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FREE COMMUNICATIONS

Deciphering APRIL's involvement in the pathogenesis of childhood IgA nephropathy

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Introduction: IgA nephropathy follows a multi-hit development involving circulating immune complexes (CICs) containing Gd-IgA1 and sCD89, contributing to renal inflammation. A Proliferation-Inducing Ligand (APRIL) is suspected to contribute to the autoimmune response in adult IgAN. However, its involvement in childhood IgAN (cIgAN), often exhibiting more inflammation, remains unknown, as does its activation mechanism.

Aim: This study aims to clarify how APRIL is activated and determine its role in cIgAN.

Material and methods: We studied 86 cIgAN and 48 control patients from France and Canada. We quantified plasma and urinary APRIL levels and plasma CICs, and compared them to biological, clinical, and histological characteristics. Immunohistochemistry of cIgAN patients' kidney biopsies was performed to visualize APRIL staining patterns. We also evaluated APRIL expression in mesangial cells (HMCs) after stimulation and assessed APRIL receptors presence on podocytes.

Results: We observed elevated levels of Gd-IgA1, sCD89-IgA1, sCD89 and circulating APRIL in the plasma, and circulating APRIL in the urine, of cIgAN patients compared to control ($p<0.05$). APRIL plasma levels correlated with histological inflammation (Oxford score). Western Blotting suggested that APRIL is trapped within CICs, colocalizing with IgA in similar-sized complexes. ELISA and immunoprecipitations confirmed IgA-APRIL and CD89-APRIL complexes presence in cIgAN samples, correlating with plasma APRIL levels. Immunostaining revealed APRIL deposits in the glomerular mesangium. Stimulating HMCs with cIgAN plasma or recombinant sCD89 induced APRIL mRNA and protein production and its secretion. It induced the production of a new form of APRIL, the same one found in CICs. APRIL production by HMCs was confirmed by immunofluorescence. TACI and BCMA seemed to be expressed by podocytes.

Conclusion: APRIL is implicated in cIgAN pathogenesis, potentially activated by sCD89 in HMCs. A novel HMC-derived APRIL form, retained in CICs, may participate in the mesangial-podocyte crosstalk. APRIL emerges as a candidate biomarker and therapeutic target in cIgAN.

Distinct Breath Volatile Organic Compound Signatures Differentiate IgA Nephropathy from Non-IgA Chronic Kidney Disease: A Novel Non-Invasive Diagnostic Approach

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Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis, yet current diagnosis still depends on invasive kidney biopsy. Non-invasive biomarkers that can distinguish IgAN from other chronic kidney diseases (CKD) remain urgently needed. Breath volatile organic compounds (VOCs) reflect metabolic changes and have emerged as promising diagnostic indicators in systemic diseases. This study investigates whether VOC profiling can discriminate IgAN from non-IgA CKD and healthy controls.

Methods: Breath samples were collected from 161 participants, including healthy controls (n=38), non-IgA CKD stage 2 (n=33) and stage 3 (n=50) patients, and IgAN stage 2 (n=20) and stage 3 (n=20) patients. VOCs were analyzed using gas chromatography after subtraction of background air values. One-way ANOVA identified VOCs with significant differences across groups.

Results: Out of 51 VOCs with significant intergroup differences ($p<0.05$), 29 compounds, such as pyrrole, 1-octen-3-ol, and 2-hexen-1-ol—showed elevated levels in non-IgA CKD but were significantly suppressed in IgAN. Conversely, 5 VOCs, including acetic anhydride and acrylonitrile, were uniquely elevated in IgAN patients. Nitric oxide, a marker of vascular and immune status, showed a marked reduction in IgAN compared to both non-IgA CKD and controls. These findings suggest a distinct breathprint for IgAN that is metabolically divergent from other CKD etiologies.

Conclusion: Breath VOC profiling reveals disease-specific metabolic signatures that effectively differentiate IgAN from non-IgA CKD and healthy individuals. This novel, non-invasive tool holds strong potential for screening and early detection of IgA nephropathy, potentially reducing the need for diagnostic biopsy in select cases.

Differential nephritogenic levels of human IgG autoantibody containing immune complexes in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common form of glomerulonephritis and represents a leading cause of end-stage renal disease. Previous studies have pointed out that galactose-deficient IgA1 (Gd-IgA1) has been recognized as an autoantigen that triggers the formation of autoantibodies (auto-Abs), leading to the formation of IgA1-containing immune complexes (ICs) that localize in the glomeruli. These complexes gradually deposit in glomeruli leading to irreversible kidney injury. However, the precise molecular mechanisms underlying this renal disease remain largely elusive.

Aims: This study aimed to generate and characterize human monoclonal IgG auto-Abs specific to Gd-IgA1 from patients with IgAN, and to investigate their roles in ICs formation and pathogenicity.

Materials and Methods: Peripheral blood mononuclear cells (PBMCs) from individual patients with IgAN were fused with SPYMEG, human fusion partner cells, and single hybridoma clones were subsequently obtained through limiting dilution.

Results/ Discussion: Six IgG auto-Abs targeting Gd-IgA1, exhibiting varying affinities and recognizing aberrantly glycosylated IgA1 autoantigens, were identified. The IgG auto-Abs were significantly more likely to detect Gd-IgA1 in IgAN patients than in healthy individuals and control diseases. These interactions led to the formation of high-molecular-weight ICs that showed enhanced renal deposition and IL-1β secretion and complement activation in vitro. Structural analysis revealed a partially flexible binding of a synthetic Gd-IgA1 hinge region peptide, suggesting heterogeneity in epitope recognition and ICs formation.

Conclusion: These results revealed novel IgG auto-Abs and characterize their binding properties, functional roles, and structural features. Therefore, these findings provided molecular insights into IgAN pathogenesis and disease heterogeneity, supporting the development of improved diagnostic strategies and targeted therapies.

Keywords: IgA nephropathy; Galactose-deficient IgA1; IgG autoantibody; Immune complexes; Human hybridoma cells

Morphometric prediction of kidney survival in IgA Nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide with a highly variable clinical course. Although the Oxford MEST-C score remains a cornerstone in histopathological assessment, digital pathology and artificial intelligence (AI) enable the extraction of morphometric features allowing for novel pathomic marker characterization that may enhance risk stratification.

Aims: Assess the prognostic value of AI-derived morphometric parameters from IgAN kidney biopsies, and their association with baseline renal function and progression to end-stage kidney disease (ESKD).

Materials and Methods: We retrospectively analyzed all biopsy-proven IgAN cases from 1998 to 2023 at ULS Coimbra with >5-year follow-up. Digitized histological slides were analyzed using the Computational Renal Pathology Suite (ComPRePS) to segment kidney structures and extract key morphometric variables (>300 features analyzed): wall-to-lumen ratio (WLR) of arteries (threshold of >0.5), glomerular eosinophilic fraction (GEF), and percentage of globally sclerotic glomeruli. Arteries were defined by a cross-sectional area >35,000µm^2. Correlations between morphometric variables and estimated glomerular filtration rate (eGFR) at biopsy were assessed, and Kaplan-Meier analysis was used to evaluate correlation with ESKD.

Results: Fifty-eight patients were included (mean age 42 years, 62,1% male). Arterial WLR>0.5 was significantly associated with lower eGFR at baseline (p=0.03), as increased GEF (p<0.01) and higher percentage of globally sclerotic glomeruli (p=0.01). In a survival curve analysis, an arterial WLR>0.5 and a GEF>0.3 were independently associated with a higher risk of progression to ESKD (p=0.033 and p=0.026, respectively).

Conclusion: AI-assisted morphometric analysis of renal biopsies enables the quantification of features which are not easily discernible through conventional histopathology, mitigating inter-observer variability. Notably, the identification of vascular lesions as prognostically relevant – despite their exclusion from the MEST-C score – illustrates the added value of these techniques. Integrating AI-driven morphometric data combining clinical variables at the time of biopsy holds promise for improving prognostic accuracy and individual risk stratification in IgAN.

Plasmacytoid dendritic cells modulate the pathogenesis of IgA nephropathy by facilitating aberrantly glycosylated IgA synthesis

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Introduction: Aberrantly glycosylated IgA plays a central role in the pathogenesis of IgA nephropathy (IgAN). The activation of Toll-like receptor (TLR) 9 induces aberrant glycosylation of IgA *via* a proliferation-inducing ligand (APRIL)-mediated pathway. TLR9 is known to be highly expressed in B cells and plasmacytoid dendritic cells (pDCs). Although the stimulation of TLR9 in B cells has been reported to promote the production of aberrantly glycosylated IgA, the effects of TLR9 stimulation on pDCs remain unclear.

Aims: We focused on the role of mucosal pDCs in the synthesis of aberrantly glycosylated IgA in patients with IgAN in present study.

Materials and Methods: We evaluated the distribution of DC subsets in tonsillar mononuclear cells (MNCs). The synthesis of aberrantly glycosylated IgA in MNCs cultured with or without pDCs was analyzed. We also evaluated the effects of pDC depletion on the production of aberrantly glycosylated IgA in ddY mice, a spontaneous murine model of IgAN, nasally immunized with CpG-oligonucleotide, a ligand for TLR9.

Results: The percentage of DCs, especially pDCs, was significantly higher in the palatine tonsils of patients with IgAN than in those of patients with chronic tonsillitis. In patients with IgAN, the abundance of pDCs was significantly correlated with the APRIL and TLR9 expressions in tonsillar MNCs. The levels of aberrantly glycosylated IgA in culture supernatants of tonsillar MNCs were found to be increased in the presence of pDCs. The pDC-depleted ddY mice exhibited significantly lower serum levels of aberrantly glycosylated IgA.

Conclusion: Mucosal pDCs contribute to the pathogenesis of IgAN by facilitating the production of aberrantly glycosylated IgA *via* TLR9 signaling. It is suggested that APRIL overexpression, triggered, by an increase in the number of pDCs in mucosal lumen, affects the production of aberrantly glycosylated IgA.

Single cell spatial transcriptomics of human kidney biopsies reveals structural and molecular features of crescent formation in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and remains a major cause of end stage renal disease. The presence of crescents in kidney biopsies of patients with IgAN is associated with a higher risk of poor renal outcome, but if and how the presence of crescents should influence treatment remains unclear.

Aim: The aim of this study was to profile cellular and molecular changes in non-crescentic and crescentic IgAN kidney biopsies within the spatial context to improve our understanding of the pathophysiologic processes associated with and underlying crescentic IgAN.

Materials and Methods: We performed single cell spatial transcriptomics targeting 5000 genes (10X Genomics Xenium) on diagnostic kidney biopsies of 6 patients with crescentic IgAN, 4 patients with non-crescentic IgAN and 2 non-IgAN kidney transplant biopsies. The presence of IgA deposits in the IgAN biopsies was confirmed with immunofluorescence staining and histology was assessed using PAS staining.

Results: Analyzing 5000 genes in over 640,000 high-quality cells identified all major cell types in the kidney and revealed changes in cellular composition between non-IgAN and IgAN kidney biopsies with an increased presence of immune cells in IgAN kidney biopsies, predominantly in crescentic IgAN. Unsupervised clustering of all glomeruli highlighted features specific to crescentic glomeruli in IgAN including increased numbers of parietal epithelial cells and decreased numbers of podocytes. Comparative transcriptomic analyses indicated altered transcriptomic programs with activation of pro-inflammatory and pro-fibrotic signaling pathways in crescentic versus non-crescentic glomeruli. In addition to an altered glomerular structure in crescentic IgAN, immune cell-dominated cellular microenvironments were observed, likely representing tertiary lymphoid structures with ongoing immune cell activation in IgAN.

Conclusion: This study provides a spatial map of IgAN kidney biopsies and highlights structural features and transcriptomic alterations relevant to disease processes in crescentic IgAN.

Pathomics-based estimation of treatment effects for corticosteroids in IgAN

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Introduction: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide, with diverse clinical presentations and response to treatments, particularly corticosteroids.

Aims: Here, we tested the potential of pathomics, i.e., a deep learning-based segmentation and automated extraction of quantitative morphometric biomarkers from digitized kidney biopsies, to improve individualized corticosteroid treatment effects in IgAN using a causal machine learning framework.

Materials and Methods: We retrospectively analyzed two multicenter (VALIGA, CureGN) and one single-center cohort (Kyoto), split into derivation and validation cohorts. The composite endpoint was a 50% decline in estimated glomerular filtration rate (eGFR) or end-stage kidney disease within 5 years of follow-up. Clinical and histopathological data were collected for each patient, and kidney biopsies were analyzed using pathomics. Treatment was defined as corticosteroid initiation during follow-up, patients receiving other immunosuppressants or novel therapies were excluded. We implemented a causal survival forest to detect and predict heterogeneous treatment effects at the individual level.

Results: Among 688 patients included, 82 (11.92%) reached the composite endpoint. Overall, patients predicted to benefit from corticosteroids experienced significantly longer progression-free survival when treated vs. untreated (4.58 years [95% CI 4.36–4.80] vs. 3.99 years [95% CI 3.71–4.28], $p < 0.01$). Patients predicted to benefit were characterized by high proteinuria, decreased eGFR, presence of E, S, and C lesions, and reduced tuft circularity (i.e., circular shape similarity). No treatment effect on progression-free survival was observed in patients with low predicted benefit, suggesting a potential 22.38% reduction in corticosteroid use in total across these retrospective cohorts. An individualized treatment assignment potentially improved overall progression-free survival by 0.42 years (95% CI 0.24–0.60, $p < 0.01$).

Conclusion: A causal machine learning framework using clinical, histopathological and pathomics predictors can identify patients likely to benefit from corticosteroid therapy while also potentially reducing overtreatment.

Investigating patient heterogeneity using deconvolution and multicellular factor analysis in IgA nephropathy

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A more comprehensive understanding of patient heterogeneity in IgAN will be crucial to improving patient stratification and directing patients to the most effective clinical trials. The increasing availability of 'omics data is moving us towards this goal by adding a molecular level of detail to standard clinical descriptors such as MEST-C score or CKD stage, and allowing us to investigate how shifts in cell behaviour and abundance contribute to IgAN pathogenesis and progression.

Here, we took advantage of a large bulk RNA-seq dataset, consisting of microdissected glomerular and rest-of-kidney fractions from 84 IgAN patients (71 adults and 13 children) and 11 reference tissue controls. We estimated cell type proportions using the deconvolution method, MuSiC, with the publicly available KPMP v1.5 as a single-cell reference dataset. We then used grouped factor analysis as implemented in MOFA, as an unsupervised method to explore inter-patient variation across both glomerular and rest-of-kidney fractions, represented in terms of latent factors. Finally, we related inter-patient variation to cell-type compositional changes by finding statistical associations between the latent factors and deconvolution scores.

Our approach allowed us to overcome a key challenge of microdissected bulk data, namely to identify a latent factor in the data accounting for contamination from tubulointerstitial transcripts in the glomerular compartment, where present. Able to separate biological from technical variation in this way, we identified two further latent factors describing compositional and expression changes, for the glomerular and rest-of-kidney fractions respectively. Both latent factors were associated with CKD stage, tubular atrophy and GFR. On the basis of these results, we show how glomerular and tubulointerstitial injury processes become decoupled in later stage IgAN, driven at least in part by the abundance of activated macrophages in the rest-of-kidney fraction.

The CARD9 S12N mutation is associated with an increased risk of IgA nephropathy in Han Chinese

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Introduction: Caspase recruitment domain family member 9 (CARD9) gene has been identified as a susceptibility gene for IgA nephropathy (IgAN) in a previous genome-wide association study, which encodes an adaptor protein that plays a pivotal role in pathogen defense and innate immunity. This study aimed to explore whether *CARD9* polymorphisms correlate with IgAN susceptibility, clinical phenotypes and progression, and to elucidate its potential roles in inflammatory and immune responses.

Methods: A total of 3,319 IgAN patients and 6,785 healthy controls were enrolled across three independent cohorts, and 10 candidate single-nucleotide polymorphisms were selected for genotyping. Molecular docking and molecular dynamics simulation were applied to characterize the mutation of residues in the protein structure and the dynamic properties of CARD9 protein. The serum levels of cytokines and galactose-deficient IgA1 were measured by a multiplex immunoassay kit and ELISA, respectively. The RNA-seq dataset was used to analyze the *CARD9* expression in renal tissues of IgAN patients.

Results: We found that rs4077515-T (S12N mutation) was significantly associated with IgAN susceptibility (OR = 1.26, 95% CI = 1.07–1.49, P = 0.006), a higher incidence of microscopic hematuria and mesangial hypercellularity. Furthermore, the S12N mutation was independently associated with renal survival after adjustments for multiple confounders. MD simulations revealed that the S12N mutation could increase the structural instability of the CARD9 protein and decrease its binding affinity with BCL10. Moreover, the S12N mutation was significantly correlated with elevated serum levels of proinflammatory cytokines (IL-5, IL-6, IL-17, and IL-8) and galactose-deficient IgA1. RNA-seq analyses revealed significant upregulation of *CARD9* expression in renal interstitial tissues of IgAN patients, which was correlated with the expression of Dectin-1, NF-κB, and the activation of B cell-mediated immune responses.

Conclusions: Our results suggest that *CARD9* S12N mutation confers susceptibility to IgAN, probably by modulating the NF-κB pathway and innate immunity.

Longer follow-up of povetacicept shows potential for treatment of IgA nephropathy (RUBY-3 study)

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Introduction: The pathogenesis of IgAN is due to genetic and environmental factors that prime B-cells to express Gd-IgA1, an auto-antigen, triggering autoantibody production, forming immune complexes that deposit in glomerular mesangium, leading to inflammation and injury. BAFF and APRIL are involved in survival and maturation of transitional and naïve B-cells, T-cell-independent B-cell responses to certain antigens, B-cell regulation, and Ig class-switch recombination. Povetacicept, a dual inhibitor of BAFF and APRIL, represents significant therapeutic advancement by targeting the root cause of IgAN.

Aims: To provide updated interim data for participants dosed with povetacicept in the RUBY-3 study.

Materials and Methods: RUBY-3 is an ongoing Phase 1/2, open-label study in adults with IgAN, receiving povetacicept 80 mg (n=21 dosed; n=8 at 48 weeks) or 240 mg (n=33 dosed; n=12 at 48 weeks) subcutaneously Q4W. Primary objective: evaluation of the safety of povetacicept. Secondary objectives: efficacy, PK, and biomarker changes with povetacicept treatment.

Results: Data at 48 weeks indicate mean 24-hour UPCR decreased 66% from baseline (from 1.3g/g to 0.5g/g) in the 80 mg cohort, and 53% (from 1.2g/g to 0.6g/g) in the 240mg cohort. In both cohorts, eGFR was stable through 48 Weeks. By Week 48, clinical remission was achieved by 63% of the 80 mg cohort and 33% of the 240 mg cohort. Gd-IgA1 declined 64% in the 80 mg cohort and 60% in the 240 mg cohort by Week 24, with sustained declines through Week 44. Povetacicept doses were generally safe and well tolerated at both dose levels.

Conclusion: Povetacicept was generally safe and well tolerated in adults with IgAN and resulted in substantial and sustained reductions in UPCR and Gd-IgA1, with stable eGFR, through 48 weeks. These updated data reinforce the potential of povetacicept as therapy for IgAN; a Phase 3 randomized, controlled study of povetacicept in IgAN is well underway.

Transglutaminase-2 specific IgA-producing plasma cells in experimental IgA nephropathy

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Introduction: The trigger and source of pathogenic IgA production in IgAN are not established. Our previous work suggested that with BAFF overexpression in experimental IgAN (BAFF-Tg mouse), IgA antibody-producing cells (IgA-APCs) are detected within the kidneys. We hypothesize that BAFF overexpression creates a de novo niche for gut-derived IgA+ plasma cells (PCs) in the kidney. Once established in the kidney, BAFF-dependent IgA+ PCs elaborate tissue-resident pathology.

Aim: We sought to localize and characterize IgA-APCs in experimental IgAN and explore mechanisms promoting their kidney localization.

Methods: We used flow cytometry, single-cell RNA sequencing (scRNA-seq), immunofluorescence, ELISPOT, and spatial transcriptomics (Xenium) to compare kidneys from BAFF-Tg and wild-type (WT) mice.

Results: We confirmed an increase in IgA+ PCs ($CD45^+B220^-CD98^+IRF4^+IgA^+$) in BAFF-Tg but not WT kidneys by flow cytometry and scRNA-seq. Ligand-receptor analysis supported interactions between kidney endothelial cells and IgA-PCs. Spatial transcriptomic data indicated that the glomerular microenvironment in BAFF-Tg mice was enriched with immune cells and exhibited increased expression of cytokines supporting the existence of an immune-activated niche. Differential scRNA-seq analysis revealed increased endothelial expression of transglutaminase 2 (*Tgm2*) in BAFF-Tg mice ($p<0.05$), a protein implicated in IgAN. We confirmed increased glomerular and tubulo-interstitial *Tgm2* RNA expression by spatial transcriptomics and corresponding increased Tgm2 protein by immunofluorescence. Since Tgm2 can be targeted by IgA in settings like celiac disease, we developed a custom ELISPOT to assess the Tgm2 specificity of IgA. Tgm2-specific IgA-PCs were observed in both intestine and kidneys of BAFF-Tg but not WT mice.

Conclusion: Tgm2-specific IgA-PCs are present in BAFF-Tg kidneys. Increased endothelial Tgm2 expression in intestines and glomeruli suggests Tgm2 may act as an autoantigen in the context of BAFF overexpression. Further study is needed to determine if Tgm2-specific IgA-PCs causally drive IgAN.

Gut Microbiome in IgA Nephropathy: Associations with Baseline Disease Presentation and Longitudinal Clinical Outcomes in South Asians

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Background: South Asians with IgA nephropathy (IgAN) have an aggressive disease presentation and progression, and the impact of gut dysbiosis has not been addressed in this population. This study investigated gut microbiome alterations in IgAN and their associations with clinical presentation and disease progression in the longitudinal prospective GRACE-IgANI cohort.

Methods: Consecutive biopsy-proven primary IgAN patients with age > 18 years, estimated glomerular filtration rate > 10 ml/min/1.73 $m^2$and no use of antibiotics or immunosuppressants in the preceding 12 weeks were recruited at the time of kidney biopsy. The disease controls included all patients other than IgAN who underwent kidney biopsy during the same period. The baseline and three-year longitudinal outcomes were analysed. Microbiome profiling is performed using 16S rRNA gene sequencing. The primary outcome is the difference in gut microbiome composition between IgAN patients and disease controls, assessed via α- and β-diversity metrics and relative abundance of bacterial taxa. Secondary outcomes include correlations between microbial profiles and clinical parameters—such as 24-hour proteinuria, eGFR, and inflammatory markers. Alpha diversity will be assessed using Shannon and Faith's phylogenetic metrics, while Bray-Curtis, Jaccard, weighted, and unweighted UniFrac will measure beta diversity. Functional pathway prediction will be performed with PICRUSt2 using the KEGG and MetaCyc databases. Random forest prediction models will be used to analyze the differences in microbiome composition.

Results: Stool samples from 112 biopsy-proven IgAN patients and 139 disease controls with non-IgAN kidney conditions are analysed using 16S rRNA gene sequencing to determine bacterial diversity and composition. Clinical data collection is complete, and microbiome analysis results are anticipated shortly.

Conclusions: This study will provide novel insights into the gut microbiome landscape of South Asian patients with IgAN and its relationship with clinical indicators and outcomes. Identification of microbial signatures associated with disease activity may inform future risk stratification strategies and microbiome-targeted interventions.

Mucosal bacteria initiate production of anti-β2-spectrin IgA autoantibody through a mechanism of molecular mimicry

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Introduction: We recently reported the presence of IgA autoantibodies targeting β2-spectrin, selectively expressed on the mesangial cell surface, in patients with IgA nephropathy (IgAN). Serum anti-β2-spectrin IgA antibodies were found to be enriched for galactose-deficient IgA1, suggesting their involvement in the pathogenesis of IgAN.

Aims: We aimed to elucidate the mechanism underlying the production of anti-β2-spectrin IgA antibodies.

Materials and Methods: We generated recombinant antibodies (trAbs) from tonsillar IgA^+ plasma cells of patients with IgAN and chronic tonsillitis (CT), and evaluated the binding of the trAbs to mesangial autoantigens and oral bacteria. BALB/c mice were subcutaneously immunized with heat-killed bacteria and CFA.

Results: We hypothesized that anti-β2-spectrin IgA antibodies production is initiated at mucosal surfaces. Based on our unbiased and paired B cell receptor repertoire sequencing analysis of mucosal IgA^+ plasma cells at the single-cell level, we cloned panels of IgAN- and CT-derived trAbs. Large-scale antibody screening using cell-based ELISA, Western blotting, and immunofluorescence staining showed that four IgAN-derived trAbs had affinity to human mesangial cells (HMCs), whereas none of the CT-derived trAbs did. Among the four clones, trAb#9 showed strong reactivity to β2-spectrin. Bacterial flow cytometry further revealed that trAb#9 also bound to the oral bacterial strain isolated from patients with IgAN (C#31-3-3: tentatively named by its colony number), suggesting structural similarity (i.e., molecular mimicry) between β2-spectrin and C#31-3-3. Restoration of the mutated sequences to the germline sequences in trAb#9 abrogated the binding to β2 spectrin, but not to C#31-3-3, indicating that somatic hypermutation is required to drive autoimmunity to β2 spectrin. Last, the mice immunized with C#31-3-3 showed an increased level of serum autoantibodies targeting HMCs and β2-spectrin, and immunoglobulin deposits in glomeruli.

Conclusion: Our data suggest that specific mucosal bacteria generate immune responses, leading to the production of anti-β2-spectrin IgA antibodies through a mechanism of molecular mimicry.

Bruton's tyrosine kinase modulates expression of C1GALT1 and production of galactose-deficient IgA1 in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is characterized by glomerular deposition of galactose-deficient IgA1 (Gd-IgA1), likely produced by mucosal IgA1-secreting cells. Dysregulated expression of *C1GALT1* is associated with Gd-IgA1 production; however, the precise mechanisms remain unclear.

Aims: To elucidate cellular-signaling events affecting Gd-IgA1 production, we investigated the role of Bruton's tyrosine kinase (Btk), the protein associated with B-cell-receptor (BCR) signaling, in *C1GALT1* expression and Gd-IgA1 production.

Materials and Methods: Immortalized IgA1-producing cell lines derived from peripheral blood mononuclear cells of IgAN patients and healthy controls were treated with a Btk inhibitor (ibrutinib) or anti-IgA antibody (to activate BCR), and Gd-IgA1 production was measured by lectin ELISA. Intracellular signaling was assessed by immunoblotting using phospho-Btk-specific antibody. Using primary tonsillar mononuclear cells (TMNCs) from patients with IgAN or chronic tonsillitis (disease controls), phospho-Btk in B-cell subsets was analyzed by FACS. IgA+ and IgD+ TMNCs were isolated, cultured, and analyzed for *C1GALT1* expression using qPCR. IgA+ TMNCs were treated with anti-IgA antibody (to activate BCR) or ibrutinib (to inhibit Btk), and *C1GALT1* expression was quantified.

Results: IgA1-producing cell lines from IgAN patients secreted more Gd-IgA1 than those from healthy controls ($p<0.01$). Ibrutinib reduced Gd-IgA1 production in IgAN-derived cells to that of healthy controls ($p<0.01$). Immunoblotting revealed elevated phospho-Btk in IgAN-derived cells ($p<0.05$). BCR stimulation with anti-IgA induced phospho-Btk in IgA+CD19+ cell lines. In TMNCs, elevated phospho-Btk activity was detected in naïve B cells from IgAN patients ($p=0.011$). In IgA+ TMNCs, IgA BCR stimulation reduced *C1GALT1* expression, whereas ibrutinib increased it. In IgAN-derived TMNCs, *C1GALT1* expression was lower in IgD+ naïve B cells and remained low in class-switched IgA+ B cells.

Conclusion: Analysis of IgA+ cells revealed opposing effects of IgA BCR activation and Btk inhibition on *C1GALT1* expression and Gd-IgA1 production in IgAN. Thus, Btk may represent a novel therapeutic target in IgAN.

Expression of MiR Triplet -192,-194,-215 in IgA Nephropathy: a Pilot Study

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Introduction: MicroRNAs are small non-coding RNA molecules that play instrumental roles in the epigenetic, negative regulation of gene expression, usually targeting, but not exclusively, the 3'UTR regions of target mRNA. In this way miRs play important roles in fine tuning the regulation of a multitude of processes. Unsurprisingly, dysregulation of miR function leads to disease pathogenesis.

Aim: Here, we investigate a closely-related cluster or triplet of miRs (-192, -194, -215) to ascertain its potential role in the pathogenesis of IgA nephropathy.

Materials and Methods: Kidney biopsy cores and sera underwent Next Generation Sequencing (NGS) to investigate miR expression profiles in IgA nephropathy patients at high (IgANp) and low risk (IgANnp) of future progression. Urine-derived exosomes were also analysed.

Results: Intrarenal expression of all three miRs was significantly downregulated in IgAN patients compared to patients with thin membrane nephropathy (TMN) that exhibited near normal histology. Validation by qPCR revealed that miR triplet expression significantly differed between IgANp and IgANnp. ROC curves confirmed these differences exhibiting AUCs of 0.8175, 0.84 and 0.7925 for miRs 192, -194 and -215 respectively. Expression of all three miRs positively correlated with eGFR, negatively with UPCR, associated with the E and T lesions of the MEST-C score and significantly correlated with the progression prediction scores of the International Risk Prediction Tool. Expression of the miR triplet in serum indicated no differences between IgAN patients and healthy subjects (HS), although expression of miR-192 and -194 was significantly lower in membranous nephropathy (MN) patients. No significant differences in miR expression were observed between patients in urine exosomes.

Conclusion: Intrarenal expression of this miR triplet more accurately predicts future progression of IgAN compared to expression of the triplet in other cellular compartments.

Glomerular C3 staining at baseline is an independent predictor of renal survival and eGFR loss in the UK National Registry of Rare Kidney Diseases (RaDaR) IgA nephropathy cohort

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Introduction: Complement plays an important role in IgAN pathogenesis. However, the prognostic significance of glomerular C3 deposition remains uncertain, particularly in non-East Asian populations. Clarifying this relationship may inform future research into the role of kidney biopsy in guiding complement-targeted therapy. This study evaluates whether glomerular C3 deposition, assessed by immunofluorescence, is associated with eGFR slope and renal survival.

Methods: UK RaDaR participants with IgAN diagnosed between 2010–2024 with an eGFR≥30 ml/min /1.73m^2 at biopsy were included. Data was extracted from original histopathology reports. Renal survival was defined as absence of kidney failure (eGFR<15ml/min/1.73m^2 for ≥4 weeks, or kidney replacement therapy) or death. Renal survival analyses were conducted using Cox Regression. Covariates were MEST-C scores (M, E, S: 0 vs 1; T, C: 0 vs ≥1), C3 intensity (<2+ vs ≥2+), age, sex, eGFR and uPCR. eGFR slope (covariates: age, sex, eGFR, uPCR) was estimated using linear mixed models.

Results: 470 patients had adequate biopsies (≥8 glomeruli). Mean age was 42 years (SD 16); 316 (67%) were male. Median eGFR at biopsy was 58ml/min/1.73m^2 (IQR 42-82) and uPCR 157mg/mmol (63-299). Median follow-up was 7.7 years (3.0-8.9). 303/470 (64%) had C3 staining reported as ≥2+. In the histology-only model, T-score (HR 3.00; 95%CI 2.11–4.35) and C3 (HR 1.49; 1.03–2.15) were independently associated with worse renal survival. In the combined model, C3 (HR 1.81; 1.08–3.07), eGFR (HR 0.81 per 5ml/min/1.73m^2; 0.75–0.88), and uPCR (HR 1.11 per 50mg/mmol; 1.06–1.17) were significant prognostic factors. Adjusted 5-year eGFR slope was –2.5 vs –4.6ml/min/1.73m^2 in patients with C3 <2+ vs ≥2+ (p=0.03).

Discussion: In this IgAN cohort, we demonstrate using real-world evidence that C3 staining ≥2+ is strongly associated with worse renal survival and steeper eGFR decline. The association is independent of clinical risk factors (eGFR, uPCR, age, sex) and histological severity (MEST-C scores).

Deciphering complement pathway activation mechanisms in childhood IgA nephropathy

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Introduction: Childhood IgA nephropathy (cIgAN) is a leading cause of glomerulonephritis, yet its mechanisms remain poorly understood. The lectin complement pathway plays a key role in IgAN pathogenesis, though its activation triggers remain unknown. Recent research highlights Collectin-11 (C-11) as a novel initiator of lectin pathway, while soluble CD89 (sCD89) has been linked to kidney inflammation in cIgAN, suggesting their involvement in disease progression.

Aims: To investigate the interplay between sCD89 and C-11 in lectin pathway activation, leading to C5b-9 formation and kidney inflammation in cIgAN.

Materials and Methods: We conducted a prospective study on one of the largest cIgAN cohorts*(n=52)*, alongside 80 controls. Plasma and urinary C-11 and soluble C5b-9 (sC5b-9) levels were quantified via ELISA and correlated with biological, histological, and clinical parameters. Kidney biopsies were analyzed for C5b-9 deposition. Human mesangial cells(HMCs) were assessed for C-11 expression and secretion via western blotting, immunofluorescence, and ELISA following stimulation with cIgAN plasma or recombinant sCD89 (rsCD89). HPLC and immunoprecipitation identified C-11 in circulating immune complexes (CICs).

Results: Elevated sC5b-9 levels correlated with proteinuria severity*(r=0.558,p<0.005)* and reliably predicted glomerulosclerosis*(AUC=0.812,p<0.005)*, surpassing proteinuria. sC5b-9 levels were linked to glomerular inflammation*(p<0.005)*, crescents*(p=0.012)*, and capillary C5b-9 deposition*(p=0.008)*. Plasma C-11 levels were significantly higher in cIgAN patients*(p<0.0001)*, contributing to proteinuria*(r=0.520,p<0.005)*, inflammation*(p=0.001)*, glomerulosclerosis*(p=0.006)*, and crescents*(p=0.013)*. Plasma sC5b-9, C-11, sCD89, and IgA-CD89 complex levels showed strong positive correlations, indicating their role in cIgAN. For the first time, we identified C-11 in CICs and confirmed its expression and secretion by HMCs. Its upregulation was induced by cIgAN plasma and rsCD89 stimulation, with colocalization alongside C3, supporting lectin pathway activation in cIgAN.

Conclusion: Plasma sC5b-9 levels above 250 ng/ml predict severe cIgAN, potentially reducing the need for invasive kidney biopsies. The interplay between C-11 and sCD89 provides mechanistic insights into complement pathway activation and offers potential for targeted therapies.

MBL2 Deficiency and Graft Survival in Transplant Patients with IgA Nephropathy: Is Complement Inhibition Always Beneficial?

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Background and hypothesis: IgA nephropathy (IgAN) is a primary cause of end-stage renal disease (ESRD), often necessitating kidney transplantation. However, graft survival varies significantly. Mannose-binding lectin (MBL), involved in the lectin complement pathway (LP), shows variable associations with IgAN outcomes. Genetic variants in *MBL2* influence MBL levels and function. We hypothesized that *MBL2* variants, MBL levels, and complement system imbalance correlate with graft survival in IgAN transplant recipients.

Methods: We investigated 64 IgAN transplant recipients, analysing *MBL2* genetic variants, serum MBL levels, and complement pathway activity. The combined influence of *MBL2* alleles and *delCFHR3-1* status on graft survival was also assessed. Graft survival was defined based on estimated glomerular filtration rate (eGFR).

Results: Patients carrying the *MBL2* "O" allele (deficient variant) had significantly lower serum MBL levels (P = .0013) and reduced graft survival compared to those with the wild-type "A" allele (P = .017). This deficiency was associated with suppressed LP activity but heightened alternative pathway (AP) activation, indicating a complement imbalance linked to allograft dysfunction. The negative impact of the "O" allele on graft survival was more pronounced in patients also lacking the *delCFHR3-CFHR1* deletion, suggesting a synergistic effect.

Conclusions: *MBL2* "O" allele associated MBL deficiency correlates with worse graft survival in IgAN transplant recipients, likely mediated by a shift towards AP overactivation. These findings, combined with the known impact of *delCFHR3-1* status, suggest genotyping for both *MBL2* and *delCFHR3-1*, along with MBL level assessment, could offer prognostic value. Identifying patients at higher risk may allow for personalized strategies, potentially involving targeted AP inhibition rather than broad complement suppression, to improve post-transplant outcomes.

Renal Progenitor Cells Can Modulate Inflammatory and Intestinal Immune Activation in IgA Nephropathy

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Background and Aims: Recent investigations explored the complex ways in which adult renal progenitor cells (RPCs) impact renal disorders. RPCs have a variety of roles in kidney disorders, including immunological regulation, tissue regeneration, and renal homeostasis maintenance. We isolated the RPCs from the urine of IgA Nephropathy (IgAN) patients and compared them with renal CD133- cells to identify genes and biological processes specifically activated in RPCs.

Method: Urine-derived cells were collected from 5 IgAN patients and 5 Healthy Subjects (HS). RPCs were isolated, characterized for the CD133 and CD24 markers by cytofluorimetric analysis, and separated from the $CD133^-$ portion by immunolabeling. RNA-sequencing was performed on both cell fractions from IgAN patients and HS. Differential analysis, Over Representation Analysis (ORA), and Gene set enrichment analysis (GSEA) were performed.

Results: We found 39 genes exclusively expressed in RPCs from IgAN patients, while 140 genes were specifically expressed in CD133- cells. Only 14 genes were shared by these two cell types. The ORA and GSEA analyses showed that RPCs modulate genes involved in immunomodulatory mechanisms only in IgAN, such as the regulation of leukocyte migration, T cell proliferation, T-reg cells, and response to molecules of bacterial origin (FDR 0.0238). Noteworthy, compared to CD133- cells, in RPCs of patients we found the downregulation of relevant genes involved in IgAN, such as IL6 (logFC -3.35,FDR 0.0002), CXCL1 (logFC -2.87,FDR 0.0178), CXCL8 (logFC -4.12,FDR 0.0007), whereas TNFRSF14, a receptor involved in the intestinal inflammation and mucosal immunity, was upregulated (logFC 2.67, FDR 0.0295).

Conclusion: Our data suggest that, in IgAN, RPCs play a role in decreasing inflammatory and immunological triggering at the renal level. By better understanding the critical role of these cells in the complex pathophysiology of IgAN, novel treatment strategies aiming to slow down the progression of IgAN can be developed.

Single-Cell Multiomic Profiling of PBMCs Reveals Immune Heterogeneity and Therapeutic Target Expression in IgA Nephropathy

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Introduction: Peripheral immune alterations may contribute to IgA nephropathy (IgAN) pathogenesis. Peripheral blood mononuclear cells (PBMCs) reflect the circulating immune landscape and may mirror disease activity. While several targeted therapies for IgAN are approved or in trials, their expression across immune cell subsets remains poorly characterized—despite its relevance for understanding disease mechanisms and therapeutic action.

Aim: To map the gene and surface protein expression of therapeutic targets in defined immune cell populations.

Methods: We used the 10x Genomics VDJ single-cell multiomic platform to analyze fresh unfrozen PBMCs from patients with biopsy-proven IgAN (N=8) and non-IgAN CKD controls (N=5). The platform enables simultaneous high-resolution profiling of gene expression, T and B cell receptor repertoires and surface protein expression (via CITE-seq antibodies). We specifically investigated the expression of known or currently targeted molecules in IgAN to identify which immune cell types are likely affected by these therapies.

Results: We profiled in total 91,000 PBMCs. We observed striking differences in the expression patterns of APRIL, BAFF, and BAFFR across immune cell subsets. BAFF was strongly enriched in several monocyte subclusters. BAFFR was expressed almost exclusively in B cells, particularly in naïve B cell populations and plasma cells. In contrast, APRIL showed expression in subsets of B cells—especially naïve B cells—and monocytes. Using antibodies targeting the respective surface proteins, we validated the observed gene expression at the protein level. Distinct expression patterns were also noted for other therapeutic targets currently investigated in IgAN, including those involved in complement inhibition and CD38.

Conclusion: High-resolution immune profiling of PBMCs in IgAN reveals distinct cellular niches for current and emerging therapeutic targets. Mapping the expression of therapeutic targets to specific immune subsets may help predict off-target effects, guide safety assessments, and inform patient stratification in future clinical trials and therapeutic decision-making.

FB-7011: A Novel, Long-Duration siRNA Dual-Targeting Both Complement Factor B (CFB) and Mannan-Binding Lectin Serine Protease 2 (MASP2) Exhibits Therapeutic Potential for Treatment of IgA Nephropathy

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IgA nephropathy (IgAN) is the most common primary glomerulonephritis. Current therapies for IgAN are limited by safety, efficacy, and patient adherence issue. The activation of alternative pathway (AP) and lectin pathway (LP), rather than the classical pathway (CP), in complement system is the major pathogenic process in IgAN. Development of specific AP and LP duel-targeted treatments holds significant potential to overcome the limitations of existing therapies.

In this study, we designed a chemically linked siRNA (FB-7011) duel-targeting both CFB and MASP2, the key proteases in the AP and LP, respectively. The mRNA/protein knockdown efficacy of CFB siRNA, MASP2 siRNA, and FB-7011 were tested in HepG2 cells *in vitro*, in humanized CFB and MASP2 transgenic mice and Cynomolgus macaques *in vivo*. A single dose of CFB siRNA or MASP2 siRNA resulted in sustained CFB or MASP2 mRNA knockdown and protein reduction *in vivo*, for 2 months in mice and 3-4 months in monkeys (>95% MASP2 protein reduction and >80% CFB protein reduction in serum). Additionally, a single dose of FB-7011 led to simultaneous and effective knockdown of CFB and MASP2 mRNA and protein expression levels in mice and monkeys.

In a BSA-induced murine IgAN model, both mouse CFB siRNA and mouse MASP2 siRNA significantly reduced albumin-to-creatinine ratio (ACR), mesangial cell number, and IgA deposition in the glomeruli, demonstrating remarkable therapeutic benefit. No hepatotoxicity, immunotoxicity, and off-target effects were observed.

FB-7011 exhibits robust and durable inhibitions of complement system and reduce renal injury in the preclinical models. The pharmacodynamic profile of FB-7011 may support a twice-yearly dosing regimen in human, addressing both efficacy and dosing challenges in current treatment regimens. Clinical studies are warranted to validate these findings in IgAN patients.

Genome-wide survival study identified variants associated with disease progression in IgA nephropathy

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Introduction IgA nephropathy (IgAN) has a poor prognosis and recent data suggested that almost all of patients may progress to kidney failure within their lifetime. Genetic variations intricately shape disease risks.

Aims This study aimed to identify genetic variants associated with IgAN disease progression.

Materials and Methods We performed genome-wide survival analyses in two independent cohorts and meta-analysis, the PKU-IgAN follow-up cohort containing 1859 IgAN patients and the TESTING cohort containing 279 patients from China. The outcome was the end-stage kidney disease or ≥40% reduction in eGFR after diagnostic kidney biopsy. Functional annotations, differential expression of the candidate genes, and the association between genotype and clinical characteristics were conducted.

Results There were three variants with $P_{meta} < 1.00\times10^{-6}$ and $P < 0.05$ in both cohorts with consistent HR direction, where the rs55776362 (HR 1.76, $P_{meta}=4.43\times10^{-7}$) located on the intron of the *TAFA5* gene had genetic support from surrounding variants within 200kb of rs55776362. Integration of eQTL analysis and epigenetic regulation data indicated that the candidate gene corresponding to rs55776362 is *TAFA5*. Chronic glomerulonephritis-based GWAS from the MVP cohort showed the *TAFA5* gene to be the most significantly associated candidate gene ($P=4.00\times10^{-13}$), and GWAS results based on kidney disease with dialysis also showed significant association of *TAFA5* ($P=2.90\times10^{-8}$). Analysis based on GEO data revealed significantly lower levels of *TAFA5* gene expression in both peripheral blood and glomeruli of IgAN patients compared to healthy controls. In addition, the expression level of TAFA5 in renal tissues from CKD patients was significantly positively correlated with eGFR and negatively correlated with the percentage of tubulointerstitial fibrosis.

Conclusions These findings may help characterize molecular mechanisms of progression of IgAN, contributing to the identification of patients at high risk of progression and the development of new therapeutic targets to slow disease progression.

Unveiling Genetic Determinants of Steroid Responsiveness in IgA Nephropathy: A TESTING Cohort Study

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Introduction: Glucocorticoid therapy shows variable efficacy and adverse effects in high-risk IgA nephropathy (IgAN) patients, potentially influenced by genetic factors.

Aims: This study aimed to identify genetic variants affecting steroid-driven proteinuria reduction.

Materials and Methods: We conducted a genome-wide pharmacogenomic analysis in 260 IgAN patients from the TESTING cohort (134 methylprednisolone-treated, 126 placebo-treated), focusing on genotype-by-treatment interaction for 6-month proteinuria reduction. Replication involved 211 glucocorticoid-naïve patients from the PKU-IgAN cohort.

Results: Three loci demonstrated genotype-by-treatment interaction ($p<5\times10^{-6}$). rs477155 (chromosome 1) was replicated (discovery $p=2.70\times10^{-6}$, replication $p=0.01$), with the GG genotype linked to complete remission (OR 2.31 (1.27-4.20), $p=6.00\times10^{-3}$) and composite clinical remission (OR 1.72 (1.14-2.59), $p=0.01$). Integrated fine-mapping, eQTL analysis, and ENCODE data revealed rs477155 as an enhancer region modulating CDA transcription via NR3C1 binding. RNA-seq confirmed NR3C1-CDA expression correlation ($r=0.43$, $p=4.40\times10^{-16}$), while GEO data showed rapid CDA upregulation post-dexamethasone (9.84±0.52 vs. 10.50±0.55, $p=7.41\times10^{-23}$). Phenome-wide analysis highlighted CDA's pleiotropic roles in immunity and renal function.

Conclusions: This study identifies rs477155 as a genetic modulator of steroid responsiveness in IgAN, implicating glucocorticoid-driven CDA regulation as a mechanistic pathway. These findings advance precision medicine strategies for predicting treatment outcomes in IgAN.

Polygenic Risk Score Predicts IgA Nephropathy Recurrence and Graft Failure in Kidney Transplant Recipients

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Introduction: IgA nephropathy (IgAN) is a complex immune-mediated glomerular disease. A genome-wide polygenic risk score (GPS) for IgAN has been associated with native IgAN risk and accelerated disease progression, but its role in post-kidney transplant (KTx) IgAN recurrence remains unclear.

Aims: We evaluated the predictive role of IgAN GPS in post-KTx IgAN recurrence and graft loss.

Methods: We genotyped and imputed 4,186 KTx recipients from 6 transplant centers. Recipient GPS for IgAN was computed and standard-normalized. The GPS was tested as predictor of kidney failure due to IgAN using logistic regression model applied to the entire cohort. In the subgroup of 369 recipients with native IgAN, the GPS was tested as predictor of time to IgAN recurrence and time to subsequent graft loss using Cox proportional hazards models adjusted for recipient, donor, and transplant predictors.

Results: Among 369 KTx recipients with native IgAN (median age 45 years, 149 living donor recipients), 96 developed recurrent IgAN over a median follow-up of 46 months. Among these, 27 experienced graft failure after median 100 months of follow up. IgAN GPS significantly predicted native IgAN among all KTx recipients (OR per standard deviation[95% CI]: 1.95[1.76,2.16], p=5.60E-07). Multivariable models showed that the GPS for IgAN was associated with IgAN recurrence independently of known risk factors (HR[95% CI]: 1.24 [1.01-1.51], p=0.03). In addition, younger age, better HLA match, and more recent transplant were independently associated with IgAN recurrence. In those with recurrent IgAN, the GPS independently predicted graft failure (HR[95% CI]: 2.33[1.29-4.23], p=0.006), but no association was observed in non-recurrent cases (HR[95% CI]: 0.97[0.66-1.43]).

Conclusions: IgAN GPS is independently associated with IgAN recurrence and subsequent graft failure in KTx recipients. Our findings support a shared genetic susceptibility between native and recurrent IgAN and suggest that the genetic risk of IgAN is mediated by extra-renal effects.

Exploring immune mechanisms in pediatric IgA nephropathy through spatial transcriptomics

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Introduction: IgA nephropathy (IgAN) involves immune cell infiltration driving renal inflammation. Spatial transcriptomics integrates gene expression with spatial topology, overcoming limitations of traditional sequencing to dissect cellular interactions. This study applies spatial transcriptomics to delineate immune-structural crosstalk in pediatric IgAN kidneys.

Aims: To characterize spatial distributions of immune and structural cells, identify intercellular communication networks, and uncover key regulators of immune dysregulation in pediatric IgAN using spatial transcriptomics.

Materials and Methods: Renal biopsies from 3 IgAN children and 3 normal controls underwent 10x genomics spatial transcriptome sequencing for clustering, differential gene analysis, pathway enrichment and cell-cell communication. Public scRNA-seq data (GSE171314) were re-analyzed. Validation cohort included renal biopsies from 26 IgAN children and 6 normal controls via multiple immunehistochemical staining (mIHC) of CD11c, CD4, CD68 and IgA.

Results: Spatial transcriptomics identified 8 cell clusters, with myeloid antigen-presenting cells (MPCs) enriched in tubulointerstitium. Dendritic cells (DCs) dominated MPCs, exceeding macrophages by 2.3-fold in scRNA-seq and 1.75-fold in mIHC ($P<0.0001$). CCL5+ proximal tubules (PTs) spatially colocalized with MPCs, were identified as potential DCs recruiters via CCL5. Cell interaction analyses implicated protease-activated receptors (PARs) in DCs activation, with PAR4 showing prominent involvement. Activated DCs exhibited spatial correlation with CD4+ T cells, which were elevated 3.7- and 3.2-fold in IgAN versus controls ($P<0.001$), respectively. Both DCs and CD4+ T cell counts positively correlated with proteinuria (24hUPro: r=0.53 and 0.58, $P<0.01$), linking DC-driven T cells activation to disease progression.

Conclusion: DCs in the kidneys of children with IgAN are mainly distributed in the tubular interstitium, and they may be recruited by CCL5+ PT. In the kidneys of children with IgAN, CCL5+ PT may activate DCs through PAR4 protein molecules, which in turn activate CD4+ T cells, thus promoting the process of immunoinflammatory injury in the kidneys of children with IgAN.

Tolerogenic dendritic cells immunotherapy protects against IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is one of the most prevalent forms of primary glomerulonephritis worldwide. Since IgAN is an autoimmune and inflammatory disease whereas DCs-induced effector T cells activation plays a pivotal role in disease progression, tolerogenic dendritic cells (tolDCs) immunotherapy holds potential as a therapeutic strategy for IgAN.

Aims: This study aimed to investigate the therapeutic efficacy of tolDCs in IgAN mice.

Materials and Methods: IgAN mouse model was established via oral mucosal immunization in C57BL/6J mice. TolDCs were generated through IL-10 exposure and subsequently characterized for their phenotypic and functional properties. Both wild-type (WT) and IgAN mice received either PBS or tolDCs treatments. Following the intervention period, comprehensive assessments were performed including renal functional parameters, histopathological changes, and inflammatory marker profiles.

Results: The IgAN mouse model was successfully established by week 8, exhibiting characteristic renal pathology including glomerular mesangial IgA deposition, mesangial cell hyperplasia, and stromal expansion. Compared with bone marrow dendritic cells (BMDCs), IL-10-induced tolDCs displayed a 3.5-fold increase in surface expression of the co-inhibitory molecule PD-L1 and a 2.7-fold upregulation of IL-10 mRNA levels, confirming their immunosuppressive phenotype. Functionally, tolDCs demonstrated migratory capacity to kidneys and enhanced regulatory T cells (Tregs) differentiation in IgAN mice. Therapeutic administration of tolDCs significantly attenuated disease progression: Compared to the IgAN-PBS group, the IgAN-tolDCs group showed 59.3% and 55.4% reductions in glomerular and tubulointerstitial IgA deposition, respectively, accompanied by 5.5-fold and 2.9-fold increases in Tregs infiltration. At the molecular level, IL-10 mRNA expression was elevated 5.0-fold in the IgAN-tolDCs group, while pro-inflammatory IL-12 and pro-fibrotic TGF-β mRNA levels were suppressed by 2.5-fold and 2.2-fold, respectively.

Conclusion: In vitro IL-10-induced tolDCs exhibiting an immunosuppressive phenotype. These tolDCs demonstrated the capacity of migrating through the circulatory system to kidneys in IgAN mice. Therapeutically, tolDCs immunotherapy significantly increased Tregs populations within the kidneys while concurrently reducing IgA deposition, which in turn attenuate renal immunoinflammatory injury in IgAN mice.

CX3CR1+ monocytes/macrophages promote regional immune injury in mesangial proliferative glomerulonephritis through crosstalk with activated mesangial cells

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Introduction: Mesangial proliferative glomerulonephritis (MsPGN) is the most common glomerulonephritis pathological type, including IgA nephrology (IgAN), in which regional immune injury leads to disease progression without targeted treatment approaches. While the mechanism of regional immune injury in MsPGN is unclear. We previously performed single-cell RNA sequencing (scRNA-seq) of IgAN and identified CX3CR1 gene increased in kidney.

Aims: To demonstrate the regulatory mechanism of CX3CR1+ monocytes/macrophages in regional immune injury of mesangial proliferative glomerulonephritis.

Materials and Methods: We first examined the expression and location of CX3CL1 and CX3CR1 in IgAN patients and animal model. Then we used CX3CR1 antagonists AZD8797 to block the CX3CL1-CX3CR1 interaction to determine the involvement of CX3CL1-CX3CR1 in MsPGN. The molecular mechanism downstream of CX3CL1-CX3CR1 was identified by Luminex multiplex immunoassay and RNA-seq, and the therapeutic effect of quetmolimab was evaluated.

Results: In this study, further scRNA-seq analysis and cellchat analysis revealed that CX3CL1 and CX3CR1 expression was increased in mesangial cells and monocytes/macrophages respectively in IgAN, mediating stronger crosstalk. This result and its association with regional immune injury was validated in clinical specimens and MsPGN animal model. Deficiency of CX3CR1+ monocytes/macrophages in MsPGN animal model attenuated proteinuria, cell proliferation and inflammation in glomerulus. Mechanistically, CX3CL1 in activated mesangial cells induced CX3CR1+ monocytes/macrophages migration and activation, and RNA-seq, Luminex multiplex immunoassay and molecular analysis revealed that CX3CR1+ monocytes/macrophages induced mesangial cells injury via MIF-CD74 interaction and activated PI3K/AKT pathway. Lastly, the therapeutic effect of CX3CL1 monoclonal antibody quetmolimab was validated for inhibiting the progression of MsPGN.

Conclusion: These findings demonstrate activated mesangial cells interact with CX3CR1+ monocytes/macrophages promoting glomerulus regional immune injury in MsPGN, providing the evidence into CX3CL1-CX3CR1 axis as a novel target of treatment for MsPGN.

Genome-wide association study meta-analysis reveals 50 susceptibility loci for IgA nephropathy and identifies B-cell receptor signaling to NF-κB pathway as a potential therapeutic target

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Introduction: IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide, yet its genetic architecture remains incompletely understood. This study aims to uncover the genetic architecture of IgAN and prioritize plausible new molecular drug targets.

Method & Materials: We conducted a comprehensive genome-wide association study (GWAS) meta-analysis of IgAN, comprising 11,931 cases and 43,772 controls, with balanced representation from East Asian (EAS) and European (EUR) populations. In addition, we leveraged state-of-the-art genomic technologies and analytical approaches, including fine-mapping, gene prioritization, and Mendelian randomization (MR), aiming to uncover novel genetic loci, identify causal variants and genes, and revealing new insights into the biological pathways underlying IgAN pathogenesis.

Result: Our analysis identified 50 genome-wide significant loci, including 17 novels, and revealed a SNP-based heritability of 35.20±1.48%. Integrative analyses prioritized causal variants and genes, revealing enrichment in pathways related to B-cell receptor signaling and NF-κB activation. Cell type phenotype Mendelian randomization analysis combined with single-cell expression data identified key cell types, while proteome-wide Mendelian randomization revealed CXCL6 as a causal factor and potential biomarker for IgAN. We developed a genome-wide polygenic score demonstrating superior discriminatory power for IgAN risk and identified significant associations with clinical phenotypes and outcomes. Druggability analysis highlighted 12 gene loci as promising therapeutic targets.

Conclusion: This study provides a wealth of new genetic insights into IgAN, offering a foundation for improved risk stratification and the development of novel therapeutic strategies. By bridging the gap between genetic discoveries and clinical applications, this research has the potential to significantly impact the management of IgAN and advance the field of precision nephrology.

MODERATED POSTERS

Revealing the Spatial Structure of IgA Immune Complexes in IgA Nephropathy Using Volume Electron Microscopy

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Introduction: The electron microscopy pathological hallmark of IgA nephropathy (IgAN) is the presence of electron-dense deposits (EDD) in the mesangial area. While it is widely accepted that immune complexes containing galactose-deficient IgA1 (Gd-IgA1) deposit outside mesangial cells, our previous research indicates Gd-IgA1 may enter these cells. However, the precise localization and quantification of Gd-IgA1-containing EDD within mesangial area remain unclear.

Aims: This study aims to clarify the precise spatial structure and quantify the deposition of IgA immune complexes within the mesangial region of IgAN patients, exploring their association with disease progression.

Materials and Methods: Utilizing volume electron microscopy: focused ion beam scanning electron microscopy (FIB-SEM), we collected renal biopsy tissues from IgAN patients and paratumor controls. Serial high-resolution images were obtained and reconstructed using a self-developed artificial intelligence program, enabling detailed three-dimensional analysis of the mesangial area.

Results: Our findings demonstrate that Gd-IgA1 forms tubular structures tightly enveloping mesangial cells, revealing close spatial associations between EDDs, mesangial cell nuclei, and vascular endothelium. We successfully reconstructed the 3D morphology of lysosomes within mesangial cells in situ and observed that lysosomes in IgAN patients were significantly larger and more electron-dense compared to those in paratumor controls. Immuno-electron microscopy confirmed that IgA1-containing EDDs localized both extracellularly and within lysosomes of mesangial cells.

Conclusion: Based on our results, we propose two models for IgA immune complex deposition in the mesangial region: (1) classic extracellular deposition and (2) an intracellular pathway involving endocytosis and lysosomal deposition. These insights not only provide new perspectives on the pathogenesis of IgAN but also suggest that future quantitative analyses could serve as a valuable reference for evaluating disease severity and progression.

Complement C3: A necessary component of pathogenic IgA1-containing immune complexes in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is an immune-complex-associated disease with mesangioproliferative kidney injury. The pathogenic immune complexes likely form in the circulation as IgG autoantibodies bind to IgA1 with some *O*-glycans deficient in galactose (Gd-IgA1); additional proteins can bind to these complexes and modulate their pathogenic potential.

Aims: As complement C3 is usually in the glomerular immune-complex deposits in IgAN, we assessed the role of C3 in the mesangioproliferative activity of soluble immune complexes using our *in vitro* models.

Materials and Methods: Immune complexes were isolated by size-exclusion chromatography from native or IgA1-depleted sera of patients with IgAN. Engineered immune complexes (recombinant polymeric Gd-IgA1 incubated with recombinant IgG autoantibodies specific for Gd-IgA1) were formed in C3-depleted and C3-repleted sera and isolated by size-exclusion chromatography. Biological activity was determined by cellular proliferation using cultured primary human mesangial cells. IgA, IgG, Gd-IgA1, and IgG-IgA and C3-IgA complexes were determined by ELISA. Non-reducing SDS-PAGE immunoblotting was used to assess covalent associations of C3 with IgA or IgG. Reducing conditions were used to assess C3 processing: alpha chain and/or its fragments indicative of C3, C3b, and iC3b.

Results: Immune complexes >700 kDa from sera of IgAN patients increased cellular proliferation of mesangial cells by 2-4 fold. These complexes contained IgA and IgG with C3 covalently associated with IgA and IgG. C3 molecular forms included C3, C3b, and iC3b. IgA1-depleted sera contained no IgA, IgG, or C3-containing stimulatory complexes. Large-molecular-mass engineered immune complexes formed in C3-repleted but not in C3-depleted serum stimulated proliferation of mesangial cells. IgG-IgA and C3-IgA complexes were confirmed by ELISA. C3 was covalently associated with IgA and IgG and consisted of C3, C3b, and iC3b.

Conclusion: Covalently associated complement C3 is required for mesangioproliferative activity of Gd-IgA1-containing immune complexes in IgAN. These C3-containing immune complexes represent a potential therapeutic target in IgAN.

Functional characterization of a novel anti-Gd-IgA1 autoantibody P4 in IgA nephropathy pathogenesis

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Introduction: IgA nephropathy (IgAN) is a common autoimmune kidney disorder characterized by the glomerular deposition of galactose-deficient IgA1 (Gd-IgA1)-containing immune complexes, which drive progressive renal injury. Despite the pivotal role of anti-Gd-IgA1 autoantibodies in IgAN pathogenesis, their incomplete characterization remains a significant barrier to understanding the disease mechanisms.

Aims: To develop a novel anti-Gd-IgA1 autoantibody and dissect its roles in the pathogenesis of IgAN.

Materials and Methods: We developed an anti-Gd-IgA1 autoantibody (P4) using flow cytometry, single-cell BCR sequencing, and in vitro expression. LC-MS confirmed galactose deficiency in recombinant IgA1. P4's roles in IgA deposition/clearance were assessed via immunohistochemistry, immunofluorescence, and in vivo fluorescence imaging in nude mice. Renal injury was evaluated by PAS staining and electron microscopy.

Results: We identified P4 as a high-affinity anti-Gd-IgA1 antibody with specific binding to galactose-deficient IgA1. Somatic hypermutation analysis revealed key amino acids within P4's CDR1 and FR2 regions critical for Gd-IgA1 binding. P4 demonstrated superior binding affinity compared to the KM55 antibody. In vivo experiments showed that P4 facilitated the rapid deposition of IgA in glomeruli in a dose-dependent manner. Notably, P4 also played a significant role in IgA clearance, as evidenced by the decreased IgA levels in both circulation and glomeruli when co-administered with IgA. Furthermore, P4-enhanced IgA deposition was associated with renal injury, as indicated by increased mesangial cell proliferation, matrix expansion, and podocyte foot process effacement.

Conclusions: Our study underscores the dual roles of anti-Gd-IgA1 autoantibody P4 in renal IgA deposition and clearance. While promoting IgA deposition within glomeruli, potentially exacerbating renal injury, P4 also facilitates IgA clearance, suggesting its potential in mitigating renal damage. These findings provide new insights into the pathogenesis of IgAN and highlight the complexity of autoantibody functions in autoimmune diseases.

Effects of anti-APRIL antibody treatment versus dual APRIL/BAFF inhibition and anti-BAFF antibody treatment in wild type mice

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IgA nephropathy is the leading cause for glomerulonephritis worldwide. The current disease hypothesis is that mucosal plasma B-cells produce excessive amounts of galactose-deficient IgA (Gd-IgA) which forms immune complexes with either IgA or IgG. These immune complexes are deposited in the kidney and trigger inflammation, scaring and subsequent function loss. A Proliferation-Inducing Ligand (APRIL) and B-cell activating factor (BAFF) are believed to be key drivers of plasma cell survival and immunoglobulins production. BAFF and APRIL have divergent roles: BAFF exerts a non-redundant role in transitional and Naive B cell survival, while human genetics studies suggest that APRIL, but not BAFF signaling, regulates IgA production. Recent clinical trials of anti-APRIL and dual anti-APRIL/BAFF molecules have shown promising results in patients with IgA nephropathy. We used flow cytometry to characterize B-cell populations in mice treated with compounds inhibiting either APRIL (anti-APRIL mAb), BAFF (anti-BAFF mAb) or both cytokines (dual inhibition, TACI-FC). We find that BAFF and dual APRIL/BAFF inhibition depletes transitional, Naive and Antigen-experienced B cells in the spleen. Inhibition of both cytokines also eliminates mature and Ag-experienced B cells in the bone marrow while single BAFF inhibition mostly impacts mature B cells in this microenvironment. In contrast, we find that single APRIL inhibition does not alter the size of any B cell compartments in lymphoid organs, suggesting that it does not strongly affect the homeostasis of the B cell lineage. Together, these data show a potential safety benefit of anti-APRIL antibodies compared to the use of dual APRIL/BAFF targeting compounds.

In vivo evidence that mesangioproliferative activity of IgA1-IgG immune complexes in IgA nephropathy requires complement C3 and can be prevented by a protein tyrosine kinase inhibitor

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Introduction: IgA nephropathy (IgAN) is an immune-complex-mediated disease with mesangioproliferative kidney injury. Our *in vitro* studies showed that the pathogenic immune complexes formed *de novo* in serum from galactose-deficient IgA1 (Gd-IgA1) and IgG autoantibodies contained complement C3 and activated multiple protein-tyrosine kinasepathways. However, it is not clear whether C3 is required for the nephritogenic activity of the Gd-IgA1-IgG complexes *in vivo*.

Aims: To assess the role of C3 in mesangioproliferative activity of IgA-IgG complexes using our passive mouse model of IgAN and test whether a protein-tyrosine kinase inhibitor, dasatinib, prevents the glomerular injury.

Materials and Methods: Immune complexes were formed from human polymeric Gd-IgA1 and recombinant human IgG autoantibodies. C3 was depleted (~99%) 1 day after intraperitoneal injection of cobra venom factor (CVF) and the depletion was maintained for at least 5 days. One day after CVF injection, the Gd-IgA1-IgG complexes were administered intravenously to a group of nude mice on 3 consecutive days. Other groups received i) immune complexes without CVF, ii) only CVF, or iii) only PBS. To test the effect of dasatinib, mice were injected intravenously with 3 doses of Gd-IgA1-IgG complexes (every other day) and daily gavaged with dasatinib (30 mg/kg). Control groups did not receive dasatinib or the immune complexes. Pathologic glomerular changes were evaluated by quantitative morphometry using H&E-stained kidney sections harvested 1 day after the last intravenous injection.

Results: Administration of immune complexes increased glomerular cellularity compared to PBS control group ($P<0.0001$). CVF-mediated C3 depletion prevented mesangioproliferative changes induced by these complexes ($P=0.021$). CVF alone did not alter glomerular cellularity. Dasatinib prevented glomerular injury induced by immune complexes ($P<0.0001$).

Conclusion: The *in vivo* mesangioproliferative activity of Gd-IgA1-IgG complexes required C3; dasatinib inhibited this glomerular injury. Thus, C3-containing Gd-IgA1-IgG complexes represent a potential therapeutic target in IgAN.

NF-kB inhibitor increases production of galactose-deficient IgA1 and modulates activation of multiple transcription factors in several subpopulations of EBV-immortalized B cells from IgAN patients and healthy controls

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Introduction: EBV-immortalized B cells from IgAN patients and healthy controls (HC) have been used to study mechanisms of production of galactose-deficient IgA1 (Gd-IgA1). GWAS identified IgAN-risk alleles in *REL* and *RELA,* suggesting NF-kB involvement. However, the role of NF-kB-signaling pathway in IgA1 *O*-glycosylation is poorly understood.

Aims: We used a small-molecule inhibitor of NF-kB (TPCA-1) to test involvement of NF-kB pathway in Gd-IgA1 production in IgA1-producing cells.

Materials and Methods: Immortalized B cells derived from peripheral blood of IgAN patients and HC were incubated with TPCA-1 for 1 hr, or for 48 hrs (followed by a second 30-min exposure) prior to collection of cells for flow cytometry. Cell-culture media were used for IgA1 and Gd-IgA1 analyses. B-cells were stained with antibodies for conventional cell-surface markers, and with HPA lectin to detect cell-surface GalNAc-containing glycoconjugates; intracellular staining detected activated transcription factors. Gene expression was determined by RT-qPCR.

Results: TPCA-1 decreased production of total IgA ($p<0.01$) whereas the proportion of Gd-IgA1 increased ($p<0.01$) in all cells. TPCA-1 decreased *C1GALT1* expression ($p=0.01$), but had no effect on *COSMC*. TPCA-1 decreased phospho-IKKa/b ($p=0.04$), pSTAT3 ($p<0.01$), and pERK1/2 ($p<0.01$). HPA-positive cells had higher CD138 and IgA staining and high SSA-A (side-scatter area) values ($p<0.01$), indicating a plasma-cell-like phenotype. These cells had a higher baseline activation of all three phospho-proteins ($p<0.01$) compared to the cells with low SSA-A values. Furthermore, 48-hr incubation with TPCA-1 increased the proportion of cells with plasma-cell-like phenotype ($p<0.01$).

Conclusion: Immortalized B cells exhibited substantial heterogeneity in both baseline transcription-factor activation and B-cell subtype. NF-kB inhibitor decreased production of IgA1, increased proportion of Gd-IgA1, and increased proportion of cells with plasma-cell-like phenotype. These IgA and cell-surface glycophenotypes were likely due to a reduced expression of *C1GALT1*. Future studies will determine the critical abnormal signaling interactions controlling IgA1 glycosylation.

Urinary biomarker analysis reveals rapid intrarenal anti-inflammatory and anti-fibrotic effects of sparsentan in IgA nephropathy in the SPARTAN study

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Introduction: SPARTAN (NCT04663204) is a single-arm, exploratory trial investigating the efficacy and safety of sparsentan, a dual endothelin angiotensin receptor antagonist (DEARA), as first-line therapy in immunoglobulin A nephropathy (IgAN). This study also examines the effects of sparsentan on pathogenic pathways in IgAN, incorporating a biomarker-focused approach to evaluation of adults who are newly diagnosed with IgAN.

Aims: We previously reported that treatment with sparsentan resulted in rapid and sustained proteinuria reductions of ≈70% over 24 weeks. Here we present the findings for urinary biomarkers up to this time point.

Materials and Methods: Twelve adults with biopsy-proven IgAN within 6 months, proteinuria ≥0.5 g/day, an eGFR of ≥30 mL/min/1.73 m^2, and no prior ACEi/ARB treatment were enrolled. Sparsentan treatment is for 110 weeks with a 4-week safety follow-up. One patient discontinued early due to hypotension. Changes in urinary biomarkers measured by ELISA and normalized to creatinine concentration were analyzed in the remaining 11 patients at baseline and at weeks 6, 12, and 24.

Results: Rapid and sustained reductions in urinary biomarkers of inflammation, immune cell recruitment/modulation, and fibrosis were observed after starting sparsentan (α2M, CHI3L1, clusterin, CXCL10, CXCL16, GDF1, IL6, MCP1, plasminogen, and sCD163). Protein-protein network mapping reveals a close relationship between affected biomarkers, suggesting a coordinated effect of sparsentan on modulation of intrarenal inflammatory and fibrotic pathways in multiple nephron segments. Marked reductions in BAFF and C5b9 were seen, indicative of actions on B-cell and complement activation.

Conclusion: Dual endothelin and angiotensin receptor antagonism targets key intrarenal pathways, promoting inflammation and fibrosis as well as B-cell and complement activation pathways. This enhances the scope of sparsentan's mode of action to cellular effects well beyond hemodynamic actions. Sparsentan may offer the possibility of limiting the consequences of IgA IC deposition in the glomerulus and tubule.

PEGylated Clostridium ramosum IgA protease clears both circulating and deposited IgA1 as a potential disease-modifying therapy for IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is a common primary glomerulonephritis caused by mesangial deposition of IgA immune complexes. Despite the approval or ongoing investigation of multiple new therapies for IgAN, they only indirectly target the deposits and generally have a delayed onset of action, limiting their effectiveness for the rapidly progressive type of the disease. In infectious diseases, many bacteria naturally produce potent IgA-degrading proteases.

Aims: To develop bioengineered IgA proteases as a first-in-class IgAN therapy, combining rapid action time, prolonged enzymatic potency, favorable administration routes, and low immunogenicity to meet clinical needs.

Materials and Methods: Based on AK183, an IgA protease from the human gut commensal bacterium *Clostridium ramosum*, we engineered a PEGylated truncation variant, designated PEG-AK183, through site-specific PEGylation. We conducted dosing studies of the drug on a humanized IgA1 transgenic model. To induce IgAN, we first primed the mice with Lactobacillus casei cell wall extract (LCWE) and complete Freund's adjuvant (CFA).

Results: Following a single subcutaneous injection of PEG-AK183 at 30mg/kgBW, circulating IgA1 was eliminated 4 hours post-administration, lasting as long as 196 hours. Plasma IgA1 did not return to pretreatment levels until day 15, demonstrating PEG-AK183's long action time and the suitability for a weekly dosing schedule. In a 4-week/dose study, plasma IgA1 levels were reduced by approximately 90% on day 7 after the last treatment. Renal immunofluorescence demonstrated complete clearance of IgA1 deposits, with significantly reduced intensity of C3 deposition as compared to the control group. No neutralizing antibodies against PEG-AK183 were detected after multiple doses.

Conclusion: PEG-AK183 demonstrated effective and sustained clearance of both circulating and renal-deposited IgA1, representing a promising therapeutic candidate for IgA nephropathy.

Sparsentan decreases mesangial IgA deposition in gddY mice; a possible role for mesangial-cell-surface autoantigen expression

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Introduction: We previously reported that sparsentan (SP), a single-molecule dual endothelin angiotensin receptor antagonist (DEARA), achieved a rapid reduction in proteinuria in a spontaneous IgA nephropathy (IgAN) model (gddY mice). We recently reported that β2 spectrin (Sci. Adv. 2023) and CBX3 (Life Sci Alliance. 2024), expressed on the surface of human mesangial cells (HMCs), are targeted by serum IgA from patients with IgAN. Here we explore a role for endothelin-1 (ET-1) and angiotensin II (Ang II) in HMC-surface expression of β2-spectrin and CBX3 and report that SP attenuates IgA deposition in the kidneys of gddY mice.

Methods: Four-week-old gddY mice were treated with either control chow or SP chow. After 12 weeks of treatment, glomerular IgA deposition was evaluated. Primary HMCs were stimulated with ET-1, Ang II, or both. Cell-surface expression of β2 spectrin and CBX3 was assessed by immunofluorescence staining following fixation with 4% paraformaldehyde.

Results: We observed that renal glomerular IgA deposition was significantly reduced in the SP group compared with the control group (6.0% vs. 45.7%, $p = 0.043$), suggesting that the reduction in glomerular IgA deposition may underlie the dramatic decrease in proteinuria observed in the SP group. We found that stimulation of HMCs with ET-1 and/or Ang II increased the surface expression of β2 spectrin and CBX3.

Conclusion: The increase in HMC-surface autoantigen expression following incubation with ET-1 or Ang II may play a role in the observation that Sparsentan significantly attenuated mesangial IgA deposition and rapidly reduced proteinuria in the gddY mice. Further studies are required to understand the mechanisms behind these novel findings.

Activation of mesangial cells via phagocytosis in IgA nephropathy

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It is still not fully understood how the mesangial cells (MCs) and the IgA containing immune complexes interact and activate the MCs in IgA nephropathy (IgAN). MCs are sometimes described as non-professional phagocytes, keeping the mesangium free from depositions. Our hypothesis is that MC activation and onset of IgAN may occur through phagocytosis of IgA.

Human primary MCs (HMCs) were stimulated with IgA1 purified from patients with IgAN and IgA1 from healthy controls. Uptake was studied by confocal microscopy, live microscopy and phagocytosis assays. Activation was studied by bioplex and q-PCR. A transcriptomic cohort of glomeruli from IgAN patients was used to confirm the findings in vitro (Liu et al, JASN 2017).

IgA1 was taken up by phagocytosis/endocytosis, but the process was slower than for professional phagocytes. Pretreating the HMCs with a phagocytosis inhibitor significantly decreased the uptake of IgA1. The IgA1 eventually ended up in the lysosomes and was degraded. Repeated stimulation with IgA1 hindered clearance, but once stimulation was stopped the IgA1 was degraded. Immunofluorescence staining of kidney biopsies from patients with IgAN revealed lysosome expression in the HMCs close to the IgA deposits. IgA1 stimulation of the HMCs induced an inflammatory response with significantly increased release of MCP1 and IL-6. Pretreatment with a phagocytosis inhibitor significantly reduced the response.

The phagosome formation pathway was one of the top upregulated pathways in the transcriptomic glomerular cohort of patients with IgAN compared to healthy controls, confirming that phagocytosis is ongoing in patients with IgAN.

In conclusion, phagocytosis of IgA by the MCs induces an inflammatory response and might be part of the onset of IgAN. It could also explain the build up of deposits in the mesangium, if the amount of IgA entering the mesangium is higher than the phagocytic capacity of the MCs.

Recommendations on diagnosis and treatment of adult-onset IgA Vasculitis proposed by the European IgA Vasculitis Study Group: focus on kidney involvement

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Background: The management of IgA vasculitis (IgAV) remains controversial especially for adults, we have been working on developing recommendations for the diagnosis and treatment of adult-onset IgAV. Here, we report the progress of this initiative with a focus on kidney involvement.

Methods: The European IgA Vasculitis Study Group (EUGAVAS), a multidisciplinary group of experts in the field of IgAV, was established in 2023. A Delphi approach was used to identify key questions to be addressed. Key questions that achieved a level of agreement ≥70% among group members drove a systematic literature review (SLR). Small working groups of 4-5 members drafted recommendation statements based on the SLR results and, where required, expert opinion. The preliminary statements were then discussed and amended by the whole group and are currently being voted on in the second round.

Results: The group consists of 38 experts, including 11 nephrologists. Following the first Delphi round, 14 out of 16 key questions were retained. The SLR identified 335 relevant publications out of 3,784 abstracts reviewed. Of the 14 preliminary statements, three focus on diagnosis and classification, three on disease staging, six on treatment, including general and organ-specific principles, and two on disease assessment and patient follow-up. Four statements are specifically dedicated to kidney involvement and discuss: 1) definition of kidney involvement and role of baseline prognostic factors; 2) indications to kidney biopsy and histological classification; 3) goals of treatment and options according to severity of kidney involvement; 4) role of nephroprotective measures. Kidney involvement is also discussed in other statements on definition of response and remission, use of biologic therapies, such as rituximab, and frequency and modality of patient follow-up.

Conclusions: A set of recommendations on diagnosis and treatment of adult-onset IgAV has been developed following a standardized approach and will soon be available for communication.

Preclinical and phase I clinical study of RG002C0106: a GalNAc-siRNA conjugate for complement-related glomerular diseases

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerular disease with a poor prognosis and lack effective etiology-based treatments. Nearly all IgAN patients exhibit substantial C3 protein deposition in renal tissue.

Aims: This study aims to develop a next-generation therapeutic novel drag for IgAN that is highly effective, long-lasting, and safe, by targeting complement C3 with small interfering RNA (siRNA).

Material and Methods: We first developed a novel N-acetyl galactosamine (GalNAc) linker structure and identified potent siRNA targeting the complement C3 gene, resulting in the investigational drug RG002C0106. We assessed preclinical pharmacokinetics (PK), pharmacodynamics (PD), and safety profiles in healthy rats, healthy and disease NHPs. Recently, a Phase I clinical study (NCT06494527) was launched to evaluate the safety, PK, and PD of RG002C0106 in healthy Chinese donors.

Result: RG002C0106 demonstrated high potent inhibition of C3 mRNA in liver tissues and C3 protein in serum in both hC3 transgenic mice and cynomolgus monkeys, especially in the NHP disease model, decreased uPCR by more than 50% compared to baseline. 50 Chinese participants received single or repeated subcutaneous doses of RG002C0106. There were no serious adverse events (SAEs), no dropouts due to adverse events (AEs), and no AEs leading to discontinuation of the study drug. RG002C0106 significantly and sustainably reduced serum C3 protein levels and inhibited both classical and alternative complement pathways during the dose range from 25 mg to 600 mg.

Conclusion: RG002C0106 effectively silences C3, improves renal function, and shows a good safety profile in preclinical and Phase I trials, it was well tolerated, with sustained reductions in C3 and suppression of complement pathways after single and repeat doses. These results support a quarterly or longer dosing regimen which will support the start of Phase 2a study in Q4 2025.

Epidemiological and Prognostic Insights into IgA Nephropathy: A Regional Cohort Study from Southern Italy

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Introduction: IgA nephropathy (IgAN) exhibits heterogeneous clinical presentations and outcomes.

Aims: To characterize the epidemiological, clinical, and histopathological features of IgAN in a regional Italian cohort and to identify predictors of complication-free survival (CFS).

Materials and Methods: A retrospective cohort analysis was conducted on patients diagnosed with IgAN in Apulia Region between 2018 and 2023. Incidence and prevalence were estimated using regional population data and disease duration metrics. Clinical and histological variables were analyzed descriptively. CFS was evaluated using Kaplan-Meier analysis. Risk factors were assessed through multivariate semiparametric Cox regression.

Results: A total of 279 patients were included, with a predominance of males (73.5%) and a mean age of 41.2 ± 18.9 years. The estimated incidence of IgAN was 1.18 per 100,000 inhabitants/year; the prevalence was 39.53 per 100,000. Over half the cohort (50.9%) presented with proteinuria exceeding 1000 mg/24h, and 45.9% were hypertensive. The incidence rate of critical events (death, transplantation, dialysis) was 8.3 per 100,000 person-days. Survival analysis demonstrated significantly reduced CFS in patients with elevated proteinuria levels (log-rank $p = 0.002$). Notably, the incidence of adverse events rose from 1.3 in patients with proteinuria <500 mg/24h to 13.9 in those with >1000 mg/24h. Multivariate Cox regression identified the following as independent predictors of poorer outcomes:

– Severe tubular atrophy/interstitial fibrosis (T2 lesions) (adjusted HR = 6.66; $p = 0.014$)

– Elevated serum creatinine (aHR = 1.41; $p = 0.039$)

– Reduced estimated glomerular filtration rate (eGFR) (aHR = 0.97; $p = 0.044$)

Conclusions: In this regional cohort, IgAN demonstrates a higher incidence and prevalence compared with national data, although still in the rare disease range. Proteinuria, histological severity, and impaired renal function are confirmed as key prognostic indicators. Comprehensive data acquisition through the National Renal Biopsy Registry is crucial to mitigating regional disparities and enhancing outcome-driven interventions.

Baseline and Longitudinal Associations between serum C3/C4 levels and tissue complement biomarkers and IgA Nephropathy in South Asia

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Background: Approximately 40% of patients with IgA nephropathy (IgAN) in India present with proteinuria and renal impairment, resulting in a dismal 10-year renal survival rate of 35%. Complement therapeutics are changing the treatment landscape for IgAN. The objective of this study was to determine the association between complement components and traditional biomarkers in IgAN in South Asia.

Methodology: The GRACE-IgANI cohort consisted of 200 prospectively recruited patients. Serum C3 and C4 levels were measured using endpoint nephelometry. Tissue C3, Tissue C3d, C4d, and C5b-9 were stained by immunofluorescence or immunohistochemistry as appropriate. The relationship between the complement components with assessment of baseline and longitudinal outcomes.

Results: The presence of hypertension and eGFR <60 ml/min/1.73 m^2 were associated with significantly lower serum C3 levels and serum albumin ≤ 4 g/dL. Lower serum C3 level was significantly associated with higher chronicity MEST-C scores (S1, T1/T2) and global glomerulosclerosis (GS>33%) in biopsy. Higher serum C3 levels correlated significantly with increased mesangial IgA deposition. Increased mesangial C3d deposition reflected severe IgAN disease at baseline, as it correlated with increased proteinuria, low albumin, and decreased eGFR. The mean positivity of C3d increased with higher chronicity in biopsy evidenced by S1 and T1/T2 and with GS>33%. Like C3d, an increase in mesangial C4d was seen with lower serum protein levels, and reduced eGFR, although the association was weaker than with C3d. In terms of histopathological factors, the average C4d positivity rose when GS exceeded 33%. In our cohort, mesangial deposition of terminal complement components (C5b-9) did not exhibit any clinical correlations.

Conclusion: Significantly lower serum C3 levels, higher levels of serum C4, and increased tissue C3d and C4d levels were observed in high-risk IgAN patients at baseline. At the three-year follow-up, the combination of lower C3 and higher C4 levels predicted worse renal outcomes.

Prognostic Significance of Persistent Hematuria in Japanese Patients with IgA Nephropathy: Findings from the Japan IgA Nephropathy Prospective Cohort Study (J-IGACS)

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Background: In IgA nephropathy (IgAN), baseline kidney function and proteinuria at the time of renal biopsy are established predictors of long-term outcomes. However, accumulating evidence suggests that persistent urinary abnormalities during the disease course may better reflect ongoing disease activity and renal prognosis. While time-averaged proteinuria (TAP) has been well validated as a prognostic marker, the role of persistent hematuria remains controversial. Moreover, studies evaluating the association between hematuria over the disease course and renal outcomes are limited, and validation in Japanese patients remains lacking. In the present study, we aimed to investigate the prognostic significance of time-averaged hematuria (TAH) in a Japanese IgAN cohort.

Methods: Data were derived from the Japan IgA nephropathy prospective cohort study (J-IGACS), a nationwide prospective observational study. Hematuria was evaluated every six months using urine sediment analysis, graded into five categories based on red blood cell (RBC) counts per high-power field. Numerical values were assigned to each grade, and the arithmetic mean over time defined the TAH score. Patients were stratified into three groups according to TAH levels. The primary composite outcome was a 1.5-fold increase in serum creatinine from baseline or progression to end-stage kidney disease.

Results: Among 991 patients, the mean age was 44.7 ± 15.8 years, mean eGFR was 75.4 ± 28.7 mL/min/1.73m^2, and median proteinuria at baseline was 0.58 g/day (IQR 0.28–1.18). Higher TAH levels were significantly associated with worse renal outcomes. In multivariable Cox models, TAH was independently associated with the primary composite outcome (HR 1.55, 95% CI 1.20–2.01). Subgroup analyses indicated that the adverse impact of TAH was more pronounced in patients with higher TAP.

Conclusion: Persistent hematuria is an independent determinant of renal prognosis in IgAN, particularly among patients with sustained proteinuria. Monitoring hematuria in addition to proteinuria may have therapeutic implications.

Prognostic impact of proteinuria recurrence in IgA nephropathy: A post hoc analysis of the Japan IgA Nephropathy Prospective Cohort Study (J-IGACS)

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Introduction: Persistent significant proteinuria is an established risk factor for kidney disease progression in IgA nephropathy (IgAN). While remission of proteinuria is generally associated with favorable renal outcomes, the clinical implications of proteinuria recurrence (flare) after remission remain unclear. This study assessed the prognostic impact of proteinuria recurrence using time-dependent analytical approaches and evaluated its effects on renal function trajectories.

Methods: We utilized data from a prospective multicenter cohort (Japan IgAN Prospective Cohort Study [J-IGACS]) designed to validate prognostic stratification based on clinicopathological parameters. Patients with biopsy-confirmed IgAN were followed every 6 months. Proteinuria remission was defined as urinary protein-to-creatinine ratio (UPCR) <0.3 g/gCr sustained for at least 6 months. Proteinuria recurrence was defined as UPCR ≥0.5, ≥0.75, or ≥1.0 g/gCr in two consecutive biannual visits. The kidney outcome was a composite of ≥30% eGFR decline or initiation of renal replacement therapy. Time-dependent Cox regression and mixed-effects models were used to examine outcomes and eGFR slope changes.

Results: Among 1130 patients, 762 achieved proteinuria remission. At cohort entry, the mean age was 36.9 ± 16.0 years, 53.0% were female, mean eGFR was 81.0 ± 26.8 mL/min/1.73 m^2, and mean UPCR was 0.86 ± 1.73 g/gCr. Histopathological findings included M1 21.7%, E1 34.4%, S1 69.4%, T1+2 13.2%, and C1+2 37.1%. The mean follow-up period was 6.2 ± 3.0 years, during which 60 patients (7.9%) experienced the composite outcome. Proteinuria recurrence at thresholds ≥0.5, ≥0.75, and ≥1.0 g/gCr occurred in 95 (12.5%), 43 (5.6%), and 26 (3.4%) patients, respectively. Proteinuria recurrence at ≥1.0 g/gCr was significantly associated with adverse renal outcomes (HR 3.82; P=0.0045) and accelerated eGFR decline by 2.2 mL/min/1.73 m^2/year (P<0.001).

Conclusion: Proteinuria recurrence at ≥1.0 g/gCr after remission independently predicts accelerated renal function decline and adverse kidney outcomes in IgAN, underscoring the need for continuous proteinuria monitoring post-remission.

Prognosis of Elderly Patients with IgA Nephropathy: A Post Hoc Analysis of the Japan IgA Nephropathy Prospective Cohort Study (J-IGACS)

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Background: As the elderly population increases, the number of elderly patients with IgA nephropathy (IgAN) is expected to rise, but research on their clinical characteristics and prognosis remains limited.

Methods: This study aimed to investigate the clinical characteristics and renal prognosis of elderly IgAN patients by categorizing them into three age groups: Group 1 (under 40 years), Group 2 (40 to under 60 years), and Group 3 (60 years and older) using data from the Japan IgA Nephropathy Prospective Cohort Study (J-IGACS). The primary outcome was progression to end-stage kidney disease or a ≥30% decrease in estimated glomerular filtration rate (eGFR). Univariable comparisons of the primary outcome were performed using Kaplan–Meier curves and the log-rank test. A Cox regression model was used to investigate the relationship between the primary outcome and histopathological or clinical variables.

Results: Among 991 patients, the median age was 37.1 years (interquartile range [IQR] 26.8–50.3), with 50.7% female. Median baseline eGFR and proteinuria were 74.8 mL/min/1.73 m^2 (IQR 55.9–94.3) and 0.58 g/day (IQR 0.28–1.18), respectively. There were 555 patients in Group 1, 298 in Group 2, and 138 in Group 3. The number of outcomes in each group was 41, 43, and 35, respectively. Patients in Group 3 had lower eGFR, higher proteinuria, and received fewer immunosuppressive treatments and tonsillectomies. The cumulative incidence of the primary outcome was significantly higher in Group 3 ($P < 0.001$). In a multivariable analysis, age category was not significantly associated with the primary outcome. Low eGFR and high proteinuria were significant risk factors, while immunosuppressive treatment and tonsillectomy were associated with a lower risk.

Conclusion: The renal prognosis of elderly patients with IgA nephropathy is poorer than that of younger patients, but this may be influenced more by patient background than age itself.

Intercontinental survey of patients with IgA nephropathy – preliminary analysis

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IgA nephropathy is the most common primary glomerulonephritis worldwide. 1074 patients with IgA nephropathy (IgAN) with a follow up of five years were examined through three different continents (Argentina from South America, India from Asia and Romania, Czech Republic from Europe).

Histological evaluation (MEST-C score) as well as clinical parameters at presentation (blood pressure, renal function, urinalysis, serum level of uric acid and albumin) and at the end of follow up were evaluated. Statistical analyses using univariant and multivariant analyses, linear discriminant analysis and logistic regression model were assessed.

We noticed best renal prognosis in Argentine patients compared to Indian, Romanian and Czech patients (renal survival with preserved renal function – 89 %, 65 %, 43 %). Immunosuppressive treatment was used mostly in Romania (80.5 % compared to Argentina in 31,5 %; 63.2 % in India and 47.2 % in the Czech Republic). Advanced interstitial fibrosis was assessed in Czech patients compared to Argentina patients (MEST-C score in patients with baseline proteinuria › 0,5 g/d: in Argentina T1+T2 40 %, India 85 %, Czech Republic 100 %, Romania 84 %) as well as crescentic forms of IgAN were noticed mainly in Czech patients compared to other countries (MEST-C score in patients with baseline proteinuria › 0,5 g/d: Czech Republic – C1 70 %, C2 6,3 %; Argentina – C 1 35.5 %; Romania – C1 27.9 %,C2 12.6 %; India C1 24.7%, C2 4.1 %).

In our study we analyzed clinical and histological data of a huge number of patients with IgAN from three continents with different renal prognosis which might be affected by various indication for renal biopsy. Renal prognosis of patients in different countries will be assessed by means of propensity-score analysis.

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Clinical Remission in IgA Nephropathy: Visualization of transition patterns and identification of an appropriate time point for prognostic assessment

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Introduction: Transition of urinary abnormalities during the clinical course is associated with renal prognosis, and clinical remission is a key therapeutic target for better renal outcomes in IgA nephropathy (IgAN). We had proposed new criteria for clinical remission in patients with IgAN (Clin Exp Nephrol, 2014), and reported the association for renal prognosis (Clin Exp Nephrol, 2021).

Aim: To better understand the clinical course and prognostic relevance of clinical remission, we investigated its patterns and the appropriate time-point for remission assessment.

Material and methods: We analyzed a previously reported multicenter cohort of Japanese adults IgAN (JAMA Netw Open. 2019). First, we applied a multi-state model to estimate transition probabilities over a 5-year period using the proposed remission criteria for patients with hematuria and proteinuria. Subsequently, to determine the appropriate time-point for assessing remission, we conducted a landmark analysis at every 0.5-year interval from biopsy to 3.0 years.

Results: Initially, 824 patients were evaluated for hematuria and 748 for proteinuria using the multi-state model. The model demonstrated a gradual increase in remission transitions for both hematuria and proteinuria, especially after 1 year post-biopsy. At 5 years, the stacked probabilities of remission were 0.32 for hematuria and 0.30 for proteinuria. Subsequently, a landmark analysis was conducted to evaluate the appropriate time point for remission assessment with respect to renal prognosis. Cox models were used to estimate renal risk, and the C-statistic improved progressively with longer follow-up which plateaued beyond the 2.0-year landmark (0.5 year: 0.64, 1.0 year: 0.68, 1.5 year: 0.71, 2.0 year: 0.75, 2.5 year: 0.76, 3.0 year: 0.78). After adjusting for age, MAP, and eGFR, similar trends were observed.

Conclusion: We elucidated the longitudinal transition patterns toward remission in patients with IgAN and demonstrated that the 2-year time point is appropriate for predicting renal prognosis based on remission status.

Long-Term Outcomes in IgA Nephropathy: Findings from the ERKNet Patient Registry (ERKReg)

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Introduction: We explored the relationships of proteinuria and age at onset with lifetime risk of kidney failure in patients followed in European reference centers and recorded in the European Rare Kidney Disease Registry (ERKReg).

Methods: Data were analyzed on 31.12.2024. At that time, the IgA nephropathy cohort within ERKReg comprised 884 adults and 385 children from 18 European countries and 49 units, all with a biopsy-proven diagnosis of IgA nephropathy.

To compare the findings with those of the RaDaR study, a matched "RaDaR Inclusion subcohort" was created by including only patients with proteinuria >0.5g/d or eGFR <60ml/min/1.73m^2 at any time.

Results: The median (IQR) age at diagnosis was 33 (17, 49) years and the median follow-up duration 6.0 (2.3, 14) years from diagnosis. During the observation period, 240 (18.9%) patients progressed to kidney failure and 7 (0.6%) died. The overall median kidney survival following diagnosis was 35.9 (95% CI: 29.0 to NE) years.

The median age at diagnosis was 41.8 (31, 57) at adult manifestation compared to 13.2 (9, 16) at childhood manifestation. Adult manifestation demonstrated a higher risk for kidney failure as compared to disease manifestation during childhood, with an adjusted hazard ratio of 2.0 (95% CI: 1.4 to 2.8, p<0.001).

Time-averaged proteinuria was strongly associated with worse kidney survival, with about threefold higher risk for kidney failure in patients with 0.5-1.0 g/d time-averaged proteinuria compared to patients with <0.5 g/d.

The RaDaR Inclusion subcohort, consisting of patients with more severe disease, had a median kidney survival of 28.3 years (95% CI: 22.0 to 35.7). These outcomes were notably better than those reported in the RaDaR study, which showed an overall median survival of 11.4 years from diagnosis.

Patient sex and the region of residence in Europe had no significant impact on kidney survival.

Investigation of gut-derived immune cell in IgA nephropathy

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IgA nephropathy (IgAN) is the most common primary glomerular disease globally, with up to 40% of patients progressing to end-stage kidney disease within 20 years. IgAN pathophysiology is driven by the "four-hit hypothesis" where elevated circulating levels of IgA1 with *O*-glycans deficient in galactose are recognized as autoantigens by autoantibodies, resulting in formation of circulating immune complexes and deposition in glomeruli. However, this model doesn't account for the variability in presentation and progression of the disease. Current research highlights the role of the mucosal immune system, linking disease flares to mucosal infections. Recent studies reveal dysregulation in the gut microbiota composition as well as an increase in circulating mucosal-derived immune cells in IgAN patients. Additionally, gut dysbiosis correlations—such as higher IgAN incidence in celiac disease and inflammatory bowel disease—suggest shared immunological pathways and disruption of the gut-kidney axis.

The gut microbiome interacts with the host and plays a regulatory role in gut-immune axis modulation. While there is initial evidence of microbiota's role in IgAN pathogenesis, the generation of gdIgA and its interaction with commensal and pathogenic bacteria remains unclear.

To gain insights into the IgG and IgA serological and cellular antibody repertoire and to address specific origin of mucosa-derived immune cells, we performed a comprehensive analysis of circulating immune cells, as well as serological assays to determine if differentially glycosylated IgA is preferentially recognized by serum immunoglobulins from IgAN patients and healthy donors.

Overall we observed differential combinatorial expression of the mucosal markers CCR9, CCR10 and α4β7 in several B and T cell subsets, with IgA+ plasmacells being the only antibody secreting cells with a small intestinal origin.

Further analyses on serological profiling of pathological autoantibodies against bacterial repertoire and on circulating B/Tcell receptors (BCRs/TCRs) may be valuable for the development of specific immunotherapeutic interventions in IgAN.

Proteomics Unveils Molecular Profiles and Potential Pathogenic Mechanisms in IgA Nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerular disease globally, characterized by IgA deposition in the glomeruli. Its pathogenesis remains incompletely understood, highlighting the need for comprehensive molecular profiling to identify key proteins and pathways involved.

Aims: This study aims to identify differentially expressed proteins between IgAN patients and healthy controls (HC) using proteomics, and to elucidate potential pathogenic mechanisms and biomarkers for IgAN.

Materials and Methods: Plasma samples from 80 IgAN patients and 80 HC were analyzed using protein corona proteomics with the Proteograph™ Assay Kit. Differential proteins were identified based on P-VALUE < 0.05 and FOLD CHANGE ≤ 0.5 or ≥ 2. Further analysis included principal component analysis (PCA), protein-protein interaction (PPI) network analysis, KEGG pathway enrichment, Gene Ontology (GO) analysis, and Cluster of Orthologous Groups (COG) classification.

Results: PCA revealed significant differences between IgAN and HC groups ($P<0.001$). A total of 216 differentially expressed proteins were identified, with 121 upregulated and 95 downregulated in IgAN. Notably, CHMP4A, NOG, FBL, TNFRSF11B, and CAPN3 were the top 5 upregulated proteins, while CD63, IGKV1D-16, VDAC2, DOCK5, and PDIA6 were the top 5 downregulated proteins. PPI analysis showed that ACTB had the highest number of interacting proteins (46, $P = 0.024$). KEGG analysis highlighted the proteasome pathway (hsa03050) as the most significantly altered, while GO analysis identified the organic nitrogen compound metabolic process as a key affected pathway. COG analysis revealed 265 proteins involved in post-translational modification and protein turnover.

Conclusion: This study provides novel insights into the molecular landscape of IgAN, identifying key proteins and pathways that may contribute to its pathogenesis. These findings could serve as potential biomarkers and therapeutic targets for IgAN, warranting further validation in future studies.

Keywords: IgA nephropathy; Proteomics; Protein corona; Biomarkers; Pathogenic mechanisms

Association of Urinary Inflammatory Biomarkers with Disease Activity and Progression Risk in IgAN and IgAVN: Findings from a Single-Center Cohort

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Background: Immunoglobulin A nephropathy (IgAN) and IgA vasculitis with nephritis (IgAVN) frequently progress to end-stage kidney disease (ESKD). Early biomarkers for disease activity and progression risk are needed. Inflammation-related proteins contribute to kidney damage and have been implicated in IgAN pathogenesis.

Aim: The objective was to identify urinary biomarkers associated with disease activity and progression risk in IgAN and IgAVN.

Methods: A Swedish single-centre cohort with IgAN or IgAVN and follow-up from 2004–2019 was studied. Urine sampled at biopsy was analysed using the OLINK Inflammation panel including 92 inflammation-related proteins. Associations with baseline eGFR, 24-hour albuminuria at biopsy (U-alb/24h), eGFR slope, time-average albuminuria (TAA), and 5-year risk of 50% eGFR decline or ESKD (International IgAN Prediction Tool, IIgAN-PT) were assessed using linear regression models, Random Forest, and Boruta analysis. Bonferroni correction ($p<0.05/92$) was applied.

Results: Urinary biomarkers were analysed in 58 patients (IgAN: n=39; IgAVN: n=19) with a median follow-up time of 9.4 years. At baseline, median U-alb/24 was 1.1 g/day, and eGFR 81.3 mL/min/1.73 m^2. Median TAA was 0.5 g/day, and eGFR slope −1.7 mL/min/1.73 m^2/year. Median IIgAN-PT risk was 8%.

TWEAK, SCF, MCP-1, ST1A1, and IL-18 were associated with U-alb/24h in all analyses. TWEAK and SCF remained associated with TAA. ST1A1 and MCP-1 were significantly associated with TAA in linear regression analysis but tentative by Boruta. No proteins were significantly associated with eGFR, eGFR slope, or IIgAN-PT risk after Bonferroni correction in linear regression analysis. However, Boruta confirmed CCL25, TNFRSF9, PD-L1, CCL19, TNF-beta, IL-10RB, FGF-5, IL-22RA1, and IL-18R1 as biomarkers associated with eGFR; ST1A1 for eGFR slope; and PD-L1, NRTN, CCL25, TGF-alpha, LIF, IL-6, TNFRSF9, and OPG for IIgAN-PT risk.

Conclusion: Urinary TWEAK, SCF, MCP-1, ST1A1, and IL-18 may reflect early glomerular damage in IgAN. Urinary markers predicting disease progression remain to be identified.

Soluble Fcγ receptor ectodomains as inhibitors of FcγR activation in immune complex-mediated diseases

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Fc gamma receptors (FcγRs) are crucial mediators in the recognition and clearance of circulating immune complexes (CICs). Under physiological conditions, they help maintain immune homeostasis; however, excessive and persistent CIC formation can lead to pathological FcγR activation and chronic inflammation. This mechanism is central to the pathogenesis of CIC-mediated diseases such as IgA nephropathy (IgAN), IgA vasculitis (IgAV), and systemic lupus erythematosus (SLE), including lupus nephritis (LN). Moreover, genetic polymorphisms in FcγRs influence susceptibility and disease progression.

In this study, we tested the ability of the soluble human FcγR2b extracellular domain (OHB-101) to interfere with FcγRIII activation by primary pathogenic CICs in sera from IgAN, IgAV, and SLE/LN patients using a cell-based FcγR activation reporter assay. In brief, mouse thymoma cells (BW5147) were stably transduced to express chimeric receptors composed of human FcγR ectodomains fused to the mouse CD3-zeta signaling module. Receptor activation results in mouse interleukin-2 (IL-2) secretion, which is quantified by ELISA.

Patient sera activated FcγRIII with variable intensity depending on the disease and individual donor. Synthetic CIC generated using recombinant trimeric human TNFα and Infliximab served as a control of CIC with known molecular size and molarity. In all conditions, OHB-101, provided by Oak Hill Bio, effectively inhibited FcγRIII activation, including activation by synthetic CIC. Furthermore, an isolated IgA fraction from IgAN patient sera also induced FcγRIII activation, correlating with activation observed using whole serum. Again, OHB-101 successfully inhibited activation, suggesting that IgG-containing CICs are present in the fraction.

We conclude that OHB-101 binds to immune complexes and prevents their interaction with cellular FcγRs. These findings support targeting the FcγR–immune complex axis as a promising therapeutic strategy for CIC-mediated diseases.

Lower urine epidermal growth factor to monocyte chemoattractant protein 1 ratio is associated with elevated biomarkers of endothelial dysfunction in IgA nephropathy

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Introduction: Circulating undergalactosylated IgA, a key mediator in IgA nephropathy (IgAN), has been shown to induce endothelial damage, which may contribute to further loss of kidney function. A decreased ratio of epidermal growth factor to monocyte chemoattractant protein-1 in urine, U-EGF/MCP-1, has been proposed as a predictive biomarker of negative kidney outcomes in IgAN, but the relationship between U-EGF/MCP-1 and endothelial dysfunction in IgAN is unknown.

Aims: The aim was to study the relationship between U-EGF/MCP-1 and plasma endothelial biomarkers in IgAN.

Materials and Methods: This single-center prospective cohort study included 39 patients (33 male, 6 female) with biopsy-proven IgAN recruited at Danderyd Hospital, Stockholm, Sweden. Plasma levels of endothelial markers ICAM-1, VCAM-1, E-selectin, VE-cadherin, Thrombomodulin and Syndecan 1 and urine levels of MCP-1 were measured at biopsy using Meso Scale® (Meso Scale Diagnostics, Maryland, USA), a multi-array electrochemiluminescence assay. Urine levels of EGF were measured using ELISA (ThermoFisher®). The relationship between U-EGF/MCP-1 and plasma endothelial markers and clinical characteristics including age, BMI, blood pressure, albuminuria (U-ACR), and eGFR (CKD-EPI 2009) was studied using Spearman rank correlation and Mann Whitney U.

Results: U-EGF/MCP-1 had a significant negative correlation to age ($r(37)=-0.25$, $p<0.05$) and systolic blood pressure ($r(37)=-.20$, $p<.05$) but not to diastolic blood pressure or BMI. There was a significant negative correlation between the U-EGF/MCP-1 ratio and U-ACR ($r(37)=-.33$, $p<0.05$) and a positive correlation to eGFR ($r(37)=0.7$; $p<0.05$). There were significant negative associations between U-EGF/MCP-1 and several endothelial biomarkers, including VCAM-1 ($r(37)=-0.33$, $p<0.05$), Syndecan 1 ($r(37)=-0.35$, $p<0.05$), and Thrombomodulin ($r(37)=-0.71$, $p<0.05$).

Conclusions: A lower U-EGF/MCP-1 ratio was associated with elevated levels of plasma endothelial markers, a sign of endothelial damage. Given the relationship between endothelial dysfunction and cardiovascular disease, the significance of the U-EGF/MCP-1 ratio as a potential biomarker of cardiovascular risk in IgAN should be further explored.

Plasma endothelial biomarkers in relation to albuminuria, kidney function and CKD progression in IgA-nephropathy (encore from 62nd ERA congress)

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Background and Aims: Circulating galactose-deficient IgA1, a key driver of IgA nephropathy (IgAN), has been shown to induce endothelial damage, which is believed to contribute to disease progression. We aimed to compare plasma endothelial biomarker levels between patients with IgAN, healthy controls and disease controls and study their association with CKD progression over time in IgAN.

Method: We conducted a single-center prospective cohort study including 44 patients with IgAN and 19 disease controls, 11 membranous nephropathy (MN) and 8 hypertensive nephropathy (HN), recruited from 2019 onwards. Plasma VCAM-1, ICAM-1, E-selectin, VE-cadherin, and Syndecan 1 were measured at time of biopsy using Meso Scale®. We also included 40 age-matched healthy controls (HC). We analyzed plasma biomarker levels and their relation to clinical parameters at baseline as well as eGFR slope during a median follow-up of 3.3 (2.1-4.1) years.

Results: Patients with IgAN had significantly higher levels of ICAM-1, VCAM-1, and Syndecan-1 compared to HC ($p=0.02$ for ICAM-1; $p<0.001$ for others), but similar levels to disease controls. Amongst patients with IgAN, there were weak positive correlations between U-ACR and E-selectin, VCAM-1 and Syndecan-1 ($p<0.05$ for all) and significant negative associations between all biomarkers and eGFR at baseline ($p<0.05$ for all). There was a significant positive association between E-selectin and eGFR slope ($r = 0.35$, $p<0.05$).

Conclusion: We found a significant elevation of endothelial biomarkers amongst patients with IgAN compared to healthy controls. Importantly, patients with IgAN had similar levels of plasma endothelial biomarkers as patients with HN and MN, despite being significantly younger and with fewer cardiovascular comorbidities. IgAN patients with the highest levels of E-selectin at baseline improved their kidney function over time, likely as an effect of treatment. Future studies should assess the association between baseline endothelial biomarkers and CKD progression in a larger and more ethnically diverse patient cohort.

Comparative proteomic analysis of glomeruli and circulating IgA-immune complexes in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide, with 30-40% of cases progressing to end-stage renal disease. Circulating IgA-immune complexes (IgA-ICs) play crucial roles in the development of glomerulonephritis. To detect proteins associated with the pathogenesis of IgAN, we performed label-free quantitative mass-spectrometry analyses of glomerular and circulatory IgA-ICs.

Methods: Glomerular proteins were extracted from remnant FFPE kidney tissues from patients with IgAN (n=31) and controls (n=10). IgA-ICs were purified from the sera of patients with IgAN (n=14) and healthy controls (n=20). Glomerular proteins and IgA-ICs were analyzed by label-free quantification using high-resolution mass spectrometry. To assess the impact of immunosuppressive therapy (tonsillectomy and steroid pulse therapy) and supportive therapy (comprehensive supportive therapy including renin-angiotensin-system inhibitor) on IgA-IC proteome, IgA-ICs proteome at pre- and post-treatment, from different treatment group were analyzed.

Results: In glomerular proteomics, complement proteins involved in the classical, alternative, and terminal complement pathways were increased in patients with IgAN compared to controls. Specifically, complement factor H-related (CFHR) protein 1, which is a complement positive regulatory protein of the alternative pathway, was significantly elevated in the glomeruli and IgA-ICs of patients with IgAN compared to controls. Furthermore, CFHR1 levels in IgA-ICs decreased after treatment in the immunosuppressive therapy group but remained unchanged in the supportive therapy group.

Conclusion: Results of this study showed that complement proteins associated with classical, alternative, and terminal pathways were more abundant in the glomeruli of patients with IgAN compared to those of controls. Furthermore, CFHR1 levels were elevated in both glomeruli and IgA-ICs. The CFHR1 levels in IgA-ICs in the immunosuppressive therapy group decreased after treatment. This study underscores the importance of IgA-ICs containing CFHR1 in promotion of glomerular complement activity in IgAN and its potential as therapeutic targets.

Targeting APRIL and BAFF pathways: Divergent effects on immune populations and protective immunity, with implications for IgAN management

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Introduction: APRIL and BAFF both regulate B-cell maturation and plasma cell survival. Therapeutic inhibition of APRIL or APRIL and BAFF has emerged as a promising strategy for IgA nephropathy, yet their broader immunological effects remain incompletely understood. This study evaluated the distinct immunological and functional impacts of selective APRIL versus APRIL/BAFF blockade in mice.

Aims: To define how APRIL only and dual APRIL/BAFF inhibition differentially alter immune composition, antibody production, splenic architecture and host defense.

Materials and Methods: Mice were treated with anti-APRIL or dual APRIL/BAFF inhibitors. Immune profiling included flow cytometry, single-cell RNA sequencing, surface proteomics, and spatial transcriptomics to map splenic architecture. Protective immunity was tested via influenza vaccination and live viral challenge.

Results: Serum IgA was reduced by ≥40% with both APRIL and APRIL/BAFF inhibition. APRIL inhibition minimally affected B-cell subsets, with reductions limited to germinal center B cells. In contrast, APRIL/BAFF blockade led to extensive depletion (80–89%) of total B cells, including naïve, follicular, and antibody-secreting cells. Single-cell multi-omics and spatial transcriptomics further characterized impacts on B cell subsets and gene programs. In an influenza challenge model, dual APRIL/BAFF inhibition significantly impaired survival (10%) compared to both APRIL-only treatment (40%) and isotype control (70%). Log-rank analysis confirmed that survival was significantly reduced in the APRIL/BAFF group versus isotype control ($p < 0.005$) and versus APRIL-only treatment ($p < 0.05$). In contrast, survival differences between APRIL-only and isotype control were not statistically significant ($p = 0.21$), suggesting APRIL inhibition is superior to APRIL/BAFF blockade for preserving protective immunity.

Conclusion: Selective APRIL inhibition reduced IgA while preserving broader immune integrity. Conversely, dual APRIL/BAFF inhibition compromised adaptive immunity, significantly impairing host defense against viral infection. These findings show the benefit of selective APRIL targeting vs. dual APRIL/BAFF inhibition on maintenance of immune competence, with potential implications for the management of IgAN.

Genetic regulation and therapeutic targeting of MTMR3 reshape TLR9-mediated IgA responses

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Background: GWAS have identified rs4823074, a noncoding variant within the MTMR3–HORMAD2 locus, as strongly associated with IgAN. Yet the mechanistic basis of this association and its downstream immunological effects remain elusive.

Aim: We aimed to define how rs4823074 regulates MTMR3, and assess its role in TLR9–IgA signaling and therapeutic relevance.

Materials and Methods: Luciferase assays, EMSA, and ChIP-qPCR were used for regulatory analysis; mRFP-GFP-LC3 imaging for autophagy and localization; Immunoprecipitation, RNA-sequencing, ELISA, mass spectrometry, Co-IP, and Malachite Green assays for signaling and enzymatic studies.

Results: Carriers of the rs4823074 risk allele exhibited elevated MTMR3 expression ($p=0.01$) and higher serum IgA levels ($p=0.08$). Dual-luciferase assays revealed increased transcriptional activity ($p<0.001$), while EMSA demonstrated stronger protein–DNA complex. SP1 was confirmed as the binding factor via super-shift. ChIP-seq and ChIP-qPCR further validated SP1 binding at both rs4823074 locus and MTMR3 promoter (~33.85% and ~18.72% of input).

The regulatory effect of the risk allele on MTMR3 prompted investigation of its downstream function. Upon TLR9 activation, MTMR3 translocated from the cytoplasm to the nucleus, suggesting a spatially-regulated inhibitory role. MTMR3 overexpression reduced TLR9-induced autophagic flux, increased the expression of TRAF3 ($p<0.001$) and promoted its K63-linked ubiquitination, leading to elevated IFN-β production. Functionally, recombinant IFN-β augmented IgA secretion from cultured splenocytes ($p<0.001$), implicating an MTMR3–TRAF3–IFN-β axis in modulating TLR9-driven humoral responses.

To evaluate MTMR3 as a therapeutic target, we assessed AUTEN-67, which inhibited MTMR3 enzymatic activity by ~ 50% at 100μM and reduced CpG-induced IgA by 34% ($p=0.002$). PARP1 was identified as a key binding partner of MTMR3. PARP1 inhibitor olaparib reduced MTMR3-PARylation and suppressed CpG-induced IgA production ($p=0.012$). These findings highlight MTMR3 as a promising immunoregulatory target.

Conclusion: Rs4823074 enhances MTMR3 transcription and downstream TLR9–TRAF3–IFN-β signaling, highlighting MTMR3 as a therapeutic target.

Deep shotgun metagenomic analysis of the oral microbiome identifies extrachromosomal mobile genetic elements associated with IgA nephropathy

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Introduction: Exogenous antigens have been implicated in the pathogenesis of IgA nephropathy (IgAN), and our recent studies have demonstrated that antigenic stimulation of the upper respiratory mucosa induces the production of nephritogenic IgA antibodies. However, the specific antigens involved have yet to be fully elucidated.

Aims: This study aimed to comprehensively analyze the oral microbiome of IgAN patients by performing deep shotgun metagenomic sequencing and to identify microorganisms associated with the disease pathogenesis.

Materials and Methods: Saliva samples were collected from 44 patients with IgAN, 25 with chronic tonsillitis, and 11 healthy individuals. Shotgun sequencing was performed on extracted DNA. Universal single copy marker genes were used to analyze bacterial species and their relative abundances. Additionally, *de novo* assembly of short reads was conducted to generate contigs. The contigs were classified into three categories—chromosome, plasmid, and phage—based on their genomic characteristics. Subsequently, the diversity and abundance of the contigs were compared among categories.

Results: Shotgun sequencing yielded an average of 56 million paired-end short reads per sample. Analysis of bacterial species identified few bacterial species were consistently enriched in IgAN patients compared to the other groups. However, contig-based analysis revealed that only plasmid contigs exhibited significant differences in beta diversity. Among these plasmid contigs, specific bacterial plasmids were significantly increased in IgAN patients compared to the other groups. To validate this finding, the host bacterial strain was isolated from the saliva of IgAN patients. Subsequent long-read sequencing confirmed that the strain harbored a plasmid. Finally, comparative genome analysis showed the plasmid was significantly more abundant in IgAN patients.

Conclusion: While previous studies on disease-associated microbiomes have primarily focused on the relationship between bacterial species and disease, our findings suggest that plasmids, as mobile genetic elements within the commensal microbiome, may play a more critical role in the pathogenesis of IgAN.

The Genetic Study Identifies Susceptibility Loci for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide and a leading cause of chronic kidney disease and end-stage kidney disease (ESKD). While environmental and immunological factors contribute to disease development, genetic susceptibility plays a critical role in the pathogenesis of IgAN.

Methods: In this study, we conducted a comprehensive genetic analysis of 36 patients with biopsy-proven IgAN using whole-genome sequencing (WGS)/whole-exome sequencing (WES) and targeted sequencing of candidate genes. Genetic data were analyzed in relation to clinical phenotypes, including proteinuria, estimated glomerular filtration rate (eGFR), and histopathological severity. We further explored polygenic risk scores (PRS) and gene-environment interactions to understand disease heterogeneity better.

Results: We identified several genetic loci significantly associated with IgAN, including variants in genes involved in mucosal immunity, complement activation, and glycosylation pathways. Notably, pathogenic and likely pathogenic (LP) genes related to IgAN in *COL4A4* and *CFI*, variants of uncertain significance (VUS) genes found PKD1 (6/36), *COL4A4* (3/36), *COL4A4* (3/36), TTR (1/36), CARD9 (2/36), CFH (2/36), especially Taiwanese population specific gene CCDC158 (4/36), BCAS3 (3/36), DLG1 (2/36). Higher polygenic risk scores correlated with earlier onset, more severe proteinuria, and faster progression to kidney failure. Functional annotation suggested these variants may modulate IgA production and immune complex deposition in the mesangium.

Conclusion: Our findings further prove that IgAN is a genetically complex disease with multiple susceptibility loci contributing to its pathogenesis. Genetic profiling may offer novel insights into personalized risk assessment, early diagnosis, and targeted therapeutic strategies for patients with IgAN.

Molecular endophenotyping of IgA Nephropathy patients reveals immune-driven subgroups with distinct clinical outcomes

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and a leading cause of kidney failure in young adults. Despite sharing a common histological diagnosis, IgAN exhibits remarkable clinical heterogeneity and variable progression rates, often limiting the effectiveness of current treatment strategies.

Aims: To explore the molecular heterogeneity of IgAN and identify transcriptomic signatures that explain disease variability and support precision medicine approaches.

Materials and Methods: We performed an unbiased analysis of kidney transcriptomic profiles from IgAN patients enrolled in the NEPTUNE cohort. RNA sequencing was conducted on microdissected glomerular and tubulointerstitial compartments. Immune cell enrichment was assessed using CIBERSORTx. We evaluated the expression of gene signatures associated with BAFF/APRIL pathways and Sparsentan response patterns (as defined in Eddy et al. MedRiv, 2025).

Results: Two distinct molecular subgroups of IgAN patients were identified, each with unique transcriptomic profiles. Subgroup 2 (45% of the cohort) showed greater immune and inflammatory activation, with upregulation of STAT1 signaling, complement cascade and B-cell related pathways. Clinically, subgroup 2 exhibited significantly lower eGFR (median 54 vs. 82 mL/min/1.73m^2), higher proteinuria (median 2.8 vs. 1.1 g/day), and more severe interstitial fibrosis and tubular atrophy at biopsy ($p<0.01$ for all comparisons). During follow-up, subgroup 2 had a 2.5-fold higher risk of kidney failure. Immune deconvolution confirmed increased infiltration of monocytes, macrophages, and plasma cells in subgroup 2. Analysis of molecular signatures revealed that subgroup 2 had a 3.2-fold higher BAFF/APRIL signature score ($p<0.001$). Additionally, Sparsentan-modulated transcripts were significantly enriched in subgroup 2 (fold change >2, $p<0.001$), correlating with disease severity and histological activity.

Conclusion: Transcriptomic profiling reveals distinct molecular subtypes of IgAN associated with clinical severity and disease progression. These findings provide a framework for future biomarker-driven clinical trials and underscore the relevance of patient stratification based on molecular disease drivers, paving the way toward precision medicine in IgAN.

The role of sCD89 myeloid receptor in glomerular hypercellularity in childhood IgA nephropathy

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Introduction: Childhood immunoglobulin A nephropathy (cIgAN) is one of the most common primary glomerulonephritis. It manifests as recurrent hematuria and proteinuria, associated with renal inflammation and mesangial hypercellularity. Without early diagnosis and targeted treatment, up to 40% of patients may progress to end-stage renal disease within 20 years.

This autoimmune disease involves glomerular deposition of circulating immune complexes (CICs). Soluble CD89 (sCD89), found in CICs, plays a key role in inflammation and mesangial proliferation in cIgAN through the involvement of the transferrin receptor 1 (TfR1) and activation of the PI3K/mTOR pathway. However, the underlying molecular mechanisms remain poorly understood.

Aims: My project aims to determine (i) the mechanisms by which sCD89 regulates TfR1, and (ii) the requirement of TfR1 in mediating sCD89-induced activation of the PI3K/Akt/mTOR signaling pathway in human mesangial cells (HMCs).

Materials and Methods: HMCs were stimulated with recombinant sCD89 (rsCD89) and treated with mTOR inhibitors (everolimus, simTOR) or siRNA targeting TfR1. Protein expression and phosphorylation of key components of the PI3K/Akt/mTOR pathway, including p70S6K1, 4E-BP1, and S6Rp, were analyzed by western blot. TfR1 expression was analyzed by RT-qPCR, western blot, immunofluorescence, and flow cytometry.

Results: HMC stimulation with rsCD89 increased Akt (p-T308, p-S473), mTOR (p-S2448), and p70S6K1 (p-T389) expression and phosphorylation, while their levels decreased when TfR1 was silenced. TfR1 was consistently expressed in HMCs and upregulated at both mRNA and protein levels 24 hours after rsCD89 stimulation.

Everolimus treatment reduced mTOR p-S2448 and the p-S2448/mTOR ratio, validating its inhibitory effect and allowing assessment of its impact on TfR1 expression.

Conclusion: These findings strongly support sCD89's role in mesangial cell proliferation via TfR1 regulation and mTOR pathway activation. This study enhances our understanding of the links between sCD89, TfR1, and mTOR signaling, offering a foundation for new therapeutic approaches targeting mesangial hypercellularity and inflammation in cIgAN.

The effects of multi-locus interaction on IgA nephropathy in Han Chinese population

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Previous genome-wide association studies (GWAS) have identified multiple susceptibility genes for IgAN, including *TNFSF13*, *ITGAX-ITGAM*, *FCRL3*, *ST6GAL1* and *CARD9*. Gene-gene interaction might have more influence on the susceptibility of IgAN and advance our understanding of the genetic pathogenesis of IgAN. This study aims to investigate the correlation between the gene-gene interaction and IgAN susceptibility.

Methods: A total of 63 single-nucleotide polymorphisms (SNPs) were selected for genotyping by using MassARRAY platform in 1,000 IgAN cases and 1,000 healthy controls. The frequency distribution of genotypes and alleles were calculated. Generalized multifactor dimensionality reduction (GMDR) method was used to analyze the multi-step gene-gene interactions.

Results: The GMDR analysis revealed that the interaction of *FCRL3* (rs7528684), *ITGAX-ITGAM* (rs7190997), and *ST6GAL1* (rs6784233, rs7634389) was significantly associated with the risk of IgAN (P=0.001, OR=2.88). In addition, the genotype–phenotype association analysis showed that the interaction of *TNFSF13* (rs3803800), *FCRL3* (rs11264793, rs7528684), *ITGAX* (rs11150619) and *ST6GAL1* (rs6784233, rs7634389) was associated with eGFR in IgAN patients (*P*=0.01, *OR*=14.03). The *TNFSF13* (rs3803800), *FCRL3* (rs11264793, rs7528684), *ITGAX* (rs11150614), and *ST6GAL1* (rs7634389) had combined effects on the low-density lipoprotein in IgAN patients (*P*=0.01, *OR*=4.81). Furthermore, the interaction of *TNFSF13* (rs3803800), *FCRL3* (rs11264793, rs7528684), *ITGAX* (rs7190997) and *ST6GAL1* (rs6784233, rs7634389) was associated with hematuria in IgAN patients (*P*=0.001, *OR*=29.66).

Conclusions: The study suggested that the interaction of *ITGAX-ITGAM*, *TNFSF13*, *FCRL3* and *ST6GAL1* genes might have some influence on the susceptibility and the disease severity to IgAN.

Engineering of IgA-specific CARs for CAR-T cell therapy against IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is an autoimmune disease characterized by the accumulation of IgA1 immune complexes in the glomerulus of the kidney, leading to inflammation, filtration impairment, and potentially end-stage kidney disease requiring transplantation. Current treatments are mostly supportive and non-specific, highlighting the need for a targeted therapeutic approach.

Aims: This study aims to develop a chimeric antigen receptor (CAR) T cell therapy targeting B cells responsible for the production of pathogenic IgA1, by specifically recognizing the M-Ig isotype specific segment (migis), a unique portion of membrane-bound IgA1.

Materials and Methods: Using a naïve human phage display library, we selected six single-chain variable fragments (scFvs) specific for the migis region. These scFvs were cloned into second-generation CAR constructs and into engineered T cell receptor fusion architectures (eTRuCs), where the scFv is fused to the CD3ε component of the T cell receptor. Primary human T cells were edited via CRISPR-Cas technology to knock-in the constructs, and surface expression was confirmed. The functional activity of the CAR-T cells was assessed through stimulation assays with an IgA1+ immortalized B cell line.

Results: Engineered CAR-T cells displayed specific activation upon engagement with the IgA1+ B cell line, as demonstrated by upregulation of T cell activation markers CD25, CD137, and CD69 and showed initial IgA1+ B-cell killing. However, the expression of activation markers and cell killing was significantly lower than for control constructs targeting the CD19 antigen, which was also expressed on the IgA1+ cell line.

Conclusion: Our findings suggest that targeting the IgA1 migis region via CAR T cells may represent a novel strategy for eliminating the B cell populations producing pathogenic IgA1 in IgAN. Future studies will focus on further optimizing the scFvs via antibody affinity maturation and evaluating whether binders with increased affinity can improve the activation capacity of the CAR constructs.

Evaluation of inhibitory oligotherapy for modulation of IgA expression

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Introduction: IgA nephropathy (IgAN) is characterized by the deposition of galactose deficient-IgA1 (gd-IgA1) containing immune complexes in the glomerular mesangium leading to mesangial cell proliferation, extracellular matrix synthesis, chemokine and cytokine release, and renal damage. Current treatment options focus on controlling symptoms and slowing disease progression.

Gapmer antisense oligonucleotides (ASOs) are short synthetic oligonucleotides that bind to target RNA forming a DNA-RNA heteroduplex which is cleaved by RNase H1, effectively silencing gene expression.

The aim of the project was to design an ASO targeting *IGHA* mRNA capable of reducing IgA synthesis without inhibiting expression of other immunoglobulin isotypes, which could be used as a potential treatment for IgAN.

Materials and methods: ASOs targeting human *IGHA1* and mouse *IGHA* were designed *in silico*. For screening, human IgA+ DAKIKI cells and mouse IgA+ MOPC cells were transfected with candidate ASO sequences or a non-targeting control. IgG+ DB cells and IgM+ Ramos cells were transfected with effective candidate sequences to determine if knockdown was isotype specific. RT-qPCR was used to determine *IGHA* mRNA expression and secreted IgA synthesis was measured using commercial IgA ELISA kits.

Results: Human IGHA1-targeting LNP-MOE-ASO2 showed 70% IGHA1 mRNA knockdown during initial screening and 50% reduction in IgA synthesis. IgG+ and IgM+ B-cell lines showed no significant difference in immunoglobulin expression. However, persistent reduction in IgA synthesis was dependent on repeated dosing with the ASO. Mouse IGHA-ASO7 showed >50% IGHA mRNA knockdown and >60% reduction in IgA synthesis compared to the untreated control.

Conclusion: ASOs are capable of specifically reducing IGHA mRNA expression and subsequent IgA protein synthesis *in vitro* without affecting the expression of other immunoglobulin isotypes. Ongoing work focuses on testing these ASOs in primary B-cells from healthy donors and *in vivo* work in a IgAN mouse model.

Tonsillar Immune Signatures in IgA Nephropathy: Elevated KLRG1 and ZBTB16 Expression in Germinal Center Regions

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Introduction: The pathogenesis of immunoglobulin A nephropathy (IgAN) remains incompletely understood; however, aberrant mucosal immunity, particularly involving the tonsils, is thought to play a central role. Although tonsillectomy has been associated with improved kidney outcomes in Japan, the immunological molecular features of B and T cells that distinguish IgAN from habitual tonsillitis remain unclear.

Aims: To characterize B and T cell–related immune signatures in tonsillar tissue distinguishing IgAN from habitual tonsillitis.

Methods: We conducted transcriptomic profiling of laser-microdissected tonsillar regions (mantle zone + germinal center and others) from five patients with biopsy-proven IgAN (three with crescent formation) and five age-, sex-, and creatinine-matched control patients with habitual tonsillitis. Gene expression was analyzed using the NanoString nCounter® Human Immunology V2 Panel (for B cell profiling) and the T cell receptor (TCR) diversity panel. Data analysis was conducted using ROSALIND® software.

Results: There were no significant differences in baseline characteristics between the groups. In IgAN patients, the mean serum creatinine was 0.83 ± 0.23 mg/dL, and urinary protein was 0.59 ± 0.28 g/gCr. Expression of KLRG1 and ZBTB16 in the mantle zone + germinal center was significantly higher in IgAN compared to controls ($p<0.001$ and $p=0.02$, respectively), whereas CCL18, FADD, and TNFRSF17 were significantly lower ($p=0.01$, $p=0.02$, $p=0.02$). Immunohistochemical analysis revealed that KLRG1-positive cells were localized to the germinal center regions in IgAN, especially in cases with crescents, whereas in habitual tonsillitis, these cells were restricted to peripheral areas. In contrast, TCR repertoire analysis showed no significant differences between groups.

Conclusion: Our data suggest that KLRG1 may serve as a key immunological marker in the tonsillar immune environment of IgAN. Further studies are warranted to validate its role in disease pathogenesis and its association with kidney function.

Causal Relationships Between Gut Microbiota and IgA Nephropathy: Evidence from Mendelian Randomization and Microbiome Validation

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Introduction & Aims: Emerging evidence suggests a strong association between gut microbiota and IgAN. However, the causal role of specific gut microbiota in IgAN remains unclear. This study aimed to identify causal relationships between gut microbiota and IgAN using a two-sample Mendelian randomization (MR) approach, validated with 16S rRNA sequencing data.

Methods & Materials: We performed MR analysis using genetic instruments for 412 gut microbiota taxa from genome-wide association studies (GWAS) as exposures and IgAN GWAS data as the outcome. The inverse-variance weighted (IVW) method was used as the primary analysis, supplemented by MR-Egger regression, weighted median methods, and Cochran's Q test to assess pleiotropy and heterogeneity. Reverse MR, multivariable MR (MVMR), and mediation MR analyses were conducted to validate significant findings. Genus-level abundances were further validated in external 16S rRNA datasets using the Conditional Quantile Regression (ConQuR) method for batch-effect correction. Statistical significance was adjusted using Bonferroni correction.

Results: Three gut microbiota species were protective against IgAN: *s_Alistipes_senegalensis* (OR=0.64, 95% CI: 0.48 – 0.87, p = 0.002), *s_Ruminococcus_bromii* (OR = 0.75, 95% CI: 0.57–0.98, p = 0.040), and *s_Bilophila_unclassified* (OR = 0.68, 95% CI: 0.47–0.98, p = 0.040). Six species were associated with increased IgAN risk, including *g_Barnesiella* (OR = 1.32, 95% CI: 1.03–1.70, p = 0.030) and *s_Rothia_mucilaginosa* (OR = 1.52, 95% CI: 1.02–2.28, p = 0.040). After multiple-testing correction, significant associations persisted for *s_Alistipes_senegalensis* (p = 0.043), *s_Bacteroides_clarus* (p = 0.035), and *s_Bilophila_unclassified* (p = 0.002). Sensitivity analyses confirmed robust results without evidence of pleiotropy or heterogeneity (p > 0.05). Genus-level validation revealed consistent microbial shifts in IgAN patients compared to controls, including *Alistipes_A_871400*, *Bacteroides_H*, *Clostridium_T*, *Ruminococcus_C_58660*, and *Rothia*.

Conclusion: This study establishes a causal relationship between specific gut microbiota and IgAN risk or protection, particularly implicating *s_Alistipes_senegalensis, s_Bacteroides_clarus,* and *s_Bilophila_unclassified*.

POSTERS

Natural history, epidemiology & risk prediction

Characterisation of IgA Nephropathy in an Australian Cohort

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Introduction: This retrospective cohort study of 104 patients with biopsy-proven immunoglobulin A nephropathy (IgAN) in the Hunter Region of New South Wales, spanning a 21-year period, aimed to identify predictors of kidney failure and disease progression.

Aim: To evaluate prognostic factors for progression of IgAN to kidney failure (defined as initiation of kidney replacement therapy or death) and all-cause mortality.

Methods: We conducted a retrospective analysis of 363 patients with biopsy-proven IgAN from 2000–2020 in the Hunter Region. Demographic data, comorbidities, biopsy features and biochemical markers were collected for at least 12 months post-biopsy. Multivariable Cox regression analysis assessed associations with renal progression.

Results: A total of 104 patients met inclusion criteria and were followed for a median of 72 months. The mean age at presentation was 45 years, with a predominantly male population. Most patients presented with haematuria and non-nephrotic range proteinuria. Patients were stratified into low, intermediate, and high-risk categories. Twenty-eight patients (26.9%) developed kidney failure, and 15 (14.4%) had >20 mL/min eGFR decline within 12 months.

Multivariable analysis revealed these key predictors of kidney failure: additional renal pathology on biopsy (HR 3.90, 95% CI 1.63–9.29), proteinuria (HR 1.15, 95% CI 1.02–1.29), and moderate-severe interstitial fibrosis/tubular atrophy (T2) (HR 7.00, 95% CI 2.32–21.05). There were 17 deaths (16.3%) with a mean survival time of 167.8 months (95% CI 152.6–183.1).

Conclusion: Unlike earlier Australian reports, our findings emphasise that progression to kidney failure is not uncommon in IgAN. We identified several consistent predictors of renal progression. This highlights the need for a change in clinical management, as IgAN should no longer be considered a benign condition.

Urinary Galactose-Deficient IgA1 as a Potential Early Biomarker for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is a chronic glomerular disease that can progress over decades and frequently leads to end-stage kidney disease (ESKD). Elevated serum levels of galactose-deficient IgA1 (Gd-IgA1) are characteristic of IgAN.

Aims: In this study, we investigated the potential of urinary Gd-IgA1 as a non-invasive biomarker for the early detection of IgAN.

Methods: Urine samples from 17 patients with biopsy-proven IgAN and 11 healthy controls were analyzed using three human monoclonal antibodies—Teddy 7 (T7), Teddy 9 (T9), and Teddy 71 (T71)—specifically developed to detect Gd-IgA1.

Results: Urinary Gd-IgA1 were significantly higher in IgAN patients compared to healthy controls when detected by T7 (0.800 ± 0.710 vs. 0.183 ± 0.173, $P = 0.009$), T9 (0.488 ± 0.485 vs. 0.119 ± 0.096, $P = 0.027$), and T71 (0.479 ± 0.453 vs. 0.137 ± 0.139, $P = 0.023$).

Conclusion: Urinary Gd-IgA1 can be reliably detected using monoclonal antibodies T7, T9, and T71, and is significantly elevated in patients with IgAN. These findings suggest that urinary Gd-IgA1 may serve as a promising non-invasive biomarker for the early diagnosis of IgA nephropathy. Further validation in larger, prospective studies is warranted.

KDIGO chronic kidney disease risk category and renal survival in patients with IgA nephropathy

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Introduction and Aims: The risk category determined by the KDIGO chronic kidney disease (CKD) heat map is widely utilized in the assessment of patients with IgA nephropathy (IgAN). The heat map incorporates two-dimensional clinical factors: estimated glomerular filtration rate (eGFR) and proteinuria. However, the significance of the association between the CKD risk category and renal prognosis in patients with IgAN remains to be elucidated, as does whether this association is influenced by pathological findings.

Methods: We used a dataset from the Japan IgAN Prospective Cohort Study (J-IGACS). Exposure was CKD risk category, which ranges from low, moderate, high to very high risk. The primary outcome was defined as dialysis initiation or a ≥ 50% increase in serum creatinine from baseline. Covariates included age, sex, mean arterial blood pressure, hematuria, MEST-C score, use of renin-angiotensin system inhibitors, use of corticosteroids, and tonsillectomy within one year of renal biopsy.

Results: Of 1130 participants in J-IGACS, 941 were enrolled. They were classified into CKD risk categories: 109, 250, 355, 227 participants were in low, moderate, high and very high, respectively. With increasing CKD risk category, the median eGFR decreased (93.9, 85.6, 79.2, 41.8 ml/min/1.73m^2) and the median proteinuria increased (0.05, 0.30, 0.87, 1.33 g/day). The association between CKD risk category and primary outcome was significant overall (hazard ratio [95% confidence interval]; 2.33 [0.28-19.6], 3.65 [0.47-28.4], 9.17 [1.14-72.3], in moderate, high, very high risk, respectively, with low risk as reference) and robust in all subgroup analyses except for crescent (C0/C1+2) in MEST-C score. The association between CKD risk category and primary outcome was weaker in C1+2 subgroup than in C0 subgroup (P for interaction 0.08).

Conclusion: CKD risk category is associated with renal survival in patients with IgAN, although its clinical impact may be differentiated by crescent formation in the MEST-C score.

Utility of A/C subclassification of histological grade classification of IgA nephropathy: a Japanese prospective cohort study

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Background and Aims: The histological grade classification (H-Grade) of IgA nephropathy (IgAN) in Japan showed sufficient predictive ability for renal function prognosis, comparable to the Oxford classification. In this study, to improve the utility of H-Grade for treatment choice, we investigated the usefulness of the A/C subclassification, consisting of active (A) and chronic lesions (C).

Materials and methods: Patients with IgAN diagnosed by renal biopsy were enrolled in the Japan IgA Nephropathy Cohort Study (J-IGACS) between 2005 and 2015. Cases with only active (cellular and fibrocellular) crescents were classified as A, those with only global sclerosis, segmental sclerosis or fibrous crescents as C, and those with both lesions as A/C. In A or A/C group and C group, multivariate analysis was performed using mean arterial pressure (MAP0), estimated glomerular filtration rate (eGFR0), urine protein excretion (UPE0) at renal biopsy, administration of steroid with/without tonsillectomy (ST), and use of renin-angiotensin system inhibitors (RASi) as variables. The endpoint was a composite of a 50% decline in eGFR and end-stage renal disease. To validate the results, prognostic comparisons were also made using log-rank tests between groups with/without ST.

Results: A total of 938 patients from J-IGACS (median follow-up: 5.5 years) were divided into three groups as non-A non-C (98 cases), A or A/C (361 cases) and C (497 cases). In Cox multivariate analysis adjusted for MAP0, eGFR0 and UPE0, H-Grade 3, 4 and ST were selected as significant variables in A or A/C group, whereas only H-Grade 3 and 4 were selected in C group. Furthermore, log-rank tests showed a significant difference in prognosis between ST-treated and untreated groups in A or A/C group, but no significant difference was found in C group.

Conclusion: By appending the A/C classification to the H-Grade, it was possible to distinguish cases in which ST was effective.

Microscopic hematuria is an early hallmark of IgA nephropathy and an indicator of disease activity

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Introduction: Microscopic hematuria is the first approach to IgA nephropathy (IgAN). Approximately 70% of patients present with hematuria as their first symptom. Microscopic hematuria correlates with disease activity and has been used to evaluate treatment responses in recent international clinical trials.

Aims: We aimed to elucidate the significance of isolated microscopic hematuria in the proportion of glomerulonephritis and pathological activities.

Materials and Methods: Among 513 patients who underwent renal biopsy in Juntendo University Urayasu Hospital, between January 2023 and December 2024, 42 patients showed hematuria without overt proteinuria. We analyzed the proportion of glomerulonephritis and pathological activities.

Results: IgAN was diagnosed with the largest number of 30 cases (71.4%), thin basement membrane disease (TBM) was in 9 (21.4%), minor glomerular abnormality in 2 (4.8%), and crescentic formed glomerulonephritis in 1 (2.4%). Among patients with IgAN, average age was 40.8 years old, endocapillary proliferation and crescentic formation were seen in 33.3% and 30%, respectively. Adhesion and segmental sclerosis were shown in 10% patients with IgAN. Global sclerosis and Oxford T lesions were rarely observed.

Conclusion: Among cases of isolated hematuria, IgAN was the most dominant. In patients with IgAN, even in cases with hematuria without overt proteinuria, active pathological findings were observed. Microscopic hematuria may be an early hallmark of pathological activity.

Validation of International risk-prediction tool and its Comparison with the JSN Classification in Japanese Patients with IgA Nephropathy: A Retrospective Cohort Study

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Introduction: The clinical course of IgA nephropathy (IgAN) is heterogeneous, necessitating accurate prognostic tools to guide management. The International IgAN Prediction Tool (IPT) was recently developed to estimate renal outcomes; however, its utility in Japanese patients remains unclear, particularly in comparison to the Japanese Society of Nephrology classification system, which incorporates clinical and histological severity.

Aim: This study aimed to validate the IPT in Japanese IgAN patients.

Materials and Methods: We retrospectively analyzed 145 patients (51.0% male) with biopsy-confirmed IgAN with a mean follow-up of 37 months, since 2014. Clinical and histopathological data were evaluated based on the Oxford classification. Patients were stratified into four groups (PS I-IV) using IPT prognostic scores and the JSN classification (low/moderate/high/super-high). The primary endpoints included progression to end-stage kidney disease (ESKD) and a ≥ 30% decline in estimated glomerular filtration rate (eGFR).

Results: At baseline, mean eGFR was 60.0 mL/min/1.73 m^2, and mean proteinuria was 1.5 g/gCr. Corticosteroid therapy was administered to 40.0%, and 36.6% underwent tonsillectomy with steroid pulse therapy. Declines in eGFR and higher proteinuria correlated with higher IPT scores. While Oxford classification lesions (M1, E1, S1, C1–2) were similar across groups, tubulointerstitial lesions (T1–2) were significantly more frequent in PS-III and PS-IV. During follow-up, 5.6% of the patients progressed to ESKD, and 15.9% of the patients reached ≥30% eGFR reduction. High and super high-risk categories in the JSN classification were more prevalent in PS-III and IV. Kaplan–Meier analysis showed significantly worse outcomes in PS-IV and super high-risk JSN groups.

Conclusion: The IPT is a reliable tool for predicting renal outcomes in Japanese IgAN patients, which is comparable to the JSN classification. Its prognostic value is particularly evident in intermediate to advanced disease stages.

Serum IgE is biomarker of benign course of IgA nephropathy

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Introduction: The role of IgE in the IgAN development and progression, as well as the allergen-specific profile of antibodies, remain not fully understood.

Aims: To determine the rate of elevated level of serum IgE in patients with IgAN and to establish its relationship with clinical, morphological and laboratory manifestations and the course of disease.

Materials and Methods: The study included 47 patients with primary IgAN, age 32 (27÷39) years.. The levels of daily proteinuria (PU), hematuria, serum creatinine, presence of arterial hypertension (AH), glomerular filtration rate (GFR) were analyzed. Total IgE in blood were measured with enzyme-linked immunosorbent assay, allergen-specific IgE antibodies to 57 allergens (household, epidermal, fungal, plant, food) were determined with using «EUROLINE Atopy Screen (IgE)» kit (Euroimmun, Germany).

Results: Elevated level of serum total IgE was found in 55% of patients with IgAN, the concentration was 89.4 (47.5÷198.7) IU/ml, correlation was established with GFR (R=0.32, p=0.02) and creatinine (R=-0.40, p=0.01). The decrease of AH rate (p=0.01), tubular atrophy and interstitial fibrosis (T1) (p=0.03) were determined in patients with elevated IgE levels as compared to those in group with IgE normal range. Correlation analysis revealed relationship between total serum IgE and endothelial proliferation (R=-0.40, p=0.02). The highest rate of occurrence among all allergens was found for specific IgE to domestic mites *Dermatophagoides farinae* (42.1%), the highest specific activity 31.4 (1.7÷71.3) c.u. was identified to *Dermatophagoides pteronyssinus*. A correlation was established between specific IgE to *Dermatophagoides pteronyssinus* and PU (R=-0.51, p=0.01) and between specific IgE to *Dermatophagoides farinae* and percentage of crescents (R=-0.55, p=0.01). Five-year event-free survival in the IgE group within the normal range was 67±19%, whereas there was 100% in patients with higher than the normal IgE level (p=0.008).

Conclusion: Higher than normal level of total and specific serum IgE testified about benign course of IgAN.

Clinical Validation of an IgA1 Galactose-Deficient Assay Kit in IgA Nephropathy

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Introduction: IgA nephropathy (IgAN) is frequently associated with elevated levels of galactose-deficient IgA1 (Gd-IgA1) in the serum. A new assay for this biomarker is currently being developed for diagnostic and prognostic purposes.

Aims: In this study, we evaluated the relationship between Gd-IgA1 levels and (1) the diagnosis of IgAN and (2) its prognosis.

Methods: This is a retrospective single-center study based on the IgAN cohort from the Saint-Etienne University Hospital. All patients with biopsy-proven IgAN and available diagnostic serum samples were included. The healthy volunteer cohort was provided by the French Blood Establishment (anonymous blood donors). The assay kit, marketed by Reliant Glycoscience™ (Birmingham, Alabama, USA), is based on the affinity of Gd-IgA1 for the HAA lectin.

Results: A total of 312 IgAN patients and 128 healthy volunteers (HVs) were included in the analysis. A significant difference in Gd-IgA1 levels was observed between patients and HVs (median 172 vs. 148 µg/ml, $p<0.001$).
Gd-IgA1 levels were significantly associated with systolic blood pressure at diagnosis (coef 0.038, p=0.009), vascular (coef 0.0014, p=0.034), interstitial (coef 0.0014, p=0.0078), and tubular (coef 0.001, p=0.015) histological lesions, as well as the T lesion in the Oxford classification (coef 0.001, p=0.027). Higher Gd-IgA1 levels were also associated with a greater likelihood of corticosteroid therapy (c-statistic: 0.628 [0.55–0.71]). Gd-IgA1 levels above the 85th percentile were linked to progression to end-stage renal disease.

Conclusion
In this case-control study, Gd-IgA1 levels were associated with the diagnosis of IgAN and, among patients, with elevated blood pressure, more severe histological lesions, increased likelihood of corticosteroid therapy, and the development of end-stage renal disease.

Outcome of Czech patients with IgA nephropathy

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We assessed 169 Czech patients with IgA nephropathy (IgAN) with a follow up of 72 months. Clinical parameters at presentation as well as histological findings (MEST-C score) of 169 Czech patients with IgAN were evaluated.

During follow up 82 patients (48,5 %) reached 50 % decline of eGFR or progression to end-stage kidney disease (ESKD), 13 patients (7,7 %) died and 74 patients (43,8 %) maintained relatively stable renal function.

We used International IgAN prediction tool (www.qxmd.com) to calculate the risk of a 50 % decline of eGFR or progression to ESKD within five years after renal biopsy. Median risk of preserved renal survival was 6.38 %; median risk of 28.86 % of 50 % decline of eGFR or progression to ESKD and 42.23 % of death.

Baseline clinical parameters (blood pressure, renal parameters, urinalysis, serum level of uric acid and albumin) were able to predict patients with preserved renal survival or 50 % decline of eGFR or progression to ESKD according to linear discriminant analysis which was confirmed also by means of logistic regression. We added exponential regression model to assess renal survival using only three clinical markers (systolic blood pressure, eGFR, proteinuria) at the time of diagnosis.

International IgAN prediction tool is suitable for the forecast of risk for renal survival but with low probability in our Czech cohort. Linear discriminant analysis or logistic regression model might be useful for the prediction of renal survival using only three clinical parameters.

Characteristics and outcome of immunoglobulin A nephropathy – a Swiss single center experience

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Introduction: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Roughly 40% of affected patients progress to end-stage kidney disease (ESKD) by ten years. Geographic differences in clinical course and treatment response are well recognized.

Aim: The purpose of this retrospective cohort analysis was to study all cases of IgAN of a Swiss tertiary single center with respect to clinical and histological characteristics, treatment practices and outcome.

Materials and Methods: This retrospective cohort analysis identified 158 cases of adult biopsy-proven IgAN by chart review diagnosed between 1980 and 2017. Detailed phenotypisation was performed. Statistical analysis included standard descriptive methods and univariate analysis corrected by the Bonferroni method.

Results: Patients were majorly male and of Caucasian descent. At diagnosis, mean estimated glomerular filtration rate (eGFR) was 55.4 ml/min/1.73 m^2, mean proteinuria was 2.4 g/d, 69.9% of the patients were hypertensive. Clinical presentation varied according to age whereas no differences according to sex were observed. Initial biopsies showed moderate to severe tubular atrophy and interstitial fibrosis in 29.1% and crescents in 36.7% of cases. Therapy included renin-angiotensin-aldosterone-inhibitors in 86.7%, immunosuppressives in 46.8% including steroids (43%) and other immunosuppressives (28.7%), most commonly azathioprin. Overall outcome included 34.1% complete and 22.2% partial remissions, relapses occurred in 32.0% of patients. Progression to ESKD occurred in 43.0% of patients during follow-up (median 100.0 months). Recurrence rate after transplantation was 18.8%. Immunosuppressive therapy was more frequently used in patients with higher proteinuria level and crescents. Patients attaining remission had higher baseline eGFR. Predictors of progression were lower eGFR, higher proteinuria and higher percentage of tubular atrophy and interstitial fibrosis on the initial biopsy.

Conclusion: This retrospective cohort analysis gives insight into clinical and histological characteristics and outcome of patients with IgAN from a Swiss tertiary center, treatment practices and predictors of outcome and therapy choices.

The clinical impact of glomerular C3 depositions on the severity and treatment responses in IgA nephropathy

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Introduction: The activation of the complement system plays a crucial role in the pathogenesis of IgA nephropathy (IgAN). Among the complement pathways, multiple studies support the involvement of the alternative pathway. However, the clinical impacts of complement deposition in the glomerulus remain fully understood.

Aim: We investigated the clinical impact of the complement deposition in the kidney biopsy tissue.

Materials and Methods: This study included 58 patients with biopsy-proven IgAN. Patients were divided into two groups based on their C3 deposition intensity. We conducted a retrospective analysis of the role of complement in the glomerulus in the clinical and pathological features, including Oxford classification and treatment responses, in these two groups.

Results: A total of 47 patients and 11 patients were classified as C3 positive and C3 negative, respectively. The levels of microscopic hematuria and estimated glomerular filtration rate were significantly severe in patients with positive C3 deposition in the glomerulus. Serum levels of C3 were lower, and serum levels of IgA/C3 rations were higher in patients with positive C3 deposition in the glomerulus. Furthermore, in cases with positive C3 deposition, glomeruli with crescents (C score) and segmental sclerosis (S score) were notable. Nevertheless, no significant difference was observed in remission rates following tonsillectomy and steroid pulse therapy (TSP).

Conclusion: Patients with positive C3 deposition in the glomerulus tend to exhibit increased microscopic hematuria, worsened kidney function, and a greater severity of both acute and chronic lesions in the kidney. Reduced serum C3 levels and increased serum IgA/C3 ratios may act as markers for the degree of C3 deposition within the glomerulus. However, the intensity of glomerular C3 deposition may not influence the therapeutic responses to TSP. We need to increase the number of patients to validate these results in more detail.

Healthcare resource utilization and costs among patients with primary immunoglobulin A nephropathy (IgAN) by proteinuria and kidney function decline in China

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Introduction: Providing up-to-date evidence on disease progression and economic burden of immunoglobulin A nephropathy (IgAN) is essential, to improve treatment strategies and allocate resources effectively to manage IgAN.

Aims: This study investigated the association between disease progression and healthcare resource utilization/costs among IgAN patients in China.

Materials and Methods: This retrospective cohort study included adult patients with biopsy-proven primary IgAN diagnosed between 01/01/2015 and 06/30/2023. Index date was the date of renal biopsy. Healthcare costs per capita per year were calculated across proteinuria levels and CKD stages over 2015–2023, and reported as CPI-adjusted CNY in 2023 (converted to USD). Inpatient and outpatient visit frequency and length per patient-year at follow-up were estimated.

Results: This study included 1,674 patients, 55.0% <40 years and 88.2% had moderate-to-severe hematuria at renal biopsy. During follow-up (median: 2 years), renin-angiotensin-aldosterone system inhibitor (RAASi) was commonly administered (62.1%), followed by corticosteroids (59.6%) and immunosuppressants (30.3%) along with a high proportion of concomitant traditional Chinese medicine (TCM) use (86.8%). On average, per follow-up year, each patient had seven outpatient nephrology visits, one hospitalization, and 14 days of hospital stay. Overall per capita healthcare cost was $1,363 in 2023. The per capita per year healthcare costs increased with higher proteinuria levels or advancing CKD stages, from $1,211 among patients with proteinuria <0.5 g/day to $2,506 among patients with proteinuria ≥3 g/day, and $1,449 among patients with CKD stage 1 to $3,136 among patients with CKD stage 4.

Conclusion: A quarter of patients experienced rapid eGFR decline, risking acute kidney injury despite use of RAASi +/- TCM. Patients with higher proteinuria levels and advanced CKD stages experienced higher healthcare costs. The economic burden associated with CKD progression and high proteinuria levels among IgAN patients highlights the need for enhanced treatment strategies to reduce proteinuria and preserve kidney function.

Serum galactose-deficient IgA1 levels in patients with IgA nephropathy and healthy controls measured with GalD®, a novel lectin-based enzyme-linked immunosorbent assay

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Introduction: Galactose-deficient IgA1 plays the central role in development of IgA nephropathy (IgAN), a common primary glomerulonephritis in many countries. Serum levels of galactose-deficient IgA1 are associated with long-term kidney outcomes. Historically, measurements of serum galactose-deficient IgA1 levels with lectin-based assays have been technically challenging. Variable sources of the lectin and inconsistent inclusion of neuraminidase treatment and standards have rendered results of lectin-based assays not comparable across studies.

Aims: To develop a robust lectin-based enzyme-linked immunosorbent assay (ELISA) to measure serum levels of galactose-deficient IgA1 based on well characterized quality-control standards.

Materials and Methods: We developed GalD® assay kit, a lectin-based ELISA to measure serum levels of galactose-deficient IgA1. Antibody specific for human IgA is pre-coated in the wells of 96-well plates. Captured IgA is analyzed in a two-step detection reaction; biotin-labeled lectin first selectively binds to galactose-deficient IgA1 and then bound biotin-labeled lectin is detected using avidin conjugated with peroxidase in a colorimetric reaction with tetra-methyl-benzidine with optical density read at 450 nm. Each plate includes a standard serum IgA1 sample and three quality-control standards. Eight sites have used GalD® assay kits. At Reliant Glycosciences, we measured serum galactose-deficient IgA1 levels in 281 IgAN patients and 281 healthy controls.

Results: Quality controls showed reproducibility within 10% at all sites. At Reliant Glycosciences, serum levels of galactose-deficient IgA1 in 85% of IgAN patients were above median level for healthy controls; 64% of IgAN patients had levels above the 75th percentile for healthy controls.

Conclusion: GalD® assay provides robust and highly reproducible measurement of serum levels of galactose-deficient IgA1, the most utilized disease-specific biomarker for IgAN. This assay can be used to track responses to disease-modifying treatments and will enable much-needed cross-study comparisons in future studies. Additonal uses may include risk-stratification of patients and monitoring for recurrent disease after kidney transplantation.

Gut Microbiome Features in IgA Nephropathy Patients with Favorable and Unfavorable Prognosis

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Introduction: IgA nephropathy (IgAN) is a heterogeneous disease with variable progression. Emerging evidence suggests the gut microbiome may influence kidney disease outcomes.

Aims: To characterize and compare gut microbiome composition and functional profiles in IgAN patients with variable prognosis, as defined by the International IgAN Prediction Tool (IIgANPT).

Materials and Methods: Adult patients with biopsy-proven IgAN were enrolled from the renal biopsy registry at Pauls Stradiņš Clinical University Hospital, Latvia (2020–2022). Prognostic risk was calculated using the IIgANPT and categorized as s favorable (<10%, FP) or unfavorable (≥10%, UP) for a 50% eGFR decline or progression to ESRD within 60 months. Stool samples were collected for metagenomic sequencing and functional profiling.

Results: A total of 48 patients (FP: 37; UP: 11) were analyzed. No significant differences in alpha or beta diversity were observed. *Prevotella* (7.86%) was the most abundant genus in FB prognosis patients, while *Blautia* (7.04%) predominated in UP patients. At the species level, *Agathobacter rectalis* (2.67%) was the most prevalent in FP patients, whereas *Prevotella sp900557255* (4.40%) in UP patients. Differential abundance analysis identified 383 species with significant variation. Notably enriched in UP patients were *CAG.605.sp900545005* (coef = 8.03, FDR = 2.90E-04), *CAG.831.sp902388455*. *Citrobacter portucalensis* was negatively associated with worse prognosis (coef = -4.68, FDR = 7.25E-03). Twenty metabolic pathways differed significantly between groups. L-lysine degradation X (coef = –4.28, FDR = 4.34E-02) and O-glycan modification via type 2 precursor disaccharide (coef = –2.55, FDR = 7.24E-02) were enriched in FP. Gd-IgA1 accounted for a greater portion of the observed pathway variations (PERMANOVA R^2=0.059, p=0.016)

Conclusion: Although global microbial diversity was similar, specific taxonomic and functional signatures distinguished IgAN patients with favorable versus unfavorable prognosis. These findings suggest potential prognostic or therapeutic targets warranting further investigation.

Paediatric disease

Alternative budesonide formulation in pediatric IgA Nephropathy as a possible therapeutic option: a case series

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Introduction: Pediatric IgA nephropathy (IgAN) is a leading cause of glomerulonephritis and progressive kidney disease. While the FDA and EMA have recently approved Nefecon for adult IgAN, pediatric data are still lacking.

Aim: Here, we report the first case series of pediatric patients treated with an alternative formulation of budesonide.

Materials and Methods: The five patients, with a mean age of 14.2 years, had biopsy-proven IgAN and variable MEST-C scores; three had previously received a 6-month prednisone course with only partial or no response. Based on recent evidence of efficacy and safety profiles, we initiated a budesonide formulation approved for IBD with pan-intestinal release, at 9 mg/m^2 daily for 9 months with a variable tapering schedule and stable dose of ACE-inhibitors.

Results: At treatment initiation, the mean eGFR and UPCR were 97 ± 23.7 mL/min/1.73m^2 and 0.5 ± 0.29 mg/mg, respectively. One patient was lost at 3 months. After 9 months, the mean eGFR was slightly reduced at 92 ± 13.4 mL/min/1.73m^2, and the mean UPCR had decreased to 0.31 ± 0.22 mg/mg (-38%), with 3/4 patients achieving proteinuria remission (UPCR <0.2 mg/mg). However, during the following 9 months, proteinuria increased again in all but one patient, reaching a mean UPCR of 0.66 ± 0.58 mg/mg at 18 months, despite stable eGFR. Microhematuria was less affected, with only one transient remission. Notably, two patients with frequent gross hematuria experienced a consistent and lasting reduction in episodes. No significant treatment-related adverse events were reported.

Conclusion: This case series highlights two critical points: alternative budesonide formulations might induce clinical improvement in pediatric IgAN; however, as observed in the NefIgArd trial cohort, proteinuria worsening after withdrawal is common, appearing even earlier in our cohort, likely due to non-standardized dosing, release and tapering profile. These findings emphasize the need for prospective pediatric trials with optimized budesonide formulations.

Secondary IgA Nephropathy in the context of disseminated tuberculosis: a pediatric case report

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Introduction: IgA nephropathy (IgAN) is the most common form of glomerulonephritis in children, with most cases being idiopathic. However, systemic conditions such as liver disease, inflammatory bowel disease (IBD), and chronic infections may cause secondary IgAN.

Aim: We report a case of secondary IgAN associated with disseminated tuberculosis (DTB).

Materials and Methods: A 14-year-old boy with Crohn's disease, in remission since 2021 and on adalimumab with previous negative immunostimulation tests, was referred for daily macroscopic hematuria lasting two months and an increase in inflammatory markers.

Results: On admission, labs showed creatinine 0.5 mg/dL, elevated C3, IgG, IgA, CRP 2.5 mg/dL, and a UPCR of 0.5 mg/mg. Since a recent vacation in Egypt, we performed urine tests for Mycobacterium tuberculosis and Schistosoma, and an abdominal ultrasound; the results were negative. Kidney biopsy confirmed IgAN (M1, E1, S0, T0, C0). Given the IBD history, budesonide was started and adalimumab discontinued. Macrohematuria turned into consistent microscopic hematuria within 10 days; after two weeks, UPCR and microhematuria slightly decreased to 0.37 mg/mg and 30–60 RBCs/HPF, respectively. However, inflammatory markers remained elevated, with fatigue, weight loss, and intermittent fever. The patient was re-admitted. Imaging showed multiple splenic hypoechoic lesions, and chest X-ray revealed findings consistent with miliary TB. Cultures confirmed Mycobacterium tuberculosis. Anti-TB therapy was initiated. Budesonide was maintained mainly for intestinal indications. After two weeks, UPCR dropped to 0.11 mg/mg, microhematuria to 15 RBCs/HPF, and systemic symptoms improved.

Conclusion: Although causality cannot be definitively proven due to coexisting Crohn's disease, this may represent the first pediatric case of IgAN secondary to DTB. The few cases described achieved remission after TB treatment. Here, the rapid proteinuria improvement after TB-therapy (unlike after budesonide, which takes months to act) supports a stronger link to DTB than to intestinal origin. TB should be excluded in IgAN with systemic inflammation, even in non-endemic areas.

An open-label phase 3 study of ravulizumab in pediatric immunoglobulin A nephropathy or immunoglobulin A vasculitis-associated nephritis

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Introduction: In immunoglobulin A nephropathy (IgAN), immune complex formation and deposition leads to complement system activation, contributing to kidney damage. IgA vasculitis-associated nephritis (IgAVN) has similar pathogenesis to that of IgAN. Ravulizumab, a complement C5 inhibitor, has shown clinically meaningful proteinuria reduction in adults with IgAN in a phase 2 trial; a phase 3 trial of ravulizumab in adults (NCT06291376; EU CT 2023-507851-31-00) is ongoing.

Aims: To describe the design of a phase 3 study of ravulizumab in pediatric patients with IgAN or IgAVN.

Materials and Methods: This phase 3, open-label, single-arm, multicenter study evaluates the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of ravulizumab in pediatric patients (N≈18) with IgAN (n=12) or IgAVN (n≈6). Patients (aged ≥2-<18 years) with a kidney biopsy-based diagnosis of IgAN/IgAVN, body weight of ≥10kg, an estimated glomerular filtration rate (eGFR) of ≥30mL/min/1.73m^2, and a urine protein-to-creatinine ratio (UPCR) of ≥0.5g/g from first morning void during screening will be included. The study consists of a 6-week screening, a 34-week primary evaluation, and a 72-week extension period. Patients will receive weight-based loading dose of ravulizumab intravenously on Day 1, then maintenance dose on Day 15, and every 8 weeks (if weight ≥20kg) or 4 weeks (if weight <20kg) thereafter up to Week (W) 106.

Results: Primary endpoints (PK and PD) are ravulizumab maximum serum concentration, trough serum concentration, and change in serum free C5 concentration through W34. Secondary endpoints include change from baseline in UPCR and eGFR up to W34 and W106, respectively, and partial remission (≥50% UPCR reduction from baseline and UPCR <3g/g) at W34. Safety, tolerability, and immunogenicity are evaluated.

Conclusion: Without proper management, IgAN and IgAVN can lead to kidney failure, requiring dialysis or transplant. This trial could inform future management of these conditions in the pediatric population.

Exploration influence of the intensity of renal immune cell infiltration on clinicopathological features and prognosis in children with IgA nephropathy

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Objective: To investigate the correlation between the intensity of renal immune cell infiltration and clinicopathologic features as well as prognosis in children with IgAN.

Methods: A total of 55 cases with IgAN were included for multiple fluorescence immunohistochemistry to detect the infiltration of immune cell subsets in renal tissue. Patients were divided into CKD stage 1-2 group and CKD stage 3-5 group according to the renal function of follow-up ≥1 year. The correlation between the intensity of renal immune cell infiltration and clinicopathological features of IgAN children in the two groups was analyzed.

Results: The median follow-up time of 55 children with IgAN was 74 months, including 35 patients in CKD stage 1-2 group and 20 patients in CKD stage 3-5 group. The age of diagnosis in CKD3-5 group was higher than that in CKD1-2 group, increased urinary protein [2.27(0.51, 3.56)g/d/1.73m2 vs 0.57(0.16, 2.30) g/d/1.73m2], increased MAP [90.65±14.11mmHg vs 81.57±9.13mmHg], increased serum uric acid [402.0(251.8, 556.3) μmol/L vs 288.0(250.0, 415.0) μmol/L] and serum albumin decreased [33.6(23.5, 39.8) g/L vs 39.0(34.0, 43.0) g/L]. There was an increase of T1/2 in Oxford Classification, and there was no statistical differences between the two groups on treatment. The percentage of CD68+ macrophage percentage, CD68+CD163+ macrophage percentage and CD20+B lymphocyte were increased in stage CKD3-5 group. CD68+ macrophage infiltration was positively correlated with the level of urinary protein quantity, MAP and serum uric acid. The percentage of CD163+ macrophage infiltration was positively correlated with urinary protein quantity and MAP level. The percentage of CD68+CD163+ macrophage infiltration was positively correlated with the level of urine protein quantity and serum uric acid. The percentage of renal CD20+B cell infiltration intensity was positively correlated with Oxford Classification E.

Conclusions: Increased infiltration of renal macrophages and B cells at renal biopsy may be the risk factors for poor prognosis of IgAN in children.

Correlation of capillary loop IgA deposition with clinicopathological features in pediatric IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerular disease in children. Clinical and histopathological heterogeneity ranges from asymptomatic hematuria/proteinuria to rapidly progressive nephritis, potentially linked to IgA deposition patterns. While most cases show mesangial IgA deposition, a subset exhibit capillary loop involvement, yet its clinical relevance remains unclear.

Aims: To analyse the relationship between capillary loop IgA deposition with clinical manifestations and renal pathology in IgAN children.

Materials and Methods: Clinical and pathological data of IgAN children at the First Affiliated Hospital of Sun Yat-sen University from 2000 to 2024 were retrospectively collected, including 24-hour urine protein (24hUPro), serum albumin (ALB), estimated glomerular filtration rate (eGFR), peripheral blood immune cell ratio, Lee's Pathological Classification, Oxford Pathological Staging, etc. According to the presence or absence of renal IgA deposition in capillary loops (CLD), IgAN children were divided into CLD(-) and CLD(+) groups.

Results: This study enrolled 408 IgAN children (male-to-female ratio 2:1) stratified into CLD(-) (n=366, 89.7%) and CLD(+) (n=42, 10.3%) groups. Clinically, CLD(+) groups exhibited significantly higher 24hUPro [2.18(1.12, 3.29) vs. 0.73(0.25, 1.86)g/d, $P<0.0001$], lower ALB [28.0 (25.0, 33.3) vs. 38.6(32.0, 42.0)g/L, $P<0.0001$], and higher rates of dyslipidemia (85.7% vs. 62.3%, $P=0.0026$), hyperuricemia (38.1% vs. 21.9%, $P=0.0188$), and acute kidney injury (AKI) (31.0% vs. 10.1%, $P<0.0001$). Histopathologically, CLD(+) groups showed increased proportions of advanced Lee grade≥IV (28.6% vs. 9.3%, $P=0.0002$) and Oxford E1 lesions (61.9% vs. 34.7%, $P=0.0006$). Immunologically, CLD(+) groups demonstrated reduced serum IgG [6.31(3.07, 9.36) vs. 8.41(5.13, 10.80)g/L, $P=0.0015$] and elevated derived neutrophil-to-lymphocyte ratio [dNLR: 1.52(0.79, 2.98) vs. 1.12(0.75, 1.75), $P=0.0459$].

Conclusion: CLD(+) IgAN children exhibit severe clinical manifestations (elevated proteinuria , hypoalbuminemia, and higher rates of dyslipidemia, hyperuricemia and AKI), along with advanced histopathological features (Lee grade ≥IV, Oxford E1 lesions) and immune dysregulation (reduced IgG, elevated dNLR). These findings underscore that IgA deposition in capillary loops correlates with aggravated disease severity in IgAN children.

Nefcon Use in Pediatric IgA Nephropathy: Three Case Reports

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Introduction Nefecon, a targeted therapy for IgA nephropathy (IgAN), has demonstrated efficacy in adult patients. However, limited data exist regarding its use in pediatric IgA nephropathy.

Aims This report explores the therapeutic effects and safety profile of Nefecon in three pediatric cases.

Results:

Case 1 A 16-year-old boy with IgA nephropathy was readmitted due to a recurrence of proteinuria. He has been diagnosed with IgA nephropathy (M1E1S1T0C1) 3.5 years prior. Remission of proteinuria was initially achieved using steroids and mycophenolate. Eight months ago, after discontinuing immunosuppressive therapy, proteinuria reoccurred, escalating to 0.8 g/day despite restarting steroids and mycophenolate. Nefecon (16 mg/day) was added, along with losartan and dapagliflozin. Side effects included weight gain (6 kg), acne, and mild facial edema. Three months later, proteinuria increased to 0.96 g/day, and the case remains under follow-up.

Case 2 A 15-year-old boy diagnosed with IgA nephropathy (M1E1S1T0C1) five years prior achieved complete remission with steroids and cyclophosphamide. One year prior, proteinuria relapsed after stopping these treatments, confirmed by a second biopsy as M1E1S1T0C0. Nefecon (16 mg/day) was initiated, combined with fosinpril and finerenone, followed by mycophenolate one month later. At three months, proteinuria decreased from 1.9 g/day to 0.61 g/day. Side effects included weight gain (3.8 kg) and acne.

Case 3 A 16-year-old boy diagnosed with IgA nephropathy (M0E1S0T0C1) two years ago received sequential treatments with steroids, cyclophosphamide, calcineurin inhibitors, and mycophenolate, achieving transient proteinuria reduction to 525 mg/day. Seven months prior, proteinuria and hematuria relapsed. Nefecon (16 mg/day) was started alongside fosinpril, and the case is ongoing. Side effects included weight gain and acne.

Conclusion These cases illustrate variable responses to Nefecon in pediatric IgA nephropathy, highlighting challenges in treatment efficacy and safety. Further research is needed to optimize its use in this population.

IgA vasculitis

A comparative study of clinical and pathological differences between adult-onset IgA vasculitis and IgA nephropathy

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Background: IgA vasculitis (IgAV) with nephritis shows bimodal onset, and studies focusing on adult-onset cases are relatively limited. IgA vasculitis and IgA nephropathy (IgAN) often exhibit remarkably similar glomerular lesions, making pathological differentiation challenging.

Objective and Methods: In this study, we retrospectively analyzed clinical and pathological differences between 32 IgAV patients and 228 IgAN patients, all aged 18 or older, who underwent renal biopsy at our hospital between January 2012 and February 2023.

Results: Clinically, IgAV was significantly presented extra-renal symptoms such as purpura and hematochezia compared to IgAN. Moreover, levels of CRP ($p=0.0141$), D-dimer ($p=0.0013$), and C3 ($p=0.0013$) were significantly higher in the IgAV.

In contrast, no significant differences were observed in hematuria ($p=0.3786$), urinary protein/creatinine ratio ($p=0.2815$), or serum creatinine levels ($p=0.2820$) at the time of renal biopsy.Pathologically, IgAV showed significantly higher incidences of endocapillary proliferation ($p=0.0005$), necrotizing lesions ($p<0.0001$), and peritubular capillaritis ($p=0.0036$) under light microscopy. On the other hand, global glomerulosclerosis ($p=0.0104$) and segmental sclerosis ($p=0.0350$) were significantly more frequent in IgAN.

Immunofluorescence findings showed higher fibrinogen deposition both in mesangium ($p<0.0001$) and along capillary walls ($p=0.0229$) in IgAV. Conversely, IgA ($p=0.0393$) and C3c ($p<0.0001$) deposition in mesangium was significantly more prominent in IgAN. Although there was no significant difference in deposit accumulation on electron microscopy, endocapillary proliferation was significantly more prominent in IgAV.

Discussion and Conclusion: Our findings showed not only clinically but also pathologically distinct differences between IgAV and IgAN possibly due to marked vascular injury resulting local hyper coagulation in the former.

Pathogenesis

When it is not IgA nephropathy: a case highlighting the diagnostic value of renal biopsy

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Introduction: IgA nephropathy (IgAN) is the most prevalent glomerular disease, diagnosed based on clinical presentation and biopsy findings. However, differential diagnosis can be challenging and confusing.

Aims: This case aims to highlight the significance of renal biopsy in the accurate diagnosis and the potential pitfalls of misdiagnosing hereditary nephropathies. It also demonstrates the importance of precise diagnosis in avoiding inappropriate treatment strategies.

Materials and Methods (Case presentation): This is a case report of a 51-year-old female who was admitted to our hospital with microhematuria and 24-h proteinuria up to 3g, elevated BP of 160/90 mmHg. Her renal function was stable with an eGFR of 60 mL/min. She had no hearing loss or visual impairment. Past medical history revealed that at age 6 she was likely misdiagnosed with acute post-infectious glomerulonephritis due to nephritic syndrome and then lost to follow-up. Thereafter, she underwent screening only during her pregnancy 15 years ago, at which time persistent microhematuria was noted. However, no further follow-up after delivery was performed. Family history was unremarkable, her parents and brother are alive and have no renal symptoms. According to these data we suggested IgAN with secondary focal segmental glomerulosclerosis.

Results: However, a renal biopsy revealed an abnormality in type IV collagen, indicating a hereditary disorder, possibly Alport syndrome or thin basement membrane nephropathy. Further genetic testing was assigned. Based on the biopsy results, a nephroprotective treatment strategy was implemented.

Conclusion: Renal biopsy was pivotal in revising the initial diagnosis and guiding the treatment plan. The patient's proteinuria initially thought to be glomerular in origin, was found to be associated with chronic kidney disease due to a hereditary disorder. Following intensive nephroprotective therapy, proteinuria started to decrease and kidney function remained stable. The correct diagnosis prevented unnecessary immunosuppressive treatments and focused the management on slowing disease progression.

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Combination of a mouse monoclonal antibody and a GalNAc-specific lectin for monitoring of IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is the common primary glomerulonephritis and a major cause of end-stage renal disease worldwide, but diagnosing IgAN requires an invasive procedure, which hinders early detection and monitoring of disease progression. Several reagents, including antibodies and lectins that recognize galactose-deficient (Gd) IgA1, the specific biomarker of IgAN, have been developed for a non-invasive and practical diagnostic strategy. However, their sensitivity and specificity have not yet met the required standards.

Aims: To develop a sensitive and specific non-invasive diagnostic assay IgAN by targeting Gd-IgA1.

Materials and Methods: We reported a newly identified anti-Gd-IgA1 antibody, ASK2, and a lectin, *Crenomytilus grayanus* lectin (CGL), with the aim of improving the development of early-stage IgAN diagnosis.

Results: These two reagents could not only specifically distinguish Gd-IgA1 from normal IgA1 with intact glycans, but they also exhibited enhanced binding with serum and urine samples from IgAN patients. They were also found to bind to synthetic antigen-mimic glycopeptides and to recognize Gd-IgA1 in the glomerulus through immunofluorescence staining. The combination of ASK2 and CGL, along with the previously reported KM55, has significantly improved the detection specificity and sensitivity in the sera of IgAN patients.

Conclusion: The potential binding mode of ASK2 and CGL in complex with Gd-IgA1 was revealed through molecular modeling using the interaction energy as evaluation criteria to provide structural insights for further mechanistic studies.

The Role of T Nodule in the Tonsil-Glomerular Axis in Patients with IgA Nephropathy: A Retrospective Cohort Study

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Tonsillectomy combined with steroid pulse therapy (SPT) has been established as an effective treatment for immunoglobulin A nephropathy (IgAN) in Japan. However, the underlying mechanisms supporting the efficacy of tonsillectomy remain unclear. This study assessed palatine tonsils from 77 patients with IgAN, including 14 and 63 who received SPT before and after tonsillectomy, respectively. Tonsils from 21 patients with chronic tonsillitis served as controls. Specific tonsillar lesions were identified in patients with IgAN and were found to correlate with both active and chronic glomerular lesions. The number of T lymphocyte nodules (T nodules), defined by an assembly of HLA-DR–positive cells at the center, was counted per 2.0 mm^2 and was termed the T nodule score. The area of involution of lymphoepithelial symbiosis (ILES), which shows reticular pattern of cytokeratin-positive tonsillar crypt epithelium in normal condition, was scored in 5 grades and designated as ILES score. T nodule and ILES scores in tonsils were correlated with the incidence of crescents and segmental sclerosis in glomeruli, respectively. The findings highlight the essential role of the tonsil–glomerular axis in both early active and late chronic phases. Interestingly, the SPT-preceding group showed no significant change in T nodule score, which correlated with crescent formation but demonstrated considerable shrinkage of lymphoid follicles producing abnormal IgA1. The ILES score was significantly higher in the SPT-preceding group compared to the tonsillectomy-preceding group indicating an effect of SPT on enhancement of ILES scores. This study underscores the involvement of innate and cellular immunity and supports tonsillectomy as a necessary treatment alongside SPT for IgAN. SPT after tonsillectomy was necessary because memory T cells already distributed in systemic circulation can undergo SPT-induced apoptosis. Suppressing glomerular vasculitis at an early stage by conducting tonsillectomy besides SPT is as a goal for the shift from “inhibiting IgAN progression” to “IgAN remission”.

Competitive Binding Between IgA and IgG Autoantibodies to Gd-IgA1 Derived from the Same IgA Nephropathy Patient

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Introduction: IgA nephropathy (IgAN) is the most prevalent form of primary glomerulonephritis worldwide and is characterized by mesangial deposition of immune complexes containing galactose-deficient IgA1 (Gd-IgA1). Both IgG and IgA autoantibodies (auto-Abs) specific to Gd-IgA1 have been identified in patients with IgAN. However, the nature of their interaction, particularly whether they compete for binding to Gd-IgA1, and the resulting effects on immune complex (IC) formation and inflammation have not been fully elucidated.

Aims: To examine the competitive binding between IgA and IgG autoantibodies to Gd-IgA1 from the same IgAN patient and its impact on immune complex formation and inflammation.

Materials and Methods: Peripheral blood mononuclear cells were collected from individual patients with IgAN, and patient-derived IgG auto-Abs, IgA auto-Abs, and Gd-IgA1 were identified using a human hybridoma platform. These components were used to perform IC formation assays, competitive binding assays, and functional inflammation assays.

Results: In present study, we found that IgA auto-Ab interfered with IC formation between IgG auto-Ab and Gd-IgA1, as demonstrated by native gel Western blot analysis. ELISA confirmed this competition, with a dose-dependent decrease in IgG binding ($p<0.01$). In macrophage assays, IL-1β secretion was significantly elevated in response to the IgG–Gd-IgA1 complex, but was reduced upon the addition of IgA autoantibody, indicating its modulatory effect on the inflammatory response.

Conclusion: This study demonstrated that IgA auto-Ags can competitively inhibit IgG auto-Abs binding to Gd-IgA1 when all components are derived from the same IgAN patient, suggesting a nuanced, patient-specific autoimmune mechanism in IgAN and offer potential avenues for antibody-targeted therapeutic interventions to modulate inflammation and disease progression.

Analysis of renal lymph node revealed the presence of IgG+ germinal center B cells in IgA nephropathy model mice

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Introduction: Recently, we showed the presence of IgA autoantibodies (auto-Abs) against mesangial cells in the serum of patients with IgA nephropathy (IgAN), suggesting that IgAN is an autoimmune disease with tissue-specific auto-Abs (*Sci. Adv.* 2023, *Life Sci. Alliance.* 2024, *Kidney Int. Reports.*2025). In some autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis, draining lymph nodes of target organs have been reported to be involved in the pathogenesis.

Aim: This study aims to investigate the role of renal lymph nodes (RLN) in the pathogenesis of IgAN.

Methods: Male and female spontaneous IgAN model mice (gddY) were used. Lymphocytes collected from the RLNs of BALB/c, IgA-deficient gddY mice, and gddY mice were evaluated using flow cytometry at 4, 8, and 12 weeks of age. The number of $CD4^+$ and $CD8^+$ T cells and B cells were analyzed. For the analysis of the B cell subset, naïve B cells, memory B cells (MBCs), and germinal center B cells (GCBs) were evaluated.

Result: The number of B cells in RLNs from gddY mice increased at 4 weeks of age compared to BALB/c mice and IgA-deficient gddY mice, whereas that of $CD4^+$ and $CD8^+$ T cells did not. In RLNs from gddY mice, naïve B cells began to increase at 4 weeks and MBCs and GCBs were significantly increased at 8 weeks. The immunoglobulin subtype of these B cells was IgG. No gender differences were observed.

Conclusion: We found that IgG^+ MBCs and GCBs increased in RLNs of gddY mice. Given that earlier papers reported that IgG antibodies against glomerular antigens are present in the sera of patients with IgAN (*J. Clin. Invest.* 1991, *Nephrology Dialysis Transplantation.*1992), the presence of IgG^+ MBCs and GCBs in RLNs further suggests the presence of IgG auto-Abs against renal antigen. Future analysis of auto-antigens is required.

Targeting human IgA autoantibodies and galactose-deficient IgA1 antigen to unravel their pathogenic roles in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is an autoimmune disease, characterized by predominant glomerular IgA immune deposits formed by autoantibodies (auto-Abs) and galactose-deficient IgA1 (Gd-IgA1) bearing Thomsen-nouveau [Tn] antigen (a mucin-type *O*-glycan). IgA auto-Abs have been detected in blood of IgAN patients, it remains largely unknown about their pathophysiological role in the pathogenesis of the renal disease. The pathogenic mechanisms remain unclear, making it difficult to develop effective treatments.

Aims: To examine the pathophysiological roles of human IgA auto-Abs and corresponding IgA1 autoantigens (auto-Ags) in IgAN.

Materials and Methods: Using a panel of human hybridoma cell lines that produce IgA auto-Abs and auto-Ags. The interaction between IgA auto-Abs and their corresponding antigens was validated through BLI, mass spectrometry, and native gel electrophoresis. The inflammatory potential of the resulting immune complexes (IC) was assessed using THP-1 cells.

Results: A total of five human hybridoma cell lines producing IgA auto-Abs were successfully generated. These IgA auto-Abs were shown to bind the Gd-IgA1 auto-Ags (from same patient) using BLI analysis and also demonstrated binding to *O*-glycans in a mini-glycan array. Furthermore, mass spectrometry revealed that the IgA auto-Abs recognized GalNAc in the hinge region of the corresponding auto-Ags. In native gel analysis, these IgA auto-Abs were shown to form high-molecular-weight IC with their corresponding auto-Ags. Notably, the five IgA auto-Abs–auto-Ags complexes were significantly increased IL-1β, IL-6, TNF-α and MCP-1 in human macrophages, suggesting a potential mechanism through which they amplify inflammatory responses in IgAN.

Conclusion: The IgA auto-Abs we identified form IC with their corresponding auto-Ags, contributing to inflammatory responses that may exacerbate the progression of IgAN.

Kidney injury and colocalization of complement C3, IgA, and IgG in glomerular immune-complex deposits in patients with IgA nephropathy and IgA vasculitis with nephritis

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Introduction: IgA nephropathy (IgAN) and IgA vasculitis with nephritis (IgAVN) are considered similar diseases with different spectra of clinical manifestations. Routine immunofluorescence microscopy of kidney-biopsy specimens of IgAN and IgAVN patients shows glomerular immune-complex deposits with IgA as (co)dominant immunoglobulin and variable staining for IgG. Complement C3 (C3) is usually present.

Aims: We sought to assess glomerular C3-IgA, C3-IgG, and IgA-IgG pairwise colocalization using confocal microscopy and correlate the data with Oxford MEST-C scoring system to assess the severity of kidney injury.

Materials and Methods: Sections of remnant frozen kidney-biopsy specimens from patients with IgAN (n=17) and IgAVN (n=23) were stained with fluorochrome-labeled reagents: a nanobody specific for IgG Fc and antibodies specific for C3 and IgA. Staining was assessed by high-resolution confocal microscopy. Pairwise colocalization in immune-complex deposits was determined by imaging software and results were correlated with Oxford classification MEST-C scores.

Results: All samples had C3, IgA, and IgG in the glomerular immune-complex deposits despite many samples being negative for IgG by routine immunofluorescence. The deposits had predominantly mesangial localization in IgAN. IgAVN had staining in both glomerular capillary walls and mesangial areas. In IgAN, the mean values of Pearson correlation coefficient were higher for C3-IgA than for C3-IgG or IgA-IgG, whereas in IgAVN they were similar for C3-IgA and IgA-IgG. In IgAN, elevated C3-IgA colocalization was associated with features of active glomerular injury: mesangial hypercellularity (M1 vs. M0; P=0.0185), endocapillary hypercellularity (E1 vs. E0; P=0.0042), and cellular/fibrocellular crescents (C1+C2 vs. C0; P=0.0043). IgAVN patients did not show statistically significant correlation between colocalization data and MEST-C scores (P=0.068 and 0.053 for E1 vs. E0 and C1+C2 vs. C0, respectively).

Conclusion: These data revealed common and distinct characteristics of glomerular immune-complex deposits in IgAN and IgAVN patients and indicated a disease-inducing role for C3-IgA-containing immune complexes in IgAN.

Evaluation of IgA1 and IgA2 coating patterns of the gut microbiota of IgA Nephropathy patients

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Introduction: Immunoglobulin A nephropathy (IgAN) is characterized by deposition of immune complexes containing de-glycosylated IgA1 (dg-IgA1), anti-glycan IgG autoantibodies and other components in the glomerular mesangium. These IgA1-immune deposits trigger inflammation and progressive renal dysfunction. We have reported an increased relative abundance of mucin-degrading bacteria in the gut microbiota of IgAN patients leading to IgA1 de-glycosylation (1) suggesting a possible link between microbial dysbiosis and disease pathogenesis. In health, secretory IgA response to bacteria is a major mediator of gut homeostasis (2). The differential role of IgA1 and IgA2 subclasses in gut-microbiota interactions remains poorly understood in IgA-related diseases such as IgAN.

Methods: Bacteria isolated from stools of healthy controls, patients with IgAN and unrelated CKD were stained with IgA subclass-specific monoclonal antibodies and anti Gd-IgA1(KM55) antibody, then analyzed by flow cytometry.

Results: We found that most bacteria from healthy controls and CKD patients are coated by both IgA subclasses. While no differences were observed in IgA1+IgA2+ bacteria, there was a significant reduction in the proportion of $IgA1^{+}IgA2^{-}$ bacteria (2.4%±3.04) in the gut microbiota of IgAN patients compare to healthy controls (15.9%±8.7), $p \leq 0.01$. Also, we observed a trend towards an increase in Gd-IgA1-coated bacteria in IgAN patients (0.33%±0.17) compared to healthy controls (0.17%±0.10), $p=0.05$.

Conclusion: These results highlight a potential role for subclass-specific IgA-microbiota interactions in IgAN pathogenesis and underscore the need for further investigation into the mechanisms underlying IgA1 and IgA2 dynamics in the gut ecosystem.

Longitudinal blood single-cell RNA sequencing study in IgAN patients from the randomized cligan trial (RCT)

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Introduction. We designed a RCT (NCT 0466272) enrolling incident patients in different arms based on active or chronic renal lesions. Peripheral blood mononuclear cells (PBMCs) were collected at established time (T) points to monitor immune system in patients undergoing corticosteroid treatment.

Aim. To explore transcriptomic heterogeneity and delineate dynamic immune cell changes at the single-cell level under therapy.

Methods. ScRNA-sequencing of PBMCs was carried out in 3 IgAN patients of whom 2 individuals with active renal lesions and one with chronic renal lesions. The longitudinal single-cell profiling was observed at T0, T2, T4 and T8 months. We compared the transcriptional profile of PBMCs from IgAN patients with health control scRNA-seq datasets and with LPS-stimulated PBMCs, offering valuable insights into disease-specific transcriptional changes.

Results. On average, 4503 cells were sequenced with a mean of 60,889 reads and 2325 median genes detected per cell. Unsupervised clustering methods identified 50 Clusters. At T0, PBMCs from IgAN patients with active renal lesions showed reduced $CD4^+$T cells, increased $CD8^+$ T cells and monocytes and a higher proportion of cells in the G2M phase. Longitudinal profiling revealed that immune cell alterations observed at T2 returned to baseline by T8. Differentially expressed genes (DEGs) across clusters decreased from 3,164 (T2 vs T0) to 172 (T4 vs T0). Monocytes were most responsive to corticosteroids, followed by CD8+ Tem and NK cells. Among the 1602 modulated genes in monocytes the most impacted canonical pathway was the macrophage alternative activation signaling pathway and pathways relating to the regulation of gene expression and protein synthesis.

Conclusions. The first longitudinal scRNA study in IgAN showed enhanced monocyte modulation during corticosteroid therapy. Corticosteroids induced a shift toward reparative (M2-like) macrophage polarization, promoting tissue repair and potentially reducing fibrosis and chronic damage. These findings support corticosteroid use in the active phase of the disease.

Dextran sulfate sodium-induced chronic inflammatory colitis reduces intestinal propionate and causes glomerular IgA-IgG deposition in HIGA mice

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Introduction: Since IgA nephropathy (IgAN) is exacerbated after upper respiratory tract inflammation and enteritis and is associated with chronic inflammatory bowel disease, there is a close association between mucosal-associated lymphoid tissue (MALT) and the pathogenesis of IgAN. IgA production in MALT is believed to interact with the mucosal bacterial flora. Recently, "short-chain fatty acids (SCFAs)", a metabolite of bacterial origin, have been reported to affect IgA production in MALT.

Aims: Here, we used a dextran sulfate sodium (DSS)-induced chronic colitis mice model with high IgA (HIGA) to show the effects of inflammation of gut-associated lymphoid tissue on the microbiota, SCFA, mucosal IgA production, and renal glomeruli.

Methods: Fourteen-week-old female HIGA mice were divided into two groups; control and DSS administration groups. DSS was dissolved in sterilized drinking water and administered in three cycles for seven days at 14 days interval. Intestinal microorganisms were analyzed using 16s rDNA sequencing, and SCFA were measured using GC/MS. Serum and fecal IgA levels were measured using enzyme-linked immunosorbent assays (ELISA). IgA glycosylation were analyzed by lectin ELISA using *Ricinus communis* agglutinin I (RCAI) and *Sambucus nigra* agglutinin (SNA). The glomerular deposition rates of IgA and IgG in renal specimens were measured using immunofluorescence.

Results: DSS administration changed the intestinal microbiota and decreased the intestinal propionate concentration (P = 0.0291). DSS administration increased IgA secretion into the intestinal lumen and significantly decreased its reactivity with RCAI compared to the control (P = 0.0175). The glomerular deposition rates of IgA and IgG were significantly increased in the DSS group (P = 0.0070 and P = 0.0175, respectively).

Conclusion: DSS-induced colonic inflammation decreased intestinal propionate and increased intestinal production of degalactosylated IgA and induced glomerular IgA-IgG deposition. Further studies are needed to clarify the relationship between these findings.

Moving from the four- to the five-hit hypothesis in IgA nephropathy. A proposal based on novel pathophysiological concepts with potential therapeutic implications

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Since its inception, the multi-hit hypothesis has been the most accepted approach to tackle the complex pathophysiology of IgA nephropathy (IgAN), underscoring four key-driving hits that intervene first in the appearance of poorly mucosal-derived O-galactosylated IgA1, outpoured into the circulation and referred to as galactose-deficient IgA1 (Gd-IgA1), then by the formation of IgG-Gd-IgA1-containing immune-complexes containing myeloid IgA Fc receptor CD89 trapped in the immune-complexes, their mesangial deposition and finally glomerular inflammation with kidney fibrosis. These hits have recently been recognized as potential targets for tailored therapies.

However, the origin of Gd-IgA1 has recently be reappraised. Genetic causes in which three enzymes, core-1-ß1,3-galactosyltransferase (C1GALT1), N-acetylgalactosaminyltransferase-2 or -14 (GALNT2 or 14) normally intervene have been reported. Variations in the former and microRNAs let-7b-mediated suppression of the latter lead to this Gd-IgA1. In addition, epigenetic mechanisms can also intervene both dependently and independently of genetic causes: Certain gut commensal can drive the switching of IgM to normal IgA as to Gd-IgA1 through BAFF/APRIL pathways; involvement of the gut microbiota dysbiosis of mucin degraders can generate mucosal Gd-IgA1 by post-translational mechanism. An active reverse transcytosis trafficking step by enterocytes can bring back from the gut lumen Gd-IgA1 to the circulation generating immune responses notably IgG anti-Gd-IgA1 autoantibodies. Finally, human defensins as α-defensin 6 (a risk locus for IgA nephropathy) inhibit the growth of *Akkermansia muciniphila*, a mucin-degrading bacteria. Host α-defensin 6 genetic defects may thus allow the increase of these bacteria with consequent Gd-IgA1 generation. These data suggest gut microbiota dysbiosis contributes to generation of auto-antigens in patients with IgAN. In conclusion, this overlooked genetic, epigenetic and environmental hit highlights a plausible target for proper treatment, both by targeting diets, microbiome and by potential genetic or epigenetic manipulations. This hit should be considered as the Hit 1 in the multi-hit hypothesis of IgAN.

Exploration of the IgA1 O-glycoforms profile and pathogenic IgA-complex compositions by mass spectrum in IgA nephropathy

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Introduction: Higher levels of galactose deficient IgA1 (GdIgA1) and poly-IgA complex are critical in the formation of immunodeposits in IgA nephropathy (IgAN). Previously, we found patients with IgA myeloma (IgAMM) without renal IgA deposition also had higher levels of plasma GdIgA1 undesignedly.

Aims: We aimed to investigate the key IgA-O glycemic profile and pathogenic IgA-complex compositions in IgA nephropathy by mass spectrum.

Materials and Methods: Plasma IgA, GdIgA1, CD89 captured poly-IgA1 and IgG-IgA complex in IgAN, IgAMM and healthy controls (HCs) were detected by ELISA. Plasma Poly-IgA1 was detected by Western-blot. The variation in O-glycoforms of IgA1 and compositions of poy-IgA complex were evaluated via mass spectrometry of EThcD-sceHCD and HCD MS/MS fragmentation modes.

Results: Levels of IgA, GdIgA1, CD89 captured poly-IgA and IgG-IgA complex were higher in IgAMM patients than those in IgAN. IgA1 O-glycoforms indicated higher abundances of O-GalNAc/HR and O-gal-deficence/HR in IgAN and HCs than those in IgAMM group, while the absolute GdIgA was higher in IgAMM group. Compositional differences of proteins in poly-IgA varied between groups (67 different proteins in IgAN and IgAMM, 14 in IgAN and HCs). Mean percentages of IgA in poly-IgA complex were 72%, 39.4% and 38.0% in IgAMM, IgAN and HCs, respectively. Relative abundances of C3, APOB-100, AMBP and fibronectin were different among groups. In IgAN, the higher APOB-100 group had heavier renal C3 deposition. AMPB abundances were negatively related to eGFR levels and associated with sever T lesions.

Conclusion: IgAMM patients also had higher levels of GdIgA1 and poly-IgA in circulation. Distinct different IgA1 O-glycoforms of IgA1 were shown in IgAN and IgAMM. IgA-APOB-100 or IgA-AMBP complex might play potential pathogenic roles or biomarkers for IgAN.

Treatment

Single-center outcomes and clinical features of persistent urinary abnormalities after tonsillectomy and steroid pulse therapy in IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is a primary glomerular disease with a significant risk of progression to end-stage renal disease. In Japan, tonsillectomy combined with steroid pulse therapy (TSP) has been widely adopted to achieve high remission rates of proteinuria and hematuria. Although TSP is considered effective, the renal prognosis based on persistent urinary abnormalities following treatment remains unclear. Therefore, we aimed to investigate renal outcomes according to patterns of urinary abnormalities post-TSP and to further examine the clinical characteristics at the time of kidney biopsy in these patients.

Methods: A retrospective study was conducted on 187 patients diagnosed with IgAN and treated with TSP at Juntendo University Hospital between 2012 and 2021. IgAN patients were classified into four groups based on urinary findings six months post-TSP: complete remission, persistent proteinuria, persistent hematuria, and persistent proteinuria and hematuria. Renal outcomes and clinicopathological data at the time of kidney biopsy of each group were analyzed. Cumulative probabilities of 30% increase in s-Cr or 30% decline in eGFR from baseline were analyzed using the Kaplan–Meier method, and differences in curves were compared using the log-rank test.

Result: Among the cohort, 73.2% achieved complete remission, while 13.9% had persistent proteinuria, 8.6% had persistent hematuria, and 4.3% exhibited both. Patients with unresolved urinary abnormalities had a higher risk of decline of renal function compared to those achieving remission. Persistent proteinuria was associated with higher blood pressure, BMI, and tubular atrophy and interstitial fibrosis. Persistent hematuria correlated with thinner glomerular basement membranes.

Conclusion: Persistent urinary abnormalities post-TSP indicate a higher risk of deterioration of renal function. Persistent proteinuria is thought to be associated with non-immunological factors, therefore early intervention with non-immunological therapies, alongside immunosuppressive treatments, may improve outcomes. Further studies are needed to optimize treatment strategies for IgAN patients with persistent urinary findings.

AFFINITY study: 1 year results of atrasentan in IgAN in patients with UPCR <1 and ≥1g/g

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Introduction: Atrasentan, a potent, selective endothelin A receptor antagonist, is being investigated to treat IgAN and other kidney diseases.

Aim: To report the efficacy and safety of atrasentan in patients with IgAN from the AFFINITY study.

Methods: AFFINITY (NCT04573920) is a Phase 2, open-label basket trial of atrasentan in patients with kidney diseases. The IgAN cohort included adults with biopsy-proven IgAN; eGFR ≥30 mL/min/1.73m^2, UPCR ≥0.5 and <1g/g (first morning void at screening), and on maximum tolerated/stable RASi for ≥12 weeks. Patients took 0.75 mg oral atrasentan daily for 52 weeks. The primary endpoint was change in 24h UPCR from baseline to Week 12.

Results: In patients with IgAN (N=20; median age 44.5 years, 50% women, 45% White, 45% Asian), baseline median 24h UPCR was 0.8 g/g; 12 patients had baseline UPCR <1g/g. Reduction in UPCR was evident by Week 6 and sustained through Week 52. Clinically meaningful reductions in UPCR were evident in patients with baseline UPCR <1 and ≥1g/g through Week 52. At baseline, Week 12, and Week 24, 1/20 (5%), 12/20 (60%), and 13/19 (68%) patients had UPCR <0.5g/g, respectively. One patient discontinued treatment at Week 13 due to an adverse event (AE) of headache considered treatment-related. There were no treatment-related serious AEs or deaths.

Conclusion: Atrasentan was well tolerated and resulted in a stable, clinically meaningful reduction in proteinuria over 1 year of treatment, comparable between patients with baseline UPCR <1 and ≥1g/g.

ALIGN post-hoc analyses: Reduction in proteinuria with atrasentan across subgroups by MEST-C score, baseline hematuria and baseline UPCR

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Introduction: Atrasentan is a potent and highly selective endothelin A receptor antagonist. In the prespecified 36-week interim analysis (IA) of the Phase 3 global ALIGN clinical trial, atrasentan demonstrated superiority versus placebo with a clinically-meaningful and statistically significant proteinuria reduction (primary endpoint) in patients with IgAN receiving supportive care.

Aim: To report additional post-hoc analyses from the ALIGN trial.

Materials and Methods: ALIGN is an ongoing, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of atrasentan versus placebo in adults with IgAN at risk of progressive loss of renal function. The main stratum included patients with biopsy-proven IgAN and proteinuria of ≥1g/day while on maximum tolerated dose of RASi. Patients were randomized to receive atrasentan 0.75 mg or placebo orally once daily for 132 weeks while continuing supportive care. These post-hoc analyses assessed the change from baseline (CFB) in 24-hour UPCR at Week 36 based on baseline proteinuria (<1 or ≥1g/g), MEST-C scores and baseline hematuria. Analyses were performed on the IA data set i.e. first 270 of 340 patients randomized to the main stratum. For MEST-C score analysis, 160 of 270 patients were included (i.e. patients with MEST-C scores available at baseline).

Results: Atrasentan demonstrated a statistically significant and clinically-meaningful proteinuria reduction of 36.1% (95% CI: 26.4%, 44.6%; p<0.0001) relative to placebo, at Week 36. The reduction in proteinuria in patients with baseline UPCR <1 g/g and ≥1g/g (LS mean % UPCR CFB relative to placebo at Week 36) was −28.7 (95% CI: −47.5, −3.2) and −38.3 (95% CI: −47.4, −27.5), respectively. In addition, efficacy benefit favoring atrasentan was shown irrespective of MEST-C score and baseline hematuria level.

Conclusion: Consistent with the primary endpoint findings, atrasentan shows favorable efficacy versus placebo in patients with IgAN regardless of baseline UPCR (<1g/g and ≥1g/g), MEST-C score, and baseline hematuria.

Changes in proteinuria and kidney function in subgroups of patients with IgAN defined by baseline Gd-IgA1 levels in a Phase 1/2 study of zigakibart

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Introduction: Zigakibart, an investigational, humanized monoclonal antibody to treat IgAN, blocks APRIL, a cytokine which promotes pathogenic Gd-IgA1 production, leading to inflammation and kidney injury.

Aims: To determine the changes in proteinuria and kidney function according to patient subgroups using categories of baseline Gd-IgA1 in the ongoing Phase 1/2 trial, ADU-CL-19, of zigakibart (NCT03945318).

Materials and Methods: Part 3 of ADU-CL-19 enrolled patients ≥18 years with biopsy-proven IgAN, total urine protein of ≥0.5g/24h or 24h UPCR of ≥0.5g/g, eGFR of ≥30mL/min per 1.73m^2, and on a stable/optimized dose of RASi for ≥3 months before screening (or RASi intolerant). Patients received zigakibart 450mg Q2W IV, transitioning to 600mg Q2W SC at ≥24 weeks (Cohort 1, n=10) or 600mg Q2W SC (Cohort 2, n=30) for up to 124 weeks. Patients were categorized into four subgroups according to quartiles of baseline Gd-IgA1 level, defined as (1) ≤Q1, (2) Q1<–≤median, (3) median<–≤Q3, and (4) >Q3. UPCR and eGFR percent changes from baseline–Week 76 were calculated for each Gd-IgA1 quartile subgroup and reported descriptively.

Results: Clinical outcomes from baseline–Week 76 were comparable in all subgroups defined by Gd-IgA1 at baseline. Mean Gd-IgA1 percent change from baseline was −74.4% for the overall population. Mean UPCR percent changes from baseline were −49.8%, −60.9%, −70.2%, and −60.9% for Gd-IgA1 subgroups 1, 2, 3, and 4, respectively. Mean eGFR percent changes from baseline were −6.93%, 6.25%, 2.63%, and 7.59% for Gd-IgA1 subgroups 1, 2, 3, and 4, respectively.

Conclusion: Following 76 weeks of zigakibart treatment, patients achieved 74.4% mean percent reduction of Gd-IgA1. Zigakibart provides clinically meaningful treatment benefits in terms of proteinuria reduction and eGFR stabilization in patients with IgAN, independent of their baseline Gd-IgA1 levels.

Effect of iptacopan discontinuation on proteinuria and complement biomarkers in patients with immunoglobulin A nephropathy (IgAN): a post hoc analysis from a Phase II trial

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Introduction: Alternative complement pathway (AP) inhibition with iptacopan, a potent oral complement factor B inhibitor, significantly reduced proteinuria in IgAN patients leading to its accelerated approval by the US FDA.

Aims: We explore the effects of iptacopan discontinuation on proteinuria and AP biomarkers using data from the Phase II (PhII) and ongoing open-label extension (OLE) studies.

Methods: In the PhII randomized, double-blind, placebo-controlled study, adults with confirmed IgAN received placebo or iptacopan (10, 50, 100 [Part 2 only] or 200mg) for 90 (Part 1) or 180 (Part 2) days followed by a 90-day off-iptacopan phase. Eligible patients could restart iptacopan 200mg in the OLE.

Results: In patients treated with iptacopan >10mg, the relative reduction (95% CI) in urine protein-creatinine ratio (UPCR) from first morning void from PhII baseline (BL) in Part 1 (n=23) was 30.0% (13.5, 43.4%) at Day (D) 90 and 35.4% (17.5, 49.5%) in Part 2 (n=38) at D180. UPCR returned to BL levels 30 days after iptacopan discontinuation in Part 1 and by OLE initiation in Part 2. At OLE Month 12, UPCR had decreased once more from PhII BL by 37.9% (8.7, 57.8%) and 31.9% (10.3, 48.3%) in patients from Part 1 (n=7) and Part 2 (n=20) respectively. AP biomarkers decreased from BL to D90 in the pooled iptacopan 200mg arms (median [interquartile range] reduction in urinary sC5b-9: 97.2% [89.3, 98.4%]; serum Wieslab: 81.4% [72.9, 92.5%]; plasma Bb: 24.5% [13.6, 40.6%]). At the first off-iptacopan visit, there was a median increase from BL in urinary sC5b-9 (18.3% [–77.8, 168.8%]) and plasma Bb (3.3% [–12.7, 11.2%]) and a reduction of BL serum Wieslab of 10.3% [0, 19.7%]).

Conclusion: Iptacopan discontinuation led to rapid reactivation of systemic and renal complement to near BL levels and an increase in proteinuria. Notably, proteinuria decreased after reinitiation of iptacopan.

Effects of nefecon on Hits 1, 2, and 3 of the pathogenic cascade of IgA nephropathy: a full NefIgArd analysis of exploratory biomarkers

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Introduction: The multi-hit paradigm of immunoglobulin A nephropathy (IgAN) pathogenesis describes an increase in circulating galactose-deficient IgA1 (Gd-IgA1) (Hit 1), leading to IgA and immunoglobulin G (IgG) antibodies that bind Gd-IgA1 (Hit 2), and formation of circulating IgA-containing immune complexes (IgA-IC) (Hit 3). These ICs accumulate in the mesangium, driving inflammation and scarring in the kidneys (Hit 4) and progressive nephron loss. Nefecon is an oral, targeted-release formulation of budesonide designed to inhibit Gd-IgA1 production in the gut-associated lymphoid tissue. The NefIgArd trial showed that nefecon stabilized estimated kidney function and reduced proteinuria over 9 months of treatment and 15 months of off-treatment follow-up in adults with primary IgAN.

Aims: Evaluate changes in markers of Hits 1–3 of the cascade with nefecon versus placebo using data for exploratory biomarker timepoints (baseline and 3/6/9/12/18 months) in the NefIgArd trial.

Materials and methods: Gd-IgA1, IgG anti-IgA, and IgA-IC levels were measured in serum samples from 216 participants (n=108 per group). Comparisons between nefecon and placebo groups were made using robust regression with multiple imputations and with a significance threshold set at $p<0.05$.

Results: Statistically significant reductions in circulating Gd-IgA1 levels were observed with nefecon versus placebo at 3/6/9/12 months but were not significantly different at 18 months. Nefecon was also associated with significant IgG anti-IgA antibody reductions versus placebo at 3/6/9 months, with levels approaching baseline by 12 months (3 months post-treatment) and remaining non-significant at 18 months. Additionally, nefecon resulted in a significant reduction versus placebo in IgA-IC at 3 months, with numerical reductions maintained at 6/9 months.

Conclusion: The 18-month NefIgArd biomarker data represent the most complete analysis of drug effects on the IgAN cascade, showing clear reductions in markers of Hits 1–3 with nefecon versus standard of care. These findings demonstrate a direct disease-modifying effect of nefecon.

Efficacy of nefecon by baseline eGFR deciles: a subanalysis from the NefIgArd trial of daily nefecon 16 mg or placebo in addition to supportive care for patients with biopsy-confirmed primary IgAN

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Introduction: Nefecon – an oral, targeted-release formulation of budesonide – reduces loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) at risk of disease progression with similar treatment effect in those with a baseline estimated glomerular filtration rate (eGFR) of <60 or ≥60 mL/min/1.73 m^2.

Aims: To evaluate efficacy of nefecon by baseline eGFR deciles, focusing on upper and lower ranges. This subanalysis reports changes in eGFR and urine protein–creatinine ratio (UPCR) across subgroups in the upper and lower deciles of kidney function at baseline.

Materials and Methods: NefIgArd study design and endpoints have been previously described. For this subanalysis, patients were divided into eGFR deciles based on the overall population at baseline (defined as the geometric mean of the two most recent measurements before randomization).

Results: Median eGFR was 55.49 mL/min/1.73 m^2 (interquartile range: 45.93–69.84) in the overall population and was balanced across nefecon and placebo groups. Patients from the full analysis population were divided into groups based on the decile boundaries of baseline eGFR: above and below 38, 43, 47, 51, 55, 60, 66, 72, and 82 mL/min/1.73 m^2. In general, UPCR reduction and eGFR benefit were observed at all time points with nefecon relative to placebo. UPCR and eGFR benefit with nefecon relative to placebo were also observed in patients below and above the lower and higher baseline eGFR decile boundaries, respectively.

Conclusion: This NefIgArd subanalysis demonstrated that the efficacy of a 9-month nefecon treatment course in the reduction of proteinuria and preservation of kidney function was independent of baseline eGFR, both at the end of 9 months of treatment and throughout the remaining 15-month, off-drug observation period.

Safety, tolerability, and efficacy of mezagitamab (TAK-079) as add-on to standard-of-care therapy in primary IgA nephropathy: Week 48 results from a phase 1b study

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Introduction: Mezagitamab is a fully human anti-CD38 monoclonal antibody that depletes plasma cells producing galactose-deficient IgA1 (Gd-IgA1) and anti-Gd-IgA1 antibodies. This mechanism of action potentially decreases immune complex formation, reducing proteinuria and stabilizing kidney function.

Aims: This open-label, global study (NCT05174221) evaluated mezagitamab as add-on to stable standard-of-care therapy.

Materials and Methods: Eligible participants had biopsy-proven disease, proteinuria (urine protein:creatinine ratio [UPCR] ≥1g/g or urine protein excretion ≥1g/24 h calculated from a 24-h urine collection) and eGFR ≥45mL/min/1.73m^2. Participants received subcutaneous mezagitamab 600mg once weekly for 8 weeks, then 600mg every 2 weeks for 16 weeks (16 doses total), followed by 24-weeks safety follow-up. The primary endpoint was percentage of participants with adverse events (AEs). Secondary and exploratory endpoints included serum IgA, Gd-IgA1, and IgG levels, percentage change from baseline in 24-h UPCR, change from baseline in eGFR, and resolution of haematuria (defined as negative or trace haematuria in those with positive haematuria at screening).

Results: Seventeen participants enrolled. Sixteen (94.1%) participants reported ≥1 AE, and none were serious. There were no study discontinuations due to AEs, Grade 3+ infections or opportunistic infections. Rapid and sustained reductions in serum IgA (52.4%; 95% CI: 46.1, 58.2), Gd-IgA1 (57.8%; 48.1, 66.9) and IgG (18.9%; 11.2, 26.8) were observed; serum IgA and IgG levels trended towards baseline by Week 48. UPCR was reduced by a model-based mean of 54.1% (95% CI: 42.0, 63.7) and model-based mean change from baseline in eGFR was +1.1mL/min/1.73m^2 (−2.6, +4.8) at Week 48. There was resolution of haematuria in 69% (44, 94) of participants (9/13) by Week 48.

Conclusion: Mezagitamab was generally well tolerated, consistent with previous reports. Rapid reductions in proteinuria, serum IgA, Gd-IgA1, and IgG were seen while the proportion of participants with haematuria declined, and renal function remained stable during the first year of study.

Zigakibart-treated patients with IgAN achieved high rates of proteinuria remission and stable eGFR over 76 weeks in a Phase 1/2 study

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Introduction: Zigakibart, an investigational, humanized monoclonal antibody to treat IgAN, blocks APRIL, a cytokine that promotes pathogenic Gd-IgA1, leading to kidney deposition, inflammation and injury.

Aims: To determine the percentage of patients achieving reductions in UPE, and trends in eGFR from baseline–Week 76, below different thresholds, in a Phase 1/2 trial of zigakibart (NCT03945318).

Materials and Methods: Part 3 of ADU-CL-19 enrolled patients ≥18 years with biopsy-proven IgAN, and total urine protein of ≥0.5g/24h or a 24h UPCR of ≥0.5g/g. Patients received zigakibart 450mg Q2W IV, transitioning to 600mg Q2W SC at ≥24 weeks or 600mg Q2W for ≥124 weeks. Key outcomes at Week 76 were the percentage of patients achieving proteinuria remission with UPE thresholds of <300mg/24h and <500mg/24h, and trends in eGFR from baseline, stratified by proteinuria remission subgroups (<300 vs. >300mg/24h and <500 vs. >500mg/24h) determined at Week 52.

Results: The mean (SD) UPE and eGFR at baseline was 1630 (1519) mg/24h and 70.7 (26.8) mL/min/1.73m^2, respectively. Of 35 patients assessed to Week 52, 28.6% (10/35) and 42.9% (15/35) achieved UPE <300mg/24h and <500mg/24h, respectively. Of 31 patients assessed to Week 76, 29.0% (9/31) and 45.2% (14/31) achieved UPE <300mg/24h and <500mg/24h, respectively. Mean eGFR remained stable from baseline–Week 76 regardless of UPE. At Week 76, mean (SE) eGFR change from baseline was 0.00 (2.37) mL/min/1.73 m^2 (patients achieving UPE <300mg/24h) and -0.17 (2.23) mL/min/1.73 m^2 otherwise. For patients with UPE <500mg/24h, mean (SE) eGFR change from baseline to Week 76 was 0.53 (2.91) mL/min/1.73 m^2 and -0.67 (2.01) mL/min/1.73 m^2 otherwise.

Conclusion: At 76 weeks, 29% and 45% of patients achieved UPE reductions below stringent thresholds of <300 and <500mg/24h with zigakibart, demonstrating clinically meaningful proteinuria remission. eGFR stabilization was sustained independent of UPE remission thresholds, supporting the disease-modifying effect of zigakibart in IgAN.

Budesonide enteric capsules for IgA nephropathy with hepatitis B virus infection: Two cases

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Introduction: Budesonide enteric capsule is a novel immunomodulatory agent targeting intestinal mucosal B cells for treatment of IgA nephropathy (IgAN). There is a complex immune interaction between hepatitis B virus (HBV) infection and IgAN. Exploring the use of budesonide enteric capsules in treatment of IgAN with HBV has clinical significance.

Aims: To evaluate the efficacy and safety of budesonide enteric capsules in patients with IgAN and chronic HBV infection.

Materials and Methods: Two young male patients were reported. Both two patients (disease durations:3 years and 1 month, respectively) presented with nephrotic-range proteinuria (2.91-3.67 g/d), microscopic hematuria, hypertension (165-180/100-110 mmHg), and hyperuricemia (429-473 μmol/L). One patient exhibited mild renal insufficiency (serum creatinine: 118 μmol/L). Renal biopsy confirmed IgAN (Oxford classification: Case 1, M0E0S0T0C1; Case 2, M1E0S0T0C0) and non-active HBV infection (HBsAg-positive, HBV-DNA <20 IU/mL). Treatment regimen include: 1) triple supportive therapy (RAS inhibitors, SGLT2 inhibitors, antihypertensive agents); 2) antiviral therapy (entecavir 0.5 mg/d); 3) targeted immunomodulation (budesonide enteric capsules 16 mg/d).

Results: After 9 months of intervention, both patients had a significant decreased in 24-hour urinary protein (Case 1: 1.17→0.5 g/d; Case 2: 3.67→0.43 g/d) with resolution of microscopic hematuria, and renal function remained stable (Case 1: eGFR 81.6→80 mL/min·1.73m^2; Case 2: eGFR 80.1→96.5 mL/min·1.73m^2). HBV reactivation markers (HBV-DNA, ALT/AST) were continuously negative, and no glucocorticoid-related metabolic abnormalities or infectious complications occurred.

Conclusion: Budesonide enteric capsules combined with intensive supportive therapy effectively improved renal outcomes in IgAN patients with HBV coinfection without triggering viral reactivation. This case report provides an evidence-based support for the use of budesonide enteric capsules in the special population, suggesting that targeted intestinal immunity modulate the number and activity of mucosal B cells in ileal Peyer's patches may be a preferred strategy under strict HBV biomarker monitoring.

Efficacy and Safety of Nefecon in IgA Nephropathy: A 6-Month Retrospective Cohort Study

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Objective: To evaluate the clinical efficacy and safety of Nefecon in patients with IgA nephropathy (IgAN).

Methods: A retrospective cohort study was conducted on 25 IgAN patients treated with Nefecon for six months. Clinical parameters, including 24-hour urinary protein excretion, serum creatinine, estimated glomerular filtration rate (eGFR), and serum albumin, were analyzed at baseline and monthly intervals. Adverse events were systematically documented.

Results: The cohort comprised 25 IgAN patients (mean age 39.1 ± 11.5 years; 64% male; 64% hypertensive). Baseline measures included BMI 23.2 ± 3.2 kg/m^2, blood pressure 139.8/90.5 mmHg, Oxford scores (M1 20%, E1 32%, S1 76%, T1 48%, C1 24%), proteinuria 1.9 g/day (IQR 1.2–2.7), creatinine 189.0 ± 93.7 µmol/L, eGFR 44.7 ± 24.4 mL/min/1.73m^2, albumin 40.3 ± 5.5 g/L, and urine RBC 36.9/HPF (IQR 10.6–136.4). Following six months of Nefecon treatment, median 24-hour urinary protein excretion decreased from 1.9 g/day (IQR: 1.2–2.7) at baseline to 0.7 g/day (IQR: 0.4–2.1) at month 6 ($P < 0.01$). Mean eGFR improved from 44.7 ± 24.4 mL/min/1.73m^2 to 50.4 ± 30.3 mL/min/1.73m^2 ($P < 0.05$), with intermediate peaks observed at month 2 (50.2 ± 27.6) and month 3 (50.1 ± 27.6). Serum creatinine exhibited fluctuations, declining to a median of 135.0 µmol/L (IQR: 95.9–227.0) by month 4 and stabilizing thereafter. Serum albumin remained stable, increasing marginally from 40.3 ± 5.5 g/L to 41.7 ± 3.6 g/L. At six months, complete remission, partial remission, and no remission of proteinuria were observed in 28.0% (n = 7), 44.0% (n = 11), and 28.0% (n = 7) of patients, respectively. Adverse events were predominantly mild, including gastrointestinal disturbances (9.4%) and infections (5.7%).

Conclusion: Nefecon significantly reduces proteinuria and improves renal function in IgAN patients, with a favorable safety profile. These findings support its potential as a first-line therapeutic option for IgAN.

Beyond Nine Months: Real-World Efficacy and Safety of Extended Nefecon Therapy in IgA Nephropathy

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Introduction: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in Asia, with about 60% of Chinese patients progressing to end-stage kidney disease (ESKD) within 15 years. Nefecon, a targeted-release budesonide, reduces pathogenic galactose-deficient IgA1 by acting on Peyer's patches. The NefIgArd trial demonstrated its efficacy over 9 months, but the benefit of longer treatment remains uncertain.

Aims: To assess the efficacy and safety of 12-month Nefecon therapy in IgAN patients in a real-world setting, compared to conventional treatment.

Materials and Methods: This retrospective study included 12 patients with biopsy-proven IgAN treated with Nefecon (16 mg/day) for 12 months and 36 propensity score-matched controls who received conventional therapy, mostly combining corticosteroids and immunosuppressants. Clinical data, including 24-hour urine protein and estimated glomerular filtration rate (eGFR), were collected at baseline and after 12 months.

Results: After 12 months, the Nefecon group had a significant reduction in 24-hour urine protein (from 1016 [490, 1296] mg to 114 [96, 139] mg; p = 0.037), which was significantly lower than in the control group (291 [167, 589] mg; p = 0.01). The eGFR slope was significantly more favorable in the Nefecon group (5.4 [1.6, 11.6] vs. -3.4 [-12.9, 8.2] mL/min/1.73 m^2/year; p = 0.032). No serious infections occurred in the Nefecon group; mild adverse effects included changes in bowel habits, sleep disturbance, and menstrual irregularities.

Conclusion: Twelve-month Nefecon therapy significantly reduced proteinuria and preserved renal function in IgAN patients, with a better safety profile compared to conventional treatment involving systemic corticosteroids and immunosuppressants.

Sparsentan as first-line treatment of incident patients with IgA nephropathy: An interim analysis of the SPARTAN trial evaluating efficacy and cardiovascular risk variables

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Introduction: SPARTAN (NCT04663204) is a single-arm, exploratory trial investigating the efficacy and safety of sparsentan, a dual endothelin angiotensin receptor antagonist (DEARA), as first-line therapy in immunoglobulin A nephropathy (IgAN).

Aims: To evaluate 24-week interim efficacy and cardiovascular risk variables.

Materials and Methods: Twelve adults with biopsy-proven IgAN, proteinuria ≥0.5 g/day, eGFR ≥30 mL/min/1.73m^2, and no prior ACEi/ARB treatment were enrolled. Sparsentan is administered for 110 weeks with a 4-week safety follow-up. One patient discontinued early due to hypotension. For cardiovascular risk factor assessments, there are occasional missing data points for 1 or 2 patients.

Results: Mean age at enrollment was 35.8 (SD, 12.2) years, with median (IQR) proteinuria of 1.7 (0.6-3.3) g/day and a mean eGFR of 70.2 (SD, 25.0) mL/min/1.73 m^2 at baseline. Proteinuria reductions were rapid and sustained over 24 weeks (−68.9% [±SE −75.7 to −60.1] from baseline to week 24); 58% of patients achieved complete proteinuria remission (<0.3 g/day) at any time during the 24 weeks of treatment. After an initial decrease from baseline, BP remained stable over 24 weeks. Minimal changes in total body water (−4.4 [SD, 14.8] L), body weight (−1.0 [SD, 3.3] kg), blood lipids (total cholesterol, −0.2 [SD, 0.7] mmol/L; HDL, 0.1 [SD, 0.2] mmol/L; non-HDL cholesterol, −0.4 [SD, 0.7] mmol/L; LDL, −0.2 [SD, 0.8] mmol/L), triglycerides (−0.3 [SD, 0.6] mmol/L), and blood glucose (0.2 [SD, 0.6] mmol/L) were observed from baseline to week 24. Following an initial marked decrease, NT-proBNP stabilized for the remaining duration of treatment. Cardiac MRI results at week 24 showed a change from baseline in left ventricular mass/BSA of −3.1 (SD, 3.5) g/m^2 and left ventricular ejection fraction of 0.3 (SD, 6.6) %.

Conclusion: In newly diagnosed patients with IgAN, sparsentan reduced proteinuria ≈70% over 24 weeks, with cardiovascular risk factors remaining stable or improving.

Efficacy and Safety of Finerenone in Immunoglobulin A Nephropathy: A 12-months Real-World Observational Study

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Introduction: Current guidelines for immunoglobulin A nephropathy (IgAN) emphasize optimized supportive care to reduce proteinuria and preserve renal function.

Aims: This study aimed to evaluate the therapeutic potential of finerenone, a novel nonsteroidal mineralocorticoid receptor antagonist (MRA), in patients with IgAN.

Materials and Methods: We retrospectively analyzed 22 biopsy-proven IgAN patients who completed 12 months of finerenone therapy. Clinical parameters including urinary protein excretion, estimated glomerular filtration rate (eGFR), serum potassium levels, and adverse events were collected during follow-up visits.

Results: The cohort comprised 22 patients (9 male, 13 female) with a mean age of 42.0 ± 13.5 years. Six patients (27.3%) had comorbid hypertension. The median disease duration of IgAN was 3.5 years (interquartile range [IQR]: 1.0–10.0). Concomitant therapies included renin-angiotensin system (RAS) inhibitors in 95.5% (21/22) and sodium-glucose cotransporter-2 (SGLT2) inhibitors in 63.6% (14/22). Baseline characteristics revealed median urinary protein excretion of 1079.50 mg/day (IQR: 872.50–2338.50), mean eGFR of 65.74 ± 19.66 mL/min/1.73 m^2, and mean serum potassium of 4.24 ± 0.37 mmol/L. After 12-month finerenone treatment, proteinuria decreased by 45.1% from baseline; complete remission (urinary protein excretion <500 mg/day) was achieved in 42.9% (9/21) and partial remission (≥50% reduction from baseline and <1000 mg/day) occurred in 14.3% (3/21); mean eGFR decline was 6.74 mL/min/1.73 m^2 (95% CI: 2.50–10.99); serum potassium remained stable at 4.47 mmol/L (95% CI: 4.32–4.62; P = 0.205 vs baseline). One transient hyperkalemia event (6.29 mmol/L) was observed, resolving spontaneously without intervention. No serious adverse events or treatment discontinuations occurred.

Conclusion: This 12-month real-world study demonstrates the potential benefits of finerenone in IgAN, showing significant proteinuria reduction and attenuated renal function decline. The favorable safety profile positions finerenone as a promising adjunct to supportive care for IgAN.

Nefecon Treatment in Patients with Primary IgA Nephropathy and Renal Insufficiency: A 6-Month Observational Study

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Introduction: IgA nephropathy (IgAN) remains the predominant cause of primary glomerulonephritis globally, especially in China. IgAN patients with renal insufficiency usually face higher risk of progressing to end-stage kidney disease (ESKD). Nefecon, a novel targeted-release formulation of budesonide acting on gut-associated lymphoid tissue, shows promise in mitigating proteinuria and preserving renal function in IgAN, while there are few data in real-world clinical situation.

Aims: To investigate the effectiveness and safety of Nefecon in patients with primary IgAN and renal insufficiency.

Materials and Methods: This single-centre observational study enrolled 16 biopsy-confirmed IgAN patients (4 males, 12 females, mean age 45±9 years old) from the First Affiliated Hospital of Dalian Medical University. All participants received ≥3 months of optimized supportive therapy including maximally tolerated RAS blockade and SGLT-2 inhibitors prior to Nefecon initiation. Urine protein-creatinine ratio (UPCR), eGFR (CKD-EPI equation), and serum albumin were collected at baseline, 3 months, and 6 months.

Results: At baseline, 8 of 16 patients received concomitant finerenone. UPCR was 2168.65 (1369.19, 2968.11) mg/g, eGFR was 43.24 (32.63, 53.85) mL/min/1.73 m^2, Mean serum albumin level was 40.7±4.7 g/L. At month 3, UPCR was 1799.55 (1000.09, 2599.01) mg/g, eGFR was 44.26 (33.66, 54.87) mL/min/1.73 m^2. Mean serum albumin level was 40.5±3.6 g/L. At month 6, UPCR was 1682.38 (882.92, 2481.84) mg/g, eGFR was 45.94 (35.33, 56.54) mL/min/1.73 m^2, Mean serum albumin was 41.0±3.3 g/L. For adverse events, 5 patients developed facial oedema during the treatment.

Conclusion: Six-month Nefecon therapy demonstrated potential stabilization of kidney function alongside modest proteinuria reduction, with favourable tolerability in high-risk IgAN populations.

Felzartamab for IgA nephropathy: final results of the IGNAZ study

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Introduction: Felzartamab is a monoclonal antibody that binds to CD38 on plasma cells, the likely source of pathogenic IgA1 forms and autoantibodies in IgA nephropathy (IgAN).

Aims: We report final 24-month data from the Phase 2a IGNAZ study (NCT05065970) assessing the efficacy and safety of felzartamab versus placebo in patients with IgAN.

Materials and Methods: Patients aged 18–80 years with biopsy-confirmed IgAN, proteinuria ≥1.0 g/day (≥0.5 g/day for Japanese patients), and eGFR ≥30 mL/min/1.73 m^2 using renin-angiotensin inhibitors ≥3 months were randomized 1:1:1:1 in Part 1 to placebo (n=12) or felzartamab in 1 of 3 arms: 2 doses in 15 days (M1; n=12), 5 doses in 2 months (M2; n=11), and 9 doses in 5 months (M3; n=13). In Part 2, 6 Japanese patients received open-label M3.

Results: Patients were 67% male (mean age: 41.6 years; UPCR: 1.7 g/g; eGFR: 74.6 mL/min/1.73 m^2). In Part 1, 40/48 patients completed treatment. Felzartamab treatment led to rapid, clinically meaningful reductions in UPCR versus placebo, with the greatest effect in the M3 arm. Mean eGFR declined less in the felzartamab arms versus placebo. Among felzartamab arms, IgA reductions were rapid and durable (lasting 19 months after the last dose); IgG recovered by 6–9 months. Efficacy in Part 2 was similar to that in Part 1 (M3). Treatment-emergent AEs were typically grade 1 or 2 and not dose-dependent. The most common treatment-related AE was infusion-related reaction (IRR), including one treatment-related serious AE. Five patients discontinued felzartamab for IRR/hypersensitivity. Infection incidence was similar across felzartamab arms; all were grade 1 or 2 and non-serious.

Conclusion: Felzartamab was generally well tolerated and led to sustained proteinuria reduction and reduced eGFR decline versus placebo, indicating potential disease modification in patients with IgAN. Investigation of felzartamab in patients at high risk for loss of kidney function is warranted.

Is IgA nephropathy a curable disease? ~case series of repeat biopsy~

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Introduction: IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis. While there is a high risk of progression to end-stage renal disease within their lifetimes, outcomes vary widely. Although the indication of immunosuppressive therapy should be determined based on histological and clinical severity, immunosuppressive therapy allows some patients to reach complete remission (CR) of urinary abnormalities.

Aims: We aimed to elucidate whether the IgAN is curable by immunosuppressive treatment.

Materials and Methods: To analyze pathological improvement in cases with CR, repeat biopsy (Re-Bx) was performed. Immune depositions were analyzed with monoclonal galactose-deficient IgA1 antibody (KM55).

Results: We performed Re-Bx in three patients with CR after immunosuppressive therapy. The interval between the first renal biopsy and the Re-Bx was 5, 12, and 24 years, respectively. A 20 years old man with M0E1S0T0C1 score was performed by tonsillectomy and steroid (PSL) pulse therapy. After 5 years, Re-Bx indicated no significant pathological changes without deposition of Gd-IgA1. A 38 years old woman with M1E1S0T0C1 score was treated with PSL. Re-Bx of 12 years interval showed only several global sclerosis without any immune deposition. A 12 years old woman with M1E0S0T0C1 score was also performed PSL pulse therapy. After 24 years, Re-Bx indicated no significant pathological changes without deposition of Gd-IgA1.

Conclusion: Our study demonstrates a series of IgAN patients cured by immunosuppressive treatment. Components of MEST-C, endocapillary hypercellularity and crescents, have been shown to correlate with response to immunosuppressive therapy. Not only existing immunosuppressive treatments, but new targeting treatments also make it possible for further curable cases worldwide.

Impact of sustained UPCR reduction on eGFR over 2 years: a secondary analysis from the NefIgArd trial of daily nefecon 16 mg or placebo in addition to supportive care for patients with biopsy-confirmed primary IgAN

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Introduction: Immunoglobulin A nephropathy (IgAN) is a chronic immune-mediated kidney disease characterized by galactose-deficient IgA1 (Gd-IgA1) deposition in the glomeruli. Nefecon, an oral, targeted-release formulation of budesonide, is released into the distal ileum – a major site of Gd-IgA1 production. The NefIgArd trial studied nefecon versus placebo in adults with IgAN.

Aims: This analysis reports the proportion of patients achieving sustained urine protein–creatinine ratio (UPCR) reduction for at least 6/9/12/18 months and the impact of sustained UPCR reduction on eGFR over 2 years.

Materials and Methods: Patients in the NefIgArd trial received nefecon 16 mg or placebo daily for 9 months (n=182 per group) plus renin-angiotensin system (RAS) inhibition versus RAS inhibition alone, followed by a 15-month, off-drug observation on RAS inhibition only. UPCR was measured at baseline and at 3/6/9/12/18 months.

Results: More nefecon recipients achieved 30% UPCR reduction, 61%/53%/51%/13% for at least 6/9/12/18 months, respectively, compared with 23%/16%/14%/5% in the placebo group. A 40% UPCR reduction was achieved by 52%/42%/40%/7% with nefecon, compared with 15%/12%/10%/3% of those treated with placebo. The effect of nefecon on UPCR reduction was clinically meaningful, with over half of patients sustaining ≥30% UPCR reduction for longer than 12 months. Sustained 30% UPCR reductions for >6/9/12 months were associated with mean eGFR change from baseline at 24 months of −4.4, −3.6, and −3.3 for nefecon and −7.6, −5.9, and −4.9 for placebo, respectively. Overall, eGFR curves showed sustained 30% UPCR reduction for ≥6 months was associated with slower eGFR decline, and nefecon recipients had slower decline than placebo recipients irrespective of UPCR reduction duration.

Conclusion: A substantial proportion of patients receiving nefecon achieved deep and sustained proteinuria reduction, highlighting the disease-modifying effect of nefecon 16 mg/day and supporting favorable effects on kidney function stabilization.

Impact of time since diagnosis on eGFR and UPCR changes over time with nefecon: a subanalysis from the NefIgArd trial of daily nefecon 16 mg or placebo in addition to supportive care for patients with biopsy-confirmed primary IgAN

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Introduction: Immunoglobulin A nephropathy (IgAN) is a chronic immune-mediated kidney disease characterized by galactose-deficient IgA1 (Gd-IgA1) deposition in the glomeruli. Results from the Phase 3 NefIgArd study demonstrated that nefecon 16 mg/day reduced proteinuria and preserved estimated glomerular filtration rate (eGFR) over 9 months of treatment, and kidney function benefits were sustained for up to 15 months of off-treatment follow-up in patients with primary IgAN.

Aims: To evaluate the effect of nefecon vs placebo in the NefIgArd trial according to time since IgAN diagnosis.

Materials and Methods: NefIgArd study design and study endpoints have been previously described. This subanalysis reports eGFR and urine protein–creatinine ratio (UPCR) change over time. Patients were divided into quartiles according to time since IgAN diagnosis at baseline.

Results: Mean time since diagnosis was 4.3 years in the overall population. Years since diagnosis in each quartile (Q) was <0.6 in Q1, 0.6–<2.4 in Q2, 2.4–<6.4 in Q3, and ≥6.4 in Q4. Compared with placebo, nefecon was associated with eGFR benefit across all quartiles. In Q1, eGFR was preserved with nefecon relative to placebo by 6.41/5.78/4.79 mL/min/1.73 m^2 at 9/12/24 months, respectively. In Q4, eGFR was preserved with nefecon relative to placebo by 6.95/3.61/5.07 mL/min/1.73 m^2 at 9/12/24 months, respectively.

Nefecon was also associated with greater reduction in UPCR vs placebo across all quartiles. In Q1, nefecon reduced UPCR versus placebo by 22.01%/51.12%/18.52% at 9/12/24 months, respectively. In Q4, nefecon reduced UPCR versus placebo by 16.74%/42.88%/35.48% at 9/12/24 months, respectively. Overall, Q1 patients maintained kidney function to a greater extent over the 2 years than other quartiles.

Conclusion: This NefIgArd subanalysis demonstrated that nefecon conferred treatment benefit in all patients versus placebo, irrespective of time since diagnosis; however, kidney function was preserved to a greater extent in patients more recently diagnosed with IgAN.

UPCR response at 12 months in patients with IgAN receiving nefecon vs placebo: analysis of NefIgArd trial data

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Introduction: In immunoglobulin A nephropathy (IgAN), absolute proteinuria reduction is a key surrogate biomarker for improved kidney outcomes. Current Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines consider an absolute reduction to <1 g/day a "reasonable treatment target." Durable proteinuria reductions were observed in NefIgArd, a Phase 3 trial of nefecon in IgAN, with a mean urine protein-creatinine ratio (UPCR) reduction of 51.3% from baseline with nefecon at 12 months.

Aims: To assess UPCR response at 12 months in patients with IgAN from the NefIgArd trial.

Materials and Methods: Patients were randomized 1:1 to 16 mg/day nefecon (n=182) or placebo (n=182) for 9 months, followed by 15 months off treatment; optimized supportive care was maintained throughout. Patients were classified by absolute UPCR response at 12 months: ≤0.3, ≤0.5, ≤1, or >1 g/gram.

Results: At 12 months, 65.4% of patients had a UPCR ≤1 g/gram with nefecon versus 33.0% with placebo, 34.6% versus 10.4% of patients had a UPCR ≤0.5 g/gram, and 18.1% vs 4.9% had a UPCR ≤0.3 g/gram. Nefecon-treated patients with a UPCR ≤1 g/gram had a smaller estimated glomerular filtration rate (eGFR) change than patients with >1 g/gram (mean [± standard error] absolute change from baseline at 12 months: 0.11 [–0.70, 0.93] and –4.82 [–6.30, –3.35] mL/min/1.73 m^2, respectively).

Conclusion: In the NefIgArd trial, two thirds of patients achieved absolute UPCR ≤1 g/gram at 12 months, after 9 months of nefecon treatment and 3 months off treatment. Lower UPCR at 12 months translated into eGFR benefit, demonstrating the disease-modifying effect of nefecon in patients with IgAN.

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Randomized Embedded Adaptive Platform Clinical Trial in South Asian Kidney Biopsy-Proven IgAN: Multi-center, Multi-arm and Multi-stage – Design Innovations and Operational Feasibility in Resource-Limited Settings

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Background: Our prospective observational GRACE-IgANI cohort (Alexander *et al.*) showed that South Asians with IgA nephropathy (IgAN) have severe and progressive disease. The lack of post-trial access to emerging biomolecules, driven by regional regulatory constraints, poses a significant risk of a rebound of the disease. Platform trials offer efficient frameworks for evaluating multiple interventions simultaneously. This is the first platform trial for glomerular diseases worldwide.

Trial Hypothesis: Among South-Asian adults with biopsy-proven primary IgAN, commonly available drugs (oral prednisolone/ gut-directed budesonide/ mycophenolate/ HCQ) in addition to maximally tolerated renin angiotensin aldosterone system inhibitors (RAASi) plus steady dose of sodium-glucose transport protein 2 inhibitors (SGLT2i) can significantly enhance kidney outcomes at two years compared to RAASi plus SGLT2i alone.

Key benefits of a platform trial: This investigator-initiated trial evaluates repurposed, regulatory-approved immunomodulatory agents with potential efficacy in IgAN. By leveraging existing data, the trial *shortens development timelines* while maintaining patient safety. The platform design allows for *flexible addition or removal of treatment arms* based on interim analyses.

Operational Strategies for Feasibility and Cost-Effectiveness: To ensure *affordability and scalability*, the trial is conducted at 10 academic centers across India. Key innovations include: A custom-built *in-house digital dashboard* for real-time trial oversight and patient tracking, use of REDCap for *secure, standardized data capture* and *integration into routine clinical workflows* to minimize operational disruption.

Challenges Encountered include regulatory navigation for a *novel trial design* unfamiliar to ethics committees, *capacity-building* at participating sites, ensuring *consistent protocol adherence* across diverse clinical settings and *limited prior experience* with embedded and adaptive trial methods in nephrology in LMICs.

Conclusions: This trial demonstrates that sophisticated trial designs, such as Adaptive Platform Trials, are feasible in South Asia with strategic planning. Investigator-led approaches, repurposing of existing drugs, and innovative cost-containment strategies may pave the way for more efficient clinical research in nephrology in LMICs.

Spot and 24-hour assessments of proteinuria and albuminuria in IgA nephropathy: A prespecified analysis of the SANCTUARY trial

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Introduction: Proteinuria is essential for disease assessment, monitoring, and guiding intervention in patients with IgA nephropathy (IgAN). 24-hour (24h) urine protein (UP) measurement is used in clinical trials because of the circadian variability in protein excretion but is challenging to operationalize, requires complete collection, and contributes to patient burden.

Aims: This prespecified sensitivity analysis of the SANCTUARY phase 2 trial explores the efficacy of ravulizumab in adults with IgAN using spot urine protein:creatinine ratio (UPCR) and urine albumin:creatinine ratio (UACR) in comparison with 24h measurements.

Materials and methods: SANCTUARY (NCT04564339), a randomized, double-blind, placebo-controlled trial evaluated efficacy and safety of ravulizumab in adults with biopsy-confirmed IgAN, eGFR ≥30 mL/min/1.73 m^2, on stable/optimal renin-angiotensin blockade, and mean UP ≥1 g/day from 2 valid 24h collections. Patients were randomized 2:1 to ravulizumab or placebo (IV every 8 weeks [wks]) for 26 wks; all patients received ravulizumab wks 26–50. The primary endpoint was percentage change from baseline to wk 26 in 24h proteinuria. As part of the prespecified schedule of activities, UP, albumin, and creatinine from morning spot urine samples were measured. In a *post hoc* analysis, we studied the correlation between spot UPCR and UACR and 24h UPCR, UP, and UACR.

Results: 43 participants were randomized to ravulizumab and 23 to placebo. 24h UP, 24h UPCR, and spot UPCR yielded similar estimates of the treatment effect on proteinuria from baseline to wk 26: −30.1%, −33.2%, and −27.0%, respectively. *Post hoc* correlation analysis indicated moderate-to-strong correlation between spot UPCR and 24h UPCR, spot UPCR and spot UACR, and spot UACR and 24h UACR.

Conclusion: The implementation of spot UPCR in trials may facilitate recruitment and encourage participants' adherence to study visits. However, caution should be exercised when interpreting results.

Treatment patterns and healthcare resource utilization among adults with primary IgA nephropathy (IgAN) in China: a longitudinal retrospective cohort study from a multi-province registry

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Introduction: Immunoglobulin A nephropathy (IgAN) is the most common glomerular disease in China. However, long-term treatment strategies remain unclear, and real-world data on treatment patterns and disease burden are limited.

Aims: To evaluate treatment patterns and healthcare resource utilization (HCRU) among newly diagnosed adults with IgAN in a real-world setting in China.

Materials and Methods: This retrospective cohort study included biopsy-confirmed adult patients with IgAN diagnosed between 2015 and 2023, using data from a nationwide registry (IgAN-Management Quality Improvement Initiative Project in China). Patient demographics, initial treatment strategies (initiated within three months of diagnosis), and treatment modifications (defined as first change to a regimen differing from initial therapy) were analyzed descriptively. HCRU was calculated as mean per-patient-per-year IgAN related outpatient and inpatient visits.

Results: A total of 2,603 patients were included, with a mean±SD age of 38.33±11.91 years at diagnosis; 46.14% were male. Initial treatment most commonly included RAS inhibitors (63.43%), corticosteroids (60.35%), immunosuppressants (52.63%), and traditional Chinese medicine (64.23%). 78.33% of patients experienced a treatment modification, with mean time to modification 258±354 (median: 132) days. In subsequent treatment, immunosuppressant use remained common (47.67%); cyclophosphamide use declined (16.71% to 8.63%), while hydroxychloroquine, Tripterygium herbal preparations, and mycophenolic acid drugs use remained stable.

Since 2021, newer therapies were observed during treatment modification, including SGLT2 inhibitors (9.30%) and B-cell–targeted biologics (3.60%). Hydroxychloroquine usage in subsequent treatment increased in 2021-2025 time-period (24.00%), compared to 2015-2019 (1.9%). Mean IgAN-related outpatient visits and hospitalizations were 3.1±3.2 and 1.0±1.1 per-patient-per-year, respectively.

Conclusion: This study reveals frequent treatment modifications and emerging use of novel therapies, highlighting an evolving and heterogenous treatment landscape for IgAN in China. The continued reliance on immunosuppressants and notable HCRU reflect the challenges of managing IgAN in China and underscore the need for more standardized, evidence-based treatment strategies to optimize outcomes.

Evaluating sibeprenlimab for Patients With IgA Nephropathy: Results From a Prespecified Interim Analysis of the Phase 3 VISIONARY Study

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Introduction: Sibeprenlimab is a selective antibody that inhibits the cytokine A PRoliferation Inducing Ligand (APRIL), a key driver of immunoglobulin A nephropathy (IgAN) pathogenesis. Phase 2 results suggested that sibeprenlimab may significantly reduce proteinuria and stabilize kidney function, defined by estimated glomerular filtration rate (eGFR).

Aims: The ongoing phase 3 VISIONARY trial evaluates subcutaneous (SC) sibeprenlimab in participants with IgAN at high risk for disease progression.

Materials and Methods: VISIONARY is a double-blind, randomized, placebo-controlled trial (NCT05248646) that includes adults on a renin-angiotensin system inhibitor (RASi) with or without a sodium-glucose cotransporter-2 inhibitor (SGLT2i). Participants were randomized 1:1 to receive SC sibeprenlimab 400 mg or placebo every 4 weeks for 26 doses. The primary endpoint for this prespecified interim analysis is the ratio of 24-hour urine protein-to-creatinine (uPCR-24h) at 9 months versus baseline.

Results: Across 31 countries, 510 participants were randomized; 320 (152 sibeprenlimab, 168 placebo) completed the 9-month uPCR-24h evaluation (63% male; 59% Asian; median age = 42 [range, 18-83] years). RASi and SGLT2i use at baseline were reported in 98% and 39% of participants, respectively. Median (range) baseline uPCR-24h was 1.3 (0.5-6.7) g/g, and mean (SD) baseline eGFR was 63.4 (24.9) mL/min/1.73m^2. After 9 months, a statistically significant reduction from baseline in geometric mean uPCR-24h was observed with sibeprenlimab (50.2% [95% CI, 44.0% to 55.6%]) versus an increase with placebo (2.1% [95% CI, 13.8% to -8.5%]), resulting in a between-group difference of 51.2% (96.5% CI, 42.9% to 58.2%; $P<0.0001$). A total of 76.3% and 84.5% of participants in the sibeprenlimab and placebo groups, respectively, had a treatment-emergent adverse event.

Conclusion: In this interim analysis, the primary study endpoint was met: sibeprenlimab demonstrated a significant and robust reduction in proteinuria after 9 months of treatment versus placebo, with a favorable safety profile.

A mechanistic biopsy study of the effect of iptacopan on immunopathology in patients with IgA nephropathy (IgAN)

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Introduction: Overactivation of the complement system via the alternative pathway (AP) is a key driver of immunoglobulin A nephropathy (IgAN) pathophysiology.

Aim: This mechanistic study aims to evaluate the effects of iptacopan, a selective complement factor B inhibitor, on the underlying immunopathology in patients with IgAN.

Methods: This Phase IIa multicenter, single-arm, open-label, repeat-biopsy study will enroll up to 20 adult patients with biopsy-proven IgAN, estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, proteinuria ≥0.8 g/g, and receiving a maximally tolerated and/or stable dose of supportive care treatment (angiotensin converting enzyme inhibitor or angiotensin receptor blocker and sodium-glucose co-transporter 2 inhibitors) for ≥90 days before baseline. Patients will receive iptacopan 200 mg bid for 9 months, with kidney biopsies at baseline and study end. The primary objective is to quantify changes in mesangial complement 3c and its C3c-containing fragment deposition from baseline to 9 months. The secondary objectives are to describe the histopathological changes after iptacopan treatment, changes in CD68 cells and immunoglobulins from baseline at 9 months. The exploratory objectives include evaluating the histopathological changes in complement biomarkers after iptacopan treatment, changes in the MEST-C scores from baseline at 9 months; describing changes in urine protein–creatinine ratio (UPCR; log-transformed ratio to baseline of UPCR), hematuria (change from baseline in dipstick and red blood cell per high power field [RBC/HPF] at 9 months), and eGFR (change from baseline at 9 months); and exploring the correlation of histopathological changes with UPCR and eGFR changes.

Conclusion: This study will explore the impact of iptacopan on IgAN immunopathology by assessing glomerular complement activation together with renal histopathology, kidney function, and key biomarkers. The findings will enhance understanding of iptacopan's mechanistic effects on IgAN and potential kidney-protective benefits.

Safety and efficacy of iptacopan in patients with IgA nephropathy (IgAN) with baseline eGFR 20-<30 mL/min: Phase 3 APPLAUSE-IgAN subcohort results

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Introduction: Treatment of patients with advanced IgAN and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 is limited to supportive care. Iptacopan specifically binds Factor B and inhibits the alternative complement pathway involved in IgAN pathogenesis. We present results from the APPLAUSE-IgAN subcohort with baseline eGFR 20-<30 mL/min/1.73 m^2.

Aim: To descriptively assess the safety, efficacy, and pharmacokinetics (PK) of the low baseline eGFR subcohort at Month 9 at time of interim analysis (IA).

Materials and Methods: APPLAUSE-IgAN (NCT04578834), a Phase 3, double-blind, placebo-controlled trial, enrolled adults with biopsy-confirmed IgAN with proteinuria ≥1 g/g despite stable supportive therapy. Patients were randomized 1:1 to iptacopan 200 mg or placebo twice daily for 24 months while remaining on supportive therapy.

Results: The IA included 27 patients (13 iptacopan, 14 placebo) randomized to the low eGFR cohort. Baseline demographics and disease characteristics were similar for iptacopan vs placebo: median (IQR) 24h urine protein-creatinine ratio (UPCR) 2.1 (1.7–2.5) vs 1.8 (1.4–2.4) g/g; mean (SD) eGFR 24.7 (2.8) vs 25.8 (2.9) mL/min/1.73m^2. All patients received maximally approved/tolerated RASi doses. In each arm, serious adverse events (AEs) occurred in two patients and AEs leading to treatment discontinuation in one patient. The most frequent AE was COVID-19 (23.1% iptacopan, 35.7% placebo). At Month 9, there was a median reduction in 24h-UPCR in the iptacopan group of 28% relative to baseline, whereas there was an increase in the placebo group of 10%. These results correspond to a 34.5% reduction in 24h-UPCR at Month 9 for iptacopan relative to placebo, which is consistent with the primary analysis. PK data will be presented.

Conclusion: In patients with baseline eGFR 20-<30 mL/min/1.73m^2, iptacopan was well tolerated with a favorable safety profile, and decreased proteinuria vs placebo at Month 9. Iptacopan may therefore represent a potential treatment option for patients with low eGFR.

Felzartamab durably reduces disease relevant biomarkers through targeting of CD38+ plasma cells and plasmablasts, the upstream drivers of IgA nephropathy

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Introduction: IgA nephropathy (IgAN) is driven by antibody-secreting cell (ASC) production of galactose-deficient IgA1 (Gd-IgA1) and anti–Gd-IgA1 autoantibodies resulting in immune complex deposition–induced kidney damage. Felzartamab is a fully human anti-CD38 monoclonal antibody that directly depletes CD38+ ASCs, the upstream cellular mediators of disease. In a placebo-controlled IgAN Phase 2 trial (NCT05065970, IGNAZ), felzartamab resulted in clinically meaningful prolonged urine protein-creatinine ratio (UPCR) reductions and estimated glomerular filtration rate (eGFR) stabilization.

Aims: Here, we evaluate disease-relevant biomarkers to understand molecular mechanisms of felzartamab efficacy and durability in IgAN.

Materials and Methods: Whole blood and serum from IGNAZ subjects were collected at baseline, on treatment, and during follow-up of a 2-year study. Samples were assessed for immune cells (flow cytometry), polyclonal immunoglobulins (turbidometry), and Gd-IgA1 (electrochemiluminescence immunoassay).

Results: Felzartamab induced rapid and durable depletion of Gd-IgA1 and total IgA. Patients who received 9 doses over a 5-month period maintained Gd-IgA1 reduction for at least 15 months after the first dose. Similar reductions in IgA were observed for 24 months after treatment start. IgG reduction was modest (<20%) and rebounded to baseline by 12 months. Circulating plasmablasts decreased on-treatment in felzartamab arms versus placebo. Treatment did not impact early or memory B-cell subsets or survival factors. Immunomodulation of other CD38+ cell types was observed.

Conclusion: Felzartamab targets and depletes the upstream cellular drivers of IgAN, resulting in rapid reduction of major disease-related biomarkers. Effects are maintained off-treatment while also preserving humoral immunity. These observations are consistent with other indications, supporting the disease-modifying potential of felzartamab in immune-mediated diseases.

Concomitant sparsentan (SPAR) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in adults with IgA nephropathy (IgAN) in the phase 2 SPARTACUS trial

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Introduction: SPAR, a non-immunosuppressive, dual endothelin angiotensin receptor antagonist (DEARA), showed sustained proteinuria reduction and kidney function preservation in patients with IgAN in PROTECT. A subgroup analysis from DAPA-CKD and EMPA-KIDNEY showed that SGLT2is reduced proteinuria and kidney failure progression in patients with IgAN.

Aims: Report the final analysis of the phase 2 SPARTACUS trial, which evaluated the efficacy and safety of SPAR added to stable SGLT2i treatment in adults with IgAN.

Materials and Methods: SPARTACUS was an open-label study of 24 weeks of SPAR added to SGLT2i in patients with IgAN at risk of disease progression. Patients previously received SGLT2i and the maximum tolerated dose of a renin-angiotensin system inhibitor (RASi) for ≥12 weeks. Endpoints included change from baseline in urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and blood pressure (BP), and adverse events.

Results: Forty-eight patients received SPAR (mean [SD] age, 48.9 [13.9] y; male, n=28 [58%]; median [IQR] baseline UACR, 0.70 [0.49-1.01] g/g); 41 completed the study. At week 24, SPAR added to stable SGLT2i led to a least-squares mean (95% CI) reduction in UACR of −56% (−66% to −43%; median [IQR] UACR, 0.33 [0.16-0.72] g/g); 12 patients (31%) reached a UACR of <0.2 g/g, and 20 (51%) and 30 (77%) had a ≥50% and ≥30% reduction in UACR from baseline, respectively. eGFR remained relatively stable through week 24, with slight decreases in BP. Thirty patients (63%) had a treatment-emergent adverse event; hypotension (15%) was the most common. No patients experienced abnormal liver function test results >3 times the upper limit of normal.

Conclusion: Switching from a RASi to SPAR on a background of an SGLT2i further reduced proteinuria in adult patients with IgAN, lowering their risk for disease progression. SPAR combined with an SGLT2i was generally well tolerated, with no unexpected safety signals.

Early Intervention with Budesonide Enteric-Coated Capsules in IgA Nephropathy: 2 Case Demonstrating Reduced Proteinuria and Stabilized Renal Function

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Introduction: IgA nephropathy (IgAN) is a renal disease closely related to immune abnormalities in the intestinal mucosa, and is one of the most important causes of renal failure. Early diagnosis and intervention is essential to slow disease progression. Budesonide enteric-coated capsule targets gut-associated lymphoid tissue and reduces circulating levels of Gd-IgA1 and immune complexes in patients with IgAN, which is expected to delay disease progression.

Aims: The aim of this study was to evaluate its efficacy and safety in the early treatment of IgAN.

Materials and Methods: The 2 young adult patients (male 21 years old, CKD stage 1, eGFR 108.4ml/min/1.73m^2; female 30 years old, CKD stage 2, eGFR 82.9ml/min/1.73m^2) diagnosed with IgAN by renal puncture biopsy were included. None of the patients wished to receive hormonal therapy, and a combination regimen containing budesonide enteric-coated capsules (16 mg/d) and based on RASi, SGLT2i or MRA and hydroxychloroquine was used. Renal function parameters were recorded at the time of diagnosis, at the beginning of treatment, 3 months, 6 months, and 9 months later.

Results: The Oxford typing of renal biopsy in both patients was M1E0S1T0C0 and renal biopsy was performed typically within the first four years of disease manifestation.. After 6-9 months of treatment, proteinuria was significantly improved (24h urine protein from 1.3g to conversion in the man and 50% decrease in urine protein-creatinine ratio from 1.35g to 0.51g in the woman); renal function remained slightly increase (eGFR from 108.4 to 131.9ml/min/1.73m^2)in male and stable in female(eGFR from 82.9 to 79.4ml/min/1.73m^2). It was well tolerated, with no serious adverse effects reported.

Conclusion: Budesonide enteric-coated capsules significantly reduced proteinuria and stabilized renal function and well tolerated in the early treatment of IgAN. Early diagnosis and treatment of patients are particularly important in IgAN.

The efficacy of Nefecon in the treatment of IgA nephropathy and IgA vasculitis nephritis: first-in-pediatrics case series

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Introduction: Nefecon, a budesonide formulation designed to target the gut-associated lymphoid tissue at Peyer's patches (a major site of Gd-IgA1 production), has been recommended by KDIGO 2024 guideline as a treatment option for adult IgA nephropathy (IgAN). Nevertheless, whether an antiproteinuric effect can be observed in in pediatric patients with IgAN/IgAVN remains unclear.

Aims: To preliminarily assess the efficacy and safety of nefecon in pediatric patients with IgAN/IgAVN within the framework of supportive care.

Materials and Methods: In this real-world study, IgAN or IgAVN children treated with nefecon at least 3 months were included between January 2025 and April 2025. All patients were stable on maximum tolerated doses of RAS inhibitors, with an eGFR >60 mL/min/1.73 m^2 and a urine protein/creatinine ratio (UPCR) >0.5 g/g.

Results: Three pediatric patients were analyzed, median age was 9 years old (7, 12), median baseline eGFR (Schwartz) was 116.6 mL/min/1.73 m^2 (111.6, 127.2), median baseline UPCR was 1.59 g/g (0.54, 2.05), and median urine red blood cell count was 251/uL (13, 699). After initiation of nefecon, UPCR significantly decreased to a median of 0.45 g/g (0.44, 1.06) in the 4-week follow-up and further declined to a median of 0.24 g/g (0.18, 1.13) after 12 weeks, equivalent to a relative reduction in proteinuria up to 55.1% (44.9%, 88.5%). Urine red blood cell count decreased to a median of 59/uL (5, 305). A marked reduction was also observed in the urine albumin/creatinine ratio. The renal function was stable during 3-month follow-up. Aside from 2 patients who presented with a distinctive "moon face" appearance, no further adverse events attributable to the drug were reported.

Conclusions: In this real-world setting, nefecon shows a significant impact on reducing proteinuria and hematuria in pediatric patients with IgAN/IgAVN. However, its potential inhibition of the hypothalamic-pituitary-adrenal axis remains a concern that warrants meticulous consideration by pediatric nephrologists.

Efficacy and Safety Profile of Nefecon in 26 Chinese Patients with IgA Nephropathy: A Real-World Observational Study

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Introduction: IgA nephropathy (IgAN), the most prevalent primary glomerulonephritis in China, progresses to end-stage kidney disease (ESKD) in 50% of high-risk patients within a decade. Pathogenesis involves gut-mediated overproduction of galactose-deficient IgA1 (Gd-IgA1). Nefecon, a novel targeted-release budesonide formulation delivering 4 mg to ileal Peyer's patches, represents China's first approved disease-modifying therapy targeting IgAN pathogenesis.

Aims: To assess real-world clinical outcomes and safety of Nefecon in Chinese IgAN patients.

Methods: This retrospective analysis included primary IgAN patients receiving ≥6 months Nefecon therapy (June 2024-April 2025). Outcome measures included urinary total protein (UTP) reduction rate, estimated glomerular filtration rate (eGFR) changes, hematuria resolution, and adverse events at 3, 6, and 9 months.

Results: The cohort (n=26, 57.7% male, mean age 42.1±13.8 years) demonstrated baseline eGFR 50.2±30.2 mL/min/1.73 m^2 and median UTP 1.31 g/d (IQR 0.65-1.76). Concomitant therapies included RAS inhibitors (65.4%) and corticosteroids/immunosuppressants (26.9%).

Key outcomes:

1. Proteinuria reduction: Median UTP decreased progressively by 13.5% (n=22), 33.6% (n=26), and 34.2% (n=5) at respective timepoints
2. Renal function: Mean eGFR increased 8.3%, 5.5%, and 19.8% from baseline
3. Hematuria resolution: Complete resolution rates increased from 25% (3-month, n=22) to 5.8% (6-month, n=26) and 66.7% (9-month, n=5)

Subgroup analysis revealed superior 9-month eGFR improvement in patients with baseline eGFR ≥35 mL/min/1.73 m^2 (36.1% vs -4.8% in <35 group, P=0.038). No serious drug-related adverse events or infectious complications were observed.

Conclusion: This real-world analysis demonstrates Nefecon's sustained renoprotective effects in Chinese IgAN patients, particularly those with preserved renal function (eGFR ≥35 mL/min/1.73m^2), with progressive proteinuria reduction and hematuria resolution. The favorable safety profile supports its clinical utility in this population.

Effects of cyclosporin a therapy combined with steroids and angiotensin converting enzyme inhibitors on childhood IgA nephropathy

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Introduction: Several mall randomized clinical trials or small uncontrolled trials have indicated potential role of Cyclosporin A (CsA) in treating IgAN with encouraging results, such as significant reduction of proteinuria.

Aim: To evaluate the clinical effects of CsA in children with IgAN.

Materials and methods: We retrospectively reviewed the charts of 14 patients (mean age 8.9±2.9 yr; 8 boys, 6 girls) with IgAN who were treated with CsA and prednisolone from 2021 to 2024. 10 of the 14 children were ≤10 years old. The median duration of follow-up was 3,2 years. CsA was administered to patients with heavy proteinuria (>2 g/day). The starting dose of CsA was 5 mg/kg/day and the blood level was maintained at 100-200 ng/mL. The mean (±SD) CsA level was 183.8±48.3 ng/ mL (range 120.7-276 ng/mL) and the mean duration of CsA therapy was 10.9±1.9 months (range 8-12 months). Prednisolone (1-2 mg/kg/day) was given or four weeks and was gradually reduced to dose of 5-10 mg/day on alternate days during CsA therapy.

Results: At the end of CsA therapy, 2 patients showed normal urinalysis and renal function findings, 9 had microscopic hematuria without proteinuria, 2 had proteinuria of <40 mg/m2/hr, and 1 had active renal disease with proteinuria of >40 mg/ m2/hr. CsA was well tolerated in all patients and none required drug discontinuation or had any adverse event that warranted hospitalization. The mean 24-hr urinary protein excretion declined from 107.1±35.1 mg/m^2/hr to 7.4±2.4 mg/m2/hr ($P<0.001$) and serum albumin increased from 3.3±0.6 g/dL to 4.3±0.3 g/dL ($P<0.001$) after CsA therapy. Serum creatinine, creatinine clearance, systolic blood pressure, and diastolic blood pressure did not differ before and after CsA therapy.

Conclusion: Our study suggests that CsA combined with steroids and ACE inhibitor may be effective in reducing proteinuria and attenuating histologic progression in aproportion of children with IgAN.

Transplantation

Telitacicept Treatment for Recurrent IgA Nephropathy after Kidney Transplantation

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Background: IgA nephropathy (IgAN) is frequently recurrent after kidney transplantation, posing significant challenges in management. In this report, we conduct a retrospective analysis to assess the efficacy and safety of telitacicept in treating recurrent IgAN among kidney transplant recipients.

Methods: A retrospective cohort study was conducted from August 2023 to April 2025. Patients with biopsy-proven recurrent IgAN following kidney transplantation who were treated with telitacicept were included. The primary outcome was the change in proteinuria levels after 12 months of treatment. Complete remission (CR) is defined as having 24-hour urinary protein excretion of less than 0.3 g/d and an increase of serum creatinine (Scr) less than 15%. Partial remission (PR) is defined as decrease in 24-hour urinary protein excretion of 50% or more (not exceeding 3.5 g/d) compared to the baseline, along with an increase in Scr of less than 15%. Secondary outcomes were changes in Scr and estimated glomerular filtration rate (eGFR) compared to baseline.

Results: The mean age of the participants was 34.6±11.8 years, 40% were female. 3 patients discontinued treatment at 3 months, and 2 patients at 6 months. The remaining patients completed the 12-month telitacicept treatment. After 6-month follow-up, 2 patients achieved CR, and 2 patients reached PR. Furthermore, 6 patients (60%) experienced a reduction of over 30% in proteinuria. At 9-month follow-up, 1 patient reached CR, 2 patients reached PR, and 5 patients (50%) exhibited a declining trend in proteinuria. Throughout the treatment, the Scr and eGFR level remained stable in 9 patients. Notably, the mean urine red blood cell count decreased by 89.47% from baseline after 12-month treatment. No serious adverse events occurred during the treatment.

Conclusions: Telitacicept shows promising safety and efficacy in lowering proteinuria for patients with recurrent IgAN following kidney transplantation.

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