

New Insights on IgA Nephropathy from the Perspective of Active Lesions and Systemic Inflammatory Responses

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Abstract: Immunoglobulin A nephropathy (IgAN) is a chronic disease. Active disease typically presents with massive proteinuria and gross hematuria, along with renal pathological features such as mesangial cell proliferation, endothelial cell proliferation, and crescents. Active lesions may achieve remission following treatment but also can relapse at any stage of the patient's life. Systemic inflammatory markers are significantly associated with IgAN disease activity indicators. Research has found that patients with high disease activity and low chronicity are more likely to benefit from immunosuppressive therapy. We speculated that “four-hit” hypothesis in IgAN may exist as the background for the recurrence of the disease. Bacterial or viral infections and vaccinations are common mucosal triggers that may induce active lesions by activating systemic inflammatory responses. The clinical manifestations triggered by these factors are diverse, which likely reflects the complex interplay between the nature of the injury and individual patient susceptibility. In this narrative review, we explore new insight on IgAN from the perspective of active disease and systemic inflammatory responses.

Keywords: IgA nephropathy, MEST-C classification, active lesion, systemic inflammation, innate immunity

Introduction

Immunoglobulin (Ig) A nephropathy (IgAN) is the highest incidence of primary glomerulonephritis, predominantly affecting young adults with a mean age at diagnosis of 34 to 45 years.¹ Its clinical manifestations are diverse, ranging from intermittent episodes of gross hematuria to microscopic hematuria and proteinuria, accompanied by impaired renal function.² Renal biopsy remains the gold standard for diagnosis, with histology systematically classified according to the Oxford MEST-C score,³ active lesions are typically characterized by mesangial hypercellularity (M1), endocapillary proliferation (E1) or crescents (C1/C2), whereas chronic lesions reflect irreversible renal damage, including segmental glomerulosclerosis (S) and tubular atrophy/interstitial fibrosis (T).^{4–6} It is reported that the epidemiology of IgAN varies significantly across different regions, with the highest incidence observed in East Asia population.⁷ Approximately 40% to 50% of patients develop renal failure within 10 years of IgAN diagnosis.^{1,2}

“Four-hit” hypothesis is the recognized pathogenesis of IgAN, and the production of galactose-deficient IgA1 (Gd-IgA1) is the first pathogenic event of IgAN.⁷ The discovery of several IgAN susceptibility loci has confirmed the role of genetic factors in IgAN.^{8,9} Although it was found that high levels of Gd-IgA1 were also observed in relatives of IgAN patients, most of relatives were asymptomatic,¹⁰ suggesting that other cofactors are required for the development of IgAN. Increasing evidence suggests that infections, food antigens, dysbiosis, and abnormal mucosal immune responses are associated with the production of Gd-IgA.⁷ After entering the systemic circulation, Gd-IgA1 is recognized by autoantibodies, forming circulating immune complexes. These complexes subsequently deposit in the glomerular mesangial region and trigger the release of pro-inflammatory and pro-fibrotic cytokines and complement activation, ultimately leading to renal injury⁷ (Figure 1). However, in clinical practice, IgAN typically presents as a chronic disease

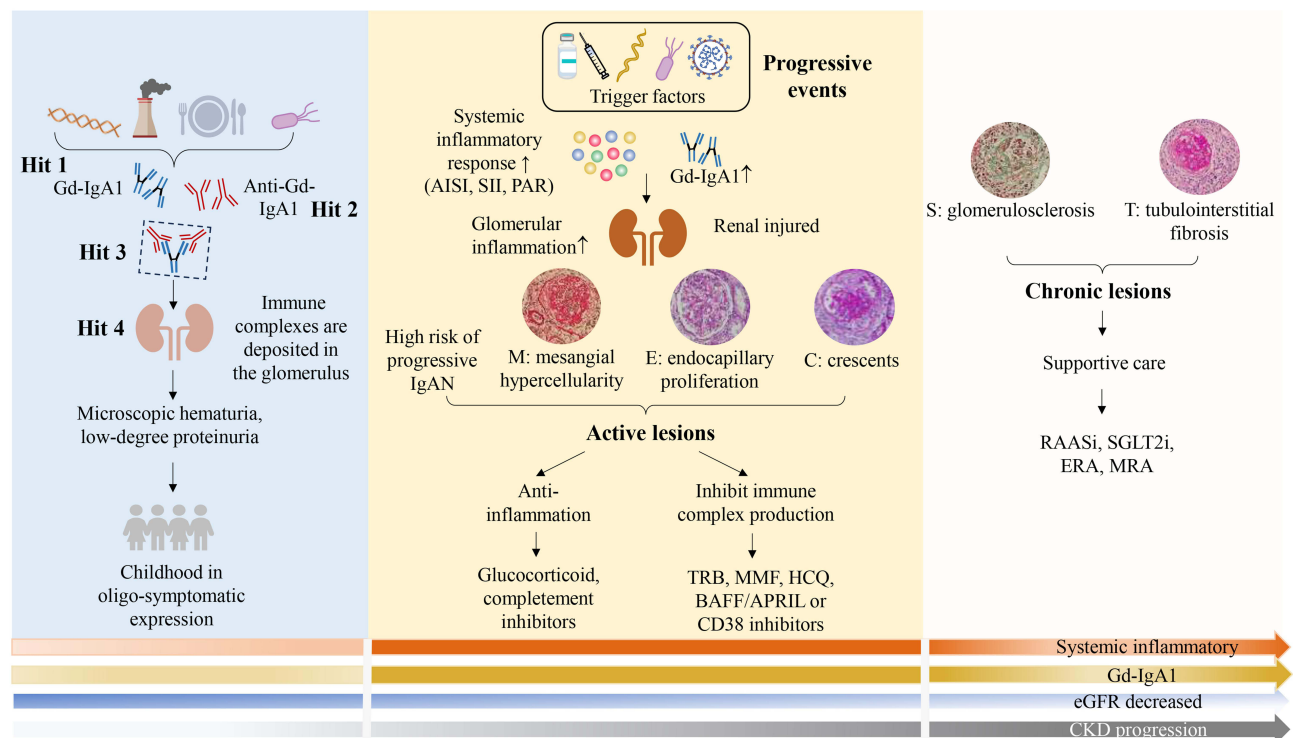


Figure 1 Onset, progression, and treatment of IgA nephropathy. The interaction between genetic and environmental factors induces the production of Gd-IgA1. Subsequent antibody generation and immune complex deposition in the kidneys lead to the development of IgAN. In the early stage, the disease may present with only oligo-symptomatic. Infections and vaccination are the triggers of disease progression, manifesting as enhanced systemic inflammatory (AISi, SII, PAR) and immune responses (Gd-IgA1), with active lesions (mesangial hypercellularity, endocapillary proliferation or crescents) representing the predominant pathological finding. Treatment in the active phase primarily focuses on reducing inflammation and inhibiting immune complex formation. With recurrent episodes or persistent slow progression, the disease ultimately manifests as chronic lesions, primarily represented by glomerulosclerosis and tubulointerstitial fibrosis lesions. At this stage, the prime therapeutic strategy shifts to supportive care.

Abbreviations: APRIL, a proliferation-inducing ligand; AISi, aggregate index of systemic inflammation; BAFF, B-cell activating factor; ERA, endothelin-1 receptor antagonist; Gd-IgA1, galactose-deficient IgA1; IgAN, IgA nephropathy; MMF, mycophenolate mofetil; MRA, mineralocorticoid receptor antagonists; PAR, platelet-to-albumin ratio; RAASi, renin-angiotensin system antagonists; SGLT2i, sodium-glucose transporter-2 inhibitors; SII, systemic immune-inflammation index; TRB, targeted-release budesonide.

with acute exacerbations. Both innate and adaptive immune responses contribute to its pathogenesis, and disease activity and fluctuations may be associated with elevated systemic inflammation levels. Clinical observations indicated that events such as bacteria or viruses infections or vaccination, can trigger systemic inflammatory responses and immune activation, resulting in the recurrence or exacerbation of IgAN.^{11,12} Several indicators of systemic inflammation have been identified as being associated with a poor prognosis in IgAN patients.^{13–15}

The 2025 KDIGO guidelines recommend comprehensive lifestyle interventions in IgAN patients, along with strict blood pressure control.³ For those at risk of disease progression, active treatment is required, with therapeutic approaches primarily focused on three key areas: anti-glomerular inflammation (eg: glucocorticoid [CS], iptacopan), suppression of pathogenic IgA production (eg: targeted-release budesonide and telitacept), and slow chronic kidney disease progression (eg: renin-angiotensin system antagonists, sodium-glucose transporter-2 inhibitors and endothelin-1 receptor antagonism).^{1,16}

Notably, active lesions may subside after treatment and can remerge at any time in a patient's lifetime in response to different triggers. It typically manifests as increased proteinuria, with histological features showing M1, E1, or C1/2 lesions.^{4–6} Patients with high activity and little chronicity who are treated with immunosuppressive therapy (IST) demonstrate a significantly lower risk of end-stage renal disease (ESRD).¹⁷

IgAN's status as a lifelong managed disease requires us to understand the major mechanisms of injury that may play a role throughout life and to implement more specific measures to reduce the global impact of IgAN. Although previous reviews have thoroughly discussed the Oxford classification or clinical risk factors for IgAN, there are limited reviews linking systemic inflammation to renal histological activity. This study summarizes the latest evidence on the treatment

and prognosis of IgAN based on pathological scoring, and preliminarily explores the hypothesis linking systemic inflammatory responses, infections, and vaccinations to active lesions, offering new insights for deepening the understanding of IgAN mechanisms.

In this narrative review, we searched relevant literatures published before 21 December 2025 through electronic databases, including PubMed, EMBASE and Web of Science, using the following keywords: (“immunoglobulin A nephropathy” OR “IgA nephropathy”) AND (“MEST” OR “MEST-C” OR “Oxford” OR “Oxford Classification”) AND (“inflammation” OR “innate immunity” OR “adaptive immunity”). Then, proceed to read, categorize and summarize the literature.

Evaluation of Treatment and Prognosis in IgAN Based on MEST-C Score

KDIGO 2025 guideline suggested that histological data at the time of biopsy can be used for the initial assessment of IgAN patients.³ The correlation between baselines total MEST-C scores and renal outcomes has been confirmed,¹⁸ with T lesions are consistently associated with poorer renal outcomes.^{19–24} There were also reported that M1 and S1 lesions were risk factors affecting proteinuria remission, requiring more intensive treatment strategies.²⁵ The antiproteinuric effect of iptacopan was independent of pathological scores, with consistent efficacy observed across various subgroups.²⁶ We summarized relevant studies on the relationship between pathological scores and disease prognosis over the past five years (Table 1).

Histopathological findings have been used to assess disease activity and chronicity.⁴ Itami et al found that patients with M1, E1, S1, or C1/2 scores demonstrate higher renal survival rates with CS therapy. Therefore, researchers added the scores of these lesions to create a “steroid responder score” (SRS) ranging from 0 to 4 points (point 0: low, 1–2: medium, and 3–4: high), while T lesions were classified separately as “steroid non-responder score” (SNRS, 0 or 1 point). Subsequently, by combining these two sets of scores, six new risk combinations were derived. The results showed that patients with a high SRS (more active lesions) benefited from CS treatment, regardless of SNRS score, and CS treatment was ineffective for moderate SRS/low or high SNRS.¹⁷ Guo et al classified the presence of crescents and at least one other active lesion (fibrillar necrosis or endocapillary hypercellularity) as severe glomerular activity. IST (CS ± cyclophosphamide [CYC], mycophenolate mofetil [MMF] or calcineurin inhibitors) was a more significant protective factor for renal outcomes in patients with severe glomerular activity and/or those with combined T0 lesions.²⁷ Recently, Keskinis et al subdivided 37 IgAN patients based on combinations of active (M and E) and chronic (S and T) histological lesions. Six (75.0%) patients with severe activity and mild chronicity and 10 (71.4%) patients with severe activity and severe chronicity achieved a reduction in proteinuria of over 30% with stable estimated glomerular filtration rate (eGFR) three months after targeted-release budesonide treatment. Authors considered that presence of tubular atrophy, combined with M1 and/or E1 cannot limit the potential benefit of targeted-release budesonide administration.⁶ Another study demonstrated that extended treatment with telitacicept was more effective in reducing proteinuria among subgroup of patients with severe pathological changes (M1, E1, T1/2 and C1/2).³² These studies suggested that high active lesions may be the most important parameter for determining IST treatment response.

Specially, the relationship between crescentic lesions and prognosis and treatment response in IgAN remains controversial.^{33,34} Chen et al used MEST score to predict composite renal outcomes, which achieved an area under curve of 0.76, with a sensitivity of 60.2%, and specificity of 83.6%. The addition of C lesion did not alter the area under curve and resulted in only a slight increase in sensitivity and specificity (63.0% and 84.8%).³⁵ When the proportion of crescentic glomeruli was below 50%, the intensive regimen of CS combined with IST (CYC, MMF, tacrolimus) did not demonstrate superior renal protection compared with CS alone.³¹ Similarly, no evidence was found in three other studies that the presence of crescents influenced prognostic assessment.^{19,21,28} However, a prospective (TESTTING) study of 279 IgAN patients showed that 17.6% were classified as C1/2 lesions. These patients experienced a significant reduction in the risk of renal outcomes following CS treatment, though this did not reach statistical significance due to the small sample size, there was a statistically difference in the entire cohort of 379 patients.²⁹ In contrast, another study found that IST therapy (CS ± MMF, leflunomide, calcineurin inhibitors) was significantly associated with a reduced risk of composite outcomes in IgAN patients with C1 lesions.³⁰ In addition, presence of C2 lesions was an independent risk

Table I Summarize the Relevant Studies of MEST-C Score with Treatment Response or Prognosis in Patients with IgAN Over the Past Five years

Authors	Research Design	Patients (Male), n	Treatments (n)	Renal Biopsy (%)	Laboratory Test			Follow-Up (Median, y)	Results	Conclusion
					24-h UP (g/d)	eGFR (mL/min/1.73m ²)	Scr (mg/dl)			
Alza-Arcila et al ¹⁹	Retrospective cohort study	397 (203)	RAASI/IST	M1: 326 (82.1); E1: 83 (20.9); S1: 252 (63.5); T1: 67 (16.9); T2: 68 (17.1); C1: 63 (15.9); C2: 19 (4.8)	1.7 (0.6–3.5)	54.0 (33.0–94.0)	1.4 (0.9–2.1)	4.6 (2.2–7.8)	122 patients (30.7%) progressed to ESRD, S1 (HR 2.1, 95% CI 1.09–4.09, $P = 0.026$), T1/T2 (HR 1.96, 95% CI 1.42–2.71, $P < 0.001$), and 24-h UP (HR 1.0002, 95% CI 1.0001–1.0002, $P < 0.001$) are independent risk factors for ESRD.	S1 and T1/T2 combined with clinical variable were independent prognostic factors for ESRD
Chen et al ²⁰	Retrospective cohort study	366 (189)	RAASI/ Statin/ Pentoxifylline	M1: 206 (58.4); E1: 105 (29.7); S1: 220 (62.3); T1/2: 103 (19.7); C1/2: 50 (14.0)	UPCR: 1159.0 (422.7, 2612.09) mg/g	53.8 (31.5, 86.1)	1.3 (0.9, 2.1)	3.04	Patients with the composite outcome had a higher rates of M (71.9 vs. 52.8%, $P = 0.03$), E (41.7 vs. 24.8%, $P = 0.012$), T1 (37.9 vs. 13.2%, $P < 0.001$), T2 (22.3 vs. 3.2%, $P < 0.001$), and C2 (6.6 vs. 1.5%, $P = 0.04$); lower baseline eGFR and higher UPCR were associated with more severe M, E, S, T, and C scores (all $P < 0.05$); T1 vs. T0 and T2 vs. T0 significantly associated with worse outcomes (OR: 5.3, 95% CI 2.96–9.58 and OR: 12.0, 95% CI 5.00–29.61, both $P < 0.001$); T score was highest predictive power (AUC 0.73, sensitivity 60.2%, specificity 83.6%).	T lesion consistently correlated with worse renal outcomes
Guo et al ²⁷	Retrospective study	1262 (630)	IST	M1: 511 (40.5); E1: 415 (32.9); S1: 807 (63.9); T1/2: 450 (35.7)	1.2 (95% CI 0.7–2.4)	85.0 $\pm$ 31.0	-	3.8 (95% CI 2.0–6.8)	C2 lesions was a significant risk factor for kidney outcome in patients without IST (HR: 1.85, 95% CI 1.03–3.31, $P = 0.040$) and in patients with T0 lesions (HR: 3.61, 95% CI 2.03–6.43, $P < 0.001$, reference to C0); IST significantly reduce the risk of kidney outcomes in IgAN patients with severe glomerular activity (HR: 0.30, 95% CI 0.12–0.74, $P = 0.009$) and in patients with T0 lesions (HR: 0.14, 95% CI 0.04–0.54, $P = 0.005$, reference to those without IST).	IST could reduce renal risk in IgAN patients with both C2 and T0 lesions, or with crescents plus another active lesion
Haaskjold et al ²¹	Retrospective study	306 (234)	IST/RAASI	M1: 103 (33.7); E1: 81 (26.5); S1: 168 (54.9); T1/2: 34 (11.1); C1/2: 70 (22.8)	1.7 $\pm$ 2.3	78.4 $\pm$ 27	-	17.1 (range 0.2–28.1)	61 (20%) patients reached ESRD; S and T lesions were significantly associated with poor outcomes (HR: 3.76, 95% CI 1.78–7.93, $P = 0.001$; HR: 6.43, 95% CI 3.73–11.07, $P < 0.001$, respectively).	S1 and T1/T2 correlated with the development of ESRD
Itami et al ¹⁷	Retrospective cohort study	858 (349)	CS/RAASI/ Tonsillectomy	M1: 420 (49.0); E1: 385 (44.9); S1: 619 (72.1); T1/2: 233 (27.2); C1/2: 409 (47.7)	0.7 (0.3–1.4)	77.0 (60.0–95.6)	-	-	Patients with M1, E1, S1, T0, and C1/2 who received CS therapy had a higher kidney survival rate than those who did not (both $P < 0.05$), while T1/2 scores were not responsive to CS.	Patients with M1, E1, S1, and C1/2 scores responded to CS therapy
Kang et al ²²	Retrospective cohort study	4151 (2137)	-	M1: 2836 (68.3); S1: 1164 (28.0); T1/2: 375 (9.0); C1/2: 930 (20.7)	UPCR: 1.1 (0.5–2.3) g/g	90.0 (64.0–112.0)	0.9 (0.8–1.2)	6.1 (2.7–9.9)	304 (7.3%) patients progressed to ESRD, and increased severity of chronicity was linked to rapid progression to ESRD; T2 were significantly associated with ESRD progression (HR: 1.47, 95% CI 1.60–2.04, $P = 0.022$).	T2 was significantly associated with renal outcome
Keskinis et al ⁶	Prospective, open label, multi-center study	37 (26)	TRB + RAASI	M1: 34 (91.9); E1: 24 (64.9); S1: 33 (89.2); T1/2: 24 (64.9); C1/2: 13 (35.1)	2.8 $\pm$ 1.6	57.3 $\pm$ 23.5	-	0.5	17 (45.94%) achieve a $> 30\%$ reduction in proteinuria with stable eGFR after 3 months of TRB treatment; TRB-treated M1, E1, and S1 patients showed significantly better renal function and proteinuria improvement than M0, E0, and S0 patients, respectively (both $P < 0.001$).	M1, E1 and S1 were parameters that favored response to TRB treatment
Perkovic et al ²⁶	Phase 3, double-blind, randomized, placebo-controlled trial	250 (131)	Treat: iptacopan (125); Control: placebo (125)	M1: 76 (60.8) vs. 80 (64.0); E1: 36 (28.8) vs. 36 (28.8); S1: 87 (69.6) vs. 89 (71.2); T1/2: 48 (38.4) vs. 53 (42.4); C1/2: 35 (28.0) vs. 22 (17.6)	24-h UPCR: 1.8 (1.4–2.7) vs. 1.9 (1.5–2.8)	62.7 $\pm$ 26.0 vs. 65.5 $\pm$ 26.7	-	0.75	Iptacopan significantly reduced 24-h UPCR by 38.3% compared to placebo (95% CI 26.0–48.6, $P < 0.001$); iptacopan consistently reduced proteinuria across all subgroups stratified by pathological scores.	Compared to placebo, iptacopan significantly reduced proteinuria in IgAN patients, regardless of pathological score.

Saleem et al ¹⁸	Retrospective study	93 (63)	RAASi/CS/IST	M1: 53 (57.0); E1: 52 (55.9); S1: 66 (71.0); T1/2: 43 (46.2); C1/2: 24 (25.8)	2.3 (0.03–11.5)	39.0 (3.0–170.0)	1.9 (0.5–14.5)	1.0	T and C scores were significantly associated with the renal outcome (both Lok-rank $P < 0.001$); baseline Scr (HR: 1.188, 95% CI 1.012–1.395, $P = 0.036$), total MEST-C scores (HR: 0.429, 95% CI 0.211–0.872, $P = 0.019$) and T-score (HR: 4.691, 95% CI 2.034–10.819, $P < 0.001$) were significant with the outcome.	T and C scores, baseline Scr, and total MEST-C score significantly affect the renal outcome
Satirapoj et al ²⁸	Retrospective cohort study	67 (21)	Treat: CS + RAASi (46); Control: RAASi (21)	M1: 24 (52.2) vs. 9 (42.9); E1: 16 (34.8) vs. 11 (52.4); S1: 33 (71.7) vs. 21 (100.0); T1/2: 17 (37.0) vs. 12 (57.1); C1/2: 15 (32.6) vs. 5 (23.8)	3.7 ± 2.4 vs. 3.1 ± 1.8	59.6 ± 32.5 vs. 40.8 ± 18.6	-	1.7 (0.6–1.9)	CS treatment was associated with a significantly slower rate of eGFR decline in patients with baseline eGFR >50 ($P = 0.011$), M0 ($P = 0.049$), or C0 ($P = 0.026$).	CS reduced kidney progression risk in IgAN patients, especially in patients with baseline GFR > 50 and Oxford M0 and C0
Shen et al ²⁵	Retrospective study	2141 (1082)	RAASi/IST	*M1: 715 (40.8), E1: 526 (30.0), S1: 1162 (66.4), T1/2: 553 (31.6), C1/2: 1062 (60.7)	1.3 (0.6–2.4)	80.0 (52.0–103.0)	-	5.8	Age at onset, baseline eGFR, baseline 24-h UP, M1 and S1 (both $P < 0.05$) significant risk factors influencing proteinuria remission	M1 and S1 lesion were risk factors influencing proteinuria remission
Shi et al ²⁹	Second analysis of the TESTING trial	279 (174)	Treat: CS (139); Control: placebo (140)	M1: 51 (36.7) vs. 38 (27.1); E1: 33 (23.7) vs. 42 (30.0); S1: 119 (85.6) vs. 120 (85.7); T1/2: 50 (36.0) vs. 56 (40.0); C1/2: 18 (12.9) vs. 31 (22.1)	2.0 (1.4–3.0) vs. 2.0 (1.5–3.0)	57.0 (44.0–75.0) vs. 61.0 (40.0–78.0)	-	5.1 (3.1–6.8) vs. 4.7 (3.0–6.4)	48 (35%) and 65 (46%) reached the combined endpoint (40% decline in eGFR or kidney failure) in CS and control groups, respectively ($P = 0.04$); patients with C lesions (C0: HR, 0.6 [95% CI, 0.4–0.9]; C1/2: HR, 0.05 [95% CI, 0.008–0.3]; $P = 0.4$) and cellular segmental sclerosis lesions were associated with a greater benefit of CS therapy ($P = 0.03$).	Presence of crescents and cellular segmental sclerosis in IgAN patients was associated with a favorable response to CS
Tang et al ³⁰	Retrospective cohort study	782 (363)	Treat: IST (391); Control: supportive care (21)	M1: 278 (71.1) vs. 291 (74.4); E1: 142 (36.3) vs. 145 (37.1); S1: 295 (75.4) vs. 294 (75.2); T1/2: 137 (35.0) vs. 133 (34.0); C1/2: 182 (46.6) vs. 183 (29.4)	1.23 (0.63, 2.09) vs. 1.09 (0.50, 2.27)	99.89 (87.52, 110.52) vs. 99.85 (86.71, 110.88)	92.00 (69.00, 118.40) vs. 89.00 (69.00, 117.50)	4.77 (4.31, 5.13)	In patients with C1 and S1 lesions, IST therapy significantly reduced the risk of the primary composite outcome compared with supportive care alone (HR 0.45, 95% CI 0.22–0.93, $P = 0.032$; HR 0.52, 95% CI 0.29–0.91, $P = 0.023$, respectively).	Patients presenting with C1 or S1 lesions had significant response to IST therapy
Thapa et al ²³	Retrospective cohort study	52 (23)	RAASi/IST	M1: 30 (57.7); E1: 25 (48.1); S1: 46 (88.5); T1: 32 (61.5); T2: 2 (3.9); C1: 30 (57.7); C2: 4 (7.7)	3.3 ± 1.5 gm/d	50.3 ± 31.4	2.3 ± 1.7	0.5	Among 46 patients with S1, 11 (24.4%) achieved complete remission, 30 (66.67%) partial remission, and 5 (11.11%) progressed to ESRD; in those with T1/2, 1 (2.94%) achieved complete remission, 14 (41.18%) partial remission, and 5 (14.71%) progressed to ESRD.	Patients with S1 and T1/2 had higher rates of progression to ESRD
Wang et al ³¹	Prospective cohort study	134 (57)	RAASi/IST	M1: 89 (82.4); E1: 76 (70.4); S1: 65 (60.2); T1: 45 (41.7); T2: 32 (29.6); C2: 57 (100)	4.4 ± 2.9	39 ± 32	-	3.3 ± 2.4	Among IgAN patients with C2 lesions, the proportions progressing to kidney failure at 3 years were 47%; T2 lesions (HR: 2.490, 95% CI 1.179–5.259, $P = 0.017$) were identified as an independent risk factor for ESRD in this population.	Patients with IgAN accompanied by C2 lesions have a poor clinical prognosis
Weng et al ³²	Retrospective study	82 (48)	Treat: telitacicept + RAASi (41); extended (26) and short-term group (15); Control: RAASi (41)	M1: 21 (51.2) vs. 15 (36.6); E1: 17 (41.5) vs. 16 (39.0); S1: 39 (95.1) vs. 37 (90.2); T1/2: 22 (53.7) vs. 13 (31.7); C1/2: 20 (48.8) vs. 23 (56.1)	2.9 (1.2–6.6) vs. 1.5 (1.0–3.0)	53.9 ± 23.4 vs. 74.1 ± 25.1	-	1	Extended telitacicept treatment significantly reduced UP at 12 months compared to RAASi alone (–56.8% vs. –0.3%, $P < 0.01$), with more pronounced clinical benefits observed particularly in IgAN patients presenting with severe pathological changes (M1, E1, T1/2, C1/2).	Extended telitacicept is associated with enhanced benefits in IgAN patients with severe pathological lesions
Zoccali et al ²⁴	Second analysis of a prospective study	1130 (791)	IST or RAASi	M1: 316 (28.0); E1: 124 (11.0); S1: 791 (70.0); T1/2: 237 (21.0); C1/2: 119 (10.5)	1.2 (0.5–2.4)	74.0 ± 31.0	-	7 (4.1–10.8)	279 (24.7%) reached the combined endpoint; M1, S1 and T1/T2 were independently related with the combined endpoint (HR: 1.34, 95% CI 1.02–1.75, $P = 0.037$; HR: 1.61 (1.10–2.36), $P = 0.01$; HR: 2.46, 95% CI 1.80–3.36, $P < 0.001$, respectively); T1/2 was significantly related to the rate of renal function loss ($P < 0.001$).	T was the pathological lesion most robustly associated with adverse renal outcomes

Notes: Laboratory test data were present median (interquartile range) or mean ± standard deviation or mean (95% CI). * MEST-C scores were available for 1751 patients.

Abbreviations: AUC, area under curve; C, crescents; CI, confidence interval; CS, glucocorticoid; eGFR, estimated glomerular filtration rate; E, endocapillary proliferation; ESRD, end-stage renal disease; HR, hazard ratio; M, mesangial hypercellularity; IgAN, Immunoglobulin A nephropathy; IST, CS or CS plus immunosuppressive agents; RAASi, renin-angiotensin-aldosterone system inhibitor; S, segmental glomerulosclerosis; Scr, serum creatinine; T, interstitial fibrosis/tubular atrophy; TRB, targeted-release budesonide; UP, urine protein, UPCR, urine protein-to-creatinine ratio.

factor for composite renal endpoint in patients without IST and in patients with T0 lesions (with or without IST). The risks were 1.85 times and 3.61 times higher than those in patients with C0 lesions, respectively.²⁷

IgAN patients with endocapillary proliferation had a higher level of proteinuria. A large number of differentially expressed genes have been found in their glomeruli, and these genes are mainly involved in innate immunity and complement activation.³⁶ Additionally, the M2 macrophage marker CD163 was highly expressed in the glomerular of this lesion,³⁶ all of which stimulate glomerular inflammation. Subsequent study further confirmed that the level of urinary soluble CD163 was positively correlated with the scores of E and C lesions, and the reduction in its levels following CS therapy was also correlated with the remission of proteinuria and a reduced risk of renal progression events during follow-up.³⁷ It has been confirmed that active glomerular lesions in IgAN patients can be reversed by IST treatment, accompanied by a significant reduction in proteinuria and hematuria.³⁸ IgAN patients with elevated level of systemic inflammation have also been found to be more prone to exhibiting E and C lesions.^{13,39} It means that the presence of this active proliferative lesion may indicate high systemic inflammatory level and glomerular inflammation.

Of course, the activity and chronicity phenotypes in IgAN are not yet well defined, MEST-C scores exist geographic variations,⁵ therefore, the efficacy prediction for each pathological lesion cannot be completely determined. Additionally, the selection of IST is influenced by racial disparities and adverse events. Limited follow-up periods constrain the assessment of long-term efficacy, and existing evidence primarily stems from observational studies, lacking randomized controlled trials to validate its long-term efficacy and safety. Future efforts are needed to develop more accurate predictive tools for assessing disease prognosis and treatment efficacy.

Systemic Inflammatory Response and the Progression of IgAN

During the early stages of IgAN, the kidneys may be only mildly involved, manifesting as microscopic hematuria or low-degree proteinuria. We speculated that the disease state of some adult IgAN patients probably originates in childhood in oligo-symptomatic expression, with unaware renal involvement due to lack of medical examination at a young age. In fact, majority of IgAN patients are diagnosed by chance.

The mucosal origin of pathogenic Gd-IgA1 in IgAN has been recognized, and episodes of disease activity accompanied by gross hematuria and proteinuria are often associated with acute respiratory or gastrointestinal infections, recurrent mucosal infections provoke episodic surges in aberrant IgA production.¹² Bacterial or viral infections, or vaccination, are factors that trigger mucosal immune response, and the activation of mucosal immunity is one of the key mechanisms including systemic inflammatory responses. Inflammation can cause changes in blood components such as neutrophils, macrophage, and lymphocyte. The aggregate index of systemic inflammation is an indicator that more thoroughly assesses systemic inflammatory by integrating this information. It was significantly positively correlated with serum creatinine, 24-hour proteinuria, total cholesterol, and triglyceride, and negatively correlated with serum albumin and eGFR.¹³ Similarly, systemic immune-inflammation index is another novel inflammatory marker. Patients with higher scores exhibit more severe clinical manifestations at baseline, stronger disease activity, and a higher incidence of renal adverse outcomes, potentially reflecting a pronounced systemic inflammatory level in IgAN patients.^{14,15} Platelet-to-albumin ratio, which is positively correlated with C-reactive protein, also indicates systemic inflammatory response in IgAN. Patients with high platelet-to-albumin ratio levels have more severe proteinuria, more obvious E and C lesions, and more aggressive treatment.³⁹ Based on the above evidence, it is reasonable to assume that systemic inflammatory markers are significantly associated with IgAN disease activity indicators, suggesting that systemic inflammatory responses may play a role in the pathogenesis and progression of the disease. In the absence of acute infection, systemic inflammatory responses may remain quiescent. However, due to the retrospective nature of this study, establishing these markers as surrogate indicators of disease activity requires further evidence from longitudinal studies and rigorous validation methods. Treatment during active lesions primarily on the anti-inflammation (CS and complement inhibitors) and inhibit immune complex production, including budesonide, telitacicept, MMF or hydroxychloroquine.⁴⁰

Subsequently, renal reserve function is activated and compensates for the early loss of glomerular function, eventually leading to chronic lesions characterized by glomerulosclerosis, tubulointerstitial fibrosis, and persistent low-grade inflammatory and immune response. At this point treatment shifts to support care represented by renin-angiotensin

system antagonists, sodium-glucose transporter-2 inhibitors, endothelin-1 receptor antagonism, and mineralocorticoid receptor antagonists¹⁶ (Figure 1).

Innate Immunity and Adaptive Immunity in IgAN

Innate immunity provides a rapid but nonspecific defense against pathogens and danger signals, it is primarily mediated by macrophages, neutrophils, dendritic cells (DCs), and granulocytes.⁴¹ The innate immune system plays a vital role in IgAN, particularly through toll-like receptors (TLRs), which are responsible for detecting pathogen-associated molecular patterns or damage-associated molecular patterns.^{42,43} In patients with IgAN, proteinuria levels are associated with the mRNA expression of TLR2, TLR3, TLR5, and TLR9 as well as TLR7 protein intensity, while serum IgA levels are correlated with TLR4 mRNA expression.^{44,45}

Infection-induced TLR activation may exacerbate IgAN by stimulating innate immune cells. Lipopolysaccharides from gram-negative bacteria walls and glycoproteins on the virus surface were recognized by TLR4. Subsequently, TLR4 interact with toll-interleukin-1 receptor domain adaptor molecule 1 and MyD88 adaptor molecule, activating the interferon regulatory factors and NF- κ B pathway, respectively, producing inflammatory cytokines, such as interferon- γ and interferon- β , interleukin (IL)-6, IL-1, tumor necrosis factor- α , a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF).^{46,47} The high expression of these cytokines induced B-cell IgA class switching and participated in abnormal IgA1 galactosylation.^{48,49} TLR9 stimulate interactions between DCs and B-cell in tonsils-associated lymphoid tissue.⁴³ DNA sequences (CpG-ODN) commonly found in bacteria and viruses are ligands for TLR9 and can induce innate immune response. They activate MyD88 signaling and promote adaptive immune responses and B-cell activation through IL-6 and APRIL pathways, including the production of Gd-IgA1 and corresponding immune complexes.⁵⁰ TLR7 is located in the endosome, where it can recognize single-stranded RNA derived from viruses and mRNA vaccines,^{46,51} and is also involved in the generation of inflammation cytokines and Gd-IgA1^{45,52} (Figure 2).

TLRs induce DCs maturation, promoting their migration to lymph nodes, where DCs become potent activators of naive T cells and act as a bridge between innate and adaptive immunity.⁵⁶ A higher proportion of DCs were observed in lymphocytes from IgAN mice that had undergone fecal microbiota transplantation.⁵⁷ B-cell trigger class switching through T cell-dependent and T cell-independent pathways, ultimately differentiating into IgA-secreting plasma cells.⁵⁶ The activation of innate and adaptive immunity may partially amplify the systemic inflammatory response, driving disease progression. Activation of TLR4 by lipopolysaccharide promotes peripheral B lymphocytes core I β 3-gal-T-specific molecular chaperone (Cosmc) methylation, thereby reducing the glycosylation level of IgA1 molecules, which is basis of the pathogenesis of IgAN.^{58,59} N-acetylgalactosamine (GalNAc) is expressed on the surface structures of pathogens including respiratory syncytial virus, Epstein-Barr virus, herpes simplex virus, and streptococci, and may induce the production of cross-reactive antibodies.^{60,61} The MTMR3/HORMAD2/LIF/OSM locus has been reported to be associated with genetic susceptibility to IgAN, and this region may influence serum IgA levels by increasing MTMR3 expression.⁶² Furthermore, animal experiments have demonstrated that MTMR3 can enhance IgA production in B cells, glomerular IgA deposition, and mesangial cell proliferation in a T cell-independent manner by mediating the activation of the TLR9 pathway.⁶²

The complement system is involved in the pathogenesis of IgAN and is also an important component of innate immunity. Multiple soluble molecules in the complement system, such as mannan-binding lectin (MBL), ficolin, and collectin-11, can also trigger immune responses by recognizing pathogen-associated molecular patterns or damage-associated molecular patterns.^{53,54} Complement and TLRs are co-activated in response to microbial infection, complement anaphylatoxin receptor signaling stimulated by C3a or C5a synergizes with TLR-MyD88 signaling to promote the activation of p38 MAP kinases and transcription factors, leading to elevated expression levels of proinflammatory cytokines and costimulatory molecules.⁵⁵ Of note, MBL can also recognize carbohydrate structures on antibodies, including the common IgG glycosylation variant IgG-G0 and polymeric IgA.⁶³ In IgAN, Gd-IgA1 revealed abnormal carbohydrate structures within the hinge region O-glycans. These aberrant structures may serve as potential ligands for MBL, activating MBL-associated serine proteases and initiating the lectin pathway. This process also establishes a complex network that bridges adaptive and innate immunity. Additionally, Gd-IgA1 immune complexes can also activate complement directly as they bind C3 and MBL.⁷ Similarly, alternative pathway is also a key effector pathway

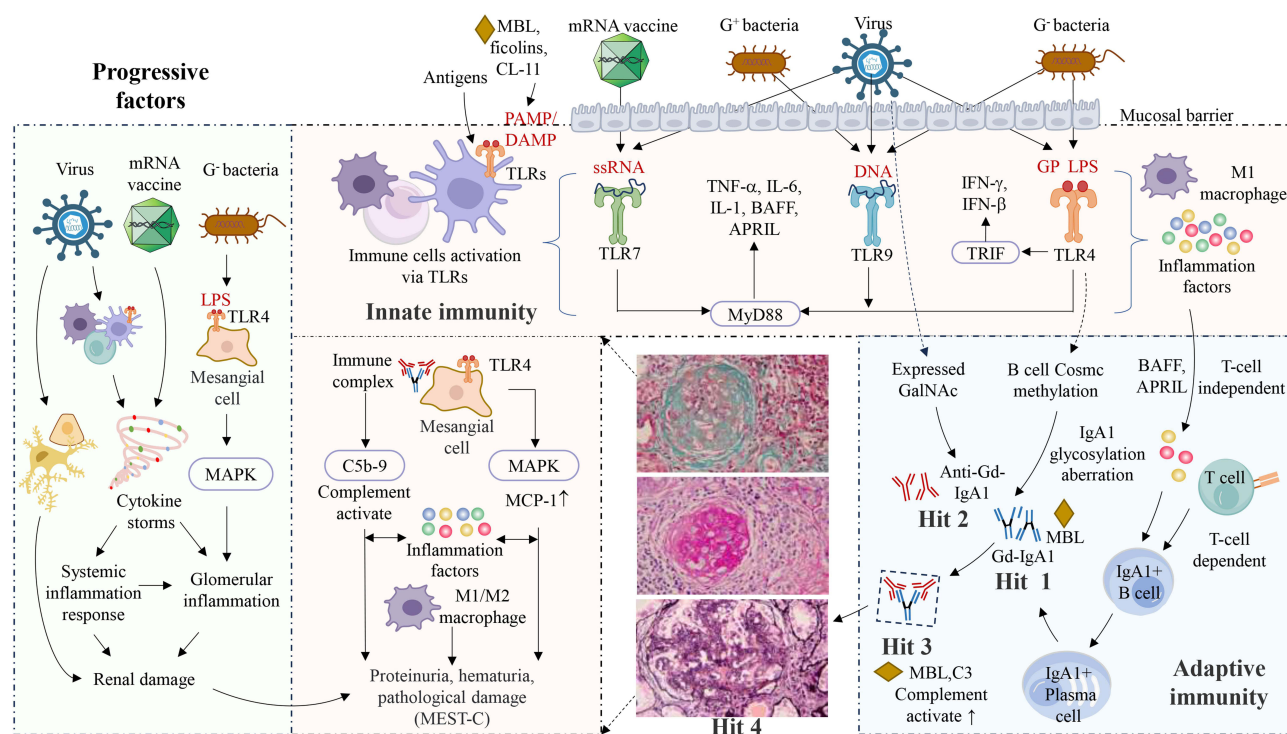


Figure 2 Innate immunity and adaptive immunity in IgAN. Pathogens invasion serves as the initiating signal for the activation of innate immune responses at mucosal sites. Upon recognition of pathogen-associated ligands, TLRs located on innate immune cells are activated, inducing the production of a large number of cytokines (IL-1, IL-6, TNF-α, BAFF, APRIL, IFN-γ, IFN-β).⁴⁶ Activated TLRs mediate the maturation of dendritic cells, thereby establishing them as a bridge between innate and adaptive immune responses, ultimately producing into IgA-secreting plasma cells. BAFF and APRIL can induce B-cell IgA class switching and participated in production of Gd-IgA1.⁴⁹ The substantial production of Gd-IgA1 can induce autoantibody generation, leading to the formation of immune complexes and deposit in the kidneys and activate the complement system.⁷ Complement system is also an important component of innate immunity, MBL, ficolin, and collectin-11, can also trigger immune responses by recognizing DAMP and PAMP;^{53,54} synergizing with TLRs to promote the release of pro-inflammatory cytokines,⁵⁵ all of which are the multiple pathogenetic hits identified in IgAN. Additionally, Gd-IgA1 immune complexes can also activate complement directly as they bind C3 and MBL.⁷ Reinfection with pathogens may contribute to the progression of IgAN, especially for individuals with immune dysregulation. Bacteria damage the kidneys by inducing cytokine production through activation of TLR4 on mesangial cells. Viruses may affect the kidneys either through direct stimulation or by indirectly inducing cytokine storms. The receptor-binding domain of vaccines can act as a superantigen, triggering cytokine storms that damage renal tissue. Different pathogens may engage distinct mechanisms to initiate disease, leading to heterogeneity in disease severity, which ultimately necessitates different treatment strategies.

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; CL-11, collectin-11; Cosmc, core 1 β3-gal-T-specific molecular chaperone; DAMP, damage-associated molecular patterns; GP, glycoprotein; IL, interleukin; LPS, lipopolysaccharide; MAPK, p38 MAP kinase; MBL, mannan-binding lectin; MCP, monocyte chemoattractant protein-1; PAMP, pathogen-associated molecular patterns; ssRNA, single-stranded RNA; TLR, toll-like receptors; TNF-α; INF, interferon; TRIF, toll-interleukin-1 receptor domain adaptor molecule 1; ↑, increased; ↓, decreased.

leading to glomerular injury in IgAN. Upon complement activation, C3 is cleaved to form C5 convertase, which subsequently cleaves C5 into the anaphylatoxins C5a and C5b fragment.⁵⁴ C5b initiates the formation of the membrane attack complex (C5b-9), induces mesangial cell activation and facilitates the release of inflammatory mediators and extracellular matrix components, thereby exacerbating glomerular injury and driving disease progression. Multiple clinical studies demonstrated that complement activation fragments such as MBL, C3, C5b-9, and factor H-related protein are elevated in patient serum or deposited in the kidneys, and are associated with disease activity and prognosis.^{54,64} Targeted therapies for specific complement components continue to achieve new breakthroughs. Compared with placebo, iptacopan (a B-factor inhibitor) reduced the 24-hour urine protein-to-creatinine ratio by an average of 38.3% at month 9.²⁶

In addition, *in vitro* studies showed that stimulation of mesangial cells with human secretory IgA and lipopolysaccharide elevates TLR4 mRNA and protein expression. TLR4 activation promotes p38 MAP kinase and enhances monocyte chemoattractant protein-1 secretion, which participate in the injury of mesangial cells in IgAN.⁶⁵ In addition, cytokines promote the polarization of macrophages into M1 and M2. M1 macrophages recruited to the glomerular facilitate inflammatory response, while M2 macrophages accelerate mesangial cell proliferation and interstitial fibrosis, showing positive correlations with proteinuria and fibrotic progression.⁶⁶ Further research confirmed by the correlation

between urinary soluble CD163 levels and eGFR, proteinuria, and serum albumin.³⁷ Increased glomerular inflammation conversely exacerbates systemic inflammatory responses and immune dysregulation.

IgAN usually onset or relapse immediately after an infection and may also be triggered by vaccination, but the severity of the disease induced by these triggers differs, necessitating distinct therapeutic approaches.¹¹ We propose a hypothesis that some individuals may have pre-existing low levels of Gd-IgA1, anti-Gd-IgA1 antibodies, or even immune complexes. The immune dysregulation within these latent individuals, analogous to the “four-hit” hypothesis in IgAN, may constitute the pathological basis for susceptibility to IgAN. Upon re-exposure to the pathogen, different triggers may activate systemic inflammation and immune responses through distinct immune pathways, thereby leading to varying degrees of IgAN. TLR4 is expressed in both mesangial cells and podocytes in the kidney,⁴² lipopolysaccharide activation of TLR4 may directly stimulate kidney damage. A retrospective study found that microscopic hematuria prior to SARS-CoV-2 mRNA vaccination is the primary predictor of gross hematuria following vaccination in IgAN patients.⁶⁷ Except for hematuria and proteinuria, vaccination may also cause systemic symptoms such as fever and pain,¹¹ reflecting a widespread inflammatory response. The mechanism linking vaccines to IgAN onset remains speculative at present. Some studies suggested that the receptor-binding domain of the vaccine itself can also act as a superantigen, triggering a cytokine storm and systemic inflammatory response that directly or indirectly lead to the occurrence of IgAN.¹¹ However, direct evidence for this pathway in vaccine-associated IgAN remains insufficient. Whether this systemic reaction directly triggers disease activity or merely coincides with it requires further investigation. While virus can directly infect the kidneys, or they can cause cytokine storms through cytokine-mediated effects, which stimulate kidney damage^{68,69} (Figure 2).

Limitations

This review has certain limitations. First, most of the treatment-related clinical studies incorporating the Oxford classification scores that we included were non-randomized controlled trials with small sample sizes. Furthermore, the association between pathological scores and treatment in IgAN patients was merely temporal, and we are unable to infer a causal relationship between the two. Second, the mechanisms we have elucidated regarding the association between systemic inflammatory responses, infections, vaccinations, and active IgAN lesions are based solely on hypotheses in the literature and remain unconfirmed.

Conclusion

The pathogenesis of IgAN is complex and multifactorial, involving the combined effects of various factors. Environmental factors such as bacterial or viral infections or vaccinations may act as potential catalysts, inducing disease activity in susceptible individuals. MEST-C scores and systemic inflammatory responses may partially reflect disease status, providing clinically meaningful information for disease assessment. Further research is warranted to elucidate the mechanisms underlying IgAN disease activation and progression. Specifically, prospective studies are needed to validate the utility of specific inflammatory markers in predicting disease onset or progression and assessing prognosis. Integrating these dynamic biomarkers with MEST-C scores into a comprehensive predictive model may enhance the ability to implement personalized treatment for patients. A longitudinal study integrating biopsy and multi-omics analysis elucidates the relationship between different triggering factors and long-term clinical trajectories. Resolving these issues is crucial for understanding IgAN disease progression and guiding individualized treatment strategies.

Abbreviations

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; CS, glucocorticoid; DCs, dendritic cells; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Gd-IgA1, galactose-deficient IgA1; IgAN, immunoglobulin A nephropathy; IL, interleukin; IST, immunosuppressive therapy; TLRs, toll-like receptors.

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Disclosure

The authors declare that they have no competing interests.

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