RECURRENT IgA NEPHROPATHY IN RENAL TRANSPLANT ALLOGRAFT

TAMAR TEVDORADZE, MD

TSMU AND INGOROKVA HIGH MEDICAL TECHNOLOGY UNIVERSITY CLINIC

Case presentation

A 31-year-old female patient

Reason for visit in 2015y:

- Hypertension
- High Creatinine (2.27 mg/dl)
- Mild proteinuria
- Hematuria

Diagnosis with kidney biopsy:

✓IgA Nephropathy

✓Arteriolosclerosis

Case presentation

In 2016_CKD, Stage 4 (GFR 17ml/min)

- 23/04/2016 Living donor pre-emptive kidney transplantation

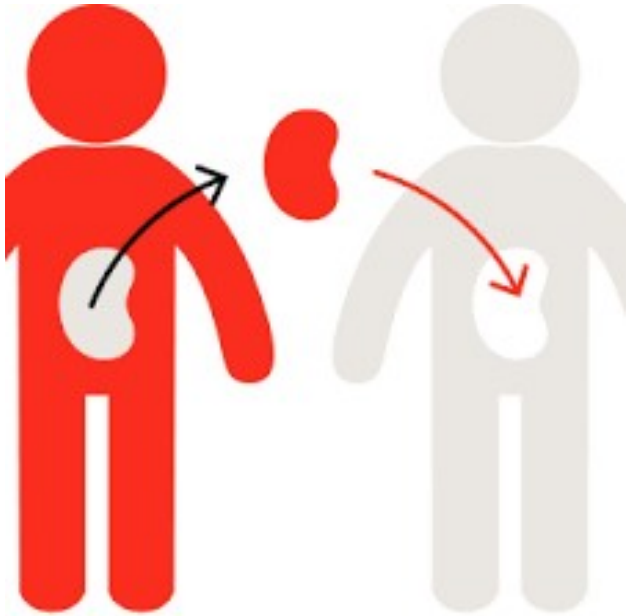
➢ Day 15_Creatinine 1.01 mg/dl

Immunosuppressive therapy:

✓Tacrolimus 5.5 mg b.i.d. (Tacrolimus conc. Target level 10-12 ng/ml)

✓Methylprednisolone 0.4mg/kg

✓Mycophenolate Mofetil 1000mg b.i.d.



Case presentation

- In May 2020_ Planning for pregnancy
- Normal kidney function
- Mycophenolate Mofetil →ı Azathioprine

Case presentation

- In May 2020_ Planning for pregnancy
- Normal kidney function
- Mycophenolate Mofetil → Azathioprine
- In November 2020_Pregnancy

Pregnancy

Readings			Average Blood Pressure (SD)							White Coat Window			
Total Readings :	39			Sys	Dia	HR	MAP	PP	Afib		Sys	Dia	HR
Successful :	25	(64.1%)	24-hr	110 (8)	69 (7)	84 (6)	77 (7)	41	1(25)	Readings	1	1	1
Afib :	1	(4.0%)								1st hr Max	124	88	99
BP Load			Awake	114 (9)	72 (8)	87 (6)	80 (9)	42	1(17)	**Night-time Dip%**			
Day readings ≥	135/85	**5.9%**									**Sys**	**Dia**	
Night readings ≥	120/70	**12.5%**	Asleep	105 (5)	65 (4)	81 (3)	74 (3)	40	0(8)	Dip%	7.6	9.5	

Comments:

24-h Normotension, Daytime Normotension, Nighttime Normotension, White Coat Hypertension, Non-Dipper

Hypertension

Methyldopa
250mg b.i.d.

Pregnancy

Tacrolimus

2021	Creatinine	Tacrolimus concentration in blood	Tacrolimus dosage
February	0.88 mg/dl	2.8 ng/ml	Tacrolimus 2g b.i.d.
March	0.91 mg/dl	1.4 ng/ml	Tacrolimus 2.5g b.i.d. + Grapefruit juice
April	0.92 mg/dl	2.7 ng/ml	Tacrolimus 3g b.i.d.
May	0.9 mg/dl	2.7 ng/ml	Tacrolimus 3.5g b.i.d.
June	0.9 mg/dl	5.2 ng/ml	Tacrolimus 3.5g b.i.d.

Pregnancy

2021	Hb	RBC	Leu	PLT	TSAT	Ferritin	Folic Acid	Vit. B12
February	10.9	3.39	8.36	251	30%	61 (4.6-200)	35 (7-46.5)	290 (139-652)
March	11.5	3.37	10.29	224				
April	10.9	3.13	10.06	220				
May	10.6	3.43	10.0	183	24%	34.57	15.91	262

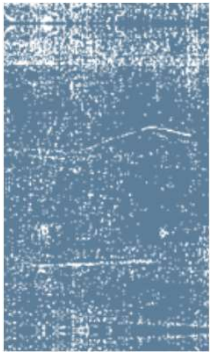
Treatment:

✓Ferrous sulfate 100mg b.i.d.

✓Folic Acid 5mg once daily

Case presentation

- In July 2021 at 37 weeks cesarean section
- Azathioprine → Mycophenolate Mofetil
- 1 year later_ Proteinuria 292 mg/24h, elevation of Creatinine



Case presentation

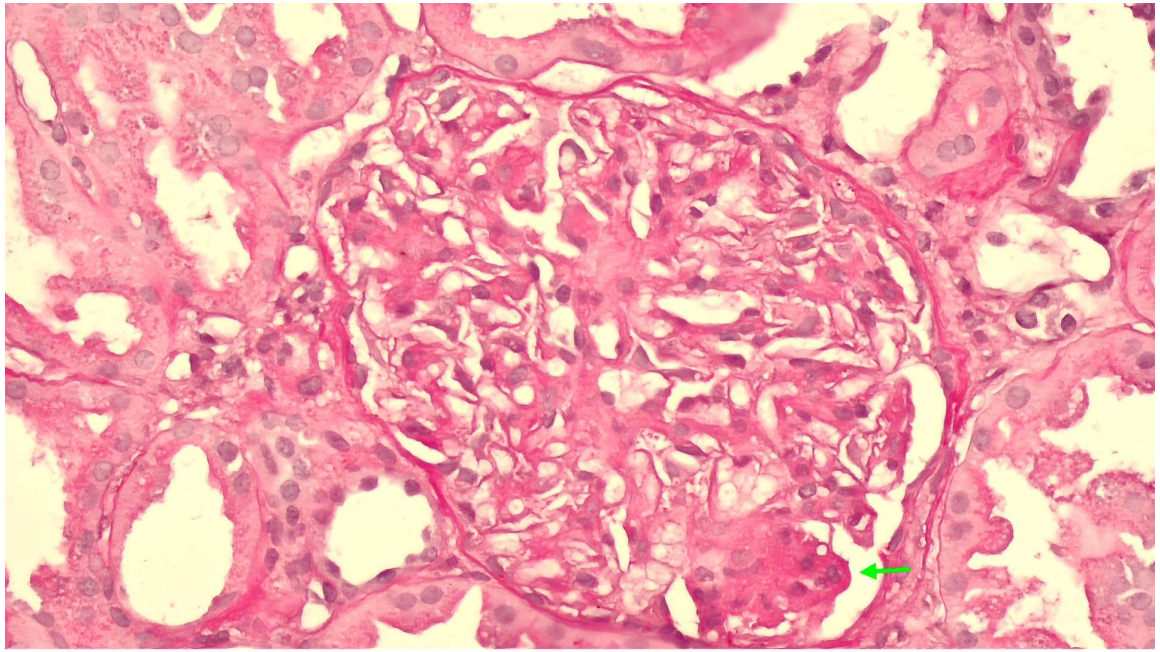
- In July 2021 at 37 weeks cesarean section
- Azathioprine → Mycophenolate Mofetil
- 1 year later_ Proteinuria, elevation of Creatinine
- Mycophenolate Mofetil withdrawal (???)

Microvascularity		Tubulointerstitial	
Glomerulitis (g)	0	Inflammation (i)	0
Peritubular capilaritis (pct)	0	Tubulitis (t)	1
C4d in peritubular capillaries		Fibrosis (ci)	1
GBM double contours (cg)		Atrophy (ct)	1
Mesangial matrix (mm)	0	SV40	
Arteries		Arterioles	
Arteriitis (v)	0	Hyalinosis (ah)	3
Vascular fibrosis, intimal thickening(cv)	3		

Transplant Kidney Biopsy 1

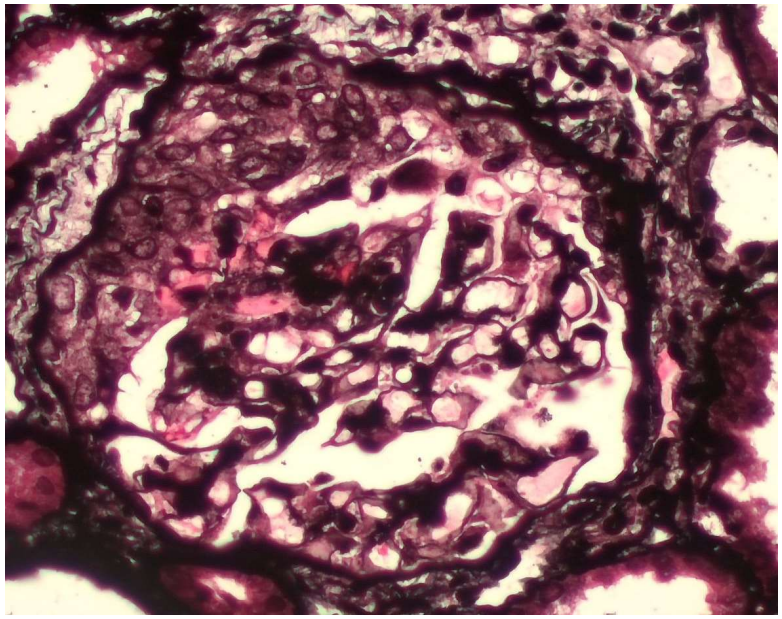
IgA Nephropathy

Oxford Classification score M3 E0 S1 T1 C1 _ S1

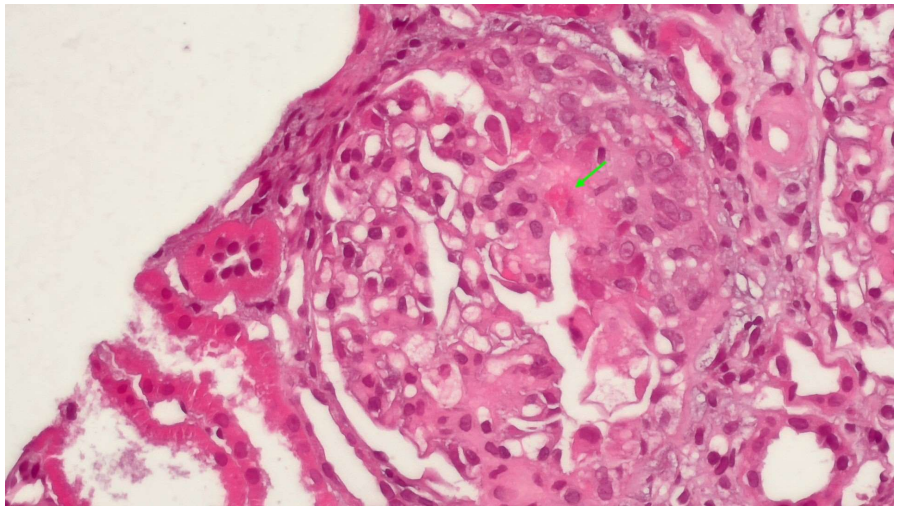


Mesangial Hypercellularity

Recurrent IgA in kidney transplant allograft

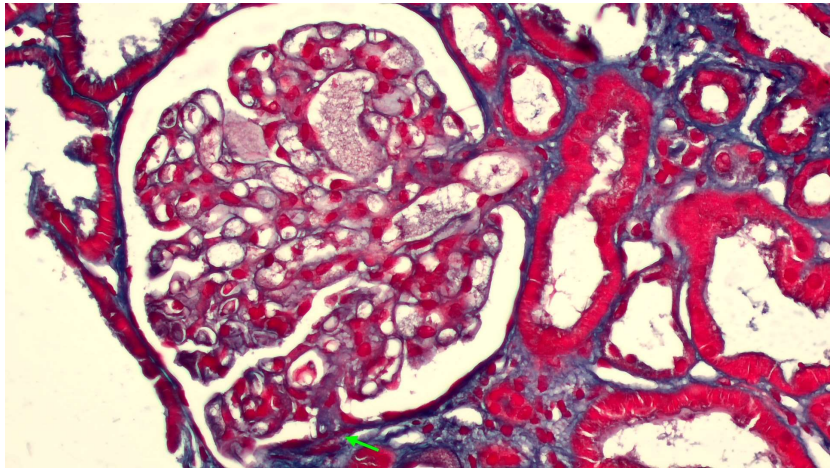


Segmental fibrocellular crescent

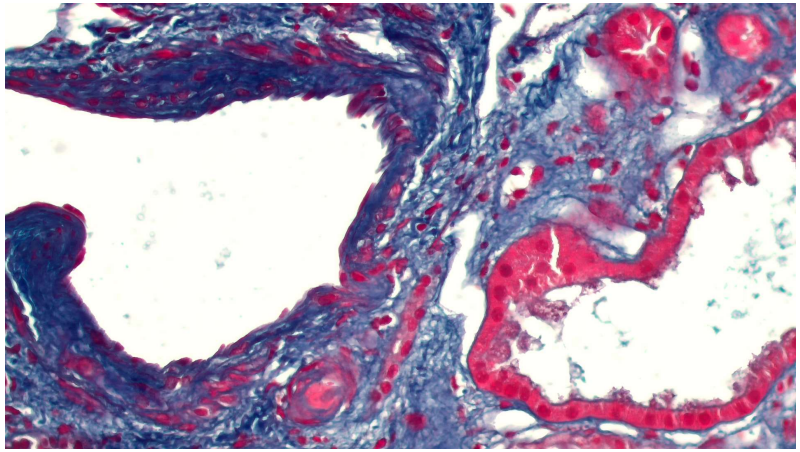


Fibrinoid necrosis and crescent

Recurrent IgA in kidney transplant allograft

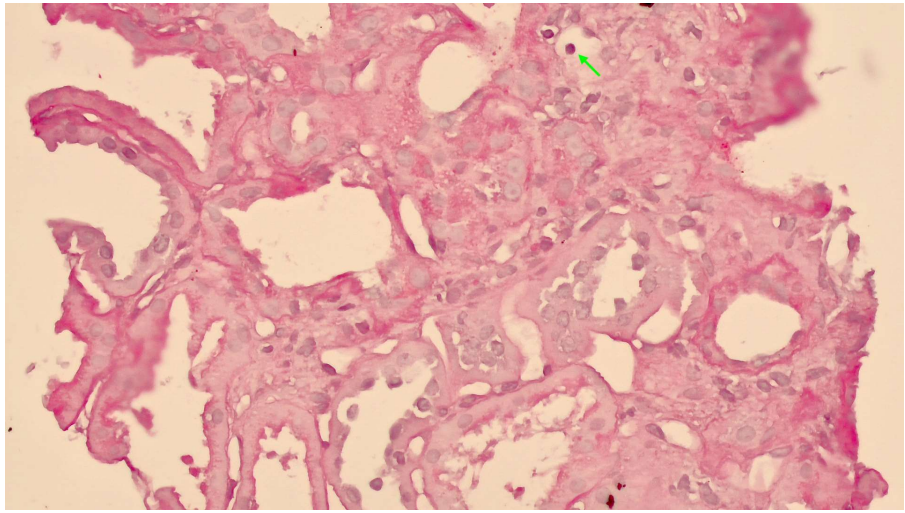


Focal segmental glomerulosclerosis

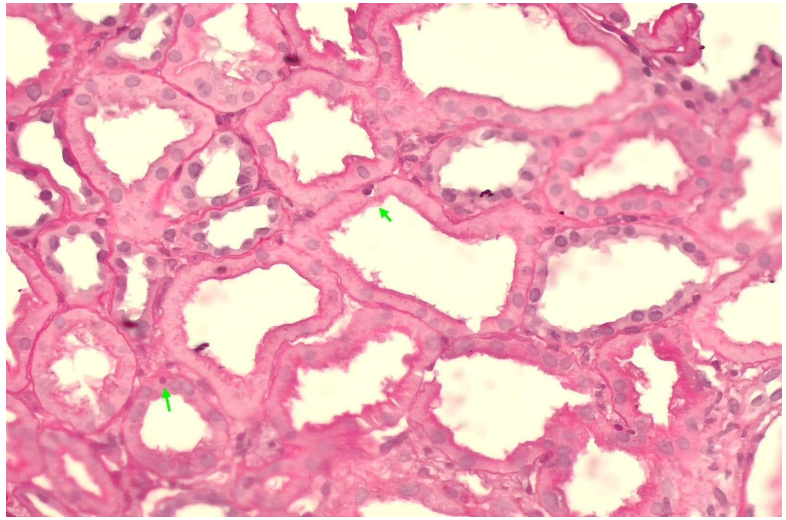


Arterial fibrosis

Recurrent IgA in kidney transplant allograft

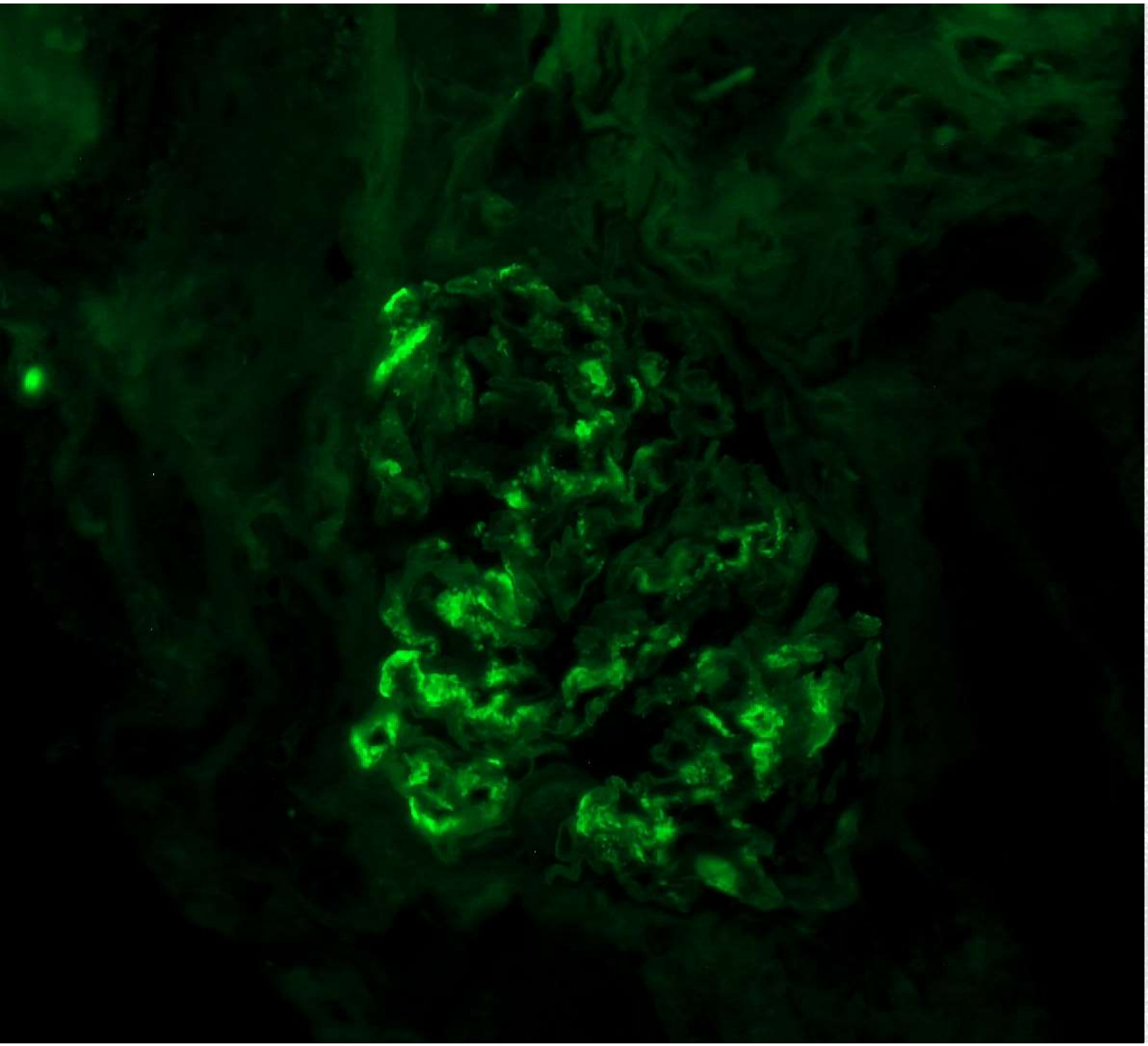


Peritubular capillarities



Tubulitis

Recurrent IgA in kidney transplant allograft

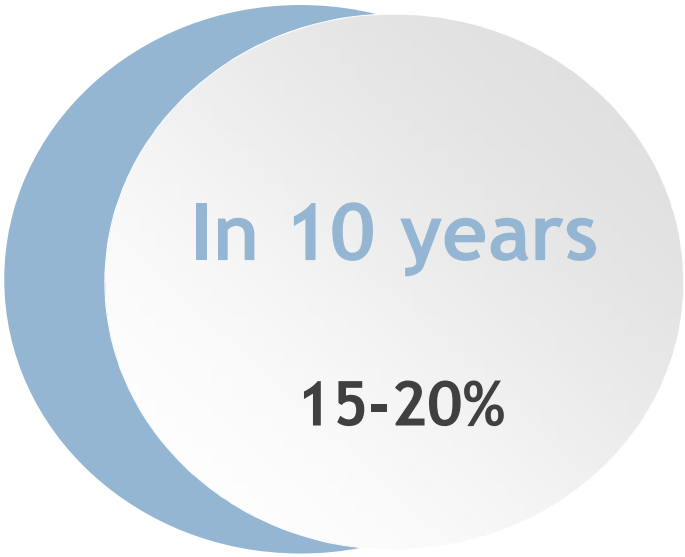


Recurrent IgA in kidney transplant allograft

- IgA staining

IgA Nephropathy

The most common form of glomerulonephritis worldwide



Current Status and Perspectives on Recurrent IgA Nephropathy after Kidney Transplantation ; Mayuko Kawabe; Izumi Yamamoto;
https://doi.org/10.1159/000530341

What do we know about IgA recurrence in adult kidney transplant recipients?

CJASN
Clinical Journal of the American Society of Nephrology

Retrospective Cohort Study

TANGO Post-Transplant Glomerular Disease (TANGO) Project

Multicenter, international
16 Centers in Europe, North America, South America

IgA nephropathy diagnosis by biopsy in native kidney
n = 504

January 2005 to December 2015

Associations with IgA Recurrence

DSA prior to transplant and recurrence

HR 2.74
(95% CI 1.22-6.14)

De novo DSA and recurrence

HR 6.65
(95% CI 3.33-13.27)

Time To IgA Recurrence

Cumulative Incidence of Recurrence

10yr 19% (95% CI 12 - 26)

15yr 23% (95% CI 14 - 34)

Median Time to Recurrence

3.4 years
(IQR 1.4-6.7 yr)

Graft Survival after IgA Recurrence

Graft Survival

1 year	94%
5 years	83%
8 years	68%

Treatment of IgA Recurrence

ACEI or ARBs	75%
Pulse steroids	24%
Increase MMF or add steroids	10%
Cyclophosphamide	4%
No treatment	11%

Conclusions In this multicenter international cohort of kidney transplant recipients, cumulative incidence of recurrent IgA was 19% at 10 years, and 23% at 15 years after kidney transplantation.

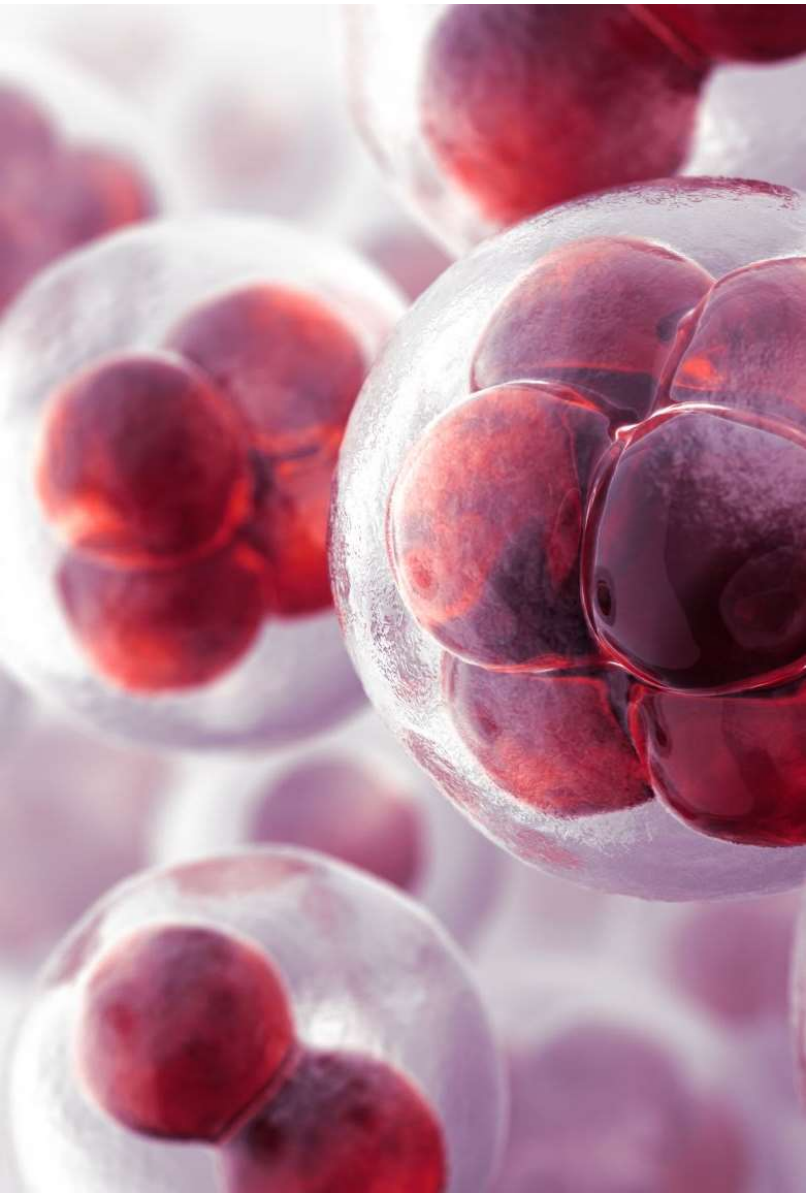
Audrey Uffing, Maria José Pérez-Saéz, Thomas Jouve, et al. ***Recurrence of IgA after Kidney Transplantation in Adults***. CJASN doi: 10.2215/CJN.00910121.
Visual Abstract by Sinead Stoneman, MB BCh BAO, MRCPI

Risk Factors

- Zero-HLA mismatched live-related donor kidney
- Preemptive transplant
- Specific human leukocyte antigen (HLA) alleles in recipient including HLA-B35, HLA-DR4, HLA-B8, HLA-DR3

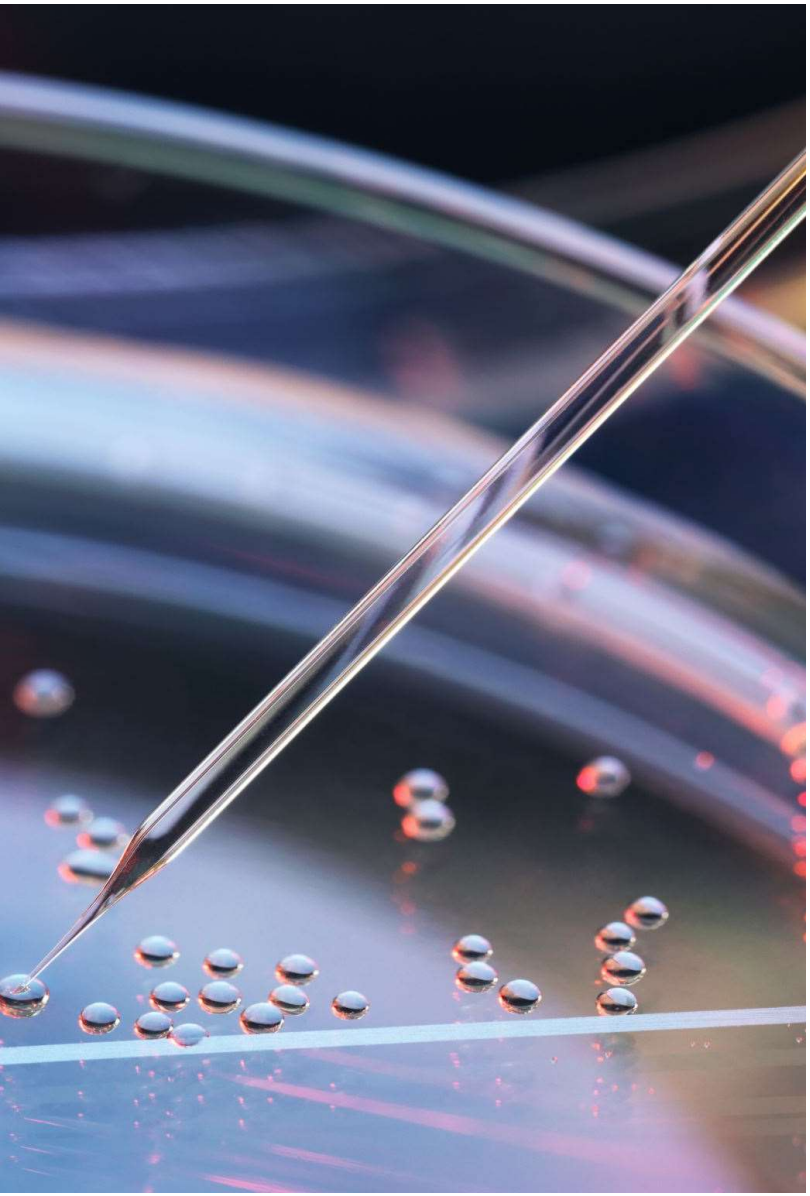
Risk Factors

- Young age
- Steroid withdrawal
- Induction therapy without anti-thymocyte globulin (ATG)
- Rare genetic variants in complement factor H-related protein 5 (CFHR5)



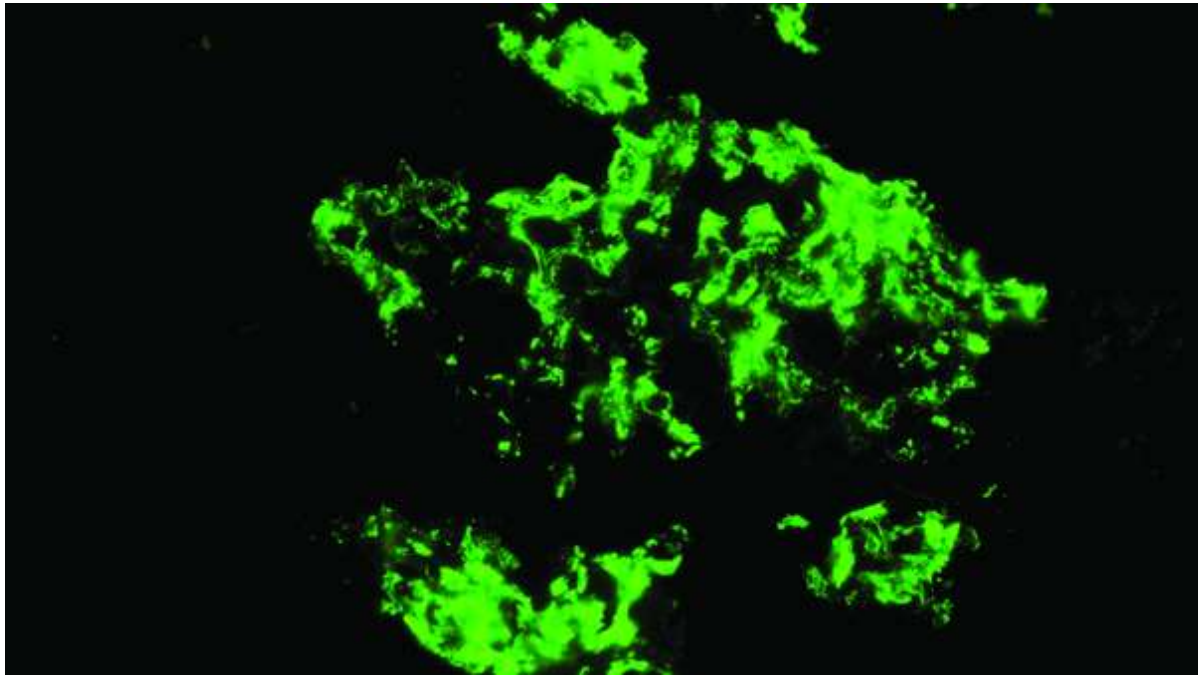
Biomarkers

- Elevated galactose-deficient (Gd)-IgA1-specific immunoglobulin G (IgG) autoantibodies
- lower levels of circulating IgA-soluble CD89 complexes
- High serum IgA concentration



Biomarkers

- B-cell-activating factor inhibitor (BAFF) and a proliferation-inducing ligand (APRIL)
- The monoclonal antibody KM55
- NanoString nCounter® platform



Mesangial C1q relatively frequent in recurrent IgAN may predict a poor outcome of kidney transplantation in native and recurrent IgAN cases

Clinical and Pathological Significance of Mesangial C1q Deposition in Kidney Transplant Recipients with Recurrent IgA Nephropathy and Patients with Native IgA Nephropathy; Ayaka Hayashi et al.

Mycophenolate mofetil inhibits rat and human mesangial cell proliferation by guanosine depletion

Prevention

I A Hauser [1], L Renders, H H Radeke, R B Sterzel, M Goppelt-Struebe

Abstract

Background: Mycophenolate mofetil (MMF) is used for immunosuppression after renal transplantation because it reduces lymphocyte proliferation by inhibiting inosine monophosphate dehydrogenase (IMPDH) in lymphocytes and GTP biosynthesis. In the present study we asked if therapeutic concentrations of MMF might interfere with mesangial cell (MC) proliferation which is involved in inflammatory proliferative glomerular diseases.

Conclusions: The results show that MMF has a concentration-dependent antiproliferative effect on cultured MCs in the therapeutic range, which might be a rationale for the use of this drug in the treatment of mesangial proliferative glomerulonephritis.

MAIN trial: Effect of mycophenolate mofetil on progression of IgA nephropathy

KidneyNews

Methods	Intervention	Outcomes		
Single center in China Patients with biopsy-proven IgAN Proteinuria >1 g/day + eGFR 30-60 mL/min/1.73 m^2 or persistent hypertension 12-Week run-in period	n = 85 Standard care + MMF 1.5 g/day	7.1% aHR, 0.23 (95% CI, 0.09-0.63)	8.2% aHR, 0.23 (95% CI, 0.10-0.57)	1.2 mL/min/1.73 m^2/y ($p < 0.001$)
	1 : 1 Median follow-up: 60 months	Doubling SCr, ESKD, or death	Progression of CKD	eGFR decline rate
	n = 85 Standard care alone	21.2%	27.1%	3.8 mL/min/1.73 m^2/y

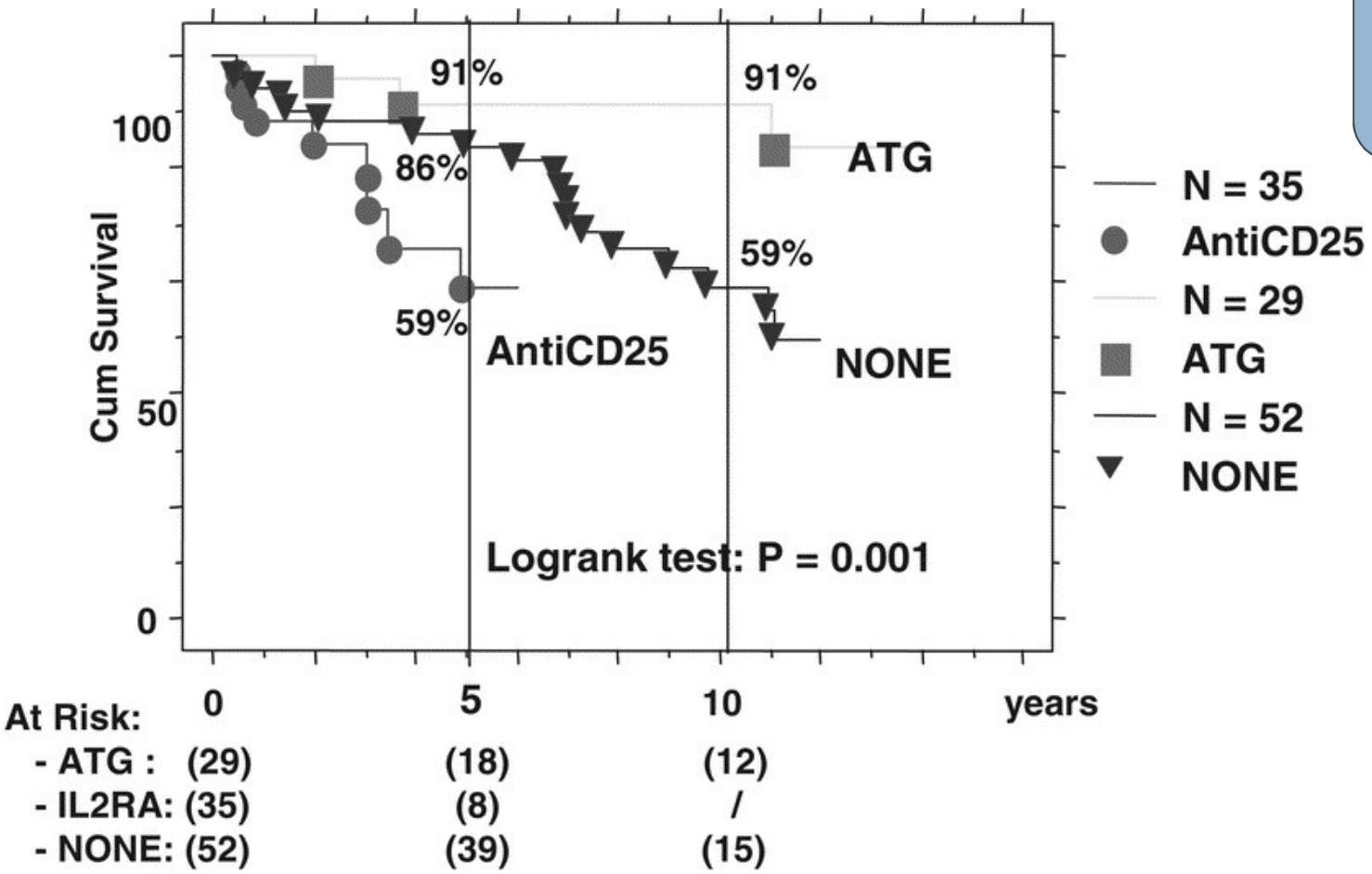
Conclusion

Among patients with IgAN at high risk of progression, adding MMF to standard care significantly reduced the risk of the primary composite outcome of doubling serum creatinine, ESKD, or death due to kidney or cardiovascular causes compared with standard care alone.

Hou FF, et. al.; MAIN Trial Investigators. Effectiveness of mycophenolate mofetil among patients with progressive IgA nephropathy: A randomized clinical trial. *JAMA Netw Open* 2023; 6(2):e2254054. doi: 10.1001/jamanetworkopen.2022.54054

VA: Dr. Alejandro Garcia-Rivera @alexgr23

Prevention



Survival without recurrence and induction therapy in IgAN recipients: endpoint, clinicopathological recurrence of IgAN; covariate: type of induction therapy.

Source:
Antithymocyte Globulin (ATG) Induction Therapy and Disease Recurrence in Renal Transplant Recipients With Primary IgA Nephropathy
Transplantation85(10):1505-1507, May 27, 2008.

Therapeutic approach

Renin-angiotensin system inhibition

Immunosuppressive therapy

Risk assessment

- **International IgAN Prediction Tool at biopsy - Adults**

Determine prognosis of the risk of a 50% decline in eGFR or progression to end-stage renal disease in adults with IgA nephropathy

- **Questions**
- 1.Estimated GFR at biopsy
- 2.Systolic blood pressure at biopsy
- 3.Diastolic blood pressure at biopsy
- 4.Proteinuria at biopsy
- 5.Age at biopsy
- 6.Race
- 7.Use of ACE inhibitor or ARB at the time of biopsy
- 8.MEST M-score
- 9.MEST E-score
- 10.MEST S-score
- 11.MEST T-score
- 12.Immunosuppression use at or prior to biopsy
- 13.At how many months after renal biopsy would you like to determine risk of renal progression?

Therapeutic approach

Systemic glucocorticoids as first-line therapy — For patients who are at **high risk** of disease progression

The initial dose of glucocorticoids is maintained for a minimum of two months, at which time the dose is tapered over four months

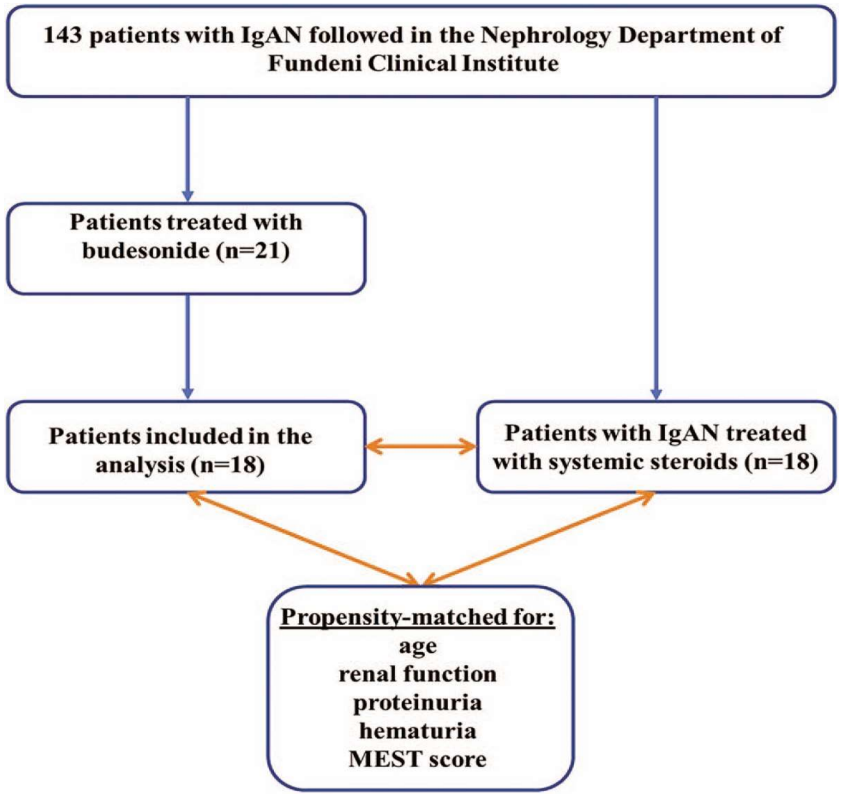
Prevention of *Pneumocystis jirovecii* pneumonia

Minimizing glucocorticoid-induced bone loss and other adverse effects

Budesonide versus systemic corticosteroids in IgA Nephropathy

A retrospective, propensity-matched comparison

Ismail, Gener MD, PhD[a,b]; Obrişcă, Bogdan MD[a,b,*]; Jurubiţă, Roxana MD[a,b]; Andronesi, Andreea MD, PhD[a,b]; Sorohan, Bogdan MD[a,b]; Vornicu, Alexandra MD[a]; Sinescu, Ioanel MD, PhD[b,c]; Hârza, Mihai MD, PhD[b,c]



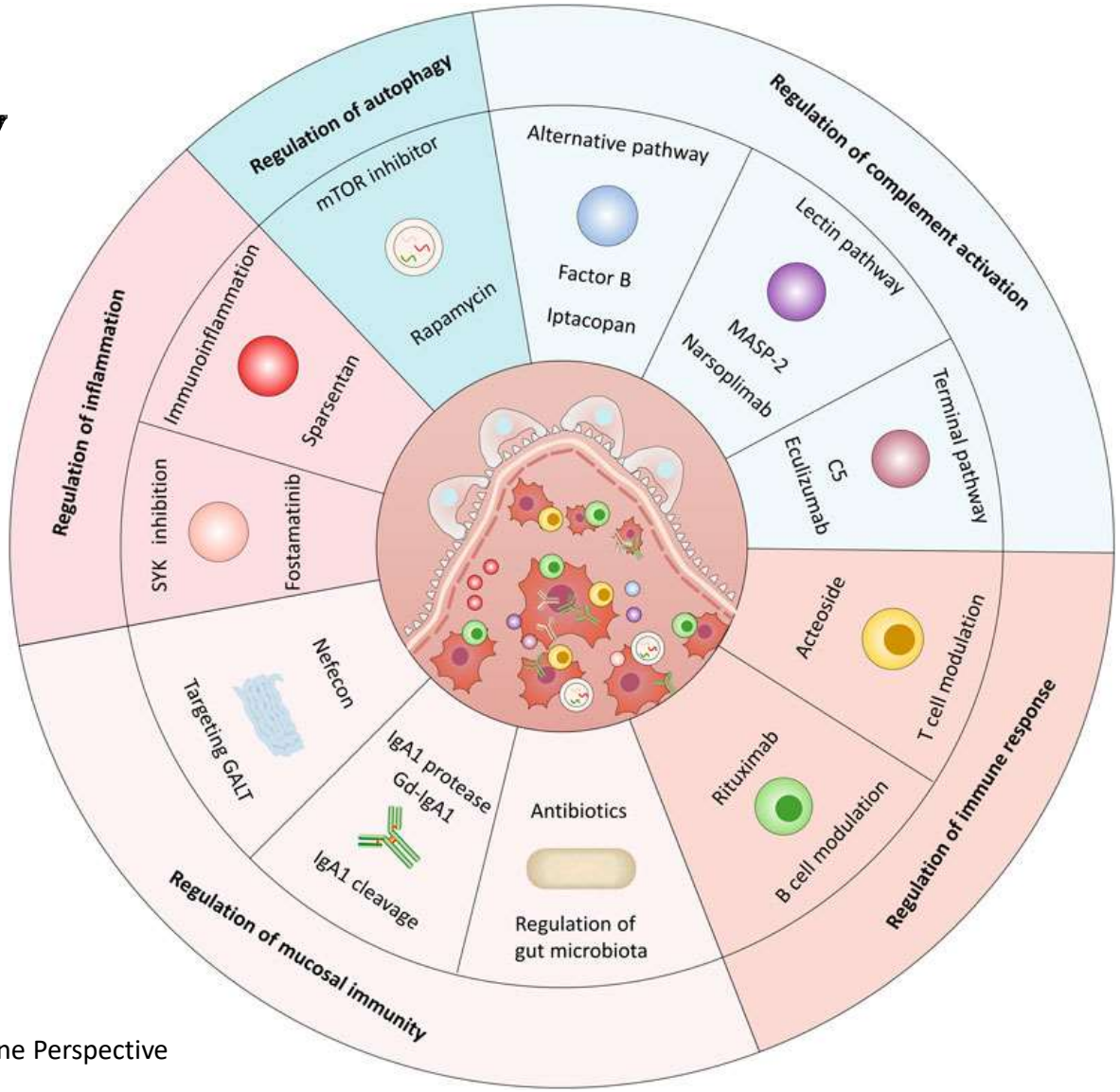
Study flow-chart.
Source: Budesonide versus systemic corticosteroids in IgA Nephropathy: A retrospective, propensity-matched comparison

Conclusions:

In summary, a pH-modified formulation of budesonide with a maximum release of active compound in the distal ileum and proximal colon was effective in the treatment of patients with IgAN at high-risk of progression in terms of reducing proteinuria, hematuria and preserving renal function over 24 months of therapy. Budesonide was well tolerated, with minimal side effects.

Targeted treatment of IgA Nephropathy

- Regulation of B and T-cell activation
- Targeting Gut-Associated Lymphoid Tissue
- Inhibition of Spleen Tyrosine Kinase Activation
- Inhibition of Endothelin-1
- Inhibition of Complement Pathways
- Regulation autophagy



An Update on Targeted Treatment of IgA Nephropathy: An Autoimmune Perspective
Xin Huang and Gaosi Xu;

REGULATION OF IMMUNE RESPONSE IN IGAN

- B-Cell Modulation

Proliferation-inducing ligand (APRIL)

- VIS649, anti-APRIL monoclonal antibody
- BION-1301, another novel humanized anti-APRIL monoclonal antibody

B-cell activation factor (BAFF)

- Blisibimod, a monoclonal antibody against BAFF

Anti-APRIL & Anti-BAFF

- Atacicept, recombinant human BLyS receptor-antibody fusion proteins that target both BAFF and APRIL
- RC-18, recombinant human BLyS receptor-antibody fusion proteins that target both BAFF and APRIL

REGULATION OF IMMUNE RESPONSE IN IGAN

- T-Cell Modulation

Artemisinin and hydroxychloroquine (AH) improves renal function and decreases mesangial matrix expansion and immune complex deposition

Acteoside, the main component of Rehmannia glutinosa, have renoprotective functions in IgAN, relieves albuminuria and reduces Th22 lymphocytosis in patients with IgAN

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

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Cohort and intervention

Randomised

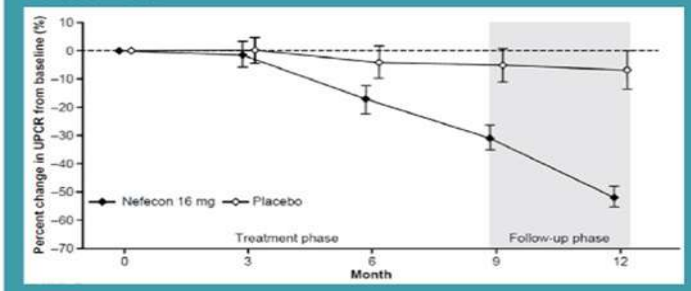
- 201 patients with **IgAN**
- **Nefecon** 16 mg od: n=97
- **Placebo**: n=102

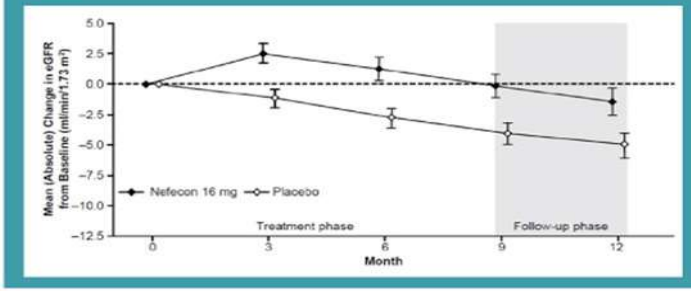
9-month treatment ➔ 3-month follow-up

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**

Outcomes





UPCR:

- At 9 months: **27% reduction** vs placebo (P = 0.0003)
- At 12 months: **48% reduction** vs placebo (P < 0.0001)

eGFR:

- At 9 months: **3.87** ml/min/1.73 m² **treatment benefit** (P = 0.0014)
- 1-year eGFR slope **improvement**: **3.37** ml/min/1.73 m² (P = 0.0111)

Safety:

- Patients with **TEAEs**: 86.6% with Nefecon vs 73.0% with placebo, mostly mild or moderate
- **No severe infections requiring hospitalisation**

Barratt et al, 2022

CONCLUSION

9 months of treatment with Nefecon, in addition to optimised and stable RAS blockade, was well tolerated and resulted in clinically important improvements in UPCR, UACR, and eGFR compared with optimised supportive care alone

ELSEVIER

Kidney International 2023 103391-402DOI: (10.1016/j.kint.2022.09.017)

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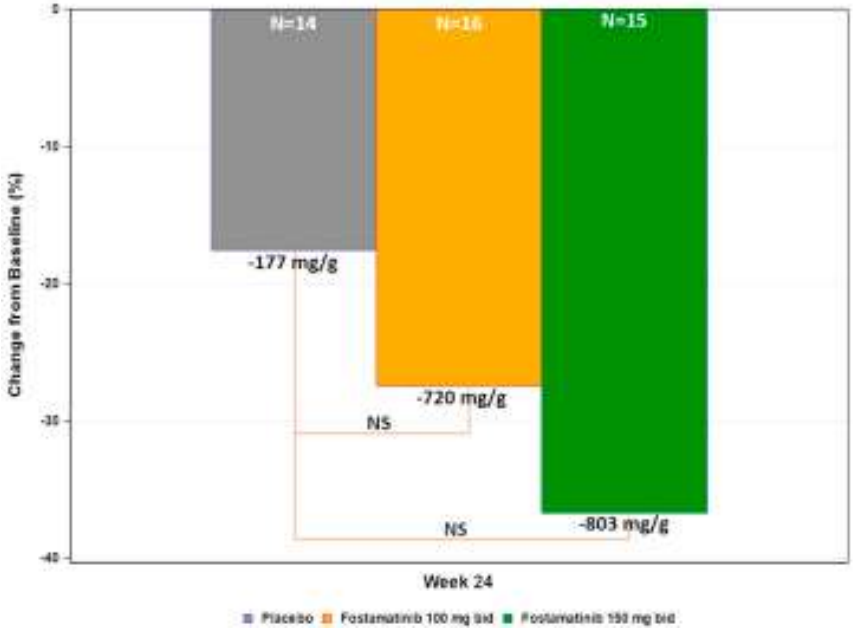
REGULATION OF INFLAMMATION IN IGAN

Inhibition of Spleen Tyrosine Kinase Activation

SUN-036 SPLEEN TYROSINE KINASE (SYK) INHIBITION IN IGA NEPHROPATHY: A GLOBAL, PHASE II, RANDOMISED PLACEBO-CONTROLLED TRIAL OF FOSTAMATINIB

F. Tam WK • J. Tumlin • J. Barratt • ... S. Tong • D. Magilavy • R. Lafayette • Show all authors



Effect of treatment on proteinuria in patients with baseline sPCR ≥1000mg/g

Conclusions

This is the first clinical trial of a new class of medication (SYK inhibitor) in patients with kidney disease. The results suggest that further investigation of fostamatinib as a novel therapy for IgAN is warranted in patients with >1g proteinuria/day

KI REPORTS
Kidney International Reports®

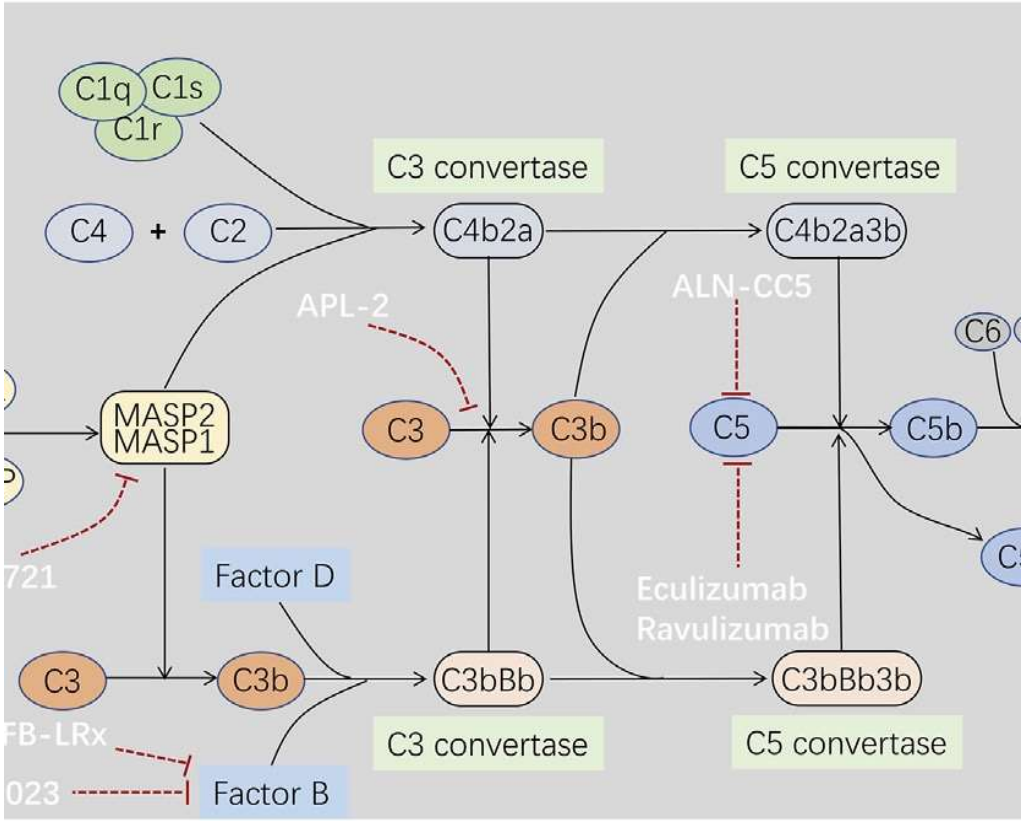
Therapeutic approach

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

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

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.

REGULATION OF COMPLEMENT ACTIVATION IN IGAN



An Update on Targeted Treatment of IgA Nephropathy: An Autoimmune Perspective; Xin Huang and Gaosi Xu;

Inhibition of the Alternative Pathway

IPTACOPAN, an oral, selective, and reversible factor B inhibitor.

Inhibition of the Lectin Pathway

NARSOPLIMAB, humanized monoclonal antibody against MASP-2, the critical effector enzyme of the lectin pathway

Inhibition of the Terminal Pathway

ECULIZUMAB, a recombinant humanized monoclonal antibody selectively against C5, can inhibit C5 cleavage

RAVULIZUMAB, first long-lasting complement inhibitor

Treatment

- Budesonide oral capsules
- Tacrolimus
- Mycophenolate Mofetil
- Candesartan

Laboratory results

	18.07.22	01.08.22	24.09.22	03.11.22	19.12.22	30.01.23	14.02.23	24.03.23
Creatinine (mg/dL)	1.03	1.09	1.04	1.04	1.24	1.3	1.1	1.01
Protein in 24 hour urine mg/24h	292	179	468	163	279	163	160	150

Transplant Kidney Biopsy 2

Microvascularity		Tubulointerstitial	
Glomerulitis (g)	0	Inflammation (i)	0
Peritubular capilaritis (pct)	1	Tubulitis (t)	1
C4d in peritubular capillaries	0	Fibrosis (ci)	1
GBM double contours (cg)		Atrophy (ct)	1
Mesangial matrix (mm)	0	SV40	
Arteries		Arterioles	
Arteriitis (v)	0	Hyalinosis (ah)	3
Vascular fibrosis, intimal thickening(cv)	2		

IgA Nephropathy

Oxford Classification score M1 E0 S1 T0 C0 _ S1

Transplant Kidney Biopsy 1

July 2022

IgA Nephropathy

Oxford Classification score

M3 E0 S1 T1 C1 _ S1

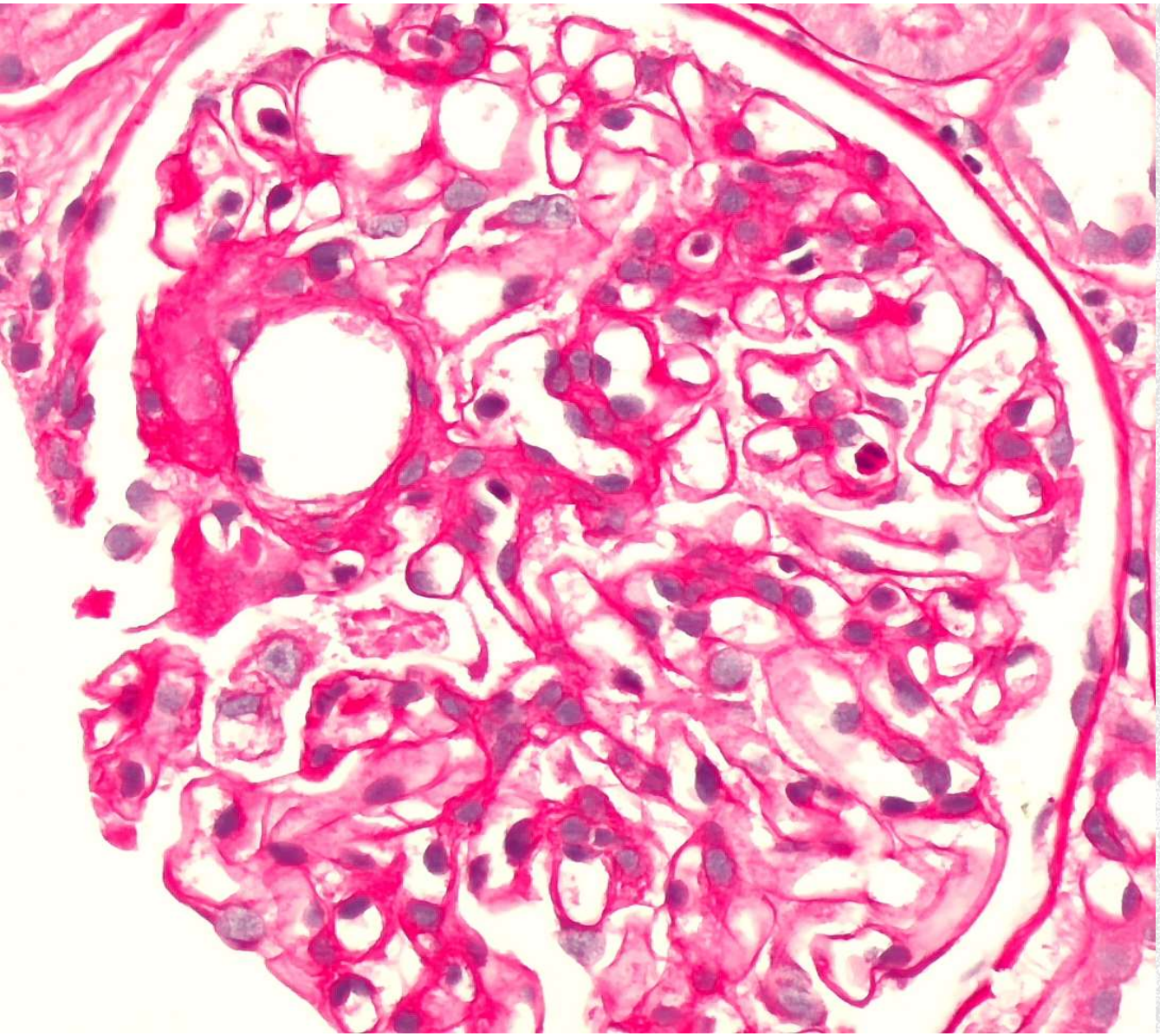
Transplant Kidney Biopsy 2

April 2023

IgA Nephropathy

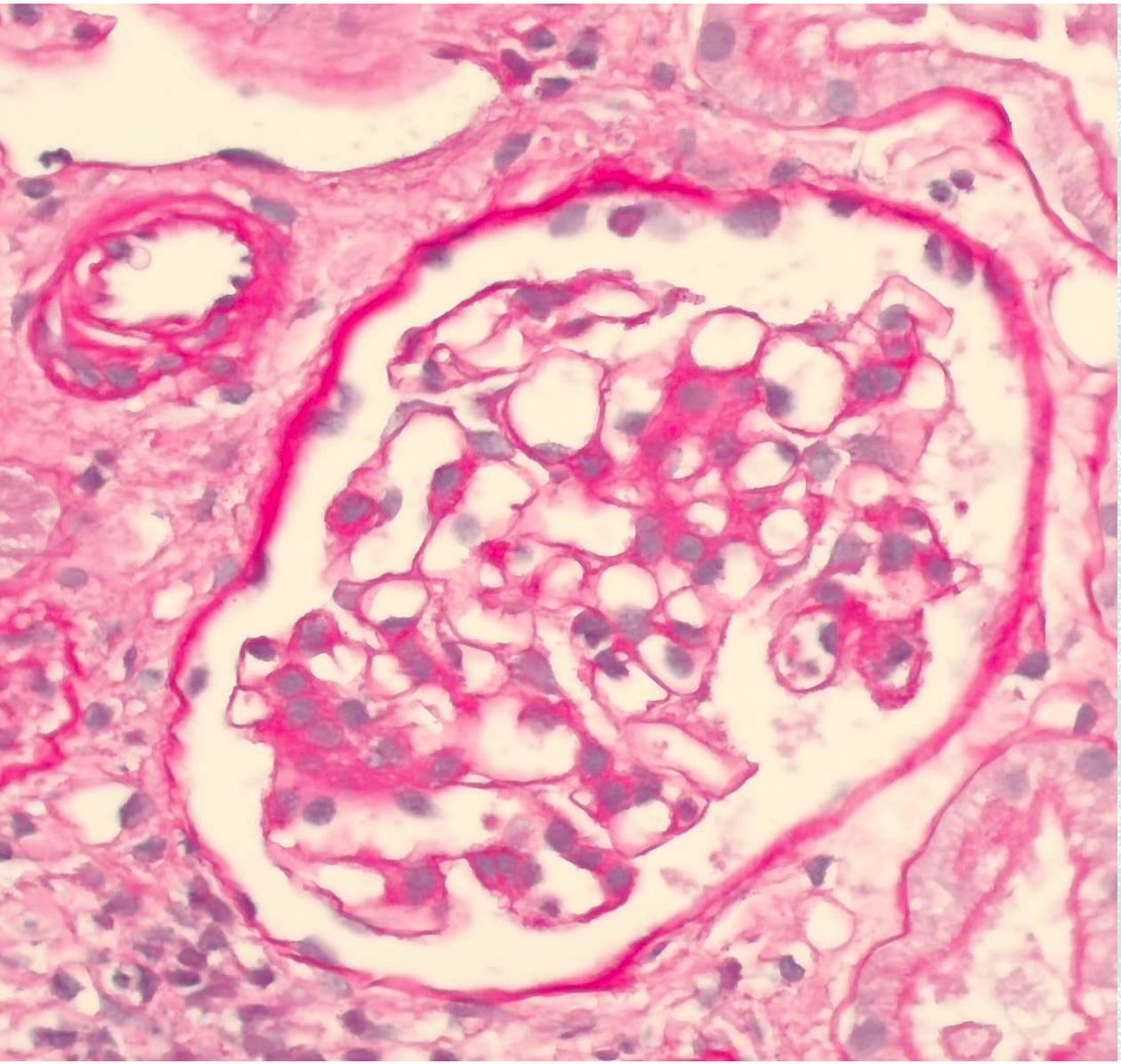
Oxford Classification score:

M1 E0 S1 T0 C0 _ S1



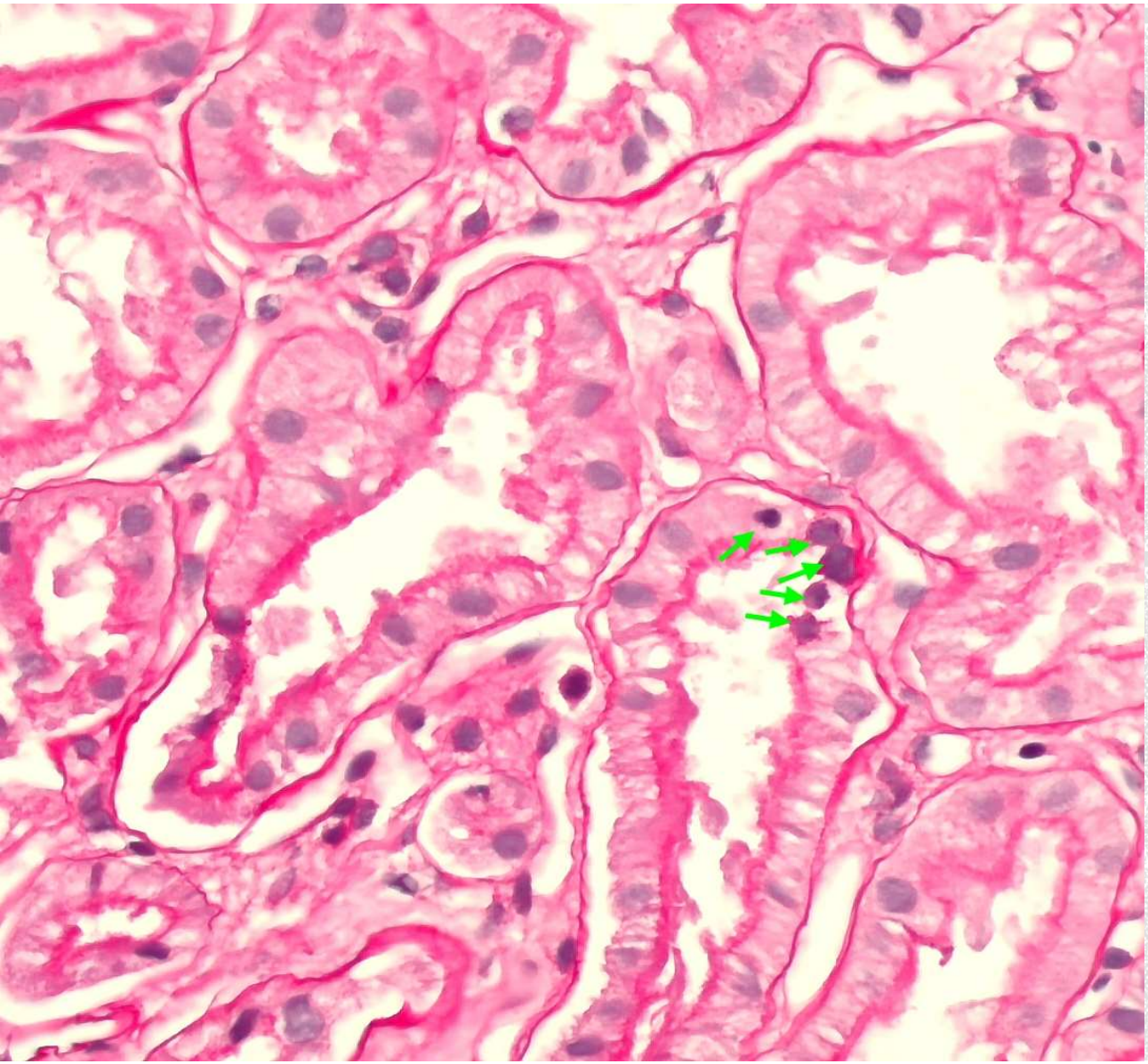
Recurrent IgA in kidney transplant allograft

Mesangial Hypercellularity



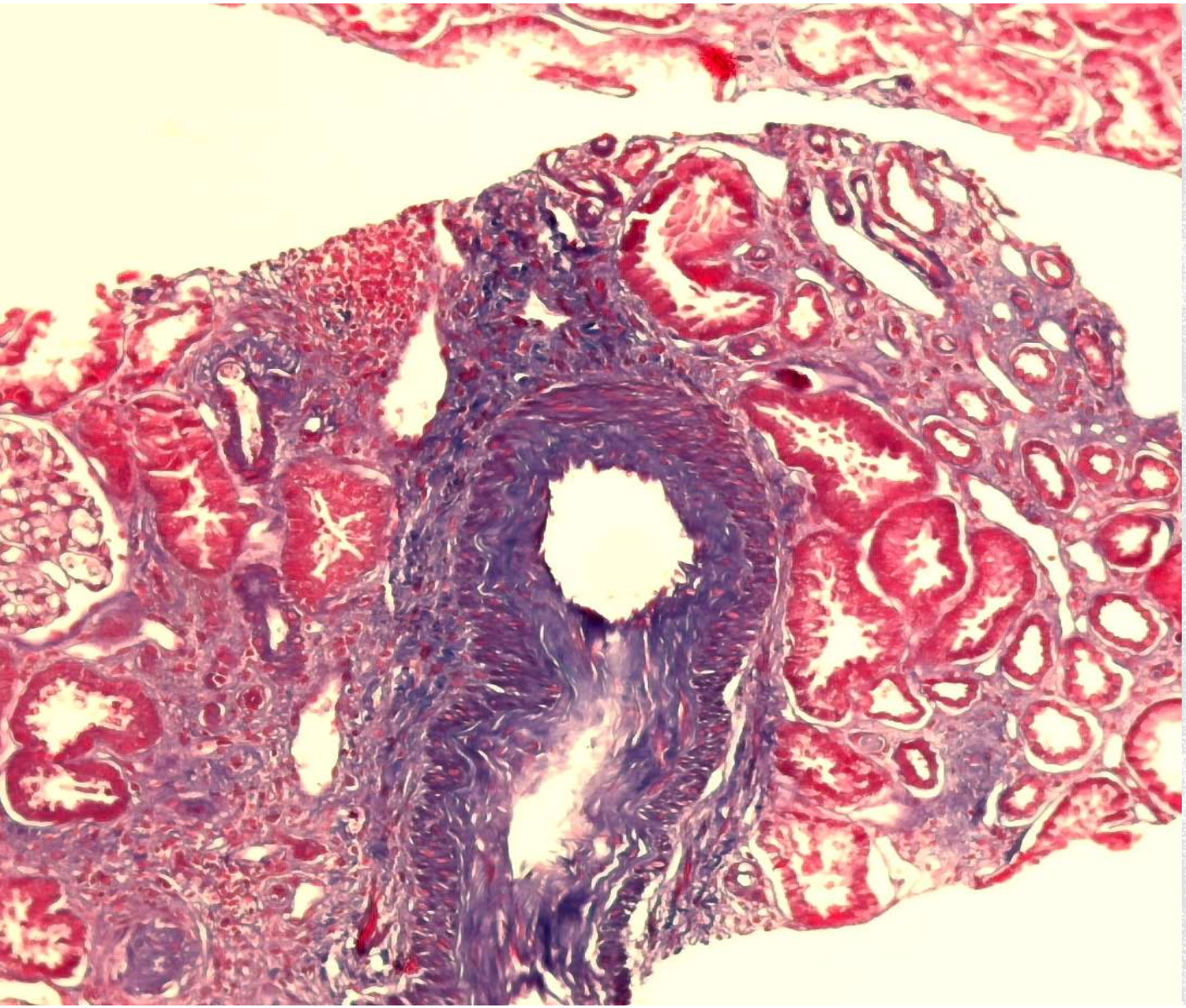
Recurrent IgA in kidney transplant allograft

Mesangial Hypercellularity



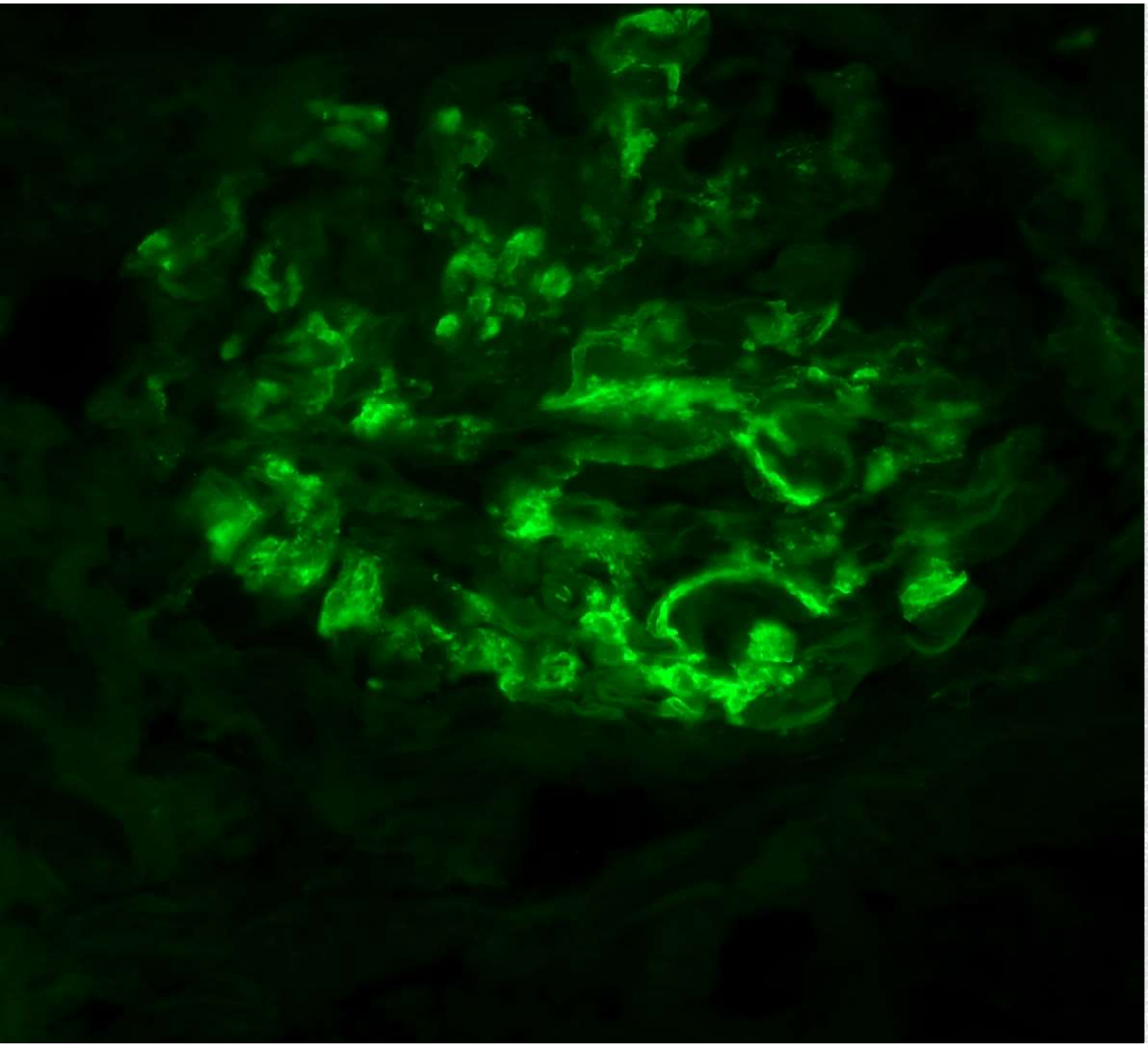
Recurrent IgA in kidney transplant allograft

Tubulitis



Recurrent IgA in kidney transplant allograft

Arterial Fibrosis



Recurrent IgA in kidney transplant allograft

- IgA staining

Conclusions

The clinical diagnosis of IgAN recurrence is often made late, so an early diagnosis by protocol biopsies is important earlier after kidney transplantation

MMF use can reduce the risk of development recurrent IgAN

Novel noninvasive biomarker are helpful for monitoring the disease severity

Budesonide is effective in the treatment of patients with IgAN at high-risk of progression with low frequency of severe adverse events

Several clinical trials have evaluated the safety, tolerability, and efficacy of novel targeted treatment of IgAN

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SEPTEMBER 2023 | 13/14

Tbilisi, Georgia

Tbilisi State Medical University

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