total IgG, IgA, and IgM levels at week 36. Although heterogeneity was significant across these analyses, sensitivity testing validated the robustness of these findings. Consistent with our findings, previous studies have indicated that atacicept markedly decreases galactose deficient IgA1, related autoantibodies, and circulating immune complexes in IgAN, while also enhancing hematuria [15,33]. This pattern corroborates the hypothesis that atacicept alleviates glomerular injury by reducing immune complex-mediated inflammation. The temporal amelioration of hematuria and proteinuria further indicates an anti inflammatory effect, potentially mediated not only through B cell modulation but also via influences on innate immune pathways, including TACI expressing cells such as macrophages [34].

While the marked reductions in GdIgA1 and total IgA observed with atacicept reflect its intended therapeutic mechanism, the concurrent reductions in total IgG and IgM are an off target consequence of broad BAFF/APRIL inhibition rather than a treatment goal, and carry distinct clinical implications. BAFF and APRIL support survival not only of autoreactive B cells but of the broader plasma cell compartment responsible for protective humoral immunity; sustained suppression of these pathways can produce clinically meaningful hypogammaglobulinemia, as has been described with other BAFF-targeted biologics such as belimumab in systemic lupus erythematosus [35,36]. In the trials included in this meta analysis, short term infection rates did not differ significantly from placebo; however, the follow up duration (24–36 weeks) is insufficient to capture the cumulative infection risk associated with chronic immunoglobulin depletion, which in other BAFF/APRIL-targeted populations has been shown to increase with longer exposure and higher cumulative dosing [37]. The dose dependent pattern of IgG/IgM suppression observed here, contrasted with the largely dose-independent renal response, suggests that lower doses may offer a more favorable benefit-risk balance for long-term use, but this requires prospective confirmation with routine immunoglobulin monitoring and pre specified infection surveillance in future trials, particularly given that hypogammaglobulinemia-related infections may manifest only after months to years of cumulative B-cell/plasma-cell suppression [38].

Atacicept showed a safety profile comparable to that of placebo. No statistically significant differences were observed in the rates of overall adverse events, drug related adverse events, serious adverse events, discontinuations, or infections. Additionally, there was little variation in safety outcomes, which supports the consistency of the tolerability findings.

Significant statistical heterogeneity was observed in immunological outcomes, including reductions in GdIgA1, total IgG, IgA, and IgM. Accordingly, a random effects model was applied to account for the between study variability arising from differences in trial design, dosing regimens, and patient populations, which would violate the fixed effects assumptions. The $I^2$ values exceeded the conventional thresholds for substantial heterogeneity, limiting the precision and interpretability of the pooled immunological estimates despite consistent directional effects in the sensitivity analyses. This heterogeneity is likely multifactorial, including varying dose arms (25, 75, and 150 mg) with distinct pharmacodynamic profiles, differences in background therapy, including RAS blockade and SGLT2 inhibitor use, non uniform GdIgA1 assay methodologies, and variation in trial phase and design affecting population selection and outcome ascertainment. Recognition of these factors is essential when interpreting pooled immunological results.

A key finding was the dissociation between the renal and immunological dose–response relationships. Antiproteinuric effects (UPCR reduction and eGFR stabilization) were largely dose independent across all arms, whereas suppression of GdIgA1 and immunoglobulins was clearly dose dependent, with maximal effects at 150 mg. This likely reflects a threshold effect in BAFF/APRIL inhibition, where partial suppression at lower doses sufficiently reduces pathogenic immune complex formation, and further cytokine inhibition yields additional immunoglobulin depletion without added renal benefit, consistent with the sigmoidal pharmacodynamics of B cell–targeted biologics. Clinically, this suggests that lower doses (e.g., 25 mg) may preserve renal efficacy while

reducing infection risk; however, inconsistent statistical significance across trials prevents confirmation of non inferiority, necessitating adequately powered dose optimization studies with combined renal and immunological endpoints.

In summary, atacicept represents a promising adjunctive therapy for IgAN, complementing supportive measures such as RAS blockade and SGLT2 inhibition through targeted modulation of upstream immunological pathways. The observed improvements in proteinuria, eGFR, and immunological biomarkers are encouraging; however, because the renal outcomes were based on surrogate endpoints, their implications for long term kidney survival remain uncertain. Future adequately powered, long term trials evaluating clinically meaningful renal outcomes including sustained eGFR decline, kidney failure, and the need for kidney replacement therapy are required before the role of atacicept in routine clinical practice can be fully established.

## Limitations

This meta-analysis has several limitations that affect the interpretation of its findings. First, only three randomized trials comprising six dosing arms were eligible for inclusion, resulting in a limited aggregate sample size and reduced statistical power, particularly for subgroup analyses and rare safety outcomes. The small number of studies also precluded the formal assessment of publication bias using Egger's regression or funnel plot asymmetry, and the possibility of selective reporting bias cannot be excluded. In addition, two trials contributed multiple dose arms that shared a single placebo group; although the pooled efficacy estimates were unchanged when these placebo groups were divided among dose arms, the participant totals in the primary forest plots and the dose-stratified safety analyses include the shared placebo participants in more than one comparison.

Second, all included trials enrolled patients with biopsy confirmed primary IgAN and preserved renal function (eGFR $\geq$30 ml/minute/1.73 $m^2$), restricting the generalizability of the findings to patients with secondary IgAN, advanced chronic kidney disease, or concurrent immunosuppressive therapy. Whether atacicept is efficacious and safe in patients with more advanced disease, who bear the highest risk of progression to kidney failure, remains unknown.

Third, and critically, UPCR and eGFR at 36 weeks were surrogate endpoints. Although these measures are validated prognostic markers for long term renal outcomes in IgAN, the magnitude of surrogate improvement observed in these trials has not been proven to translate into a reduced long term risk of kidney failure. This uncertainty can only be resolved by trials incorporating hard renal endpoints, defined as a sustained 40% decline in eGFR, end stage kidney disease, or renal death, over a minimum follow up of 2-5 years.

Fourth, all included trials were industry sponsored, introducing the potential for design, conduct, and reporting biases that are systematically documented in the context of commercially funded clinical research. This limitation is distinct from and additive to the risk of publication bias and should be acknowledged explicitly when interpreting the consistency and magnitude of efficacy estimates.

Fifth, the small number of patients in individual dosing subgroups, particularly the 25 mg arm, limits the power to draw conclusions regarding dose response relationships for renal outcomes. The conflicting statistical significance observed in the 25 mg arm for certain endpoints reflects this underpowering rather than a genuine null effect.

Sixth, methodological heterogeneity across trials, including variation in trial phase, background therapy, concomitant RAS blockade, and GdIgA1 assay methodology, introduces clinical and measurement variability that limits the precision of pooled estimates and qualifies the robustness of sensitivity analyses.

## Conclusion

This meta-analysis of three randomized trials demonstrated that atacicept produces significant antiproteinuric efficacy and favorable immunological modulation in patients with IgAN, with an acceptable tolerability profile across dosing regimens at 36 weeks. A clinically important dissociation was identified between renal and immunological dose response relationships: renal benefits appeared largely dose independent, whereas suppression of GdIgA1 and circulating immunoglobulins was dose dependent, being most pronounced at 150 mg. These findings support the therapeutic potential of atacicept in reducing disease activity and stabilizing renal function in IgAN. However, definitive conclusions regarding long term efficacy, optimal dosing, safety during chronic use, and the place of atacicept within the broader IgAN treatment algorithm require large scale, long term randomized trials incorporating hard renal endpoints, extended follow up, and inclusion of more diverse patient populations.


## Acknowledgments

None.


**Conflict of interest**

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this study.


**Funding**

The authors did not receive any extramural funding for this study.


**Consent for publication**

Not applicable.

**Consent to participate**

Not applicable.

**Availability of data and materials statement**

The dataset supporting the conclusions of this study is included in this article.

**Clinical trial number**

Not applicable.

## Ethical approval

Not applicable.

## Author details

Abdulrahman Alkhamis[1], Khalid Aldawsari[2], Abdulrahman Aljaafar[3], Hammad Altemani[4], Turki Alhazmi[3], Naif Abdullah Alrommani[5], Mohammad Allumaylim[6], Musaad Alsulaim[6], Sami Alsweed[1], Jaber Abdullah Alshahrani[7]

1. College of Medicine, Qassim University, Buraydah, Saudi Arabia
2. College of Medicine, Prince Sattam bin Abdulaziz University, Al-Kharj, Saudi Arabia
3. College of Medicine, King Abdulaziz University, Jedda, Saudi Arabia
4. College of Medicine, University of Tabuk, Tabuk, Saudi Arabia
5. College of Medicine, Sulaiman Alrajhi University, Al-Bukairiyah, Saudi Arabia
6. College of Medicine, King Saud bin Abdulaziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia
7. Family Medicine Department, Armed Forces Hospital Southern Region, Ministry of Defense Health Services, Khamis Mushait, Saudi Arabia

*Supplementary content (if any) is available online.*

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