Iga Nephropathy (IgAN)

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Disclosures

- I have previously received honoraria from Amgen, Astellas, Astra Zeneca, Faran, Genesis, GSK

Outline

- Epidemiology and Pathophysiology of IgAN (gut-kidney axis)
- Risk stratification for disease progression
- Supportive care/new agents
- Immunosuppressive therapy in high-risk patients
- Other investigational agents
  - Inhibition of Immune Complex-Activated Complement Activity
  - Inhibition of BAFF/APRIL Signaling
  - Plasma Cell and B Cell Depletion
  - Inhibition of Endothelin A Receptor and Angiotensin II Subtype 1 Receptor
- Conclusions

IgA Nephropathy (IgAN)

- **45% of all GN** (most common)
- **2.5/100,000** Global incidence (screening policies, threshold for biopsies)
- Asians > Caucasians > Black patients
- Male:Female = 2:1 (in Asia→ 1:1)
- Heterogenous clinical presentation (from asymptomatic to RPGN)
- Mucosal surfaces play a key role
- Up to **40% progress to ESRD** within 20 years of diagnosis
- Until now, SOC has been the use of supportive measure

Int J Immunogenet 2022;49:8-21
Int J Nephrol Renovasc Dis 2018;11:137-148

Long term risk of kidney failure in IgAN (RaDaR cohort)

Materials & Methods

Retrospective cohort study

UK National Registry of Rare Kidney Diseases
RaDaR

2,299 adults &
140 children with
biopsy-proven IgA nephropathy

Proteinuria **>0.5 g/day**
or eGFR **<60 ml/min**

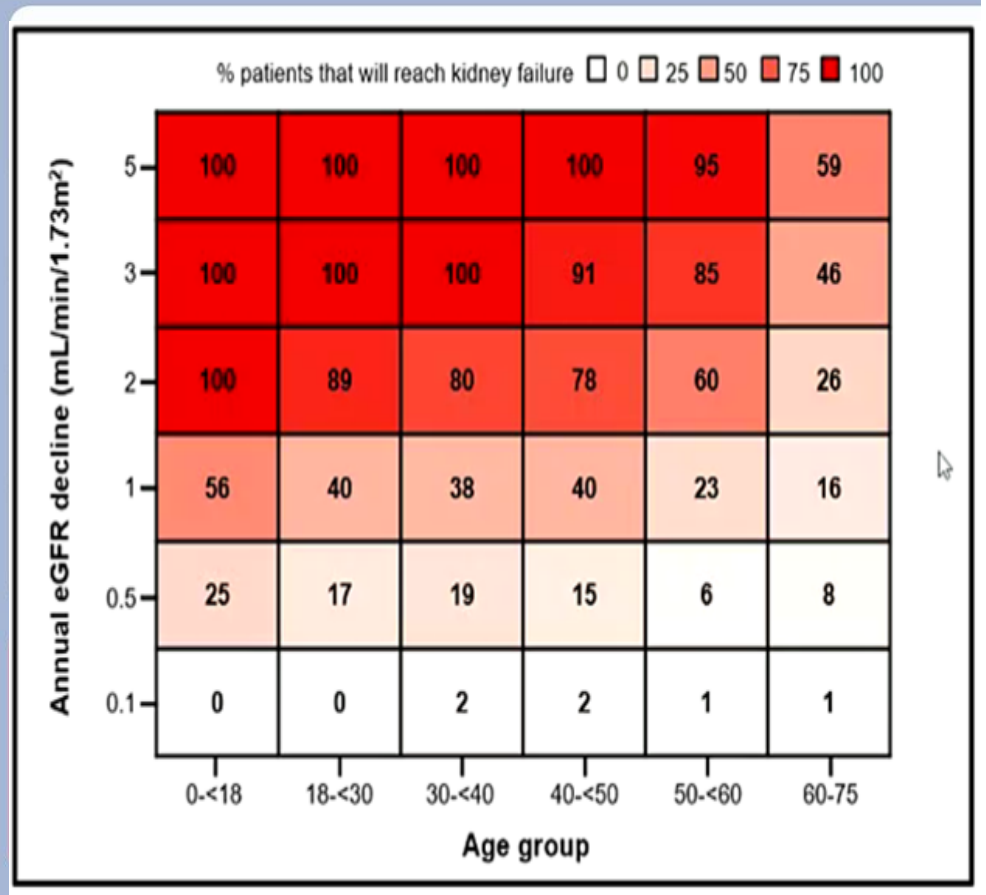
Results

5.9 years — **Median follow-up**

45.3 years — **Median age at diagnosis** (in 2020)

48 years — **Median age at kidney failure/death**

50% — **Percentage of patients who reached kidney failure or died**



- Almost all patients are at risk of progression to ESRD within their lifetime, unless eGFR declines <1ml/min/year
- Even patients traditionally regarded as being “low risk”, with proteinuria <880 mg/mg, also had high rates of kidney failure within 10yrs

Clin J Amer Soc Nephrol 2023;18(6) 727-38

Genome wide association studies (GWAS)

Identification of several genetic variants associated with increase risk for disease development

CARD9 locus

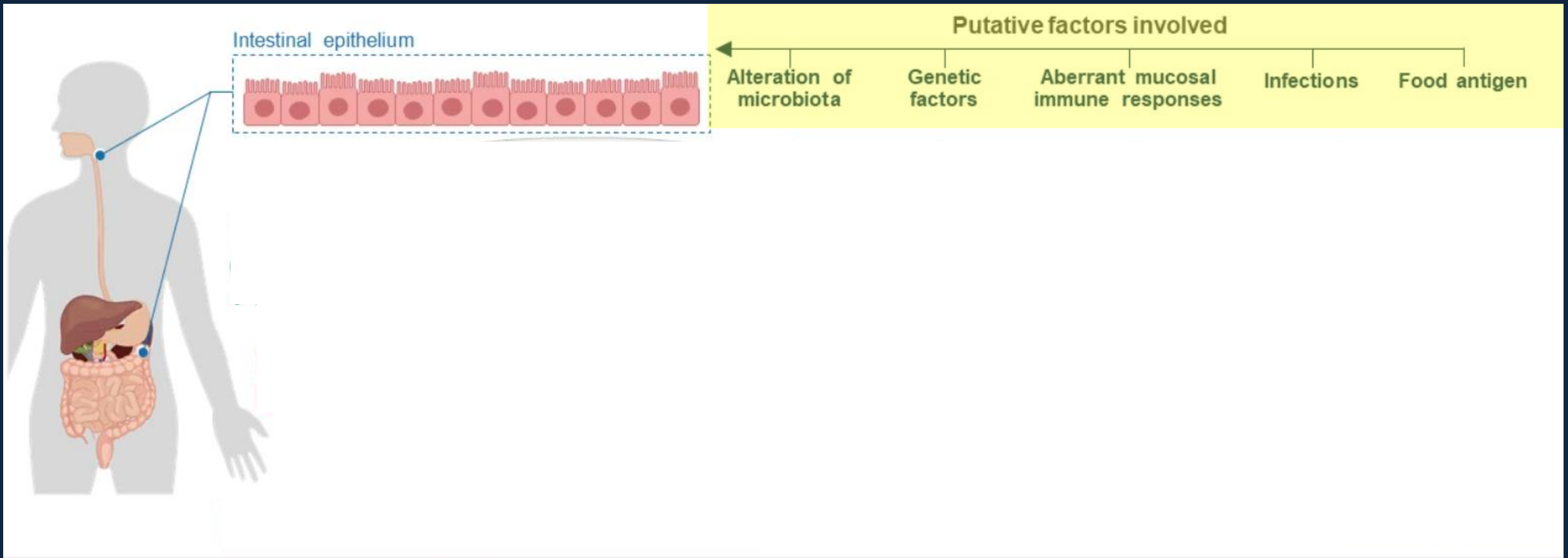
- Variant associated with ↑ *risk for IBD*

Chromosome 22q12

- LIF and OSM genes encode two cytokines important for mucosal immunity and inflammation
- *Two additional loci* encoding genes related to mucosal immunity were identified *in Chinese cohorts*

Clin J Am Soc Nephrol. 2021;16:458-466

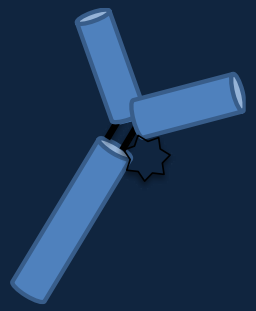
IgA and Gut-kidney axis: the “multi-hit” theory



- The formation of Gd-IgA1 is the **initial hit** in the pathogenesis of IgAN; indeed, it can act as an autoantigen leading to the synthesis of autoantibodies (IgG-IgA: **second hit**)
- The creation of immunocomplexes (ICs) and their deposition in the kidney have been found to provoke cellular proliferation and inflammation, leading to kidney damage (**third and fourth hits**)

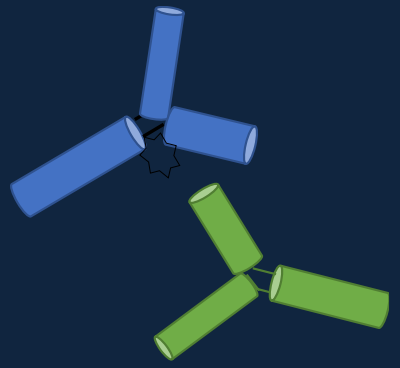
Semin Immunopathol 2021; 43:657-668
J Am Soc Nephrol. 2022 May;33(5):873-875

1. Increased circulating levels of Galactose deficient-IgA1



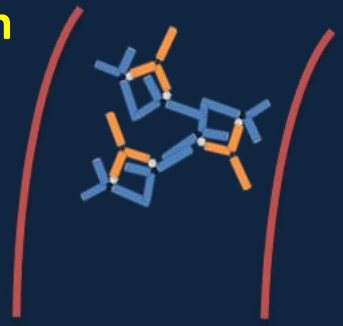
- *Genetic predisposition*
- *Epigenetics*
- *Enzymatic variants*
- *Mis-trafficking of B cells from mucosal to systemic sites*

2. Production of Anti-IgA1 autoantibodies (IgA or IgG)

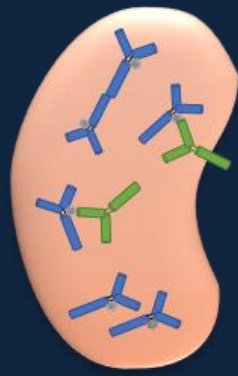


- *Genetic predisposition, HLA haplotype*
- *Germline mutations*
- *Molecular mimicry*
- *Viral infection*
- *Streptococcal antigens*

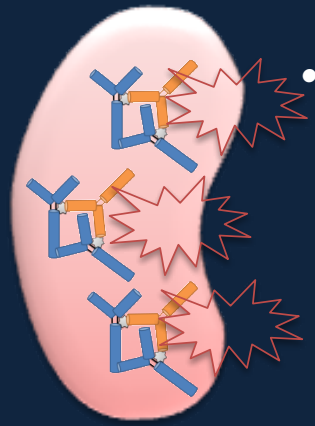
3. Immune complexes form in the circulation



4. Deposition of immune complexes in the kidney



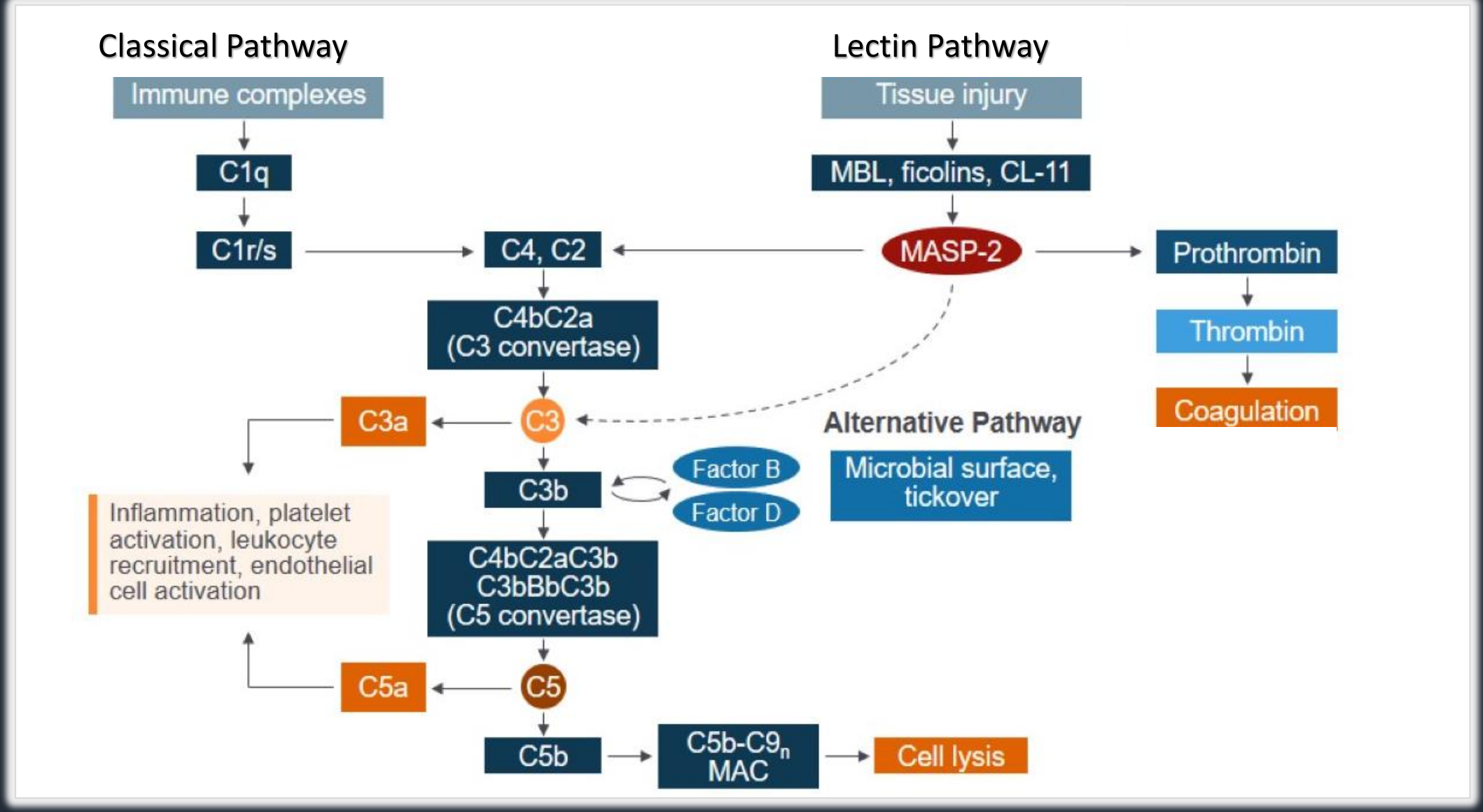
5. Immune complexes in the mesangium cause local immune activation & injury → Worse prognosis



- *Complement activation*
- *Cytokine/chemokine release*
- *Monocyte recruitment*
- *Matrix production*
- *Mesangial proliferation*
- *Glomerular sclerosis*
- *Interstitial fibrosis*

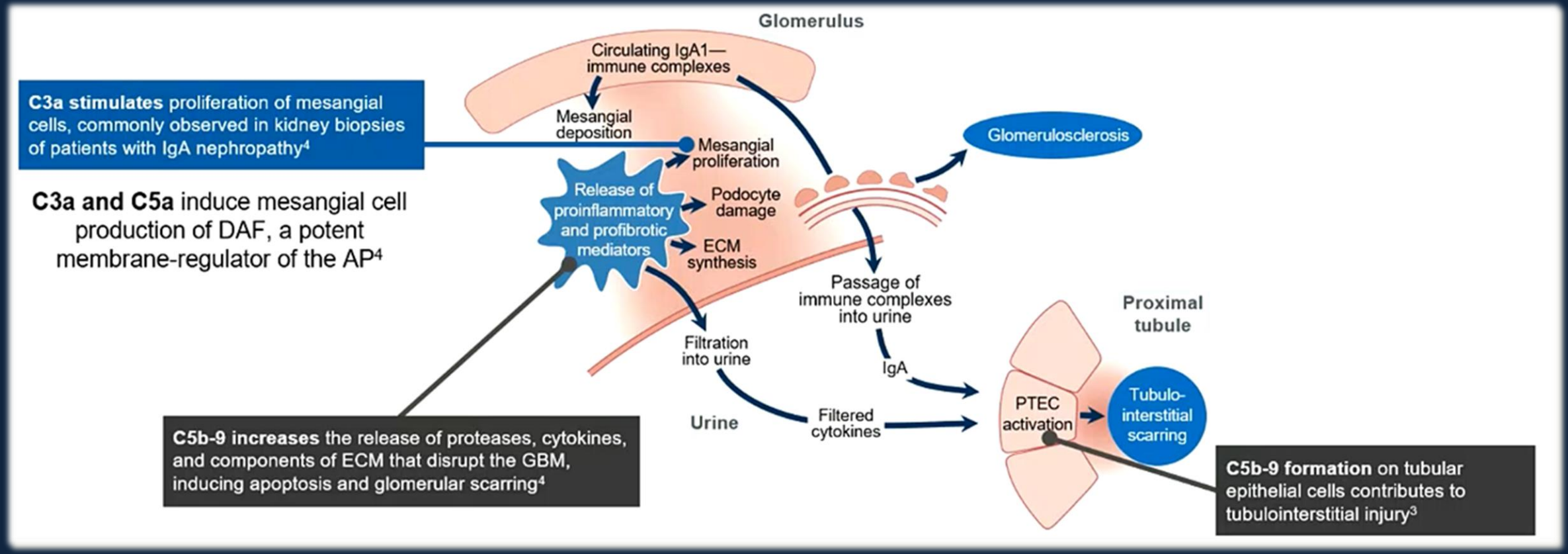
"the 5th element "

Complement Activation in Glomerular Disease



Exp Hematol Oncol. 2021;10:57

Hit 5: IgA immune complex deposition leads to overactivation of the alternative pathway in IgAN



- IgA immune complex deposition→
- Activation of the alternative pathway of the complement trigger inflammation (proteinuria and hematuria)
- Leads to tubulointerstitial and glomerular scarrinng and eventually to CKD

Front Immunol 2019; 10:504
Am J Nephrol 2018; 47:43-52

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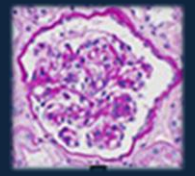
The histologic components of Oxford classification (MEST-C score) are independently associated with clinical outcomes

Histological feature	Score
Mesangial hypercellularity **(M)**	**M0:** in <50% of glomeruli; **M1:** in >50% of glomeruli
Endocapillary hypercellularity **(E)**	**E0:** absent; **E1:** present
Segmental glomerulosclerosis **(S)**	**S0:** absent; **S1:** present
Tubular atrophy/interstitial fibrosis **(T)**	**T0:** 0–25%; **T1:** 26–50%; **T2:** >50%
Cellular or fibrocellular crescents **(C)**	**C0:** absent; **C1:** present 0–25% glomeruli; **C2:** ≥25% of glomeruli

Kidney biopsy is essential for both diagnosis and predicting risk using the international IgAN prediction tool



The score predicted outcomes independently of BP, proteinuria and eGFR

Nat Rev Nephrol 2017;13:385-86
JAMA Internal Med. 2019;179:942-52

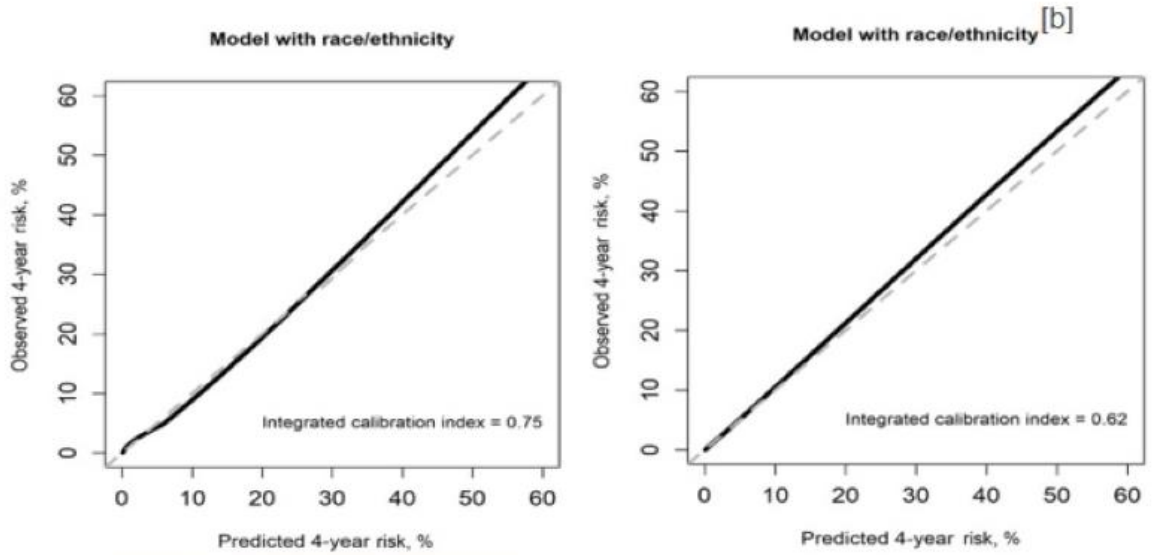
International IgAN Prediction Tool at Biopsy

Determining risk of 50% decline in eGFR or progression to ESRD in 5 yrs from biopsy

Parameters

1. Estimated GFR at biopsy
2. SBP at biopsy
3. DBP pressure
4. Proteinuria at biopsy
5. Age at biopsy
6. Race
7. Use of ACEi or ArB at the time of biopsy
8. MEST score
9. Immunosuppression use at or prior to biopsy

Validated prognostic biomarkers for IgAN



R^2_D: 61.2%
C-statistic: 0.87
(95% CI 0.86, 0.87)

R^2_D: 60.1%
C-statistic: 0.85
(95% CI 0.84, 0.87)

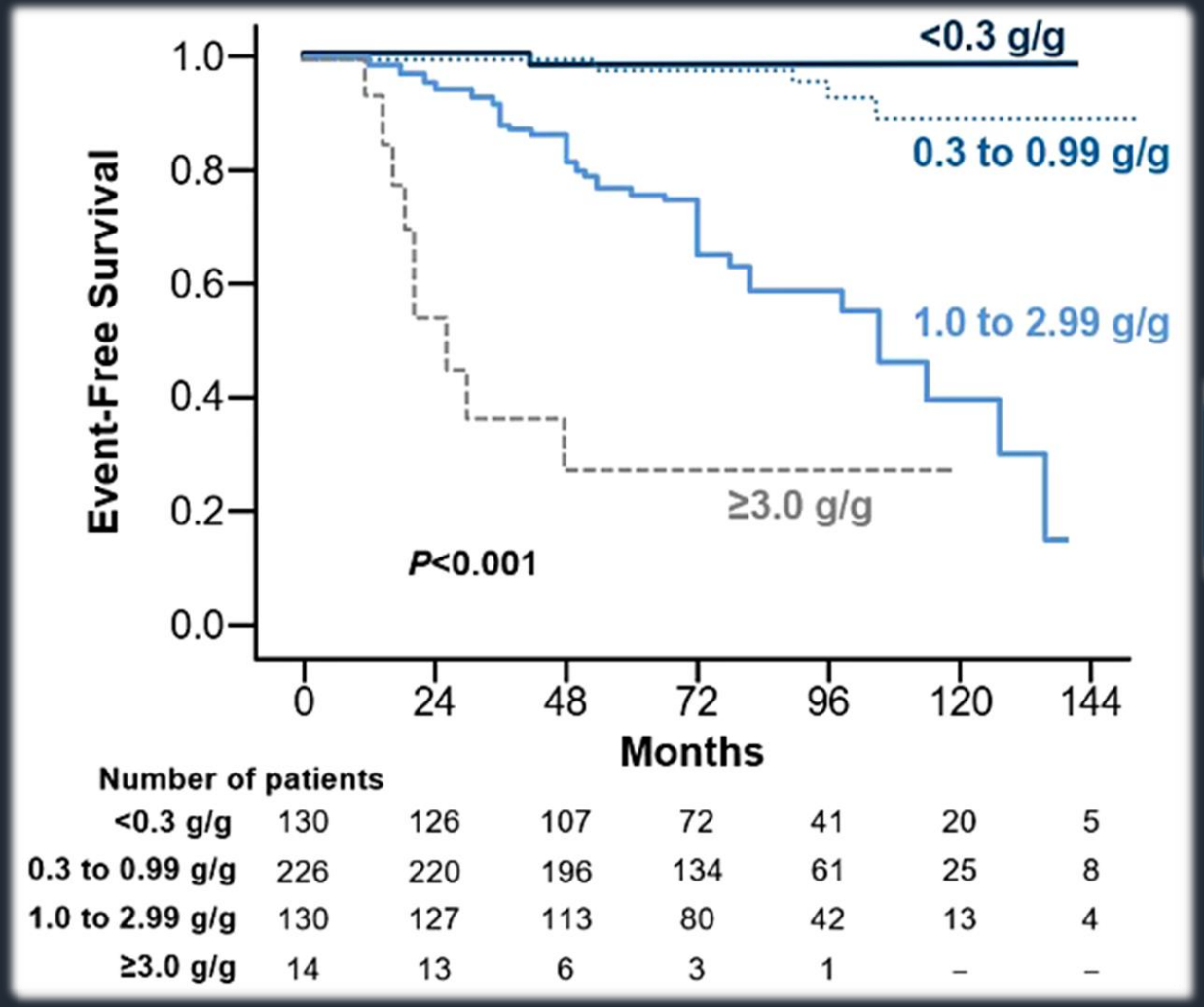
- Results were similar for model without ethnicity

The updated International IgAN Prediction Tool
can be used for accurate risk stratification <u>1-2 years post biopsy</u>

Mobile app: https://qxcalc.app.link/igarisk

Kidney Int 2022; 102:160-172

KDIGO guidelines: high-risk patients



KDIGO guidelines define high-risk patients as those with proteinuria >0.75–1 g/day despite 3 months of optimized supportive care[3]

Proteinuria of > 1g/d → 9.4 fold increased risk of ESRD

JAMA Intern Med 2019; 179: 942-52
Kidney Int. 2021;100:S1-S276

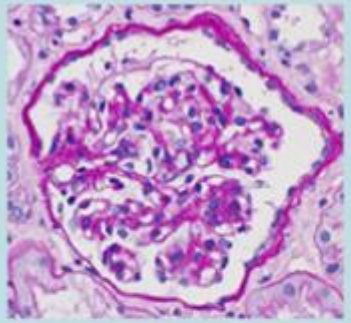
Improving treatment decisions in IgAN using personalized risk assessment from the International IgAN Prediction Tool

International IgAN cohort → **Simulated allocation of immunosuppression** → **Evaluated using net benefit**

↑ net benefit = better treatment allocation

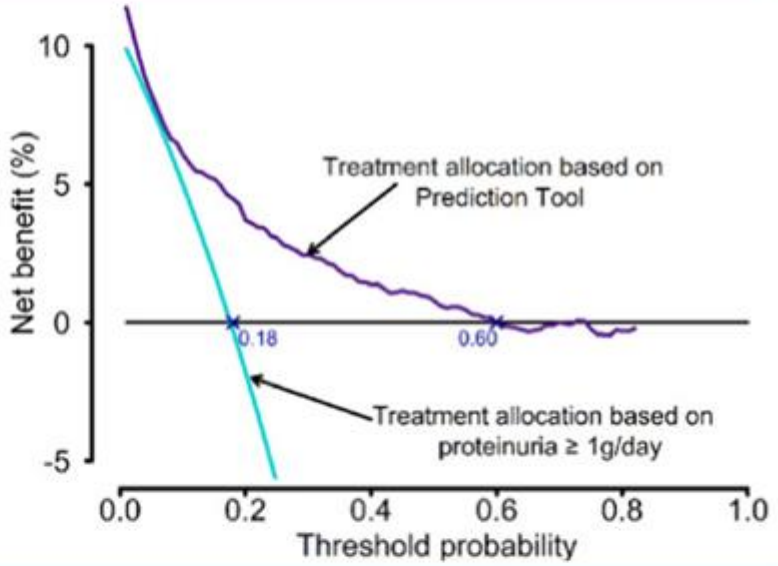
3,299 adults

Biopsy-proven IgAN



Treatment allocation based on

- Predicted risk from IgAN Prediction Tool ≥ threshold probability
- Proteinuria ≥1g/day



larger net benefit up to 23.4%

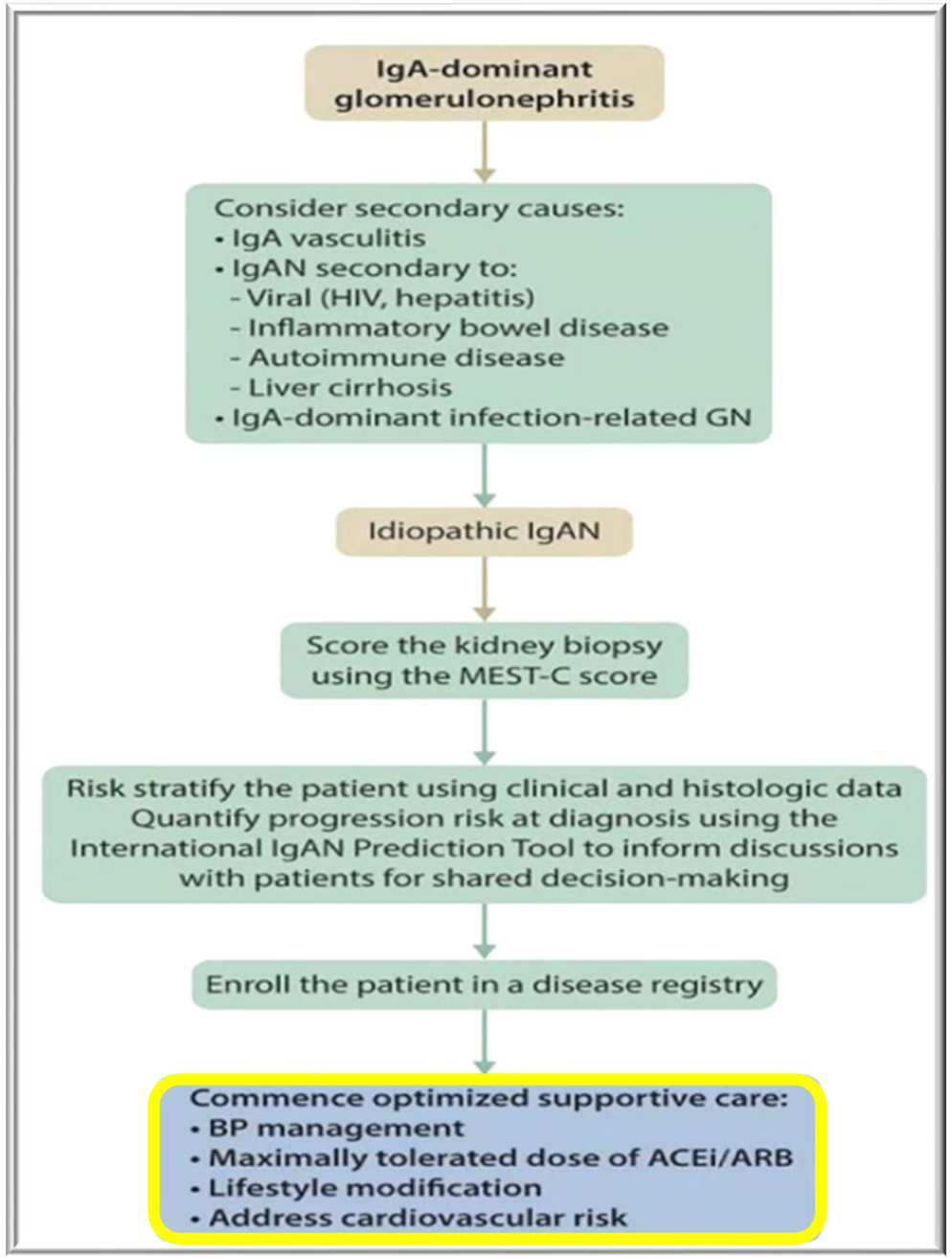
larger net ↓ in treatment up to 35.1%

CONCLUSION:

The accuracy of any immunosuppression treatment allocation in IgAN can be substantially improved using the IgAN Prediction Tool instead of relying solely on proteinuria

Kidney Int. 2020 Oct;98(4):1009-1019

2021 update



Kidney Int. 2021 Oct;100(4S):S1-S276

2021 KDIGO Guidelines

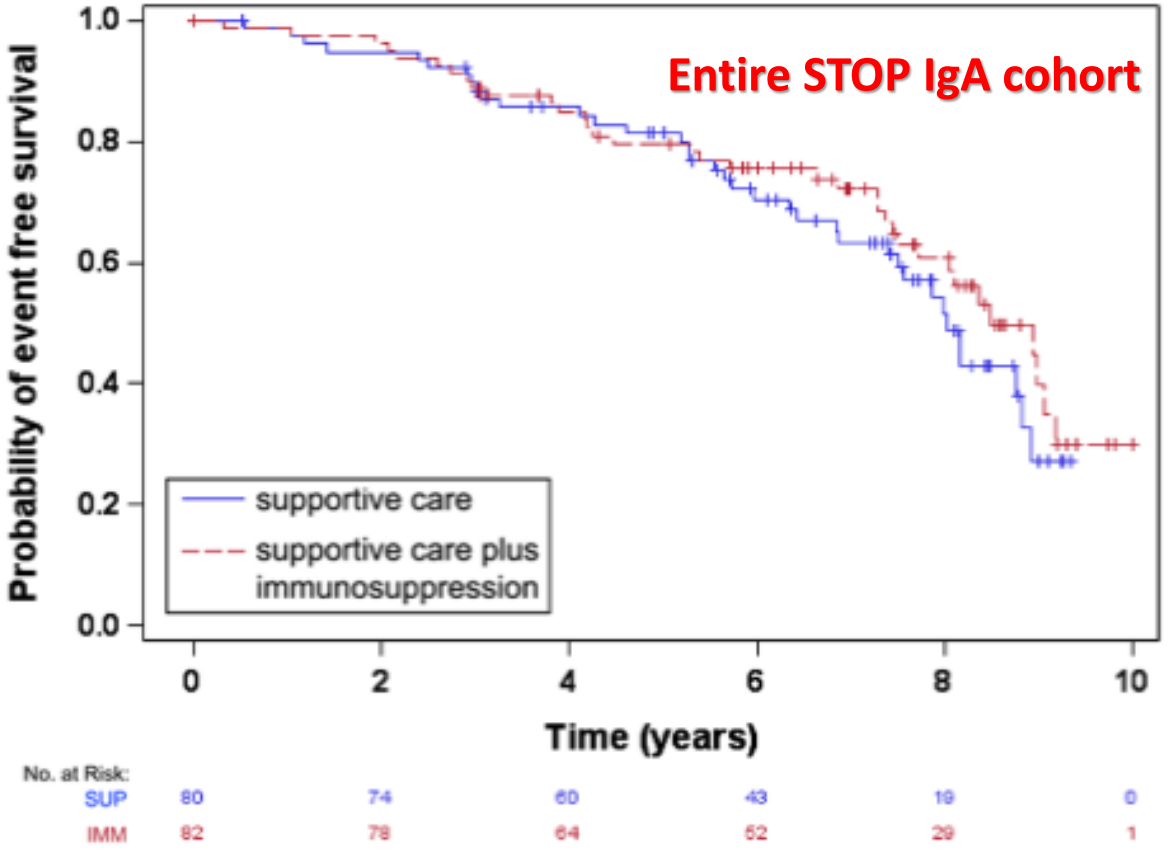
Supportive therapy in IgAN (at least for 3 months)

Blood pressure management	Dietary advices and fluid management	Lifestyle modifications	Additional measures
• target sitting systolic BP <120 mmHg • <u>preferred antihypertensives:</u> - first choice: ACE inhibitors <u>or</u> 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 • <u>avoid</u> 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)

Kidney International 2021 100, 753-779

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

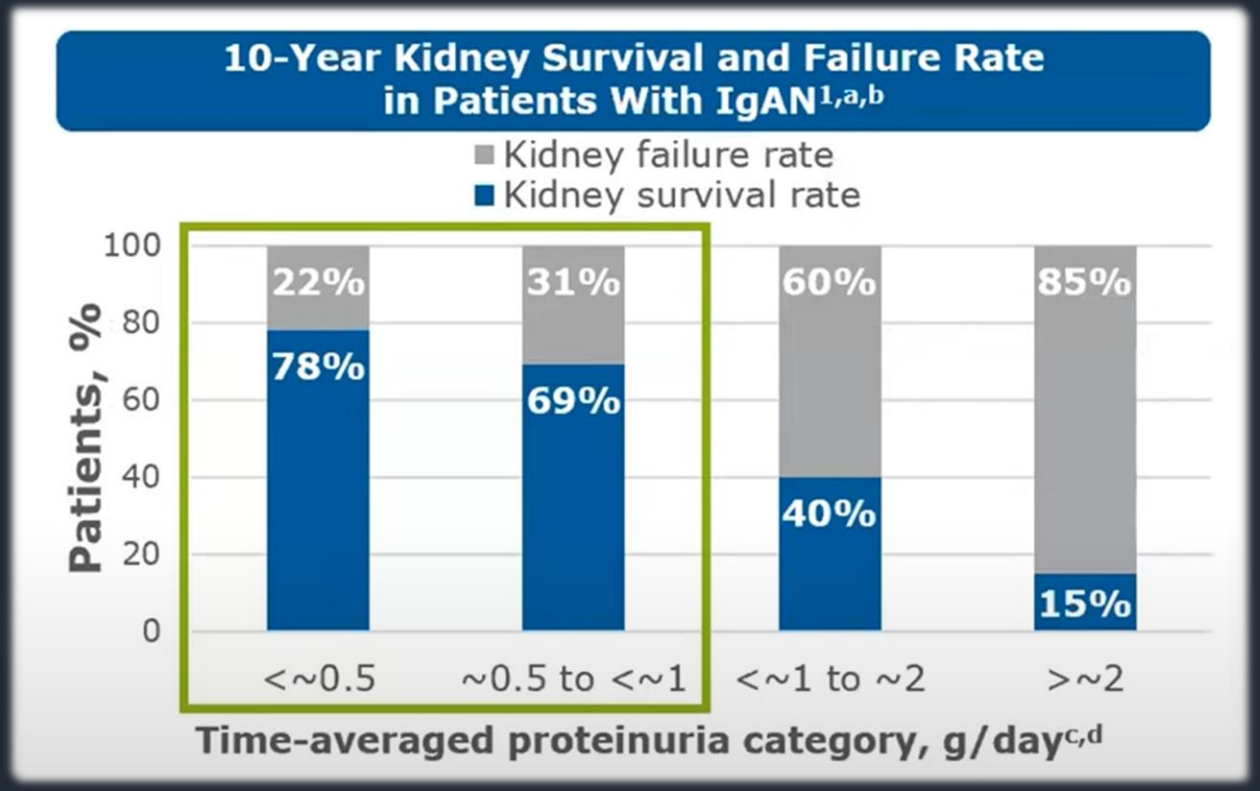
Thomas Rauen [1], Stephanie Wied [2], Christina Fitzner [2], Frank Eitner [3], Claudia Sommerer [4], Martin Zeier [4], Britta Otte [5], Ulf Panzer [6], Klemens Budde [7], Urs Benck [8], Peter R Mertens [9], Uwe Kuhlmann [10], Oliver Witzke [11], Oliver Gross [12], Volker Vielhauer [13], Johannes F E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



50% of patients in the stop IgA trial on maximal supportive care reached ESRD

Kidney Int. 2020 Oct;98(4):1044-1052

RaDaR database



There may be an unmet need for disease management in "low risk" patients with proteinuria < 1g/d

JAMA Intern Med 2019; 179: 942-52
Kidney Int. 2021;100:S1-S276

There is no minimum duration of proteinuria remission that is associated with improved outcomes in IgAN

1864 adults from 7 international cohorts

Biopsy-proven IgA nephropathy

Time-varying exposure
Duration of first proteinuria remission (≥25% ↓ to < 1g/day)

Primary outcome
ESKD or 50% drop in eGFR

Characteristics of Cohort

47% Chinese
16% Japanese
35% White
3.9 years follow-up

At time of first remission:

Proteinuria 0.55 g/day

eGFR 78mL/min/1.73m^2

Results

Non-linear, dose-response relationship with no minimum duration of remission

Lower risk of primary outcome for each 3 months in remission:

Up to 4 years in remission	HR 0.91 (95% CI 0.89 - 0.93)
After 4 years in remission	HR 0.99 (95% CI 0.96 - 1.03)

There is a strong dose-response relationship between the longer duration of proteinuria remission and a lower risk of disease progression in IgAN

J Am Soc Nephrol. 2021 Feb;32(2):436-447

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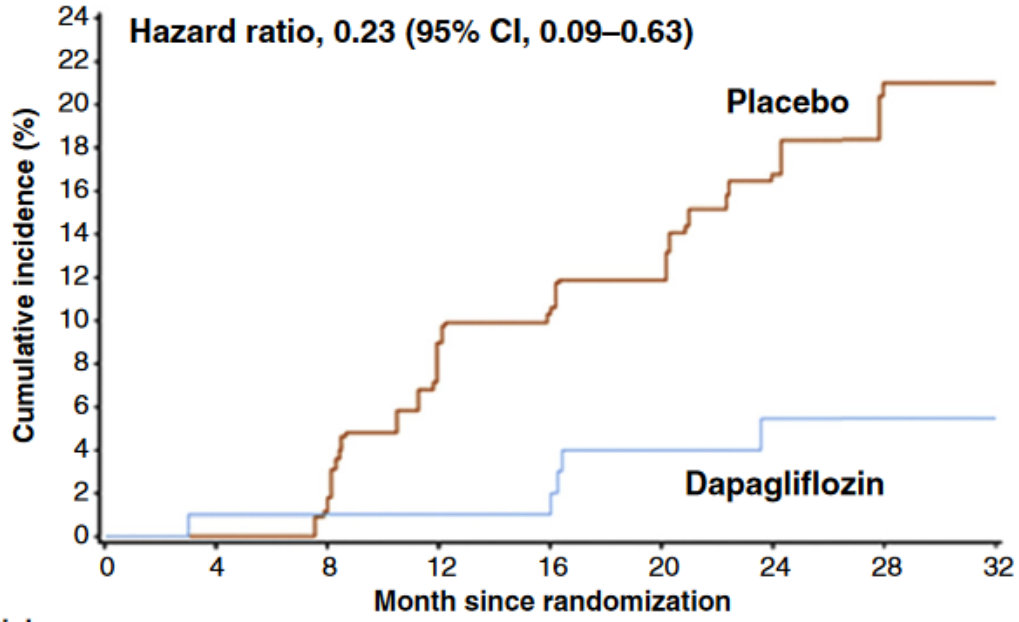
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

David C. Wheeler[1,2], Robert D. Toto[3], Bergur V. Stefánsson[4], Niels Jongs[5], Glenn M. Chertow[6,7], Tom Greene[8], Fan Fan Hou[9], John J.V. McMurray[10], Roberto Pecoits-Filho[11,12], Ricardo Correa-Rotter[13], Peter Rossing[14,15], C. David Sjöström[4], Kausik Umanath[16,17], Anna Maria Langkilde[4] and Hiddo J.L. Heerspink[5]; for the DAPA-CKD Trial Committees and Investigators

- **270 pnts** with biopsy proven **IgA nephropathy**
- Addition of dapagliflozin to RAAS inhibitors led to reduction of the risk of progression *(>50% eGFR reduction or ESRD)*
- **Renal endpoint: HR 0.23**
- **Reduction of UACR by 26%**
- Good safety profile

Conclusion: In pnts with IgAN, dapagliflozin added to ACE/ARB therapy, significantly reduced the risk of CKD progression

Renal endpoint (IgA-biopsy)



Approval of dapagliflozin in USA and Europe in CKD

Kidney Int. 2021 Jul;100(1):215-224

Deposition of IgA-immune complexes in the mesangium increases ET-1 and AngII production which contribute to:

- inflammation
- fibrosis
- changes to the shape of podocytes, podocyte loss, mesangial cell proliferation
- increased permeability of the glomerular filtration barrier
- Vasoconstriction
- Increased glomerular pressure

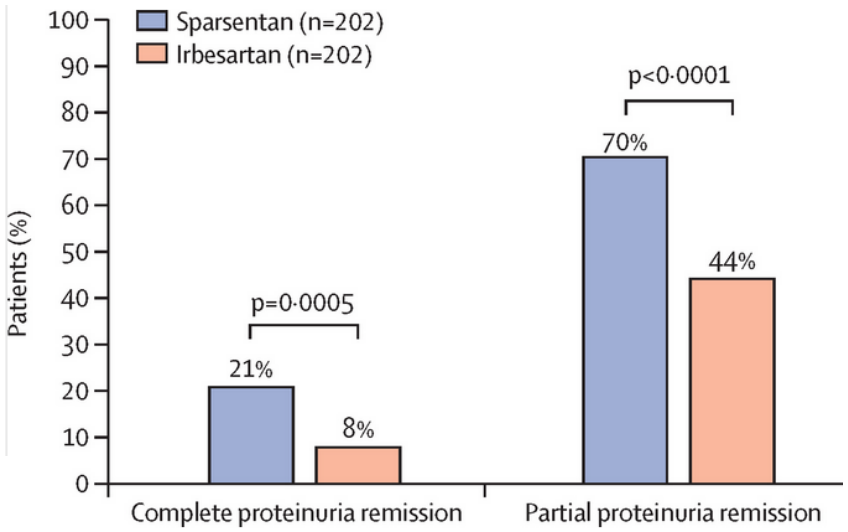
Kidney Dis. 2020, 6, 22–34
Kidney Int. 2014, 86, 896–904

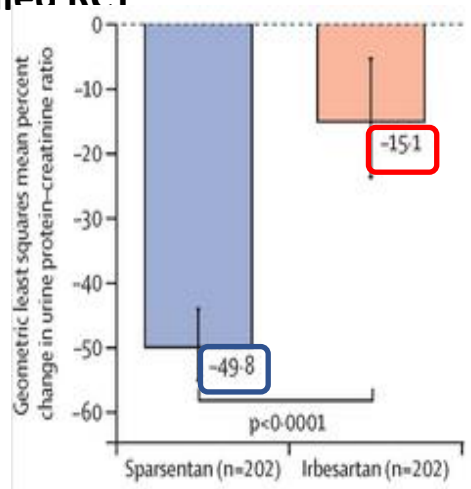
Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial *Interim analysis at 36 weeks*

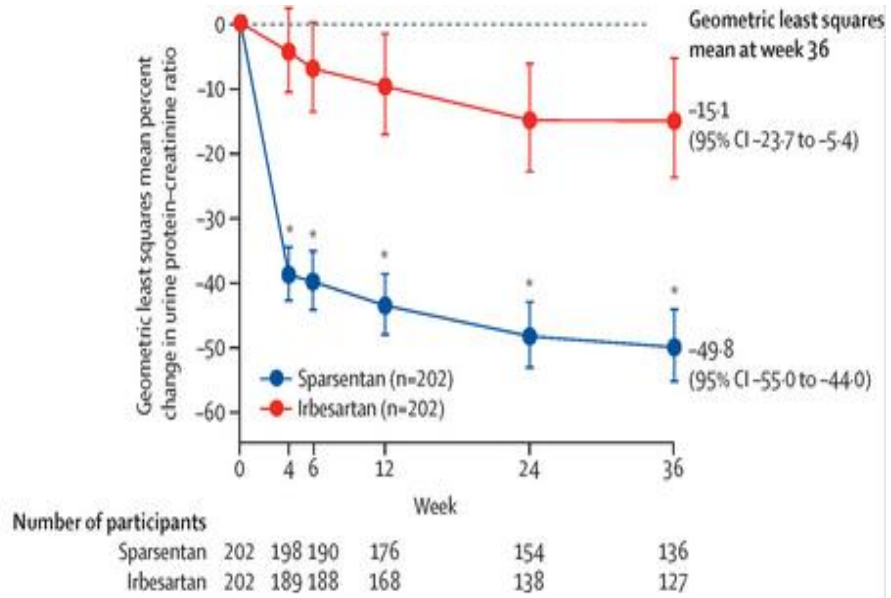
Hiddo J L Heerspink 1 , Jai Radhakrishnan 2 , Charles E Alpers 3 , Jonathan Barratt 4 , Stewart Bieler 5 , Ulysses Diva 6 , Jula Inrig 6 , Radko Komers 6 , Alex Mercer 7 , Irene L Noronha 8 , Michelle N Rheault 9 , William Rote 6 , Brad Rovin 10 , Howard Trachtman 11 , Hernán Trimarchi 12 , Muh Geot Wong 13 , Vlado Perkovic 14 ; PROTECT Investigators

PROTECT trial: **international, double-blind, active-controlled RCT**

Compared 400 mg Sparsentan vs 300mg Irbesartan
404 pnts with IgAN
eGFR >30 ml/min/1.73m^2
Proteinuria > 1g/day
Duration: 270 wks







Sparsentan= Dual Endothelin Angiotensin Receptor Antagonist (DEARA)

Lancet. 2023 May 13;401(10388):1584-1594.

TREATMENT- EMERGENT ADVERSE EVENTS

	Sparsentan (n=202)	Irbesartan (n=202)
Any TEAE, n (%)	177 (88)	158 (78)
TEAEs in ≥2% of participants treated with sparsentan, n (%)		
Peripheral edema (mostly mild, none severe)	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalemia	27 (13)	21 (10)
Anemia	10 (5)	5 (2)
Acute kidney injury[a]	9 (4)	2 (1)
Transaminase elevations >3 × ULN	5 (2)	4 (2)

- No cases of heart failure, no treatment discontinuations due to edema, and no treatment-related fluid retention serious AEs
- The liver enzyme elevations >3 × ULN all occurred without concurrent >2 × elevation in total bilirubin and were asymptomatic and reversible
- 23 (11%) sparsentan-treated and 39 (19%) irbesartan-treated patients discontinued study treatment

Sparsertan (Filspari): accelerated FDA approval in pnts with IgAN and risk of rapid kidney function decline (e.g UPCR ≥1.5g/g or ≥2g/day)

Lancet. 2023 May 13;401(10388):1584-1594.

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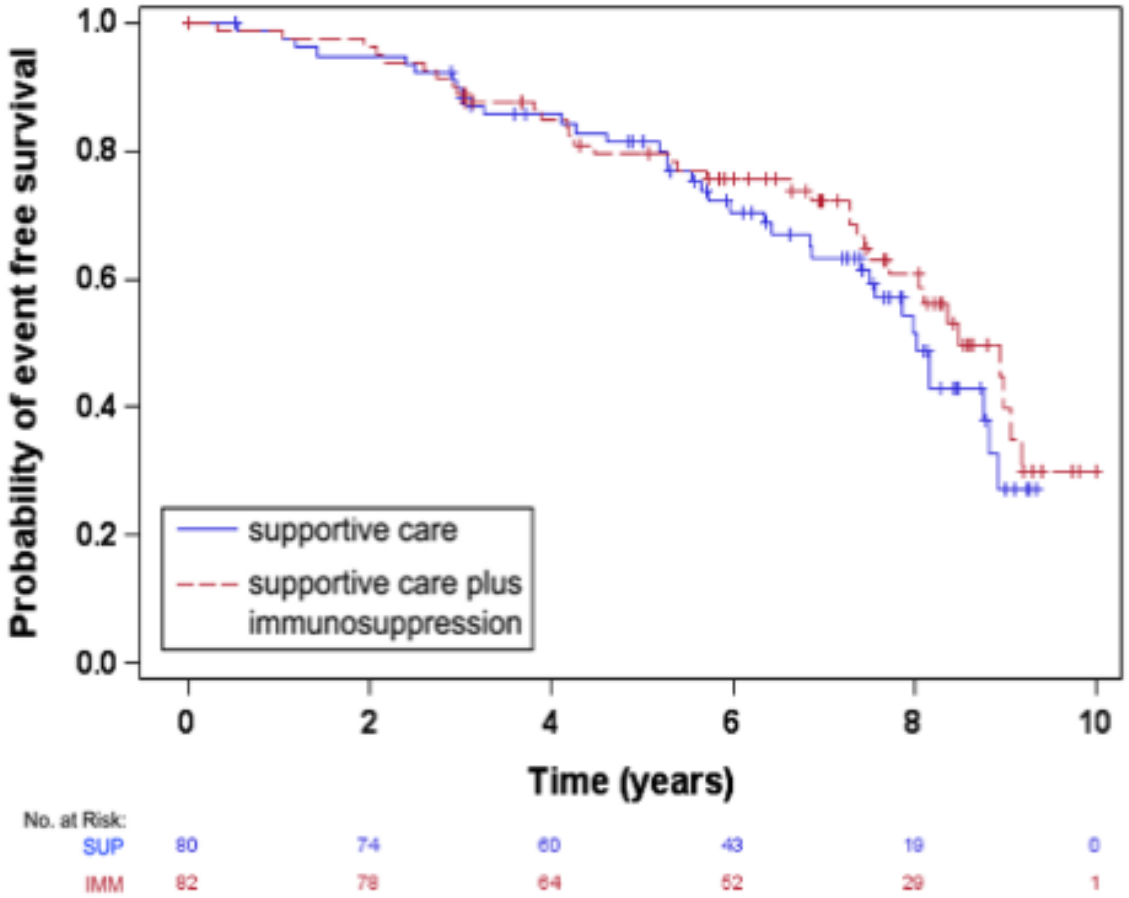
Systemic Steroids Treatment

STOP-IgAN



NEJM 2015;373:2225-2236

JAMA 2017;318:432-442

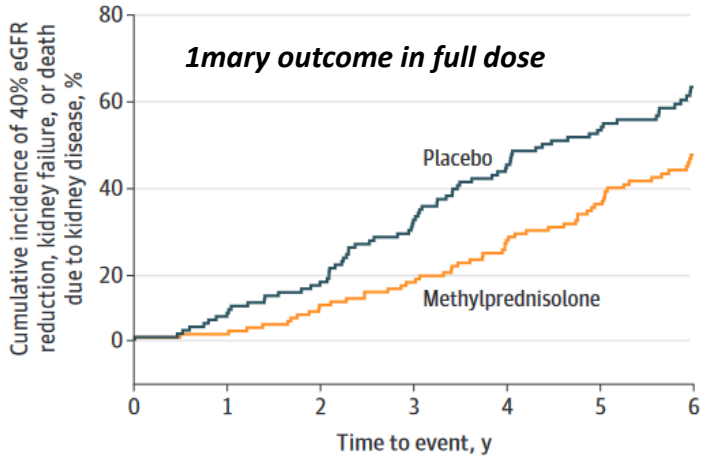
Research

JAMA | Original Investigation

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

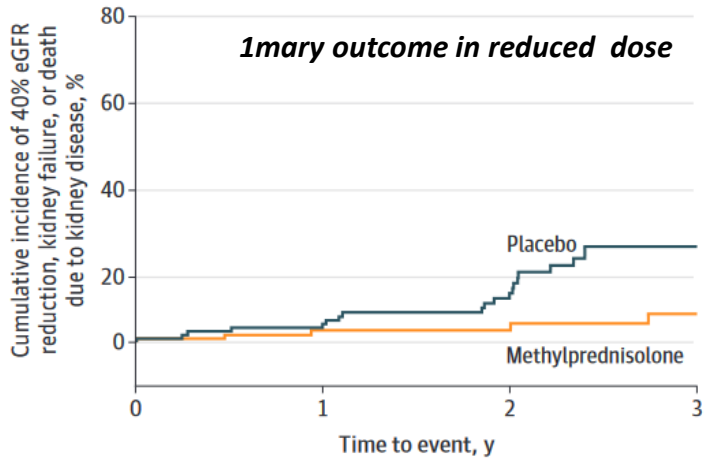
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Muh Geot Wong, PhD; Michelle A. Hladunewich, MD; Vivekanand Jha, MD; Lai Seong Hooi, MB, BChir; Helen Monaghan, BSc; Minghui Zhao, MD; Sean Barbour, MD, PhD; Meg J. Jardine, PhD; Heather N. Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, MD; David C. Wheeler, MD; Mark Woodward, PhD; Laurent Billot, MSc, MRes; Sandrine Stepien, MSc; Kris Rogers, PhD; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MBBS, PhD; Alan Cass, PhD; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hong Zhang, MD, PhD; Vlado Perkovic, MBBS, PhD; for the TESTING Study Group



No. of patients at risk

Methylprednisolone	136	133	124	117	104	92	66
Placebo	126	119	110	92	76	66	44



No. of patients at risk

Methylprednisolone	121	117	91	44
Placebo	120	115	78	35

Reduced corticosteroid dose:

From **0.6-0.8mg/Kg/d to 0.4mg/Kg/d for 2 mo** with 6-8 mo tapering
Total 503 pnts (1:1, high:low dose)
Median follow up 4.6 yrs

76% Chinese ethnicity
35 yrs median age
Initiation of therapy since biopsy: in 5 mo
Median proteinuria 2g/d

The benefit of methylprednisolone was evident on the 1mary outcome of 40% reduction in GFR and was independent of the dose as it was both on full and in reduced dose

JAMA. 2022 May 17;327(19):1888-1898

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JAMA | Original Investigation

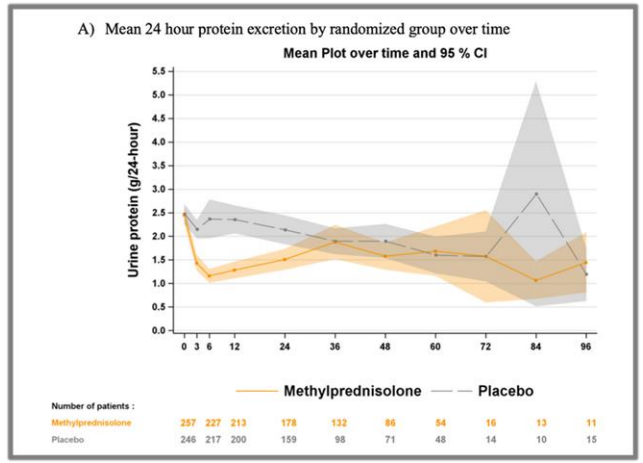
Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy

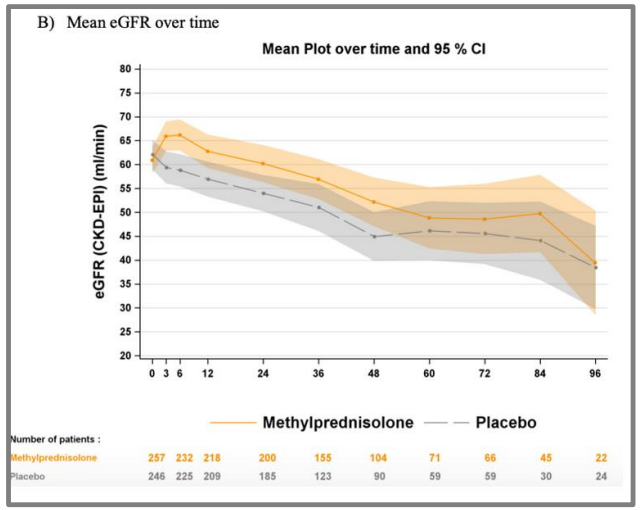
The TESTING Randomized Clinical Trial

Outcome	Methylprednisolone (n = 257)[a,b] No. of events	Methylprednisolone (n = 257)[a,b] Annual event rate (95% CI), %	Placebo (n = 246)[a,b] No. of events	Placebo (n = 246)[a,b] Annual event rate (95% CI), %	Rate difference (95% CI), %[b]	Hazard ratio (95% CI)[c]	*P* value[c]
Primary							
40% eGFR reduction, kidney failure, or death due to kidney disease[d,e]	74	7.3 (5.7 to 9.4)	106	12.1 (9.7 to 15.1)	−4.8 (−8.0 to −1.6)	0.53 (0.39 to 0.72)	<.001
Secondary							
30% eGFR reduction, kidney failure, or all-cause death	86	8.4 (6.7 to 10.6)	113	12.8 (10.3 to 15.8)	−4.4 (−7.7 to −1.0)	0.56 (0.42 to 0.75)	<.001
40% eGFR reduction, kidney failure, or all-cause death	78	7.7 (6.1 to 9.8)	106	12.2 (9.8 to 15.2)	−4.5 (−7.7 to −1.2)	0.56 (0.42 to 0.76)	<.001
50% eGFR reduction, kidney failure, or all-cause death	71	7.0 (5.5 to 9.1)	94	10.8 (8.6 to 13.7)	−3.8 (−6.9 to −0.7)	0.62 (0.46 to 0.85)	.003
Kidney failure requiring dialysis/transplant	50	4.9 (3.7 to 6.6)	67	7.8 (5.9 to 10.2)	−2.9 (−5.4 to −0.3)	0.59 (0.40 to 0.87)	.008
eGFR reduction							
30%	67	6.7 (5.2 to 8.7)	98	11.4 (9.1 to 14.3)	−4.7 (−7.8 to −1.6)	0.47 (0.34 to 0.65)	<.001
40%	57	5.8 (4.4 to 7.7)	91	10.9 (8.6 to 13.7)	−5.0 (−8.0 to −2.0)	0.44 (0.31 to 0.62)	<.001
50%	49	5.0 (3.7 to 6.7)	76	9.1 (7.0 to 11.7)	−4.1 (−6.8 to −1.3)	0.52 (0.36 to 0.74)	<.001
Death due to kidney failure[f]	1	0	1	0	0	NA	NA
Death due to any cause	6	0.5 (0.2 to 1.3)	3	0.3 (0.1 to 1.0)	0.2 (−0.4 to 0.8)	2.62 (0.53 to 13.05)	.24
Rate of eGFR decline, mL/min/1.73 m^2/y	Mean (95% CI)[g]				Mean difference (95% CI)[g]		*P* value[g]
Using all visits	−2.50 (−3.56 to −1.44)		−4.97 (−6.07 to −3.87)		2.46 (0.94 to 3.99)		.002
Excluding values from those receiving high-exposure treatment	−2.18 (−3.16 to −1.20)		−4.94 (−6.01 to −3.87)		2.76 (1.32 to 4.21)		<.001
Excluding values from those receiving treatment	−2.11 (−3.03 to −1.20)		−4.76 (−5.81 to −3.72)		2.65 (1.27 to 4.03)		<.001
Time-averaged proteinuria, g/d	1.70 (1.54 to 1.86)		2.39 (2.15 to 2.63)		−0.69 (−0.98 to −0.41)		<.001

Maximal proteinuria reduction at 6mo (-1.4g/day)
Proteinuria reduction was lost at 3yrs

eGFR increased at 6mo
Benefit was lost at 5yrs





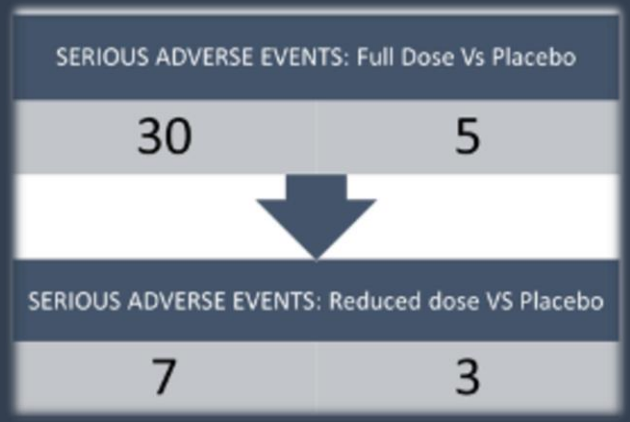
JAMA. 2022 May 17;327(19):1888-1898

Re-TESTING Steroids for IgA Nephropathy

TESTING trial: Serious adverse events

	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)

Discontinuation of trial due to ASE



JAMA. 2022 May 17;327(19):1888-1898

Curr Opin Nephrol Hypertens. 2023 May

2021 update

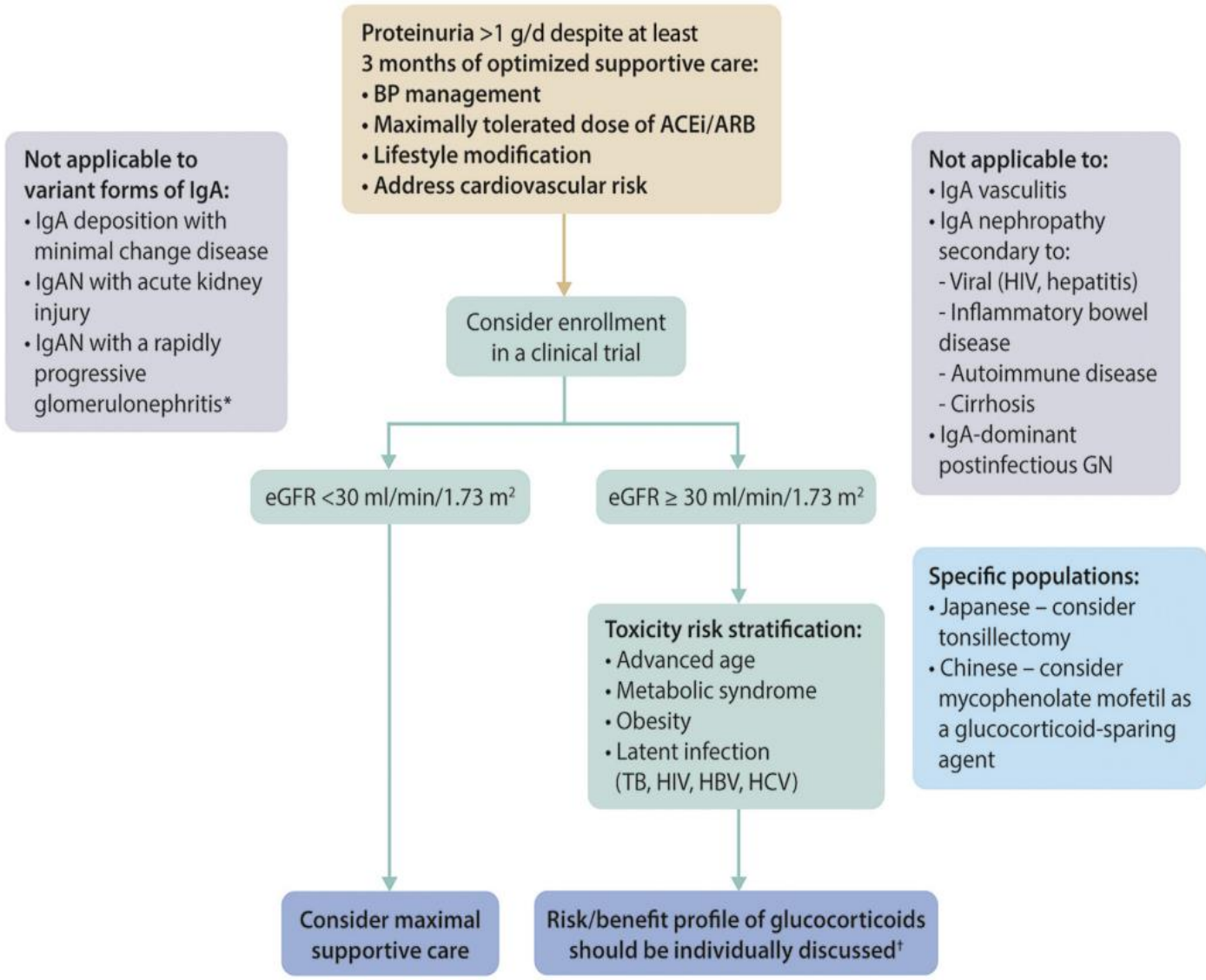
STOP IgAN RCT: CS induced a transient reduction in UP over 3 years without impact on eGFR. Significant increase in adverse events in CS-IS.

TESTING IgAN RCT: Discontinuation due to high risk of adverse events

Practice Point 2.3.1.3: Use of glucocorticoids in IgAN:

- Clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution or avoided entirely

High risk patients



Kidney Int. 2021 Oct;100(4S):S1-S276

Systemic vs topical glucocorticosteroids

NeflgArd phase III trial (Part A)

Long term efficacy in Part B → 360 pnts

Nefecon: Oral Targeted release formulation (TRF) budesonide

Cohort and intervention

Randomised

- 201 patients with **IgAN**
- **Nefecon** 16 mg od: n=97
- **Placebo**: n=102

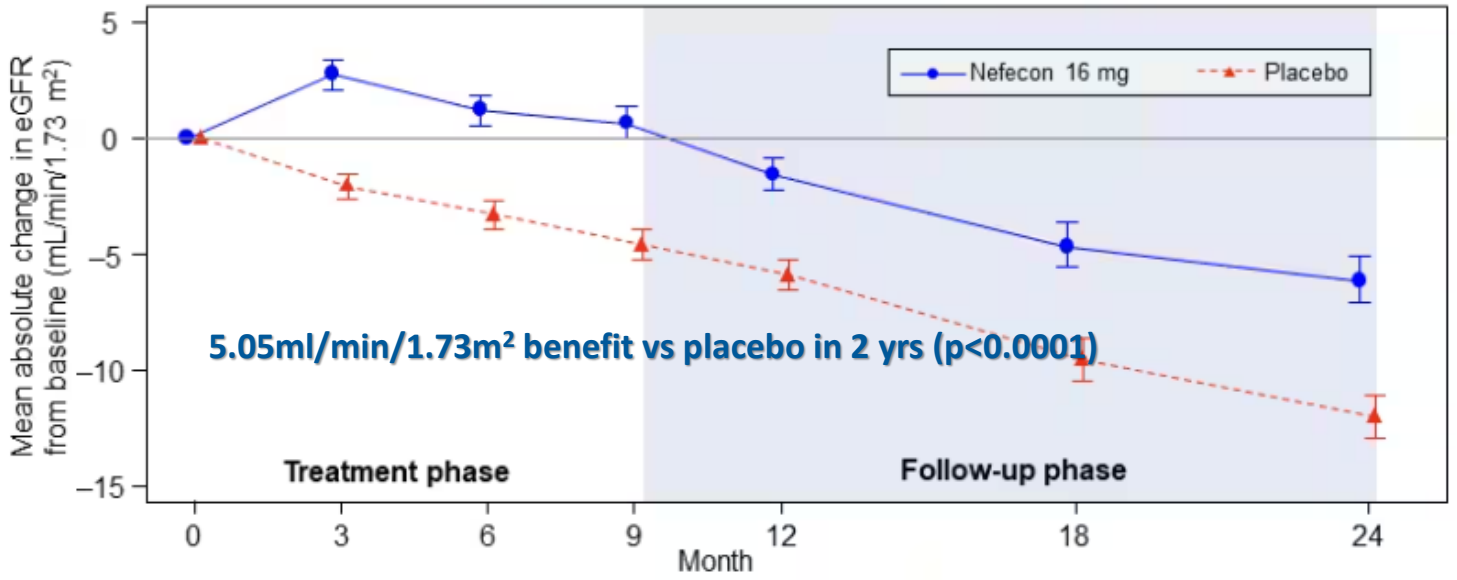
9-month treatment → 3-month follow-up

Key baseline characteristics

- Optimised RAS blockade: **ALL**
- Median UPCR: **1.26 g/g**
- Median proteinuria: **2.26 g/24 h**
- ≥2g/24h proteinuria: **58%**
- Median eGFR: **55 ml/min/1.73 m²**

Reduced loss of eGFR

Mean (SEM) absolute change in eGFR from baseline



Nefecon 16 mg/d, mL/min/1.73 m²	0.66	−1.52		−6.11
Placebo, mL/min/1.73 m²	−4.56	−5.85		−12.00
Absolute difference, mL/min/1.73 m² (95% CI)	5.21 (3.35-7.58)	4.33 (2.44-6.66)		5.89 (3.35-9.15)

Kidney International (2023) 103, 391–402

Lafayette et al. Presented at 60th annual ERA congress; June 15-18 2023; Milan

- *NefIgArd adverse events: 86.6% with Nefecon vs 73% with placebo*
- *No severe infections requiring hospitalisation*

NefIgArd RCT
Treatment adverse events (TEAE)

	Placebo (n = 100)		Nefecon 16 mg/d (n = 97)	
Adverse event descriptors	n (%)	Events	n (%)	Events
All TEAEs	73 (73.0)	300	84 (86.6)	429
Maximum severity of TEAEs				
Mild	46 (46.0)	243	49 (50.5)	330
Moderate	26 (26.0)	56	31 (32.0)	95
Severe	1 (1.0)	1	4 (4.1)	4
AE of infection	41 (41.0)	–	38 (39.2)	–
Any AESI	0 (0.0)	–	2 (2.1)	–
Severe infection that required hospitalization	0 (0.0)	–	0 (0.0)	–
New onset of diabetes mellitus[a]	0 (0.0)	–	2 (2.1)	–
Confirmed fracture	0 (0.0)	–	0 (0.0)	–
New osteonecrosis	0 (0.0)	–	0 (0.0)	–
GI bleeding requiring hospitalization	0 (0.0)	–	0 (0.0)	–
Reported occurrence of cataract formation	0 (0.0)	–	0 (0.0)	–
Reported onset of glaucoma	0 (0.0)	–	0 (0.0)	–
Any treatment-emergent SAE	5 (5.0)	5	11 (11.3)	16
Any study treatment related treatment-emergent SAE	2 (2.0)	2	2 (2.1)	2
Any AE leading to death	0 (0.0)	0	0 (0.0)	0
Any TEAE leading to discontinuation of study treatment[b]	1 (1.0)	5	9 (9.3)	27

Kidney International (2023) 103, 391–402

	STOP	TESTING	NEFIgARD
age	43±12	35 (29-46) >50 yo 10%	43 (23-73)
Time since renal biopsy (months)	9.5 (4.5-95)	5 (4-11)	33 (6-84)
eGFR	57	59	55
Proteinuria g/day	1.6	1.9	2,2
Severe AE	33%	11%	1%
Serious infections	2% 1 death	2,2% full dose 0.8% low dose Fatal in 4 cases (3 high dose, 1 low dose)	0 Mild infections in 2% no hospitalization

Ethnicity	100% Caucasian	75% Chinese	84% White

Increased frequency of peripheral edema, acne, hypertension (11-15% of the treated cases)→ some systemic CS exposure

→ ***Treatment up to 9 montns***

FDA approved in December 2021 in pnts with IgAN and risk of progression (UPCR ≥ 1.5g/g)

Systemic Glucocorticosteroids

- Rapid anti-inflammatory action
- May vanish over 1-3 years at the low doses
- Validation awaited in all ethnicities
- 4mg of methylprednisolone
- More SE

VS

Delayed released budesonide

- 90% cleared by 1st liver passage → less systemic SE
- 2nd generation synthetic GS
- Slow decrease in proteinuria (decrease in Gd-IgA)
- Possible benefits last longer
- Validation awaited in all ethnicities
- Awaiting results of Part B Nefigard
- Equivalent is 0.375mg of budesonide

Who will have a significant benefit from the treatment?

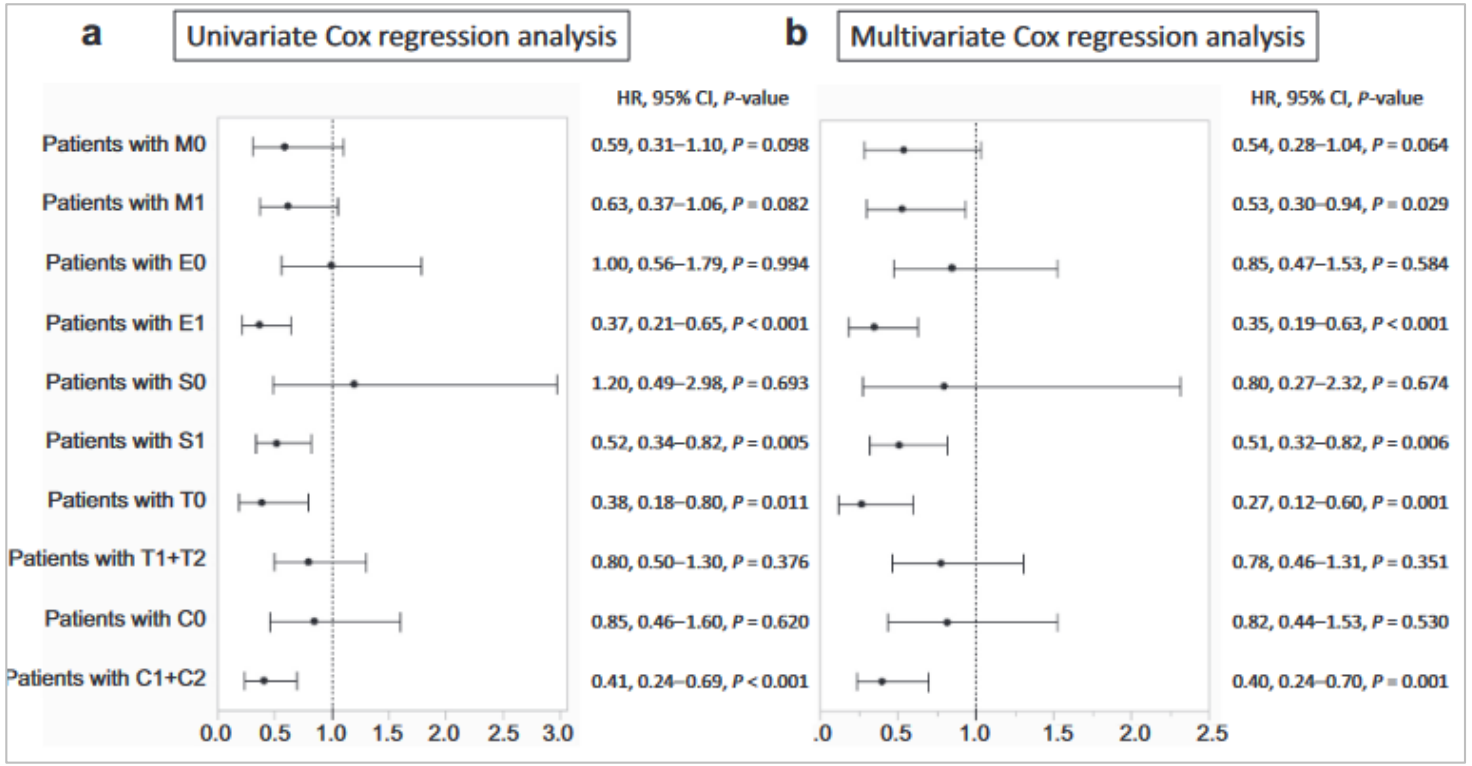
2021 update: *Insufficient evidence supporting use of Oxford classification MEST-C score to determine whether GS shoud be used in the treatment*

https://www.fda.gov/drugs/fda-approves-first-drug-decrease-urine-protein-iga-nephropathy-rare-kidney-disease

KI REPORTS
KIReports.org
CLINICAL RESEARCH

A Novel Scoring System Based on Oxford Classification Indicating Steroid Therapy Use for IgA Nephropathy

Shusaku Itami[1], Takahito Moriyama[1], Yoei Miyabe[1], Kazunori Karasawa[1] and Kosaku Nitta[1]



858 pnts with IgAN
GS benefit with MEST-C score 2-4

Pnts with M1, E1, S1, and C1+2 scores responded to GS
Pnts with T1+2 scores did not respond to GS

Kidney Int Rep. 2021 Oct 14;7(1):99-107

Intensity of macrophage infiltration in the glomerulus predicts the response to immunosuppressive therapy in IgAN

- 621 Chinese pnts and IgAN and proteinuria ≥ 1g/g
- Treated with MMF and GS for median of 18 mo
- Levels of glomerular CD68 and CD206 of MΦ

Value of

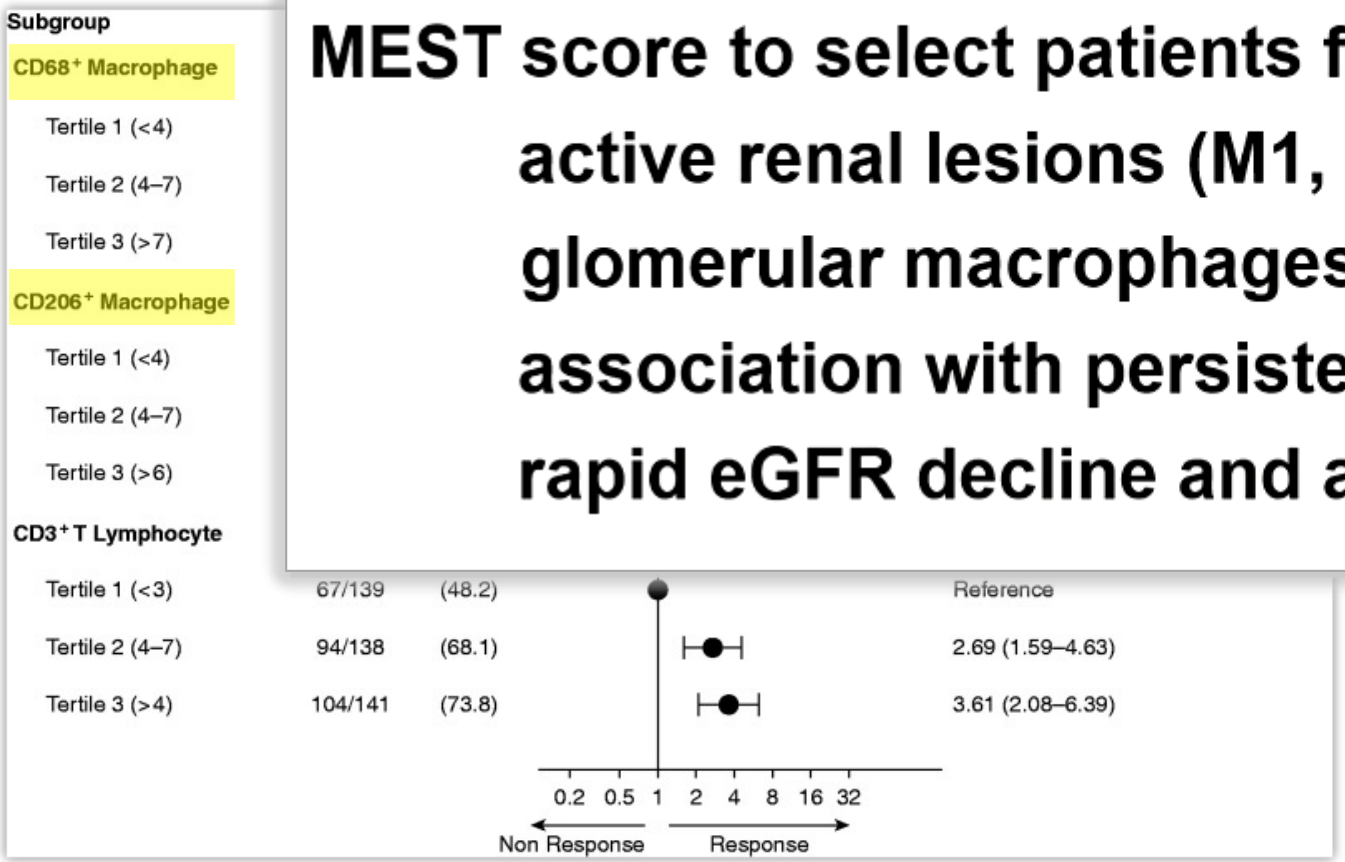
MEST score to select patients for CS/IS treatment

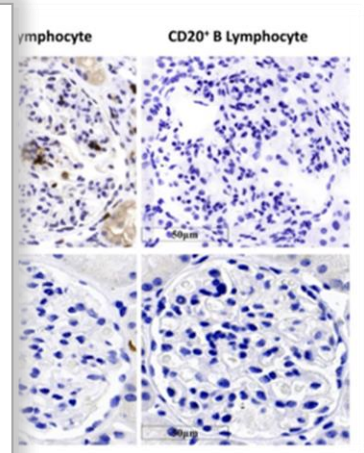
active renal lesions (M1, E1, S1, C1-2, T0)

glomerular macrophages

association with persistent severe hematuria

rapid eGFR decline and active features





rular infiltrates,

eased probability

ion in adjusted analysis compared with having lower levels

Outcome of stable UP and stable eGFR after 1 year

J Am Soc Nephrol. 2021 Dec 1;32(12):3187-3196

Emerging targeted therapies

Inhibition of Immune Complex Activated Complement Activity

Avacopan	II	NCT02384317	anti-C5a receptor antagonist
Ravulizumab	II	NCT04564339	long-acting C5-blocking antibody
Cemdisiran	II	NCT03841448	small interfering RNA-targeting C5
APL-2	II	NCT03453619	cyclic peptide inhibitor of C3 and C3b
Iptacopan	III	NCT04578834	small-molecule inhibitor of complement factor B
IONIS-FB-LRx	II	NCT04014335	antisense inhibitor of complement factor B messenger ribonucleic acid
Narsoplimab	III	NCT03608033	human monoclonal antibody against (MASP-2)

APPLAUSE-IgAN trial

ARTEMIS trial

Inhibition of BAFF/APRIL Signaling (Prevent Gd-IgA1 production)

Blisibimod	II/III	NCT02062684	monoclonal antibody against both soluble and membrane BAFF
Sibeprenlimab		NCT05248646	monoclonal IgG2κ antibody targeting APRIL
BION-1301	I/II	NCT03945318	monoclonal IgG4 antibody targeting APRIL
Atacicept	IIb	NCT04716231	BAFF/APRIL dual inhibitor
Telitacicept	II	NCT04905212	BAFF/APRIL dual inhibitor

JANUS trial

Plasma Cell Depletion

Felzartamab	II	NCT05065970	monoclonal IgG1 antibody targeting CD38
Bortezomib	NA	NCT05383547	proteasome inhibitor that depletes plasma cells

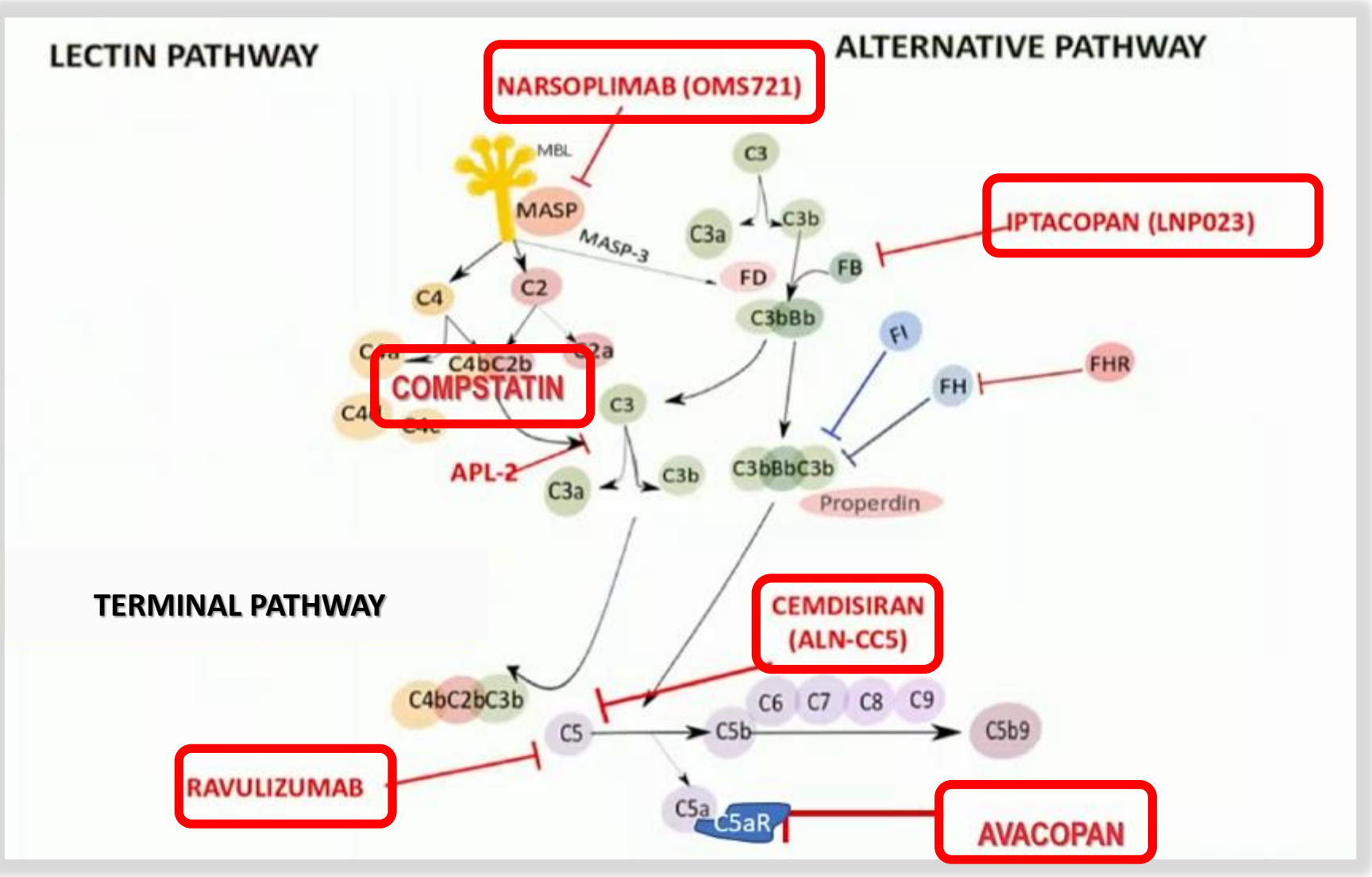
Pilot trial

Inhibition of Endothelin A Receptor and Angiotensin II subtype 1 receptor inhibitor

Sparsentan	III	NCT03762850	endothelin A receptor and angiotensin II subtype 1 receptor inhibitor
Atrasentan	III	NCT04573478	endothelin A receptor antagonist

ALIGN trial

PATHWAY-SPECIFIC COMPLEMENT INHIBITORS IN IGAN: ONGOING STUDIES



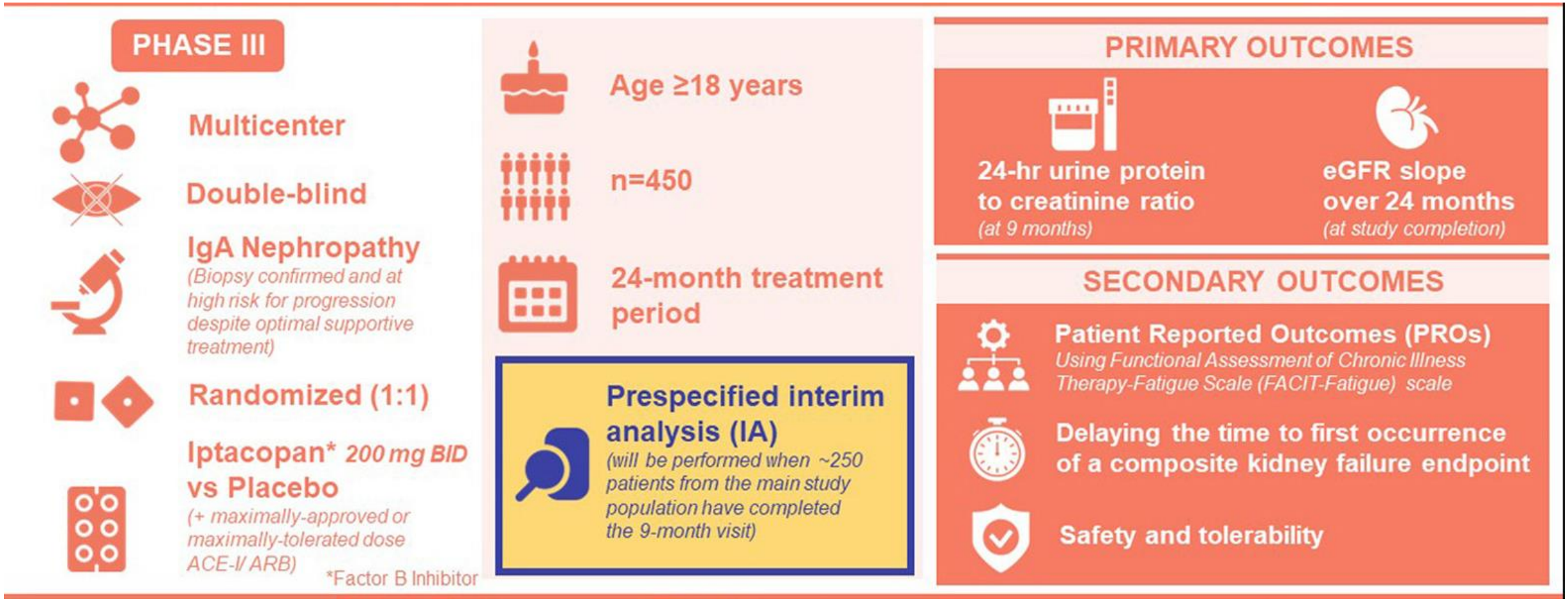
Evidence for complement activation

1. **Clinical**
2. **Genetic**
3. **Histopathological**
4. **Biochemical**

Compliment activation associates with more severe disease prognosis

Targeting the alternative complement pathway with iptacoban to treat IgAN: APPLAUSE-IgAN study (NCT04578834)

Iptacoban: is a proximal compliment inhibitor that specifically binds to factor B



APPLAUSE-IgAN will evaluate the benefits and safety of iptacoban in reducing complement mediated kidney damage and thus slowing or preventing disease progression

Safety, Tolerability and Efficacy of Narsoplimab, a Novel MASP-2 Inhibitor for the Treatment of IgA Nephropathy

mannan-binding lectin-associated serine protease-2 (MASP-2)

METHODS

Substudy 1: 18-week single-arm, open-label

Substudy 2: 18-week randomized 1:1, double-blind; open-label extension through 104 weeks

Key inclusion criteria

- Age ≥18 years
- Biopsy-confirmed IgAN diagnosis
- 24hr UPE >1g/day on ACEI/ARBs, eGFR >30 mL/min/1.73 m²
- Blood pressure < 150/90 mmHg
- Corticosteroid dose of >10 mg/day (Substudy 1 only)

Treatment

Narsoplimab 4 mg/kg once-weekly for 12 weeks. Steroid were tapered during study.

Treatment

Narsoplimab 370 mg fixed-dose or vehicle weekly for 12 weeks, then 12-week courses of open-label therapy as indicated.

Primary objective

Safety of narsoplimab in IgA nephropathy patients on corticosteroids.

Primary objective

Safety of narsoplimab in IgA nephropathy patients not on corticosteroids

Secondary objective

24-hr Urine Protein Excretion (UPE)

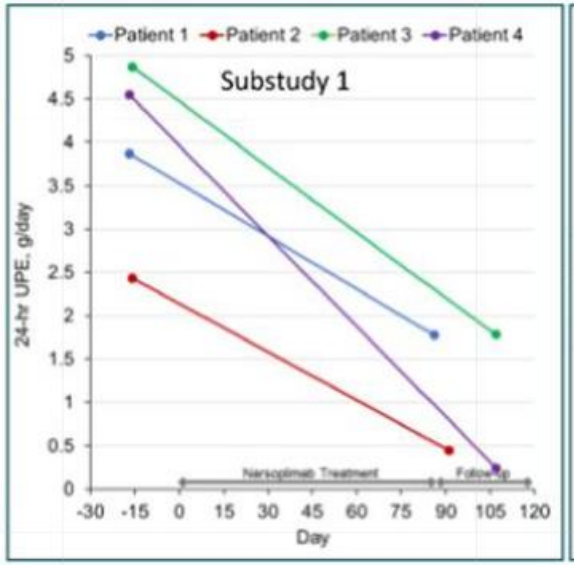
Secondary objective

24-hr Urine Protein Excretion (UPE)

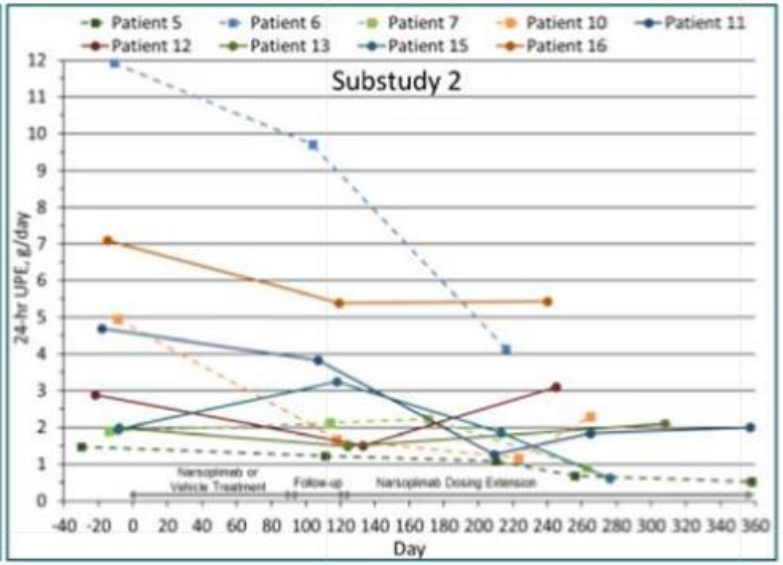
SAFETY

Narsoplimab was well tolerated in this study. The most commonly reported adverse events (AEs) included headache, upper respiratory infection, and fatigue. Most AEs were mild or moderate and transient. No treatment-related serious AEs were reported.

RESULTS



24-hr UPE at baseline and last follow-up visit in substudy 1. Median reduction of proteinuria was 72% at 13-15 weeks post-baseline.



24-hr UPE at baseline through last available follow-up visit for evaluable patients in substudy 2. Dashed lines represent patients that were initially randomized to vehicle and patients with solid lines were initially randomized to narsoplimab. All patients in dosing extension period received narsoplimab. Overall median

This interim analysis suggests that narsoplimab treatment is safe, is well tolerated, and may result in clinically meaningful reductions in proteinuria and stability of eGFR in high-risk patients with advanced IgAN.

ARTEMIS-IGAN trial

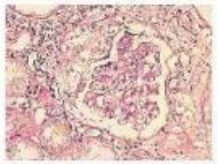
Kidney Int Rep. 2020 Nov; 5(11): 2032–2041.

C5a receptor inhibitor avacopan in immunoglobulin A nephropathy: an open-label pilot study

Methods

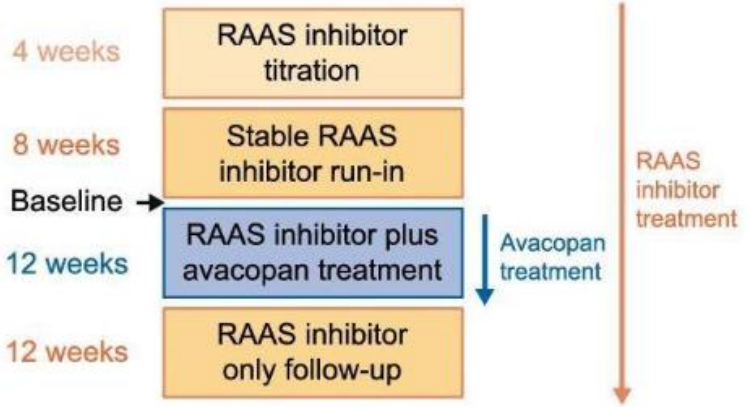
Open-label pilot trial

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

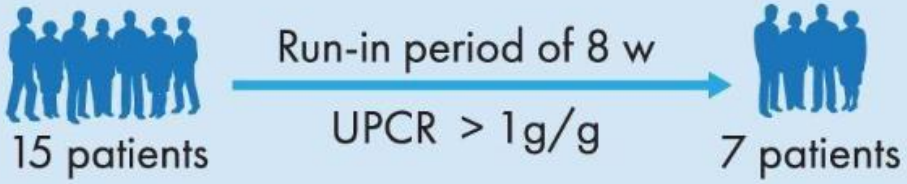


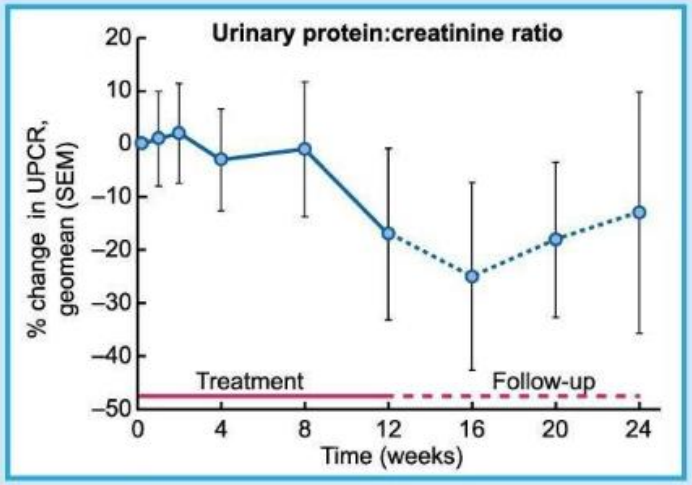
OR

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

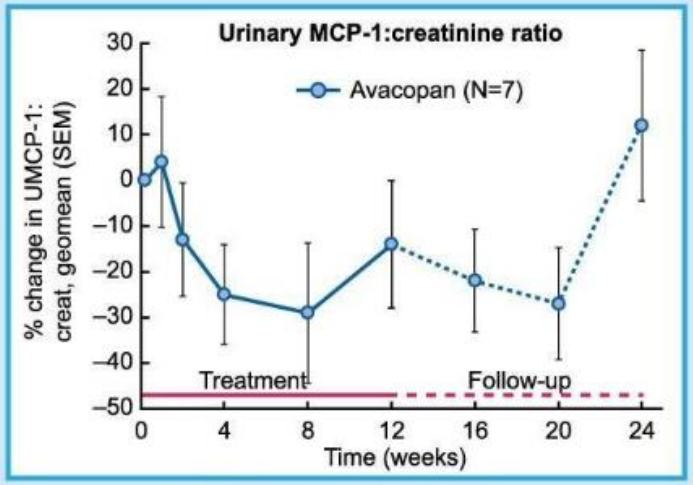


Results





Improvement in UPCR during treatment



Urinary MCP-1: creatinine decreased 30%

⚠ 1 event: unstable angina – unrelated to avacopan

improvement in the slope of the UPCR, with ~50% improvement in three of seven patients with IgAN. Longer avacopan treatment duration may be indicated for maximal benefit.

Clin Kidney J. 2022 May; 15(5): 922–928.

Emerging targeted therapies

Inhibition of Immune Complex Activated Complement Activity

Avacopan	II	NCT02384317	anti-C5a receptor antagonist
Ravulizumab	II	NCT04564339	long-acting C5-blocking antibody
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← APPLAUSE-IgAN trial

← ARTEMIS trial

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Atrasentan	III	NCT04573478	endothelin A receptor antagonist

← ALIGN trial

JANUS RCT: Atacicept binds and inhibits B lymphocyte stimulator (BLyS) and A proliferation inducing ligand (APRIL)→

Population

Adults
Japan, UK, USA

IgA Nephropathy
✓ w/ Proteinuria*
✓ on RAASi >12 wk

RAASi, renin angiotensin aldosterone system inhibitor

Intervention

Double-blinded
1:1:1 Randomization

Weekly subcutaneous injection drug or placebo

72 wk treatment
+ 24 wk safety monitoring

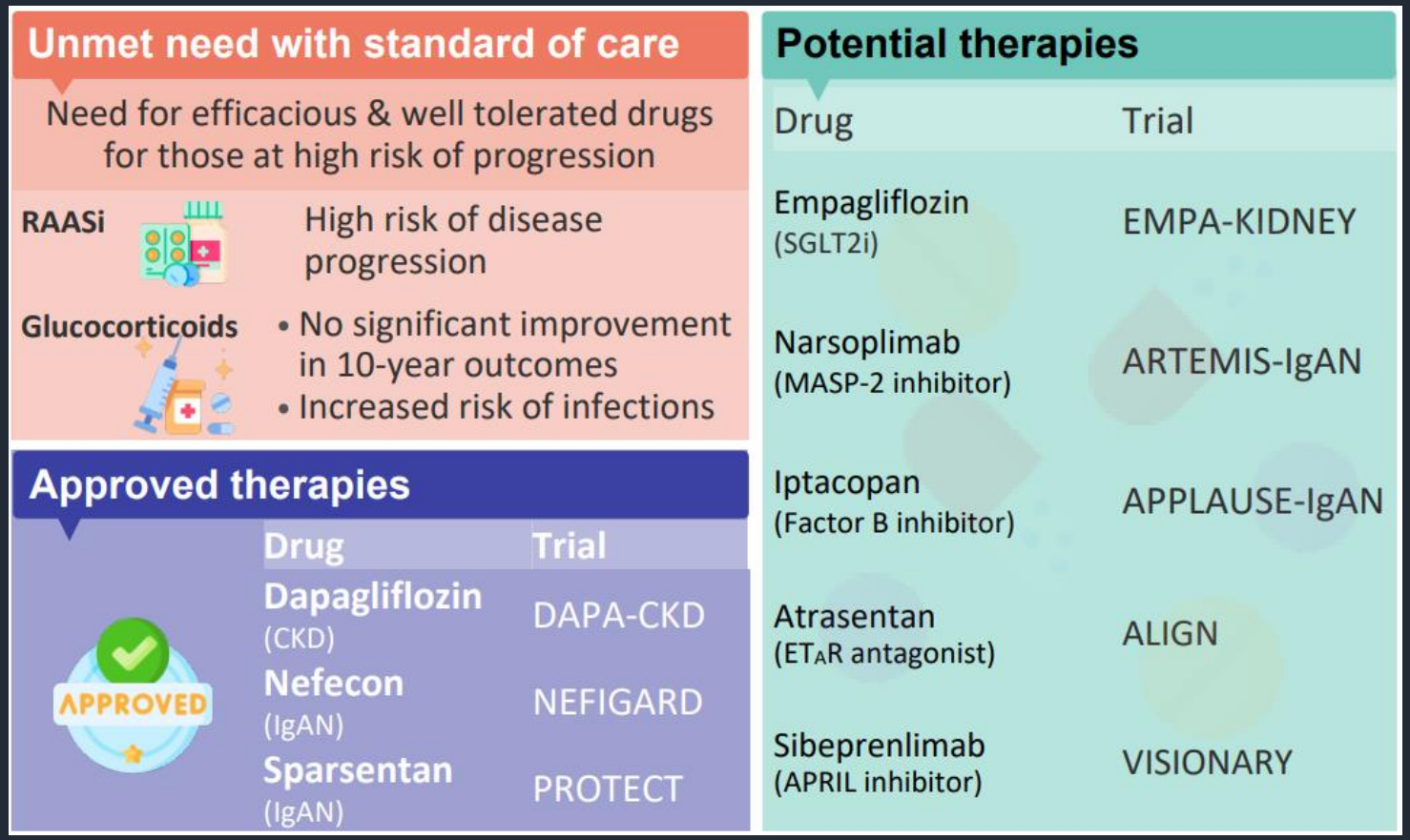
	Adverse Events		Outcomes	
	Treatment-Related	Serious†	%Δ Gd-IgA1	%Δ Proteinuria
Placebo n=5	20% (1/5)	20% (1/5)	2% (-3, 5)	24% (-24, 64)
Atacicept 25 mg n=6	83% (5/6)	50% (3/6)	-25% (-26, -24)	-24% (-61, 17)
Atacicept 75 mg n=5	60% (3/5)	None (0/5)	-60% (-66, -47)	-25% (-41, -15)

** Protein to creatinine ratio ≥ 1 mg/mg by 24-hr urine collection; † None were considered treatment-related; %Δ, percent change from baseline at 24 wk of modified intent to treat population, as Median (Q1,Q3); Gd-IgA1, galactose-deficient immunoglobulin A1*

Kidney Int Rep. 2022 Aug; 7(8): 1831–1841.

…. What does the future hold?

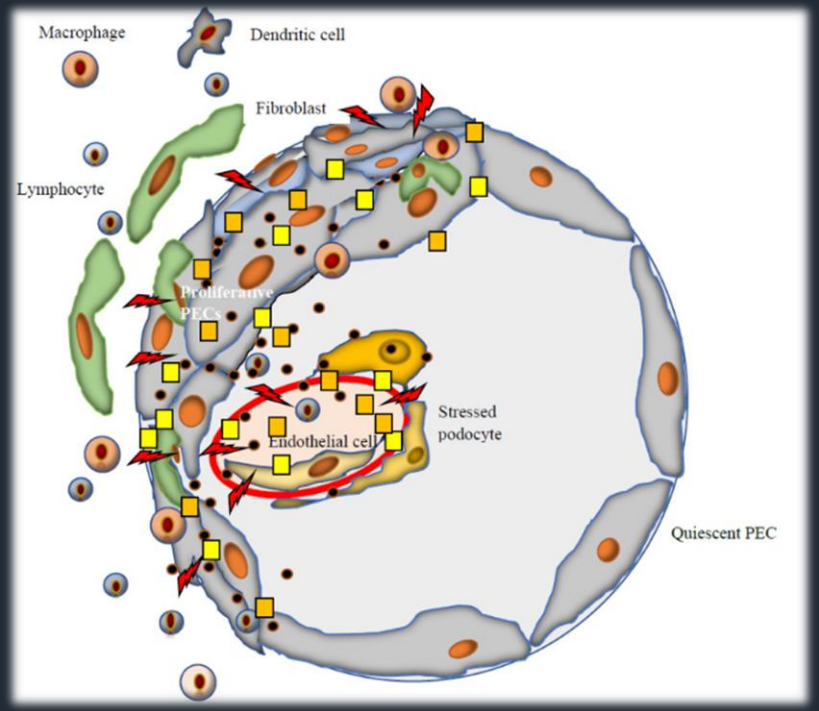
- ✓ *Earlier identification*/ diagnosis/ enrollment in clinical trials
- ✓ Better risk stratification with *novel biomarkers* ***(e.g G-IgA1, autoantibodies)***
- ✓ *Personalize* the best therapy
  - Different treatments at different stages
  - Concomitant or sequential therapies?
- ✓ Better assessment of treatment response ***(repeat biopsy?)***
- ✓ *Pediatric population? Tx population?*
- ✓ *IgAVN?*
- ✓ …AI → pathomis=automated morphometry and comprehensive quantitative data→ prediction who will respond to CS



"This is an awesome time to be a Nephrologist! We are at the entry level of an explosion in new therapies that show very little safety concern and yet are providing us the mechanism to move in a direction hopefully of both early and precise treatment for individual patients"

- https://vmx.m-anage.com/era/era23/en-GB/presentation/496667
- https://cme.healio.com/nephrology/20230320/pathogenesis-and-management-of-iga/content
- https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01554-4/fulltext
- https://www.youtube.com/watch?app=desktop&v=LV3PCkEgjFU

What about presence of crescents regarding the decision of treatment?



J. Clin. Med. 2022, 11, 356

Is there long-term value of pathology scoring in immunoglobulin A nephropathy? A validation study of the Oxford Classification for IgA Nephropathy (VALIGA) update

Multivariable Cox regression analysis for the risk of reaching the combined renal endpoint of 50% decline in eGFR or kidney failure

Characteristics	All patients ($n = 1130$)	Patients never treated with corticosteroid/immunosuppressors during the follow-up ($n = 582$)
M1	1.34 (1.02–1.75), P=0.037*	1.83 (1.23–2.75), P=0.003*
E1	1.17 (0.79–1.74), P=0.43	0.83 (0.45–1.53), P=0.55
S1	1.61 (1.10–2.36), P=0.01*	1.54 (0.89–2.66), P=0.13
T1–2	2.46 (1.80–3.36), P<0.001*	2.73 (1.66–4.47), P<0.001*
Crescents (C1–2)	0.85 (0.55–1.30), P=0.44	1.81 (0.90–3.64), P=0.10

**after 7 yrs follow up crescents maintain a negative predictive value*

Nephrol Dial Transplant (2020) 35: 1002–100

Barratt et al.

What is the relationship between proteinuria, eGFR slope, and long-term risk of kidney failure in patients with IgA nephropathy?

CJASN
Clinical Journal of the American Society of Nephrology

Materials & Methods

Retrospective cohort study

RaDaR — UK National Registry of Rare Kidney Diseases RaDaR

2,299 adults & **140** children with **biopsy-proven IgA nephropathy**

Proteinuria **>0.5 g/day** or eGFR **<60 ml/min**

Results

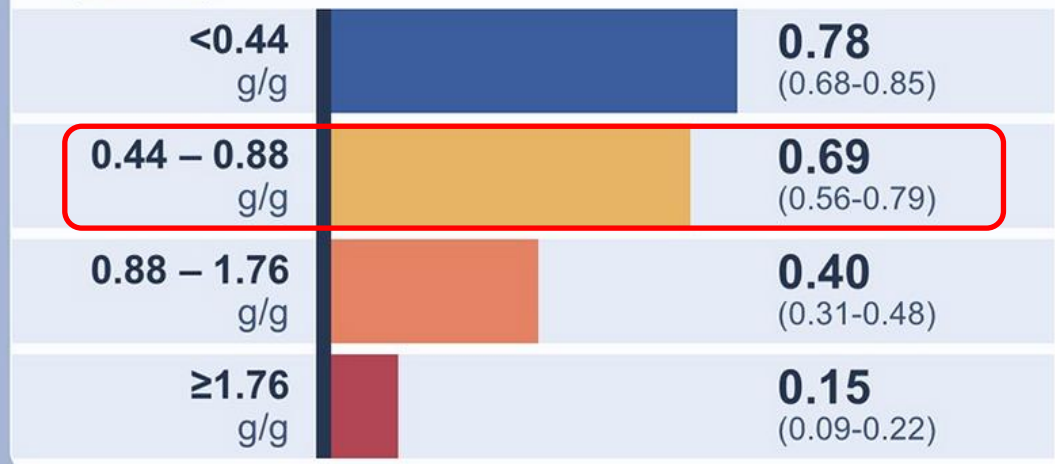
5.9 years — **Median follow-up**

45.3 years — **Median age at diagnosis** (in 2020)

48 years — **Median age at kidney failure/death**

50% — **Percentage of patients who reached kidney failure or died**

Estimated kidney survival rates within 10 years based on time-averaged proteinuria (95% CI)



At a 1 ml/min/year decline in eGFR, **~40% of adult patients** aged <50 years at diagnosis reach kidney failure within lifetime

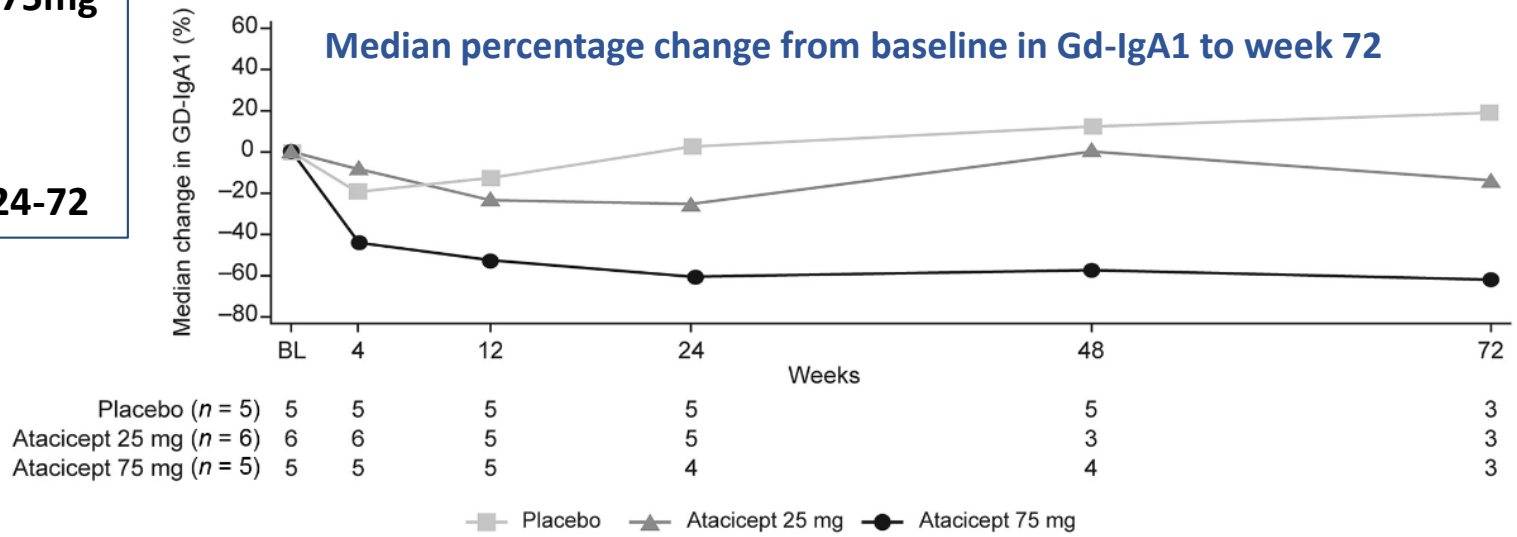
Patients traditionally regarded as being low risk, with proteinuria <0.88 g/g (<100 mg/mmol), had high rates ESRD within 10 years

Clin J Am Soc Nephrol. 2023 Jun 1;18(6):727-

KI REPORTS
KIReports.org

Randomized Phase II JANUS Study of Atacicept in Patients With IgA Nephropathy and Persistent Proteinuria

- 16 pnts (1:1:1), placebo:atacicept 25mg: atacicept 75mg
- Once weekly, SC
- 72 weeks
- 24 weeks follow up
- Dose dependent reduction in Gd-IgA1 from week 24-72



Kidney Int Rep. 2022 May 26;7(8):1831-1841

Bortezomib

IgA nephropathy is an autoimmune disease in which autoantibodies directed against Gd-IgA1 or other endogenous proteins act as autoantigens.

Proteasome inhibition is a potential treatment for autoantibody-associated autoimmunity.

Bortezomib is a proteasome inhibitor that targets plasma cells, which are professional antibody-producing cells. It is approved by the FDA for treatment of multiple myeloma.

- 8 patients received and tolerated 4 doses of bortezomib over a 2-week period during enrollment.
  - The median baseline daily proteinuria was 2.46 g (interquartile range, 2.2-3.16 g).
- At 1-year follow-up, 3 patients (38%) had achieved proteinuria <300 mg/day (full remission; primary endpoint).
  - The 3 patients who had complete remission had Oxford classification T scores of 0 before enrollmen.t
- Of the remaining 5 patients, 1 was lost to follow-up within 1 month of enrollment and 4 (50%) did not have any response or had progression of disease.

Hartono C, et al. *Kidney Int Rep.* 2018;3(4):861-866.

RCT	Authors/Year	Study drug	ST timing	Data on kidney biopsy
STOP- IgAN	Rauen T et al. 2015	ST + immunosuppression vs ST	6 months	NRD
TESTING	Lv J et al. 2017	High dose of MPL vs Placebo	At least 3 months	C lesions not reported
NEFIgAN	Fellström BC et al. 2017	TRF Busedonide vs Placebo	6 months	NRD
DAPA-CKD	Heerspink HJL et al. 2020	Dapaglifozine vs Placebo	At least 3 months	NRD
NEFIgArD	Barratt J et al. 2023	TRF Busedonide vs Placebo	At least 3 months	NRD
PROTECT	Heerspink HJL et al. 2023	Sparsentan vs Irbersartan	3 months	NRD

Schena F.P. and Cox SN, JN 2023 (in press)

What's New with IgA Nephropathy?

With Dr Muh Geot Wong
Royal North Shore Hospital
George Institute for Global Health

Steroid Regimens

Pozzi (1999, n=86): IV MP 1 g/d x 3 d M1,3,5 + PO PDN 0.5 mg/kg q.o.d. x 6 m

Manno (2009, n=97): PO PDN 1 mg/kg/d (max 75 mg/d) x 2 m, taper 0.2 mg/kg/d qmonthly

Lv (2009, n=63): PO PDN 0.8-1 mg/kg/d x 8 w, then taper by 5-10 mg q2 w over 4-6 m

STOP-IgAN (2015, n=162; 2020, n=149): Pozzi regimen
→ no renal benefit (and serious adverse effects) from immunosuppression added to supportive care measures

TESTING (2017, n=262): PO MP 0.6-0.8 mg/kg/d (max 48 mg/d) x 2 m, taper by 8 mg/d qmonthly over 4-6 m
→ temporarily halted published interim analysis due to serious adverse effects

TESTING low dose steroids: PO MP 0.4 mg/kg/d (max 32 mg/d, min 24 mg/d) x 2 m, taper by 4 mg/d qmonthly, stop within 6-9 m
→ ongoing

NEFIGAN (2017): Phase 2b trial, Nefecon (TRF-budesonide)
NEFIGARD: Phase 3

Optimize kidney protective measures:
BP control
RAAS blockade
Lifestyle modification (e.g., ↓ salt, protein)
CV risks addressed (e.g., statins)

If proteinuria >1 g/d after 3 m of optimized support, and if with risk of progression based on International IgAN Risk-Prediction Tool

If eGFR ≥ 30 ml/min/1.73m^2 and risk/benefit profile for steroid use acceptable: may consider individualized steroid regimen

Consider enrollment in clinical trial

Not recommended:
Anti-platelet agents, Anticoagulants, AZA, CYC, RTX, Fish oil

May consider in specific populations:
Tonsillectomy: Japanese
MMF: Chinese

Ongoing Phase III Trials

Trial name	Drug	Mechanism
PROTECT	Sparsentan	Combined endothelin-A/ Angiotensin II inhibitor
ALIGN	Atrasentan	ET-A receptor antagonist
	OMS721 (Narsoplimab)	MASP inhibitor
	LNP023 (Iptacopan)	CFB inhibitor

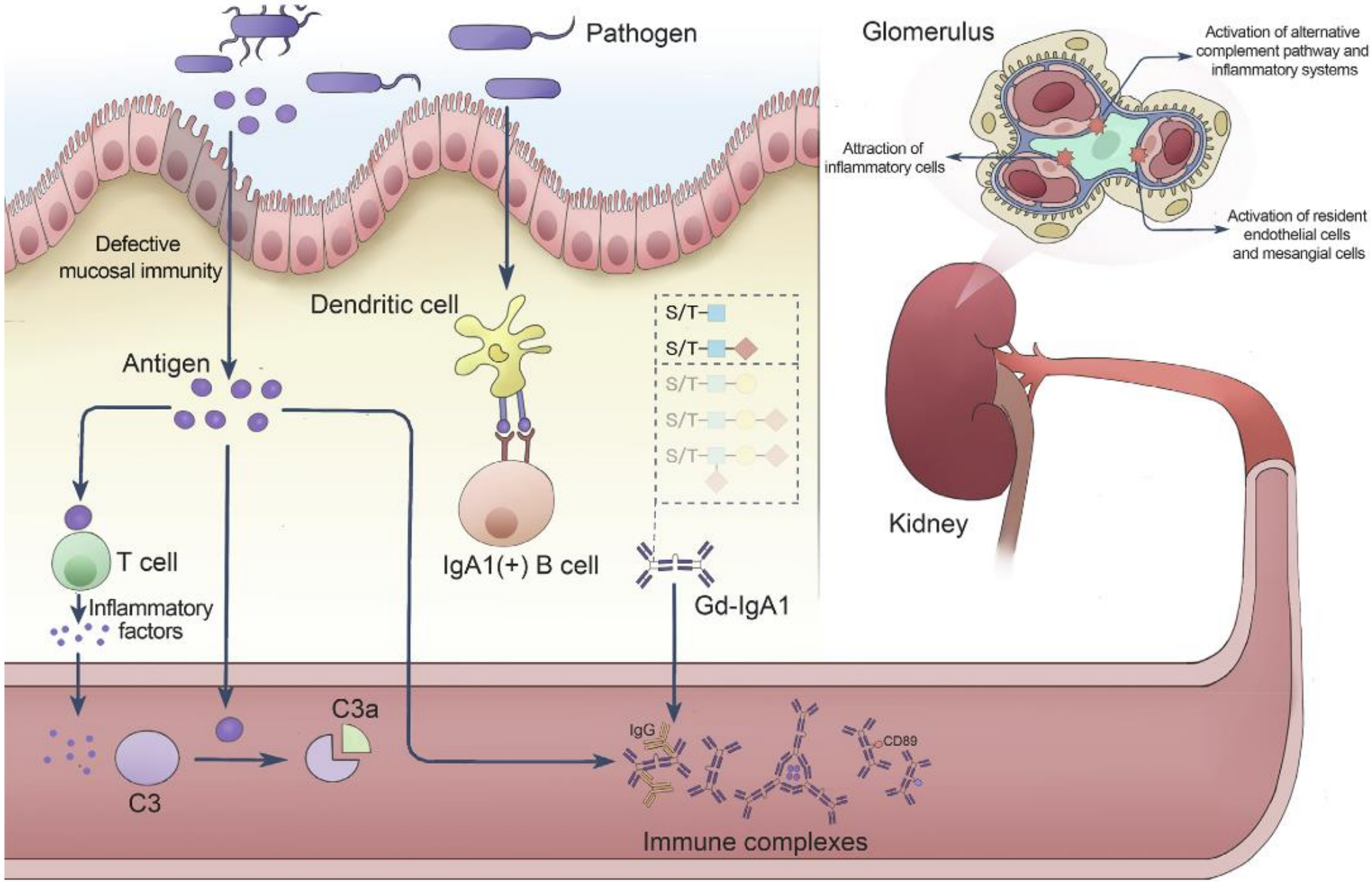
Some Ongoing Phase II Trials

Trial name	Drug	Target
enVISion	VIS649	APRIL
JANUS	Atacicept	Blys-APRIL
BRIGHT-SC	Blisibimod	BAFF
	Hydroxychloroquine	TLR9
	IONIS-FB-LRx	Factor B/C5
	ALN-CC5 (Cemdisarin)	C5
	APL-2	C3b

Adapted from: GlomCon Podocin Session 2021-01-14
Figure IgAN2 of KDIGO Clinical Practice Guideline on Glomerular Diseases Public Review Draft 2020

Infographic by: Paolo Nikolai So @nikkonephro

GlomCon edu

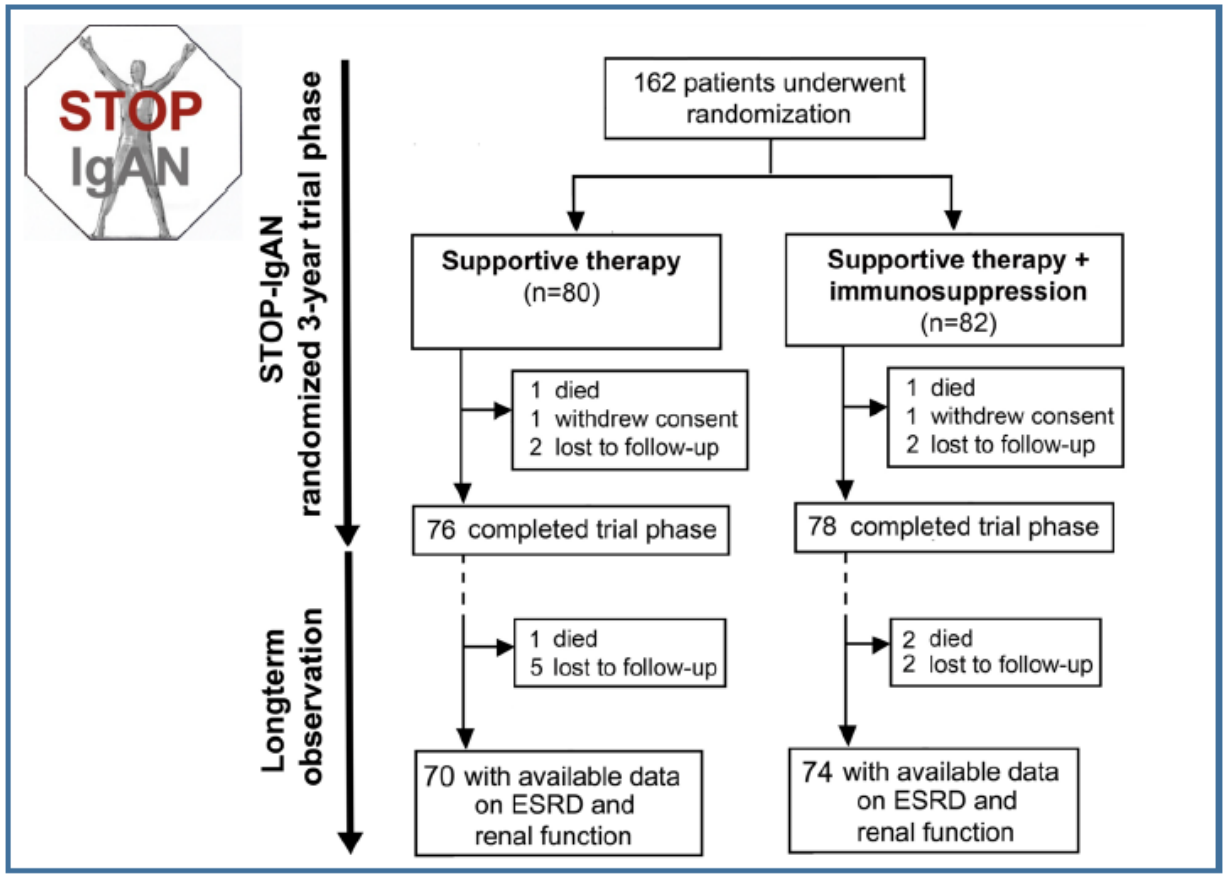


Kidney Int Rep (2017) 2, 318–331

Supportive therapy in IgAN

Blood pressure management	Dietary advices and fluid management	Lifestyle modifications	Additional measures
• target sitting systolic BP <120 mmHg • <u>preferred antihypertensives:</u> - first choice: ACE inhibitors <u>or</u> 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 • <u>avoid</u> 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)

Seminars in Immunopathology (2021) 43:717–72



Composite of all-cause death, ESRD or eGFR loss >40%	50.0%	45.5%	n.s.
All-cause death	2.8%	3.9%	n.s.
ESRD onset	23.6%	26.0%	n.s.
eGFR loss >40%	40.0%	27.4%	n.s.

- eGFR < 30 ml/min/1.73 m^2.
- Diabetes.
- Obesity (body mass index > 30 kg/m^2).
- Latent infections (e.g., viral hepatitis, tuberculosis).
- Secondary IgAN (e.g., liver cirrhosis).
- Acute peptic ulceration.
- Uncontrolled psychiatric illness.
- Severe osteoporosis.

Seminars in Immunopathology (2021) 43:717–72

Risk of Disease Progression
Need for Treatment Escalation

A subgroup of patients with IgAN are at high risk of disease progression

Pathologic and clinical features that increase the risk of disease progression include abnormal kidney function at the time of diagnosis and proteinuria

For patients at high risk of disease progression, treatment needs to be escalated to prevent progression to ESKD

Traditionally patients would be started on a course of systemic corticosteroids

ESKD, end-stage kidney disease.

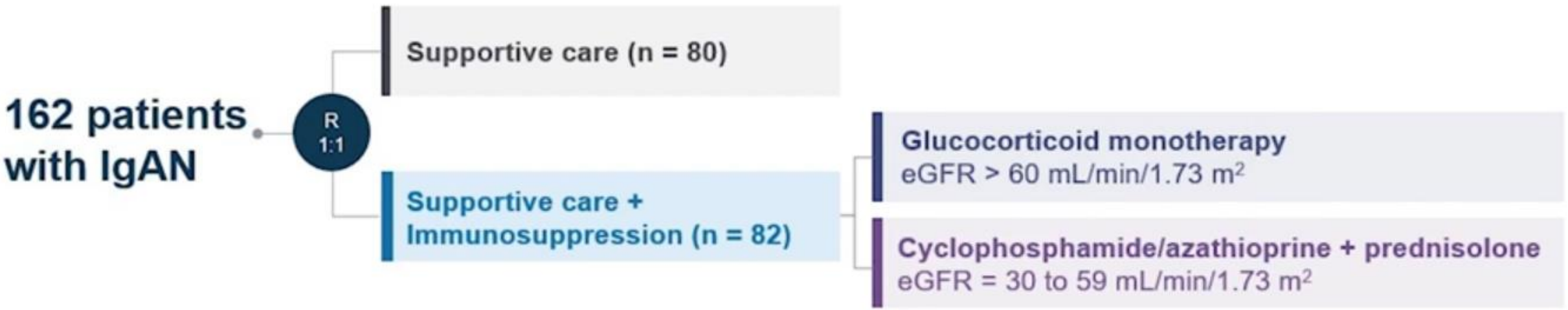
Gutiérrez E, et al. Nephron. 2020;144:555-571.

Glucocorticoid regimens used in clinical trials of IgAN

Study	Medication	Initial Dose	Taper	Total Exposure
TESTING 2022 (Lv) [36]	Methylprednisolone	0.4 mg/kg orally once daily (maximum dose: 32 mg/day) for 2 months	Reduce daily dose by 4 mg every month for 4 months	6 months
TESTING 2017 (Lv) [37]	Methylprednisolone	0.6 to 0.8 mg/kg orally once daily (maximum dose: 48 mg/day) for 2 months	Reduce daily dose by 8 mg every month for 4 months	6 months
Manno et al. [41]	Prednisone	1 mg/kg orally per day (maximum dose: 75 mg/day) for 2 months	Reduce daily dose by 0.2 mg/kg every month for 4 months	6 months
Lv et al. [42]	Prednisone	0.8 to 1 mg/kg orally per day for 2 months	Reduce daily dose by 5 to 10 mg every 2 weeks for 4 months	6 months
Pozzi et al. [43] STOP-IgA (Rauen) [44]	Methylprednisolone (IV) and Prednisolone/prednisone (oral)	Methylprednisolone 1 g IV for 3 days at the start of months 1, 3, and 5 and Prednisolone or prednisone 0.5 mg/kg orally every other day on remaining days for 6 months	None	6 months
NEFIGAN (Fellström) [45]	TRF-budesonide	16 mg orally daily for 9 months	Reduce dose to 8 mg once daily for 2 weeks, then discontinue	9 months

Antibodies (Basel). 2023 Jun 19;12(2):40

STOP-IgAN
Study Design



Primary endpoints:

- **UPCR < 0.2 g/g and decrease in eGFR < 5 mL/min/1.73 m² from baseline**
- **Decrease in eGFR ≤ 15 mL/min/1.73 m² at the end of the trial**

eGFR, estimated glomerular filtration rate; UPCR, urine protein/creatinine ratio.

Rauen T, et al. N Engl J Med. 2015;373:2225-2236.

STOP-IgAN
Efficacy and Safety Results

1. **Importance of supportive care**
   After run-in period, 34% of patients had proteinuria < 0.75 g/g

2. **Corticosteroids associated with a high rate of clinical remission at the expense of more serious adverse events**

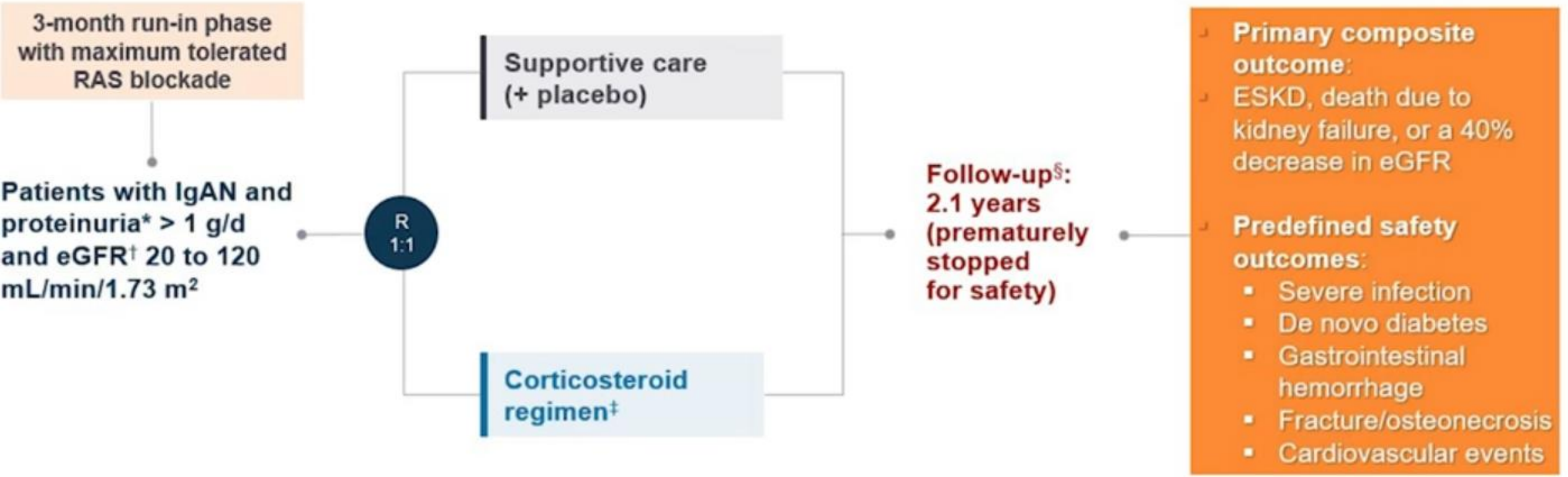
3. **Proteinuria improved with corticosteroids, but no kidney function preservation in the long-term follow-up**

4. **10-year follow-up showed no difference between supportive care with immunosuppression vs supportive care alone**

Rauen T, et al. N Engl J Med. 2015;373:2225-2236.

TESTING I
Study Design

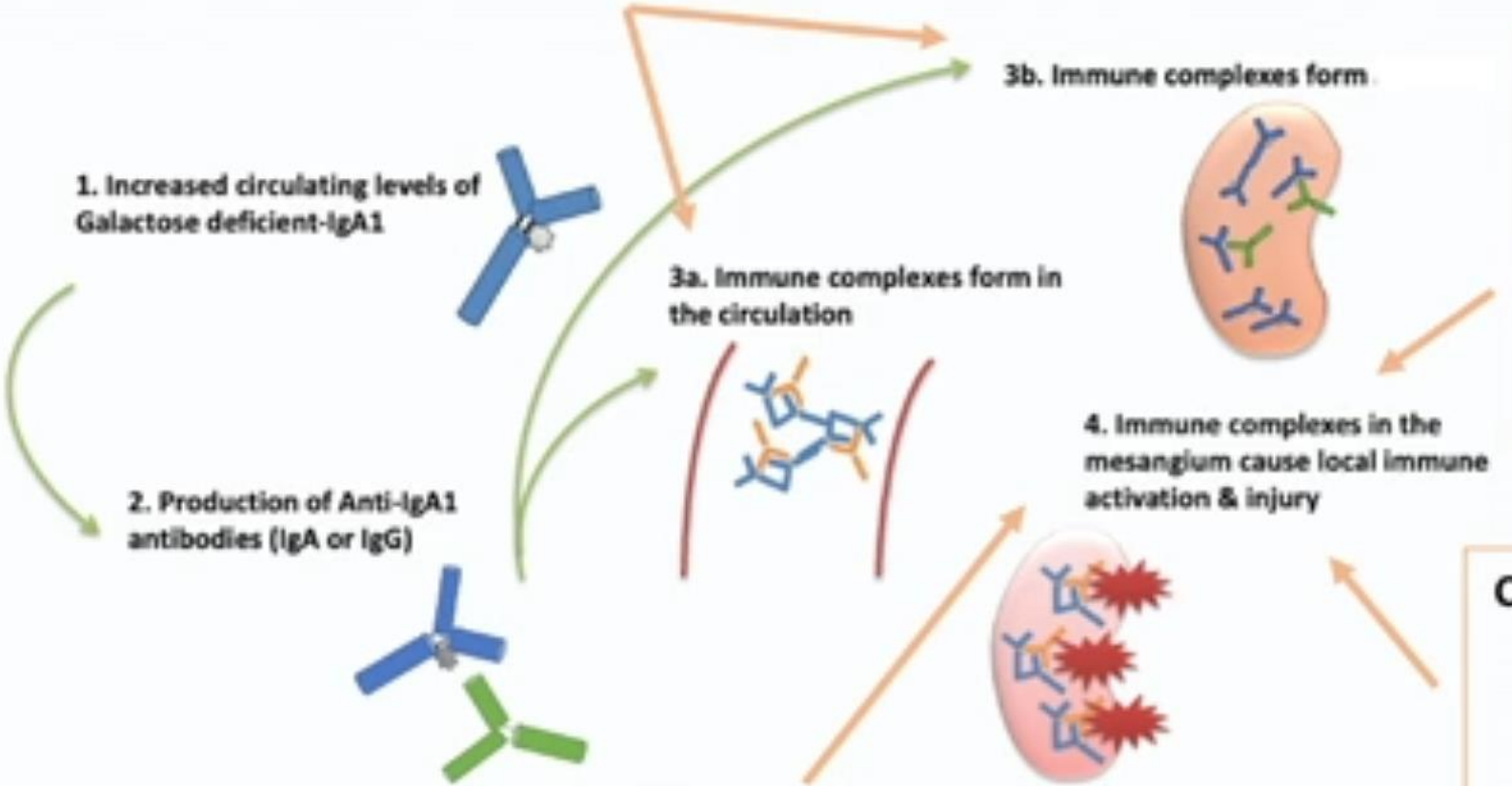
Multicenter, double-blind study, which randomized patients with IgAN to supportive care or corticosteroid



*Baseline proteinuria = 2.4 ± 1.2 g/d; †Baseline eGFR = 59.4 ± 25 mL/min/1.73 m²; ‡Daily oral methylprednisolone 0.6 to 0.8 mg/kg/d (maximum 48 mg/d) × 2 months – taper over next 4 to 6 months; §Follow-up was intended until 335 primary outcomes occurred.
RAS, renin-angiotensin system.
Lv J, et al. JAMA. 2017;318:432-442.

Novel Targets

Reduce Gd-IgA1 production
localized Budesonide



B-cell Activation Inhibitors
Prevent Gd-IgA1 production

Atacicept
Telitacicept
BION-1301

Complement Activation Inhibitors

Iptacopan
IONIC-FB-LRx
APL-2
OMS721
Cemdisiran
Ravulizumab

Endothelin Receptor Antagonists
Sparsentan (Endothelin A, AngII)
Atrasentan (Endothelin A)

1. Lai KN et al. IgA nephropathy. *Nat Rev Dis Primers*. 2016;2:16001. Published 2016 Feb 11. doi:10.1038/nrdp.2016.1
2. Rajasekaran A et al. IgA Nephropathy: An Interesting Autoimmune Kidney Disease. *Am J Med Sci*. 2021;361(2):176-194. doi:10.1016/j.amjms.2020.10.003

Gaps in other management strategies

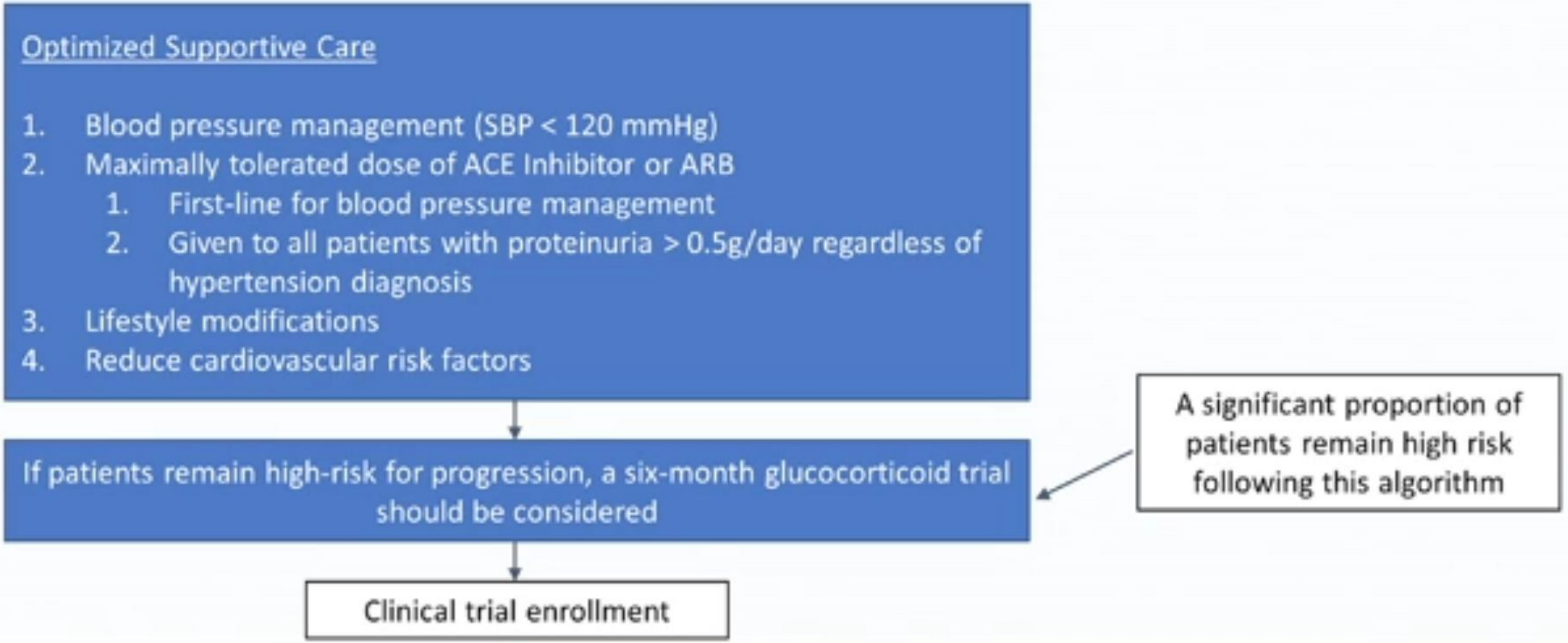
KDIGO recommends against the use of:

- Antiplatelet agents
- Anticoagulants
- Azathioprine
- Cyclophosphamide
- Calcineurin inhibitors
- Rituximab
- Fish oil
- Mycophenolate mofetil*
- Hydroxychloroquine*

**not recommended in non-Chinese patients*

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021

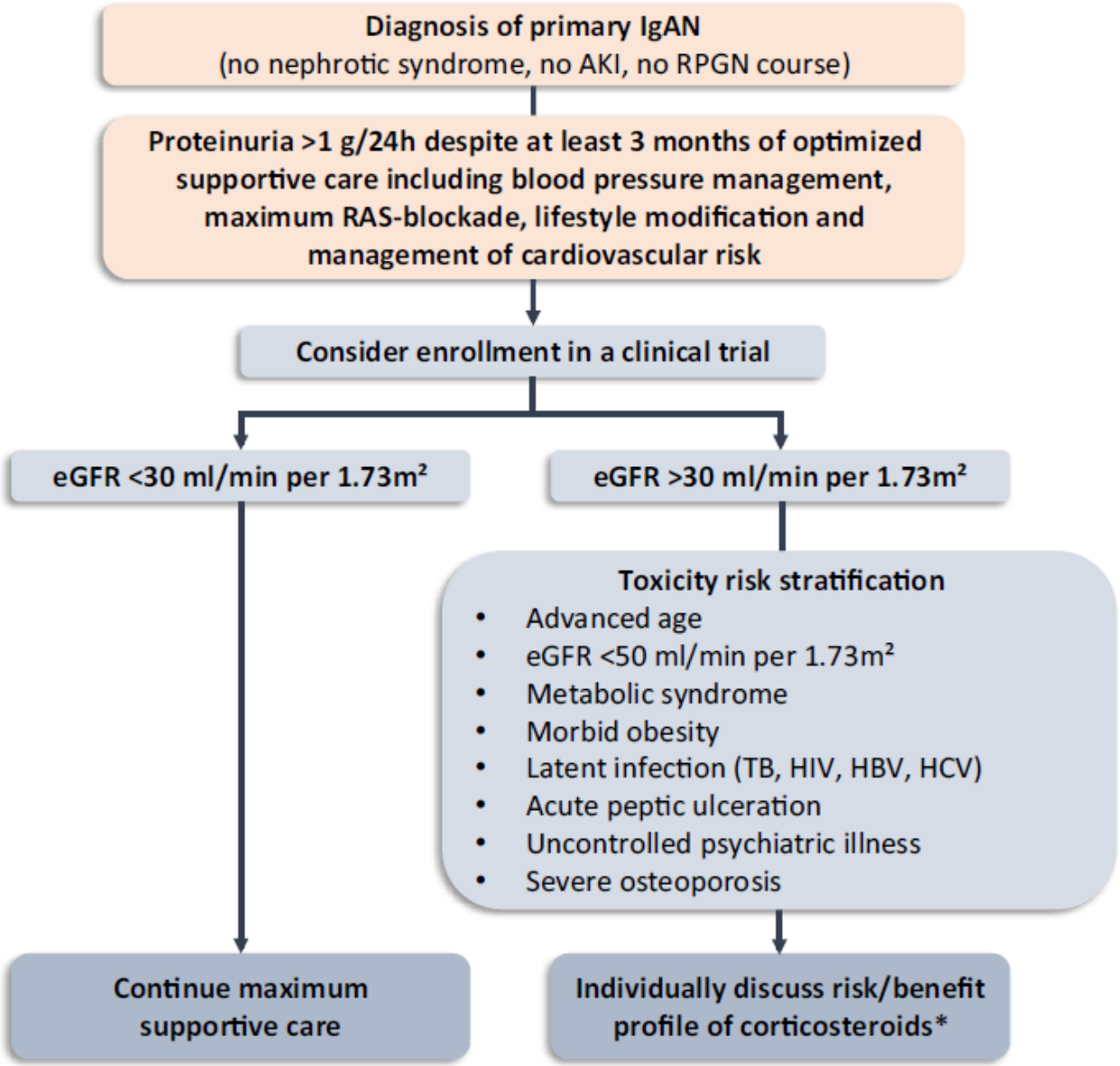
KDIGO Treatment Algorithm



1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney int.* 2021;100(45):S1-S276. doi:10.1016/j.kint.2021.05.021

Treatment of primary IgAN

(adapted from KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES



Seminars in Immunopathology (2021) 43:717–72

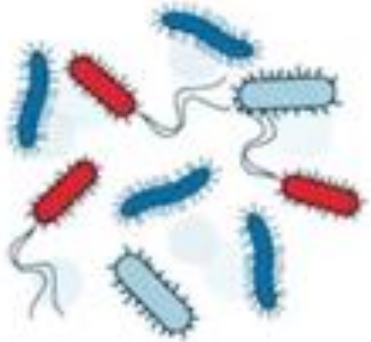
The Complement System Under Physiologic Conditions

Protection of host cells

Regulators

Non-inflammatory removal of modified host cells

Regulators



Complement activation and removal of infectious microorganisms

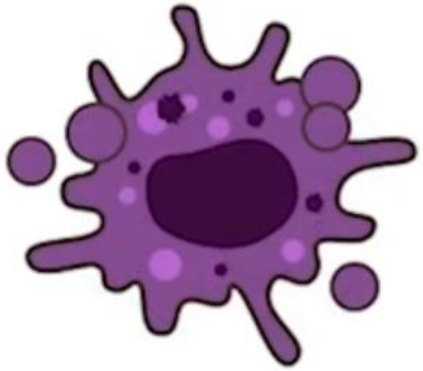
No regulators

Complement

© WebMD Global, LLC

Zipfel PF, et al. Nat Rev Immunol. 2009;9:729-740.

The Complement System Under Pathologic Conditions

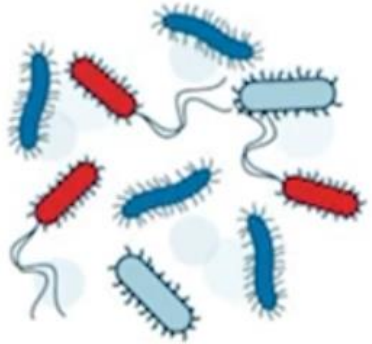


Inappropriate action of regulators leads to host cell damage

No or defective regulators

Inefficient removal of modified host cells can lead to pathology

No or defective regulators



Pathogens acquire host regulators and avoid complement attack

Acquired regulators

© WebMD Global, LLC

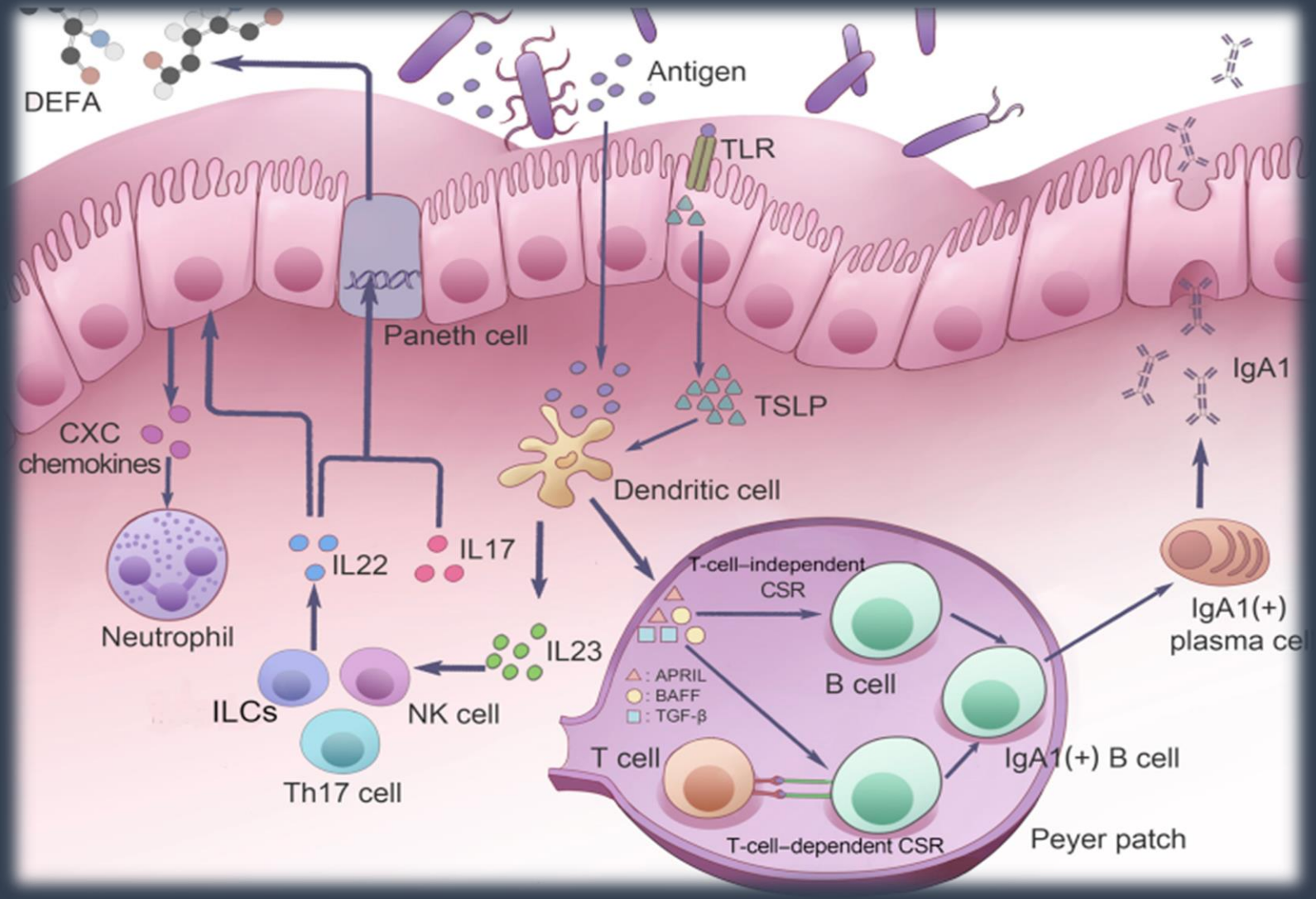
Complement

Zipfel PF, et. Nat Rev Immunol. 2009;9:729-740.

Medscape EDUCATION

The innate and adaptive immune mechanisms that drive protective mucosal immunity against pathogens

Gut associated lymphoid tissue (GALT) and IgAN

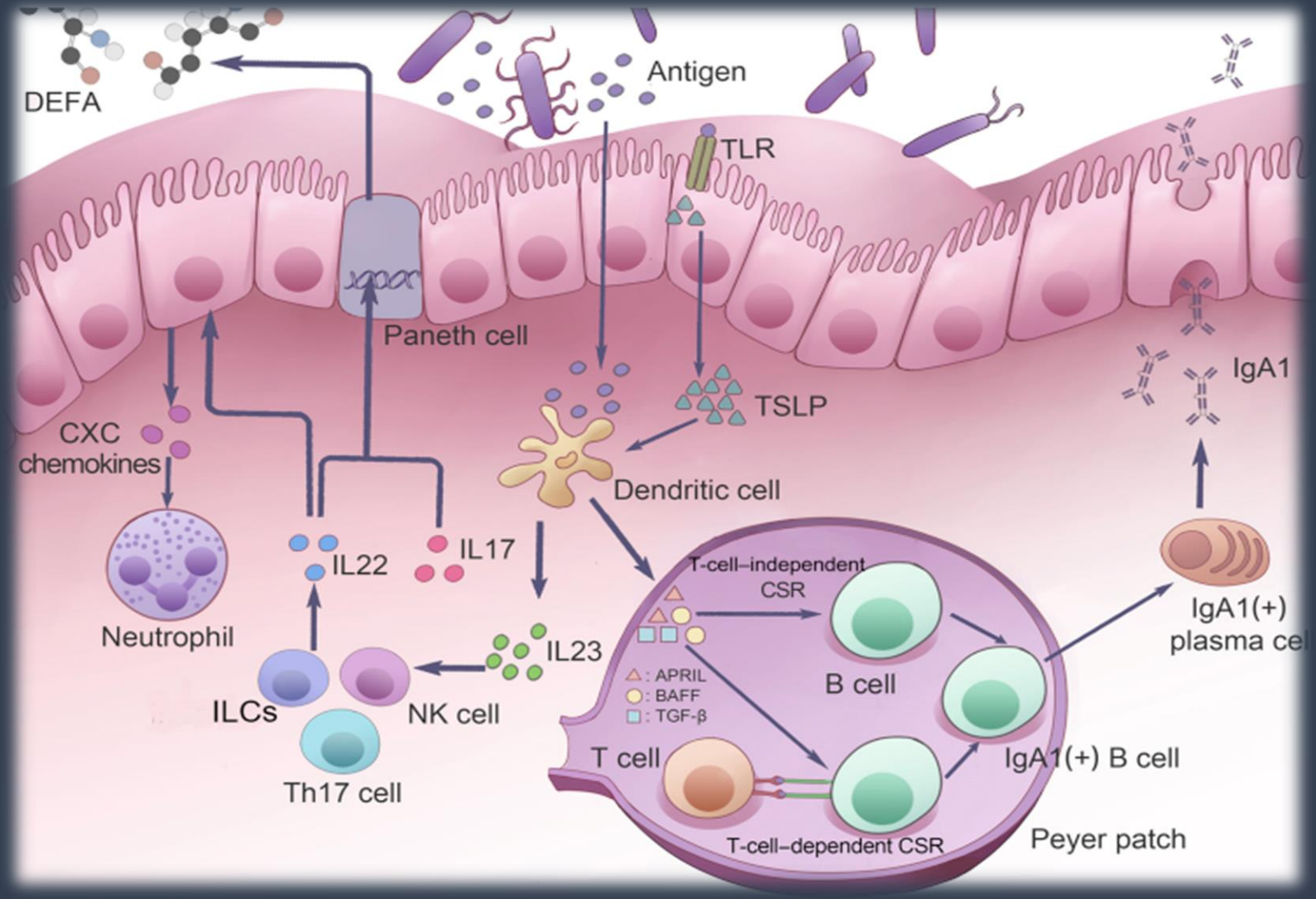


- *Genetic*
- *Epigenetic*
  - ✓ *Microbiota*
  - ✓ *Food antigens*
  - ✓ *Infections*

Kidney Int Rep (2017) 2, 318–331

The innate and adaptive immune mechanisms that drive protective mucosal immunity against pathogens

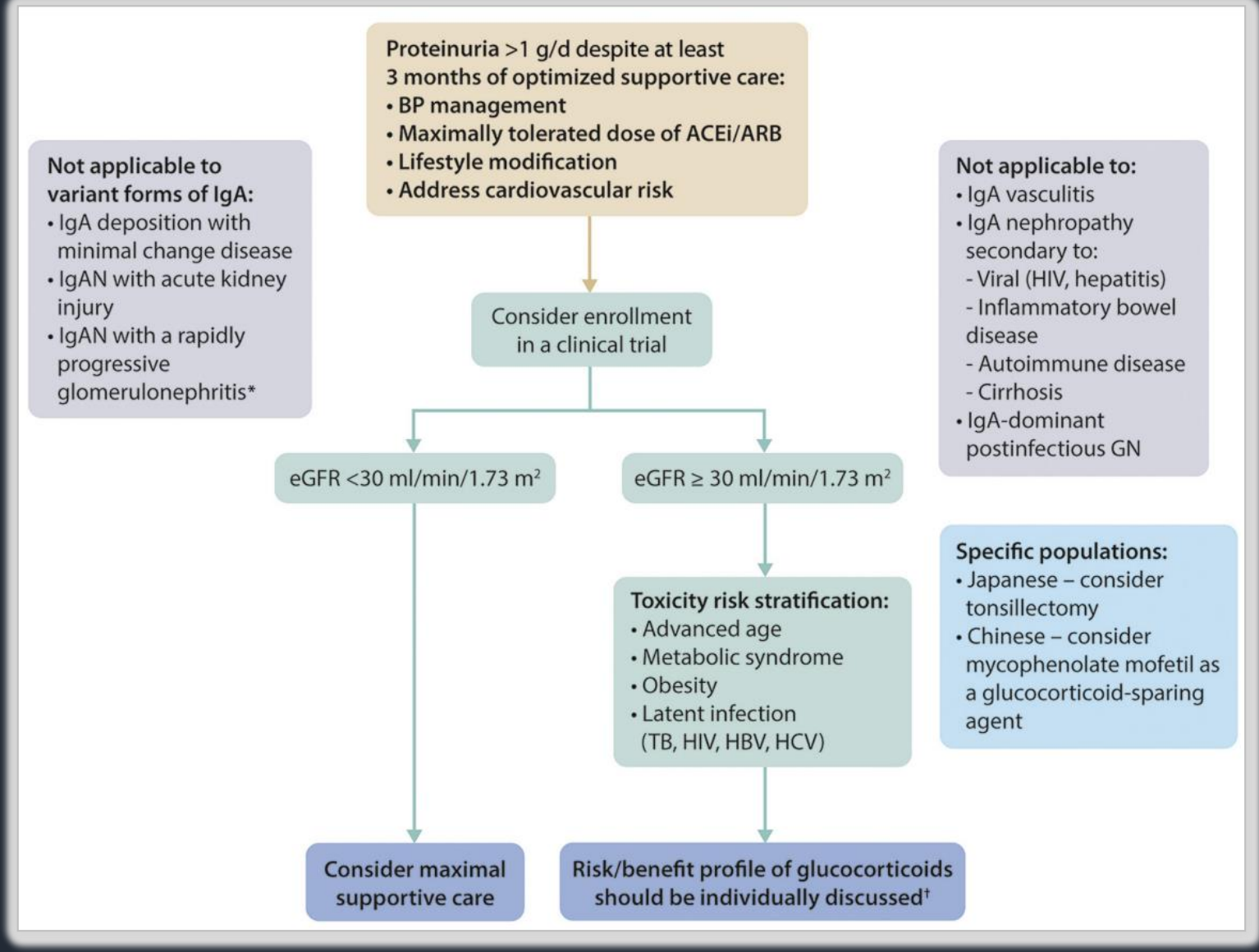
Gut associated lymphoid tissue (GALT) and IgAN



- *Genetic*
- *Epigenetic*
  - ✓ *Microbiota*
  - ✓ *Food antigens*
  - ✓ *Infections*

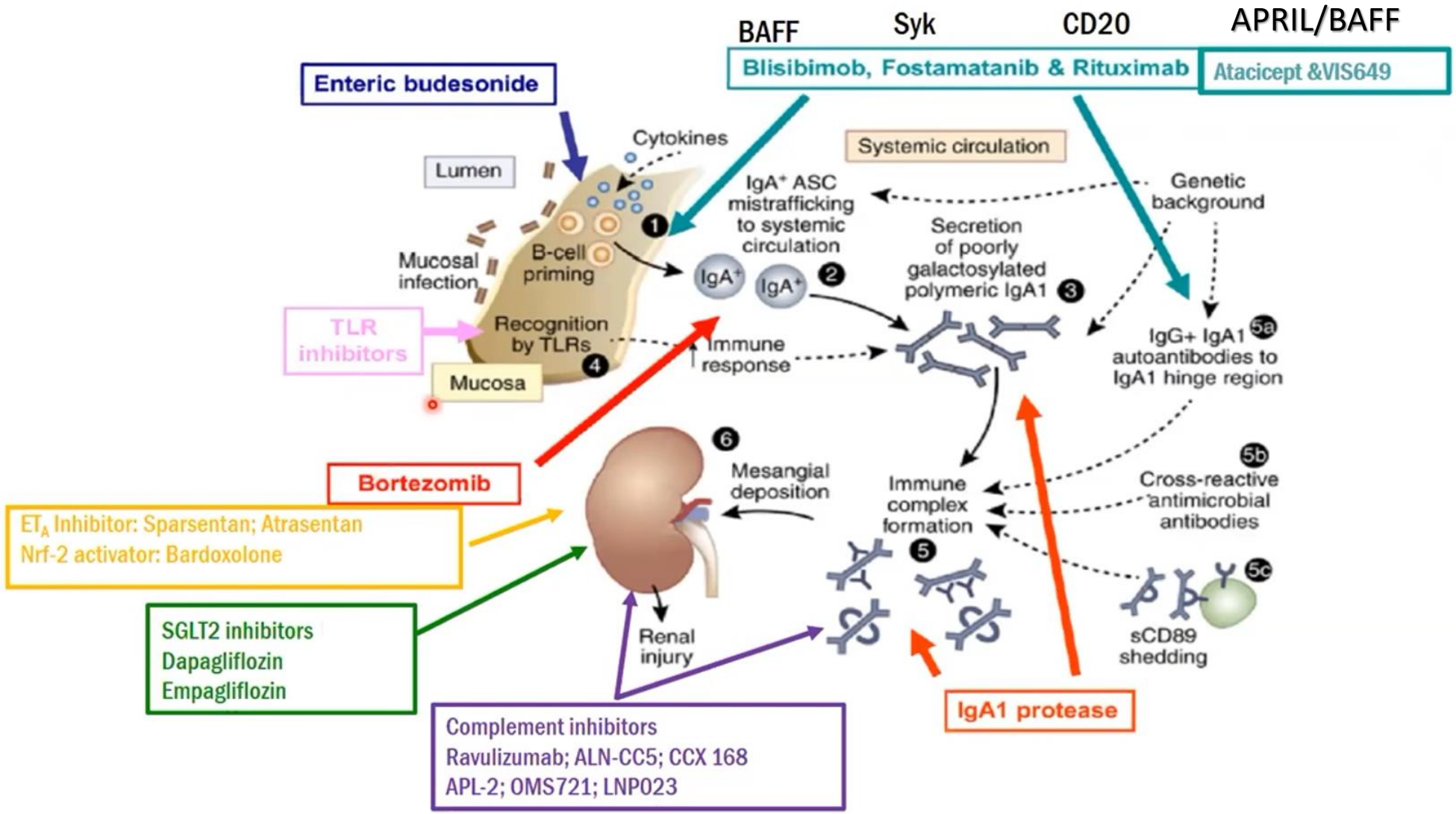
Kidney Int Rep (2017) 2, 318–331

2021 KDIGO Guidelines



Kidney International 2021 100, 753-779

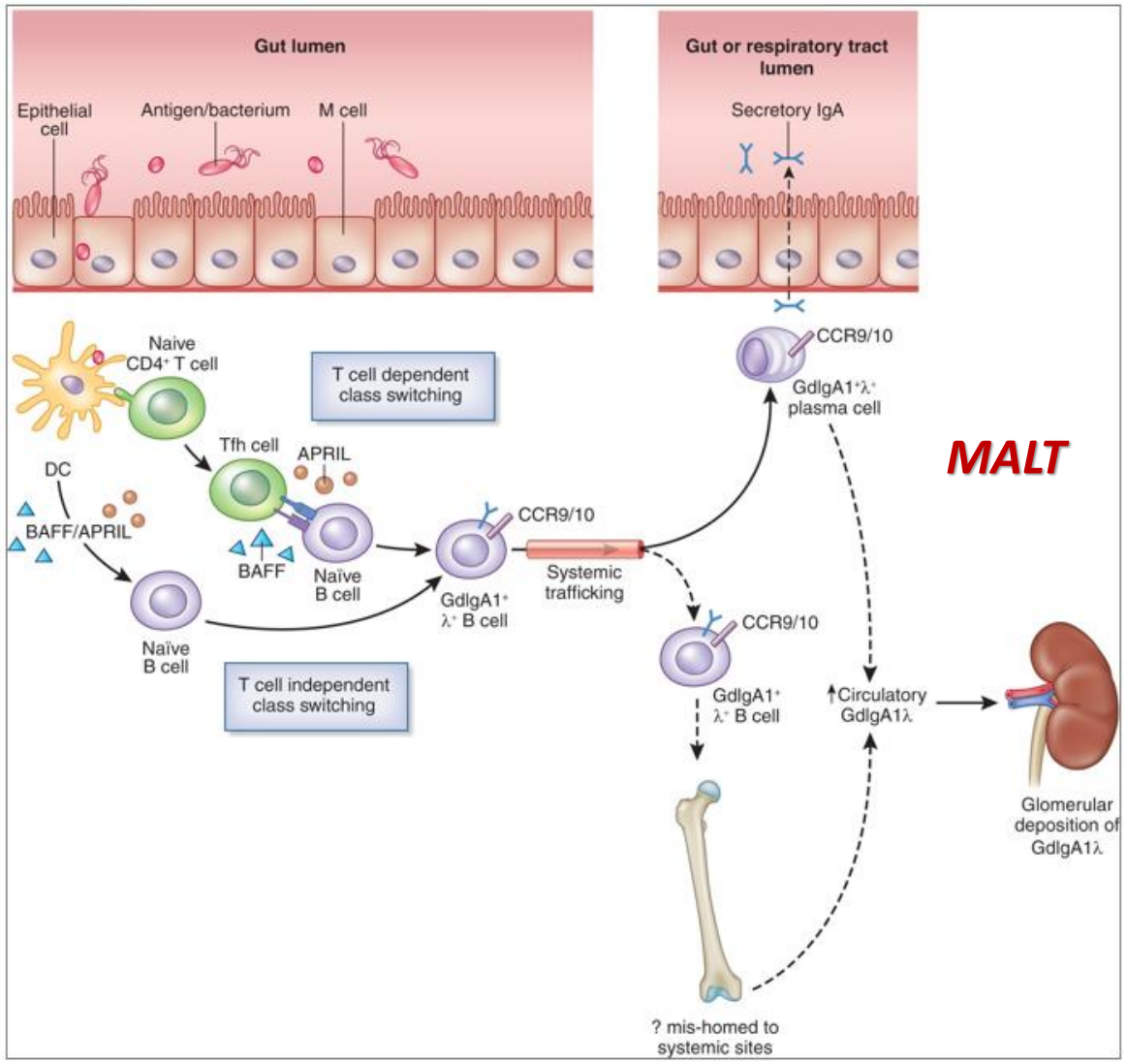
New drugs targeting complement in IgAN: ongoing studies



ATACICEPT

- Binds and inhibits B lymphocyte stimulator (BLyS) and A proliferation inducing ligand (APRIL)→ interferes with B call maturation, function and survival
- Blocks the BLyS and APRIL-mediated Ig isotope class switching and reduces IgG and IgA levels in patients with IgAN

The mucosal immune system plays a key role in the production of GdIgA1 in IgA nephropathy



Agent	Target	Modality	Mechanism of action	Desired effect
Tarpeyo	Glucocorticoid receptors	Corticosteroid	Depletes B cells and plasma cells in the small intestine	Reduced GD-IgA1 synthesis in the GALT
Ataticept and Telitacicept	BAFF and APRIL	Fusion protein/antibody	Inhibits maturation and activation of B cells and plasma cell survival	
BION-1301 and Sibeprenlimab	APRIL	Monoclonal antibody	Inhibits maturation and activation of B cells	Reduced GD-IgA1 and IgG autoantibodies
Bortezomib	Proteasome	Peptide	Inhibits proteasome activity in plasma cells	Reduced Ig synthesis
Felzartamab	CD38	Monoclonal antibody	Depletes CD38+ plasma cells	Depletes long-living plasma cells

- ✓ *Mucosal innate immunity*
- ✓ *Adaptive immunity*
- ✓ *Complement activation*

JASN 33(5):p 873-875, 2022

Indication for corticosteroids in IgA nephropathy: validation in the European VALIGA cohort of a treatment score based on the Oxford classification

Alexandra Cambier, Stéphan Troyanov, Vladimir Tesar, Rosanna Coppo; Validation Study of Oxford Classification (VALIGA) Group

Nephrol Dial Transplant. 2022 May 25;37(6):1195-1197