Update on the Management of IgA Nephropathy

3rd GCC Organ Transplant and Nephrology Congress

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IgAN: Understanding the Natural History

- The first step is to determine the risk of poor outcome

- In order to measure risk/benefit of interventions or to critically evaluate clinical trial data you must understand:
  - *What is the natural history at a population level?*
  - *How do we tailor therapy at the individual level, targeting patients at highest risk of progression?*

Slides courtesy of Dr. Heather Reich

Risk Stratification: What We Know

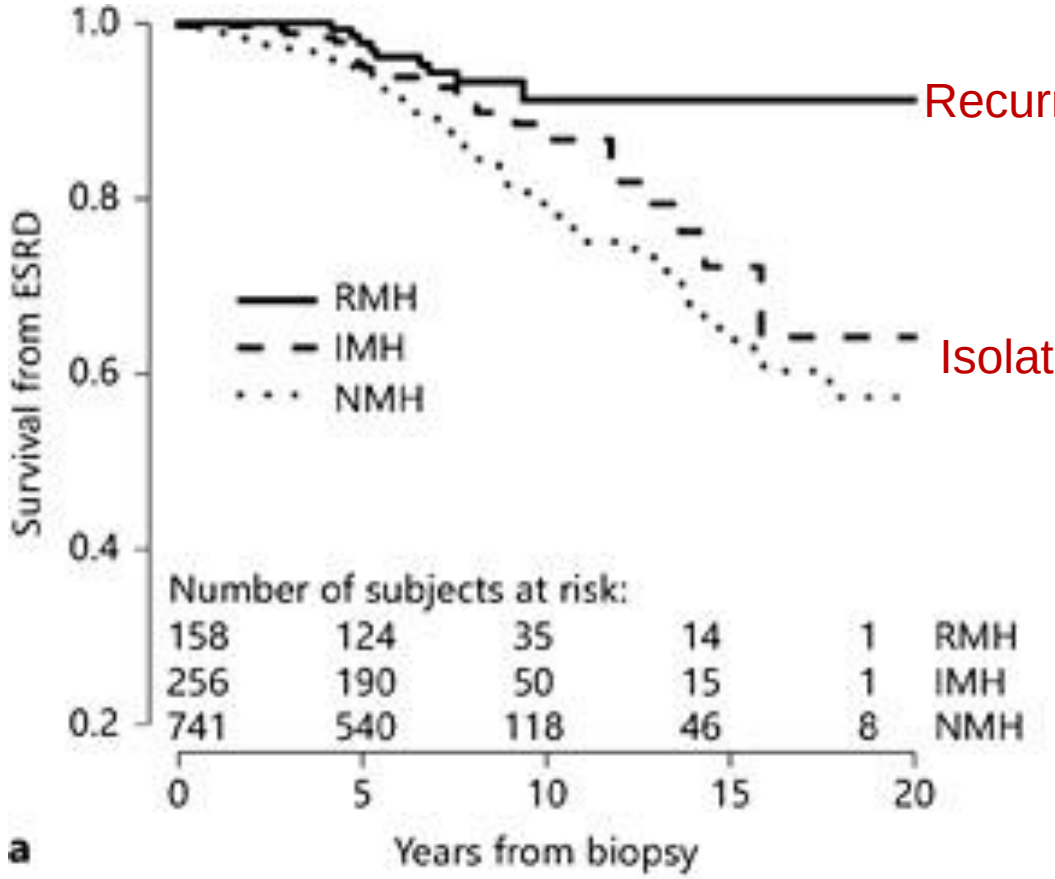
- Favourable
  - microhematuria alone
  - recurrent macrohematuria only
- Unfavourable
  - age
  - **proteinuria**
  - **hypertension**
  - tenal insufficiency
  - **specific histologic features**
  - **?race**

Macroscopic Hematuria

- Classically associated with a favourable outcome
- Recent study of cohort of 1555 patients from Jinling Hospital:
  - recurrent macrohematuria n= 158
  - isolated macrohematuria n = 256
  - no macrohematuria n = 741

Le W. et al. Am J Nephrol 2014: 40, 43

Adjusted Renal Survival



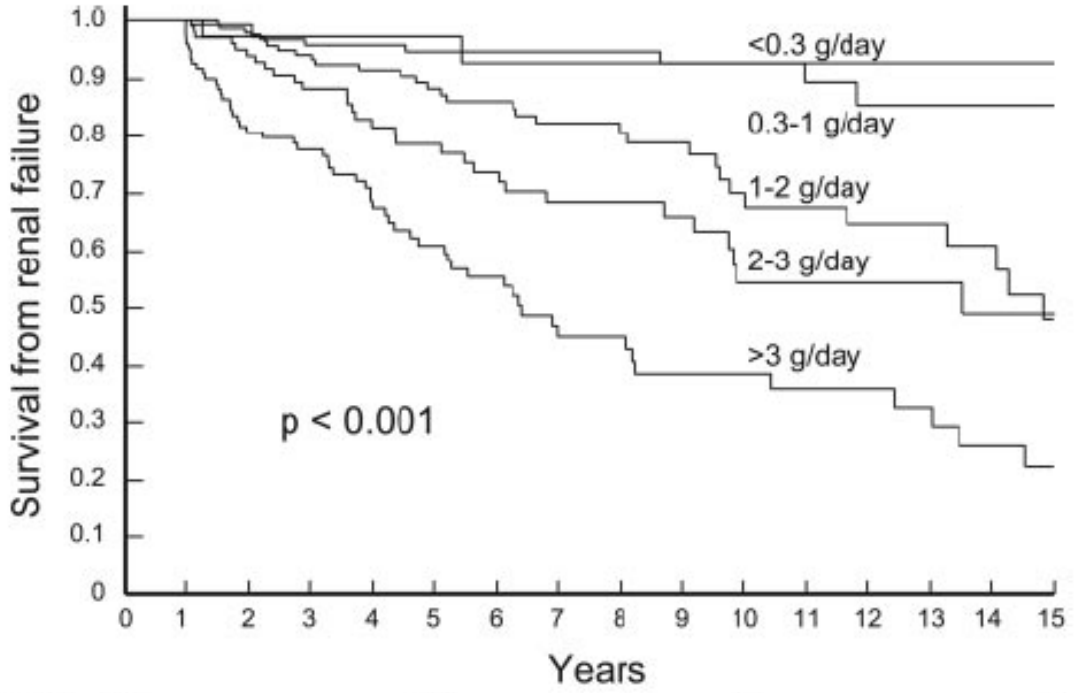
Recurrent macrohematuria

Isolated or no macrohematuria

Risk stratification of IgA Nephropathy
(continued)

- Proteinuria: The strongest prognostic factor

Proteinuria and Renal Survival in IgA Nephropathy

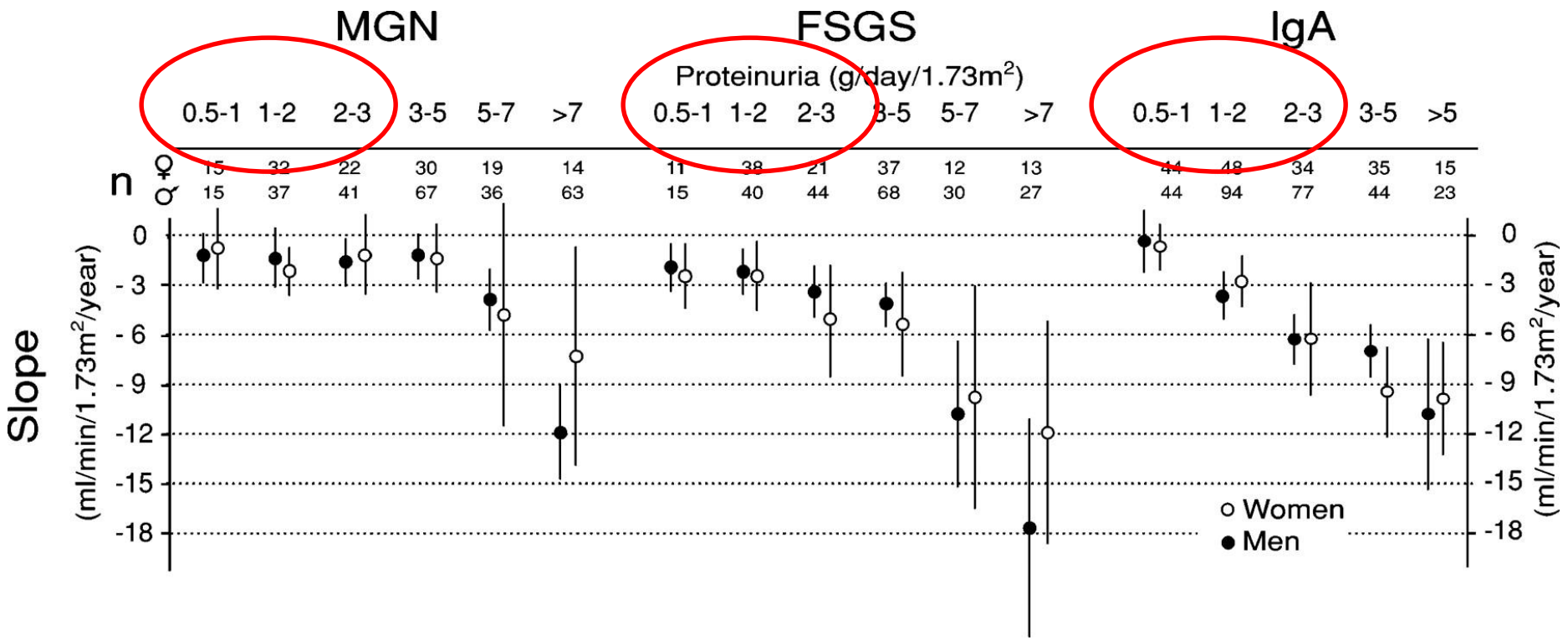


<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

Figure 1. Renal survival by category of TA-proteinuria.

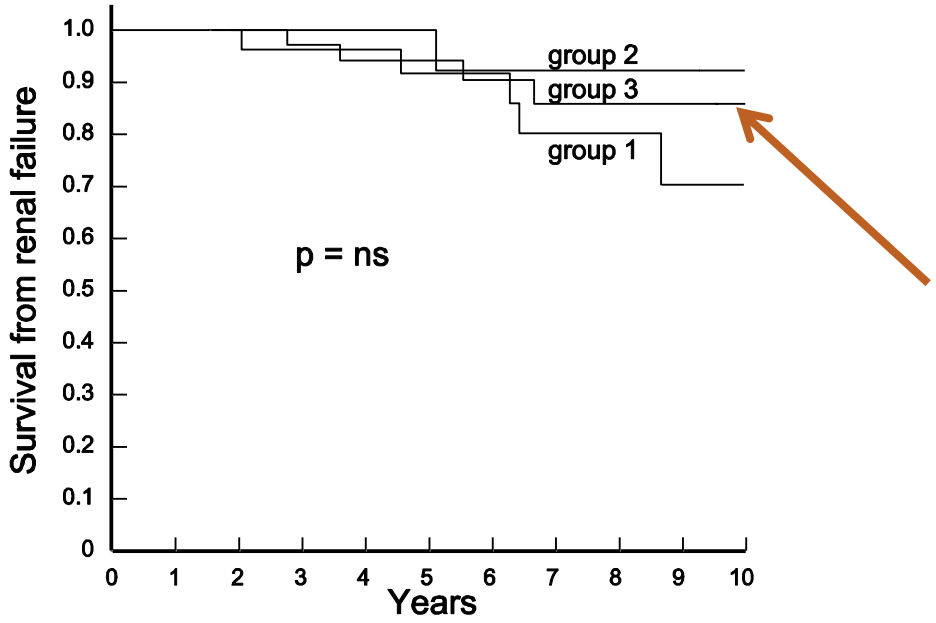
Reich J Am Soc Nephrol 2008

Modest Proteinuria in IgA Nephropathy is More Worrisome than in Other GNs



Cattran, D, Reich H, Troyanov S.
Nephrol. Dial. Transplant. 2008

Patients Attaining Partial Remission (<1g/day) Have Similar Favorable Outcome No Matter How Much Their Original Proteinuria Was



Group 1	29	18	6
Group 2	21	13	2
Group 3	39	26	10

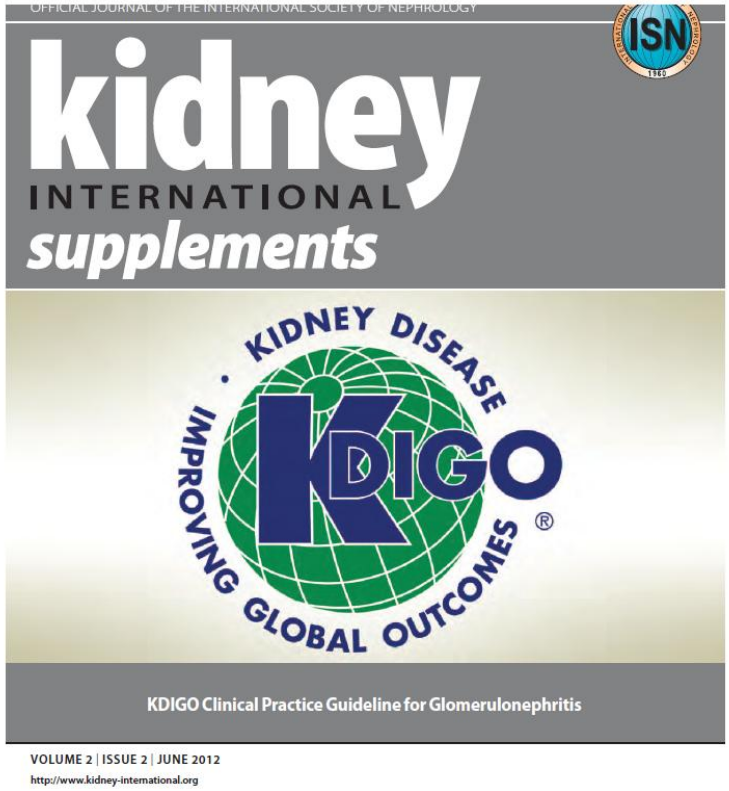
Group 1: 1-2g/day peak proteinuria

Group 2: 2-3g/day peak proteinuria

Group 3:>3g/day peak proteinuria

Reich, H. N. et al. J Am Soc Nephrol 2007;18:3177-3183

Check Out the KDIGO Guidelines for Treatment of Glomerulonephritis



Why I Like These Guidelines

- they’re sensible
- written by practising clinicians with expertise in GN, not “ivory tower” academics
- almost a handbook of GN: lots of good advice about management

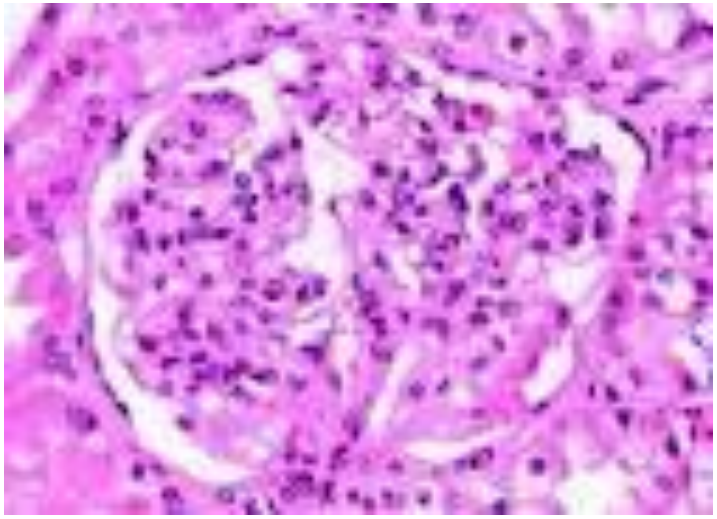
The Terminology

Grade*	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

"Not Graded": recommendations about monitoring intervals, counselling and referral to other specialists

KDIGO Guidelines for IgA Nephropathy

- rule out secondary causes
- risk-stratify the patients
  - proteinuria
  - blood pressure
  - slope of eGFR



IgA Nephropathy: Antiproteinuric and Antihypertensive Therapy (KDIGO)

- ACE/ARB therapy if 24h protein > 0.5 g
  - dose can be titrated to try to get 24h protein < 1g
  - target bp < 130/80 if < 1g/day proteinuria
  - target bp < 125/75 if > 1g/day proteinuria

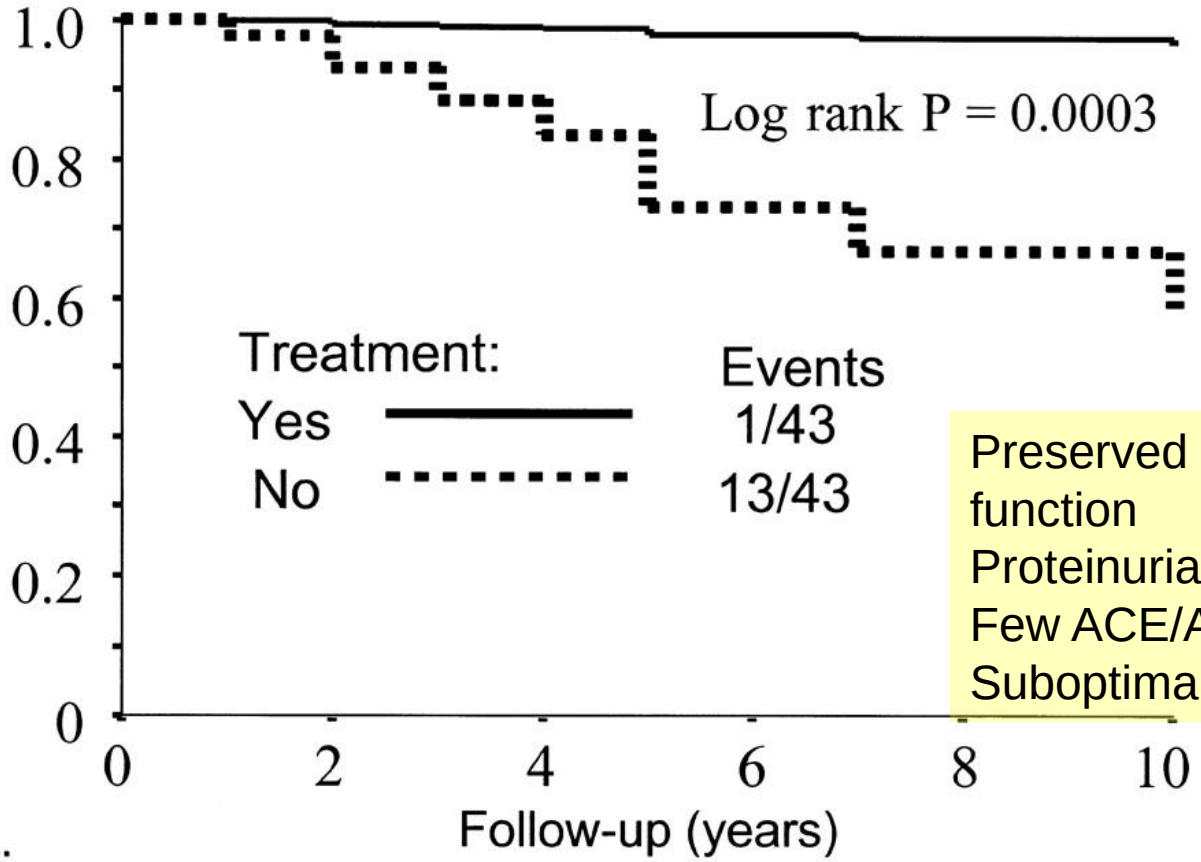
IgA Nephropathy: Corticosteroids (KDIGO)

- Suggest corticosteroids if 24h protein > 1g after 6 months of antihypertensive/antiproteinuric therapy

Table 10.1. Corticosteroid regimens in patients with IgAN

References	Pozzi C et al. [42]	Manno C et al. [43]; Lu J et al. [44]
Regimen	i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months	6-month regime of oral prednisone* starting with 0.8-1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

Survival without endpoint (creatinine doubling from baseline)



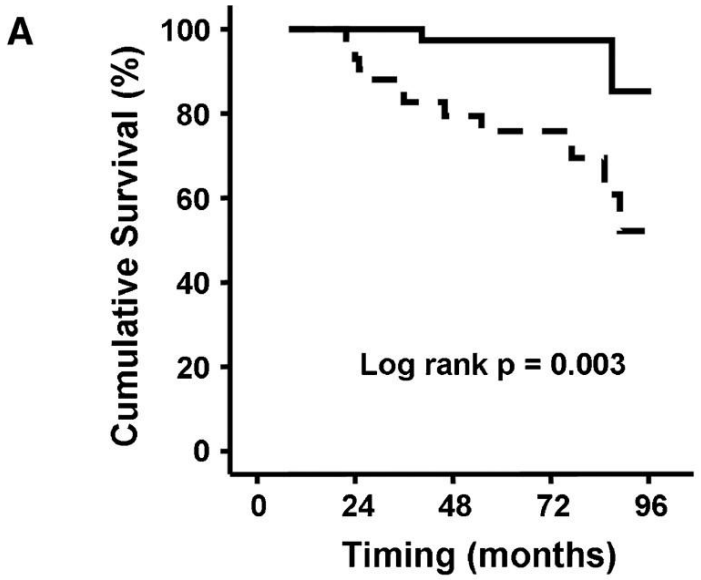
Preserved renal function
Proteinuria ~1.9 g/d
Few ACE/ARB (15%)
Suboptimal BP

Treatment:						
Yes	43	42	39	33	20	12
No	43	40	33	23	14	7

Pozzi C et al. JASN 2004;15:157-163

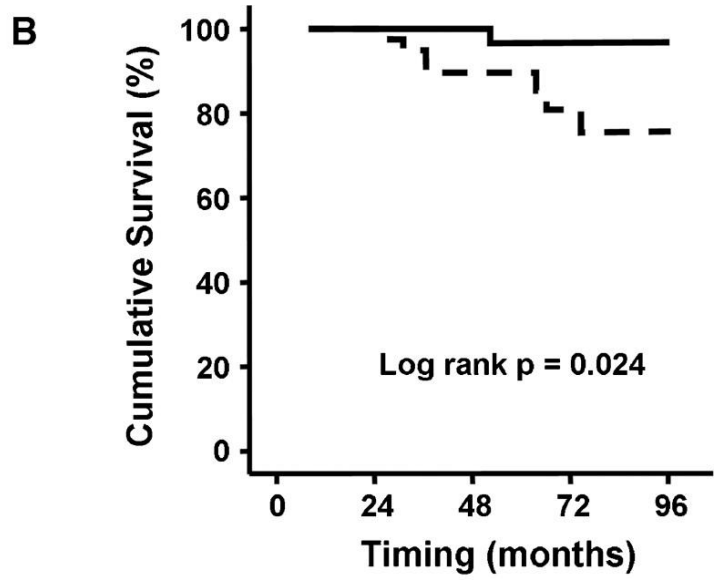
Kidney Survival in Two Treatment Groups: Ramipril alone versus Prednsione

Doubling of creatinine or ESRD



Patients at risk					
Prednisone + Ramipril	48	37	32	19	4
Ramipril	49	40	24	13	6

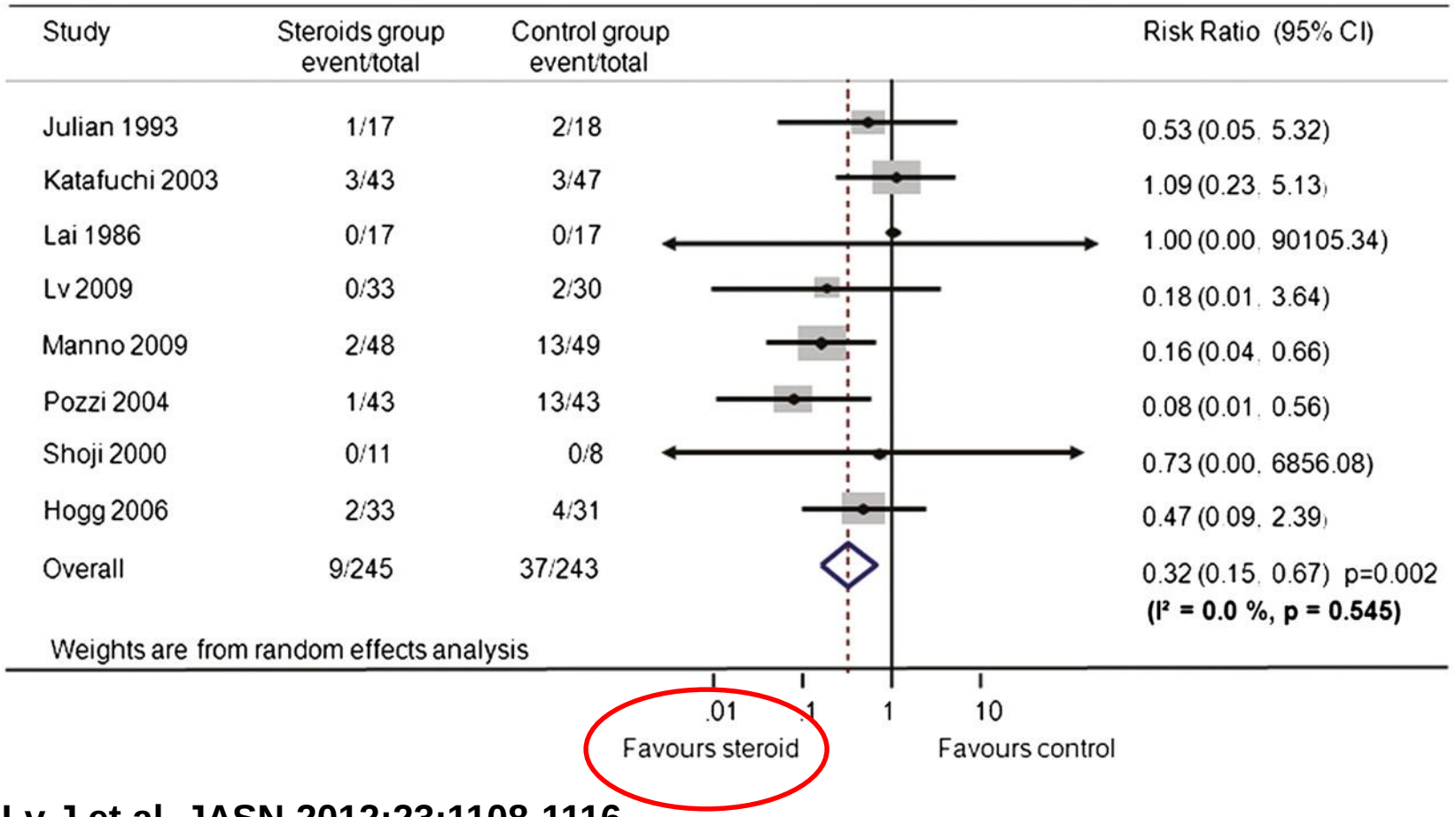
ESRD only



Patients at risk					
Prednisone + Ramipril	48	29	29	19	4
Ramipril	49	39	28	15	6

Manno C et al. Nephrol. Dial. Transplant.2009

Effect of steroids on composite renal endpoint (ESRD or doubling of serum creatinine or halving of GFR) in patients with IgA nephropathy.



Lv J et al. JASN 2012;23:1108-1116

Other Suggestions for IgA Nephropathy (KDIGO)

- don’t use cyclophosphamide or azathioprine unless it is the rare, crescentic form of IgA
- don’t use MMF
- don’t use immunosuppressive/steroid therapy in advanced CKD (eGFR < 30 ml/min)
- treat the minimal lesion with IgA deposits like “usual” minimal lesion

IgA Nephropathy: The AKI/Macrohematuria Syndrome

- if no spontaneous improvement, do a renal biopsy
  - if ATN: supportive care
  - if crescentic IgA, treat like an ANCA vasculitis

And What About Fish Oil in IgA Nephropathy?

- "We suggest using fish oil in IgA nephropathy"
  - low quality evidence, but given potential CV benefits and minimal risk, it is not unreasonable
- Not suggested
  - antiplatelet agents
  - tonsillectomy

My Kudos and Quibble: KDIGO

- addresses the issue of the “low-risk” patient (normotensive, trivial proteinuria, normal and stable renal function) who constitute the majority of patients
  - no indication for ACE/ARB therapy
- I agree with this: many colleagues consign these patients to lifelong ACE/ARB therapy
- the BP goals may be unrealistic in some patients with IgA nephropathy

What We Need is a Large, Randomized Trial of Corticosteroids with Long Followup

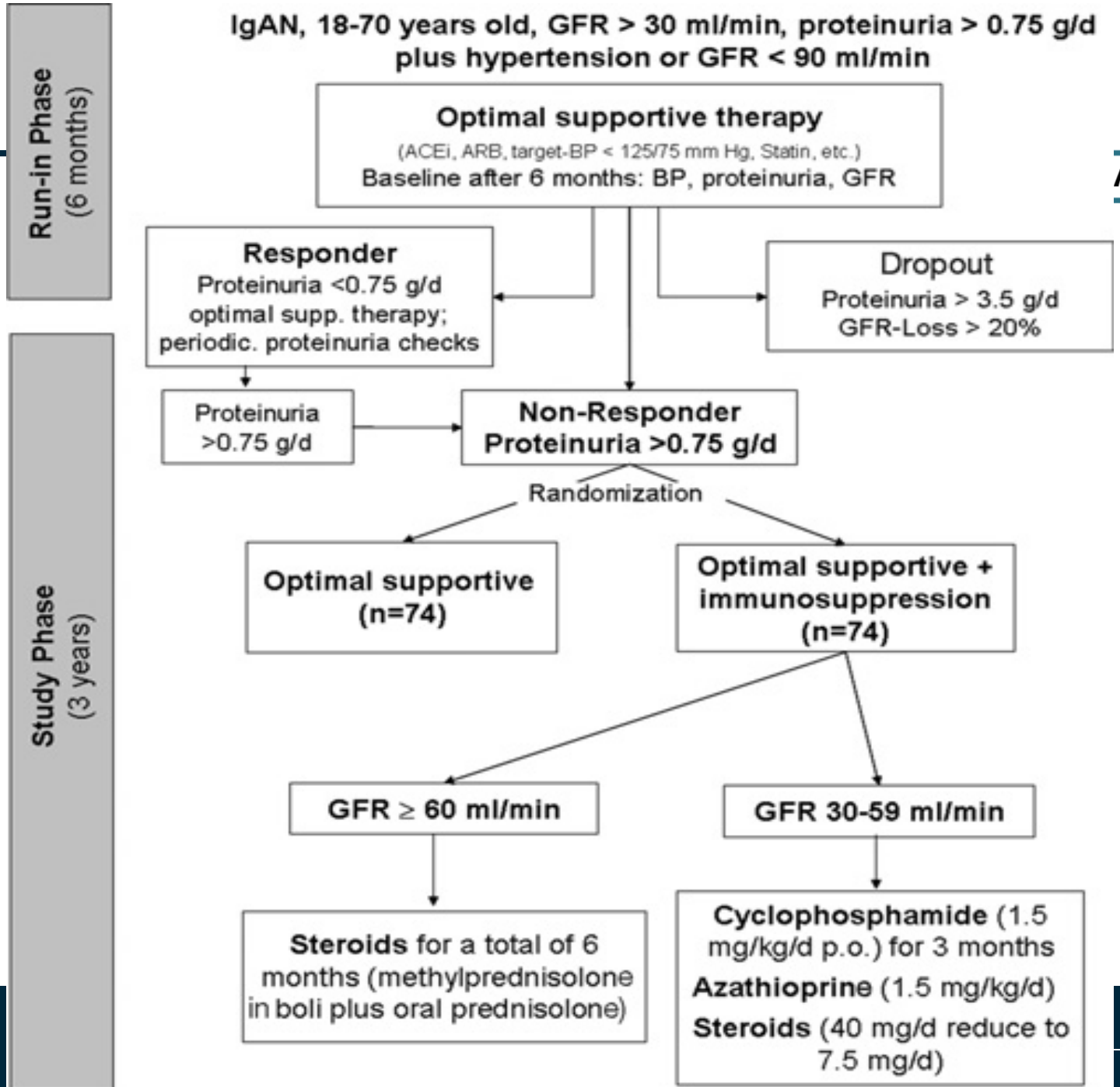
Original Article

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

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

N Engl J Med
Volume 373(23):2225-2236
December 3, 2015

The NEW ENGLAND JOURNAL of MEDICINE


IgAN, 18-70 years old, GFR > 30 ml/min, proteinuria > 0.75 g/d
plus hypertension or GFR < 90 ml/min
Run-in Phase
(6 months)
Optimal supportive therapy
(ACEi, ARB, target-BP < 125/75 mm Hg, Statin, etc.)
Baseline after 6 months: BP, proteinuria, GFR
Responder
Proteinuria <0.75 g/d
optimal supp. therapy;
periodic. proteinuria checks
Dropout
Proteinuria > 3.5 g/d
GFR-Loss > 20%
Study Phase
(3 years)
Proteinuria
>0.75 g/d
Non-Responder
Proteinuria >0.75 g/d
Randomization
Optimal supportive
(n=74)
Optimal supportive +
immunosuppression
(n=74)
GFR ≥ 60 ml/min
GFR 30-59 ml/min
Steroids for a total of 6
months (methylprednisolone
in boli plus oral prednisolone)
Cyclophosphamide (1.5
mg/kg/d p.o.) for 3 months
Azathioprine (1.5 mg/kg/d)
Steroids (40 mg/d reduce to
7.5 mg/d)

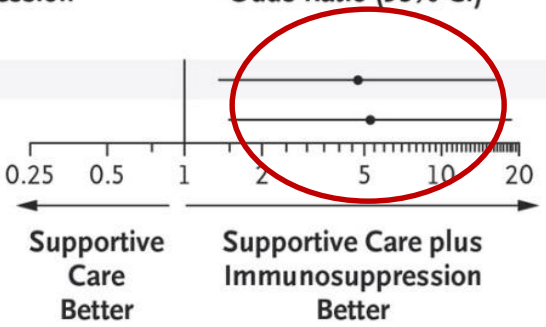
STOP IgA N: Findings #1

- After 6 month run-in of conservative therapy, one third no longer eligible because of improvement!
  - target BP was <125/75 with maximally- tolerated ACEi, patients provided home measurements
  - cholesterol <5.2 mmol/L with statin
  - visits q4 weeks, counselling to stop smoking, dietary salt restriction
- Only 162 subsequently randomized

Findings #2: Immunosuppression Group Had More Complete Remissions, but No Difference in GFR

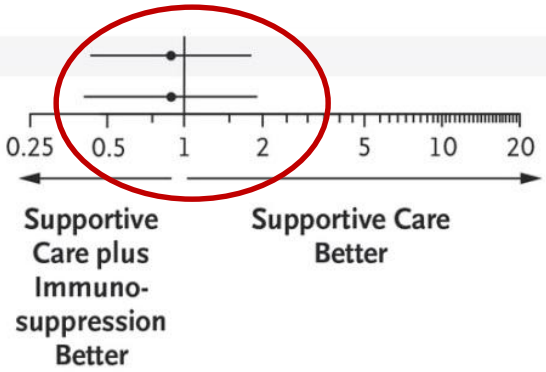
A In Full Clinical Remission

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	4/80	14/82	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72	14/71	5.38 (1.55–18.66)	0.008



B eGFR Decrease ≥15 ml/min/1.73 m²

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	22/80	21/82	0.89 (0.44–1.81)	0.75
Available-case analysis	18/76	17/78	0.89 (0.41–1.90)	0.76



STOP IgA N Results Summarized

Table 3. The STOP Trial: Summary of protocol and results[52]

Variable	Supportive Care, *n*=80	Supportive Care Plus Immunosuppression, *n*=82	*P* Value
Age, yr	45.8±12.5	42.8±13.1	NS
eGFR, ml/min per 1.73 m^2	57.4±24.9	61.1±29.0	NS
Proteinuria, g/d	1.6±0.7	1.8±0	NS
Systolic BP	131±14.0	127±8.5	NS
Diastolic BP	78±7.0	77±7.0	NS
Outcomes			
Full clinical remission, (%)	4/80 (5)	14/82 (17)	0.01*
eGFR decrease >15 ml/min per 1.73 m^2	22/80 (28)	21/82 (26)	NS
AEs			
Patients with one or more serious AEs	21/80	29/80	NS
Total no. of events of infection	111	174	0.07*
Impaired glucose tolerance or diabetes mellitus	1	9	0.02*

Coppo J Am Soc Nephrol 2017

Findings #3: Secondary Endpoints at 3 Years

- Absolute ∆eGFR: NS
- Difference in slope: NS
- eGFR loss >30: NS
- ESRD: NS
- Hematuria resolution: OR 3.73 (1.52-9.14) favouring immunosuppression

Stop IgAN: Conclusions

- we should not underestimate the impact of conservative Rx
- immunosuppression reduces proteinuria, however this is not sustained beyond 12 months (need maintenance?)
- at 3 years more patients have had remission of proteinuria and hematuria but this is not associated with a demonstrable improvement in outcome
- Note: Adverse events
  - overall similar. More non-severe AE in immunosuppressed group including DM. One sepsis death in CS/CYC.
- we need less toxic Rx!

Again, What About Adherence?

- most patients with IgA nephropathy are asymptomatic
- will patients continue to take large doses of prednisone over time because maybe it might slow progression of renal disease?
  - and what about worsening of blood pressure?
  - and what about new onset diabetes?
  - what about Cushingoid side effects?

BRIEF REVIEW www.jasn.org

Corticosteroids in IgA Nephropathy: Lessons from Recent Studies

Rosanna Coppo

- Given the slow rate of progression to ESRD, even 3 year followup may not be enough
- Steroids reduce proteinuria, and reduction in proteinuria is associated with better outcome, but it's still not clear that steroids improve outcome
- Maybe we need to risk-stratify by histology also (MEST score)

Coppo J Am Soc Nephrol 2017

Rituximab is So New and Expensive, It Has to Work, Right?

- IgG and/or IgA autoantibodies against galactose-deficient IgA1 are increased in most patients with IgA nephropathy
- Increased levels of autoantibody correlate with higher risk of progression
- Rituximab depletes antibody-producing B cells that may drive progression of the nephropathy

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Rituximab in IgA Nephritis *(continued)*

- High risk IgA patients on RAAS inhibition
- Median baseline serum creatinine 1.4 mg/dl, baseline proteinuria about 2g/day
- 34 patients total, 17 in each group
  - (control RAAS only vs RAAS and rituximab)

Lafayette J Am Soc Nephrol 2016

Rituximab in IgA Nephritis *(continued)*

- Excellent and sustained CD 19+ cell depletion
- No difference, however, in levels of anti-Gd-IgA1 antibodies
- No serious adverse events

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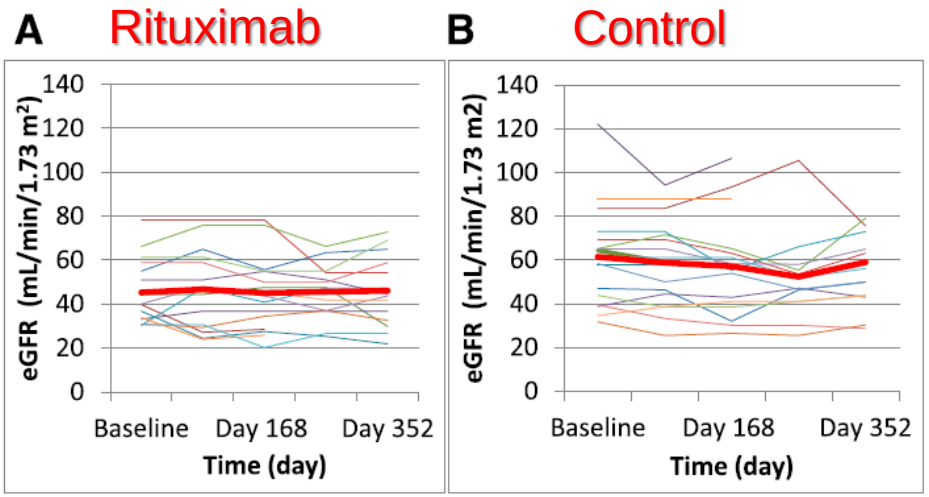
Rituximab in IgA Nephropathy: A Negative Randomized, Controlled Trial

- Neither control nor rituximab group had significant reduction in proteinuria
- No significant difference in kidney function over 1 year of follow-up



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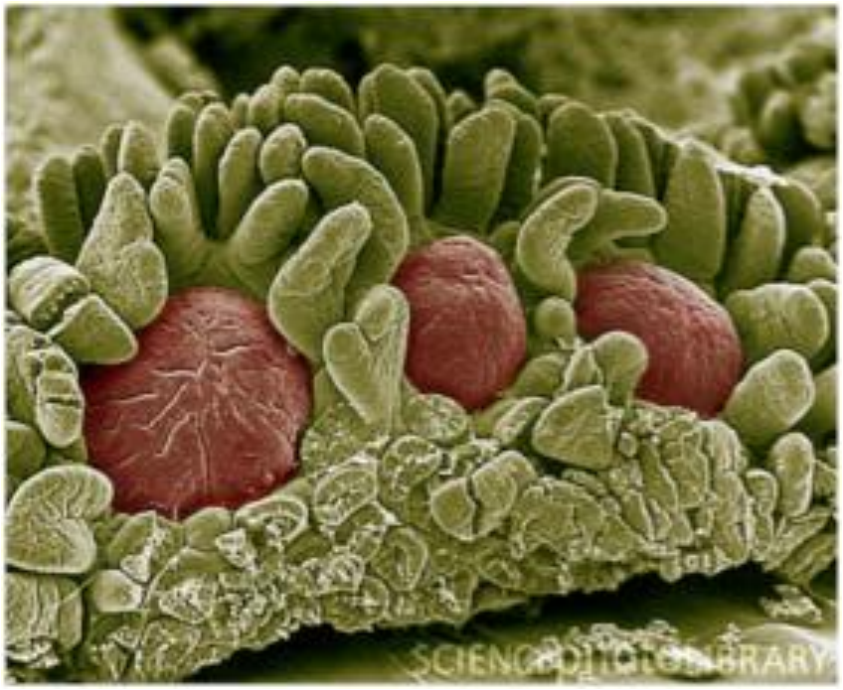
The NEFIGAN Trial

NEFECON, a novel targeted-release formulation of budesonide, reduces proteinuria and stabilizes eGFR in IgA nephropathy patients at risk of ESRD

Bengt Fellström, Rosanna Coppo, John Feehally, Jürgen Floege, Johan de Fijter, Alan Jardine, Francesco Locatelli, Bart Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren Sørensen, Vladimir Tesar.

• Nefecon

- Intraluminal introduction of steroid delivered to gut Peyer's patches
- met the primary endpoint of reduction in proteinuria at 9 months, surprisingly also showed improved eGFR
- was generally well-tolerated, consistent with low systemic exposure
- eGFR results beyond expectations
- Phase III next



IgA Nephropathy: Summary and Conclusions

- even sub-nephrotic proteinuria carries a poor prognosis
- ACE and ARB therapy and good blood pressure control are cornerstones of therapy
- corticosteroids are associated with reduction in proteinuria, but it is unclear if this leads to better renal survival
- there is little evidence for the use of other immunosuppressive regimens