The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Updates In IgA Nephropathy

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TEHRAN 2023

Introduction

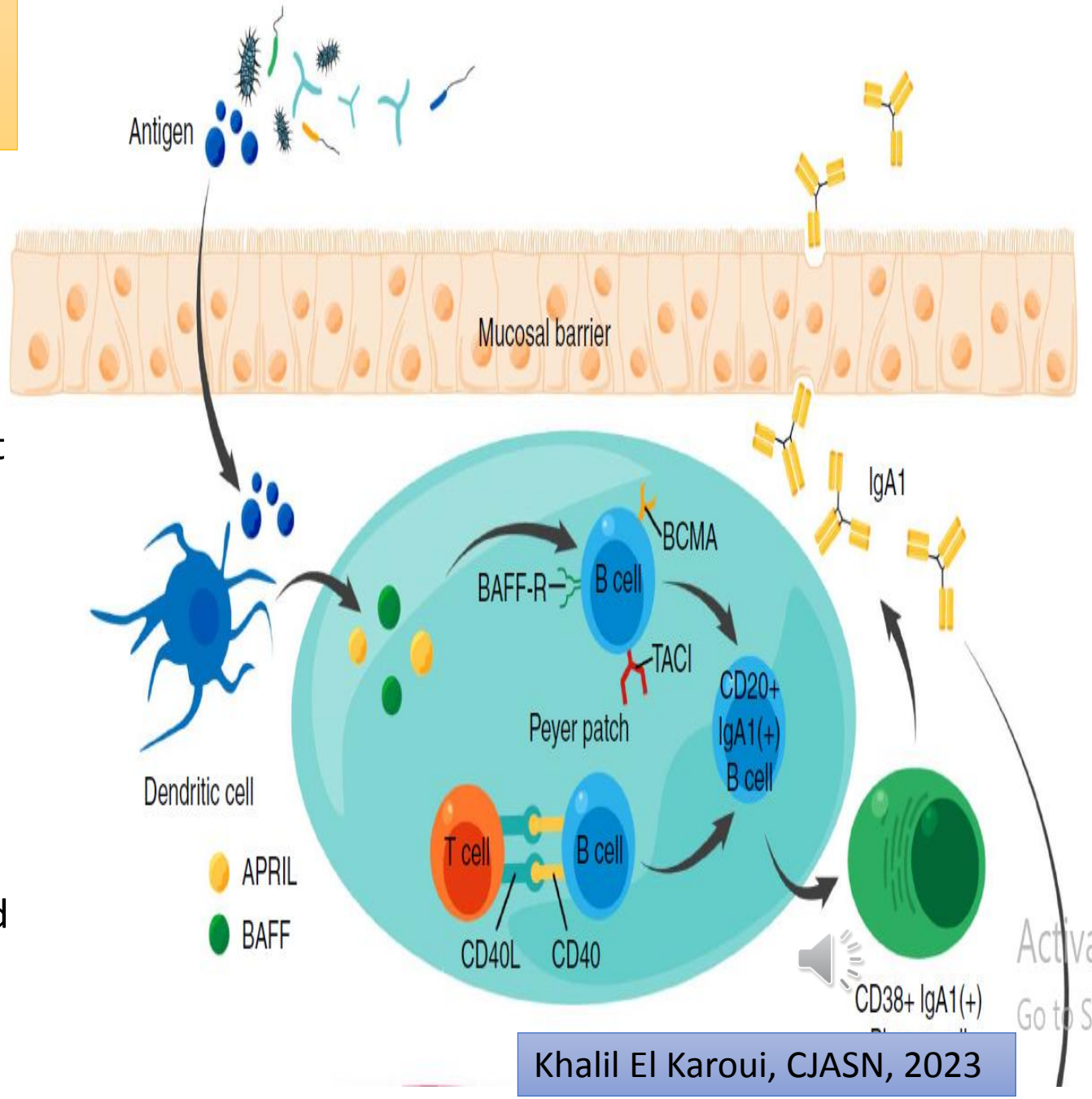
- ✓IgA nephropathy (IgAN) is the most common primary glomerular disease with a marked heterogeneity in its clinical and pathological features.
- ✓Most common cause of kidney failure in Asia, has lower prevalence in Europe, and is very infrequent among populations of African.
- ✓Among patients with reduced renal function and proteinuria >1g/24 h, outcomes remain poor and up to 50% of such patients will progress to ESKD over 10 years.

Pathogenesis of IgA nephropathy

Mucosal IgA is produced within the MALT, more particularly in the GALT, including the Peyer patches, and the NALT, where it plays a key role in the host defense against pathogens.

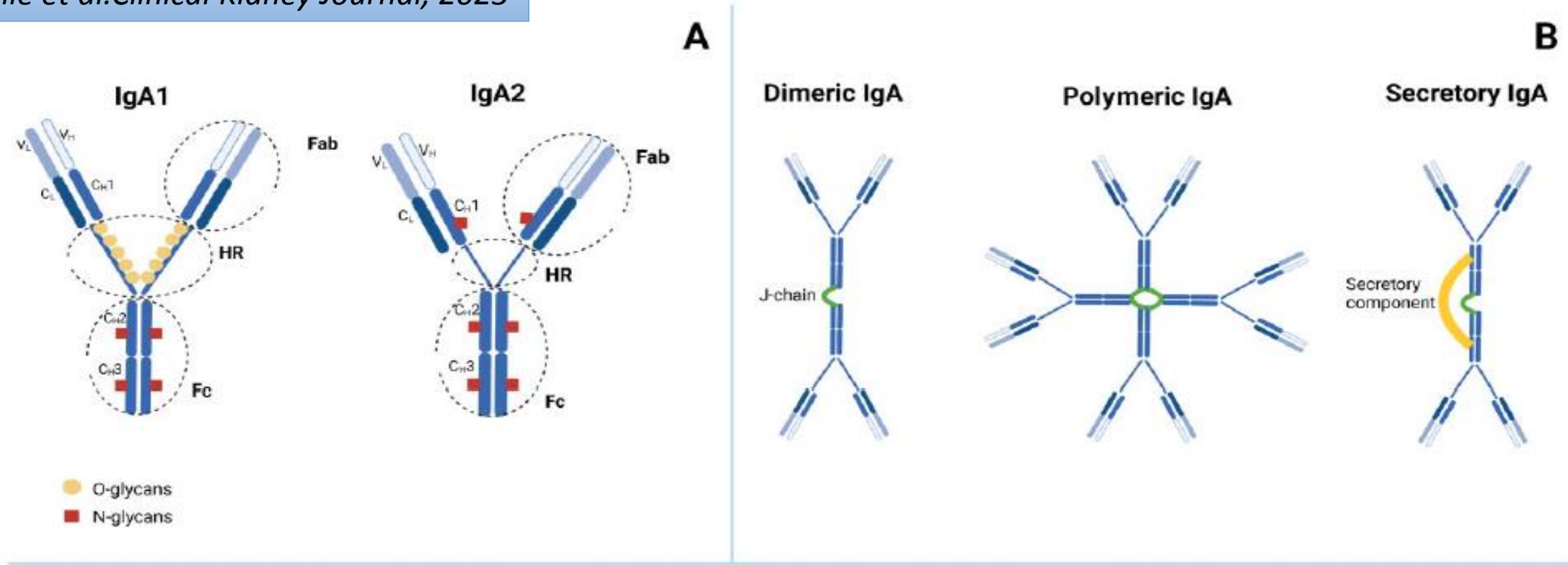
Antigens from the gastrointestinal and respiratory tract are processed by the innate immune system, among which dendritic cells Class switching of naïve B cells to IgA1+ B cells occurs via T-cell–dependent (including CD40–CD40L interaction) and T-cell–independent mechanisms, the latter with a critical role for BAFF and APRIL.

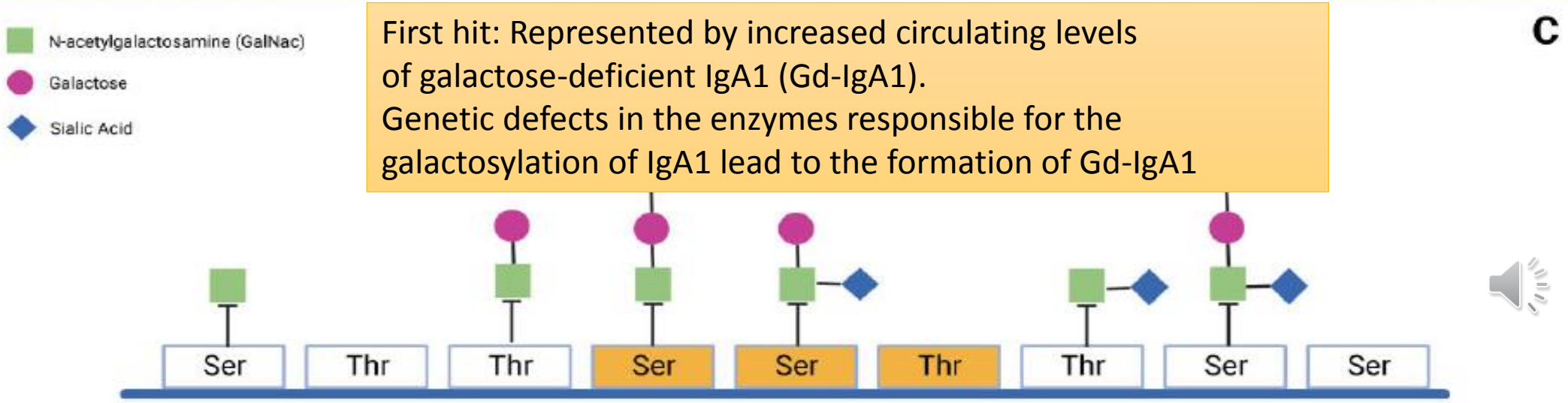
Both cytokines stimulate B cells via TACI, BCMA, or BAFF-R. IgA1(+) B cells differentiate into IgA1(+) B plasma cells that traffic toward the mucosal surface and produce IgA1, which subsequently enters the lumen.



Khalil El Karoui, CJASN, 2023

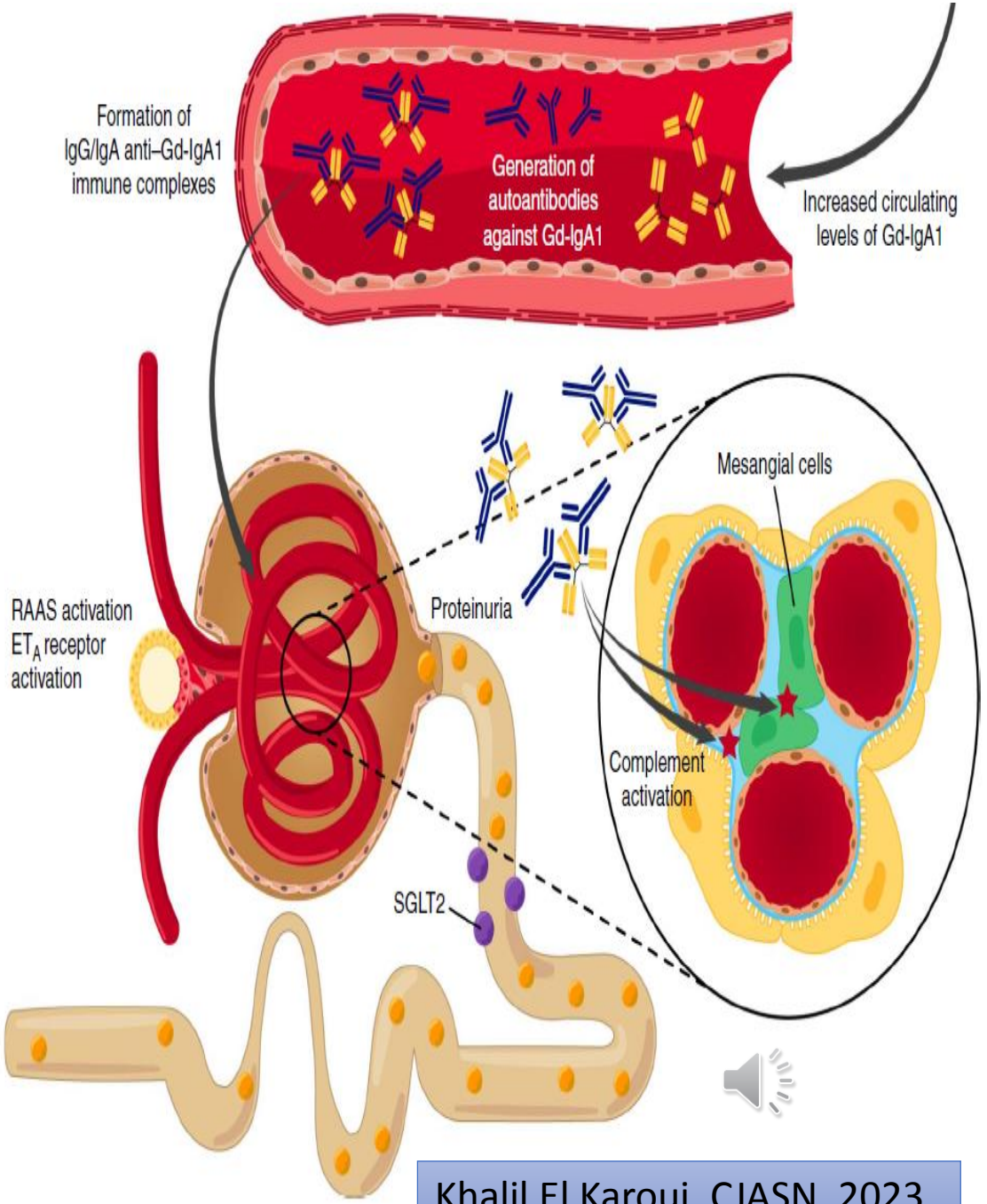
Gentile et al.Clinical Kidney Journal, 2023





First hit: Represented by increased circulating levels of galactose-deficient IgA1 (Gd-IgA1).
Genetic defects in the enzymes responsible for the galactosylation of IgA1 lead to the formation of Gd-IgA1

The second hit: the development of autoantibodies directed against the poorly galactosylated region of IgA1.
The third hit: subsequent circulating immune complex formation consisting of Gd-IgA1 and anti–Gd-IgA1-IgG, IgA, and/or IgM antibodies.
The fourth hit: binding of these immune complexes to mesangial cells, leading to mesangial cell activation.



Khalil El Karoui, CJASN, 2023

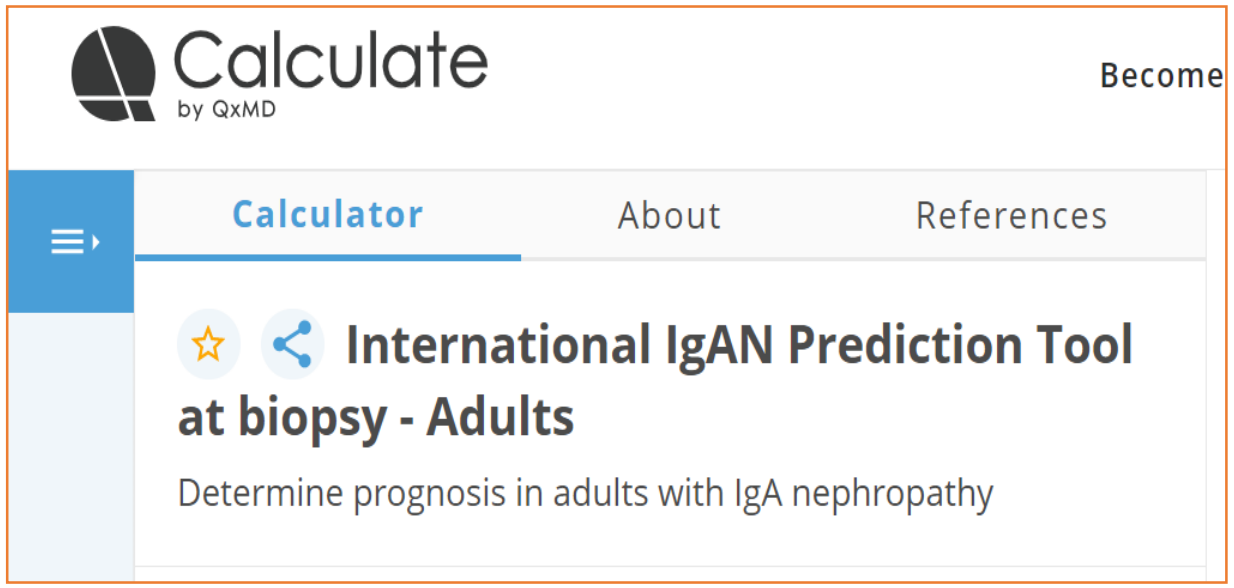
Risk Factors to disease progression

- ✓Proteinuria > 1gram/ 24 hours
- ✓Hypertension
- ✓Reduced GFR
- ✓Microscopic Hematuria
- ✓Histologic Predictors (MESTC Classification): The presence of predominantly active proliferative lesions (higher M and/or E scores), crescents (higher C score) or S1 lesions with podocytopathic features.

Considerations for the prognostication of primary IgAN:

- ✓Clinical and histologic data at the time of biopsy can be used to risk stratify patients.
- ✓ The International IgAN Prediction Tool is a valuable resource to quantify risk of progression and inform shared decision-making with patients.
- ✓**Calculate by QxMD**
- ✓**No validated prognostic serum or urine biomarkers** for IgAN other than eGFR and proteinuria.

KDIGO, Kidney International (2021), 100, S115



Risk Assessment 1-2 year after biopsy
Hematuria and crescent not included
No recommendation for treatment based on calculator
Needs more work on different ethnicity
New adjustment for children

Risk factors for progression

- ✓Estimated GFR
- ✓Blood pressure
- ✓Proteinuria
- ✓Age
- ✓Race/ethnicity (White, Japanese, Chinese, or other)
- ✓Prior use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- ✓Oxford classification of IgAN MEST histology scores
- ✓Immunosuppression use at or prior to biopsy

Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy

- ✓A strong and consistent relationship between the level and duration of proteinuria and loss of kidney function.
- ✓Trial-level analyses of data from 13 controlled trials(830 subjects) showed an association between treatment effects on percent reduction of proteinuria and treatment effects on a composite of time to doubling of serum creatinine, ESKD.

Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, and reduction to under 1 g/d is a reasonable treatment target.(KDIGO 2021)

Thompson et al , Clin J Am Soc Nephrol, 2019

Supportive therapy in IgAN

Blood pressure management	Dietary advices and fluid management	Lifestyle modifications	Additional measures
• target sitting systolic BP <120 mmHg • preferred antihypertensives: - first choice: ACE inhibitors or ARBs (with dosage uptitration as tolerated) in all patients with proteinuria > 0.5 g/d; no combination therapy - non-diydropyridine calcium channel blockers (e.g. verapamil, diltiazem) - aldosterone antagonists - beta blockers • avoid dihydropyridine calcium-channel blockers (e.g. amlodipine, nifedipine)	• restrict sodium intake to less than 2 g/d or 90 mmol/d and/or use diuretics • control protein intake • control fluid intake (less than 1.5 to 2 L/d)	• quit smoking • normalize body weight • encourage regular endurance sports, avoid strenuous exercise	• avoid NSAIDs • avoid prolonged severe hyperkalemia • consider hydroxychloroquine in proteinuric patients despite maximal dosage of RAS blocker • SGLT-2 inhibitor (currently off-label; status 8/2021)

High Risk of progression

- ✓Proteinuria >0.75–1 g/d despite ‡90 days of optimized supportive care.
- ✓The utility of the Oxford classification in guiding therapy such as immunosuppression remains uncertain.However, the presence of active proliferative lesions (ie, higher M and/or E scores) or crescents (higher C score) may be an indication to treat more aggressively
- ✓Dynamic assessment of patient risk over time should be Performed.
- ✓Adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m2.

KDIGO 2021

✓Recommendation 2.3.1.1: We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 ml/min per 1.73 m2 (2B).

Study	Medication	Start dose	Duration high dose	Taper	Total exposure
TESTING[1]	Methylprednisolone	0.6–0.8 mg/kg/d (per investigator), rounded to nearest 4 mg. Max 48 mg/d	2 months	8 mg/month	6–8 months
Manno[2]	Prednisone	1 mg/kg/d, max 75 mg/d	2 months	0.2 mg/kg/ month	6 months
Lv[3]	Prednisone	0.8–1 mg/kg/d	8 weeks	5–10 mg/d every 2 weeks	8 months

KDIGO, Kidney International (2021), 100, S115

Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	In a single RCT conducted in China, MMF with low-dose glucocorticoids was noninferior to standard-dose glucocorticoids 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. There were significantly fewer glucocorticoid-related side effects in the combination-therapy arm.[1, 5]
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy.[2–5]
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.[6]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

KDIGO, Kidney International (2021), 100, S115

Effect of immunosuppression, compared with supportive care, in real-world setting of IgA nephropathy

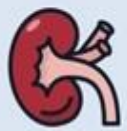
CJASN
Clinical Journal of American Society of Nephrology

China

January 2019
to May 2022

Patients with
IgA Nephropathy
n=3946

36 years
Mean age



eGFR 85
mL/min/1.73 m^2

1.4 g/ 24 hr
Mean proteinuria

INTERVENTION

New users of
immunosuppressive
agents
n=1973

Propensity score
matched recipients
of supportive care
n=1973

Composite of 40% decrease in eGFR, kidney failure, and all-cause mortality

PRIMARY OUTCOME

8%

aHR 0.60
(95% CI 0.48-0.75)

12%

Comparable effect size was observed for glucocorticoid monotherapy and mycophenolate mofetil alone

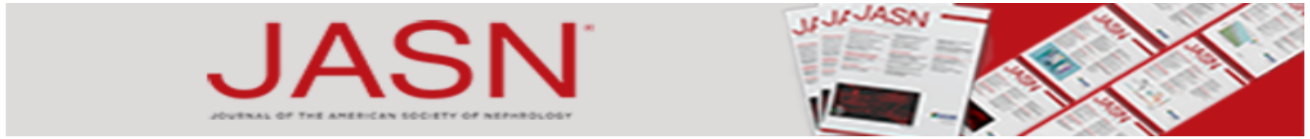
In the prespecified subgroup analysis, treatment effects of immunosuppression were consistent across ages, genders, levels of proteinuria, and the values of eGFR at baseline

Serious adverse events were more frequent in the immunosuppression group compared with the supportive care group

Conclusions: Immunosuppressive therapy, compared with supportive care, was associated with a 40% lower risk of clinically important kidney outcomes in patients with IgA nephropathy.

Hao Zhao, Yang Li, Jingdi Sun, et al. ***Immunosuppression versus Supportive Care on Kidney Outcomes in IgA Nephropathy in the Real-World Setting***. CJASN doi: 10.2215/CJN.0000000000000215.

Visual Abstract by Edgar Lerma, MD, FASN



A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction

Richard A. Lafayette, Pietro A. Canetta, [...], and Fernando C. Fervenza

- ✓Open label, multicenter study, 1-year follow-up, randomized
- ✓34 adult patients proteinuria >1 g/d, maintained on ACE or ARB, well controlled BP and eGFR<90 ml/min per 1.73 m^2,
- ✓Receive standard therapy or rituximab with standard therapy.
- ✓**Rituximab did not alter the level of proteinuria** compared with that at baseline or in the control group.

These results imply that the cells pivotal for Gd-IgA1 and anti–Gd-IgA1 antibody formation may be CD20 negative and thus unaffected by rituximab.

J Am Soc Nephrol. 2017

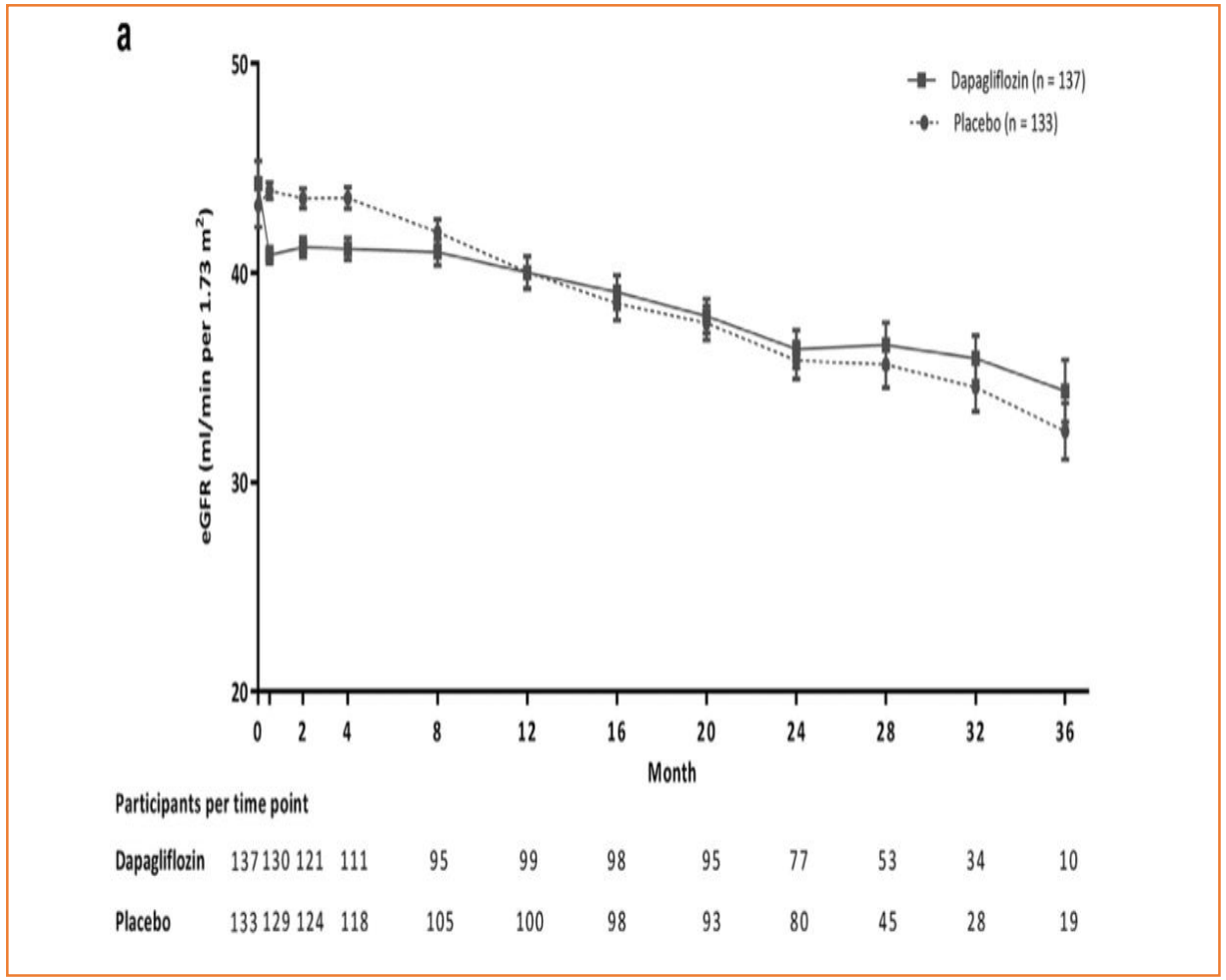
Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented 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.

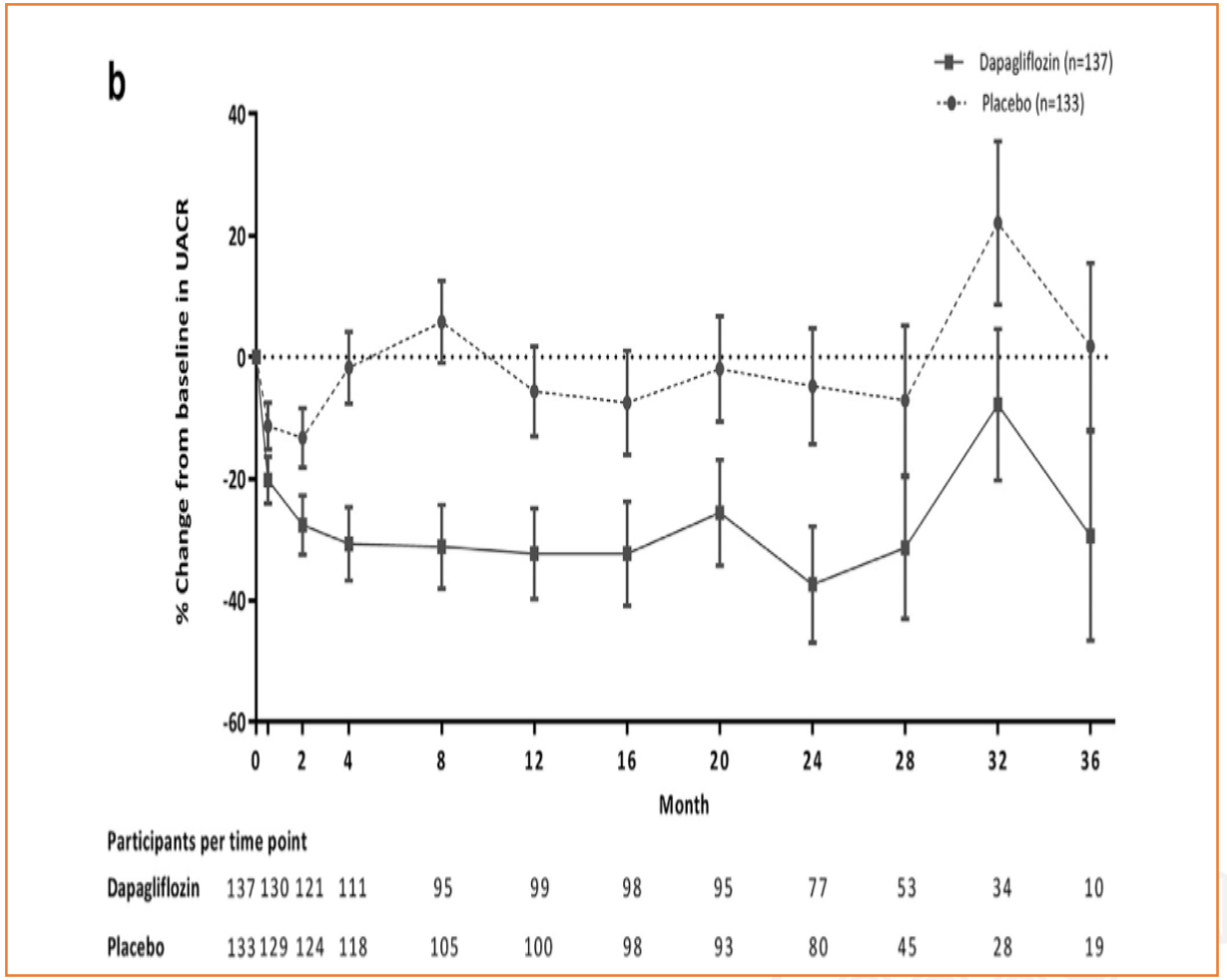
- ✓Practice Point 2.3.1.6: Tonsillectomy in IgAN: Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.
- ✓ Tonsillectomy is suggested in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.
- ✓ Multiple studies from Japan have reported improved kidney survival and partial or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed glucocorticoids

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

- ✓**270 Participants** (386 study sites in 21 countries) with estimated (eGFR) 25-75 mL/min/1.73m 2 and urinary albumin-to-creatinine ratio 200-5000 mg/g 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.
- ✓Mean rates of eGFR decline with **Dapagliflozin and placebo were 3.5 and 4.7 mL/min/1.73m 2 /year,** respectively. Dapagliflozin reduced the urinary **albumin-to-creatinine ratio by 26%** relative to placebo.
- ✓Dapagliflozin significantly and substantially reduces the risk of CKD progression with a favorable safety profile.

Wheeler et al,Kidney International (2021) 100, 215–224



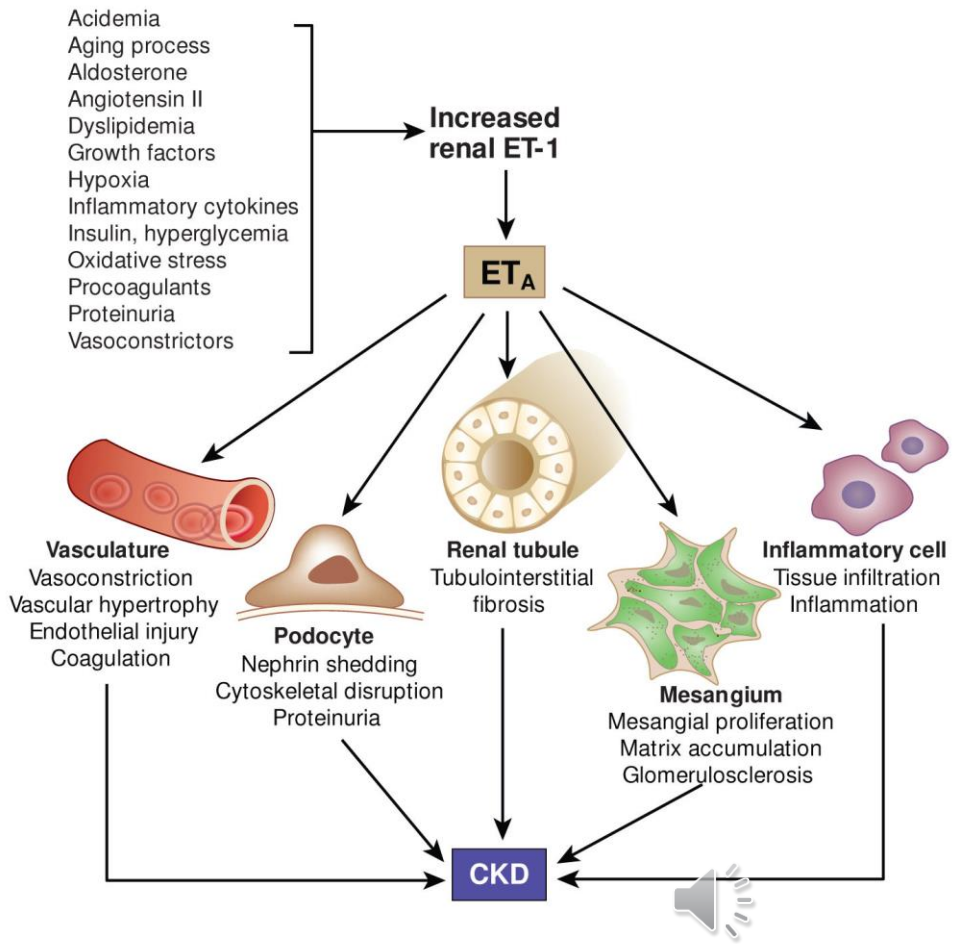


Changes over time estimated glomerular filtration rate

Changes over time Urine albumin to creatinine ratio

Pathophysiological role of Endothelin in CKD development

- ✓ET-1 is the most biologically relevant to kidney function in health and disease.
- ✓Endothelins bind to two receptor isoforms,ETA and ETB
- ✓ETA promotes vasoconstriction, cell proliferation and matrix accumulation
- ✓ETB can promote tissue injury and scarring in pathological condition however in normal condition ,ETB activation is asodilatory,antiproliferative and antifibrotic effect.

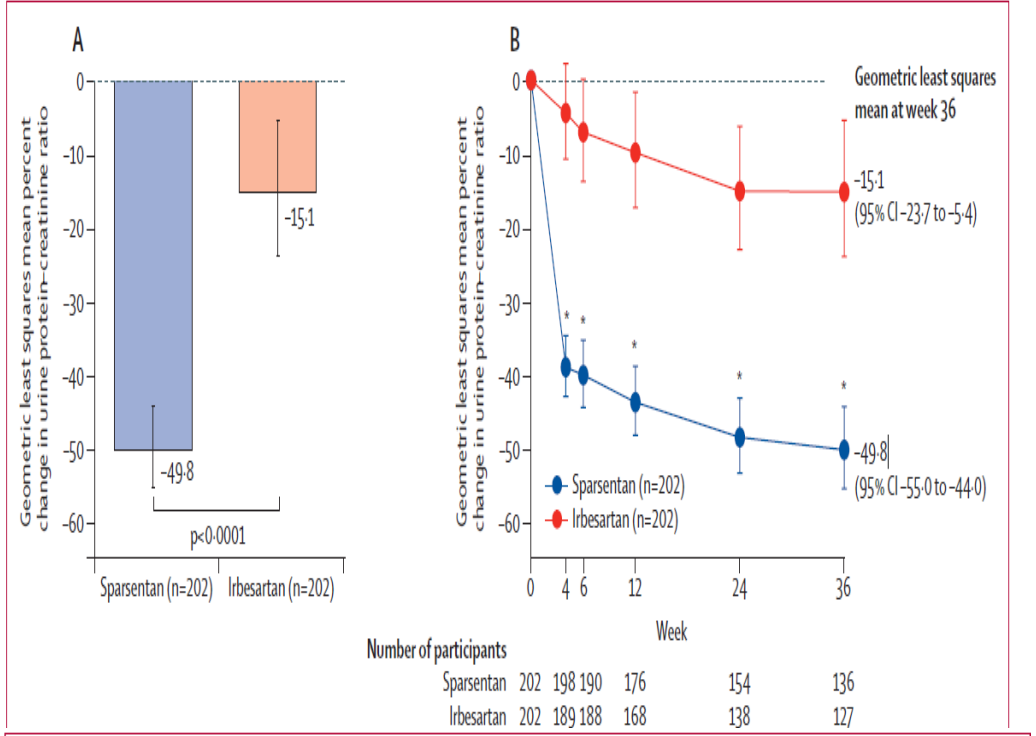


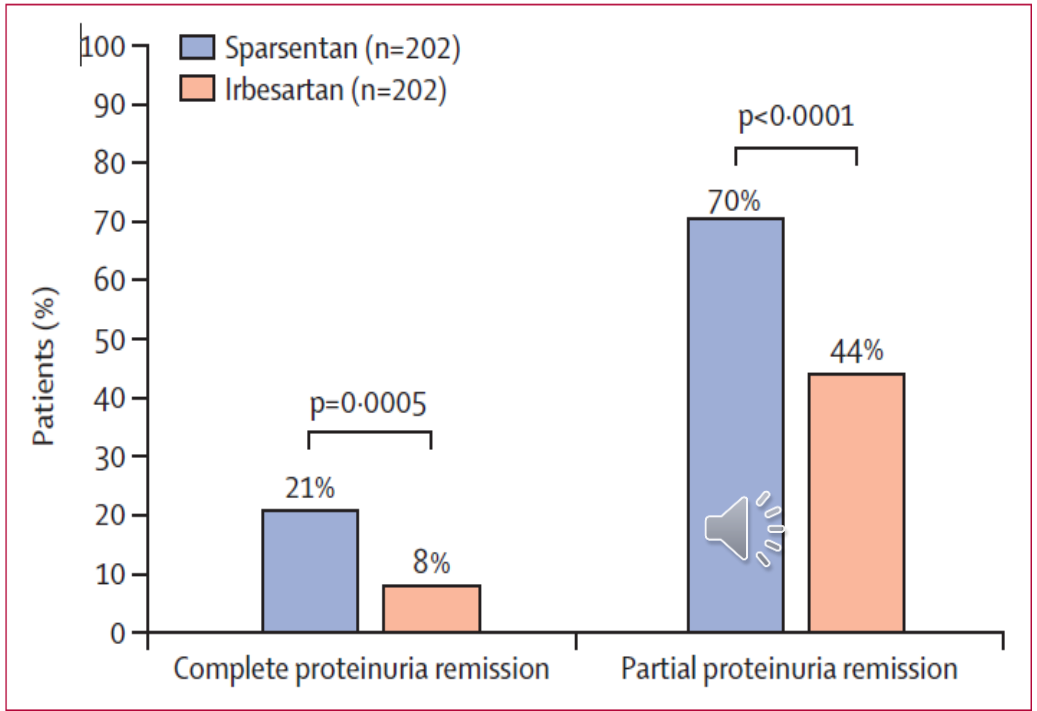
Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial

- ✓**PROTECT** is an international, randomised, double-blind, active-controlled study, being conducted in 134 clinical practice sites in 18 countries
- ✓Between Dec 20, 2018, and May 26, 2021, 404 participants were randomly assigned to sparsentan 400 mg (n=202) or irbesartan 300 mg (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).

Hiddo J L Heerspink et al, Lancet 2023

- ✓Sparsentan, a single molecule with dual antagonism of ETA receptors and AT1 receptors.
- ✓ 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.
- ✓ Completion of the study will show whether these beneficial effects translate into a long-term nephroprotective potential of Sparsentan.





Hiddo J L Heerspink et al , www.thelancet.com **May 13, 2023**

Anti Endothelin A receptors side effects

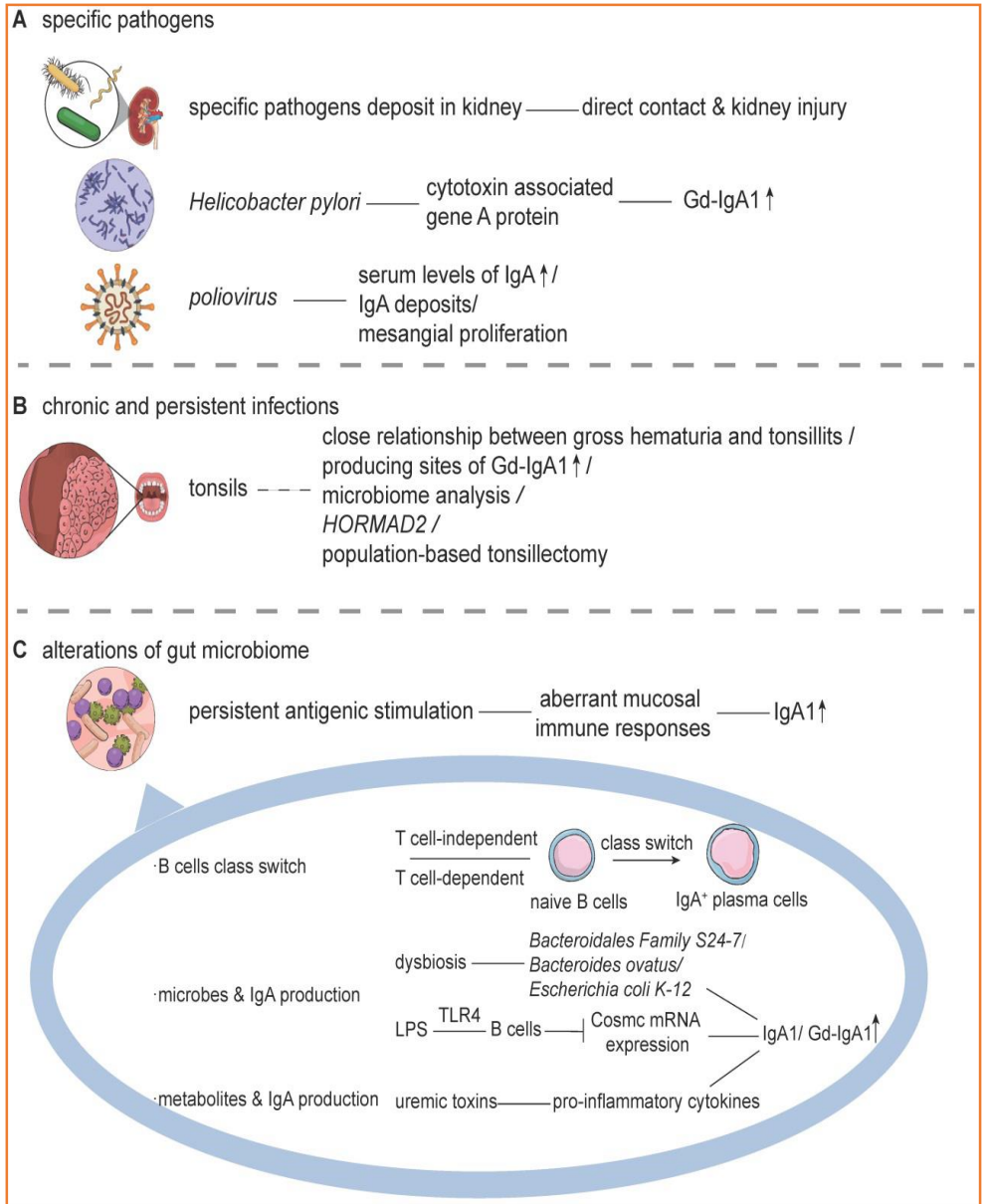
- ✓Edema : 14% *vs 9% with irbesartan*
- ✓ Hyperkalemia *:* 13% *vs 10% with irbesartan*
- ✓Dizziness (13% *vs 5% with irbesartan)*
- ✓Hypotension: (including orthostatic hypotension; 14% *vs 6% with irbesartan)*
- ✓Sulfonamide-based ERAs can cause hepatotoxicity
- ✓Absolutely contraindicated during pregnancy
- ✓Potentially testicular toxicity
- ✓In CKD and CHF needs careful prescription due to edema

The Intestine – Renal Connection In Iga Nephropathy

- ✓A gross hematuria follows mucosal infection
- ✓Association of celiac disease , dermatits herpetiformis, IBD and with IgA nephropathy.
- ✓High association of IgA against gliadin ,bovine serum albumin and lactoglobulin in 20-30 % of cases

Coppo ,NDT 2015

Mucosal Infections and Immune Responses

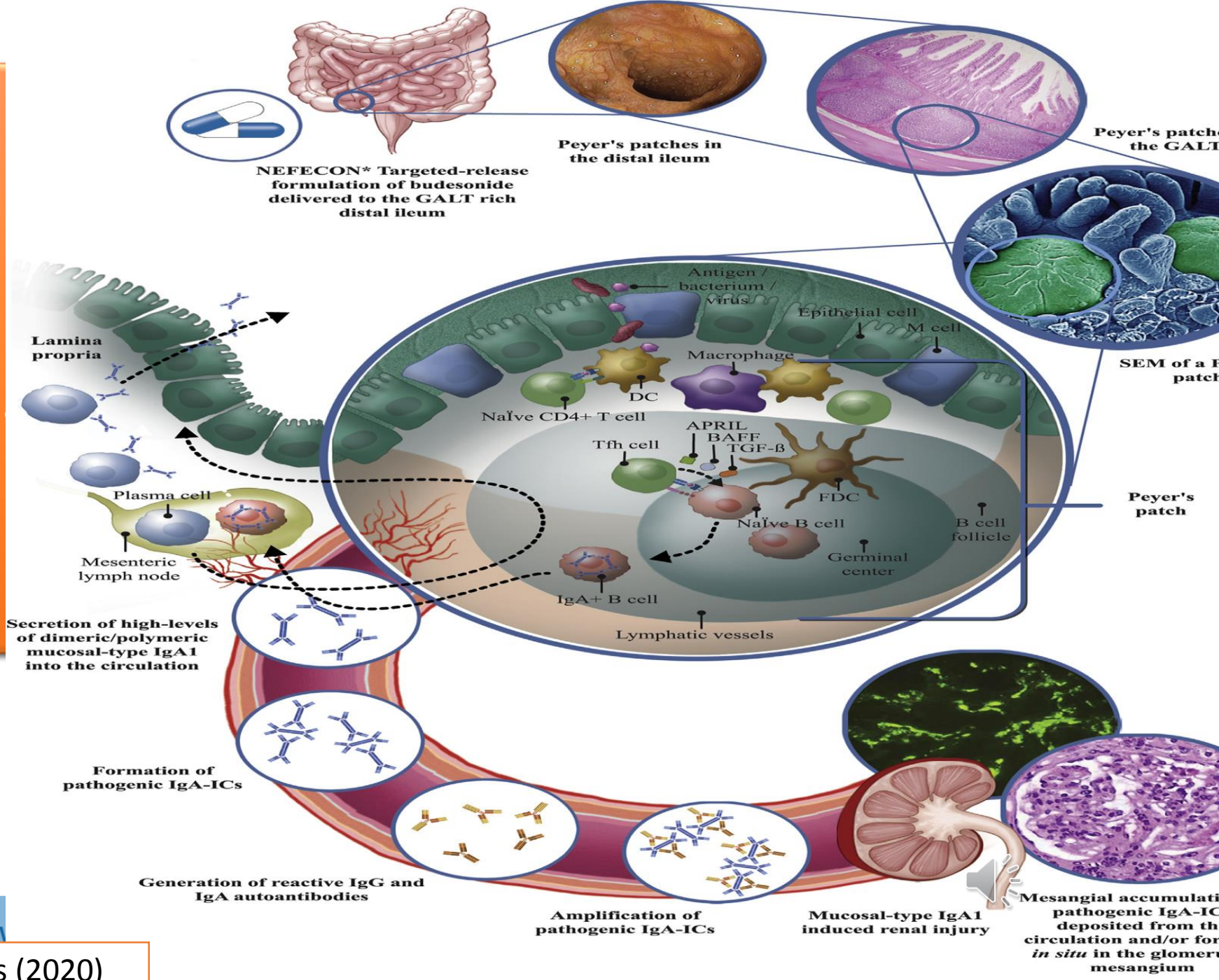


A- Specific pathogens :
believed to be involved in the initiation and progression of IgAN.

B- Chronic and persistent infections:
The occurrence of tonsillitis is believed to be related to IgAN. Clinically, there is a close relationship between upper respiratory infections and hematuria

C- Intestinal infections :
caused by the alterations of the gut microbiome and Persistent antigenic stimulation causes aberrant mucosal immune responses.

The Peyer’s patch, mucosal IgA synthesis, nephropathy, and a role for NEFECON in treatment of IgAN



Barratt et la,Kidney International Reports (2020)

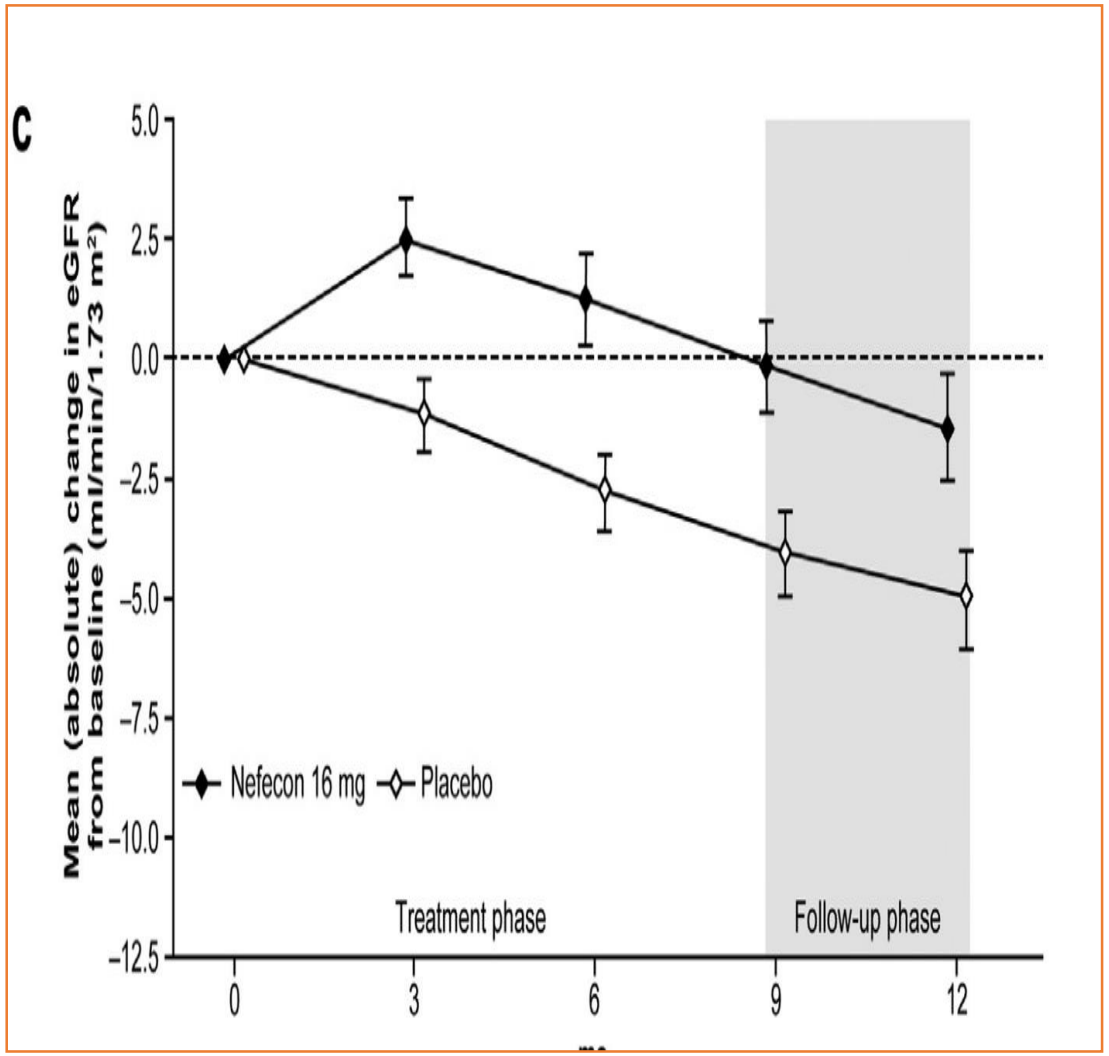
*NEFECON is an investigational treatment for IgAN and is not FDA approved

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

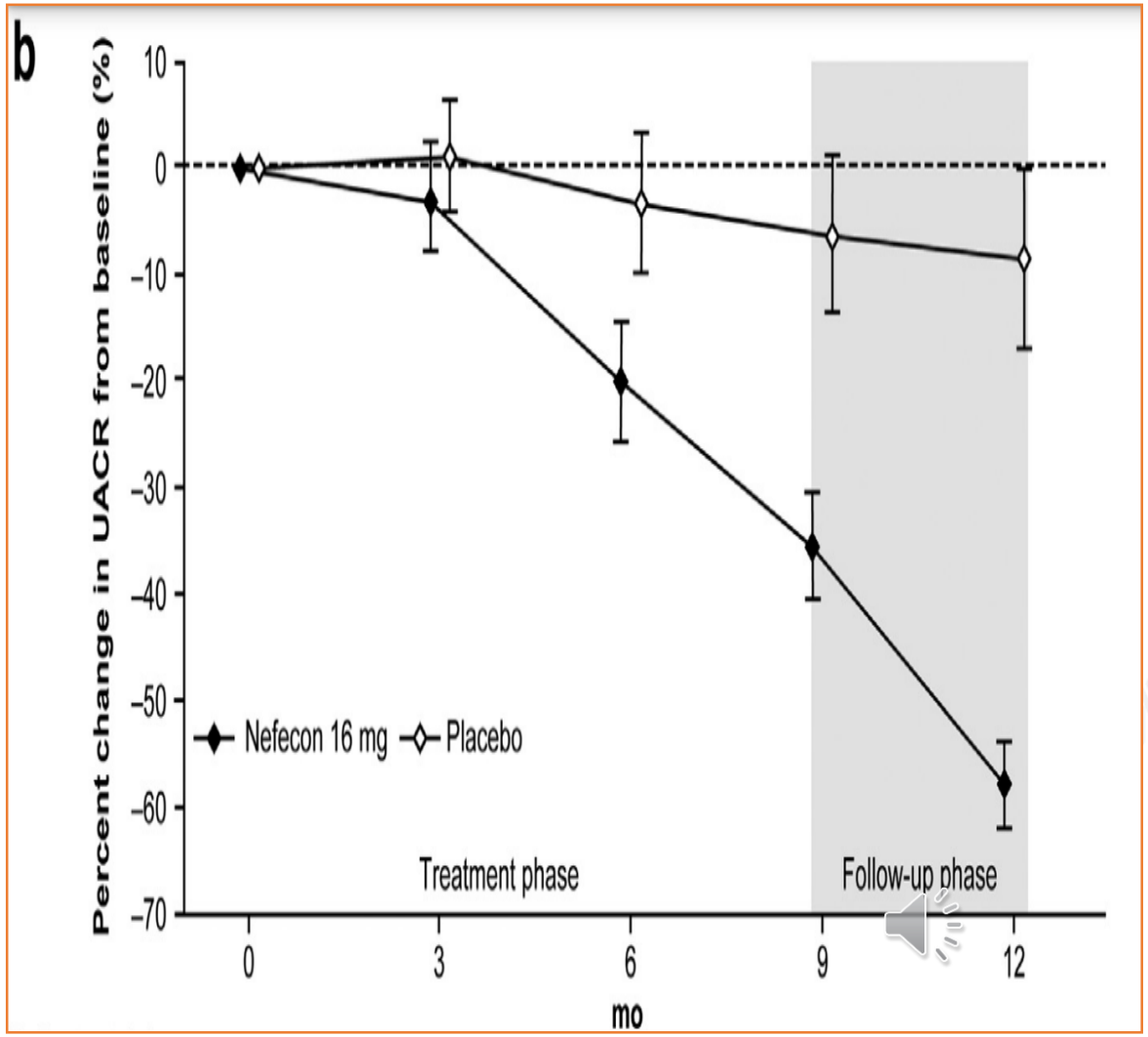
- ✓NefIgArd was a multicenter, randomized, double-blind, placebo-controlled two-part trial.
- ✓In Part A, 199 patients with IgAN were treated with Nefecon 16 mg or placebo for nine months and observed for an additional three months.
- ✓At nine months, UPCR was 27% lower in the Nefecon group compared with placebo, along with a benefit in eGFR preservation corresponding to a 3.87 ml/min/1.73 m2 difference versus placebo (both significant).

Kidney International (2023) 103, 391–402

Estimated glomerular filtration rate (CKD-EPI)



Urine albumin-to-creatinine ratio (UACR) (g/g)



Role of Complement in IgA nephropathy

Hit 1 :Increased circulating galactose-deficient IgA1

Hit 2 :Production of unique antiglycan antibodies

Activation in formation of C3 participates in the formation of pathogenic immune complexes

Hit 3 :Formation of pathogenic IgA1-containing circulating immune complexes

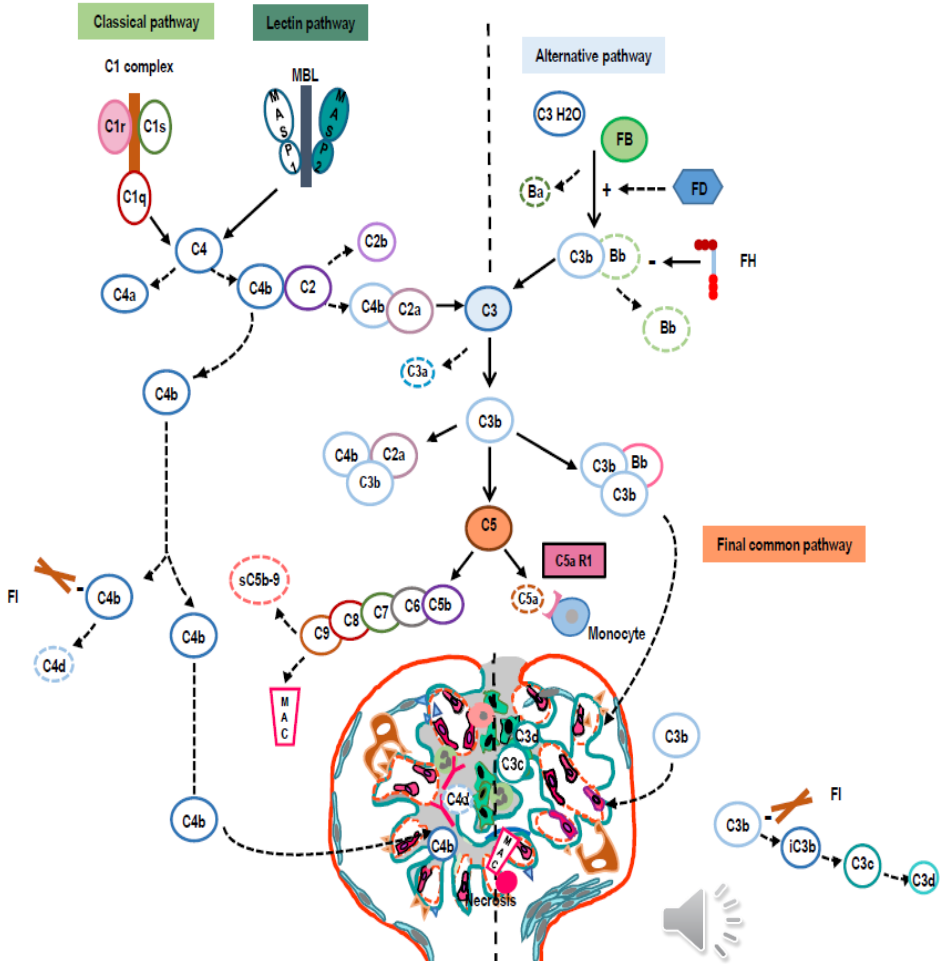
Hit 4:Mesangial deposition and mesangial cells activation leading to glomerular injury

Mesangial cells have an active role in complement activation Lectin and alternative pathways are activated and contribute to tissue injury

Maillard, Jasn 2015

Complement Activation In IgA Nephropathy

- ✓ C4d, MBL, and C5b-9 deposits are characteristic pathologic features of IgA nephropathy.
- ✓ Markers of glomerular activation of the lectin pathway (MBL, L-ficolin, MASP2,MASP1/3, and C4d) have been associated with a worse outcome of IgA Nephropathy.
- ✓ Variations in complement genes have been associated with better (CFHR3,1deletion) or worse outcome (CFH, CFHR5) of IgA nephropathy.
- ✓ Plasma levels of FHR-1 and FHR-1/FH ratio are associated with a progressive course of IgA nephropathy.
- ✓ C3a receptor/C5a receptor deficiency in mice alleviates IgA nephropathy in mice.



Main targets of complement inhibitors

Fakhouri et al. Kidney International Reports (2022)

Clinical Kidney Journal

C5a receptor inhibitor avacopan in IgA nephropathy – an open-label pilot study

This study evaluates the safety and efficacy of avacopan in patients with IgAN with persistent proteinuria despite RASi blockage

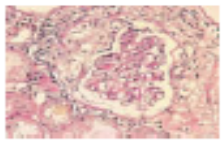
Methods

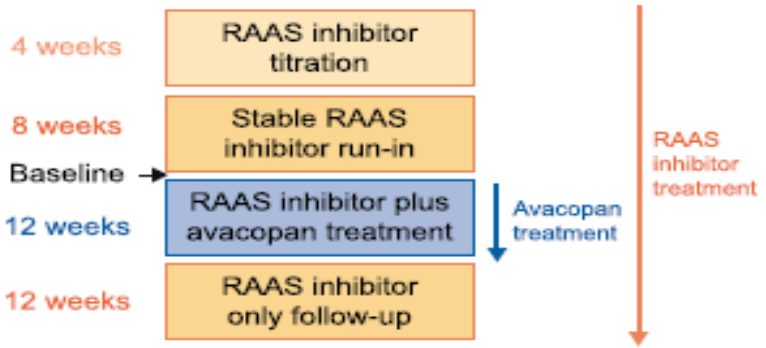
Open-label pilot trial

- ✓ UPCR > 1g/g
- ✓ eGFR > 60 mL/min/1.73 m²

OR

- ✓ eGFR > 45 mL/min/1.73 m² (if eGFR has not declined > 10 mL/min/1.73 m² in 24w)





Results

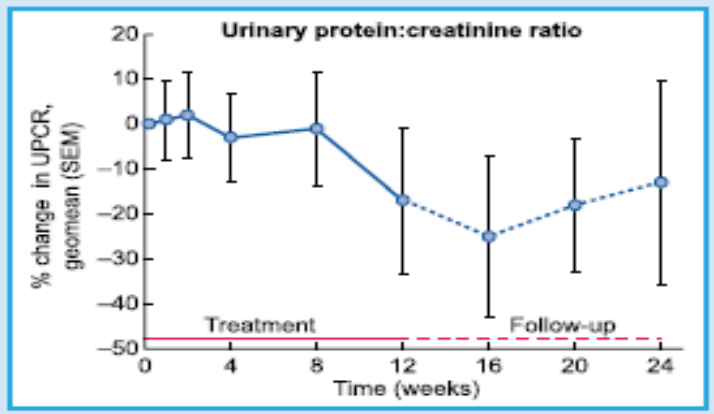

15 patients

Run-in period of 8 w

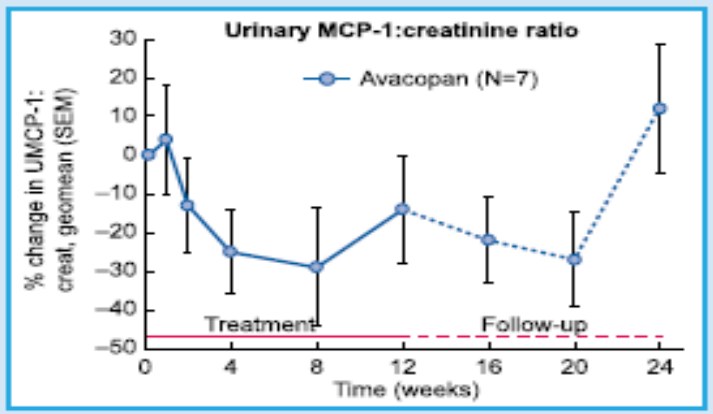
UPCR > 1g/g


7 patients

Avacopan 30 mg × 2 day



Improvement in UPCR during treatment



Urinary MCP-1: creatinine decreased 30%

⚠ 1 event: unstable angina – unrelated to avacopan

Conclusion: This short-term trial showed an improvement in the slope of UPCR in 6 out of 7 patients, with ~ 50% improvement in 3 out of 7 patients with IgAN. Longer avacopan treatment duration may be indicated for maximal benefit.

Bruchfeld, A. et al.
Clinical Kidney Journal (2021)
annette.bruchfeld@liu.se
@CKJsocial

Complement inhibitors undergoing development in IgA nephropathy

Treatment		Target	Phase	Identifier	Outcome	Estimated Study Completion Date
Complement						
Iptacopan	APPLAUSE-IgA nephropathy	CF B		NCT04578834	24 h-UPCR+eGFR	October 25
Narsoplimab		MASP-2	III	NCT03608033	24 h-UPE	April 23
Vermicopan		CF D	II	NCT05097989	24 h-UPE	August 26
Pegcetacoplan		C3	II	NCT03453619	UPCR	December 23
Ravulizumab	SANCTUARY	C5	II	NCT04564339	24 h-UPE	June 25
Cemdisiran		C5 RNA	II	NCT03841448	24 h-UPCR	February 25
IONIS-FB-LRx		CF B RNA	II	NCT04014335	24 h-UPE	December 23
RO7434656	IMAGINATION	CF B RNA	III	NCT05797610	24 h-UPCR	September 30
KP 104		C3 convertase+C5	II	NCT05517980	24 h-UPCR	September 25

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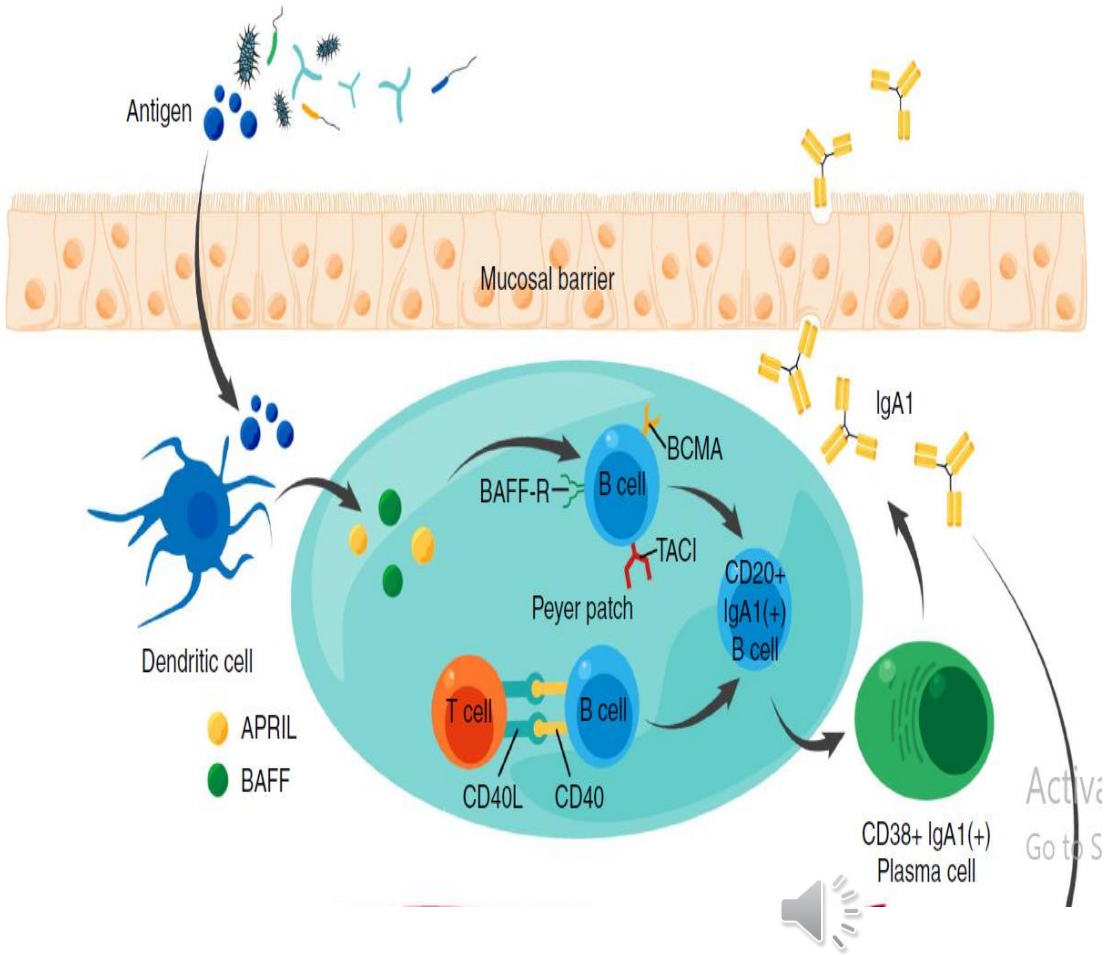
BAFF AND APRIL in IgA nephropathy

- ✓Patients with IgA nephropathy have increased the levels of CD38+ B cells and plasma cells.
- ✓B-cell-activating factor (BAFF) and A proliferation-inducing ligand (APRIL) , produced by antigen-exposed dendritic cells and intestinal epithelial cells.
- ✓Increased serum levels of BAFF and APRIL in patients with IgAN that correlate with gd-IgA1 levels and disease severity.
- ✓Therapies that specifically target these cytokines can be effective.
- ✓Atacicept is a fusion protein that binds B-lymphocyte stimulator (BlyS) and a proliferation inducing ligand(APRIL) inhibiting maturation and class-switching of B-cells and plasma cells.



B-cell directed therapies currently being evaluated in IgAN

Table 1. B-cell directed therapies currently being evaluated in IgAN.

Drug	Mechanism	Phase	Design	Primary Outcome	Identifier
Mezagitamab	mAb against CD38	I	Open label single arm trial	Incidence of adverse events	NCT05174221
BION-1301	mAb against APRIL	I/II	Double blinded, placebo controlled single ascending dose study	Incidence and severity of adverse events	NCT03945318
		I/II	Open label multiple dose study		
Atacicept	TACI fusion protein, acts as a BAFF and APRIL inhibitor	II	Double blinded placebo-controlled trial	Proteinuria Reduction	NCT04716231
Belimumab	mAb against BAFF	II	Double blinded placebo-controlled trial	Proteinuria reduction, Change in eGFR, Adverse events	EudraCT: 2017–004366-10
Felzartamab	mAb against CD38	II	Double blinded, placebo-controlled trial	Proteinuria reduction	NCT05065970
Telitacicept	TACI fusion protein, acts as a BAFF and APRIL inhibitor	II	Double blinded placebo-controlled trial	Proteinuria Reduction	NCT04905212
Blisibimod	Peptibody inhibitor of BAFF	II/III	Double blinded, placebo-controlled trial	Proteinuria Reduction	NCT02062684
Sibeprenlimab	mAb against APRIL	II	Double-blinded, placebo-controlled, multiple dose trial	Proteinuria Reduction	NCT04287985
		III	Double-blinded, placebo-controlled trial	Proteinuria Reduction	NCT05248646
Rituximab	mAb against CD20	IV	Single blinded randomized trial against supportive care	Proteinuria reduction	NCT04525729

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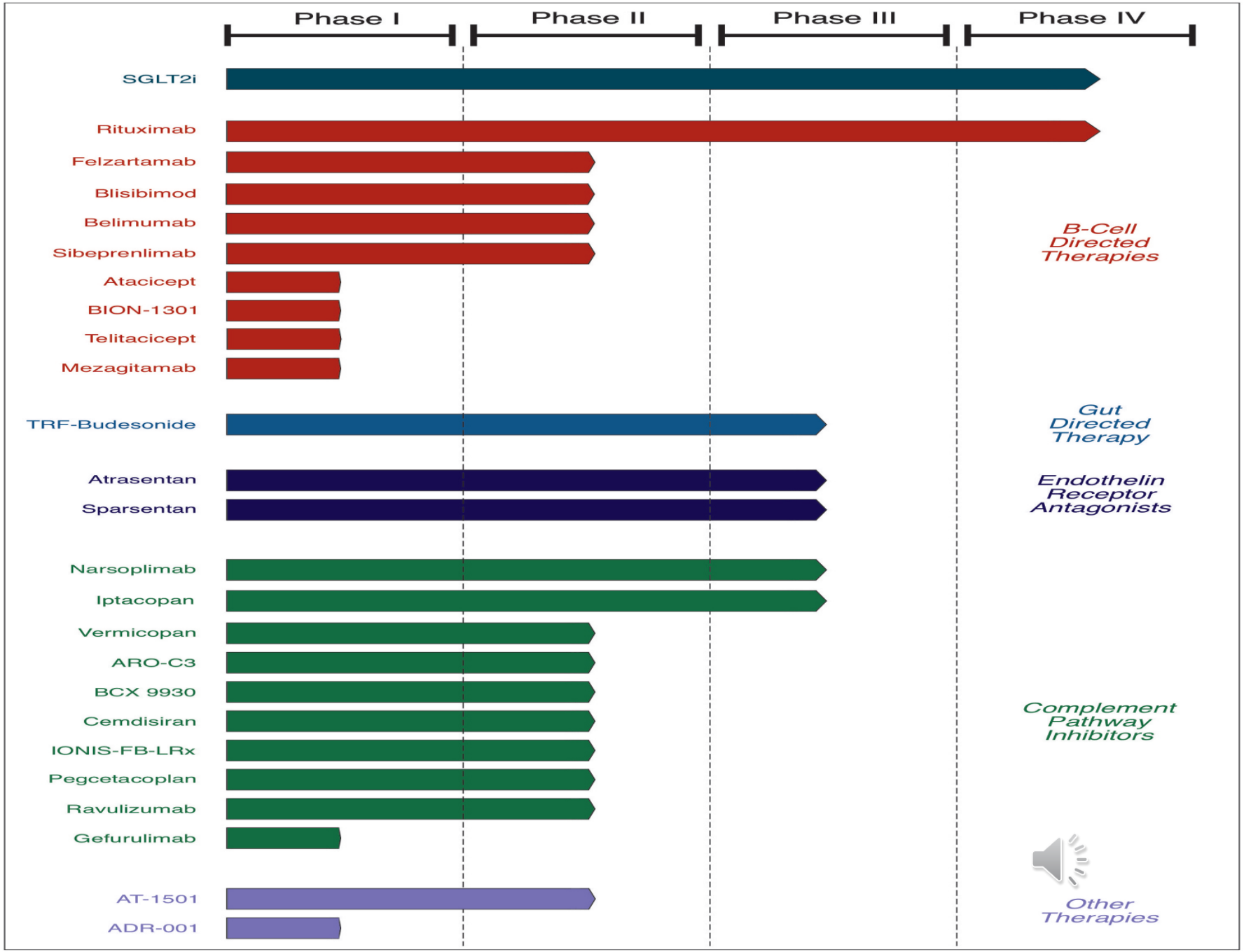
Current Clinical Trials In Iga Nephropathy



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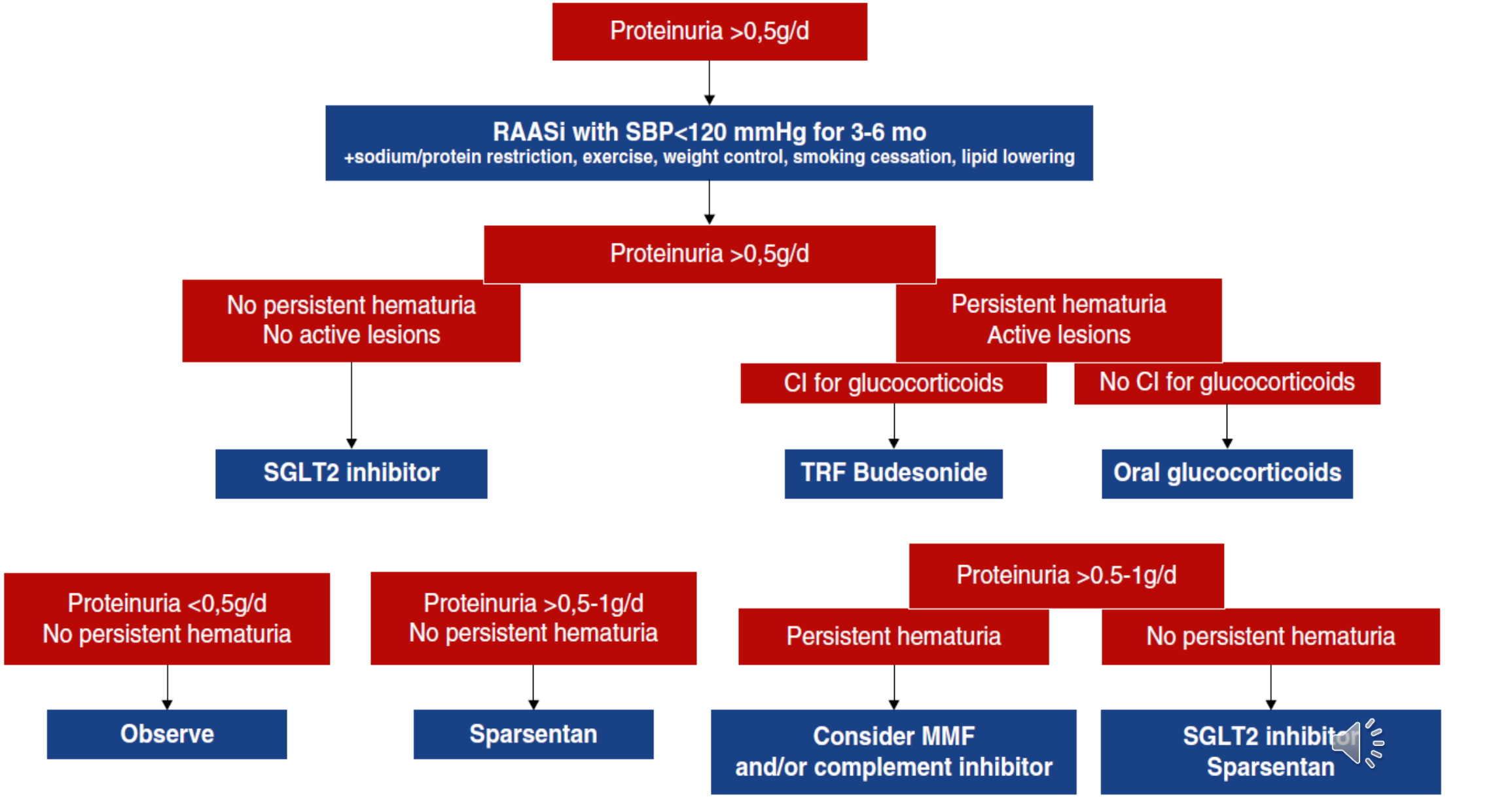

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