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Leicester IgA Nephropathy Research Group

The Rapidly Evolving Treatment Paradigm

For IgA Nephropathy

Professor Jonathan Barratt

University of Leicester

&

John Walls Renal Unit, Leicester

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Speaker Declarations

Jonathan Barratt	
Consulting and Speaker Fees	Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra
Grant Support	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra
Clinical trials	ADU-CL-19 & ALIGN (Chinook), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NeflgARD (Calliditas), ORIGIN (Vera Therapeutics)
Research projects	Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra

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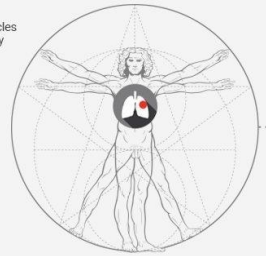
TRADITIONAL MEDICINE vs. PRECISION MEDICINE

Traditionally, radiation, chemotherapy, and surgery were the only means by which doctors could treat cancer.
With precision medicine, doctors use a patient's genes to uncover clues for treating the disease.

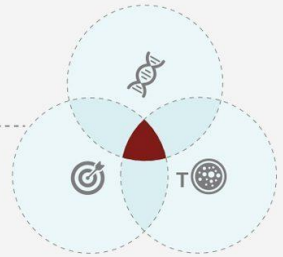
RADIATION
- High-energy particles damage or destroy cancer cells

CHEMOTHERAPY
- Chemicals attack cancer

SURGERY
- Operate on part of the body to diagnose or treat cancer



Advanced Personalized Treatment



GENETICS
- Gene sequencing
- Locate cancer-causing genes

IMMUNOTHERAPY
- Identify ways to customize treatment
- Find ways to turn immune system on
- Personalize treatment with immune-activating drugs

TARGETED THERAPIES
- Drugs turn specific genes on or off

+ TRADITIONAL THERAPIES

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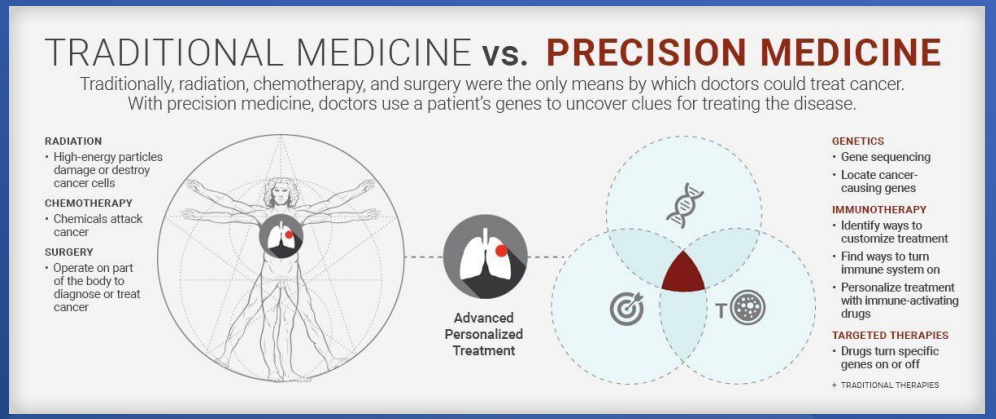

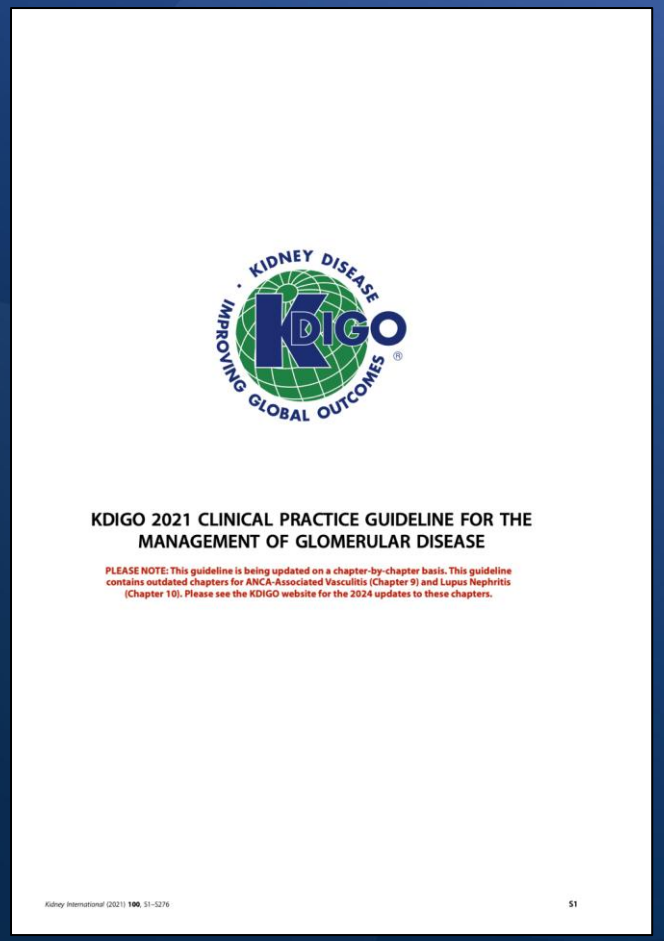
KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES

KDIGO

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASE

PLEASE NOTE: This guideline is being updated on a chapter-by-chapter basis. This guideline contains outdated chapters for ANCA-Associated Vasculitis (Chapter 9) and Lupus Nephritis (Chapter 10). Please see the KDIGO website for the 2024 updates to these chapters.

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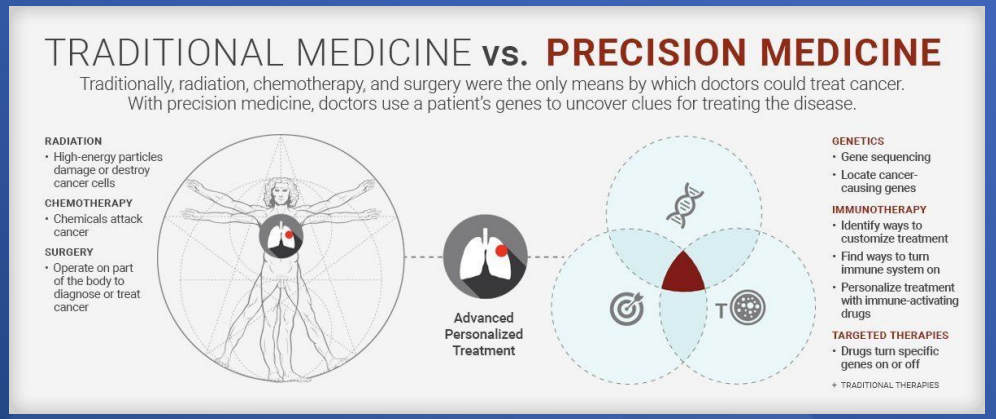

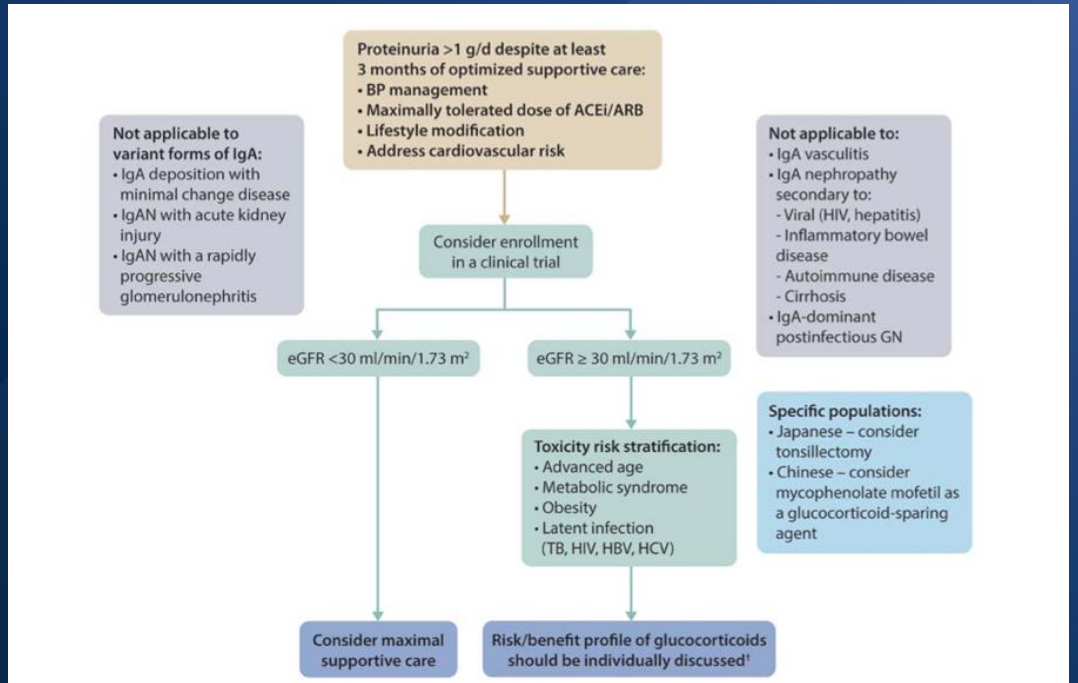

Figure 24 | Management of patients with IgAN who remain at high risk for progression after maximal supportive care. *IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3. †The TESTING study[109] shows early evidence of efficacy in patients who had marked proteinuria (2.4 g/d average) at the expense of treatment-associated morbidity and mortality. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure, eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; TB, tuberculosis.

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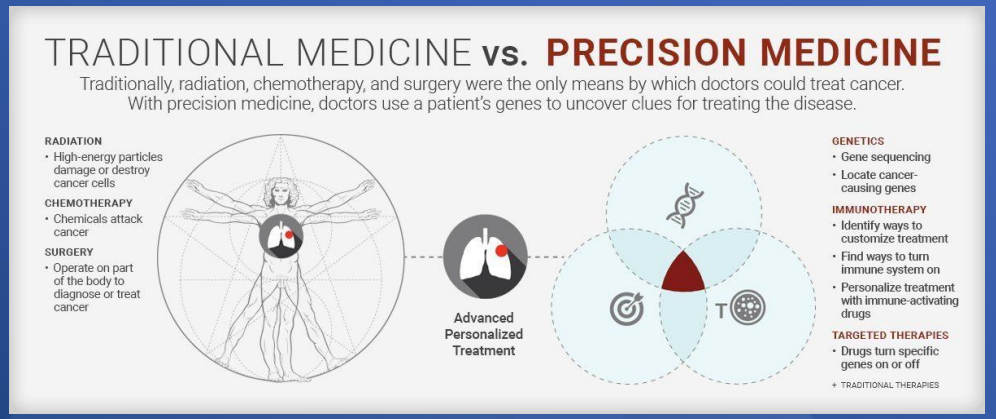

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

SUPPLEMENT TO

kidney INTERNATIONAL

KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV)

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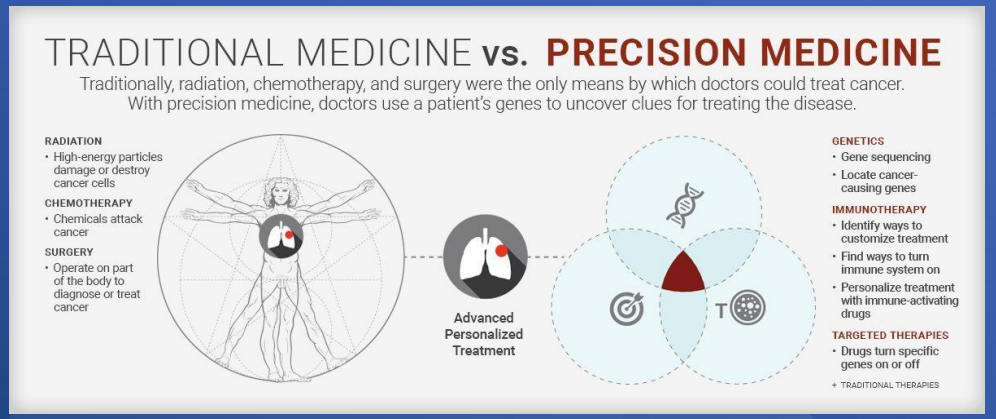

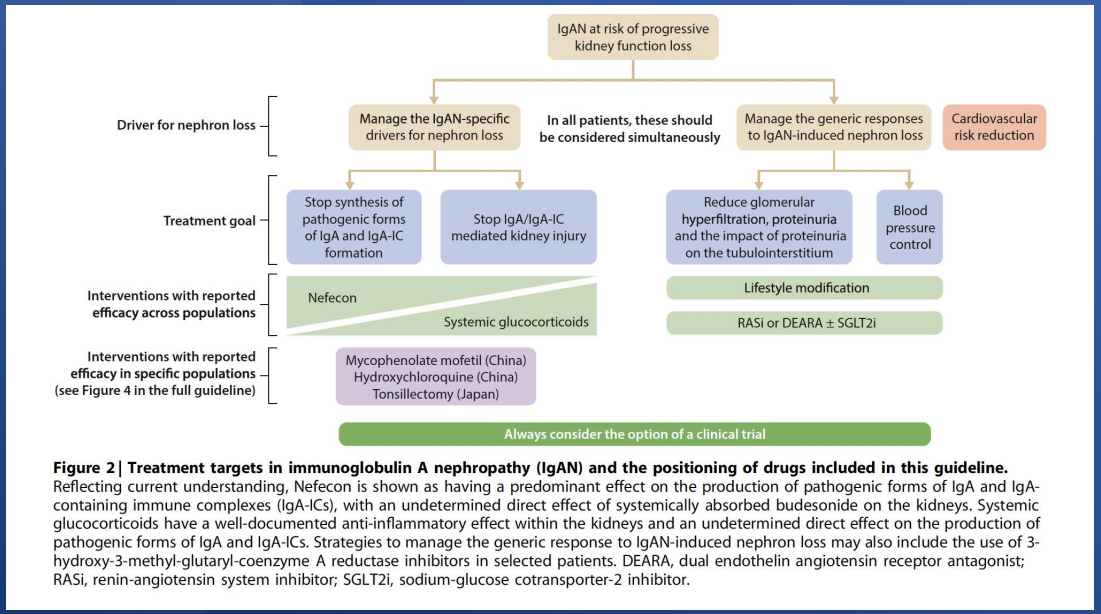

Figure 2 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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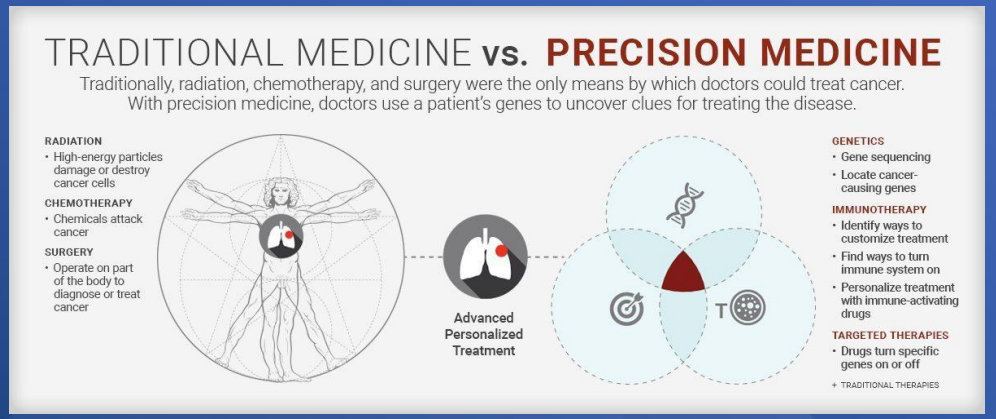

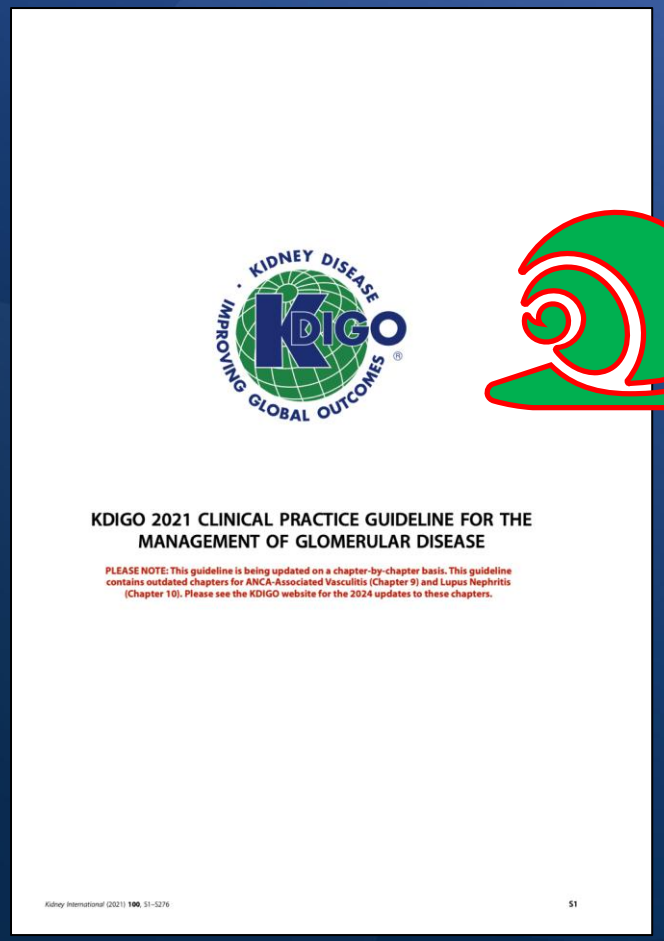

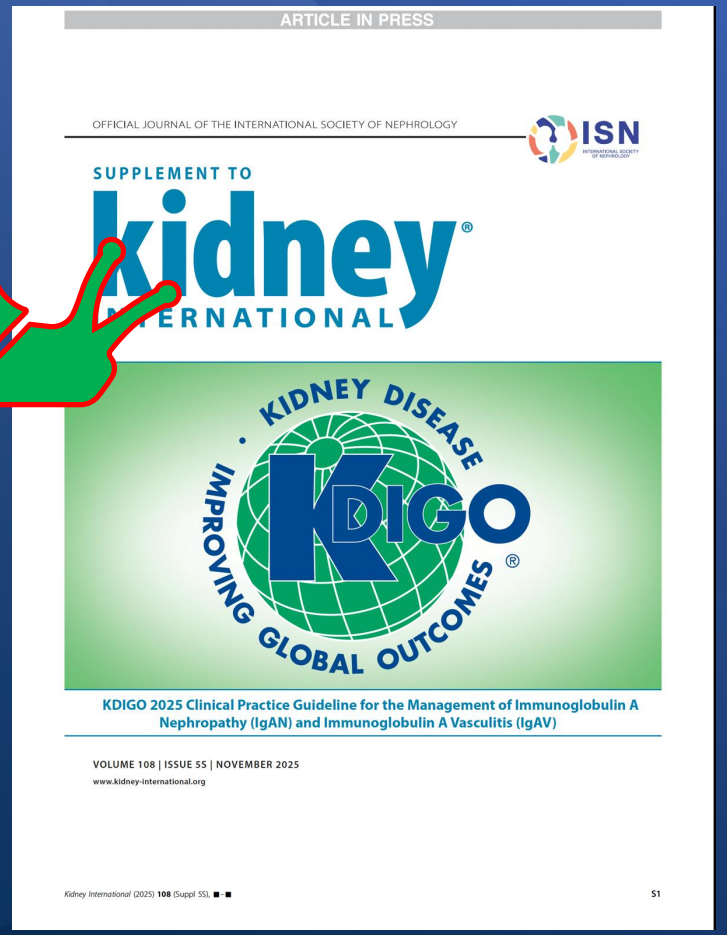

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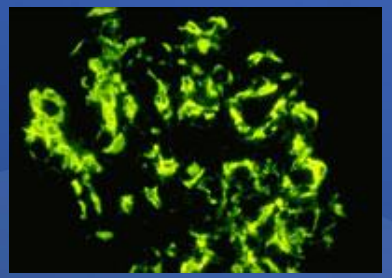


early **Disease natural history** *late*

Relative contribution to nephron loss

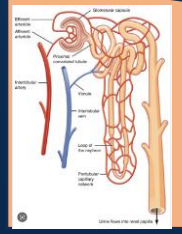
Immune complex-mediated nephron loss

Intrarenal response to nephron loss

glomerular hyperfiltration

tubulointerstitial response to proteinuria

systemic HTN



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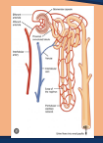

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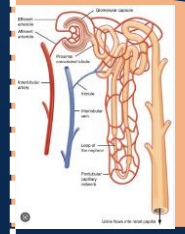

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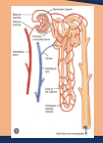

Therapeutic window to address drivers of nephron loss

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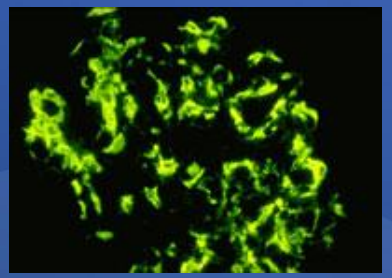

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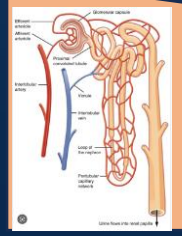

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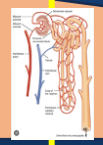

Typical time point IgAN is diagnosed

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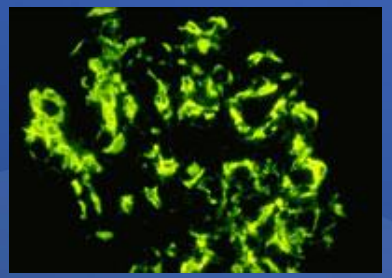

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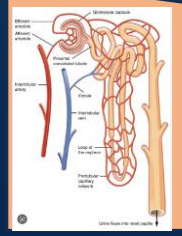

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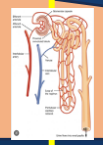

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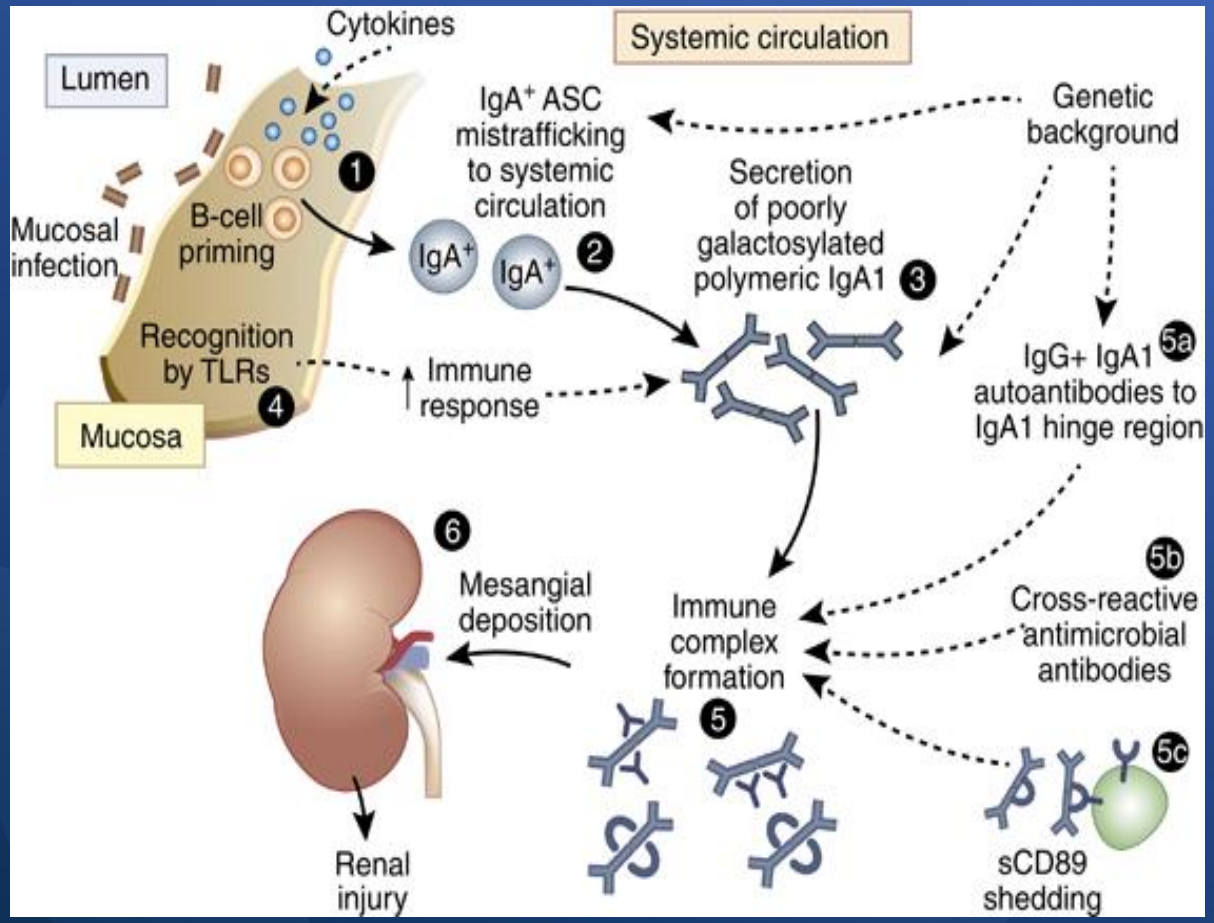
Cytokines
Systemic circulation
Lumen
IgA+ ASC mistrafficking to systemic circulation
Genetic background
Mucosal infection
B-cell priming
1
IgA+
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2
Secretion of poorly galactosylated polymeric IgA1
3
Recognition by TLRs
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Immune response
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Mucosa
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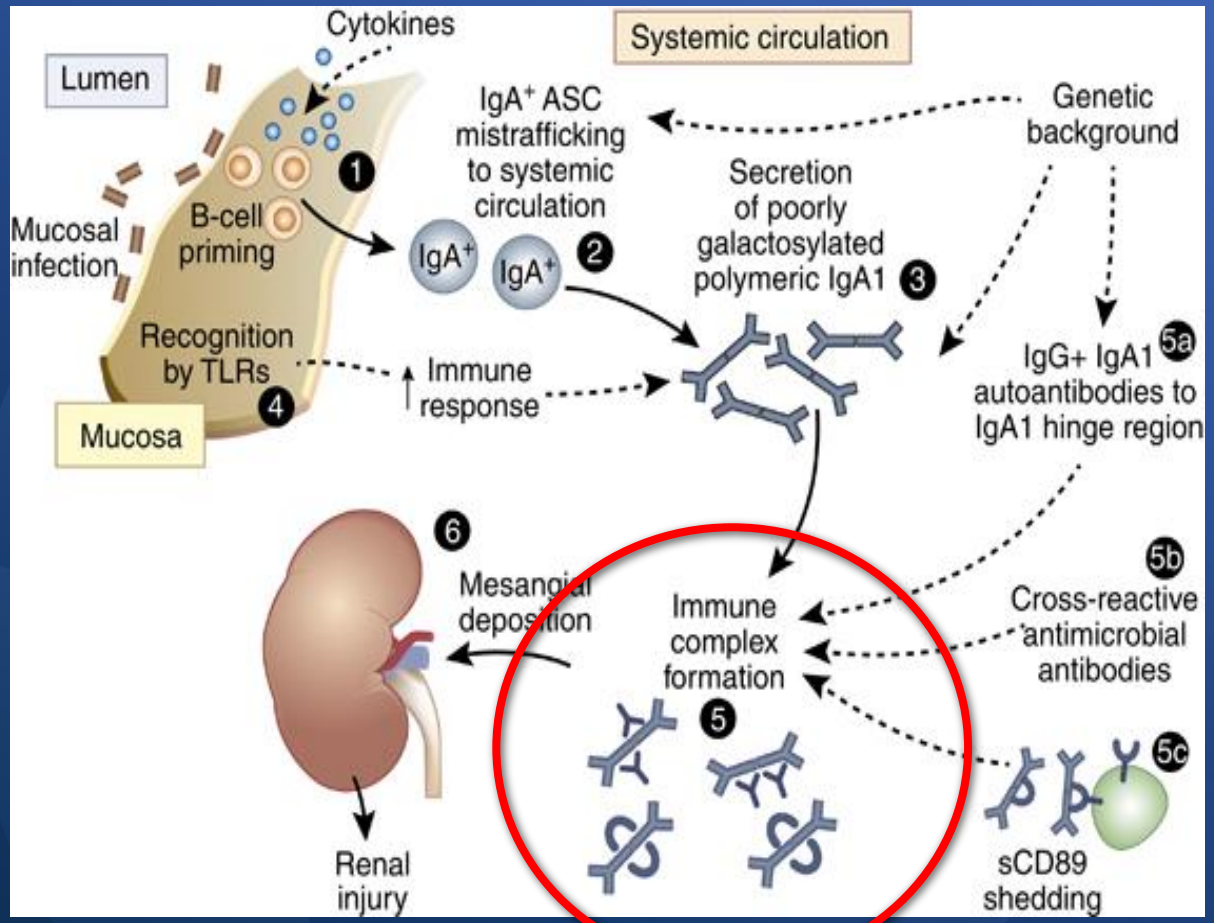
Mesangial deposition
5b
Cross-reactive antimicrobial antibodies
Immune complex formation
5
5c
Renal injury
sCD89 shedding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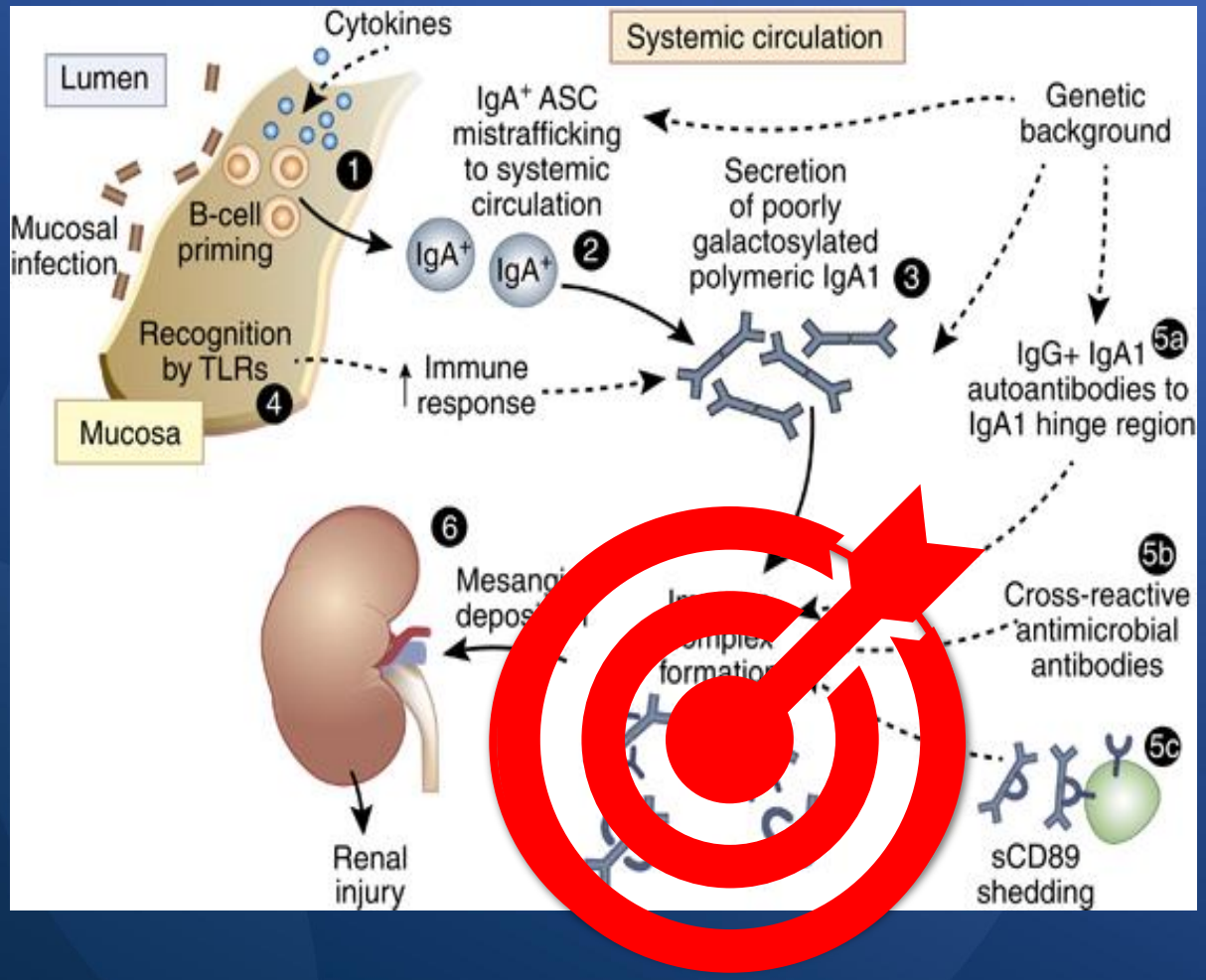

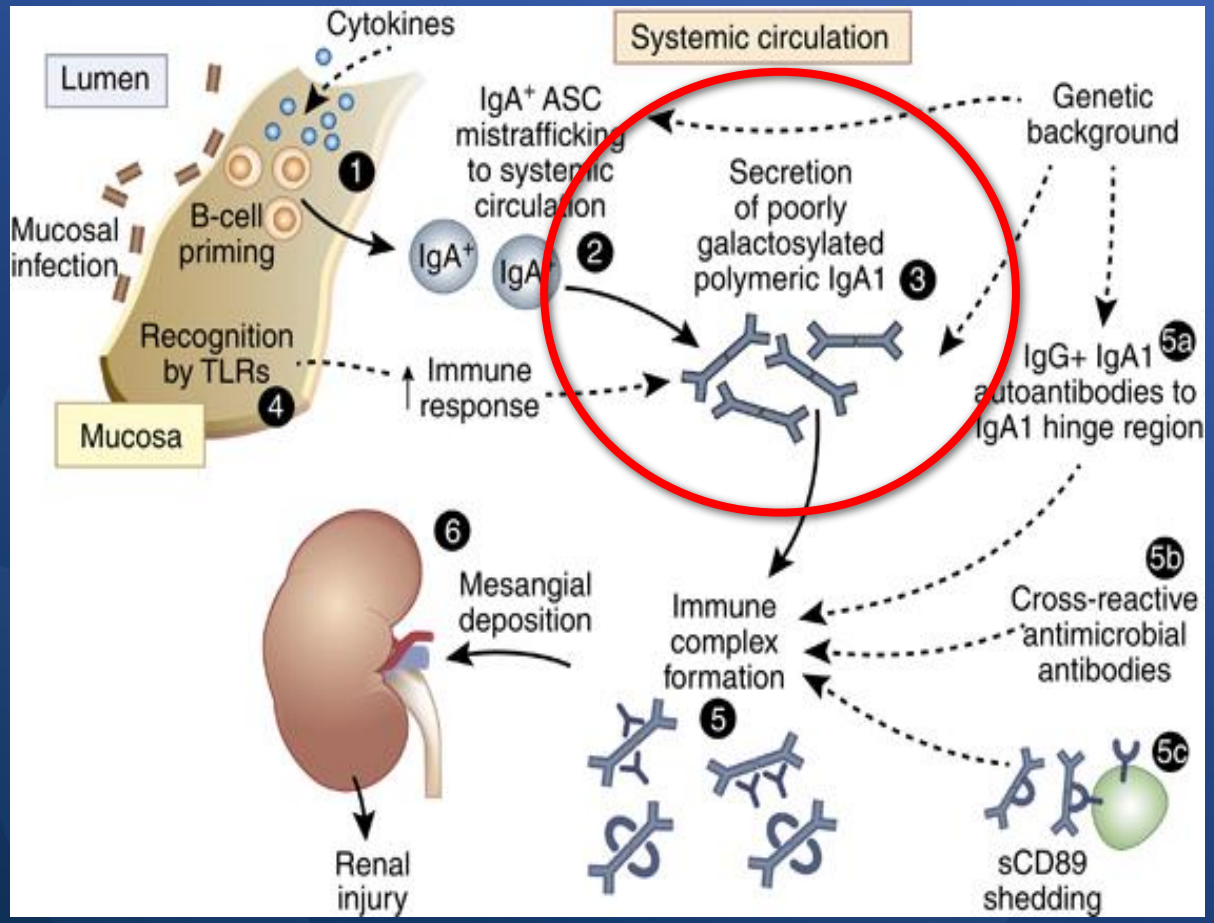
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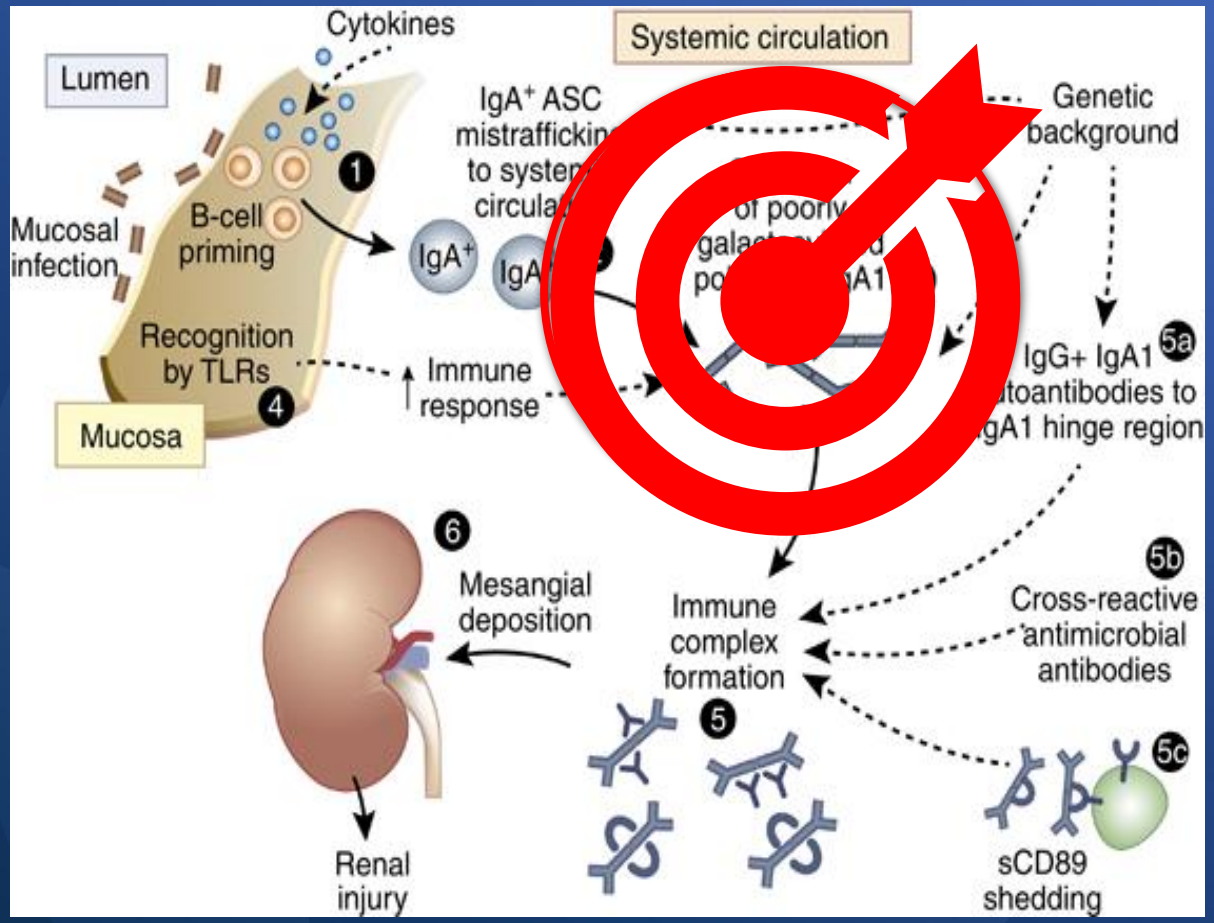

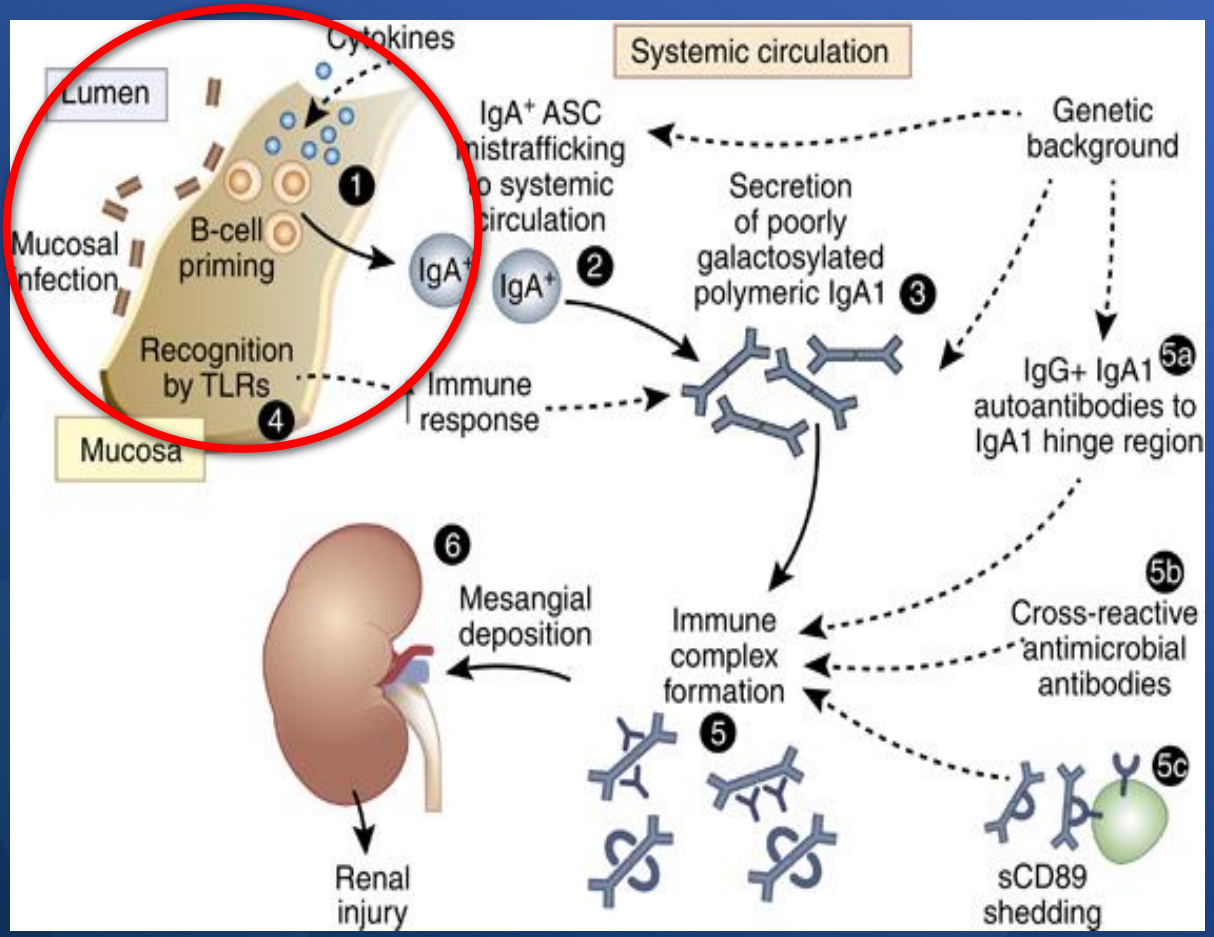
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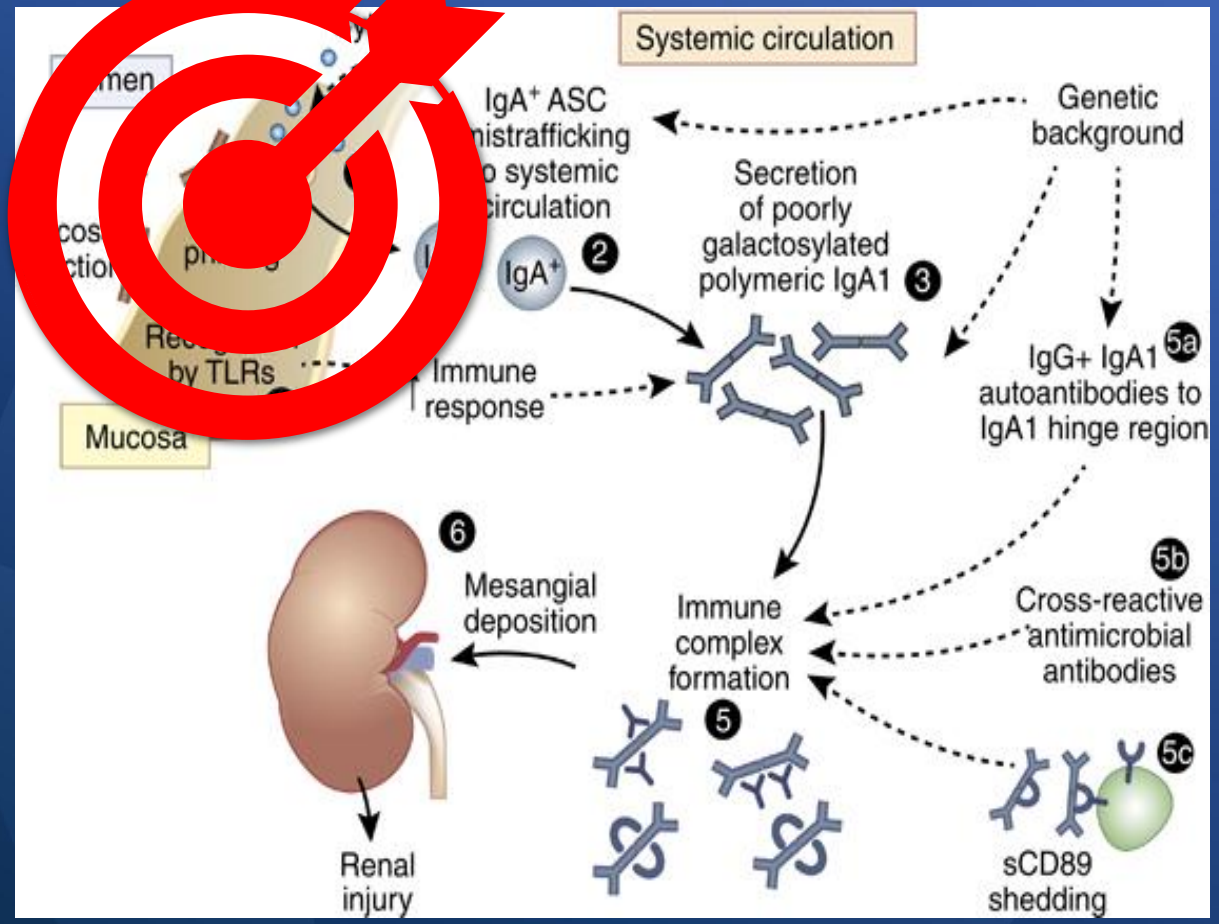

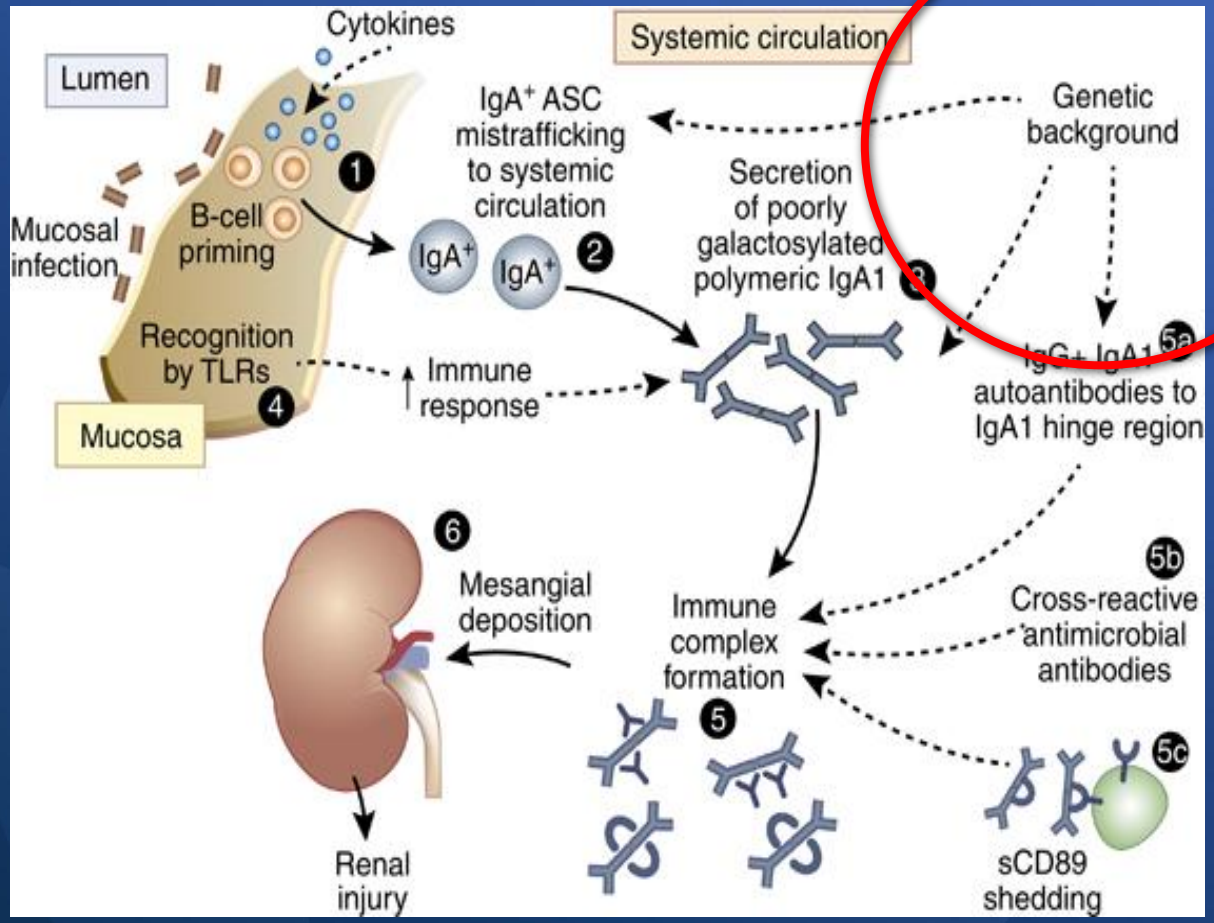
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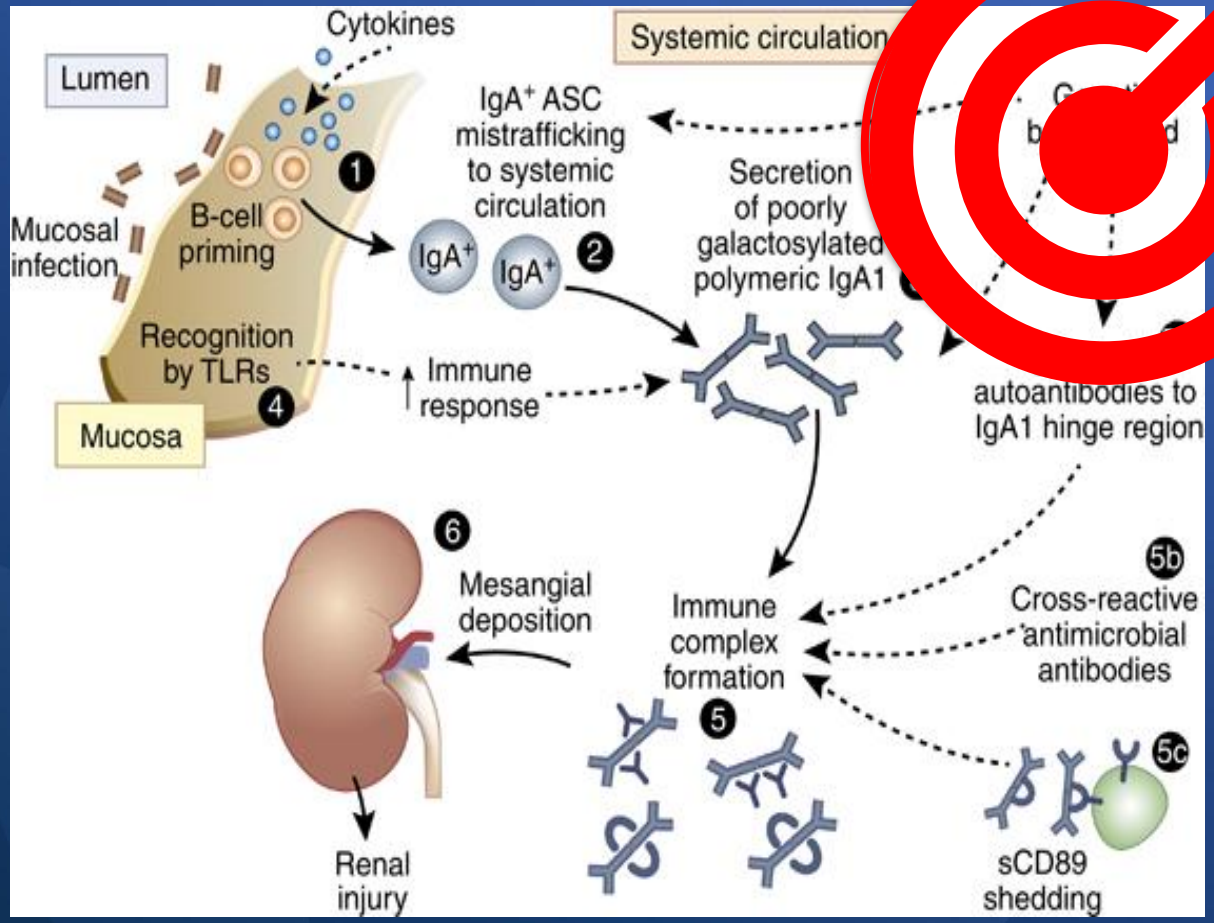

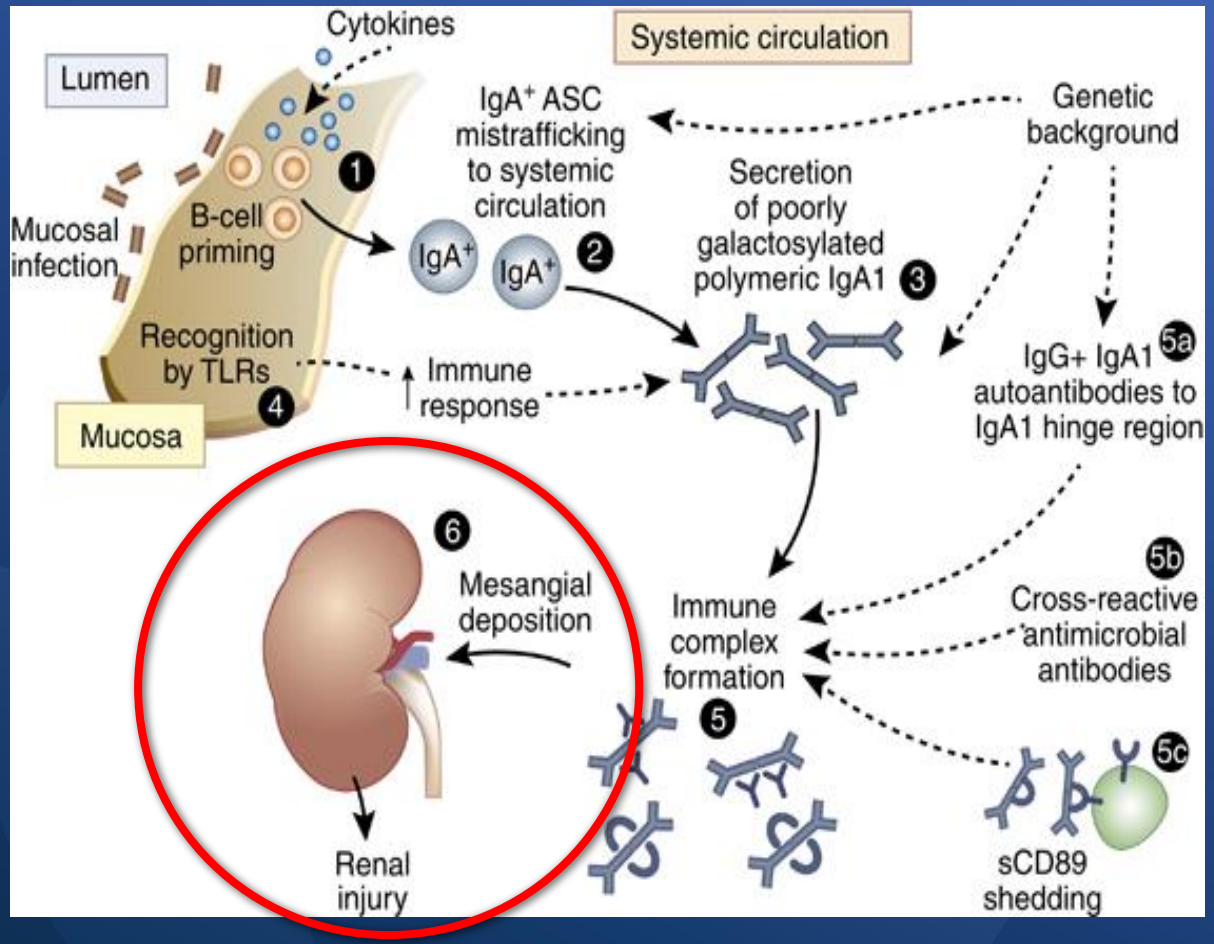
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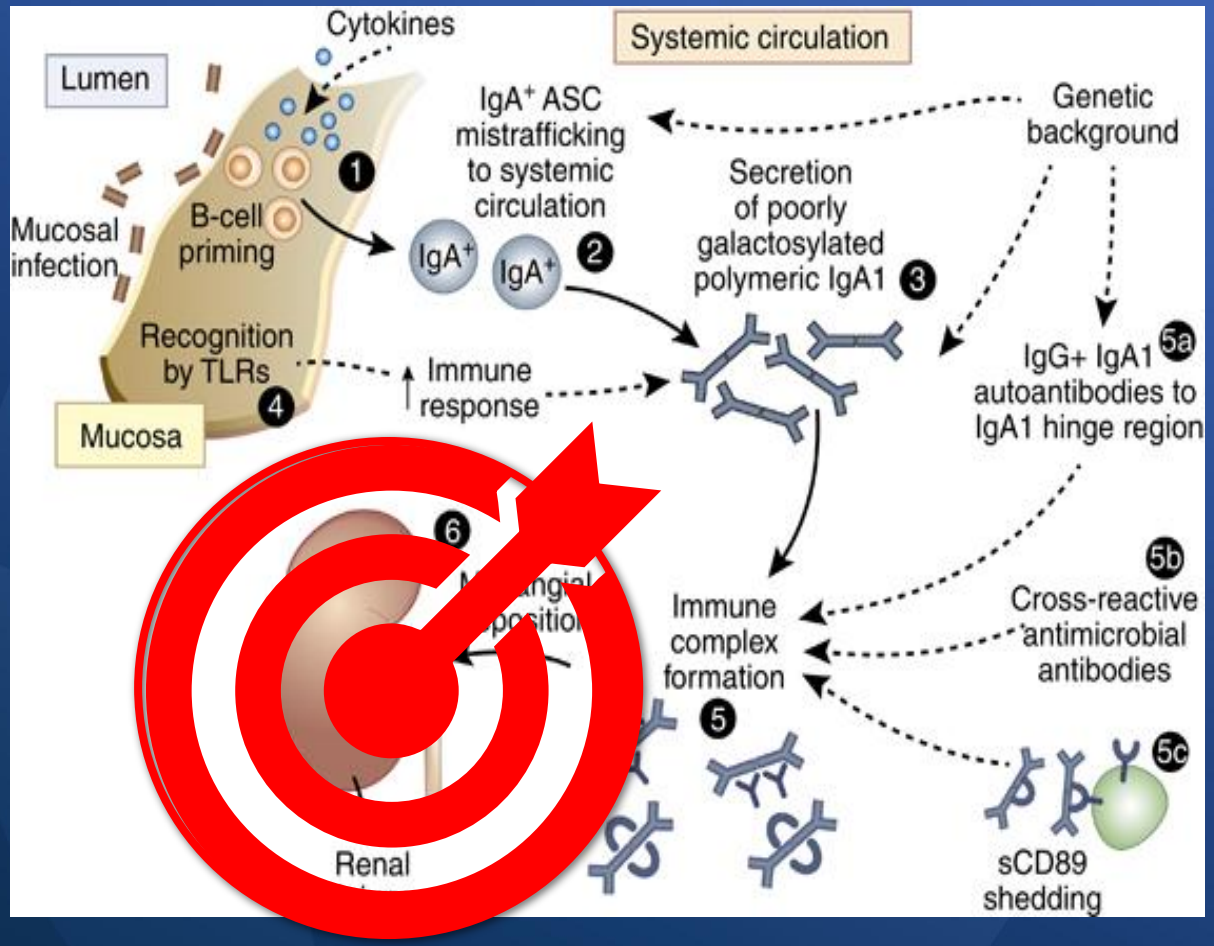
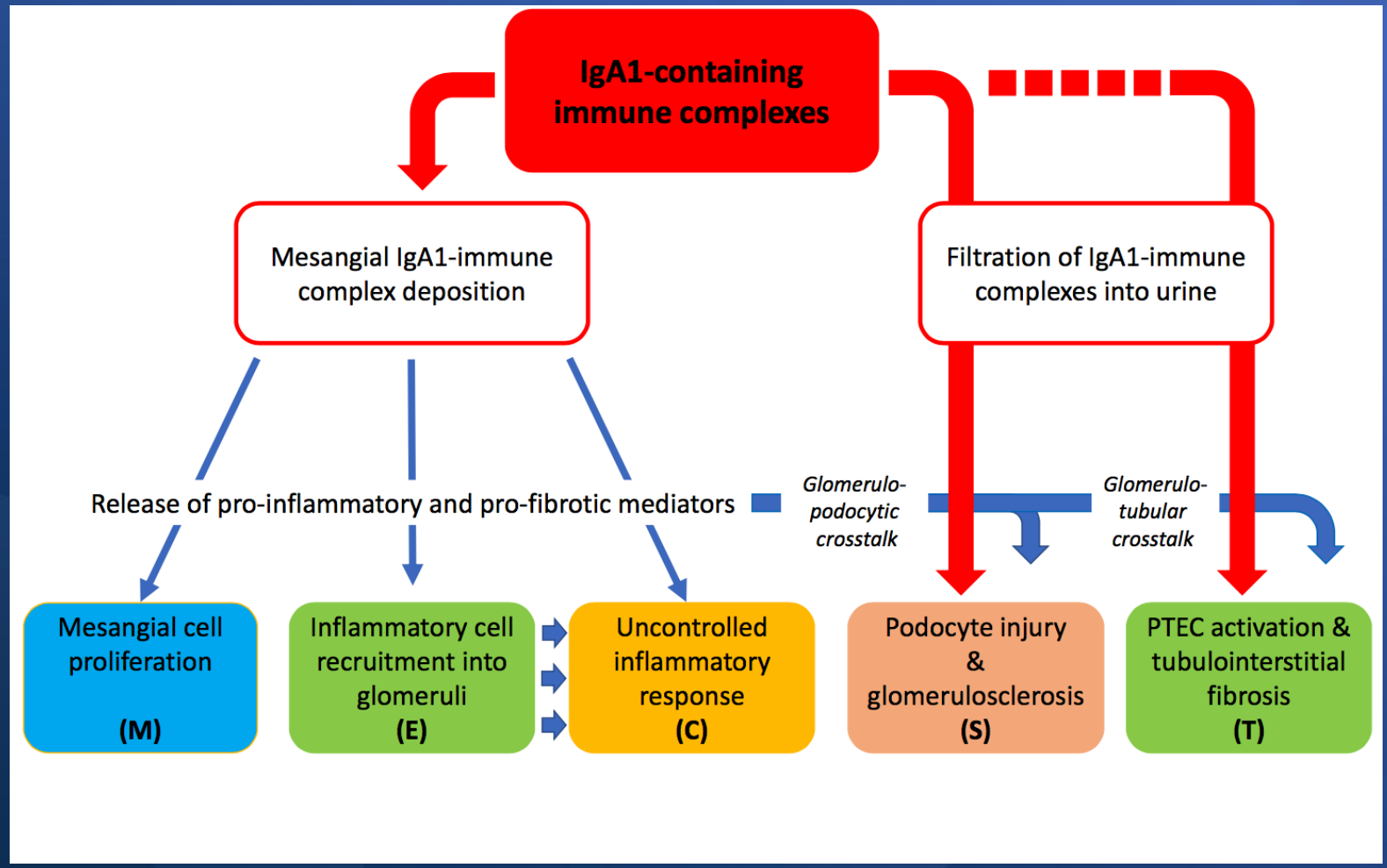
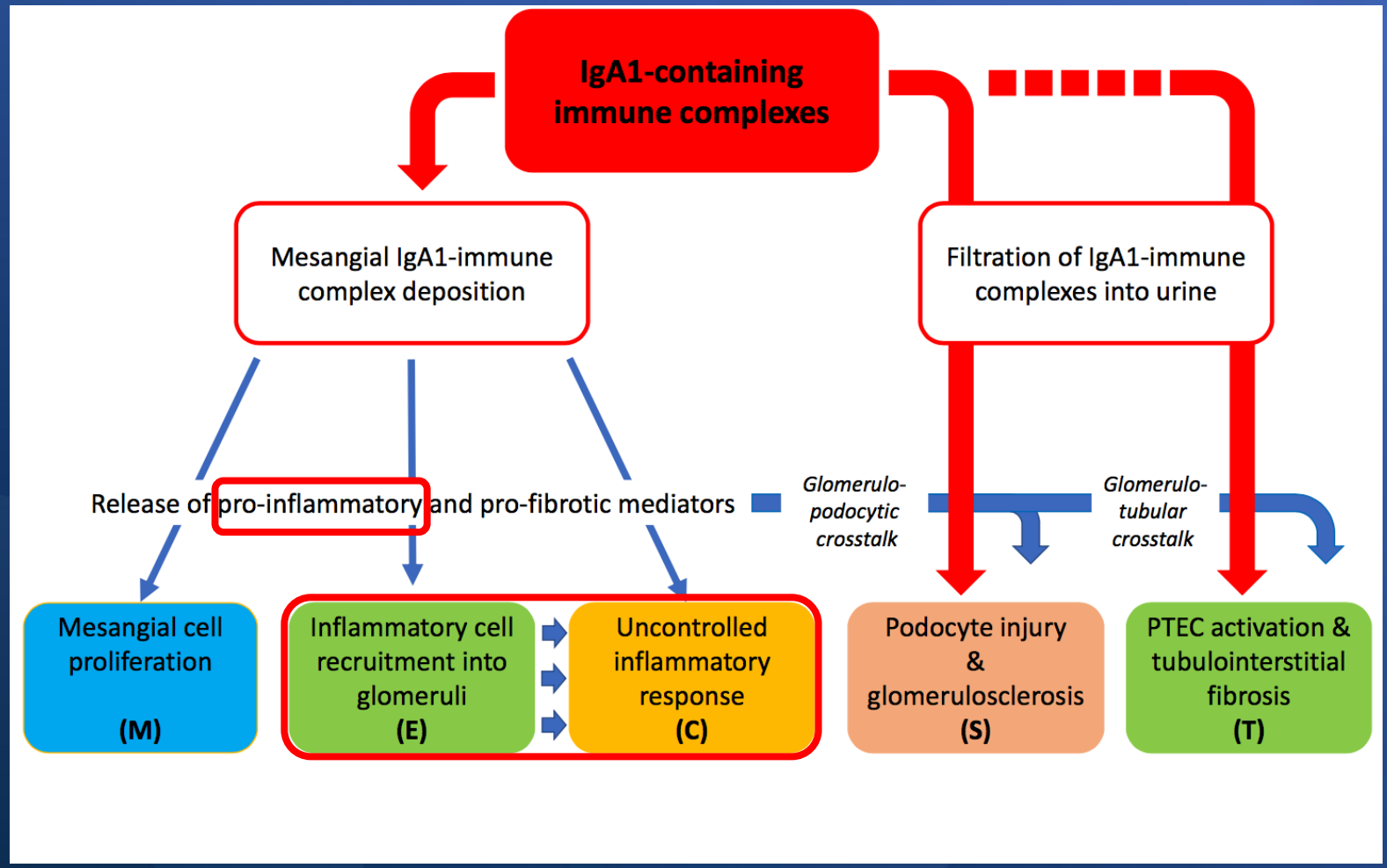



IgA1-containing immune complexes
Mesangial IgA1-immune complex deposition
Filtration of IgA1-immune complexes into urine
Release of pro-inflammatory and pro-fibrotic mediators
Glomerulo-podocytic crosstalk
Glomerulo-tubular crosstalk
Mesangial cell proliferation (M)
Inflammatory cell recruitment into glomeruli (E)
Uncontrolled inflammatory response (C)
Podocyte injury & glomerulosclerosis (S)
PTEC activation & tubulointerstitial fibrosis (T)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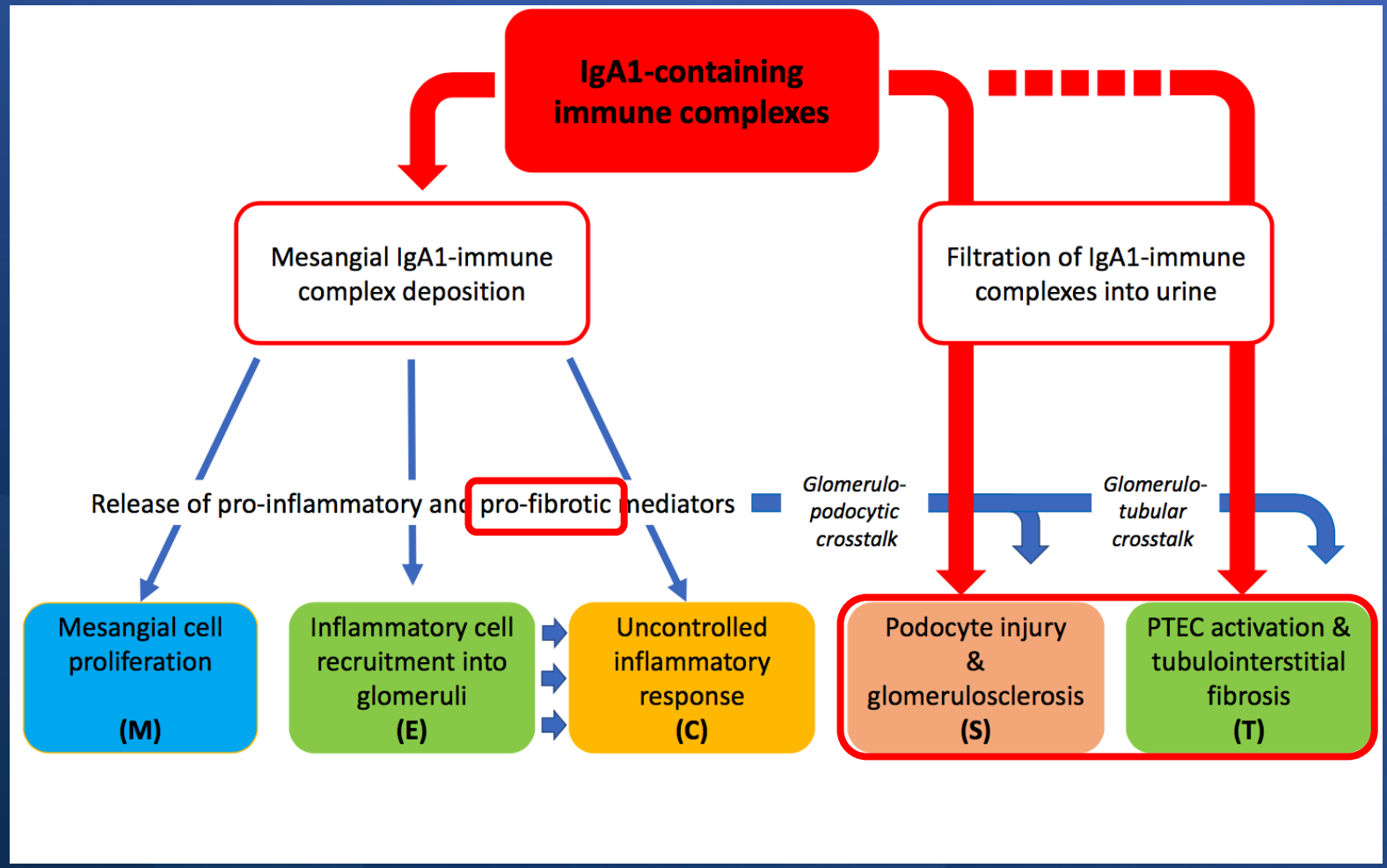
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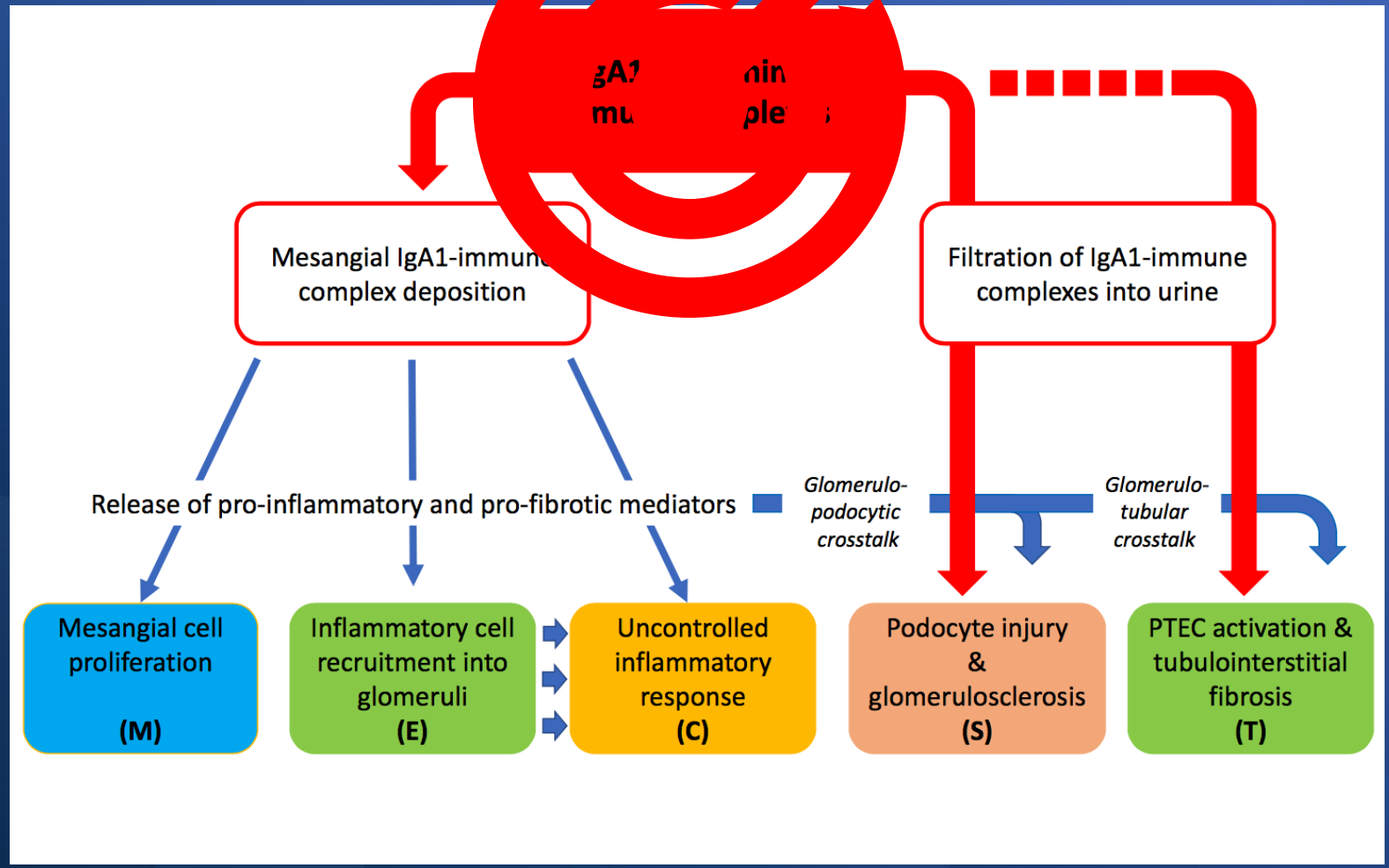
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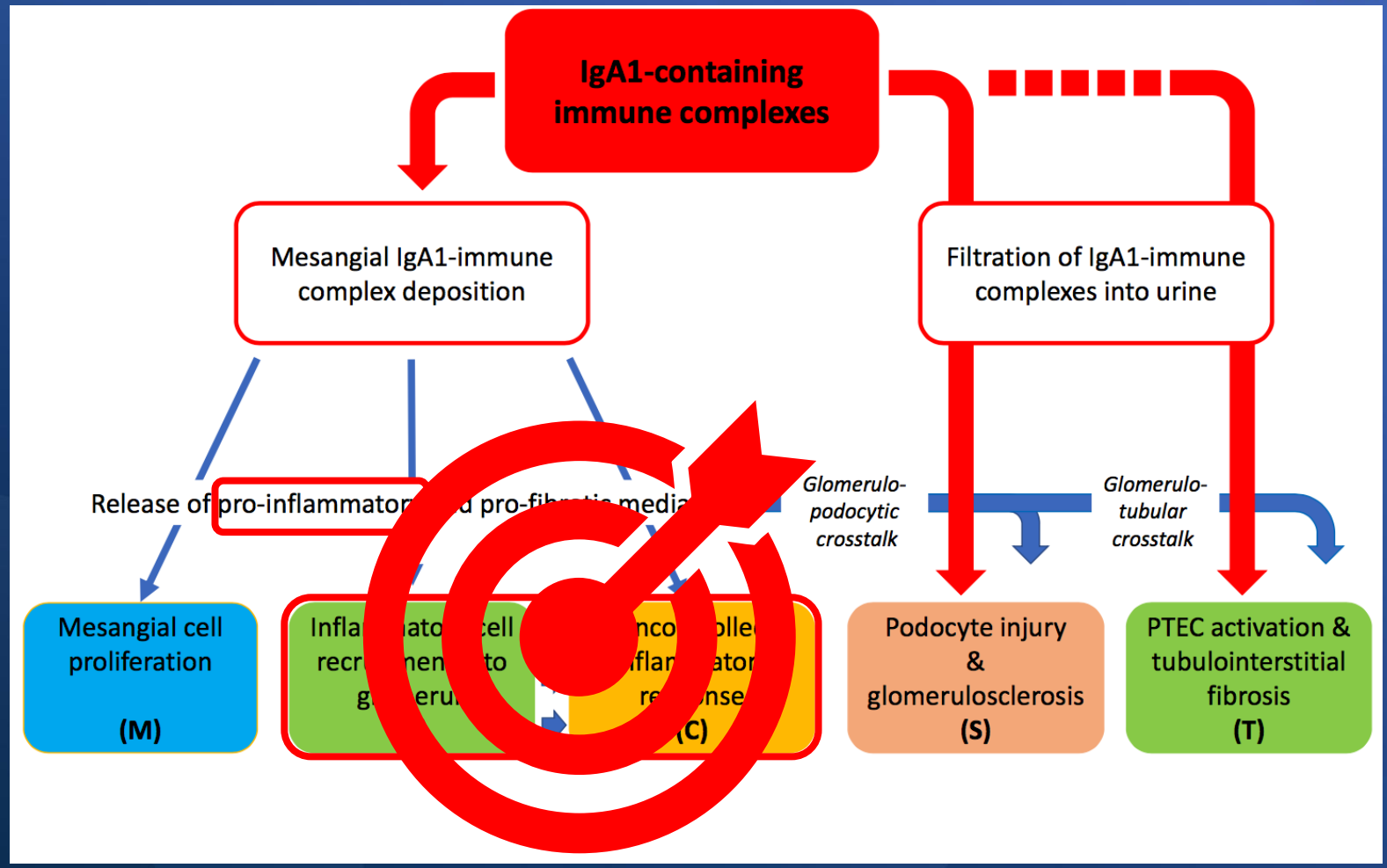
IgA1-containing immune complexes
Mesangial IgA1-immune complex deposition
Filtration of IgA1-immune complexes into urine
Release of pro-inflammator
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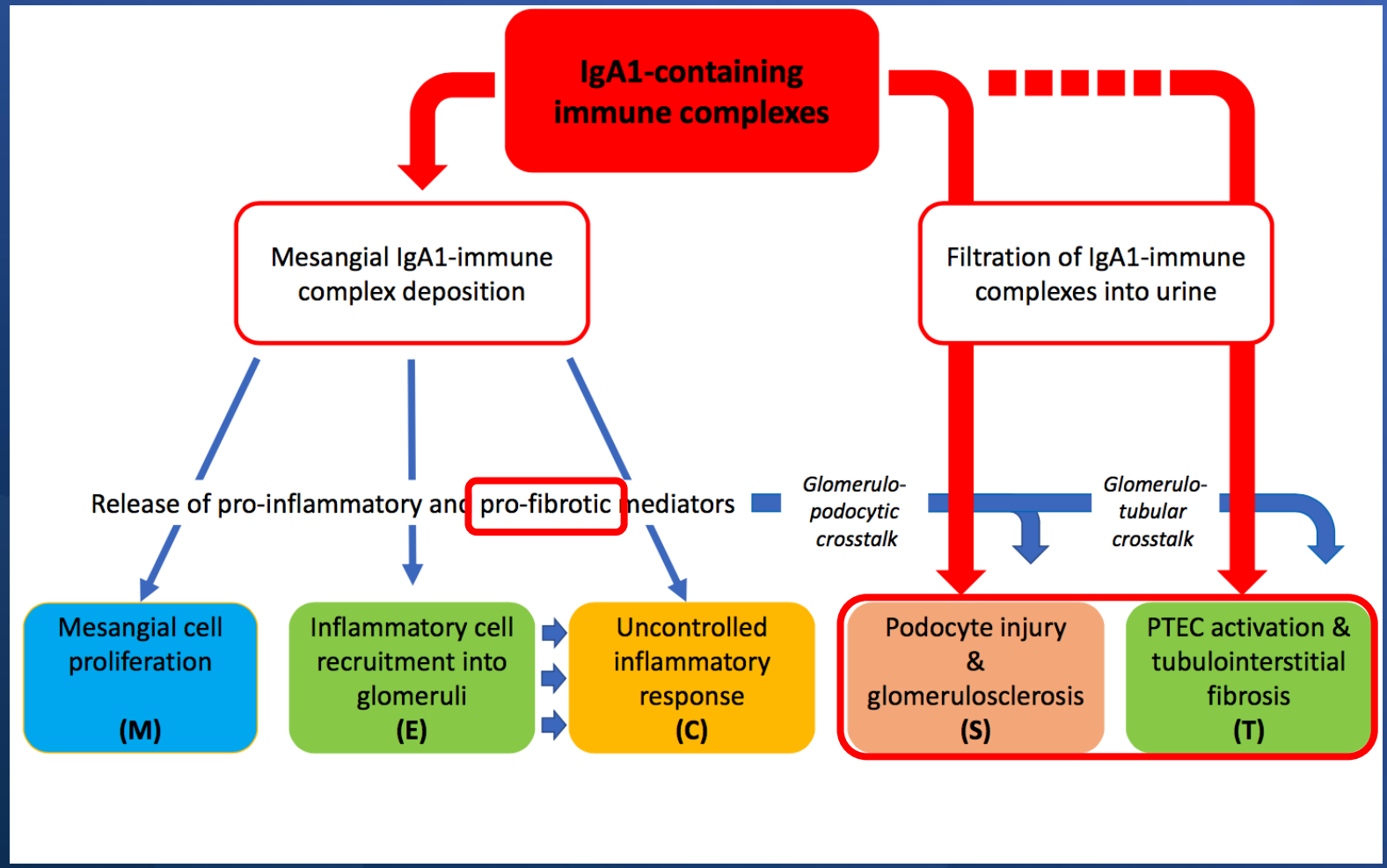
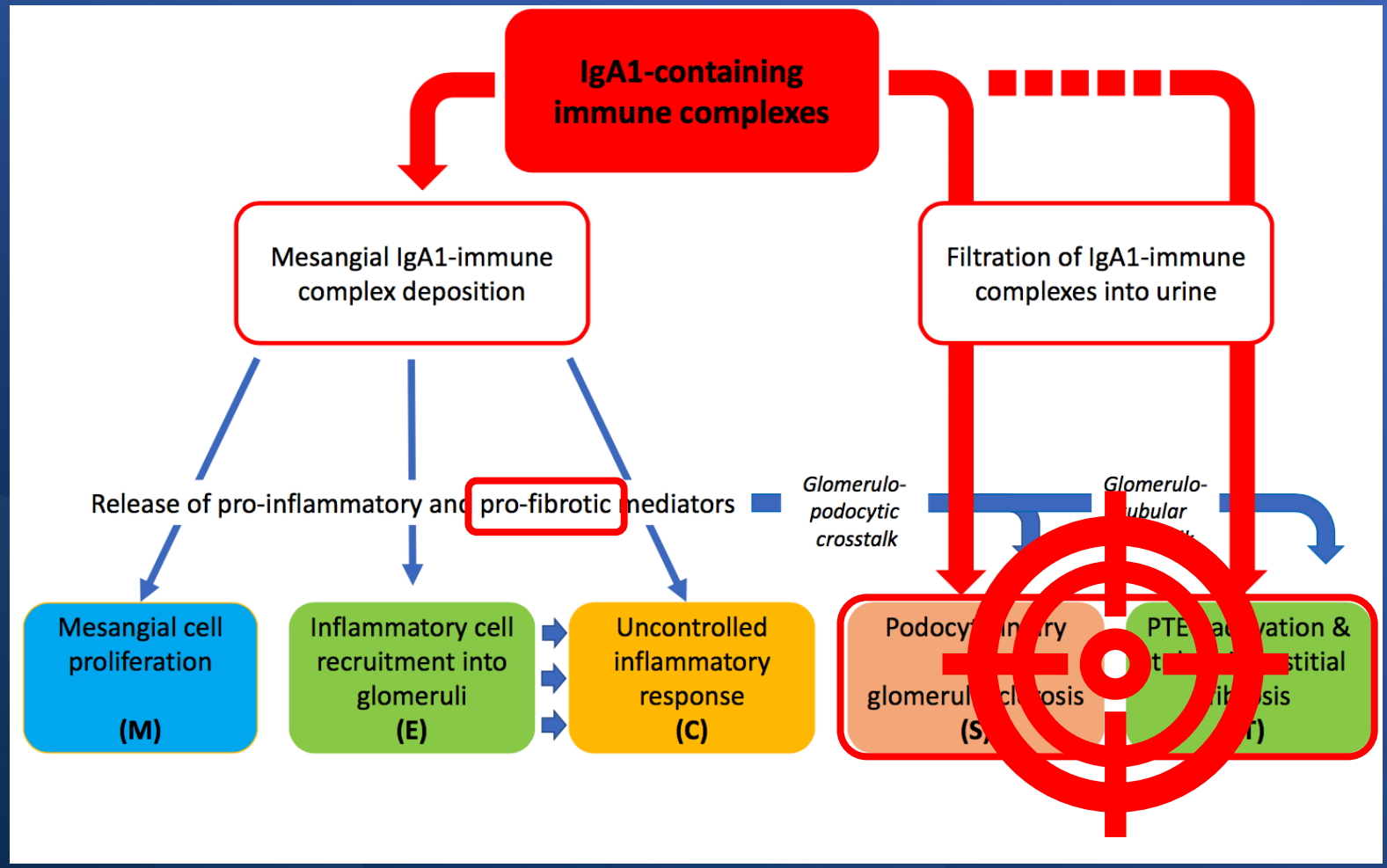
Glomerulo-podocytic crosstalk
Glomerulo-tubular crosstalk
Mesangial cell proliferation
(M)
Podocyte injury & glomerulosclerosis
(S)
PTEC activation & tubulointerstitial fibrosis
(T)


IgA1-containing immune complexes
Mesangial IgA1-immune complex deposition
Filtration of IgA1-immune complexes into urine
Release of pro-inflammatory and pro-fibrotic mediators
Glomerulo-podocytic crosstalk
Glomerulo-tubular crosstalk
Mesangial cell proliferation (M)
Inflammatory cell recruitment into glomeruli (E)
Uncontrolled inflammatory response (C)
Podocyte injury & glomerulosclerosis (S)
PTEC activation & tubulointerstitial fibrosis (T)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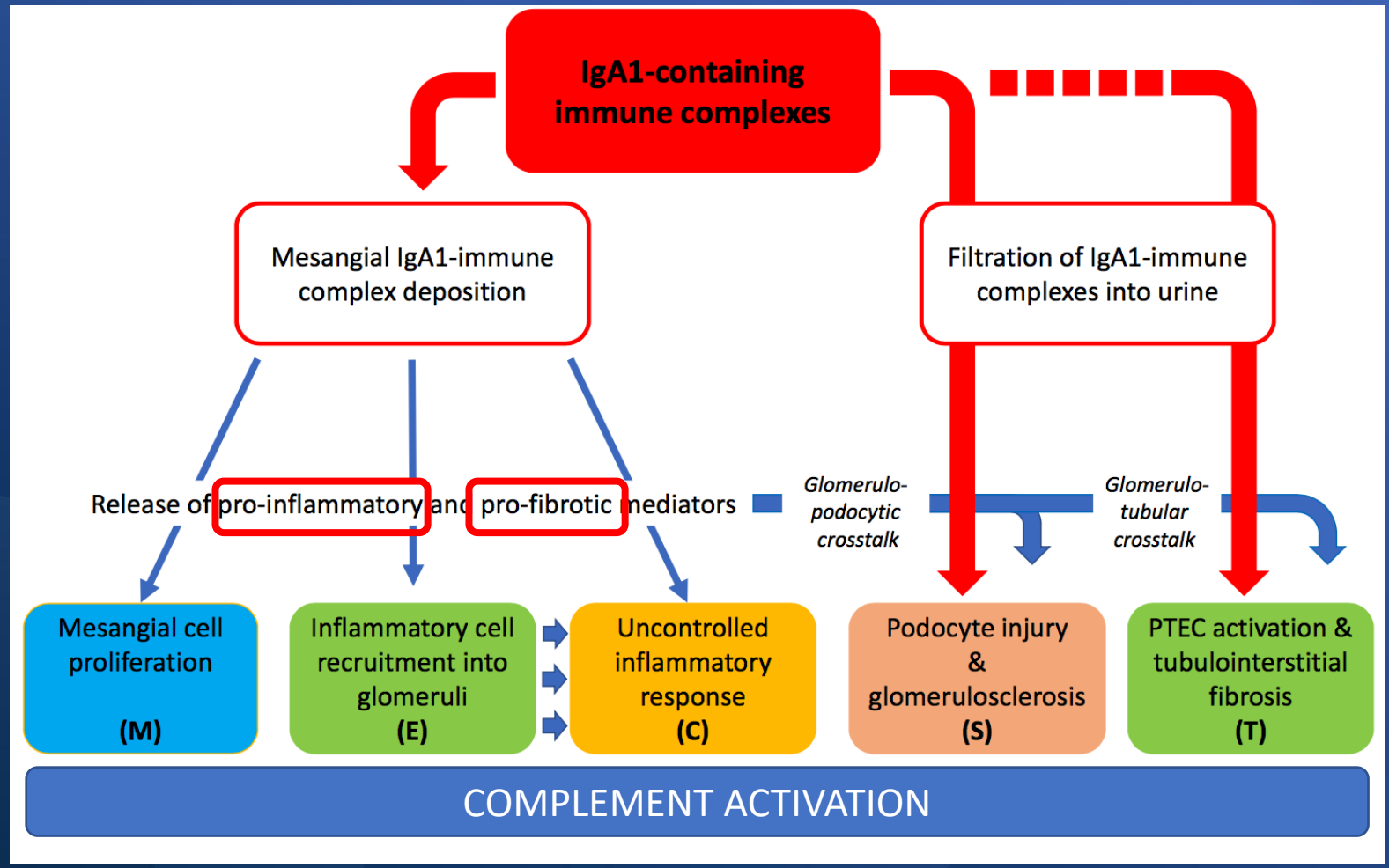
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Podocyte injury & glomerulosclerosis (S)
PTEC activation & tubulointerstitial fibrosis (T)
COMPLEMENT ACTIVATION

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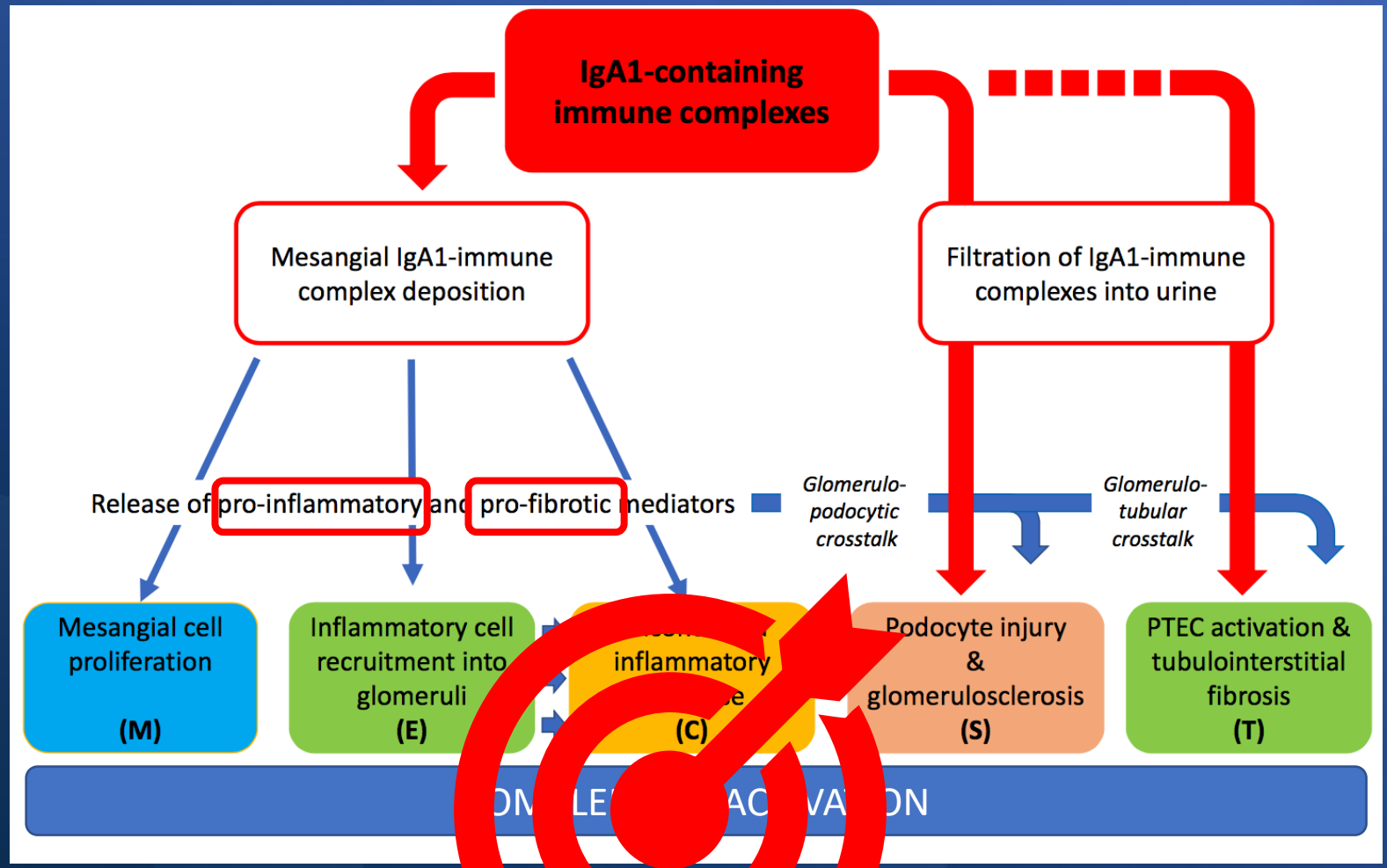


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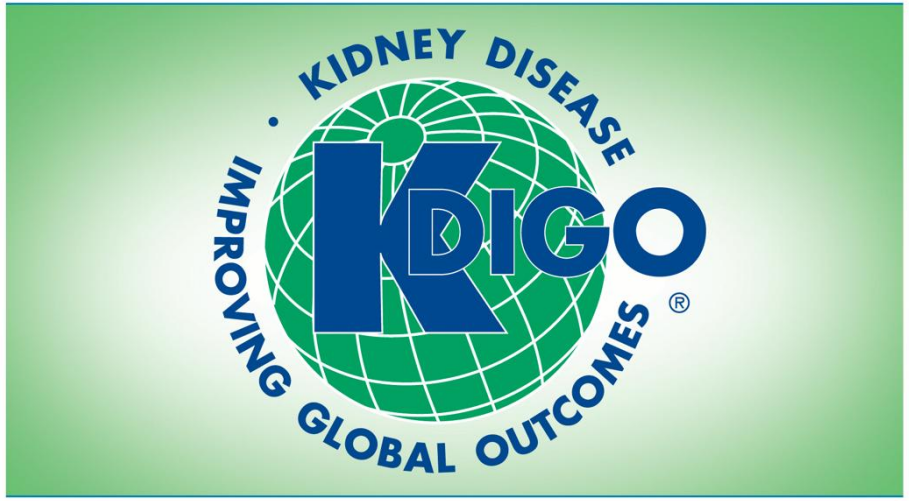

KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV)

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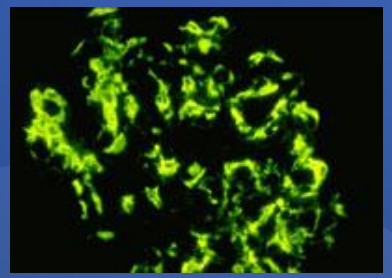

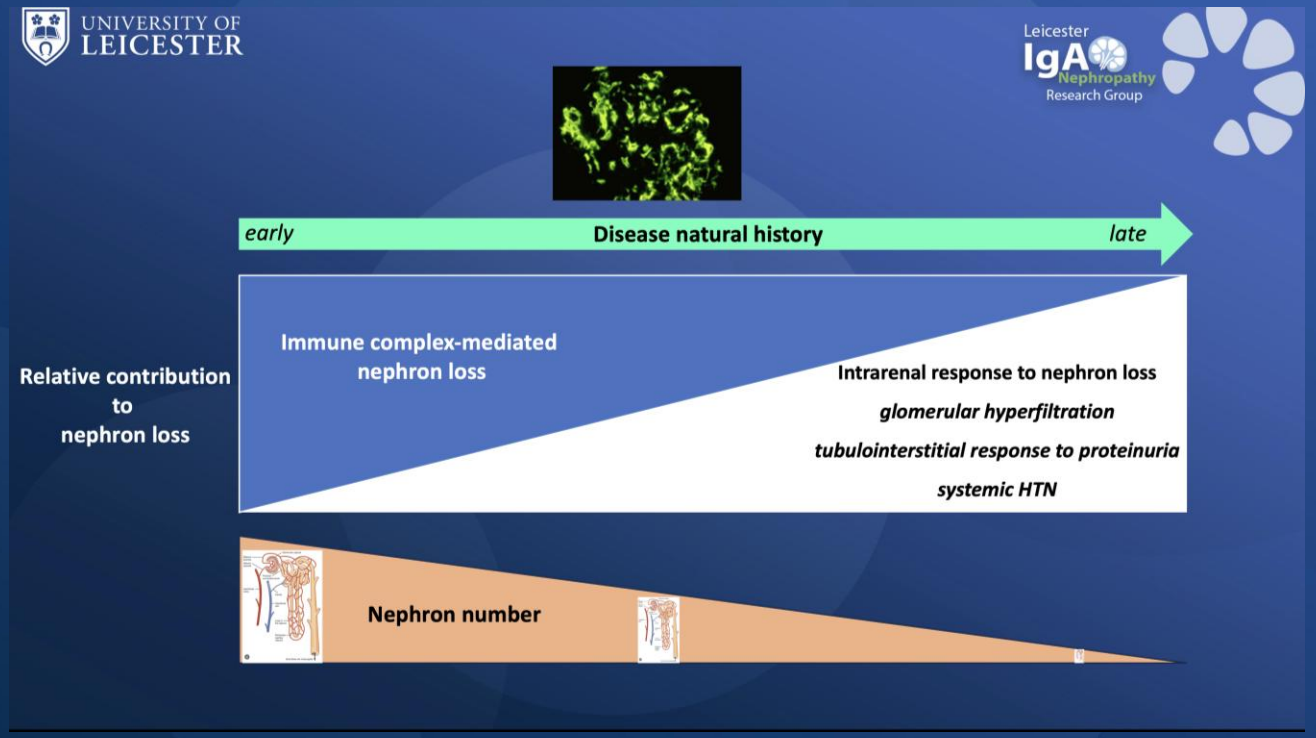

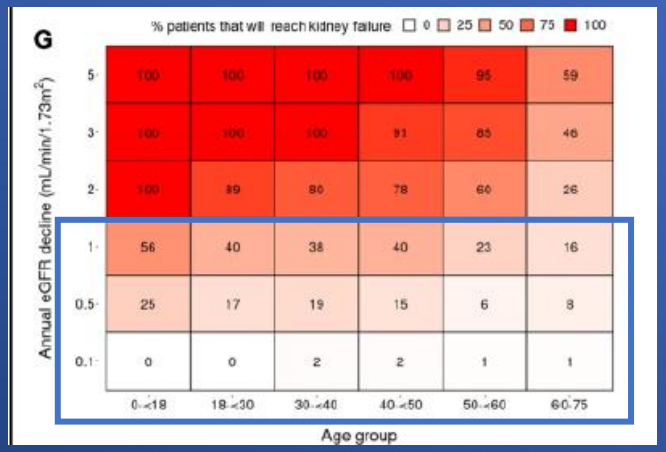

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Diagnosis of IgA nephropathy

1.2 Diagnosis

Practice Point 1.2.1: Considerations regarding the diagnosis of immunoglobulin A nephropathy (IgAN):

- IgAN can be diagnosed only with a kidney biopsy, as there are no validated serum or urine biomarkers for the diagnosis of IgAN.
- To ensure an early diagnosis and prompt treatment of IgAN, a kidney biopsy should be considered in all adults with proteinuria ≥0.5 g/d (or equivalent) in whom IgAN is a possible diagnosis and kidney biopsy is not contraindicated.
- Once a diagnosis of IgAN is made, assess for secondary causes.
- In cases of primary IgAN, determine the MEST-C (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) score according to the revised Oxford Classification.[3]

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Predicting Risk of progression in IgA nephropathy

1.3 Prognosis

Practice Point 1.3.1: Considerations regarding the prognosis of primary IgAN:

- Clinical and histologic data at the time of kidney biopsy can be used for risk stratification.
- The International IgAN Prediction Tools are a valuable resource to quantify short-term (up to 7 years from kidney biopsy) risk of progression and inform shared decision-making with patients.
  - International IgAN Prediction Tool at biopsy – Adults
  - International IgAN Prediction Tool post-biopsy – Adults
  - International IgAN Prediction Tool at biopsy – Pediatrics
  - International IgAN Prediction Tool post-biopsy – Pediatric
- The International IgAN Prediction Tools incorporate clinical information at the time of kidney biopsy or at 1 or 2 years post-biopsy (Figure 1).
- There are no validated prognostic serum or urine biomarkers for IgAN other than estimated glomerular filtration rate (eGFR) and proteinuria.

Practice Point 1.3.2: The initial assessment of the patient with IgAN is shown in Figure 2.

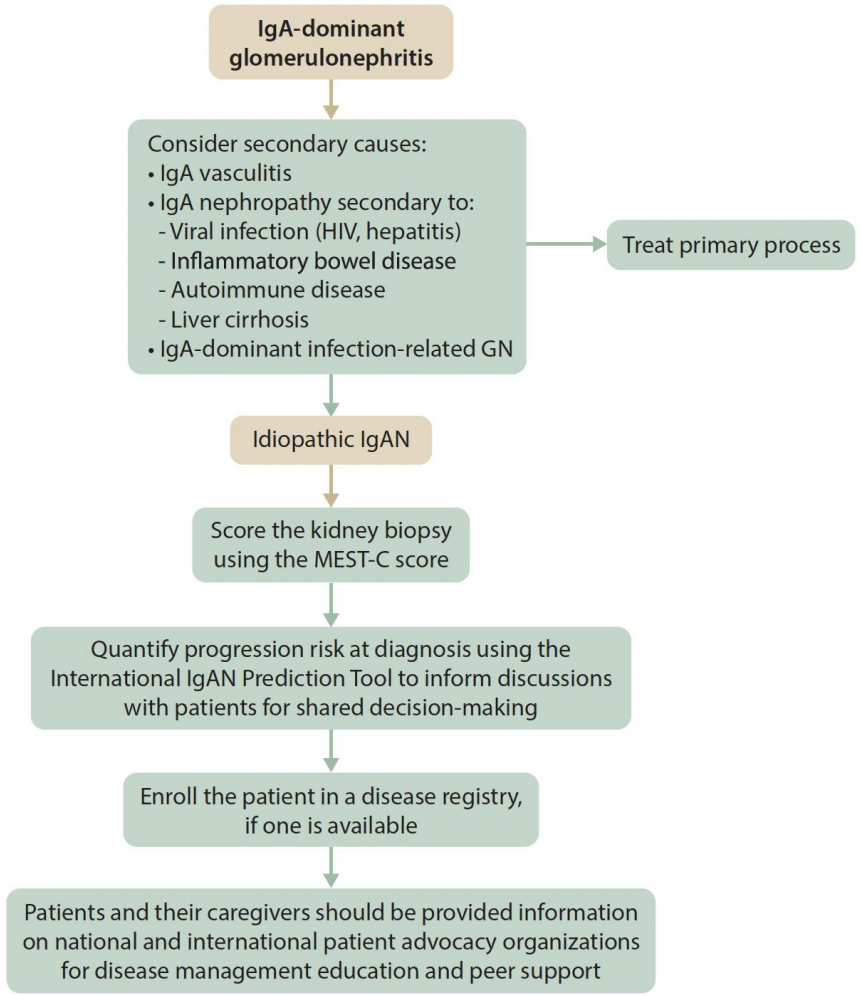

Figure 2 | Initial assessment and management of the patient with immunoglobulin A nephropathy (IgAN). GN, glomerulonephritis; HIV, human immunodeficiency virus; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

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Threshold for treatment in IgA nephropathy

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1.4 Treatment

1.4.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

Practice Point 1.4.1.1: Because patients with IgAN are at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/d (or equivalent) while on or off treatment of IgAN, treatment or additional treatment should be considered in all such cases.

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Treatment goal in IgA nephropathy

1.4.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 1.4.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to the physiological state (i.e., <1 ml/min/yr for most adults) for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at a minimum of <0.5 g/d (or equivalent), and ideally at <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring, this may not be possible and that multiple treatment strategies, including non-pharmacologic interventions, may be needed to achieve this.

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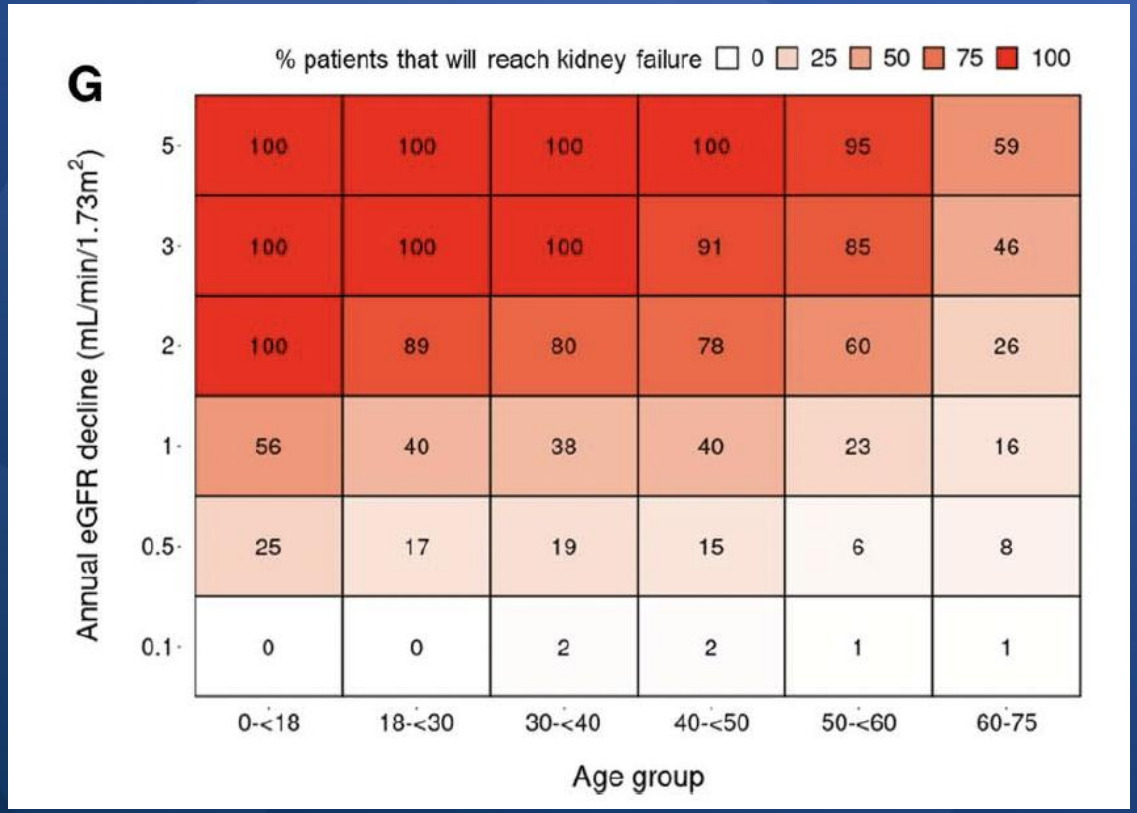

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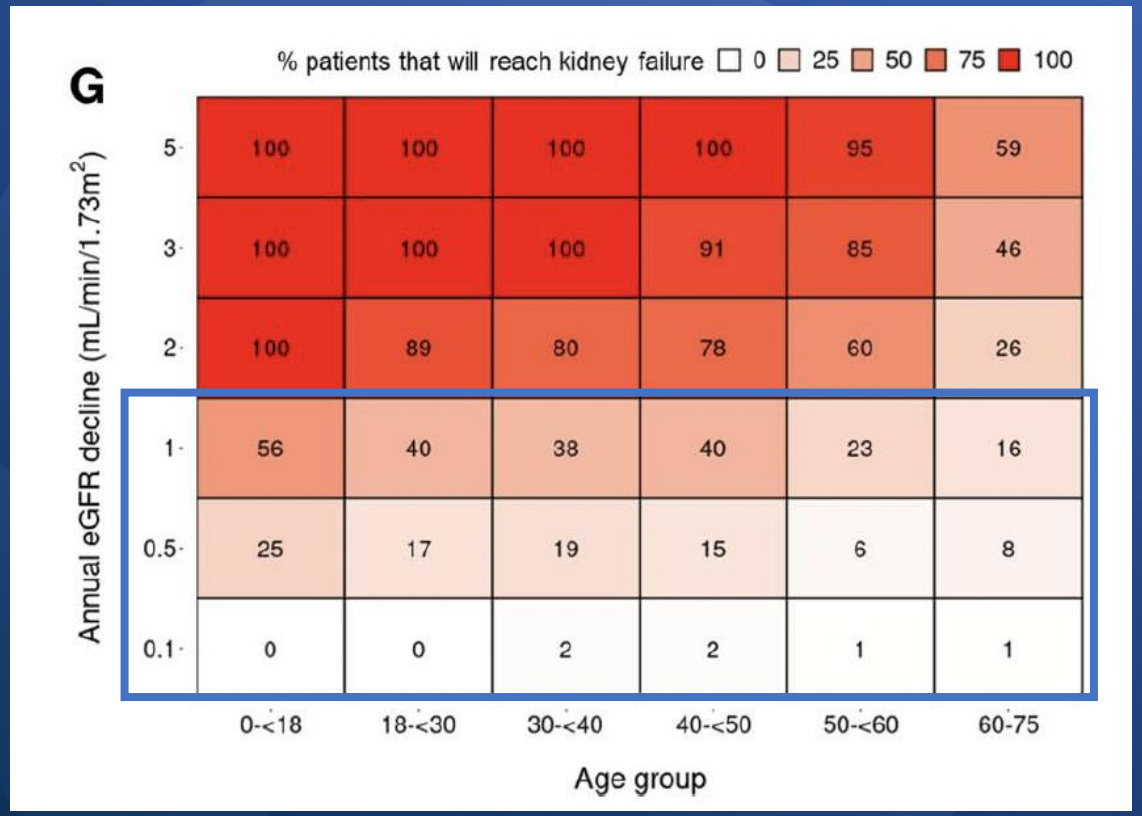

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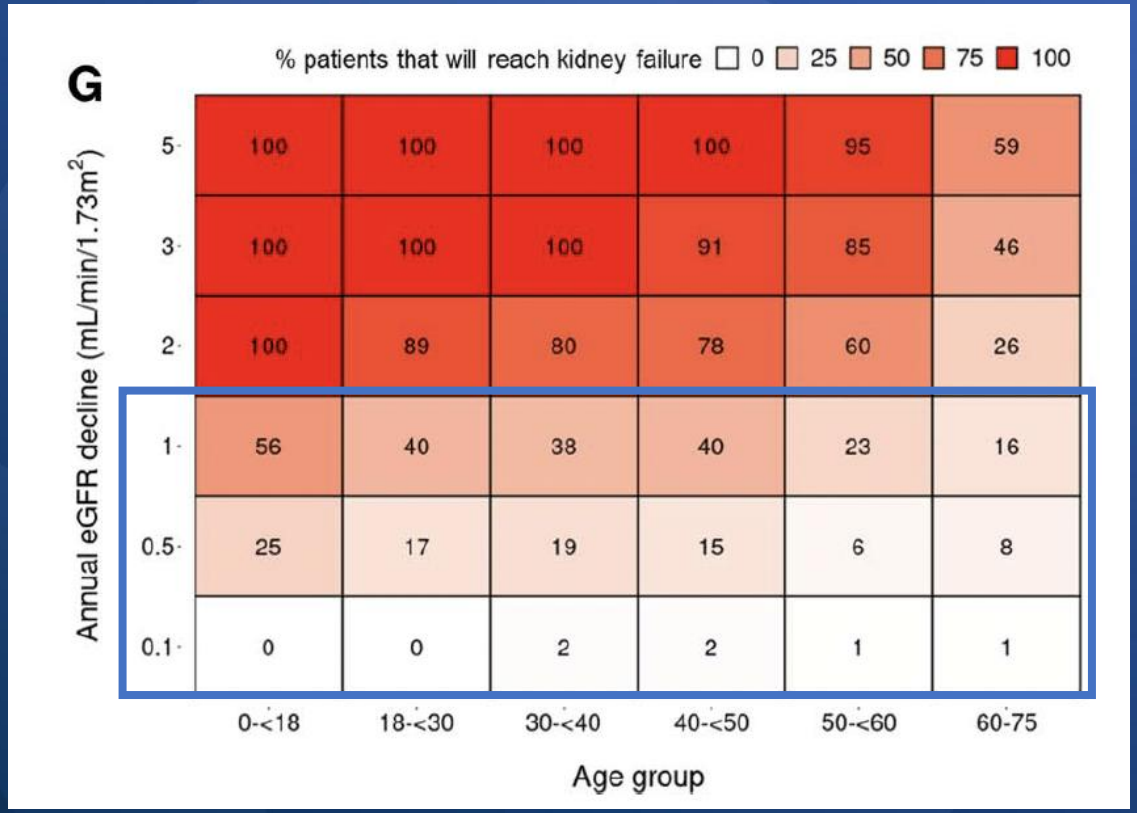
"The Future"



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Treatment of IgA nephropathy

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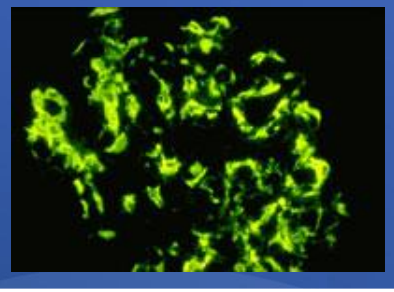

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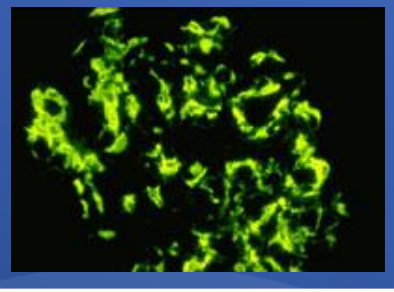

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Address immune & inflammatory drivers of continued nephron loss

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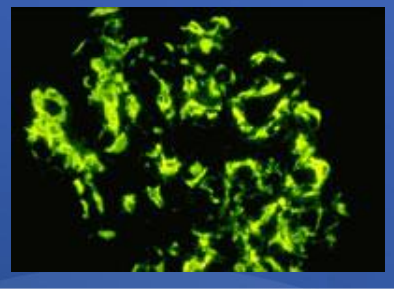

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Address immune & inflammatory drivers of continued nephron loss

Stop mesangial IgA-IC accumulation

Reduce formation of circulating IgA-IC

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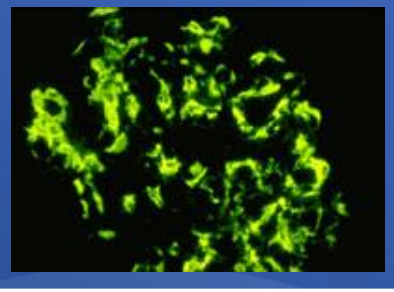

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Address immune & inflammatory drivers of continued nephron loss

Stop mesangial IgA-IC accumulation

Reduce formation of circulating IgA-IC

Stop IgA-IC mediated injury

Reduce inflammation & fibrosis

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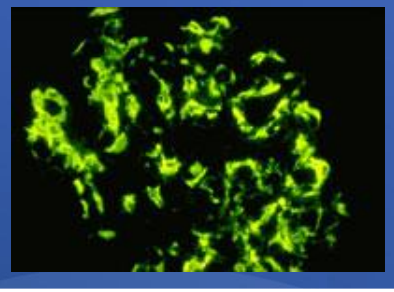

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Address immune & inflammatory drivers of continued nephron loss

Address generic CKD drivers of continued nephron loss

Stop mesangial IgA-IC accumulation

Stop IgA-IC mediated injury

Reduce formation of circulating IgA-IC

Reduce inflammation & fibrosis

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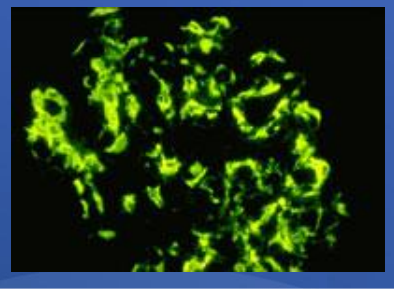

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Address immune & inflammatory drivers of continued nephron loss

Address generic CKD drivers of continued nephron loss

Cardiovascular risk reduction

Stop mesangial IgA-IC accumulation

Reduce formation of circulating IgA-IC

Stop IgA-IC mediated injury

Reduce inflammation & fibrosis

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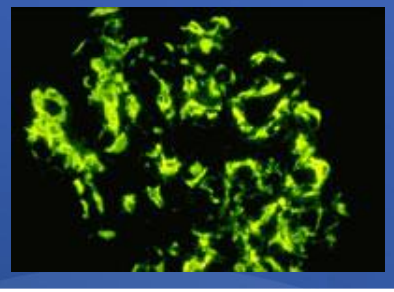

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Address immune & inflammatory drivers of continued nephron loss

IN ALL PATIENTS THESE SHOULD BE CONSIDERED SIMULTANEOUSLY

Address generic CKD drivers of continued nephron loss

Cardiovascular risk reduction

Stop mesangial IgA-IC accumulation

Reduce formation of circulating IgA-IC

Stop IgA-IC mediated injury

Reduce inflammation & fibrosis

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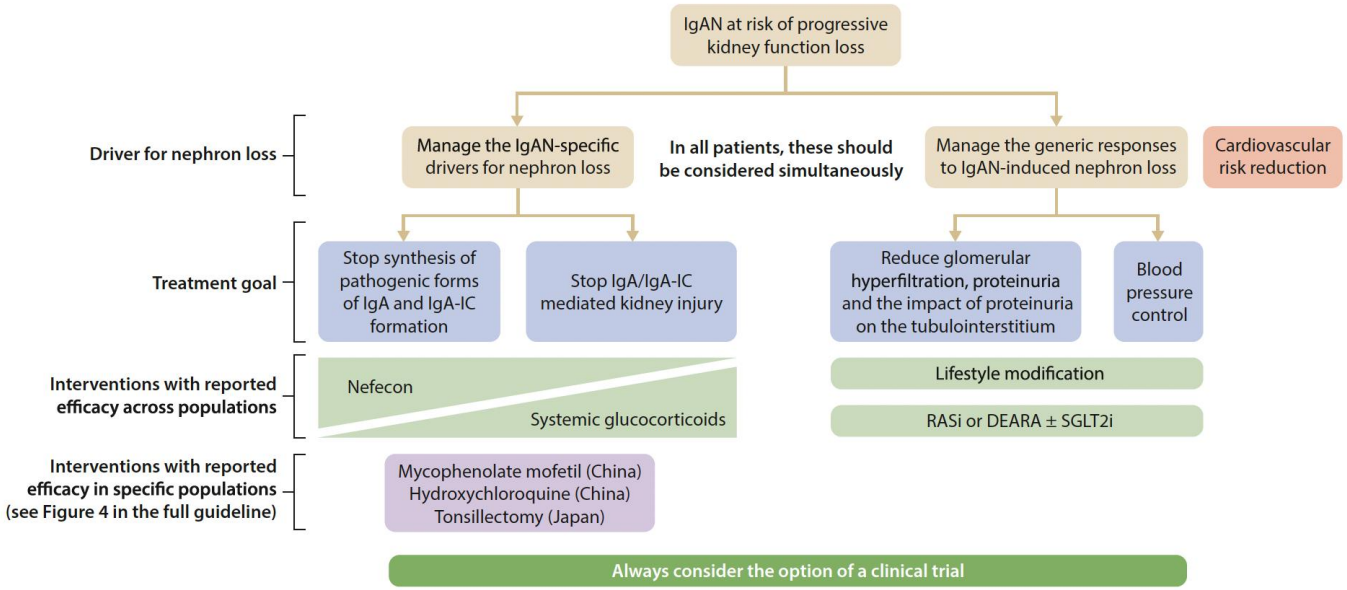

Figure 2 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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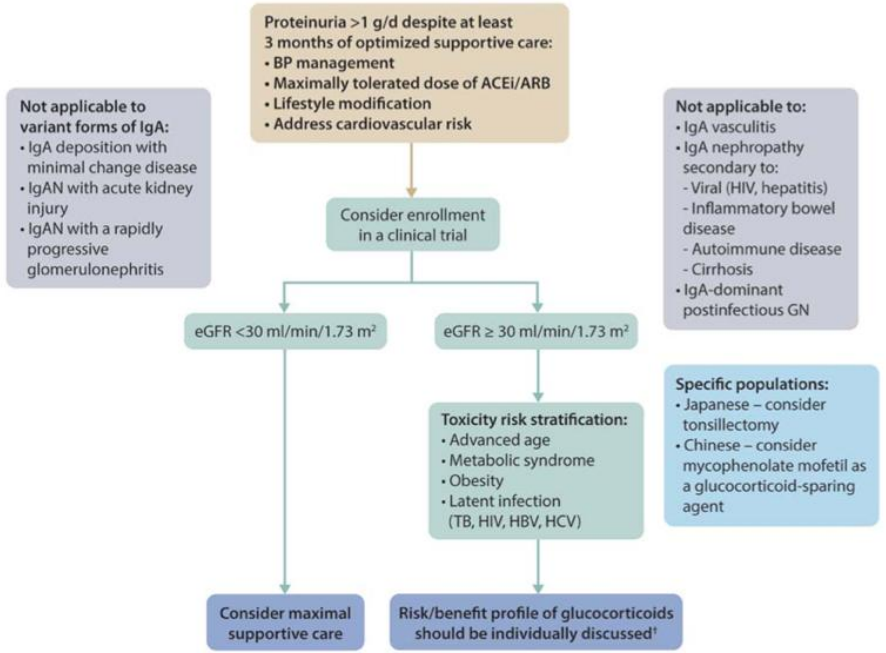

Figure 24 | Management of patients with IgAN who remain at high risk for progression after maximal supportive care. *IgAN with rapidly progressive glomerulonephritis is covered in Practice Point 2.4.3. †The TESTING study[109] shows early evidence of efficacy in patients who had marked proteinuria (2.4 g/d average) at the expense of treatment-associated morbidity and mortality. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure, eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; TB, tuberculosis.

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

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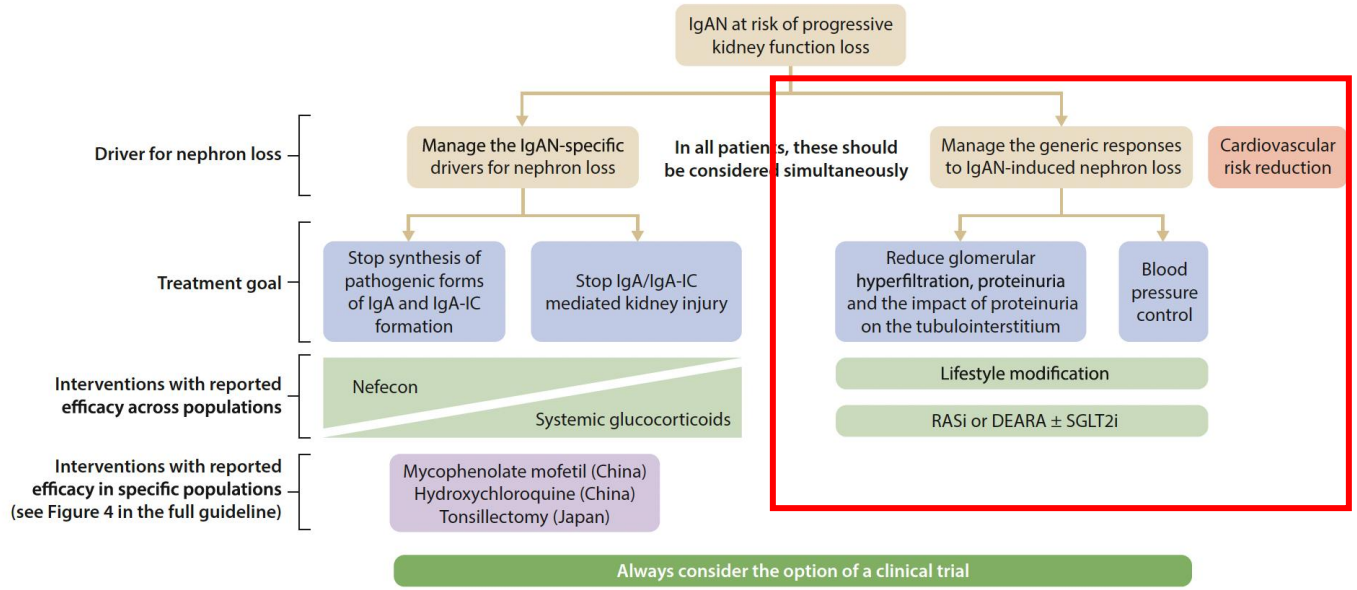

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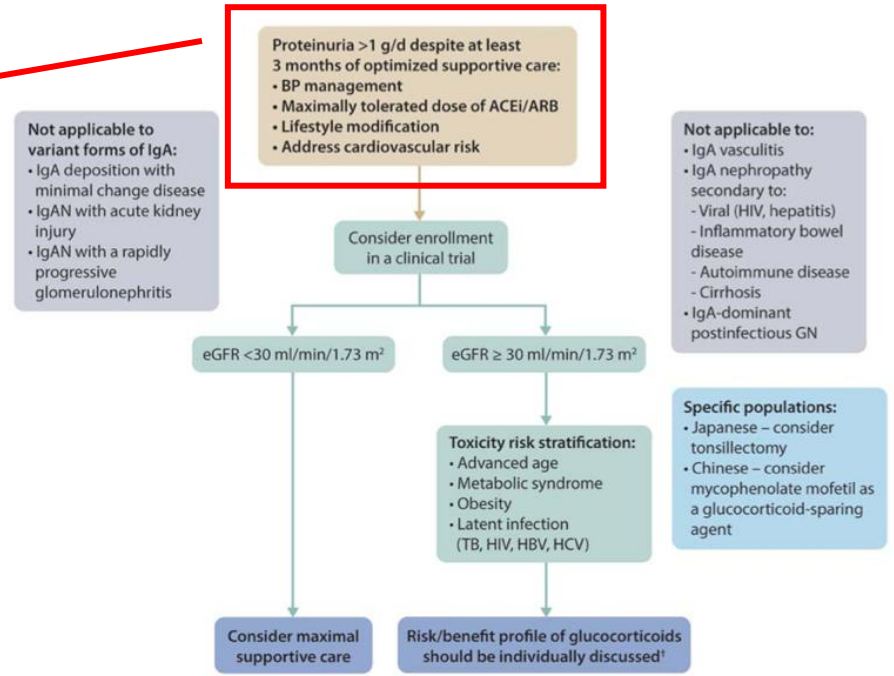

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KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

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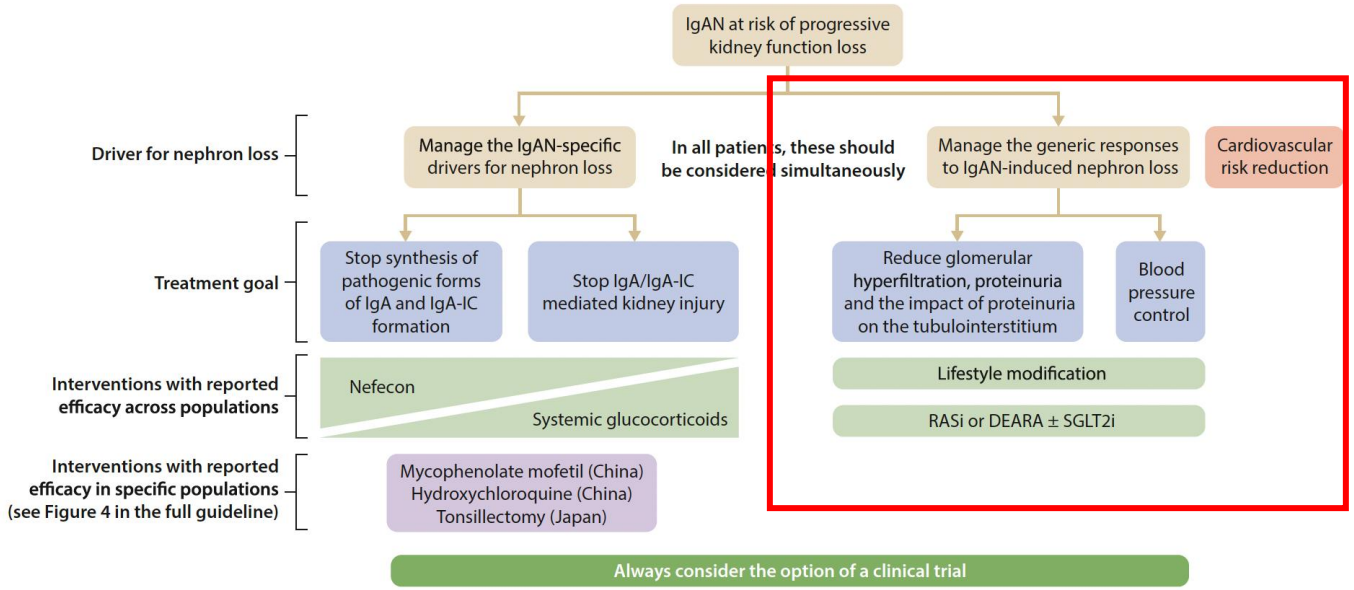

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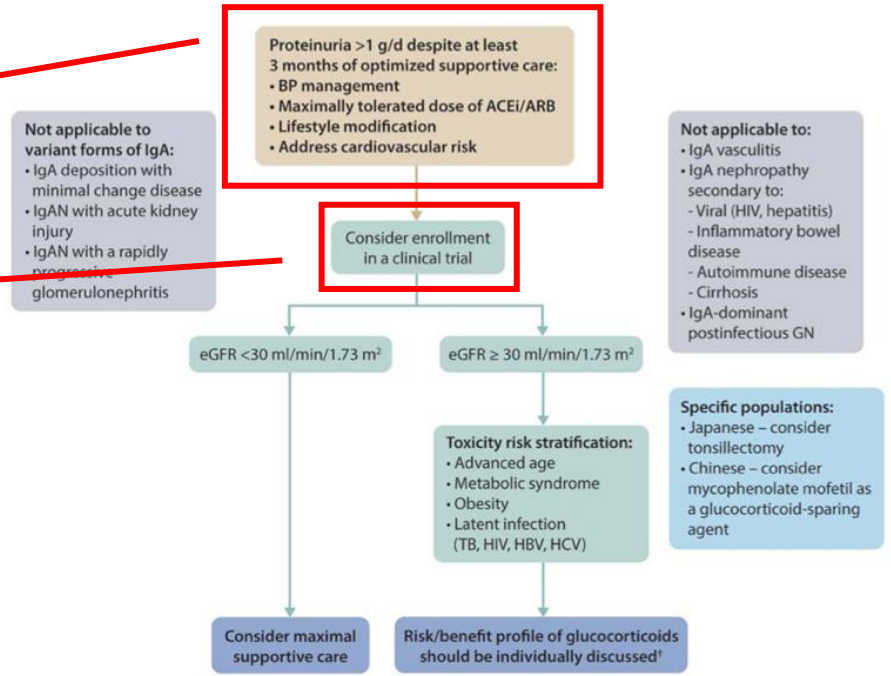

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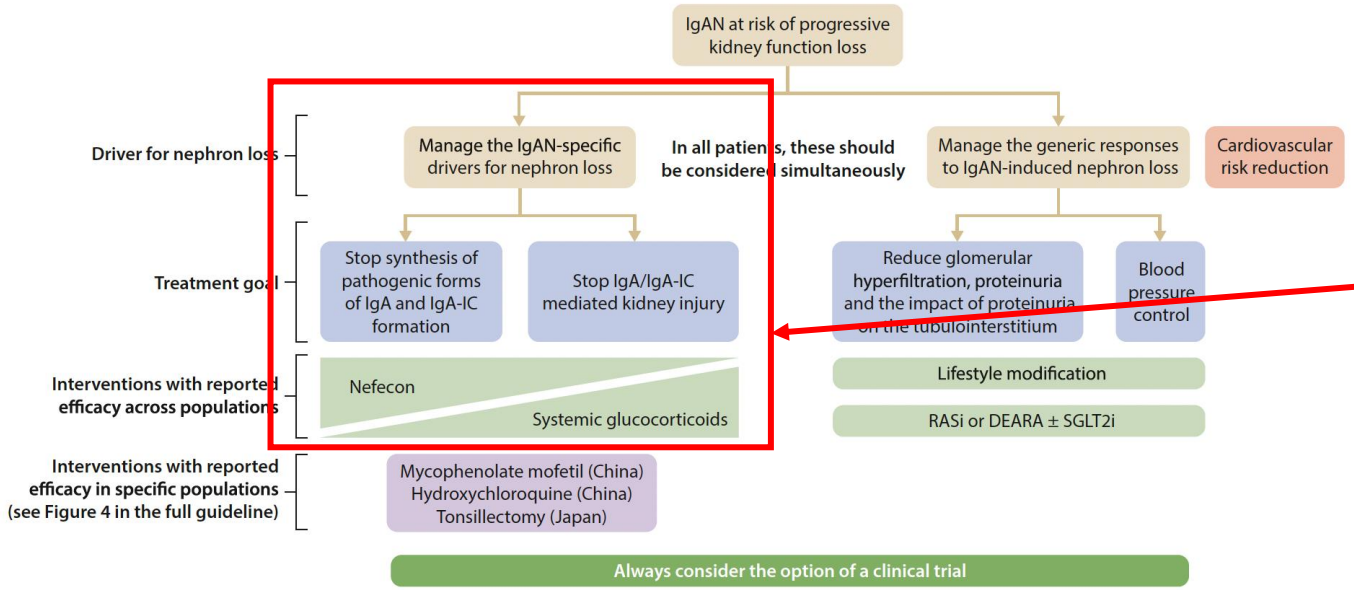

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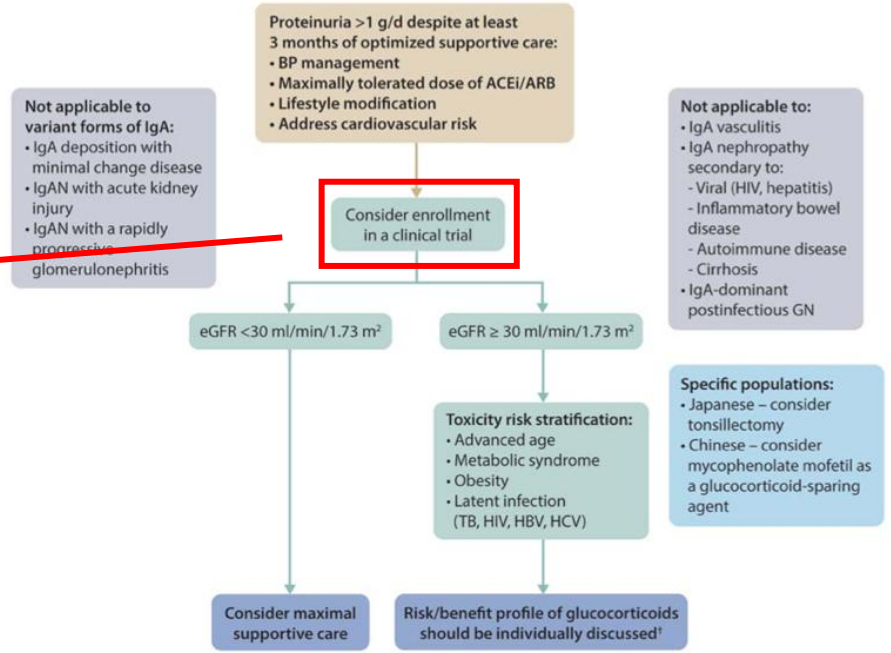

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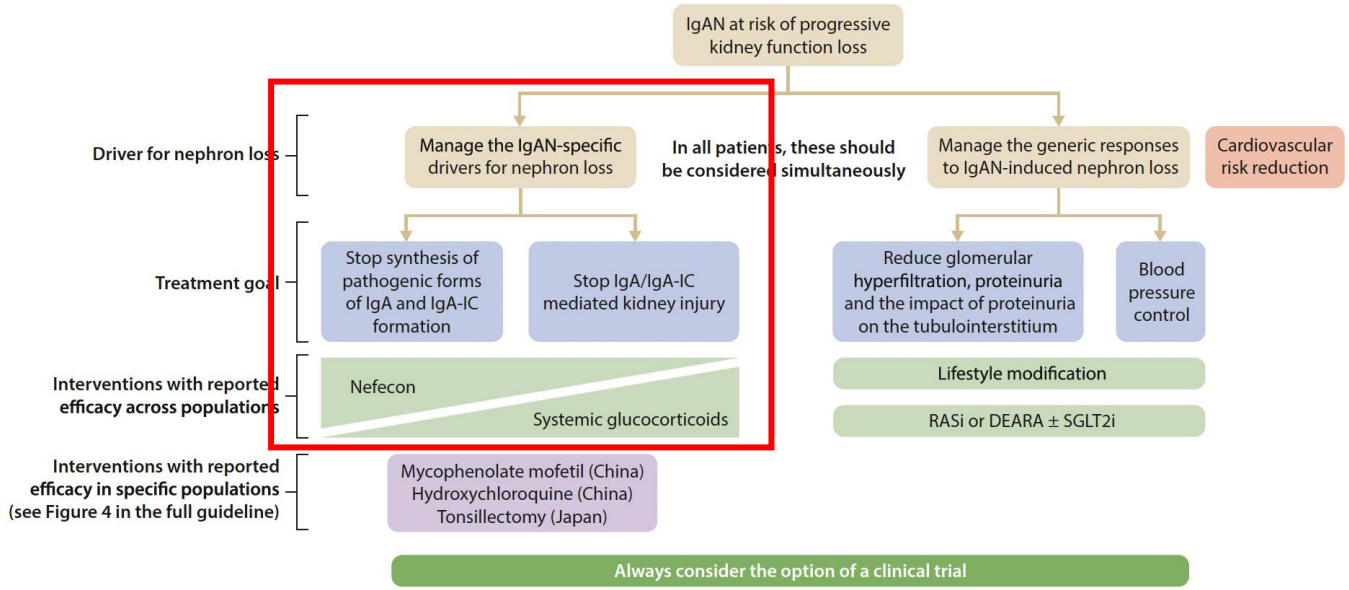
KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO



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1.4.3 Managing the IgAN-specific drivers of nephron loss

Recommendation 1.4.3.1: We suggest treatment with a 9-month course of Nefecon for patients who are at risk of progressive loss of kidney function with IgAN *(2B)*.

Practice Point 1.4.3.1: Factors to consider before using Nefecon in patients with IgAN:

- A 9-month treatment course of Nefecon, a targeted-release formulation of budesonide, may not result in a sustained clinical response in terms of proteinuria reduction or eGFR stabilization.
- Data on the safety and efficacy of additional courses of Nefecon are awaited.
- Nefecon's approval status, labeled indication, and availability vary globally.

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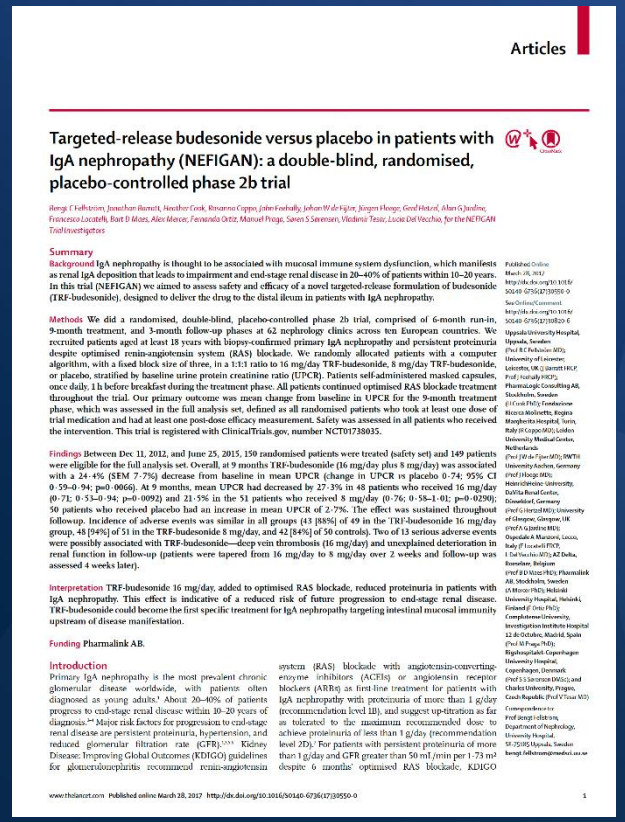

Articles

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

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Summary

Background IgA nephropathy is thought to be associated with mucosal immune system dysfunction, which manifests as renal IgA deposition that leads to impairment and end-stage renal disease in 20–40% of patients within 10–20 years. In this trial (NEFIGAN) we aimed to assess safety and efficacy of a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver the drug to the distal ileum in patients with IgA nephropathy.

Methods We did a randomised, double-blind, placebo-controlled phase 2b trial, comprised of 6-month run-in, 9-month treatment, and 3-month follow-up phases at 62 nephrology clinics across ten European countries. We recruited patients aged at least 18 years with biopsy-confirmed primary IgA nephropathy and persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. We randomly allocated patients with a computer algorithm, with a fixed block size of three, in a 1:3:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo, stratified by baseline urine protein creatinine ratio (UPCR). Patients self-administered masked capsules, once daily, 1 h before breakfast during the treatment phase. All patients continued optimised RAS blockade treatment throughout the trial. Our primary outcome was mean change from baseline in UPCR for the 9-month treatment phase, which was assessed in the full analysis set, defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement. Safety was assessed in all patients who received the intervention. This trial is registered with ClinicalTrials.gov, number NCT01738035.

Findings Between Dec 11, 2012, and June 25, 2015, 150 randomised patients were treated (safety set) and 149 patients were eligible for the full analysis set. Overall, at 9 months TRF-budesonide (16 mg/day plus 8 mg/day) was associated with a 24·4% (SEM 7·7%) decrease from baseline in mean UPCR (change in UPCR vs placebo 0·74; 95% CI 0·59–0·94; p=0·0066). At 9 months, mean UPCR had decreased by 27·3% in 48 patients who received 16 mg/day (0·71; 0·53–0·94; p=0·0092) and 21·5% in the 51 patients who received 8 mg/day (0·76; 0·58–1·01; p=0·0250); 50 patients who received placebo had an increase in mean UPCR of 2·7%. The effect was sustained throughout follow-up. Incidence of adverse events was similar in all groups (43 [88%] of 49 in the TRF-budesonide 16 mg/day group, 48 [94%] of 51 in the TRF-budesonide 8 mg/day, and 42 [84%] of 50 controls). Two of 13 serious adverse events were possibly associated with TRF-budesonide—deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up (patients were tapered from 16 mg/day to 8 mg/day over 2 weeks and follow-up was assessed 4 weeks later).

Interpretation TRF-budesonide 16 mg/day, added to optimised RAS blockade, reduced proteinuria in patients with IgA nephropathy. This effect is indicative of a reduced risk of future progression to end-stage renal disease. TRF-budesonide could become the first specific treatment for IgA nephropathy targeting intestinal mucosal immunity upstream of disease manifestation.

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Introduction

Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.[1] About 20–40% of patients progress to end-stage renal disease within 10–20 years of diagnosis.[2–4] Major risk factors for progression to end-stage renal disease are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).[3,5,6] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerulonephritis recommend renin-angiotensin system (RAS) blockade with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for patients with IgA nephropathy with proteinuria of more than 1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated to the maximum recommended dose to achieve proteinuria of less than 1 g/day (recommendation level 2D).[7] For patients with persistent proteinuria of more than 1 g/day and GFR greater than 50 ml/min per 1·73 m² despite 6 months' optimised RAS blockade, KDIGO

Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

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The therapeutic potential of a novel, targeted-release formulation of oral budesonide (Nefecon) for the treatment of IgA nephropathy (IgAN) was first demonstrated by the phase 2b NEFIGAN trial. To verify these findings, the phase 3 NefigArd trial tested the efficacy and safety of nine months of treatment with Nefecon (16 mg/d) versus placebo in adult patients with primary IgAN at risk of progressing to kidney failure (ClinicalTrials.gov: NCT03643965). NeflgArd was a multicenter, randomized, double-blind, placebo-controlled two-part trial. In Part A, 199 patients with IgAN were treated with Nefecon or placebo for nine months and observed for an additional three months. The primary endpoint for Part A was 24-hour urine protein-to-creatinine ratio (UPCR) after nine months. Secondary efficacy outcomes evaluated included estimated glomerular filtration rate (eGFR) at nine and 12 months and the UPCR at 12 months. At nine months, UPCR was 27% lower in the Nefecon group compared with placebo, along with a benefit in eGFR preservation corresponding to a 3.87 ml/min/1.73 m² difference versus placebo (both significant). Nefecon was well-tolerated, and treatment-emergent adverse events were mostly mild to moderate in severity and reversible. Part B is ongoing and will be reported on later. Thus, NeflgArd is the first phase 3 IgA nephropathy trial to show clinically important improvements in UPCR and eGFR and confirms the findings from the phase 2b NEFIGAN study.

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KEYWORDS: glomerular disease; glucocorticoids; gut-associated lymphoid tissue; IgA nephropathy

IgA nephropathy (IgAN) is a mesangioproliferative glomerulonephritis, characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1)–containing immune complexes in the glomerular mesangium.[1] These immune complexes initiate a cascade of inflammatory events, eventually causing irreversible glomerulosclerosis and tubulointerstitial inflammation and fibrosis with loss of kidney function; in patients with progressive disease (i.e., proteinuria >1 g/24 h), the risk of kidney failure may be up to 50% within 20 years.[2–5] At the time the present study was initiated, no IgAN-specific treatments were available, and guidelines recommended goal-directed supportive care comprising lifestyle change, optimal blood pressure control, and renin-angiotensin system (RAS) blockade to reduce proteinuria.[6–8]

There is accumulating evidence for the gut mucosal immune system and mucosal-derived Gd-IgA1 in the pathogenesis of primary IgAN. Peyer's patches are aggregations of lymphoid follicles, located in the mucosal layer of the intestine, and concentrated in the ileum. They are part of the gut-associated lymphoid system and serve as antigen sampling

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Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NeflgArd): 2-year results from a randomised phase 3 trial

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Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NeflgArd trial of Nefecon in patients with IgA nephropathy.

Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

Findings Patients were recruited to the NeflgArd trial between Sept 5, 2018, and Jan 20, 2021, with 364 patients (182 per treatment group) randomly assigned in the full analysis set. 240 (66%) patients were men and 124 (34%) were women, and 275 (76%) identified as White. The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min per 1·73 m² [95% CI 3·24 to 7·38]; p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7·52 mL/min per 1·73 m² (−8·83 to −6·18) reported with placebo. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] patients, *vs* placebo, seven [4%] patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%]), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]). No treatment-related deaths were reported.

Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

Funding Calliditas Therapeutics.

Introduction

IgA nephropathy is a chronic immune-mediated kidney disease characterised by IgA deposition in the glomeruli.[1] IgA nephropathy is the most common primary glomerular disease globally and has serious consequences, including reduced life expectancy; most patients with IgA nephropathy are expected to develop kidney failure, with up to 50% doing so within 20 years of presentation.[1,2] Therefore, IgA nephropathy places a substantial burden on patients and health-care services worldwide. With no cure for IgA nephropathy, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2021, recommend providing optimised supportive care (blood pressure management, lifestyle modification, maximally tolerated renin-angiotensin system [RAS] inhibition to reduce proteinuria, and addressing cardiovascular risk).[3] After supportive care, patients who remain at high risk for progressive chronic kidney disease should be considered for a clinical trial, or for systemic glucocorticoids (if they

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Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial

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KEYWORDS: chronic kidney disease; complement; cytokines; glomerulus; IgA nephropathy; proteinuria

Nefecon is the first approved treatment for patients with immunoglobulin A nephropathy (IgAN) at high risk of progression to kidney failure (accelerated approval: US Food and Drug Administration; conditional approval: European Medicines Agency).[1–3] Nefecon delivers budesonide, in a targeted formulation, to the gut-associated lymphoid tissue (GALT) of the ileum directly addressing immune dysregulation within this Peyer's patches–rich area of the GALT and downregulating the local production of the polymeric poorly O-galactosylated form of IgA1 or galactose-deficient IgA1 (Gd-IgA1) and generation of pathogenic IgA-containing immune complexes (IgA-IC).[4] The aim of the current analysis is to explore the biochemical pathways through which Nefecon exerted its effects in patients treated in the NEFIGAN study.

METHODS

NEFIGAN (ClinicalTrials.gov: NCT01738035) was a randomized, double-blind, placebo-controlled, phase 2b trial to assess the safety and efficacy of Nefecon in patients (≥18 years) with IgAN and overt proteinuria despite optimized renin-angiotensin-aldosterone system blockade therapy.[5] Patients (n = 150) were stratified according to the baseline urine protein–creatinine ratio (≥0·8 g/g and >0·8 g/g) and were randomized (1:1:1) to Nefecon 8 mg/d, Nefecon 16 mg/d, or placebo. After a 6-month run-in phase, patients underwent a 9-month treatment phase followed by a 3-month follow-up phase. Blood and urine samples were collected during the trial and exploratory analyses of a range of IgAN related biomarkers were conducted, using in-house enzyme-linked immunosorbent assays, commercial enzyme-linked immunosorbent assay duo kits, and multiplex immunoassays. A full description of the methods is provided in Supplementary Methods. All ELISAs are listed in Supplementary Table S1, and the Luminex assays used for the biomarker analyses are shown in Supplementary Table S2.

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RESULTS

Patient demographics and baseline characteristics are given in Supplementary Table S3.[5] Changes from baseline in multiple biomarkers were observed at 9 months, as described below,

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158 (87%) of 182 patients in the Nefecon group and 165 (91%) of 182 in the placebo group received 9 months of randomised treatment. Compliance with study treatment was high (171 [94%] patients in each treatment group took at least 80% of the total capsules). The overall rate of study completion was high and similar in both

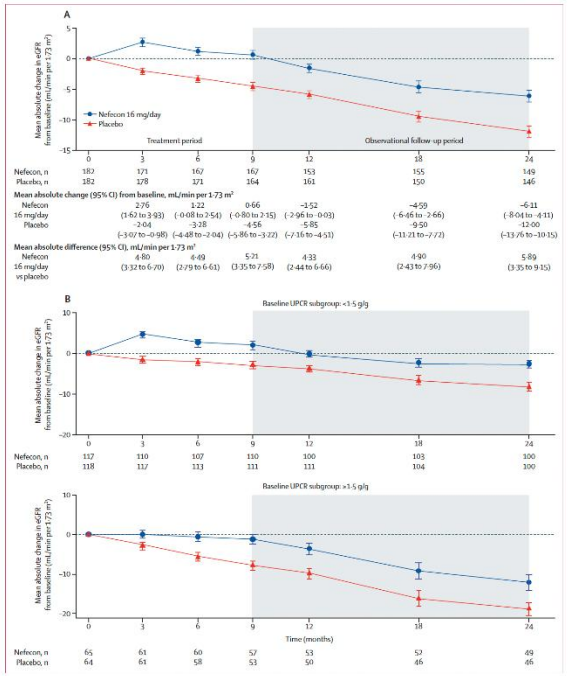

Figure 1: **Mean absolute change in eGFR from baseline to 24 months (full analysis set)**
All patients (A) and patients stratified according to baseline UPCR, <1·5 g/g and ≥1·5 g/g (B). Estimated mean absolute change (and standard error) was calculated from multiple-imputation robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months, and transformed back into the original scale. eGFR was calculated by the central laboratory with the Chronic Kidney Disease Epidemiology Collaboration formula.[16] Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. eGFR=estimated glomerular filtration rate. UPCR=urine protein-creatinine ratio.

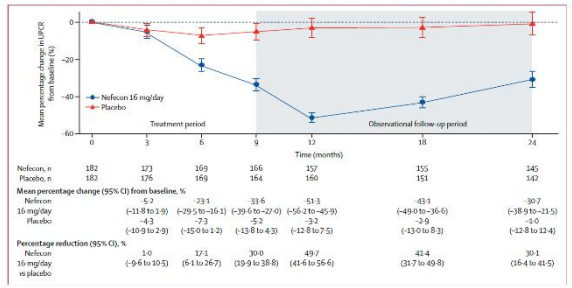

Figure 2: **Mean percentage change in UPCR (g/g) from baseline to 24 months (full analysis set)**
Estimated geometric mean percentage change (and standard error) was calculated from a mixed-effects model for repeated measures of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months. Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. The corresponding percentage reduction and confidence interval was derived from (1− ratio of geometric least squares means) × 100. UPCR=urine protein-creatinine ratio.

12 months, with a reduction in UPCR of 49·7% (41·6–56·6).

Results from the UACR analysis were consistent with those for UPCR, with the Nefecon group showing a 46·3% (36·5–54·5) reduction in time-averaged UACR between 12 and 24 months compared with the placebo group (p<0·0001; appendix p 11). The proportion of patients without microhaematuria during the observational follow-up period was significantly higher in the Nefecon group than in the placebo group (in patients with two or more urine dipstick results during the observational period, 94 [59%] of 158 *vs* 59 [39%] of 152; odds ratio for Nefecon *vs* placebo 2·5 [95% CI 1·6–4·1], p=0·0001; appendix p 12). Results of other secondary efficacy analyses were generally supportive of the overall beneficial effect of Nefecon treatment (appendix pp 13–14).

During the 9-month treatment period, Nefecon 16 mg/day was well tolerated, with a safety profile as expected for a locally acting oral budesonide product. Discontinuations due to treatment-emergent adverse events occurred in 17 (9%) of 182 patients in the Nefecon group and three (2%) of 182 in the placebo group (table 3). Treatment-emergent serious adverse events were reported in 18 (10%) patients in the Nefecon group and nine (5%) patients in the placebo group, with most considered unrelated to study treatment (table 3), and no discernible patterns in terms of body system or organ (appendix p 15). During the 15-month observational follow-up, the incidence of treatment-emergent adverse events and treatment-emergent serious adverse events was similar between the groups.

One death due to SARS-CoV-2 infection was reported during Nefecon treatment in a patient with several risk factors for COVID-19 mortality, and another patient treated with Nefecon died from a cerebral haemorrhage 10·5 months after their last dose. Neither death was considered to be related to study treatment. No treatment-emergent adverse events leading to death were reported in the placebo group.

The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] of 182 patients *vs* placebo, seven [4%] of 182 patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%] patients), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]); appendix p 15). These were generally non-serious adverse events and were of mild severity, and reversible during or after treatment. In the Nefecon group, two patients had hypertension events, and one patient had both peripheral and face oedema events, all of which were classed as serious; a fourth patient had a peripheral oedema event that was graded as severe (appendix p 15). During the observational follow-up, frequencies of the most commonly reported treatment-emergent adverse events were similar in both treatment groups, including of SARS-CoV-2 infection, which was the most frequently reported event (26 [15%] of 175 patients in the Nefecon group and 30 [17%] of 174 in the placebo group), among patients who had a study visit during the observational follow-up; appendix p 16).

The incidence of infections during treatment was similar between treatment groups (63 [35%] of 182 patients

Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial

Richard J Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, on behalf of the NefIgArd trial investigators

Summary

Background IgA nephropathy is a chronic immune-mediated kidney disease and a major cause of kidney failure worldwide. The gut mucosal immune system is implicated in its pathogenesis, and Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. We present findings from the 2-year, phase 3 NefIgArd trial of Nefecon in patients with IgA nephropathy.

Methods In this phase 3, multicentre, randomised, double-blind, placebo-controlled trial, adult patients (aged ≥18 years) with primary IgA nephropathy, estimated glomerular filtration rate (eGFR) 35–90 mL/min per 1·73 m², and persistent proteinuria (urine protein–creatinine ratio ≥0·8 g/g or proteinuria ≥1 g/24 h) despite optimised renin-angiotensin system blockade were enrolled at 132 hospital-based clinical sites in 20 countries worldwide. Patients were randomly assigned (1:1) to receive 16 mg/day oral capsules of Nefecon or matching placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Randomisation via an interactive response technology system was stratified according to baseline proteinuria (<2 or ≥2 g/24 h), baseline eGFR (<60 or ≥60 mL/min per 1·73 m²), and region (Asia-Pacific, Europe, North America, or South America). Patients, investigators, and site staff were masked to treatment assignment throughout the 2-year trial. Optimised supportive care was also continued throughout the trial. The primary efficacy endpoint was time-weighted average of eGFR over 2 years. Efficacy and safety analyses were done in the full analysis set (ie, all randomly assigned patients). The trial was registered on ClinicalTrials.gov, NCT03643965, and is completed.

Findings Patients were recruited to the NefIgArd trial between Sept 5, 2018, and Jan 20, 2021, with 364 patients (182 per treatment group) randomly assigned in the full analysis set. 240 (66%) patients were men and 124 (34%) were women, and 275 (76%) identified as White. The time-weighted average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min per 1·73 m² [95% CI 3·24 to 7·38], p<0·0001), with a time-weighted average change of −2·47 mL/min per 1·73 m² (95% CI −3·88 to −1·02) reported with Nefecon and −7·52 mL/min per 1·73 m² (−8·83 to −6·18) reported with placebo. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] patients, *vs* placebo, seven [4%] patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%]), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]). No treatment-related deaths were reported.

Interpretation A 9-month treatment period with Nefecon provided a clinically relevant reduction in eGFR decline and a durable reduction in proteinuria versus placebo, providing support for a disease-modifying effect in patients with IgA nephropathy. Nefecon was also well tolerated, with a safety profile as expected for a locally acting oral budesonide product.

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Introduction

IgA nephropathy is a chronic immune-mediated kidney disease characterised by IgA deposition in the glomeruli.[1] IgA nephropathy is the most common primary glomerular disease globally and has serious consequences, including reduced life expectancy; most patients with IgA nephropathy are expected to develop kidney failure, with up to 50% doing so within 20 years of presentation.[1–4] Therefore, IgA nephropathy places a substantial burden on patients and health-care services worldwide. With no cure for IgA nephropathy, current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2021, recommend providing optimised supportive care (blood pressure management, lifestyle modification, maximally tolerated renin-angiotensin system [RAS] inhibition to reduce proteinuria, and addressing cardiovascular risk).[2] After supportive care, patients who remain at high risk for progressive chronic kidney disease should be considered for a clinical trial, or for systemic glucocorticoids (if they

158 (87%) of 182 patients in the Nefecon group and 165 (91%) of 182 in the placebo group received 9 months of randomised treatment. Compliance with study treatment was high (171 [94%] patients in each treatment group took at least 80% of the total capsules). The overall rate of study completion was high and similar in both

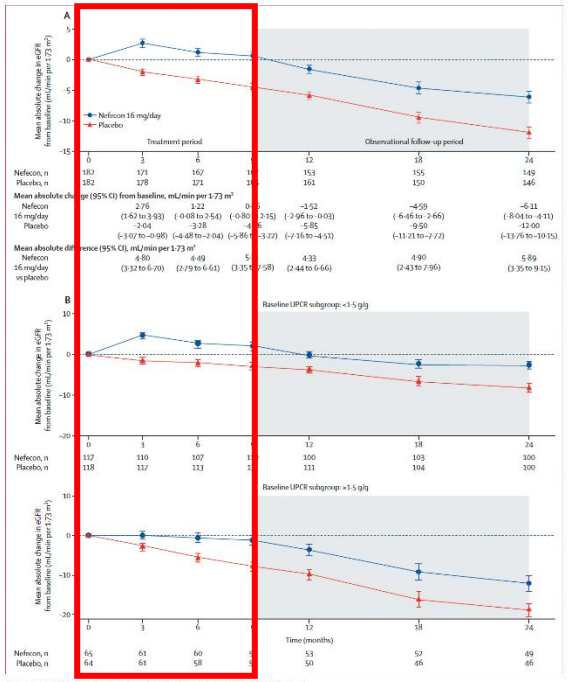

Figure 1: **Mean absolute change in eGFR from baseline to 24 months (full analysis set)**
All patients (A) and patients stratified according to baseline UPCR, <1·5 g/g and ≥1·5 g/g (B). Estimated mean absolute change (and standard error) was calculated from multiple-imputation robust regression analysis of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months, and transformed back into the original scale. eGFR was calculated by the central laboratory with the Chronic Kidney Disease Epidemiology Collaboration formula.[16] Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. eGFR=estimated glomerular filtration rate. UPCR=urine protein–creatinine ratio.

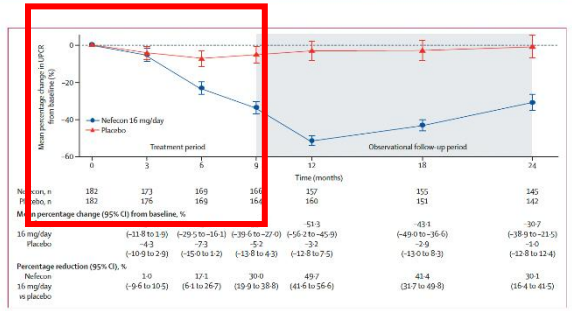

Figure 2: **Mean percentage change in UPCR (g/g) from baseline to 24 months (full analysis set)**
Estimated geometric mean percentage change (and standard error) was calculated from a mixed-effects model for repeated measures of log-transformed post-baseline to baseline ratios at 3, 6, 9, 12, 18, and 24 months. Data included at baseline and 24 months are the log of the geometric mean of the two replicate values recorded at each timepoint, respectively. The corresponding percentage reduction and confidence interval was derived from (1− ratio of geometric least squares means) × 100. UPCR=urine protein–creatinine ratio.

12 months, with a reduction in UPCR of 49·7% (41·6–56·6).

Results from the UACR analysis were consistent with those for UPCR, with the Nefecon group showing a 46·3% (36·5–54·5) reduction in time-averaged UACR between 12 and 24 months compared with the placebo group (p<0·0001; appendix p 11). The proportion of patients without microhaematuria during the observational follow-up period was significantly higher in the Nefecon group than in the placebo group (in patients with two or more urine dipstick results during the observational period, 94 [59%] of 158 *vs* 59 [39%] of 152; odds ratio for Nefecon *vs* placebo 2·5 [95% CI 1·6–4·1], p=0·0001; appendix p 12). Results of other secondary efficacy analyses were generally supportive of the overall beneficial effect of Nefecon treatment (appendix pp 13–14).

During the 9-month treatment period, Nefecon 16 mg/day was well tolerated, with a safety profile as expected for a locally acting oral budesonide product. Discontinuations due to treatment-emergent adverse events occurred in 17 (9%) of 182 patients in the Nefecon group and three (2%) of 182 in the placebo group (table 3). Treatment-emergent serious adverse events were reported in 18 (10%) patients in the Nefecon group and nine (5%) patients in the placebo group, with most considered unrelated to study treatment (table 3), and no discernible patterns in terms of body system or organ (appendix p 15). During the 15-month observational follow-up, the incidence of treatment-emergent adverse events and treatment-emergent serious adverse events was similar between the groups.

One death due to SARS-CoV-2 infection was reported during Nefecon treatment in a patient with several risk factors for COVID-19 mortality, and another patient treated with Nefecon died from a cerebral haemorrhage 10·5 months after their last dose. Neither death was considered to be related to study treatment. No treatment-emergent adverse events leading to death were reported in the placebo group.

The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral oedema (31 [17%] of 182 patients *vs* placebo, seven [4%] of 182 patients), hypertension (22 [12%] *vs* six [3%]), muscle spasms (22 [12%] *vs* seven [4%] patients), acne (20 [11%] *vs* two [1%]), and headache (19 [10%] *vs* 14 [8%]); appendix p 15). These were generally non-serious adverse events and were of mild severity, and reversible during or after treatment. In the Nefecon group, two patients had hypertension events, and one patient had both peripheral and face oedema events, all of which were classed as serious; a fourth patient had a peripheral oedema event that was graded as severe (appendix p 15). During the observational follow-up, frequencies of the most commonly reported treatment-emergent adverse events were similar in both treatment groups, including of SARS-CoV-2 infection, which was the most frequently reported event (26 [15%] of 175 patients in the Nefecon group and 30 [17%] of 174 in the placebo group), among patients who had a study visit during the observational follow-up; appendix p 16).

The incidence of infections during treatment was similar between treatment groups (63 [35%] of 182 patients

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	9-month treatment period*		15-month observational follow-up period†	
	Nefecon 16 mg/day (n=182)	Placebo (n=182)	Nefecon 16 mg/day (n=175)‡	Placebo (n=174)‡
All treatment-emergent adverse events	159 (87%)	125 (69%)	127 (73%)	124 (71%)
Mild	93 (51%)	75 (41%)	62 (35%)	73 (42%)
Moderate	57 (31%)	46 (25%)	49 (28%)	43 (25%)
Severe	9 (5%)	4 (2%)	16 (9%)	8 (5%)
Any treatment-emergent serious adverse events	18 (10%)	9 (5%)	14 (8%)	14 (8%)
Any treatment-related treatment-emergent serious adverse events	4 (2%)	4 (2%)	0	1 (1%)
Any treatment-emergent adverse events leading to death	1 (1%)	0	1 (1%)	0
Any treatment-emergent adverse events leading to discontinuation of study treatment	17 (9%)	3 (2%)	NA	NA

Data are number of patients (%). NA=not applicable. *Includes adverse events that started or worsened during treatment, up to 14 days (inclusive) after the last treatment dose (ie, the last dose the patient received including the tapering period, regardless of treatment duration). Five patients (two in the Nefecon group and three in the placebo group) did not start study treatment. †Includes adverse events that started more than 14 days after the last treatment dose. ‡Number of patients who had a study visit during the observational follow-up period.

Table 3: **Key safety variables (full analysis set)**

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Why target the gut to treat the kidneys?

A New treatment paradigm for IgA nephropathy

Professor Jonathan Barratt
University of Leicester
&
John Walls Renal Unit,
Leicester

December 7th 12.30—13.30

1.4.3 Managing the IgAN-specific drivers of nephron loss

Recommendation 1.4.3.1: We suggest treatment with a 9-month course of Nefecon for patients who are at risk of progressive loss of kidney function with IgAN *(2B)*.

Practice Point 1.4.3.1: Factors to consider before using Nefecon in patients with IgAN:

- A 9-month treatment course of Nefecon, a targeted-release formulation of budesonide, may not result in a sustained clinical response in terms of proteinuria reduction or eGFR stabilization.
- Data on the safety and efficacy of additional courses of Nefecon are awaited.
- Nefecon's approval status, labeled indication, and availability vary globally.

Recommendation 1.4.3.2: In settings where Nefecon is not available, we suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis *(2B)*.

Practice Point 1.4.3.2: Reduced-dose systemic glucocorticoid regimen:

- Methylprednisolone (or equivalent) 0.4 mg/kg/d (maximum 32 mg/d) for 2 months followed by dose tapering by 4 mg/d each month for a total of 6–9 months.
- The conversion of methylprednisolone to commonly used forms of systemic glucocorticoids is as follows: 1 mg of methylprednisolone equals 1.25 mg of prednisone or prednisolone.
- Treatment with systemic glucocorticoids should incorporate antimicrobial prophylaxis against *Pneumocystis jirovecii* and antiviral prophylaxis in hepatitis B carriers, along with gastroprotection and bone protection according to national guidelines.

Practice Point 1.4.3.3: Factors that increase the risk of toxicity of systemic glucocorticoids:

- eGFR <30 ml/min per 1.73 m^2
- Diabetes and prediabetes
- Obesity
- Latent infections (e.g., viral hepatitis and tuberculosis)
- Active peptic ulceration
- Uncontrolled psychiatric illness
- Osteoporosis
- Cataracts

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

Research

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Hong Zhang, PhD; Muh Geot Wong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, FRCPC; David Wheeler, FRCP; Mark Woodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hai-Yan Wang, MD; Vlado Perkovic, PhD; for the TESTING Study Group

clinical trial www.kidney-international.org

After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy

see commentary on page 836

Thomas Rauen[1], Stephanie Wied[2], Christina Fitzner[2], Frank Eitner[1,3], Claudia Sommerer[4], Martin Zeier[4], Britta Otte[5], Ulf Panzer[6], Klemens Budde[7], Urs Benck[8], Peter R. Mertens[9], Uwe Kuhlmann[10], Oliver Witzke[11], Oliver Gross[12], Volker Vielhauer[13], Johannes F.E. Mann[14], Ralf-Dieter Hilgers[2] and Jürgen Floege[1]; for the STOP-IgAN Investigators[15]

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Research

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy
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Research

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Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy

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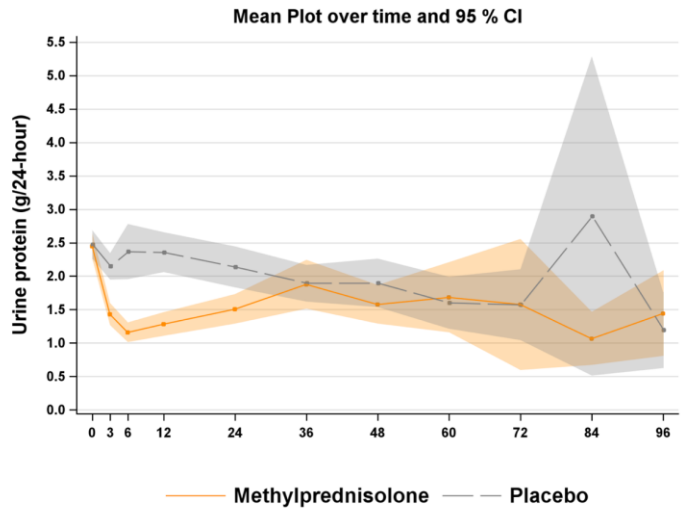
A) Mean 24 hour protein excretion by randomized group over time



eTable 4 (modified): Serious Adverse events randomized by group overall

	Methylprednisolone (N = 257)	Placebo (N = 246)
Number of SAE	37	8
Number of patients with atleast one SAE (%)		
Hospitalization/prolonged hospitalization	28 (11)	7 (2)
Resulted in death	4 (2)	0 (0)
Life-threatening	4 (2)	0 ()
Important medical event	2 (0.8)	0 ()
Persistent/significant disability/incapacity	1 (0.4)	0 (0)
Number of patients reporting the following SAE of special interest per protocol		
Severe infection requiring hospitalization	17 (7)	2 (1)
Pneumocystis Jirovecii pneumonia	4 (2)	0 (0)
Pneumonia or respiratory tract infection	3 (1)	0 (0)
Sepsis	2 (0.8)	1 (0.4)
Urinary tract infection	2 (0.8)	0 (0)
Multiple skin infection	1 (0.4)	0 (0)
Nocardia infection	1 (0.4)	0 (0)
Cryptococcal meningitis	1 (0.4)	0 (0)
Tuberculosis with bacterial infection	1 (0.4)	0 (0)
Perianal abscess	1 (0.4)	0 (0)
Acute febrile illness	0 (0)	1 (0.4)
Other	1 (0.4)	1 (0.4)
Gastrointestinal bleeding requiring hospitalization	3 (1)	1 (0.4)
Clinical evidence fractures or osteoporosis	3 (1)	0 (0)
New onset diabetes mellitus	2 (0.8)	0 (0)

Practice Point 1.4.3.4: Other pharmacologic therapies evaluated in IgAN:

- **Multiple agents have been evaluated, often in small studies in restricted populations, and they failed to show a consistent benefit in IgAN (Figure 4).**

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence of efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No evidence of efficacy
Rituximab	Not recommended	No evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China. The first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m²) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients.[2] The second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m²), showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm. The third from Guangdong (n=170, eGFR 50 ml/min/1.73 m²), showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In three smaller RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy: these were from Belgium (n=34, inulin clearance ~71 ml/min/1.73 m²),[5] New York (n=32, eGFR ~39 ml/min/1.73 m² and required glomerulosclerosis or tubulointerstitial atrophy and fibrosis on kidney biopsy reflecting relatively advanced CKD already)[6] and US/Canada (n=44, eGFR >90 ml/min/1.73 m², MMF versus omega-3 fatty acid).[7]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[8]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 4 | Other pharmacologic therapies evaluated in immunoglobulin A nephropathy (IgAN). [1]Tang *et al.*,[43] [2]Tang *et al.*,[44] [3]Hou *et al.*,[38] [4]Hou *et al.*,[45] [5]Maes *et al.*,[46] [6]Frisch *et al*,[47] [7]Hogg *et al.*,[48] [8]Liu *et al.*[49] ACEi, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial; SC, standard of care.

Practice Point 1.4.3.5: Tonsillectomy in IgAN:

- Tonsillectomy alone or with pulsed glucocorticoids may extend kidney survival and increase the likelihoods of partial or complete remission of hematuria and proteinuria based on multiple, mostly retrospective studies from Japan (Supplementary Table S5[50–54]).[40,50–52,54,55]
- Tonsillectomy alone or with pulsed glucocorticoids is recommended in the Japanese Society of Nephrology guidelines for the treatment of patients with IgAN.
- Tonsillectomy should not be performed as a treatment of IgAN in non-Japanese patients.

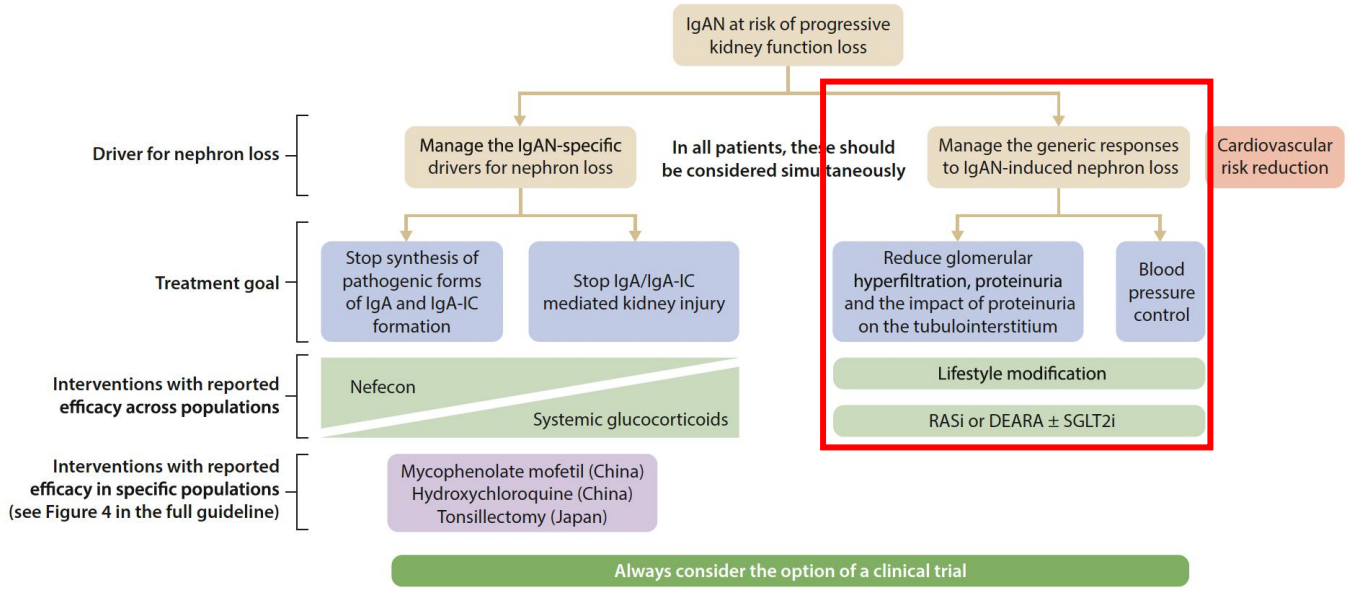


Figure 2 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

1.4.4 Managing the responses to IgAN-induced nephron loss

Practice Point 1.4.4.1: For lifestyle and blood pressure targets for all patients with IgAN, please refer to Practice Point 1.4.2.2.

Recommendation 1.4.4.1: We recommend that all patients with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) *(1B)*.

Practice Point 1.4.4.2: Factors to consider before using an ACEi or ARB:

- All patients with IgAN should receive an ACEi or ARB at the maximally tolerated dose, except patients with contraindications such as low blood pressure, bilateral renal artery stenosis, or hyperkalemia, especially due to advanced CKD.
- As ACEi or ARB do not mitigate the IgAN-specific drivers of nephron loss, their use should not preclude the concomitant introduction of therapies that target the drivers of IgAN or glomerular inflammation as stated in Section 1.4.3 for patients who will likely benefit from them.

1.4.4 Managing the responses to IgAN-induced nephron loss

Practice Point 1.4.4.1: For lifestyle and blood pressure targets for all patients with IgAN, please refer to Practice Point 1.4.2.2.

Recommendation 1.4.4.1: We recommend that all patients with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) *(1B)*.

Practice Point 1.4.4.2: Factors to consider before using an ACEi or ARB:

- All patients with IgAN should receive an ACEi or ARB at the maximally tolerated dose, except patients with contraindications such as low blood pressure, bilateral renal artery stenosis, or hyperkalemia, especially due to advanced CKD.
- As ACEi or ARB do not mitigate the IgAN-specific drivers of nephron loss, their use should not preclude the concomitant introduction of therapies that target the drivers of IgAN or glomerular inflammation as stated in Section 1.4.3 for patients who will likely benefit from them.

Recommendation 1.4.4.2: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with sparsentan *(2B)*.

Practice Point 1.4.4.3: Factors to consider before using sparsentan in patients with IgAN:

- Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a renin-angiotensin system inhibitor (RASi), because sparsentan already combines RASi with an endothelin antagonist in a single molecule.
- Sparsentan's approval status, labeled indication, and availability vary globally.

Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial

Hiddo J L Heerspink, Jai Radhakrishnan, Charles E Alpers, Jonathan Barratt, Stewart Bieler, Ulysses Diva, Jula Inrig, Radko Komers, Alex Mercer, Irene L Noronha, Michelle N Rheault, William Rote, Brad Rovin, Howard Trachtman, Hernán Trimarchi, Muh Geot Wong, Vlado Perkovic, for the PROTECT Investigators*

Summary

Background Sparsentan is a novel, non-immunosuppressive, single-molecule, dual endothelin and angiotensin receptor antagonist being examined in an ongoing phase 3 trial in adults with IgA nephropathy. We report the prespecified interim analysis of the primary proteinuria efficacy endpoint, and safety.

Methods PROTECT is an international, randomised, double-blind, active-controlled study, being conducted in 134 clinical practice sites in 18 countries. The study examines sparsentan versus irbesartan in adults (aged ≥18 years) with biopsy-proven IgA nephropathy and proteinuria of 1·0 g/day or higher despite maximised renin-angiotensin system inhibitor treatment for at least 12 weeks. Participants were randomly assigned in a 1:1 ratio to receive sparsentan 400 mg once daily or irbesartan 300 mg once daily, stratified by estimated glomerular filtration rate at screening (30 to <60 mL/min per 1·73 m² and ≥60 mL/min per 1·73 m²) and urine protein excretion at screening (≤1·75 g/day and >1·75 g/day). The primary efficacy endpoint was change from baseline to week 36 in urine protein–creatinine ratio based on a 24-h urine sample, assessed using mixed model repeated measures. Treatment-emergent adverse events (TEAEs) were safety endpoints. All endpoints were examined in all participants who received at least one dose of randomised treatment. The study is ongoing and is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 404 participants were randomly assigned to sparsentan (n=202) or irbesartan (n=202) and received treatment. At week 36, the geometric least squares mean percent change from baseline in urine protein–creatinine ratio was statistically significantly greater in the sparsentan group (–49·8%) than the irbesartan group (–15·1%), resulting in a between-group relative reduction of 41% (least squares mean ratio=0·59; 95% CI 0·51–0·69; p<0·0001). TEAEs with sparsentan were similar to irbesartan. There were no cases of severe oedema, heart failure, hepatotoxicity, or oedema-related discontinuations. Bodyweight changes from baseline were not different between the sparsentan and irbesartan groups.

Interpretation Once-daily treatment with sparsentan produced meaningful reduction in proteinuria compared with irbesartan in adults with IgA nephropathy. Safety of sparsentan was similar to irbesartan. Future analyses after completion of the 2-year double-blind period will show whether these beneficial effects translate into a long-term nephroprotective potential of sparsentan.

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Introduction

Immunoglobulin A (IgA) nephropathy is the most common primary glomerulonephritis and an important cause of kidney failure.[1,2] Proteinuria has been consistently shown to be a risk factor for progressive kidney function loss in patients with IgA nephropathy,[3] and remission of proteinuria is associated with improved kidney outcomes.[3] Despite the risk of progressive kidney disease and kidney failure, few therapeutic options are available. The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends the use of renin-angiotensin system (RAS) inhibitors in patients with proteinuria more than 0·5 g/day.[4] Following 3 months of RAS inhibitor treatment, patients with proteinuria of 1 g/day or higher have a greater risk of disease progression, and additional treatment is recommended.

The use of RAS inhibitors as standard of care in IgA nephropathy is based on their well established pleiotropic nephroprotective actions in a variety of kidney diseases and indicates a contribution of its main effector, angiotensin II, in the pathophysiology of IgA nephropathy.[5] More recently, advances in our understanding of the pathogenesis of IgA nephropathy show that endothelin-1 (ET-1) contributes to the pathophysiology of IgA nephropathy via activation of ET_A receptors, leading to a variety of effects including vasoconstriction, podocyte dysfunction, tubular injury, inflammation, and fibrosis.[6]

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin*, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald F Kohan, Radko Komers, Laura Ann Kooienga, Richard J Lafayette, Bart Maes, Robert Maiecki, Alex Mercer, Irene L Noronha, Se Won Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William E Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†

Summary

Background Sparsentan, a novel, non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist, significantly reduced proteinuria versus irbesartan, an angiotensin II receptor blocker, at 36 weeks (primary endpoint) in patients with immunoglobulin A nephropathy in the phase 3 PROTECT trial's previously reported interim analysis. Here, we report kidney function and outcomes over 110 weeks from the double-blind final analysis.

Methods PROTECT, a double-blind, randomised, active-controlled, phase 3 study, was done across 134 clinical practice sites in 18 countries throughout the Americas, Asia, and Europe. Patients aged 18 years or older with biopsy-proven primary IgA nephropathy and proteinuria of at least 1·0 g per day despite maximised renin–angiotensin system inhibition for at least 12 weeks were randomly assigned (1:1) to receive sparsentan (target dose 400 mg oral sparsentan once daily) or irbesartan (target dose 300 mg oral irbesartan once daily) based on a permuted-block randomisation method. The primary endpoint was proteinuria change between treatment groups at 36 weeks. Secondary endpoints included rate of change (slope) of the estimated glomerular filtration rate (eGFR), changes in proteinuria, a composite of kidney failure (confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality), and safety and tolerability up to 110 weeks from randomisation. Secondary efficacy outcomes were assessed in the full analysis set and safety was assessed in the safety set, both of which were defined as all patients who were randomly assigned and received at least one dose of randomly assigned study drug. This trial is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 203 patients were randomly assigned to the sparsentan group and 203 to the irbesartan group. One patient from each group did not receive the study drug and was excluded from the efficacy and safety analyses (282 [70%] of 404 included patients were male and 272 [67%] were White) . Patients in the sparsentan group had a slower rate of eGFR decline than those in the irbesartan group. eGFR chronic 2-year slope (weeks 6–110) was −2·7 mL/min per 1·73 m² per year versus −3·8 mL/min per 1·73 m² per year (difference 1·1 mL/min per 1·73 m² per year, 95% CI 0·1 to 2·1; p=0·037); total 2-year slope (day 1–week 110) was −2·9 mL/min per 1·73 m² per year versus −3·9 mL/min per 1·73 m² per year (difference 1·0 mL/min per 1·73 m² per year, 95% CI −0·03 to 1·94; p=0·058). The significant reduction in proteinuria at 36 weeks with sparsentan was maintained throughout the study period; at 110 weeks, proteinuria, as determined by the change from baseline in urine protein-to-creatinine ratio, was 40% lower in the sparsentan group than in the irbesartan group (−42·8%, 95% CI −49·8 to −35·0, with sparsentan versus −4·4%, −15·8 to 8·7, with irbesartan; geometric least-squares mean ratio 0·60, 95% CI 0·50 to 0·72). The composite kidney failure endpoint was reached by 18 (9%) of 202 patients in the sparsentan group versus 26 (13%) of 202 patients in the irbesartan group (relative risk 0·7, 95% CI 0·4 to 1·2). Treatment-emergent adverse events were well balanced between sparsentan and irbesartan, with no new safety signals.

Interpretation Over 110 weeks, treatment with sparsentan versus maximally titrated irbesartan in patients with IgA nephropathy resulted in significant reductions in proteinuria and preservation of kidney function.

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Immunoglobulin A nephropathy is the most common primary glomerular disease worldwide[1] and is associated with significant lifetime risk of kidney failure.[2] Current treatment options are limited,[3] and it is only since December, 2021, that a small number of approved treatments have become available in Europe and the USA.[4,5] IgA nephropathy is usually found in

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Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

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Introduction

Immunoglobulin A nephropathy is the most common primary glomerular disease worldwide[1] and is associated with significant lifetime risk of kidney failure.[2] Current treatment options are limited,[3] and it is only since December, 2021, that a small number of approved treatments have become available in Europe and the USA.[4,5] IgA nephropathy is usually found in

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: Change in eGFR

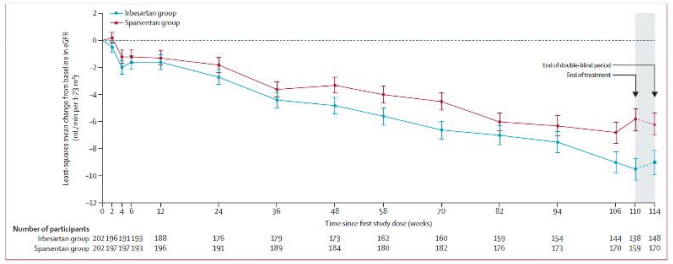

Figure 2: eGFR by visit up to week 114

Change from baseline in eGFR at week 6 or 114 was assessed with ANCOVA, and change from baseline in eGFR to other timepoints up to week 110 were analysed via a mixed model for repeated measures. Error bars indicate SEs. eGFR=estimated glomerular filtration rate.

chronic and total slopes up to week 110, as were results from all other prespecified sensitivity analyses (figure 3; appendix p 10). An imbalance in intercurrent events was observed, particularly rates and reasons for premature treatment discontinuation (figure 1) and initiation of rescue immunosuppressive therapy (appendix p 11). A prespecified sensitivity analysis that used a modified intention-to-treat approach (including data from all randomly assigned and treated patients during the double-blind period irrespective of premature treatment discontinuations) was supportive of benefit (difference 1·2 mL/min per 1·73 m² per year, 95% CI 0·2–2·2; figure 3; appendix p 10). Rescue immunosuppressive medications were initiated sooner and more frequently with irbesartan than sparsentan (16 [8%] of 202 *vs* six [3%] of 202) and were mostly corticosteroids (appendix p 11). In a prespecified sensitivity analysis excluding assessments after immunosuppressive therapy use, the difference in chronic and total slopes again favoured sparsentan, with CIs excluding the null (total slope: difference 1·0 mL/min per 1·73 m² per year, 95% CI 0·03–1·99; figure 3; appendix p 10).

The composite kidney failure endpoint of confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality was reached by 18 (9%) of 202 patients in the sparsentan group versus 26 (13%) of 202 in the irbesartan group (relative risk 0·7, 95% CI 0·4–1·2; figure 4). Within this endpoint, 18 (9%) patients in the sparsentan group versus 22 (11%) patients in the irbesartan group had confirmed 40% eGFR reduction, nine (4%) versus 11 (5%) had end-stage kidney disease, and zero versus one (<1%) died.

At week 110, the geometric least-squares mean percentage change from baseline in the urine protein-to-creatinine ratio was −42·8% (95% CI −49·8 to −35·0) with sparsentan versus −4·4% (−15·8 to 8·7) with irbesartan (geometric least-squares mean ratio 0·60, 95% CI 0·50 to 0·72; table 3; figure 5). At week 110,

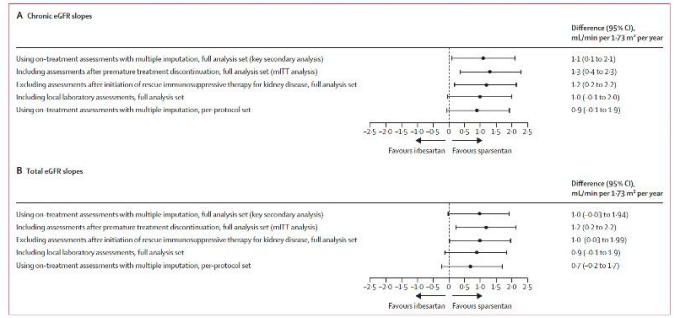

Figure 3: Prespecified sensitivity analyses of rate of change in eGFR up to week 110

(A) Chronic slope between-group difference. (B) Total slope between-group difference. The full analysis set included 202 patients in each group. The mITT approach included 202 patients in each group. The per-protocol set included 188 patients in the sparsentan group and 182 patients in the irbesartan group. eGFR=estimated glomerular filtration rate. mITT=modified intention to treat.

decreases from baseline were observed in 24 h urine protein excretion, urine albumin-to-creatinine ratio, and urine albumin excretion with sparsentan versus irbesartan. Geometric least-squares mean percentage change from baseline in the urine albumin-to-creatinine ratio at each visit is shown in the appendix (p 12).

Patients in the sparsentan group had complete proteinuria remission (urine protein excretion <0·3 g per day) earlier and more frequently than those in the irbesartan group (62 [31%] of 202 *vs* 23 [11%] of 202; relative risk 2·5, 95% CI 1·6–4·1; appendix pp 13–14). Partial proteinuria remission (<1·0 g per day) occurred in 157 (78%) patients in the sparsentan group versus 106 (53%) patients in the irbesartan group (relative risk 1·5, 95% CI 1·1–1·9). In the post-hoc analysis, urine protein excretion of less than 0·5 g per day occurred in 103 (51%) patients in the sparsentan group versus 48 (24%) patients in the irbesartan group (relative risk 2·1, 95% CI 1·5–2·9).

Blood pressure values over 110 weeks are reported in the appendix (p 15). Least-squares mean change from baseline at week 110 in systolic and diastolic blood pressure was −3·8 mm Hg (95% CI −5·5 to −2·1) and −3·4 mm Hg (−4·6 to −2·2), respectively, with sparsentan and −2·5 mm Hg (−4·3 to −0·8) and −1·2 mm Hg (−2·5 to 0·0), respectively, with irbesartan.

Treatment-emergent adverse events were reported in 187 (93%) of 202 patients in the sparsentan group and 177 (88%) of 202 in the irbesartan group (table 4). Treatment-emergent adverse events that occurred more frequently with sparsentan than irbesartan (≥5 percentage points) included dizziness (30 [15%] *vs* 13 [6%] patients) and hypotension (26 [13%] *vs* eight [4%] patients). Serious treatment-emergent adverse events were reported in 75 (37%) patients in the sparsentan group and 71 (35%) patients in the irbesartan group, and treatment-emergent adverse events led to treatment discontinuation in 21 (10%) and 18 (9%) patients, respectively. Treatment-emergent adverse events of acute kidney injury occurred in 12 (6%) patients in the sparsentan group and five (2%) patients in the irbesartan group (four [2%] *vs* one [<1%] were serious and three [1%] *vs* none led to treatment discontinuation).

Treatment-emergent adverse events of COVID-19 were reported in 53 (26%) of 202 patients in the sparsentan group and 46 (23%) of 202 patients in the irbesartan group. Hepatic treatment-emergent adverse events of interest of ALT or AST increasing to more than 3 times the ULN occurred in five (2%) patients in the sparsentan group and seven (3%) patients in the irbesartan group. In the sparsentan and irbesartan groups, serious hepatic treatment-emergent adverse events were reported in zero and two (1%) patients. No cases of drug-induced liver injury occurred in either group.

Hypotension-associated treatment-emergent adverse events (hypotension, orthostatic hypotension, and blood pressure systolic decreased) were reported in 33 (16%) patients in the sparsentan group and 13 (6%) patients in the irbesartan group, and led to treatment discontinuation in three (1%) patients in the

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

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Background Sparsentan, a novel, non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist, significantly reduced proteinuria versus irbesartan, an angiotensin II receptor blocker, at 36 weeks (primary endpoint) in patients with immunoglobulin A nephropathy in the phase 3 PROTECT trial's previously reported interim analysis. Here, we report kidney function and outcomes over 110 weeks from the double-blind final analysis.

Methods PROTECT, a double-blind, randomised, active-controlled, phase 3 study, was done across 134 clinical practice sites in 18 countries throughout the Americas, Asia, and Europe. Patients aged 18 years or older with biopsy-proven primary IgA nephropathy and proteinuria of at least 1·0 g per day despite maximised renin–angiotensin system inhibition for at least 12 weeks were randomly assigned (1:1) to receive sparsentan (target dose 400 mg oral sparsentan once daily) or irbesartan (target dose 300 mg oral irbesartan once daily) based on a permuted-block randomisation method. The primary endpoint was proteinuria change between treatment groups at 36 weeks. Secondary endpoints included rate of change (slope) of the estimated glomerular filtration rate (eGFR), changes in proteinuria, a composite of kidney failure (confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality), and safety and tolerability up to 110 weeks from randomisation. Secondary efficacy outcomes were assessed in the full analysis set and safety was assessed in the safety set, both of which were defined as all patients who were randomly assigned and received at least one dose of randomly assigned study drug. This trial is registered with ClinicalTrials.gov, NCT03762850.

Findings Between Dec 20, 2018, and May 26, 2021, 203 patients were randomly assigned to the sparsentan group and 203 to the irbesartan group. One patient from each group did not receive the study drug and was excluded from the efficacy and safety analyses (282 [70%] of 404 included patients were male and 272 [67%] were White) . Patients in the sparsentan group had a slower rate of eGFR decline than those in the irbesartan group. eGFR chronic 2-year slope (weeks 6–110) was −2·7 mL/min per 1·73 m² per year versus −3·8 mL/min per 1·73 m² per year (difference 1·1 mL/min per 1·73 m² per year, 95% CI 0·1 to 2·1; p=0·037); total 2-year slope (day 1–week 110) was −2·9 mL/min per 1·73 m² per year versus −3·9 mL/min per 1·73 m² per year (difference 1·0 mL/min per 1·73 m² per year, 95% CI −0·03 to 1·94; p=0·058). The significant reduction in proteinuria at 36 weeks with sparsentan was maintained throughout the study period; at 110 weeks, proteinuria, as determined by the change from baseline in urine protein-to-creatinine ratio, was 40% lower in the sparsentan group than in the irbesartan group (−42·8%, 95% CI −49·8 to −35·0, with sparsentan versus −4·4%, −15·8 to 8·7, with irbesartan; geometric least-squares mean ratio 0·60, 95% CI 0·50 to 0·72). The composite kidney failure endpoint was reached by 18 (9%) of 202 patients in the sparsentan group versus 26 (13%) of 202 patients in the irbesartan group (relative risk 0·7, 95% CI 0·4 to 1·2). Treatment-emergent adverse events were well balanced between sparsentan and irbesartan, with no new safety signals.

Interpretation Over 110 weeks, treatment with sparsentan versus maximally titrated irbesartan in patients with IgA nephropathy resulted in significant reductions in proteinuria and preservation of kidney function.

Funding Travere Therapeutics.

Introduction

Immunoglobulin A nephropathy is the most common primary glomerular disease worldwide[1] and is associated with significant lifetime risk of kidney failure.[2] Current treatment options are limited,[3] and it is only since December, 2021, that a small number of approved treatments have become available in Europe and the USA.[4,5] IgA nephropathy is usually found in

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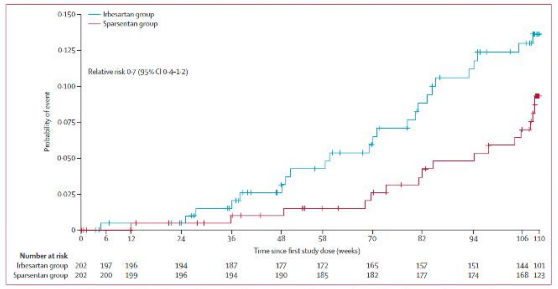

Figure 4: Time to reach the composite kidney failure endpoint of confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality
Vertical bars indicate censored patients. eGFR=estimated glomerular filtration rate.

	Sparsentan group (n=202)	Irbesartan group (n=202)	Geometric least-squares mean ratio (95% CI)
Urine protein-to-creatinine ratio, g/g	−42·8% (−49·8 to −35·0)	−4·4% (−15·8 to 8·7)	0·60 (0·50 to 0·72); 40% reduction
Urine protein excretion, g per day	−46·9% (−53·4 to −39·5)	−5·9% (−17·9 to 7·9)	0·56 (0·47 to 0·68); 44% reduction
Urine albumin-to-creatinine ratio, g/g	−56·0% (−62·1 to −49·1)	−17·3% (−29·1 to −3·5)	0·53 (0·43 to 0·66); 47% reduction
Urine albumin excretion, g per day	−58·8% (−64·7 to −52·0)	−17·9% (−30·1 to −3·6)	0·50 (0·40 to 0·63); 50% reduction

Data are geometric least-squares mean (95% CI) change in proteinuria from baseline to week 110 unless otherwise stated.

Table 3: Change in proteinuria

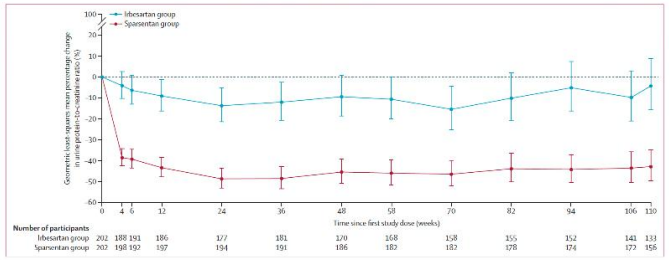

Figure 5: Geometric least-squares mean percentage change from baseline in the urine protein-to-creatinine ratio at each visit up to week 110
Error bars indicate 95% CIs.

sparsentan group (two [1%] had hypotension, and one [<1%] had orthostatic hypotension). No patients discontinued treatment due to heart failure or oedema. There were no serious treatment-emergent adverse events of study drug-related oedema. Change in semiquantitative oedema from no oedema at baseline to severe oedema occurred in two (1%) patients in the irbesartan group, and to moderate oedema occurred in two (1%) patients in the sparsentan group. Diuretic use (started on or after initial study dose) was reported in 49 (24%) patients in the sparsentan group and 54 (27%) patients in the irbesartan group, and the most frequently used class was thiazides (35 [17%] vs 42 [21%]). One patient died in the irbesartan group (cardiorespiratory arrest) and none died in the sparsentan group (table 4).

Mean bodyweight was 84·2 kg (SD 20·1) at baseline and 83·8 kg (20·9) at week 110 with sparsentan and 84·7 kg (19·7) at baseline and 85·0 kg (19·0) at week 110 with irbesartan (appendix p 16). Mean potassium concentration remained stable over 110 weeks (appendix p 9).

	Sparsentan group (n=202)	Irbesartan group (n=202)
Any treatment-emergent adverse event	187 (93%)	177 (88%)
Treatment-emergent adverse events in ≥5% of patients in ≥1 group		
COVID-19	53 (26%)	46 (23%)
Hyperkalaemia	32 (16%)	26 (13%)
Peripheral oedema	31 (15%)	24 (12%)
Dizziness	30 (15%)	13 (6%)
Headache	27 (13%)	26 (13%)
Hypotension	26 (13%)	8 (4%)
Hypertension	22 (11%)	28 (14%)
Upper respiratory tract infection	18 (9%)	18 (9%)
Fatigue	17 (8%)	11 (5%)
Anaemia	16 (8%)	9 (4%)
Nasopharyngitis	15 (7%)	16 (8%)
Blood creatine phosphokinase increased	15 (7%)	10 (5%)
Cough	15 (7%)	7 (3%)
Muscle spasms	14 (7%)	17 (8%)
Arthralgia	14 (7%)	13 (6%)
Proteinuria	13 (6%)	15 (7%)
Back pain	12 (6%)	16 (8%)
Lipase increased	12 (6%)	9 (4%)
Acute kidney injury	12 (6%)	5 (2%)
Gout	11 (5%)	10 (5%)
Pruritus	11 (5%)	8 (4%)
Diarrhoea	10 (5%)	19 (9%)
Blood creatinine increased	10 (5%)	14 (7%)
Alanine aminotransferase increased	10 (5%)	8 (4%)
Gastro-oesophageal reflux disease	10 (5%)	8 (4%)
Nausea	10 (5%)	5 (2%)
Myalgia	10 (5%)	4 (2%)
Renal impairment	7 (3%)	12 (6%)
Urinary tract infection	7 (3%)	12 (6%)
Hyperuricaemia	7 (3%)	11 (5%)
Pain in extremity	6 (3%)	12 (6%)
Aminotransferase elevations*	5 (2%)	7 (3%)
Serious treatment-emergent adverse events	75 (37%)	71 (35%)
Serious treatment-emergent adverse events in ≥2 patients in ≥1 group		
COVID-19	42 (21%)	38 (19%)
Chronic kidney disease	6 (3%)	6 (3%)
Acute kidney injury	4 (2%)	1 (<1%)
Dizziness	2 (1%)	1 (<1%)
Proteinuria	1 (<1%)	2 (1%)
Malaise	2 (1%)	0
Appendicitis	1 (<1%)	2 (1%)
Cellulitis	1 (<1%)	2 (1%)
COVID-19 pneumonia	1 (<1%)	2 (1%)
IgA nephropathy	1 (<1%)	2 (1%)
Meniscus injury	1 (<1%)	2 (1%)

(Table 4 continues on next page)

Discussion

Sparsentan received accelerated regulatory approval for treatment of IgA nephropathy based on the results of PROTECT, which showed that patients in the sparsentan group had significantly greater reductions in proteinuria versus irbesartan (relative reduction of 41%) during 36 weeks of treatment.[4,5] PROTECT continued until week 114 to determine whether the proteinuria advantage for patients who received sparsentan was durable and to verify that this large decrease in proteinuria translated into superior preservation of kidney function versus those titrated to the maximal approved irbesartan dose. Importantly, patients and investigators remained masked to treatment during this period. Over the course of the double-blind period, the superior reduction of proteinuria in the sparsentan group versus the irbesartan group was maintained with a relative reduction of 40% at 110 weeks, similar to the relative reduction observed at 36 weeks.[4] As expected for patients with IgA nephropathy,[6] the relationship between the magnitude of proteinuria reduction and rate of loss of kidney function was successfully shown in PROTECT. Kidney function decline, assessed as chronic or total eGFR slope up to week 110, was lower with sparsentan versus irbesartan, indicating better preservation of kidney function (chronic slope −2·7 mL/min per 1·73 m² per year *vs* −3·8 mL/min per 1·73 m² per year; total slope −2·9 mL/min per 1·73 m² per year *vs* −3·9 mL/min per 1·73 m² per year). The difference in chronic slope (1·1 mL/min per 1·73 m² per year) between treatment groups reached significance (p=0·037). For the total slope, although the difference between groups was of similar magnitude, favouring sparsentan, significance was narrowly missed (p=0·058). Sensitivity analyses for chronic and total slopes that used a modified intention-to-treat approach (all participants who received study drug) and therefore had somewhat greater statistical power, or that excluded data subsequent to initiation of rescue

1.4.4 Managing the responses to IgAN-induced nephron loss

Practice Point 1.4.4.1: For lifestyle and blood pressure targets for all patients with IgAN, please refer to Practice Point 1.4.2.2.

Recommendation 1.4.4.1: We recommend that all patients with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) *(1B)*.

Practice Point 1.4.4.2: Factors to consider before using an ACEi or ARB:

- All patients with IgAN should receive an ACEi or ARB at the maximally tolerated dose, except patients with contraindications such as low blood pressure, bilateral renal artery stenosis, or hyperkalemia, especially due to advanced CKD.
- As ACEi or ARB do not mitigate the IgAN-specific drivers of nephron loss, their use should not preclude the concomitant introduction of therapies that target the drivers of IgAN or glomerular inflammation as stated in Section 1.4.3 for patients who will likely benefit from them.

Recommendation 1.4.4.2: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with sparsentan *(2B)*.

Practice Point 1.4.4.3: Factors to consider before using sparsentan in patients with IgAN:

- Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a renin-angiotensin system inhibitor (RASi), because sparsentan already combines RASi with an endothelin antagonist in a single molecule.
- Sparsentan's approval status, labeled indication, and availability vary globally.

Recommendation 1.4.4.3: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with an SGLT2i *(2B)*.

Practice Point 1.4.4.4: Factors to consider before using an SGLT2i in patients with IgAN:

- There was no requirement for patients with IgAN to be on an optimized maximally tolerated dose of RASi for a minimum of 3 months for inclusion in the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) or the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.
- Patients with IgAN included in EMPA-KIDNEY and DAPA-CKD likely had long-standing disease, based on their age and eGFR at randomization; therefore, there is uncertainty over the value of SGLT2i, especially in younger patients with IgAN and relatively preserved kidney function (eGFR >60 ml/min per 1.73 m^2) (see Table 2).

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Leicester IgA Nephropathy Research Group

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ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m² of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

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*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2024816

A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

see commentary on page 24
OPEN

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Immunoglobulin A (IgA) nephropathy is a common form of glomerulonephritis, which despite use of renin-angiotensin-aldosterone-system blockers and immunosuppressants, often progresses to kidney failure. In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial, dapagliflozin reduced the risk of kidney failure and prolonged survival in participants with chronic kidney disease with and without type 2 diabetes, including those with IgA nephropathy. Participants with estimated glomerular filtration rate (eGFR) 25-75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200-5000 mg/g (22.6-565 mg/mol) were randomized to dapagliflozin 10mg or placebo, as adjunct to standard care. The primary composite endpoint was a sustained decline in eGFR of 50% or more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause. Of 270 participants with IgA nephropathy (254 [94%] confirmed by previous biopsy), 137 were randomized to dapagliflozin and 133 to placebo, and followed for median 2.1 years. Overall, mean age was 51.2 years; mean eGFR, 43.8 mL/min/1.73m²; and median urinary albumin-to-creatinine ratio, 900 mg/g. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (hazard ratio, 0.29; 95% confidence interval, 0.12, 0.73). Mean rates of eGFR decline with dapagliflozin and placebo were −3.5 and −4.7 mL/min/1.73m²/year, respectively. Dapagliflozin reduced the urinary albumin-to-creatinine ratio by 26% relative to placebo. Adverse events leading to study drug discontinuation were similar with dapagliflozin and placebo. There were fewer serious adverse events with dapagliflozin, and no new safety findings in this population. Thus, in participants with IgA nephropathy, dapagliflozin reduced the risk of chronic kidney disease progression with a favorable safety profile.

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KEYWORDS: chronic kidney disease; dapagliflozin; DAPA-CKD; IgA nephropathy; randomized controlled clinical trial; sodium-glucose cotransporter inhibitor

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IgA nephropathy is the most common primary glomerular disease worldwide.[1] Despite advances in our understanding of its pathogenesis, treatment strategies have changed little over the last 2 or 3 decades.[2] Over a period of 4 to 15 years (mean, 6.1 years), approximately 30% of patients with IgA nephropathy progress to kidney failure, and risk factors for

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RESEARCH SUMMARY

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group DOI: 10.1056/NEJMoa2204233

CLINICAL PROBLEM

Sodium–glucose cotransporter 2 inhibitors appear to slow the progression of kidney disease in patients with diabetes and albuminuria. However, most patients with chronic kidney disease do not have diabetes and have low levels of albuminuria, and the effects of empagliflozin therapy in these patients are unclear.

CLINICAL TRIAL

Design: This international, randomized, parallel-group, double-blind, placebo-controlled trial assessed the efficacy of empagliflozin in patients with chronic kidney disease, with or without diabetes and with a range of albuminuria levels.

Intervention: 6609 patients with an estimated glomerular filtration rate (eGFR) of 20 to <45 ml per minute per 1.73 m² of body-surface area, or with an eGFR of 45 to <90 ml per minute per 1.73 m² and a urinary albumin-to-creatinine ratio of ≥200 (with albumin measured in milligrams and creatinine measured in grams), were assigned to receive 10 mg of empagliflozin or placebo daily. In this study, 54% of patients had chronic kidney disease without diabetes and 34% had an eGFR of <30 ml per minute per 1.73 m². The primary outcome was the first occurrence of progression of kidney disease or death from cardiovascular causes.

RESULTS

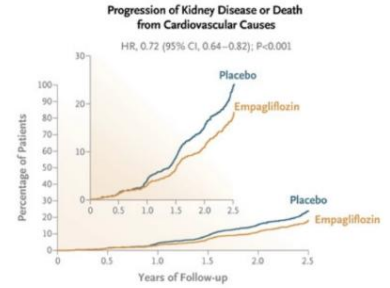
Efficacy: During a median follow-up of 2 years, progression of kidney disease or death from cardiovascular causes occurred in a significantly smaller percentage of patients in the empagliflozin group than in the placebo group.

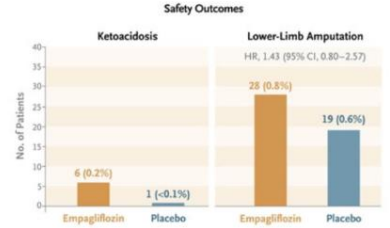
Safety: Ketoacidosis occurred in numerically more patients in the empagliflozin group than in the placebo group, as did lower-limb amputations. The incidence of serious adverse events overall and according to major organ class was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Fewer cardiovascular events occurred than expected, potentially affecting secondary and tertiary outcome assessments.
- Further study of patients with a urinary albumin-to-creatinine ratio of less than 300 may be useful.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for progression, empagliflozin therapy was associated with a lower risk of disease progression or death from cardiovascular causes than placebo.

Table 3 | Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial Registration number	Status as of July 2024
Drugs targeting the production of pathogenic forms of IgAN	Sibeprenlimab (VIS649)	APRIL	VISIONARY NCT05248646	In follow-up
	Zigakibart (BION-1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	In follow-up
	Povetacicept	APRIL/BAFF	RAINIER NCT06564142	Recruiting
Drugs targeting IgA-containing immune complex–mediated inflammation	Iptacopan (LNP023)	Complement alternative pathway factor B	APPLAUSE-IgAN NCT04578834	In follow-up
	Sefaxersen (RO7434656)	Complement alternative pathway factor B	IMAGINATION NCT05797610	Recruiting
	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376	Recruiting
Drugs targeting the generic downstream consequences of IgAN-induced nephron loss	Atrasentan	Endothelin A receptor	ALIGN NCT04573478	In follow-up

ALIGN, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Atrasentan in Patients With IgA Nephropathy at Risk of Progressive Loss of Renal Function; APPLAUSE-IgAN, A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients; APRIL, a proliferation-inducing ligand; BAFF, B cell–activating factor of the tumor necrosis factor family; BEYOND, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of BION-1301 in Adults With IgA Nephropathy; I CAN, A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis or Immunoglobulin A Nephropathy; IgAN, immunoglobulin A nephropathy; IMAGINATION, A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RO7434656, an Antisense Inhibitor of Complement Factor B, in Patients With Primary IgA Nephropathy at High Risk of Progression; ORIGIN3, A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With IgA Nephropathy (IgAN); RAINIER, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Povetacicept in Adults With Immunoglobulin A Nephropathy; VISIONARY, A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy.

Table 3 | Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial Registration number	Status as of July 2024
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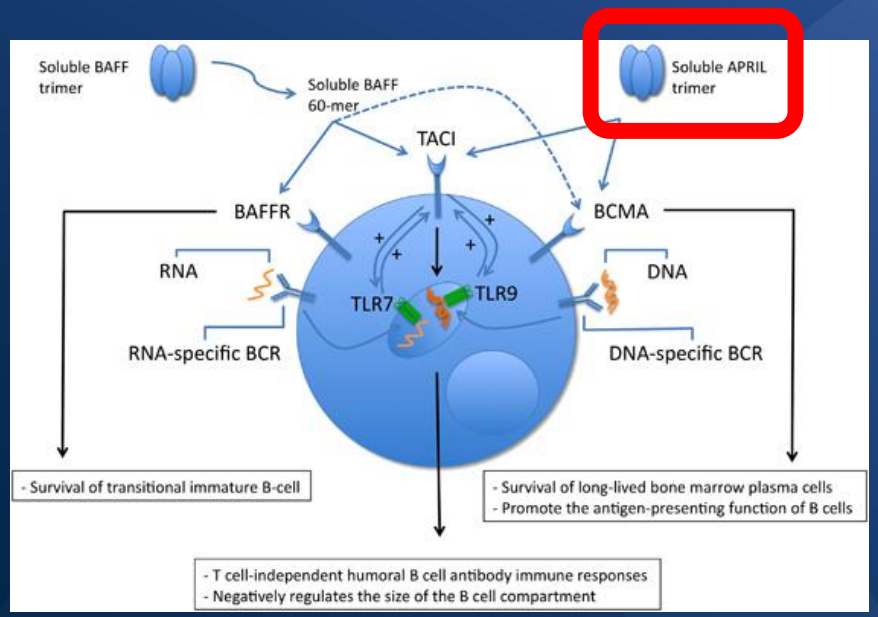
	Zigakibart (BION-1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	In follow-up
	Povetacicept	APRIL/BAFF	RAINIER NCT06564142	Recruiting
Drugs targeting IgA-containing immune complex–mediated inflammation	Iptacopan (LNP023)	Complement alternative pathway factor B	APPLAUSE-IgAN NCT04578834	In follow-up
	Sefaxersen (RO7434656)	Complement alternative pathway factor B	IMAGINATION NCT05797610	Recruiting
	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376	Recruiting
Drugs targeting the generic downstream consequences of IgAN-induced nephron loss	Atrasentan	Endothelin A receptor	ALIGN NCT04573478	In follow-up

ALIGN, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Atrasentan in Patients With IgA Nephropathy at Risk of Progressive Loss of Renal Function; APPLAUSE-IgAN, A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients; APRIL, a proliferation-inducing ligand; BAFF, B cell–activating factor of the tumor necrosis factor family; BEYOND, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of BION-1301 in Adults With IgA Nephropathy; I CAN, A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis or Immunoglobulin A Nephropathy; IgAN, immunoglobulin A nephropathy; IMAGINATION, A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RO7434656, an Antisense Inhibitor of Complement Factor B, in Patients With Primary IgA Nephropathy at High Risk of Progression; ORIGIN3, A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With IgA Nephropathy (IgAN); RAINIER, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Povetacicept in Adults With Immunoglobulin A Nephropathy; VISIONARY, A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy.



ACTIVE, NOT RECRUITING

Visionary Study: Phase 3 Trial of Sibeprenlimab in Immunoglobulin A Nephropathy (IgAN)

ClinicalTrials.gov ID NCT05248646

Sponsor Otsuka Pharmaceutical Development & Commercialization, Inc.

Information provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (Responsible Party)

Last Update Posted 2024-03-26

RESEARCH SUMMARY

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mathur M et al. DOI: 10.1056/NEJMoa2305635

CLINICAL PROBLEM

Among patients with IgA nephropathy, kidney failure develops in ≥30% within 20 to 30 years, despite the receipt of optimized standard care. A critical step in the pathogenesis of IgA nephropathy is the production of galactose-deficient IgA1 and resulting autoantibody release. Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL), a member of the tumor necrosis factor α superfamily that regulates IgA production.

CLINICAL TRIAL

Design: A phase 2, multicenter, double-blind, randomized, placebo-controlled, multiple-dose trial examined the efficacy and safety of sibeprenlimab in adults with IgA nephropathy at high risk for disease progression.

Intervention: 155 patients were assigned to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months. The primary end point was the change from baseline to month 12 in the log-transformed 24-hour urinary protein-to-creatinine ratio.

RESULTS

Efficacy: The 24-hour urinary protein-to-creatinine ratio decreased significantly more in the sibeprenlimab groups than in the placebo group. The decreases in the sibeprenlimab groups were dose-dependent.

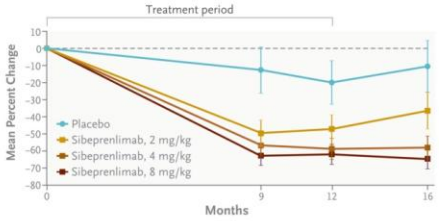
Safety: The incidence of adverse events, including serious adverse events, was similar in the sibeprenlimab groups and the placebo group.

LIMITATIONS AND REMAINING QUESTIONS

- Evidence of a return to baseline levels of APRIL in the 4 months after discontinuation of sibeprenlimab suggests that ongoing treatment will be needed.
- A phase 3 trial has been started to confirm these results in a larger patient population.

Links: Full Article | NEJM Quick Take | Editorial

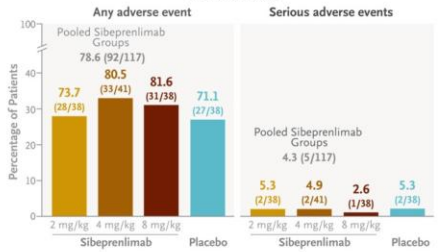
Change in 24-Hr Urinary Protein-to-Creatinine Ratio



Geometric Mean Percent Reduction in 24-Hr Urinary Protein-to-Creatinine Ratio

End Point	Sibeprenlimab 2 mg/kg (N=38)	Sibeprenlimab 4 mg/kg (N=41)	Sibeprenlimab 8 mg/kg (N=38)	Placebo (N=38)
Month 9	49.6±7.7	56.7±6.2	62.8±5.5	12.7±13.4
Month 12	**47.2±8.2**	**58.8±6.1**	**62.0±5.7**	**20.0±12.6**
Month 16	36.5±10.6	58.0±6.6	64.6±5.7	10.6±15.0

Adverse Events



CONCLUSIONS

Among patients with IgA nephropathy at high risk for disease progression, 12 months of treatment with sibeprenlimab resulted in a significantly greater reduction in proteinuria than placebo.

ORIGINAL ARTICLE

Sibeprenlimab in IgA Nephropathy — Interim Analysis of a Phase 3 Trial

V. Perkovic,[1] H. Trimarchi,[2] V. Tesar,[3] R. Lafayette,[4] M.G. Wong,[5] J. Barratt,[6] Y. Suzuki,[7] A. Liew,[8] H. Zhang,[9] K. Carroll,[10] V. Jha,[11-13] A. Quevedo,[14] S.H. Han,[15] M. Praga,[16] B. Chacko,[17] M. Sahay,[18] C.K. Cheung,[6] L. Kooienga,[19] M. Walsh,[20,21] J. Xia,[22] C. Fajardo,[22] L. Shah,[22] J. Hafkin,[22] and D.V. Rizk,[23] for the VISIONARY Trial Investigators Group*

ABSTRACT

BACKGROUND

The cytokine A proliferation-inducing ligand (APRIL) is considered a key driver of the pathogenesis of IgA nephropathy. Sibeprenlimab, a humanized IgG2 monoclonal antibody, selectively binds to and inhibits APRIL.

METHODS

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, we assigned adults with biopsy-confirmed IgA nephropathy in a 1:1 ratio to receive either subcutaneous sibeprenlimab at a dose of 400 mg or placebo administered every 4 weeks for 100 weeks. The primary end point for this interim analysis was the 24-hour urinary protein-to-creatinine ratio at 9 months as compared with baseline. The key secondary end point, to be reported at trial completion, is the annualized slope of estimated glomerular filtration rate over 24 months. Other secondary end points included the change in the level of serum immunoglobulin and safety. Exploratory end points included the change in galactose-deficient IgA1 and APRIL concentrations, the spot 24-hour urinary protein-to-creatinine ratio, hematuria, and remission of proteinuria.

RESULTS

A total of 510 patients underwent randomization — 259 to the sibeprenlimab group and 251 to the placebo group. The prespecified interim analysis included the first 320 patients (152 who received sibeprenlimab and 168 who received placebo) who had the opportunity to complete the 9-month evaluation of the 24-hour urinary protein-to-creatinine ratio. At 9 months, a significant reduction in 24-hour urinary protein-to-creatinine ratio was observed with sibeprenlimab (–50.2%) as compared with an increase with placebo (2.1%), corresponding to an adjusted geometric least-squares mean 24-hour urinary protein-to-creatinine ratio that was 51.2% (96.5% confidence interval [CI], 42.9 to 58.2) lower with sibeprenlimab than with placebo (P<0.001). The levels of APRIL and pathogenic galactose-deficient IgA1 at week 48 were reduced from baseline by 95.8% and 67.1%, respectively, with sibeprenlimab. The safety profile appeared to be similar with sibeprenlimab and placebo. No deaths were reported, and the incidence of serious adverse events that occurred during the treatment period was 3.5% with sibeprenlimab and 4.4% with placebo.

CONCLUSIONS

Sibeprenlimab resulted in a significant reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Otsuka Pharmaceutical Development and Commercialization. VISIONARY ClinicalTrials.gov number, NCT05248646.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Vlado Perkovic can be contacted at vlado.perkovic@unsw.edu.au or at University of New South Wales, Sydney, NSW 2052, Australia.

*A list of the VISIONARY trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 8, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2512133

The NEW ENGLAND JOURNAL of MEDICINE

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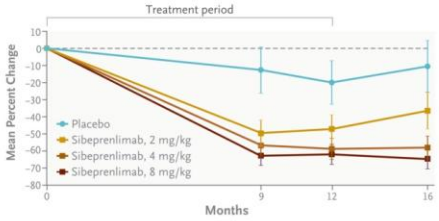

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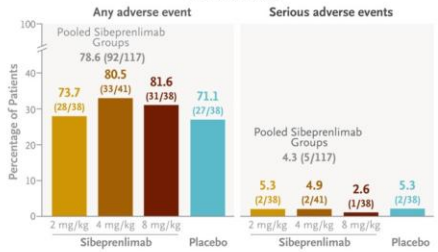

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The NEW ENGLAND JOURNAL of MEDICINE

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eGFR

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Leicester IgA Nephropathy Research Group

Novel Drug Approvals for 2025

What are "Novel" Drugs?

"Novel" drugs are new drugs never before approved or marketed in the U.S. See Drugs@FDA for information about all of CDER's approved drugs and biological products.

FDA Novel Drug Therapy Approvals for 2025

Search:

Export Excel

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date*
39.	Voyxact	sibeprenlimab-szsi	11/25/2025	To reduce proteinuria in primary immunoglobulin A nephropathy in adults at risk for disease progression
38.	Hyrnuo	sevabertinib	11/19/2025	To treat locally advanced or metastatic non-squamous non-small cell lung cancer with tumors that have activating HER2 tyrosine kinase domain activating mutations in patients who received a systemic therapy
37.	Redemplo	plozasiran	11/18/2025	To reduce triglycerides in adults with familial chylomicronemia syndrome
36.	Komzifti	ziftomenib	11/13/2025	To treat adults with relapsed or refractory acute myeloid leukemia with a susceptible nucleophosmin 1 mutation who have no satisfactory alternative treatment options
35.	Kygevvi	doxecitine and doxribtimine	11/3/2025	To treat thymidine kinase 2 deficiency in patients who start to show symptoms when they are 12 years old or younger
34.	Lynkuet	elinzanetant	10/24/2025	To treat moderate-to-severe vasomotor symptoms due to menopause
33.	Jascayd	nerandomilast	10/7/2025	To treat idiopathic pulmonary fibrosis
32.	Rhapsido	remibrutinib	9/30/2025	To treat chronic spontaneous urticaria in adults who remain symptomatic despite H1 antihistamine treatment
31.	Palsonify	paltusotine	9/25/2025	To treat acromegaly in adults who had an inadequate response to surgery and/or for whom surgery is not an option
30.	Inluriyo	imlunestrant	9/25/2025	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, estrogen receptor-1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy

Table 3 | Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial Registration number	Status as of July 2024
Drugs targeting the production of pathogenic forms of IgAN	Sibeprenlimab (VIS649)	APRIL	VISIONARY NCT05248646	In follow-up
	Zigakibart (BION-1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	In follow-up
	Povetacicept	APRIL/BAFF	RAINIER NCT06564142	Recruiting
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	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376	Recruiting
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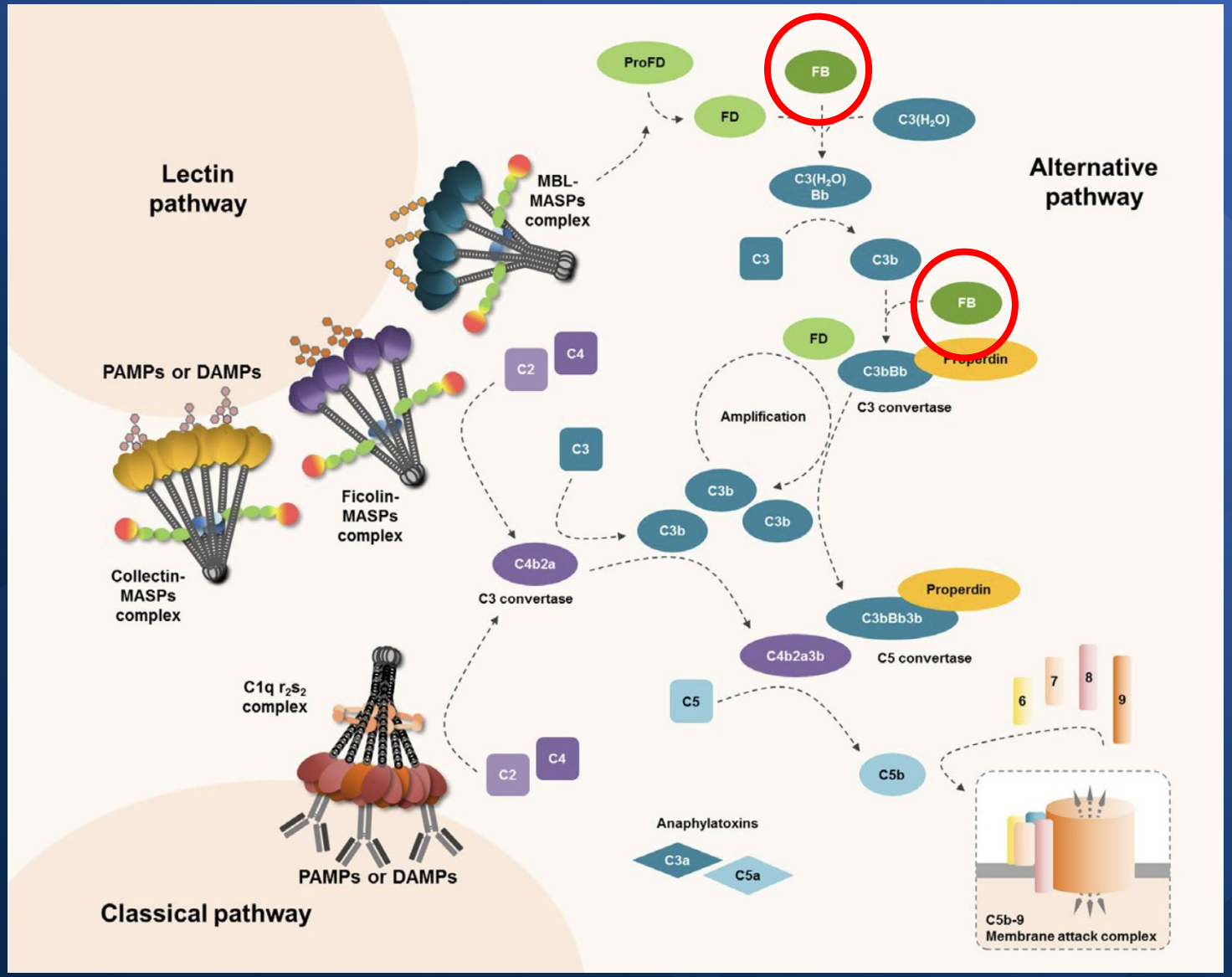

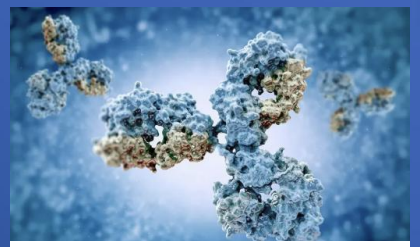

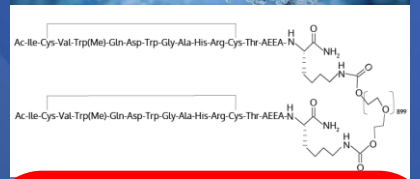

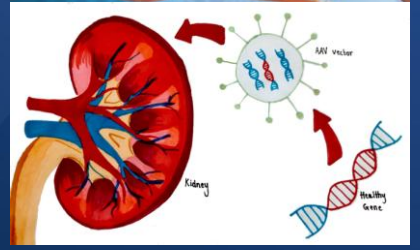

Results of a randomized double-blind placebo-controlled Phase 2 study propose iptacopan as an alternative complement pathway inhibitor for IgA nephropathy

see commentary on page 28

OPEN

Hong Zhang[1], Dana V. Rizk[2], Vlado Perkovic[3], Bart Maes[4], Naoki Kashihara[5], Brad Rovin[6], Hernán Trimarchi[7], Ben Sprangers[8,9], Matthias Meier[10], Dmitrij Kollins[10], Olympia Papachristofi[10], Julie Milojevic[11], Guido Junge[11], Prasanna Kumar Nidamarthy[12], Alan Charney[13] and Jonathan Barratt[14,15]

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Targeting the alternative complement pathway is an attractive therapeutic strategy given its role in the pathogenesis of immunoglobulin A nephropathy (IgAN). Iptacopan (LNP023) is an oral, proximal alternative complement inhibitor that specifically binds to Factor B. Our randomized, double-blind, parallel-group adaptive Phase 2 study (NCT03373461) enrolled patients with biopsy-confirmed IgAN (within previous three years) with estimated glomerular filtration rates of 30 mL/min/1.73 m^2 and over and urine protein 0.75 g/24 hours and over on stable doses of renin angiotensin system inhibitors. Patients were randomized to four iptacopan doses (10, 50, 100, or 200 mg bid) or placebo for either a three-month (Part 1; 46 patients) or a six-month (Part 2; 66 patients) treatment period. The primary analysis evaluated the dose–response relationship of iptacopan versus placebo on 24-hour urine protein-to-creatinine ratio (UPCR) at three months. Other efficacy, safety and biomarker parameters were assessed. Baseline characteristics were generally well-balanced across treatment arms. There was a statistically significant dose-response effect, with 23% reduction in UPCR achieved with iptacopan 200 mg bid (80% confidence interval 8-34%) at three months. UPCR decreased further through six months in iptacopan 100 and 200 mg arms (from a mean of 1.3 g/g at baseline to 0.8 g/g at six months in the 200 mg arm). A sustained reduction in complement biomarker levels including plasma Bb, serum Wieslab, and urinary C5b-9 was observed. Iptacopan was well-tolerated, with no reports of deaths, treatment-related serious adverse events or bacterial infections, and led to strong inhibition of alternative complement pathway activity and persistent proteinuria reduction in patients with IgAN. Thus, our findings support further evaluation of iptacopan in the ongoing Phase 3 trial (APPLAUSE-IgAN; NCT04578834).

Kidney International (2024) **105,** 189–199; https://doi.org/10.1016/j.kint.2023.09.027

KEYWORDS: alternative pathway; biomarkers; complement; IgA nephropathy; iptacopan (LNP023); proteinuria

IgA nephropathy (IgAN) is the most common form of glomerulonephritis,[1] with a global incidence of approximately 25 per million per year.[2] There are regional variations in biopsy practices and in the occurrence of IgAN, with a higher prevalence rate and a higher risk of progression to kidney failure observed in Asians.[3–5] Around 15% to 40% of patients with IgAN may develop kidney failure within 10 to 20 years of diagnosis, placing considerable socioeconomic burden on individuals, caregivers, and health care systems globally.[6,7] Risk factors for progression to kidney failure include persistent high proteinuria (>1 g/d), hypertension, reduced glomerular filtration rate (GFR), and histologic MEST-C score at diagnosis.[8–10]

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

V. Perkovic, J. Barratt, B. Rovin, N. Kashihara, B. Maes, H. Zhang, H. Trimarchi, D. Kollins, O. Papachristofi, S. Jacinto-Sanders, T. Merkel, N. Guerard, R. Renfurm, T. Hach, and D.V. Rizk, for the APPLAUSE-IgAN Investigators*

ABSTRACT

BACKGROUND

The alternative complement pathway plays a key role in the pathogenesis of IgA nephropathy. Iptacopan specifically binds to factor B and inhibits the alternative pathway.

METHODS

In this phase 3, double-blind, randomized, placebo-controlled trial, we enrolled adults with biopsy-confirmed IgA nephropathy and proteinuria (defined as a 24-hour urinary protein-to-creatinine ratio of ≥1 [with protein and creatinine both measured in grams]) despite optimized supportive therapy. Patients were randomly assigned, in a 1:1 ratio, to receive oral iptacopan (200 mg) or placebo twice daily for 24 months while continuing to receive supportive therapy. The primary objective of this prespecified interim analysis was to assess the efficacy of iptacopan as compared with that of placebo in reducing proteinuria at month 9; the primary end point was the change from baseline in the 24-hour urinary protein-to-creatinine ratio at month 9. The proportion of patients who had a 24-hour urinary protein-to-creatinine ratio of less than 1 at month 9 without receiving rescue or alternative medication or undergoing kidney-replacement therapy (dialysis or transplantation) was a secondary end point. Safety was also assessed. The effect of iptacopan on kidney function will be assessed at the end of the 2-year double-blind treatment period.

RESULTS

The main trial population included 222 patients in the iptacopan group and 221 in the placebo group. The interim efficacy analysis included the first 250 patients who underwent randomization in the main trial population (125 patients in each group) and who remained in the trial until month 9 or discontinued the trial by month 9. Safety was assessed in all the patients in the main trial population. At month 9, the adjusted geometric mean 24-hour urinary protein-to-creatinine ratio was 38.3% (95% confidence interval, 26.0 to 48.6; two-sided P<0.001) lower with iptacopan than with placebo. The reduction in proteinuria was supported by consistent results in secondary end point analyses. There were no unexpected safety findings with iptacopan. The incidence of adverse events that occurred during the treatment period was similar in the two groups; most events were mild to moderate in severity and reversible. No increased risk of infection was observed.

CONCLUSIONS

Among patients with IgA nephropathy, treatment with iptacopan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo. (Funded by Novartis; APPLAUSE-IgAN ClinicalTrials.gov number, NCT04578834.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Perkovic can be contacted at vlado.perkovic@unsw.edu.au or at the University of New South Wales, Sydney, NSW 2052, Australia.

*A complete list of the APPLAUSE-IgAN Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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www.kidney-international.org

Results of a rando placebo-controllec iptacopan as an al pathway inhibitor

Hong Zhang[1], Dana V. Rizk[2], Hernán Trimarchi[7], Ben Sprar Julie Milojevic[11], Guido Jung Jonathan Barratt[14,15]

[1]Renal Division, Peking University First Nephrology, Department of Medicine, Wales, Sydney, New South Wales, Aust Hypertension, Kawasaki Medical Schoc Columbus, Ohio, USA; [7]Nephrology Ser [8]Department of Microbiology, Immunc [9]Department of Nephrology, University for BioMedical Research, Basel, Switze Corporation, East Hanover, New Jerse John Walls Renal Unit, University Hosp

**Targeting the alternative complem attractive therapeutic strategy give pathogenesis of immunoglobulin A Iptacopan (LNP023) is an oral, pro complement inhibitor that specific Our randomized, double-blind, par Phase 2 study (NCT03373461) enrc biopsy-confirmed IgAN (within pre estimated glomerular filtration rate and over and urine protein 0.75 g/ stable doses of renin angiotensin s Patients were randomized to four 100, or 200 mg bid) or placebo for (Part 1; 46 patients) or a six-montl treatment period. The primary anal response relationship of iptacopan hour urine protein-to-creatinine ra months. Other efficacy, safety and were assessed. Baseline characteris balanced across treatment arms. T significant dose-response effect, w UPCR achieved with iptacopan 200 interval 8-34%) at three months. U through six months in iptacopan 1 (from a mean of 1.3 g/g at baseline

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include persistent high proteinuria (>1 g/d), hypertension, reduced glomerular filtration rate (GFR), and histologic MEST-C score at diagnosis.[8–10]

NOVARTIS

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Home > News > Novartis Fabhalta® (iptacopan) meets Phase III primary endpoint, slows kidney function decline in patients with IgA nephropathy (IgAN)

Novartis Fabhalta® (iptacopan) meets Phase III primary endpoint, slows kidney function decline in patients with IgA nephropathy (IgAN)

Oct 16, 2025

- *In APPLAUSE-IgAN final analysis, Fabhalta demonstrated statistically significant, clinically meaningful improvement in estimated glomerular filtration rate (eGFR) slope vs. placebo over two years*[1]
- *eGFR is key marker of kidney function; IgAN is progressive autoimmune kidney disease that leads to kidney failure in many patients*[1-3]
- *Fabhalta is first and only approved complement inhibitor for adults with IgAN and has potential to delay disease progression*[4,5]
- *Fabhalta received accelerated approval for reduction of proteinuria in adults with IgAN in US in 2024; data support 2026 submission for traditional FDA approval*[4,5]

Basel, October 16, 2025 – Novartis today announced positive final results from APPLAUSE-IgAN, a Phase III study evaluating Fabhalta® (iptacopan) in adults living with IgA nephropathy (IgAN). Fabhalta, an oral alternative complement pathway inhibitor, demonstrated statistically significant, clinically meaningful superiority compared to placebo in slowing IgAN progression measured by annualized total slope of estimated glomerular filtration rate (eGFR) decline over two years[1].

"Progressive diseases such as IgAN present an urgent need for interventions that can ultimately improve kidney health. Many people with IgAN commonly experience fear and anxiety of disease progression," said Ruchira Glaser, Development Unit Head, Cardiovascular, Renal & Metabolic, Novartis. "We are excited about today's positive Phase III APPLAUSE-IgAN results showing slowed eGFR decline, which add to the growing evidence of Fabhalta as a targeted therapy to preserve long-term kidney function, giving hope to people living with this condition."

Novartis intends to use these data to support Fabhalta submissions in 2026. Alongside Fabhalta, Novartis continues to advance its multi-asset IgAN portfolio, which also includes Vanrafia® (atrasentan) and investigational compound zigakibart.

IgAN is a progressive autoimmune kidney disease with approximately 25 per million people newly diagnosed worldwide each year[3]. IgAN is highly debilitating as it leads to glomerular inflammation, proteinuria, and a gradual decline in eGFR[2]. Up to 50% of patients with persistent proteinuria progress to kidney failure within 10 to 20 years of diagnosis, often requiring dialysis or kidney transplantation as part of long-term disease management[2,6,7]. Furthermore, people living with IgAN often face mental,

Table 3 | Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial Registration number	Status as of July 2024
Drugs targeting the production of pathogenic forms of IgAN	Sibeprenlimab (VIS649)	APRIL	VISIONARY NCT05248646	In follow-up
	Zigakibart (BION-1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	In follow-up
	Povetacicept	APRIL/BAFF	RAINIER NCT06564142	Recruiting
Drugs targeting IgA-containing immune complex–mediated inflammation	Iptacopan (LNP023)	Complement alternative pathway factor B	APPLAUSE-IgAN NCT04578834	In follow-up
	Sefaxersen (RO7434656)	Complement alternative pathway factor B	IMAGINATION NCT05797610	Recruiting
	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376	Recruiting
Drugs targeting the generic downstream consequences of IgAN-induced nephron loss	Atrasentan	Endothelin A receptor	ALIGN NCT04573478	In follow-up

ALIGN, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Atrasentan in Patients With IgA Nephropathy at Risk of Progressive Loss of Renal Function; APPLAUSE-IgAN, A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients; APRIL, a proliferation-inducing ligand; BAFF, B cell–activating factor of the tumor necrosis factor family; BEYOND, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of BION-1301 in Adults With IgA Nephropathy; I CAN, A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis or Immunoglobulin A Nephropathy; IgAN, immunoglobulin A nephropathy; IMAGINATION, A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RO7434656, an Antisense Inhibitor of Complement Factor B, in Patients With Primary IgA Nephropathy at High Risk of Progression; ORIGIN3, A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With IgA Nephropathy (IgAN); RAINIER, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Povetacicept in Adults With Immunoglobulin A Nephropathy; VISIONARY, A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy.

ORIGINAL ARTICLE

Atrasentan in Patients with IgA Nephropathy

Hiddo J.L. Heerspink, Ph.D., Meg Jardine, M.B., B.S., Ph.D., Donald E. Kohan, M.D., Ph.D., Richard A. Lafayette, M.D., Adeera Levin, M.D., Adrian Liew, M.D., Hong Zhang, Ph.D., Amit Lodha, M.B., B.S., Todd Gray, M.S.P.H., Yi Wang, Ph.D., Ronny Renfurm, M.D., and Jonathan Barratt, M.D., for the ALIGN Study Investigators*

ABSTRACT

BACKGROUND

Patients with IgA nephropathy and severe proteinuria have a high lifetime risk of kidney failure. The efficacy and safety of the selective endothelin type A receptor antagonist atrasentan in reducing proteinuria in patients with IgA nephropathy are incompletely understood.

METHODS

We are conducting a phase 3, multinational, double-blind, randomized, controlled trial involving adults with biopsy-proven IgA nephropathy, a total urinary protein excretion of at least 1 g per day, and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m^2 of body-surface area. Patients were randomly assigned to receive atrasentan (0.75 mg per day) or matched placebo for 132 weeks. The primary outcome, assessed at a prespecified interim analysis of data from the first 270 patients in the main stratum, was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36; the change was estimated with the use of a repeated-measures model. (An exploratory stratum of patients who were receiving a sodium–glucose cotransporter 2 inhibitor were included in a separate analysis.) Safety analyses were based on adverse events across the entire main stratum.

RESULTS

A total of 340 patients were recruited into the main stratum. Among the first 270 patients in the main stratum (135 per trial group) who completed the week 36 visit, the geometric mean percentage change in the urinary protein-to-creatinine ratio relative to baseline was significantly greater with atrasentan (–38.1%) than with placebo (–3.1%), with a geometric mean between-group difference of –36.1 percentage points (95% confidence interval, –44.6 to –26.4; P<0.001). The percentage of patients with adverse events did not differ substantially between the two groups. Fluid retention was reported by 19 of 169 patients (11.2%) in the atrasentan group and in 14 of 170 (8.2%) in the placebo group but did not lead to discontinuation of the trial regimen. No apparent cases of cardiac failure or severe edema occurred.

CONCLUSIONS

In this prespecified interim analysis, atrasentan resulted in a significant and clinically meaningful reduction in proteinuria as compared with placebo in patients with IgA nephropathy. (Funded by Novartis; ALIGN ClinicalTrials.gov number, NCT04573478.)

From the Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands (H.J.L.H.); the National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (M.J.); the Division of Nephrology, University of Utah Health, Salt Lake City (D.E.K.); Stanford University, Stanford, CA (R.A.L.); the University of British Columbia, Vancouver, Canada (A. Levin); Mount Elizabeth Novena Hospital, Singapore (A. Liew); Peking University First Hospital, Beijing (H.Z.); Chinook Therapeutics, Seattle (T.G.); Novartis, East Hanover, NJ (A. Lodha, Y.W.); Novartis, Basel, Switzerland (R.R.); and the University of Leicester, Leicester, United Kingdom (J.B.). Dr. Heerspink can be contacted at h.j.lambers.heerspink@umcg.nl or at University Medical Center Groningen, Hanzeplein 1, PO Box 30 001, 9700 RB Groningen, the Netherlands.

*A complete list of the ALIGN Study Investigators is available in the Supplementary Appendix, available at NEJM.org.

This article was published on October 25, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2409415

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eGFR

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Role of B cell-targeted therapies in the management of IgAN

Professor Jonathan Barratt

University of Leicester

&

John Walls Renal Unit, Leicester

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

December 5th 16.25—17.40

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

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Leicester IgA Nephropathy Research Group

Future Clinical Trials in IgA Nephropathy

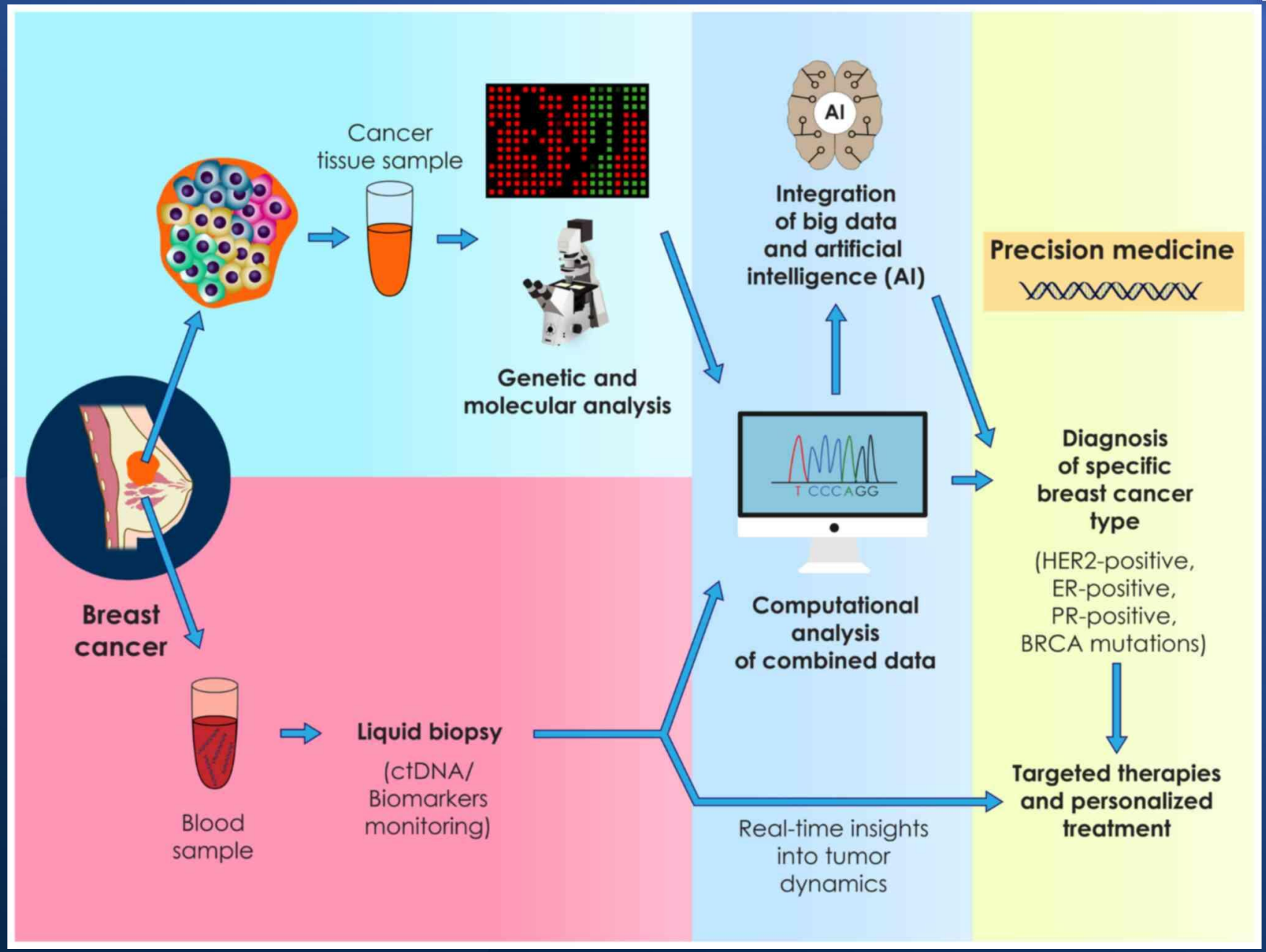
Professor Jonathan Barratt

University of Leicester

&

John Walls Renal Unit, Leicester

December 6th 11.10—12.25


Cancer tissue sample
Genetic and molecular analysis
AI
Integration of big data and artificial intelligence (AI)
Precision medicine
Breast cancer
T CCCAGG
Computational analysis of combined data
Diagnosis of specific breast cancer type
(HER2-positive, ER-positive, PR-positive, BRCA mutations)
Blood sample
Liquid biopsy
(ctDNA/ Biomarkers monitoring)
Real-time insights into tumor dynamics
Targeted therapies and personalized treatment

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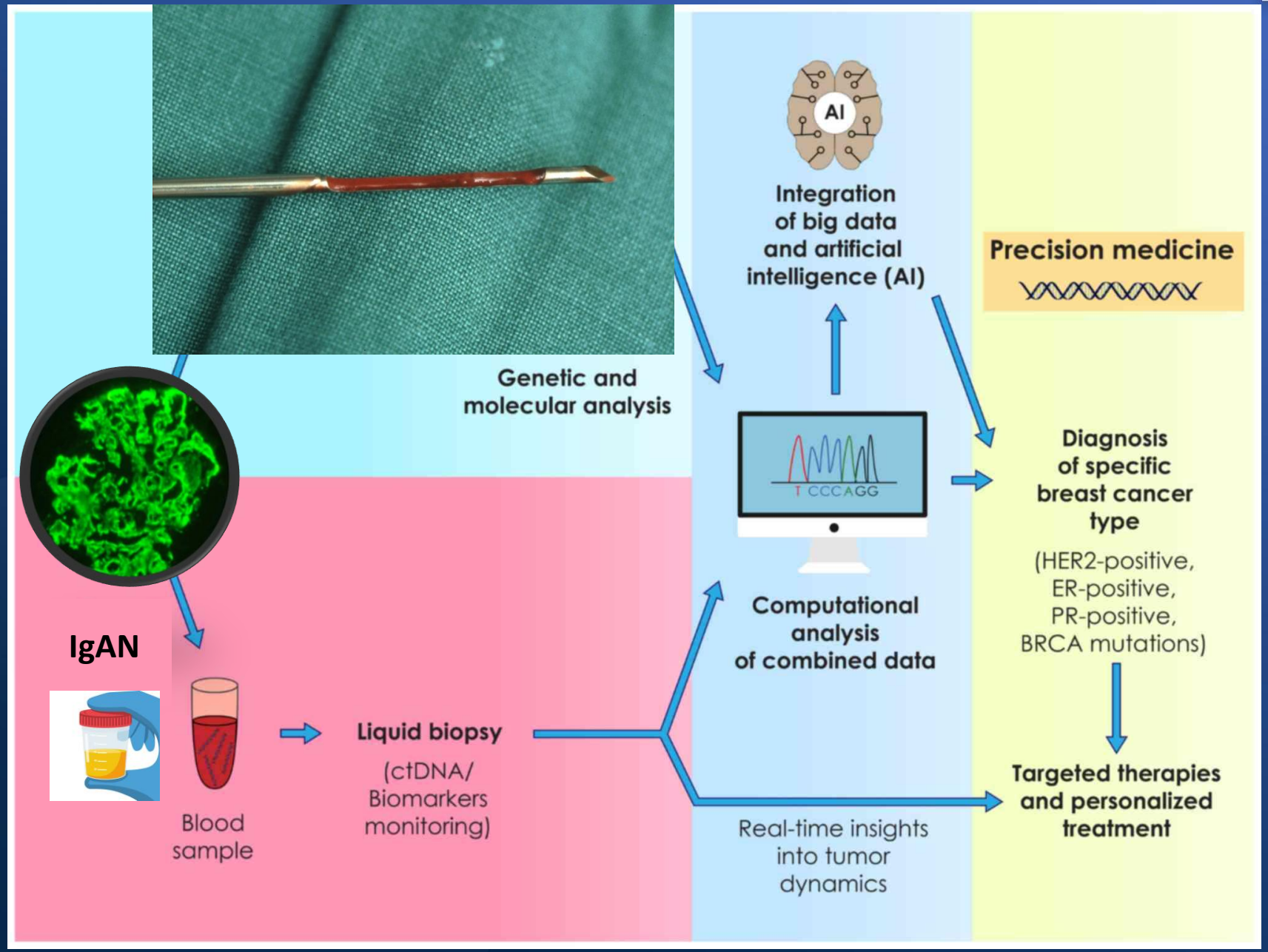

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Recruiting

Trial of the Impact of Sibeprenlimab on Immunoglobulin A Nephropathy Kidney Tissue

ClinicalTrials.gov ID NCT06740526

Sponsor Otsuka Pharmaceutical Development & Commercialization, Inc.

Information provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (Responsible Party)

Last Update Posted 2025-04-06

62nd ERA CONGRESS VIENNA & VIRTUAL JUNE 4-7, 2025 Beyond Nephrology

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

DANA V. RIZK[1], BART MAES[2], HONG ZHANG[3], MATTHIAS KRETZLER[4], FRANK EITNER[5], CLINT W. ABNER[6], MARIE-ANNE VALENTIN[6], VIPIN N[7], MARIA FERNANDA DI TATA[8], JONATHAN BARRATT[9]

[1]The University of Alabama at Birmingham, Alabama, United States of America, [2]Delta General Hospital, West Flanders, Belgium, [3]Peking University First Hospital, Beijing, P.R. China, [4]University of Michigan, Ann Arbor, MI, United States of America, [5]Novartis Pharma AG, Basel, Switzerland, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States of America, [7]Novartis Healthcare Ltd, Hyderabad, India, [8]Novartis Farmaceutica SA, Barcelona, Spain, [9]University of Leicester & Leicester General Hospital, Leicester, United Kingdom

INTRODUCTION

- Overactivation of the alternative pathway is one of the key drivers of IgAN. Targeting the alternative pathway may address an unmet need for targeted immunomodulation and result in the improvement of kidney function and prevention of disease progression.[1,2]
- Iptacopan is a proximal complement inhibitor that targets factor B to specifically inhibit the alternative complement pathway while leaving signaling from the lectin and classical pathways intact.[1,3,4]

AIM

- This repeat-biopsy mechanistic study aims to evaluate the effects of iptacopan on the underlying immunopathology in patients with IgAN and to better understand the role of complement activation in IgAN

ABBREVIATIONS

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; bid, twice a day; C3c, complement 3c; eGFR, estimated glomerular filtration rate; FMV, first morning void; IgAN, IgA nephropathy; RBC/HPF, red blood cell per high power field; SGLT2i, sodium-glucose co-transporter 2 inhibitors; UPCR, urine protein–creatinine ratio.

METHOD

- This Phase IIa multicenter, single-arm, open-label, repeat-biopsy study will enroll up to 20 adult patients with IgAN (**Figure**).
- Key inclusion criteria include biopsy-proven IgAN; eGFR ≥30 mL/min/1.73 m^2; proteinuria ≥0.8 g/g from FMV; receiving a maximally tolerated and/or stable dose of supportive care treatment (ACEi or ARB and/or SGLT2i) for ≥90 days before baseline. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* must be completed, and—if available and per local regulations—*Haemophilus influenzae* vaccination should be administered, at least 2 weeks before starting study treatment.
- The primary, secondary, exploratory objectives are listed in the **Table**.

bid, twice a day; D, day; EOT, end of treatment; n, number of participants. *Eligible participants may enroll in the roll-over extension study, contingent upon local regulations.

Table: Key Study Objectives

Objective	Endpoint (s)
Primary	
Quantifying the change after treatment with iptacopan in mesangial C3c and C3c-containing fragments	Achievement of a minimum one-grade reduction from baseline at 9 months in mesangial C3c and C3c-containing fragments
Secondary	
Describing the histopathological changes after iptacopan treatment	Change from baseline at 9 months in CD68+ cells and immunoglobulins
Exploratory	
Evaluating the histopathological changes in complement biomarkers after treatment with iptacopan	Change from baseline at 9 months in MEST-C score
Describing changes in UPCR, hematuria, and eGFR after treatment with iptacopan	Log-transformed ratio to baseline of UPCR at 9 months. Change from baseline at 9 months in dipstick and RBC/HPF, and in eGFR
Exploring the correlation of histopathological changes with proteinuria and eGFR changes after treatment with iptacopan	Correlation between changes in histology and eGFR changes

CONCLUSIONS

- This repeat-biopsy 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 the mechanistic effects of iptacopan on IgAN and potential kidney protective benefits.

REFERENCES

1. Zhang H, et al. *Kidney Int.* 2024;105(1):189-199
2. Rizk DV, et al. *Kidney Int Rep.* 2023. 9;8(5):968-979
3. Schubart A, *et al. Proc Natl Acad Sci USA.* 2019;116(16):7926-7931
4. Novartis Pharmaceuticals Corporation. Fabhalta prescribing information. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/218276s000lbl.pdf (accessed May 2025).

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CONTACT INFORMATION

In case of any questions, please contact Dr. D.V. Rizk at: drizk@uabmc.edu.

RECRUITING

A Study to Evaluate the Efficacy and Safety of RO7434656 in Participants With Primary Immunoglobulin A (IgA) Nephropathy at High Risk of Progression (IMAGINATION)

ClinicalTrials.gov ID NCT05797610

Sponsor Hoffmann-La Roche

Information provided by Hoffmann-La Roche (Responsible Party)

Last Update Posted 2024-05-10

RECRUITING

Study of Ravulizumab in Immunoglobulin A Nephropathy (IgAN) (ICAN)

ClinicalTrials.gov ID NCT06291376

Sponsor Alexion Pharmaceuticals, Inc.

Information provided by Alexion Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2024-05-03

Recruiting

Evaluation of Efficacy of Povetacicept in Adults With Immunoglobulin A Nephropathy (IgAN)

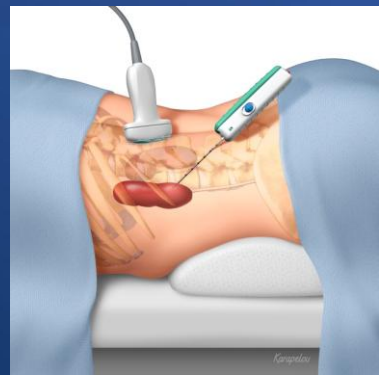
ClinicalTrials.gov ID NCT06564142

Sponsor Alpine Immune Sciences Inc, A Subsidiary of Vertex

Information provided by Alpine Immune Sciences, Inc. (Alpine Immune Sciences Inc, A Subsidiary of Vertex) (Responsible Party)

Last Update Posted 2024-12-05

SPARTAN



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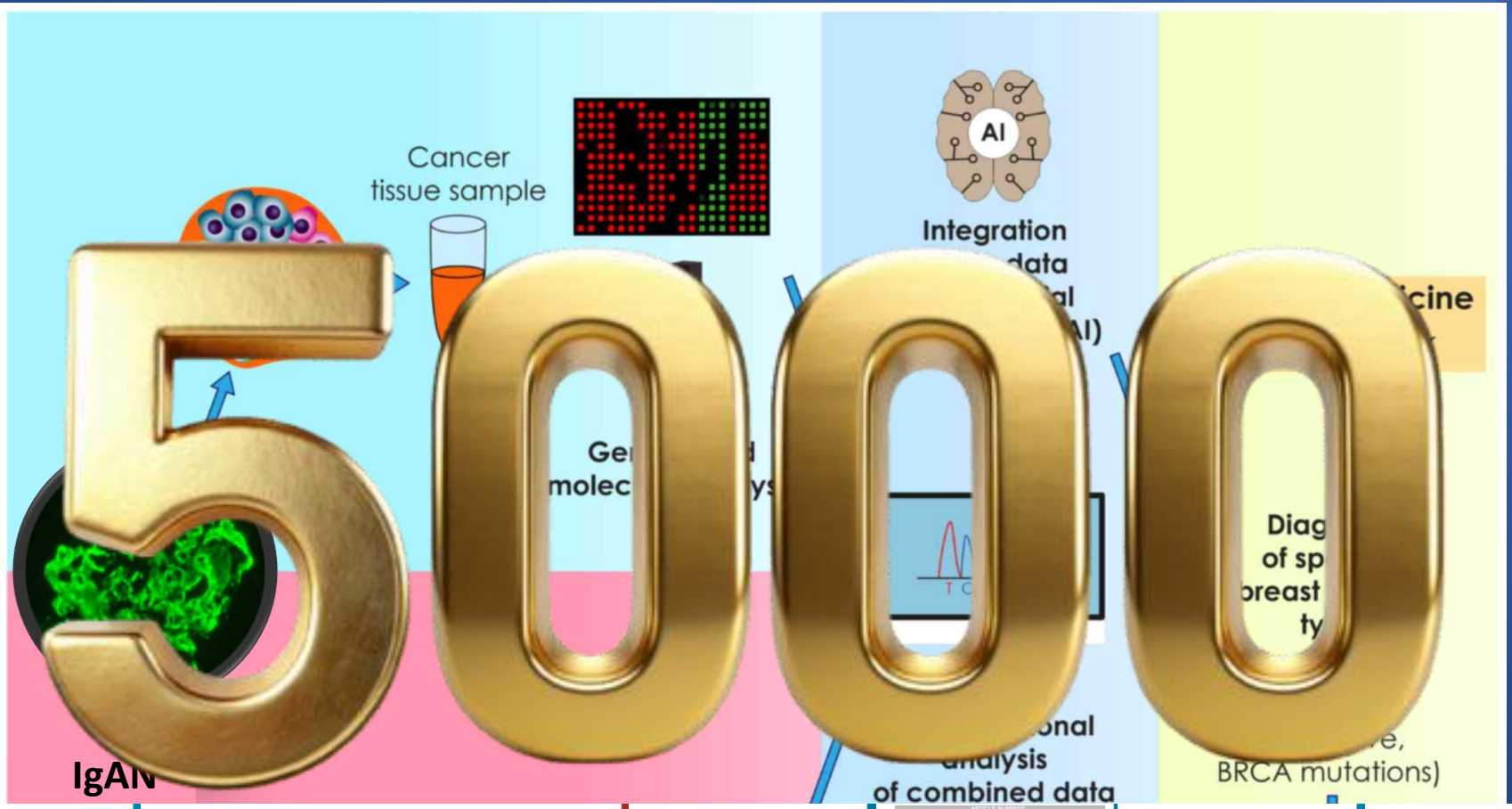

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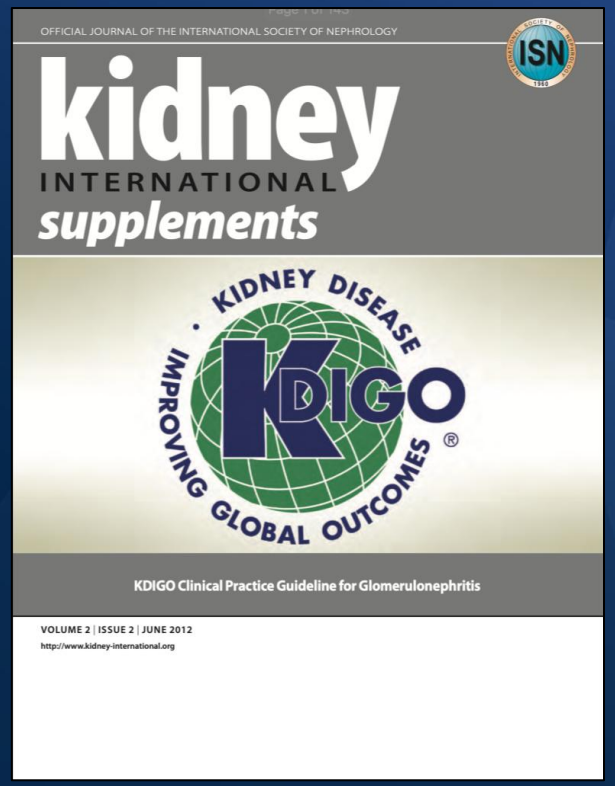

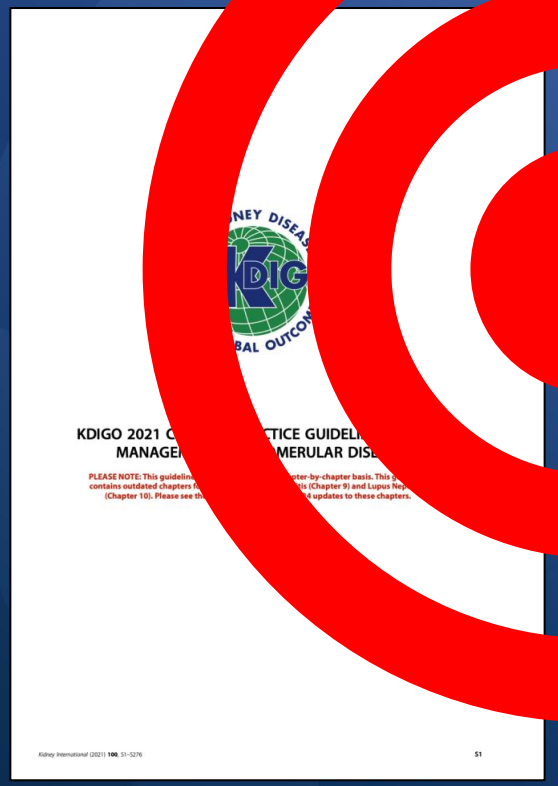

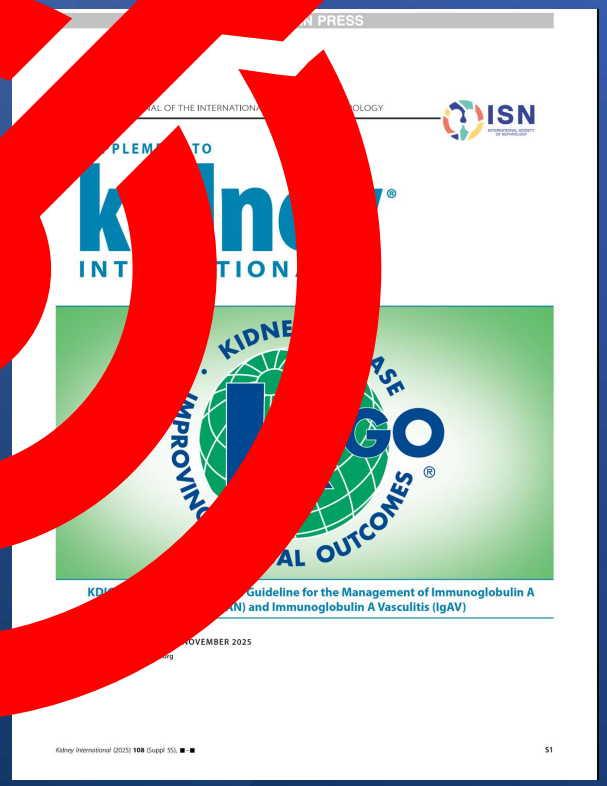

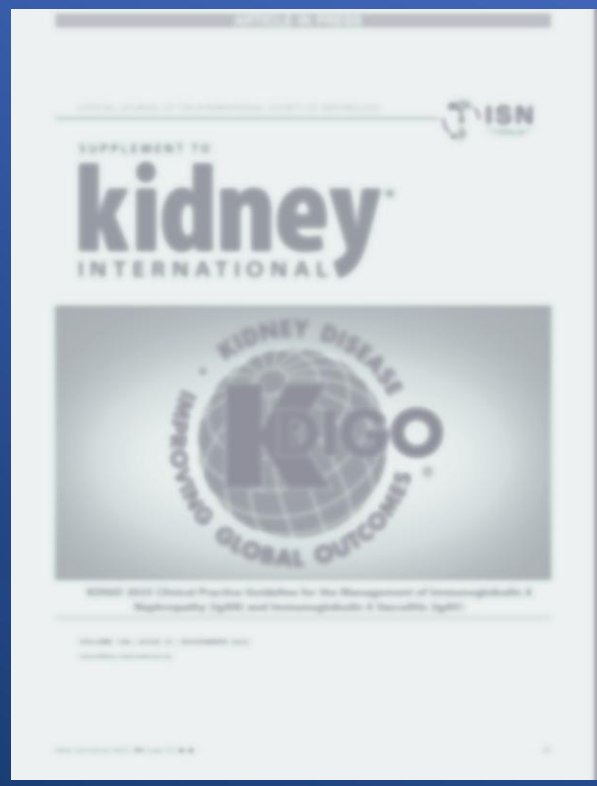

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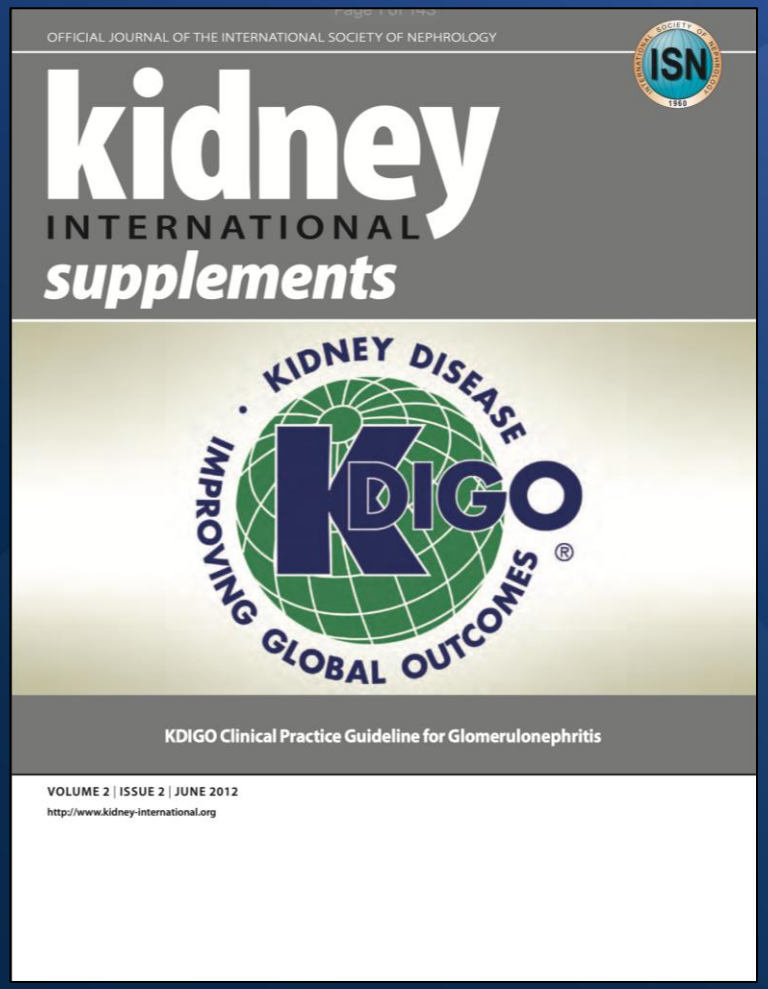

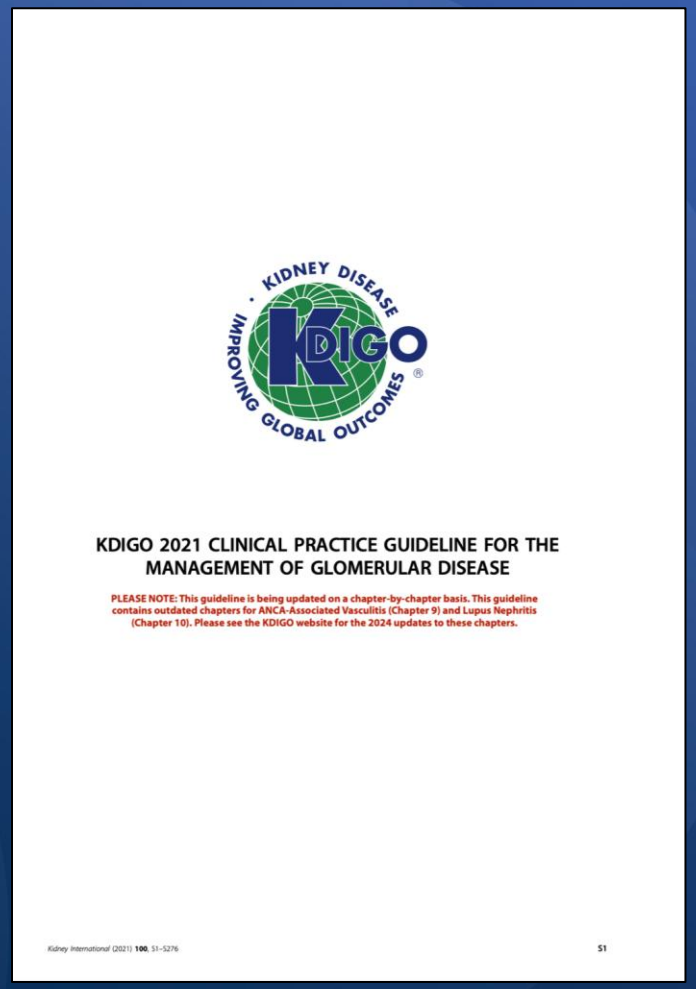

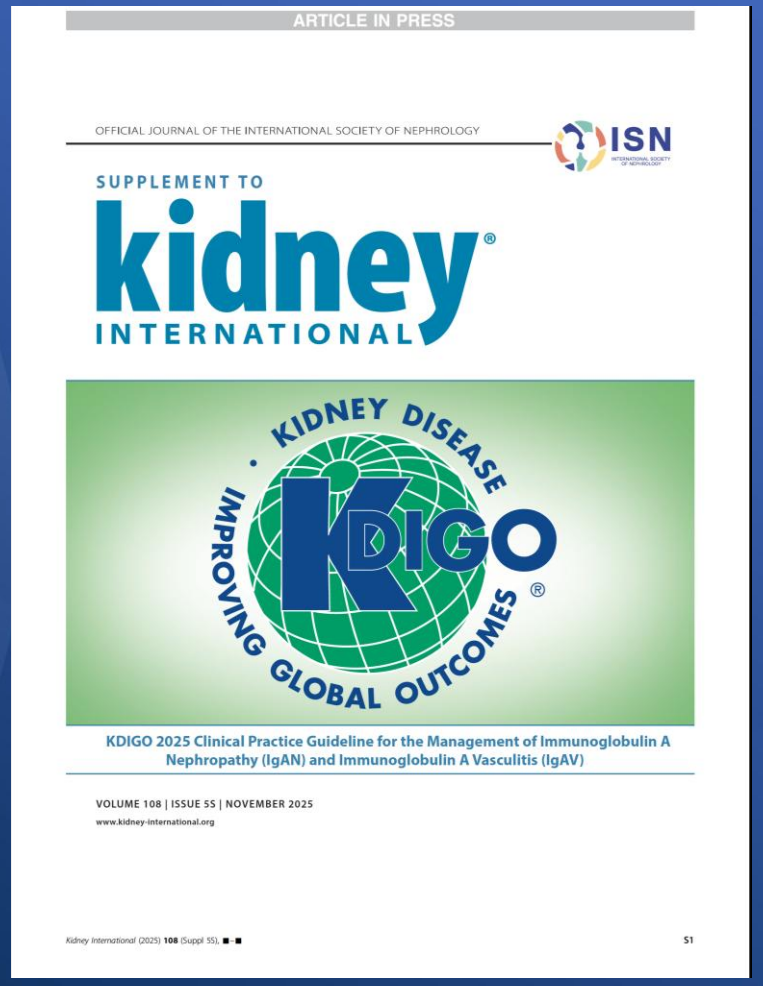

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