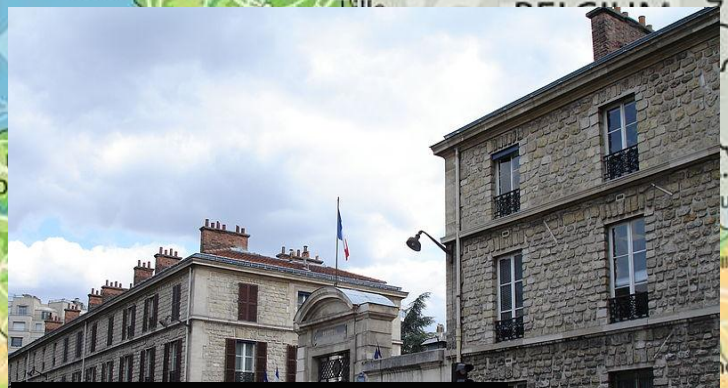
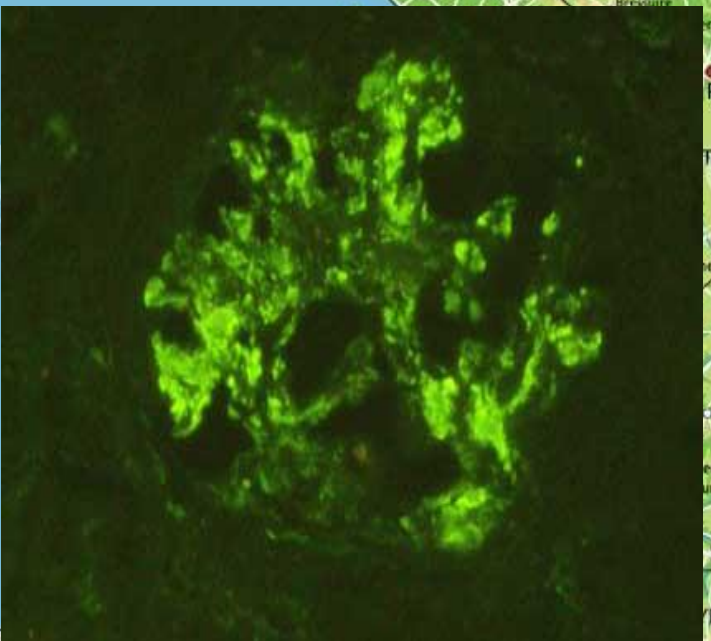
Actualités Néphrologiques
Jean Hamburger - Hôpital Necker
2018
Dominique Joly – Christophe Legendre

Treatment of IgA nephropathy: recent advances and prospect

Rosanna Coppo
Turin, Italy



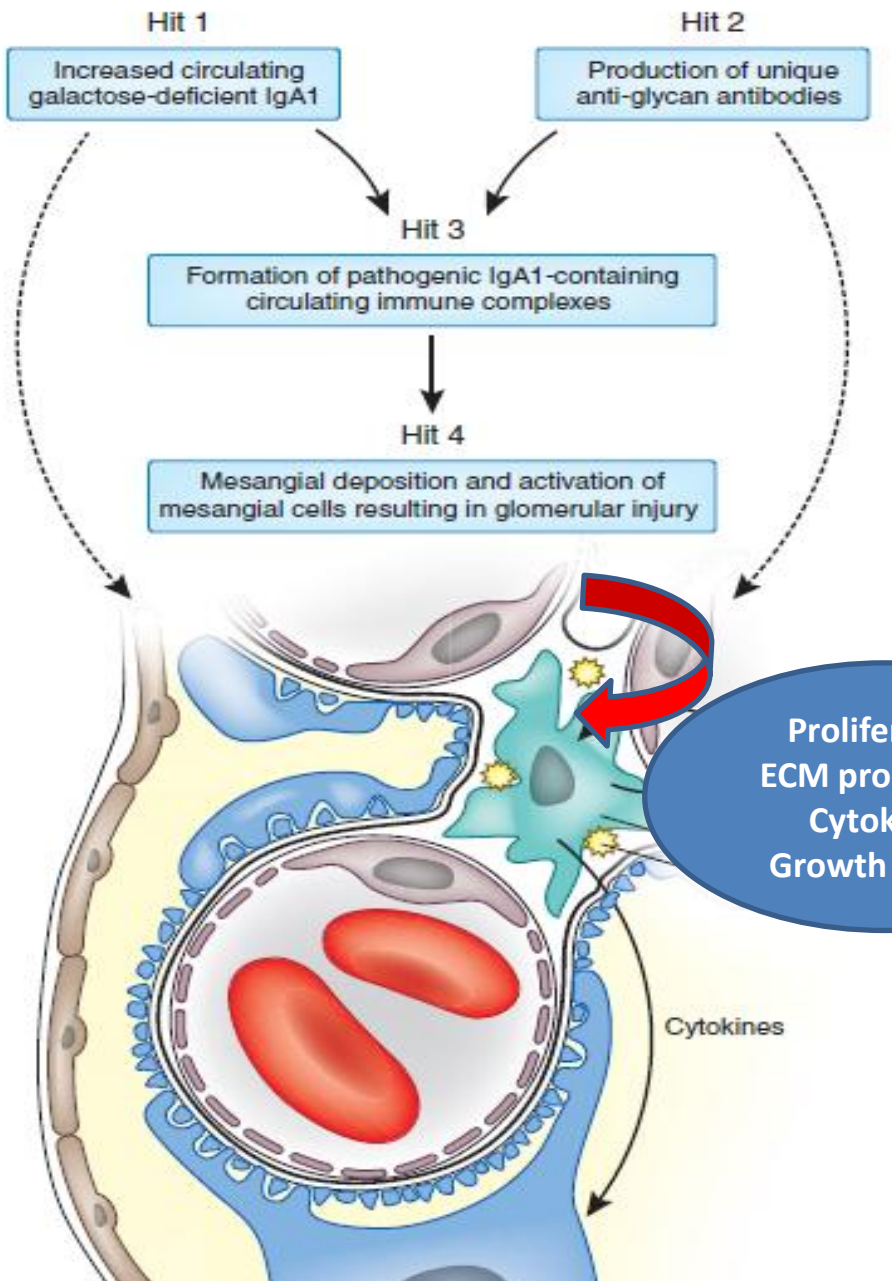


In 1967 at the
Actualités Néphrologiques de l'Hôpital Necker
glomerular IgA deposits were reported

Berger J, Hinglais N. Intercapillary deposits of IgA-IgG
J Urol Nephrol (Paris) 1968

First targeted treatments aimed at reducing IgA levels:
no effects of phenitoin
no effect of tonsillectomy

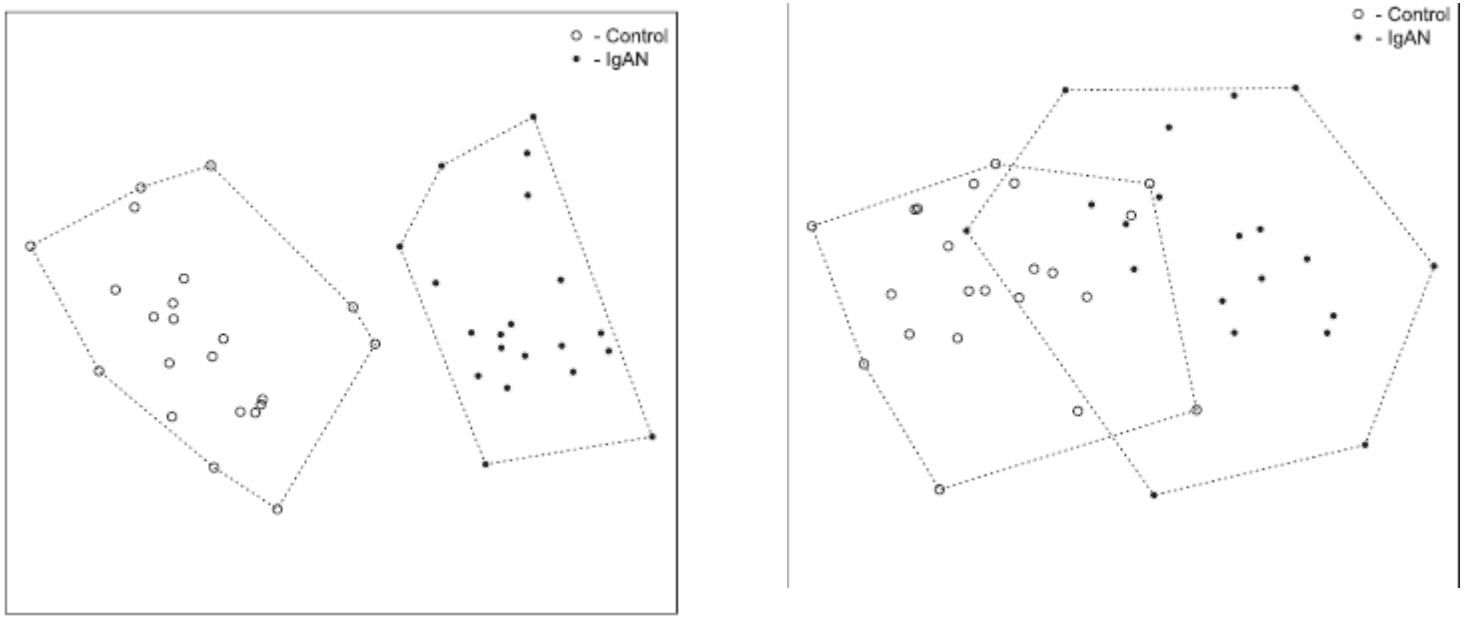
several hits are needed for the development of IgA nephropathy



J Am Soc Nephrol. 2017 28 :2961-2972.

Transcriptomic and Proteomic Profiling Provides Insight into Mesangial Cell Function in IgA Nephropathy

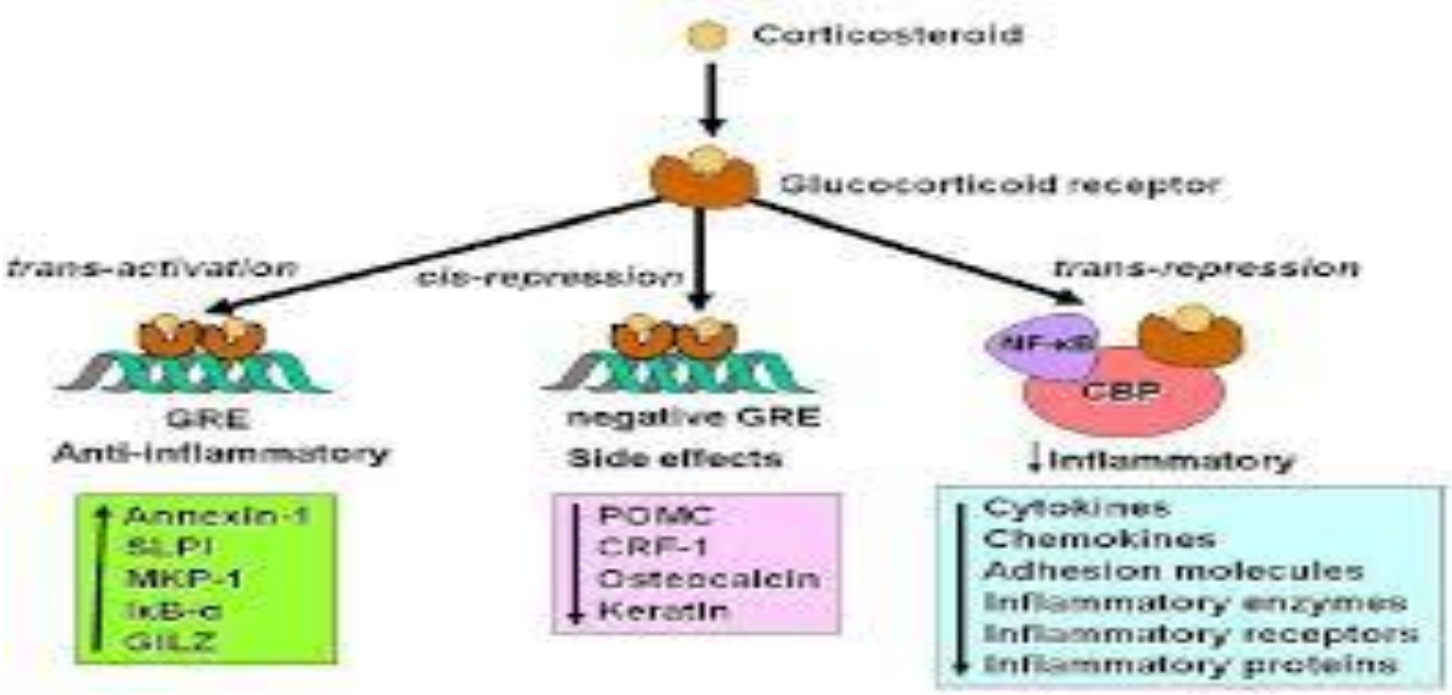
Peidi Liu,* Emelie Lassén,* Viji Nair,† Celine C. Berthier,† Miyuki Suguro,‡ Carina Sihlbom,§ Matthias Kretzler,† Christer Betsholtz,‖¶ Börje Haraldsson,* Wenjun Ju,† Kerstin Ebefors,* and Jenny Nyström*



22 pathways are induced in mesangial cells by Galactose-deficient IgA1, most of which mediate inflammation

IgAN is an inflammatory disease:

corticosteroids have pronounced anti–inflammatory effects and rather weak immunosuppressive activity.



how to select patients that will benefit from corticosteroid therapy?

Berger J, Hinglais N. Intercapillary deposits of IgA-IgG. 1968

Kobayashi Y.
Q J Med 61: 935-943, **1986**

Oral prednisone (40 mg/d tapered over 1–2 years)
in early phase of IgAN (GFR >70 ml/min and proteinuria of 1–2 g/day)

- **reduction in proteinuria**
- **protection from functional decline at 10 years follow-up.**

	Pozzi [9]		Manno [10]		Lv [11]	
	Steroid group	Control group	Steroid group	Control group	Steroid group	Control group
Sample size	43	43	48	49	33	30
Patient characteristics:						
Age (years)	38	40	31.8	34.9	27.8	30.4
Proteinuria (g/day)	2.0	1.8	1.7	1.5	2.5	2.0
eGFR (ml/min/1.73 m^2)	93	87	100.4	97.5	101.2	101.5
RASB during follow-up (%)	44%	40%	100%	100%	100%	100%
Follow-up duration (years)	4.0	4.0	4.8	5.3	2.2	2.3
Risk of experiencing the primary renal outcome	5%	26%	14.8%	47.9%	3.4%	33.8%
Study design	Randomized, open-label, nonblinded		Randomized, open-label, nonblinded		Randomized, open-label, nonblinded	

KDIGO Clinical Practice Guideline for Glomerulonephritis

Treatment of IgAN

10.3.1: We suggest that patients with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

Table 2. Corticosteroid monotherapy

Trial	Pozzi *et al.*, Italy[37,38]	Katafuchi *et al.*, Japan[38]	Hogg *et al.*, United States[26]	Manno *et al.*, Italy[35]	Lv *et al.*, China[34]
Corticosteroid regimen	Intravenous methylprednisolone 1 g/d for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg every other day for 6 months	Oral prednisolone 20 mg/d tapered to 5 mg/d at 18 months	Oral prednisone every other day 60 mg/m^2 for 3 months, then 40 mg/m^2 for 9 months, and then 30 mg/m^2 for 12 months	Oral prednisone for 6 months (1 mg/kg/day for 2 months, then reduced by 0.2 mg/kg/day per month)	Oral prednisone for 6–8 months (0.8–1 mg/kg/day for 2 months, then reduced by 5–10 mg every 2 wk)
Control regimen	Supportive only	Dipyridamole	Placebo	Supportive only	Supportive only
RAS blockade	14% at baseline; allowed during follow-up	2% at baseline; allowed during follow-up	Enalapril if hypertensive	Ramipril in all patients	Cilazapril in all patients
Key outcome in steroid group *versus* control	Ten-year renal survival (=absent doubling of serum creatinine), 53% in controls *versus* 97% in the steroid group	Significant reduction in proteinuria but not ESRD frequency	No benefit in the steroid group *versus* placebo at 2 years	Mean annual loss of GFR 6.2 ml/min in controls *versus* 0.6 ml/min in the steroid group	Significantly fewer patients with a 50% increase in serum creatinine in the steroid group

Therapeutic regimens and outcomes in randomized controlled trials in IgAN patients. RAS, renin-angiotensin system; ESRD, end-stage renal disease.

Relatively high-dose and short-term therapy (P>30 mg/day or high-dose i.v MP pulses for ≤1 year) produced significant **renal protection**,
whereas low-dose, long-term steroid use did not.

(Lv J et al, JASN 2012)

Unmet needs and unanswered questions about the use of corticosteroids (CS) in IgAN

- Effectiveness of CS in patients with
  - suboptimal renal function (eGFR<50 ml/min)
  - advanced CKD (eGFR<30 ml/min)
  - mild-moderate proteinuria (>0.5 <1 g/day)

  - different renal lesions (MEST scores)
  - different clinical phases of activity (attack therapy versus maintenance therapy)

- Exhaustive attention and documentation of adverse events.

BRIEF REVIEW www.jasn.org

JASN 2017; 28:25-33

Corticosteroids in IgA Nephropathy: Lessons from Recent Studies

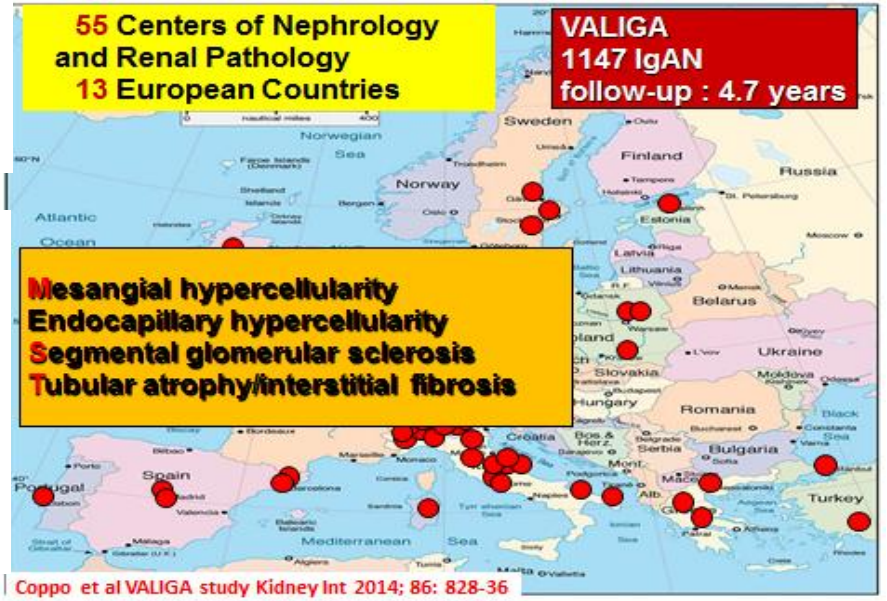
Rosanna Coppo

http://www.kidney-international.org clinical investigation

OPEN

Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments

Rosanna Coppo[1,7], Stéphan Troyanov[2,7], Shubha Bellur[3,8], Daniel Cattran[4,7], H. Terence Cook[5,7], John Feehally[6,7], Ian S.D. Roberts[3,7], Laura Morando[8], Roberta Camilla[8], Vladimir Tesar[8], Sigrid Lunberg[8], Loreto Gesualdo[8], Francesco Emma[8], Cristiana Rollino[8], Alessandro Amore[8], Manuel Praga[8], Sandro Feriozzi[8], Giuseppe Segoloni[8], Antonello Pani[8], Giovanni Cancarini[8], Magalena Durlik[8], Elisabetta Moggia[8], Gianna Mazzucco[8], Costantinos Giannakakis[8], Eva Honsova[8], B. Brigitta Sundelin[8], Anna Maria Di Palma[8], Franco Ferrario[8], Eduardo Gutierrez[8], Anna Maria Asunis[8], Jonathan Barratt[8], Regina Tardanico[8], Agnieszka Perkowska-Ptasinska[8] and on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group[8]



Coppo et al VALIGA study Kidney Int 2014; 86: 828-36

CLINICAL RESEARCH www.jasn.org

Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

Vladimir Tesar,* Stéphan Troyanov,† Shubha Bellur,‡ Jacobien C. Verhave,† H. Terence Cook,§ John Feehally,‖ Ian S.D. Roberts,‡ Daniel Cattran,¶ Rosanna Coppo,** and on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group

Propensity-matched patients in VALIGA cohort: renal outcomes were better in Corticosteroid (CS) +RASB than RASB alone

Outcomes	RASB (184 cases)	RASB+CS (184 cases)	
Change in proteinuria during entire follow-up (g/day)	**-0.3** (-1.1, 0.3)	**-0.8** (-1.6, -0.2)	**<0.001**
Reduction proteinuria to <1 g/day (%)	**54%**	**84 %**	**<0.001**
Rate of renal function decline (mL/min/1.73m^2/year)	-**3.2**± 8.3	**-1.0** ± 7.3	**0.004**
ESRD (%)	**20**	**7**	**0.003**
Combined end-point 50% decrease in eGFR or ESRD (%)	**27**	**12**	**0.008**

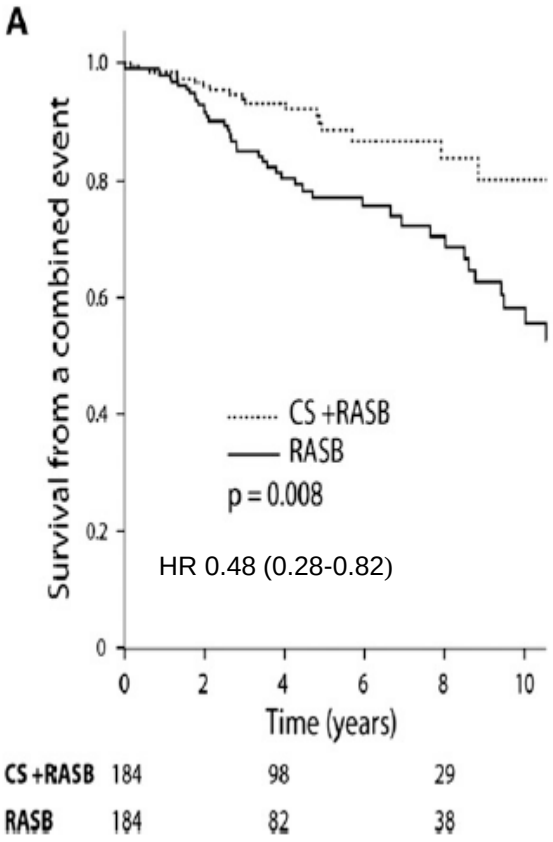
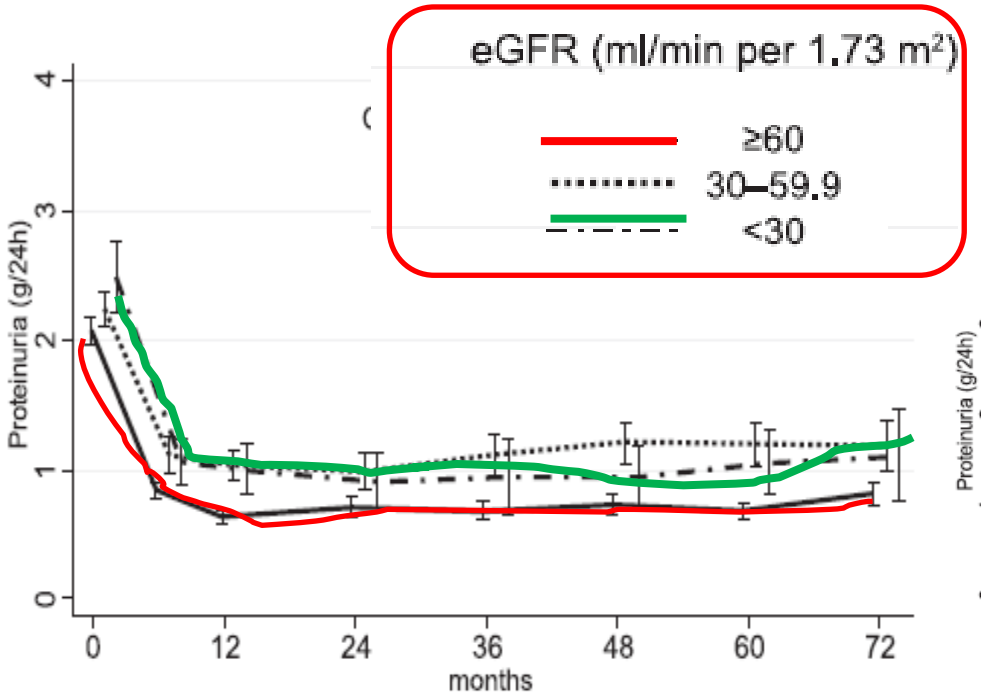
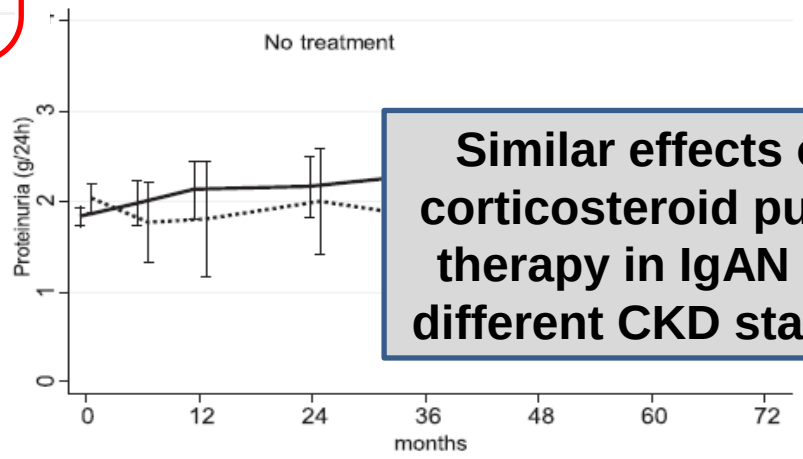


Figure 2. Response to CS and RASB compared with RASB alone in propensity-matched individuals. (A) Entire propensity-matched cohort. (B) Stratified by initial eGFR. *P* values obtained using time-dependent Cox regression.

Changes in proteinuria in IgAN after corticosteroids .
Sarcina C … and Pozzi C Clin J Am Soc Nephrol. 2016, 11:973-81

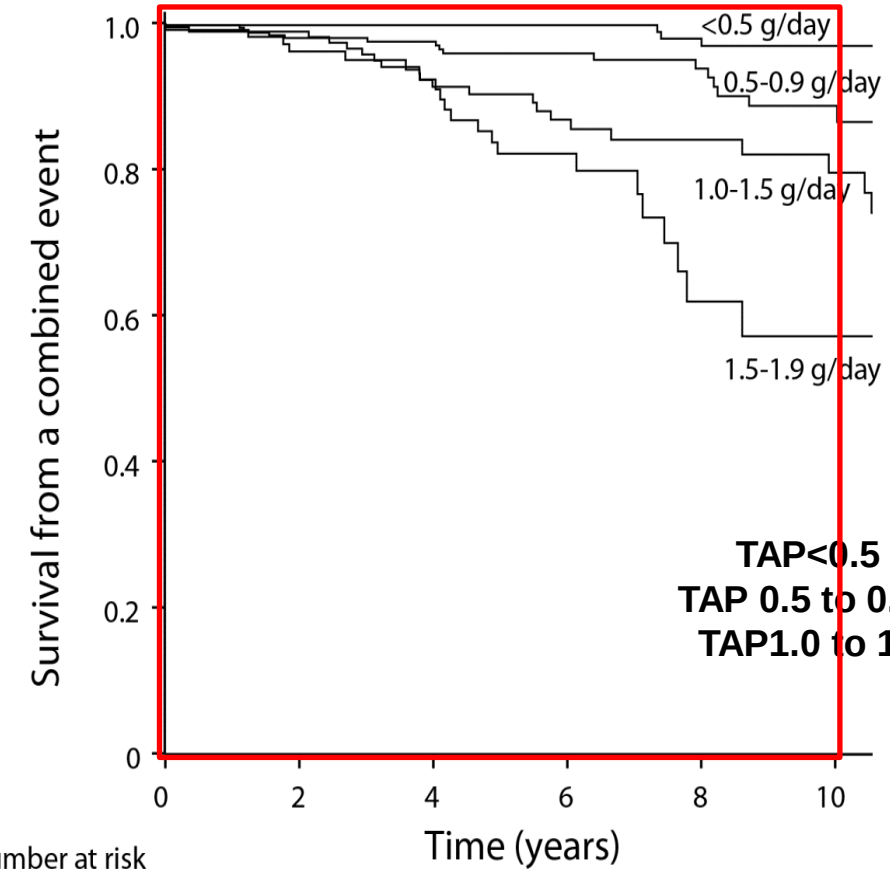




Similar effects of corticosteroid pulse therapy in IgAN in different CKD stages

Predictive value of time average proteinuria (follow-up proteinuria)

(survival from 50% decrease in eGFR and/or ESRD)



TAP<0.5 g/day vs 0.5 to 0.9 g/day : p<0.001
TAP 0.5 to 0.9 g/day vs 1.0 to 1.4 g/day: p= 0.001
TAP1.0 to 1.4 g/day vs 1.5 to 1.9 g/day: p= 0.04

Number at risk

<0.5 g/day	338	198 (59%)	97 (29%)
0.5-0.9 g/day	315	185 (59%)	77 (24%)
1.0-1.5 g/day	167	97 (58%)	46 (28%)
1.5-1.9 g/day	108	68 (63%)	14 (13%)

Coppo et al VALIGA 2014 Kidney Int

Propensity score matched IgAN patients

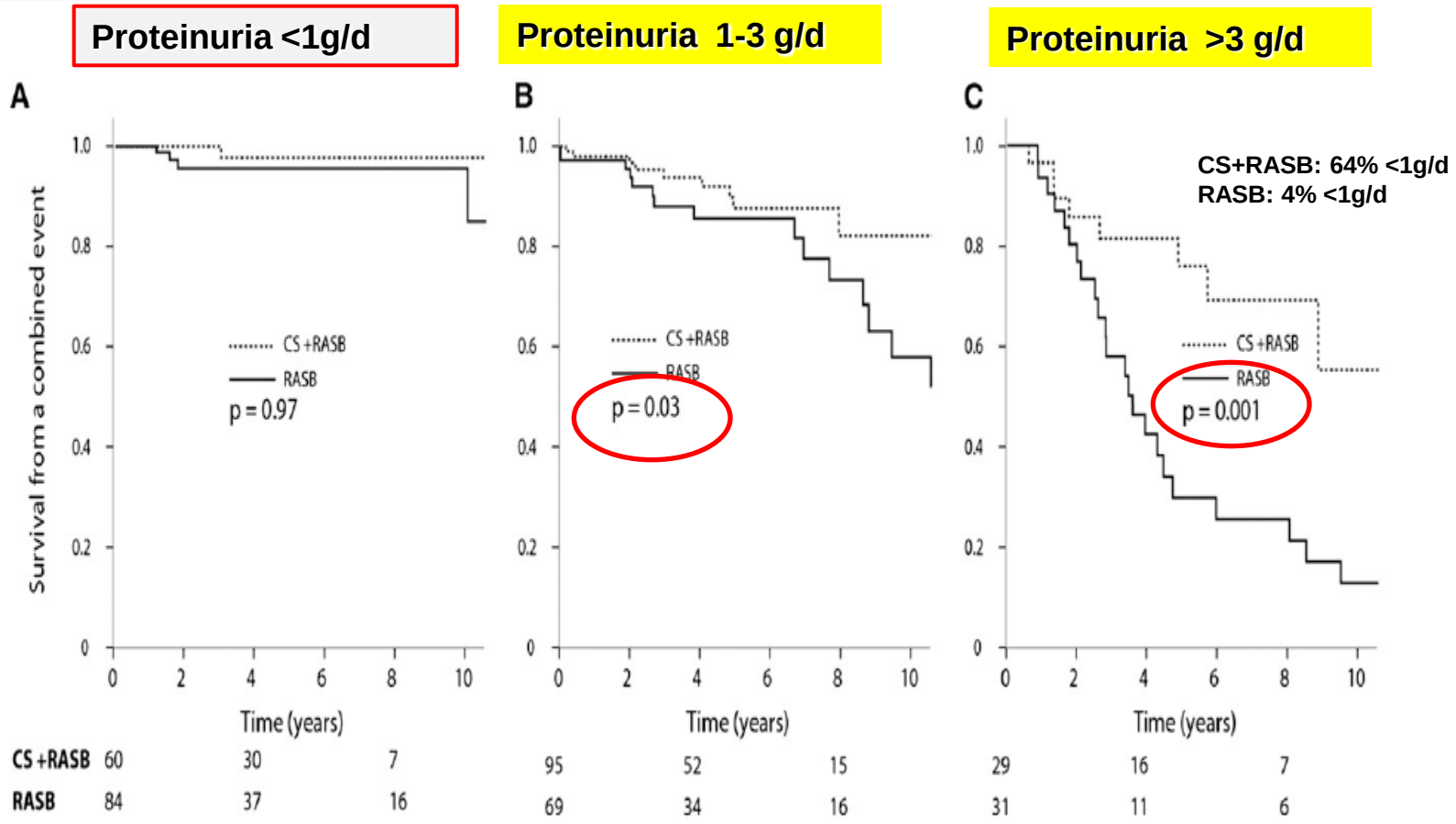


Figure 3. Response to CS and RASB compared with RASB alone in propensity-matched individuals stratified by proteinuria during follow-up, prior to CS in the CS-RASB group. (A) Proteinuria <1 g/d. (B) Proteinuria 1 to <3 g/d. (C) proteinuria ≥3 g/d. Time-average proteinuria was prior to CS in the treated group. *P* values obtained using time-dependent Cox regression. There was no evident benefit of CS in those with a proteinuria <1 g/d.

Questions still open about Corticosteroids in IgAN
- **suboptimal renal function (eGFR<50 ml/min)**
- **advanced CKD (eGFR<30 ml/min)**
- **mild-moderate proteinuria (>0.5 <1 g/day)**

Benefits of CS in addition to RASB in IgAN patients
with proteinuria >1 g/day, even with an initial eGFR <50 ml/min/ 1.73 m2
CS benefits extended to CKD 3-4.
No rapid benefits when proteinuria <1g/day, but need of long term follow- up

N ENGL J MED 373;23 NEJM.ORG DECEMBER 3, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

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

Persistent proteinuria > 0.75 g/day, <3.5 g/day is spite of

6 months of comprehensive supportive care

- **supportive care alone**
- **supportive care with the addition of immunosuppressive therapy**

a) **eGFR of > 60 ml/min: 6 months glucocorticoid (9 x1g IV MP pulses+ OP 0.5mg/kg.eod**

b) **eGFR > 30 <59 ml/min: 3 years immunosuppression : cyclophosphamide 1.5 mg/kg for 3 months, followed by azathioprine 1.5 mg/kg for months 4-36**

plus

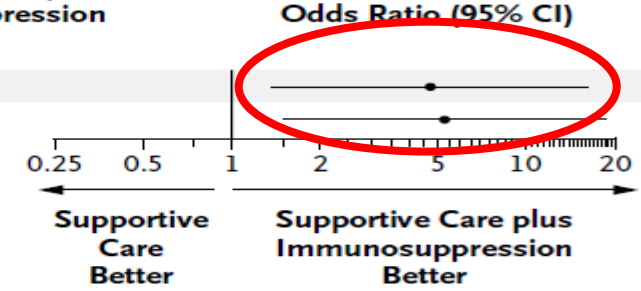
oral prednisolone 40 mg/day, tapered to discontinuation at month 36

full clinical remission :

<0.2 UP/Ucr with stable eGFR (decrease in eGFR < 5 ml/min /1.73m2)

A In Full Clinical Remission

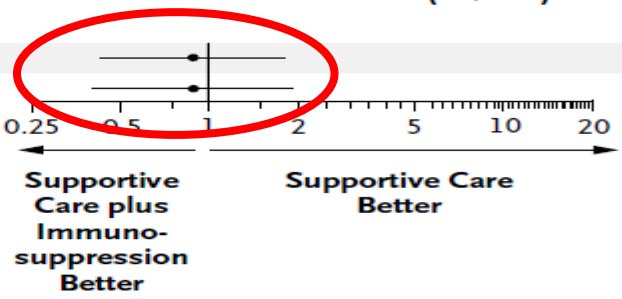
Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	4/80	14/82	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72	14/71	5.38 (1.55–18.66)	0.008



decrease in the eGFR of at least 15 ml/min/1.73 m2

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



J Am Soc Nephrol 29: 317–325, 2018.

CLINICAL RESEARCH www.jasn.org

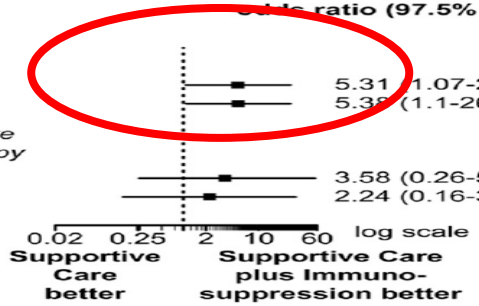
Effects of Two Immunosuppressive Treatment Protocols for IgA Nephropathy

Thomas Rauen,[1] Christina Fitzner,[2] Frank Eitner,[1,3] Claudia Sommerer,[4] Martin Zeier,[4] Britta Otte,[5] Ulf Panzer,[6] Harm Peters,[7,8] Urs Benck,[9] Peter R. Mertens,[10] Uwe Kuhlmann,[11] Oliver Witzke,[12,13] Oliver Gross,[14] Volker Vielhauer,[15] Johannes F.E. Mann,[16] Ralf-Dieter Hilgers,[2] and Jürgen Floege[1]

A

In Full Clinical Remission

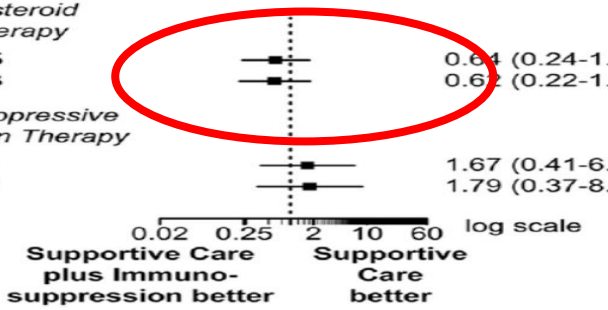
subgroup	no. of events/total no.		odds ratio (97.5% CI)	p value
high-GFR	*Supportive Care*	*Corticosteroid Monotherapy*		
full analysis set	3/54	11/55	5.31 (1.07-26.36)	0.02
available cases	3/51	11/47	5.38 (1.1-26.28)	0.018
low-GFR	*Supportive Care*	*Immunosuppressive Combination Therapy*		
full analysis set	1/26	3/27	3.58 (0.26-55.89)	0.302
available cases	1/21	3/24	2.24 (0.16-30.72)	0.491



B

GFR Decrease at least 15 ml/min/1.73 m²

subgroup	no. of events/total no.		odds ratio (97.5% CI)	p value
high-GFR	*Supportive Care*	*Corticosteroid Monotherapy*		
full analysis set	16/54	12/55	0.64 (0.24-1.75)	0.324
available cases	14/52	10/53	0.62 (0.22-1.8)	0.318
low-GFR	*Supportive Care*	*Immunosuppressive Combination Therapy*		
full analysis set	6/26	9/27	1.67 (0.41-6.79)	0.415
available cases	4/24	7/25	1.79 (0.37-8.64)	0.41



The STOP-IgAN trial

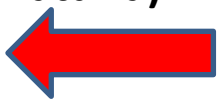
- **Was powered to detect differences in clinical remission, which did it in favour of CS/IS. Changes of proteinuria during the follow-up need a long observation to produce effects on GFR decline protection**

- **Small changes in eGFR 15 ml/min are not a valid surrogate end-point. The RCT was too short and underpowered to detect established outcomes like 50% change in eGFR**

nejm.org March 10, 2016

The New England Journal of Medicine correspondence

The STOP-IgAN trial is the best evidence yet that adding an aggressive immunosuppressive regimen to aggressive kidney-protective therapies provides some benefit after 3 years of treatment (e.g., greater likelihood of complete remission of proteinuria and clearing of microscopic hematuria) but at a substantial cost (infection and one death from sepsis).



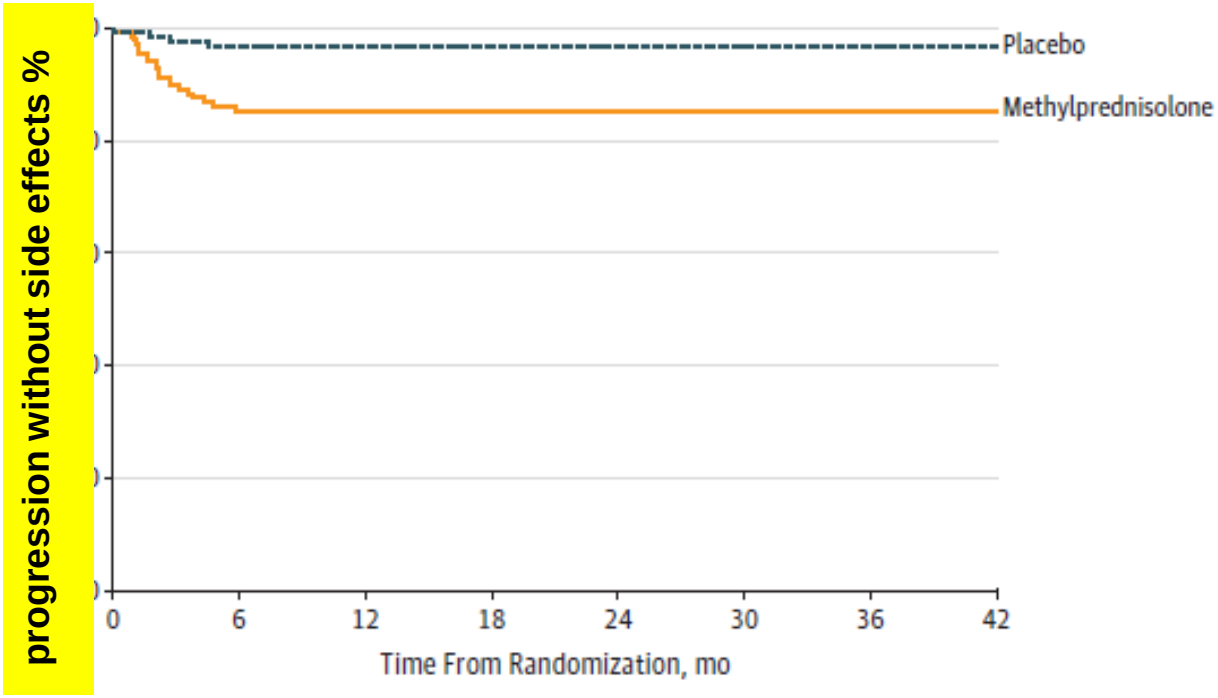
Isabelle Ayoub, Lee Hebert, Brad H. Rovin, M.D.

JAMA | Original Investigation

JAMA. 2017;318(5):432-442.

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

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



TESTING RCT

- **Proteinuria > 1 g/day in spite of 3 months of optimized RASB supportive care,**
- **eGFR 20 to 120 mL/min/1.73m2.**

- **Randomized to oral methylprednisolone (0.6-0.8mg/kg/day) or placebo for 2 months, then weaning over 4 to 6 months.**

- **262 participants randomized (eGFR, 59 mL/min, proteinuria 2.40 g/d)**
  followed over a median of 2.1 years

recruitment was discontinued because of excess serious adverse events.

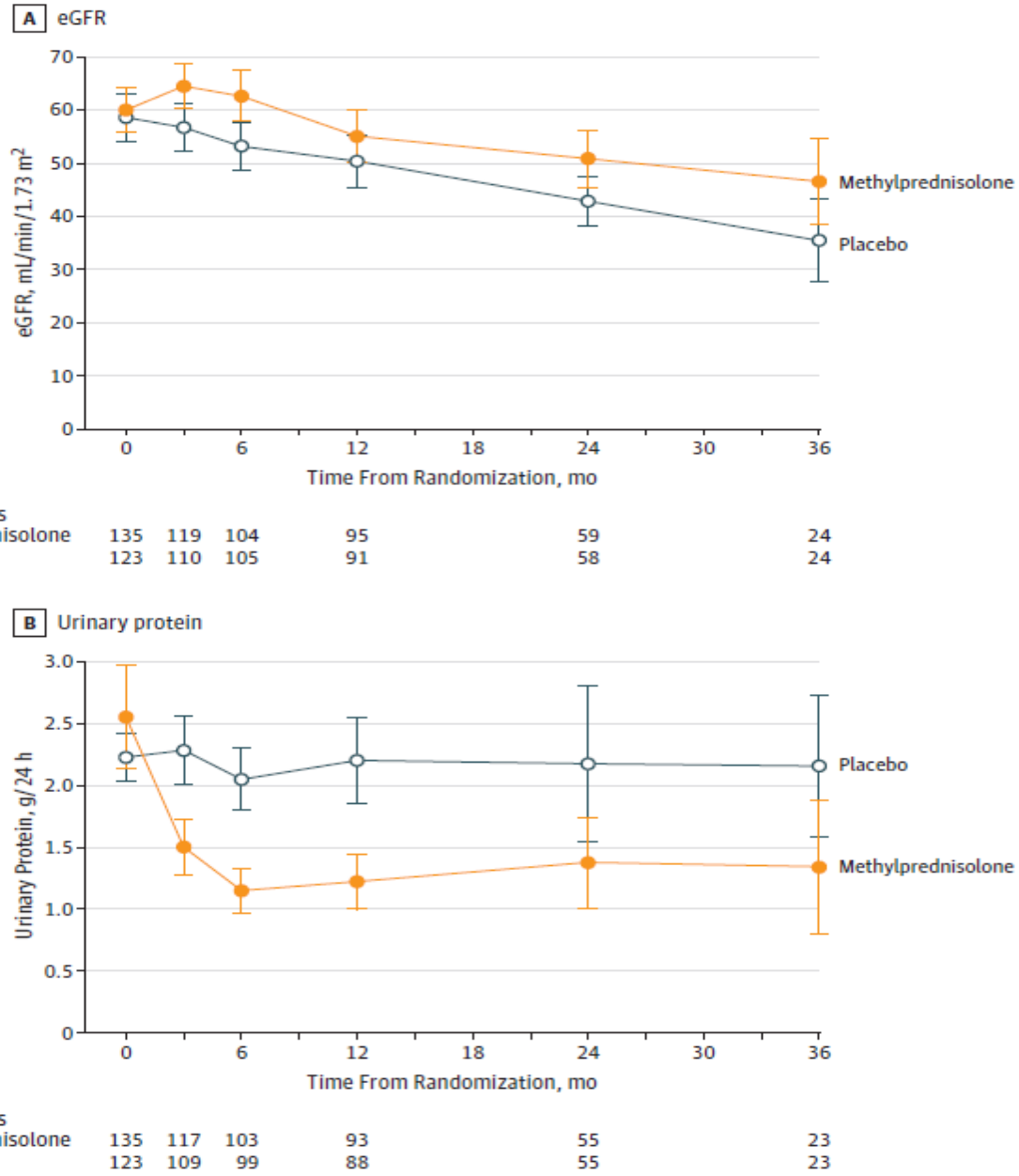
15% in methylprednisolone group vs 3.2% in placebo (P = .001)

mostly due to serious infections (8.1% vs 0; P < .001), including 2 deaths.

- **Primary renal outcome (ESRD or a 40% decrease in eGFR)**

in 6% in methylprednisolone group vs 16% in placebo group (P = .02)

Figure 4. Effect of Methylprednisolone Therapy on eGFR and Proteinuria During Follow-up



(Sarcina C and Pozzi C, CJASN 20

Adverse events (AE) and renal function

Renal function	AE in CS alone	AE in CS+azathioprine
Study 1 (Lancet 1999) **eGFR 90 ml/min**	**2.3%**	-
Study 2 (JASN 2010) **eGFR 81 ml/min**	**5.7%**	**16.8%**
Study 3 (JN 2013) **eGFR 34 ml/min**	**15.4%**	**30.0%**

STOP
Rauen et al , NEJM 2015
33% of patients eGFR <60 ml/min

TESTING
Lv et al, JAMA 2017
38.5% of patients eGFR<50 ml/min

Patients enrolled in all the RCTs were selected only on the basis of persistent proteinuria >1 g/day

histopathology was not considered (active versus sclerotic lesions)

Kidney Int. 2016 Jan;89(1):167-75.

www.kidney-international.org clinical investigation

The MEST score provides earlier risk prediction in IgA nephropathy

see commentary on page 19

Sean J. Barbour[1,2,3], Gabriela Espino-Hernandez[2], Heather N. Reich[4], Rosanna Coppo[5], Ian S.D. Roberts[6], John Feehally[7], Andrew M. Herzenberg[4,8] and Daniel C. Cattran[4]; for the Oxford Derivation, North American Validation and VALIGA Consortia

901 IgAN from
the Oxford Classification study (167 cases)
North American validation study (87 cases)
VALIGA validation study (647 cases)
Primary outcome (50% decrease in eGFR or ESRD).

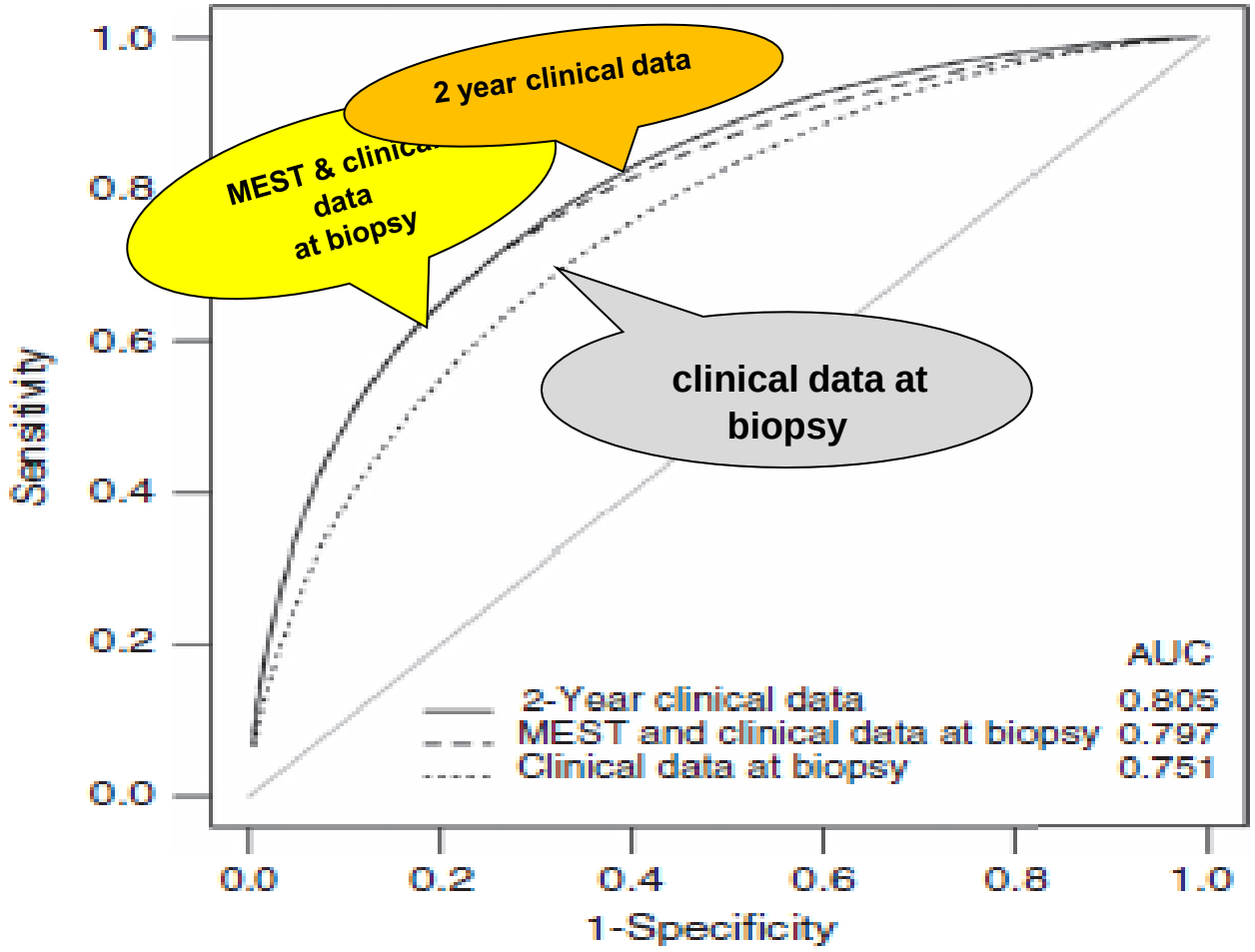


Figure 3 | The receiver operating curves for models predicting the 5-year risk of a 50% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD) using clinical data at biopsy with or without MEST, and 2-year clinical data alone. AUC, area under the curve.

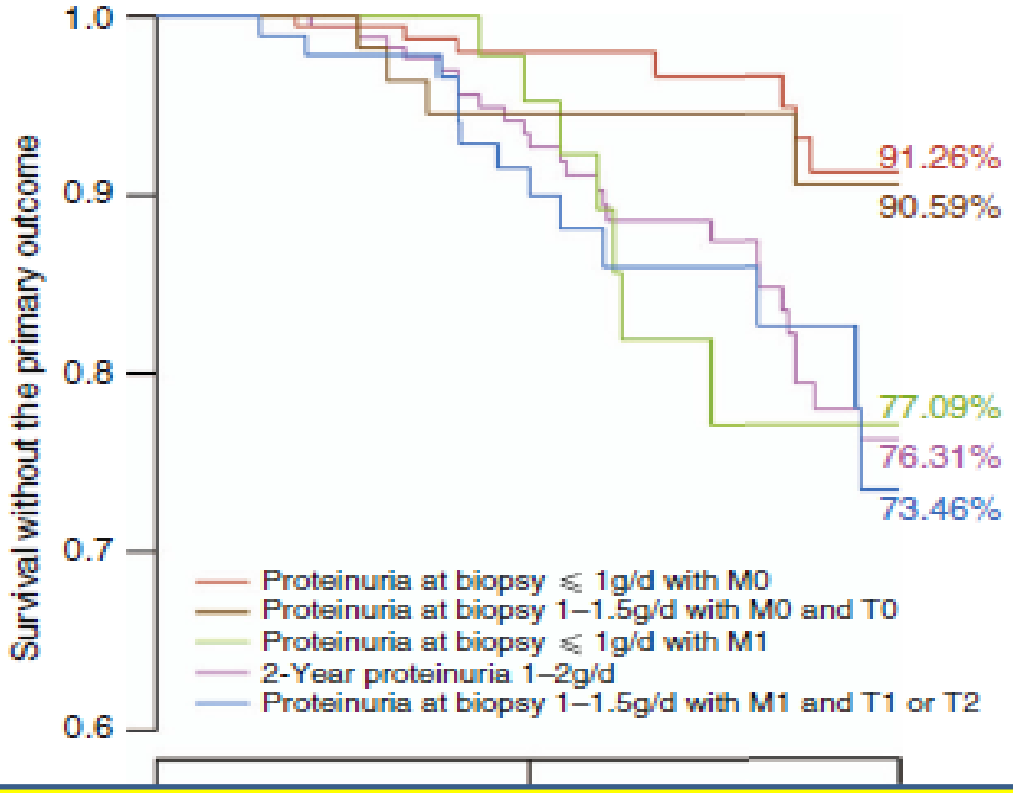
www.kidney-international.org

Kidney Int. 2016 Jan;89(1):167-75.

The MEST score provides earlier risk prediction in IgA nephropathy

see commentary on page 19

Sean J. Barbour[1,2,3], Gabriela Espino-Hernandez[2], Heather N. Reich[4], Rosanna Coppo[5], Ian S.D. Roberts[6], John Feehally[7], Andrew M. Herzenberg[4,8] and Daniel C. Cattran[4]; for the Oxford Derivation, North American Validation and VALIGA Consortia



proteinuria (UP) at RB < 1g/d with M0

UP at RB ≤ 1g/d, and M1

2-yrs follow-up UP 1-2 g/d qualified for steroids by KIDGO

UP at RB 1-1.5 g/d, and M1 and T1/2

Patients with M0 and T0 have low risk even if UP 1-1.5 g/day

Patients with M1 and UP at biopsy < 1g/day are at high risk

VALIGA observational study study

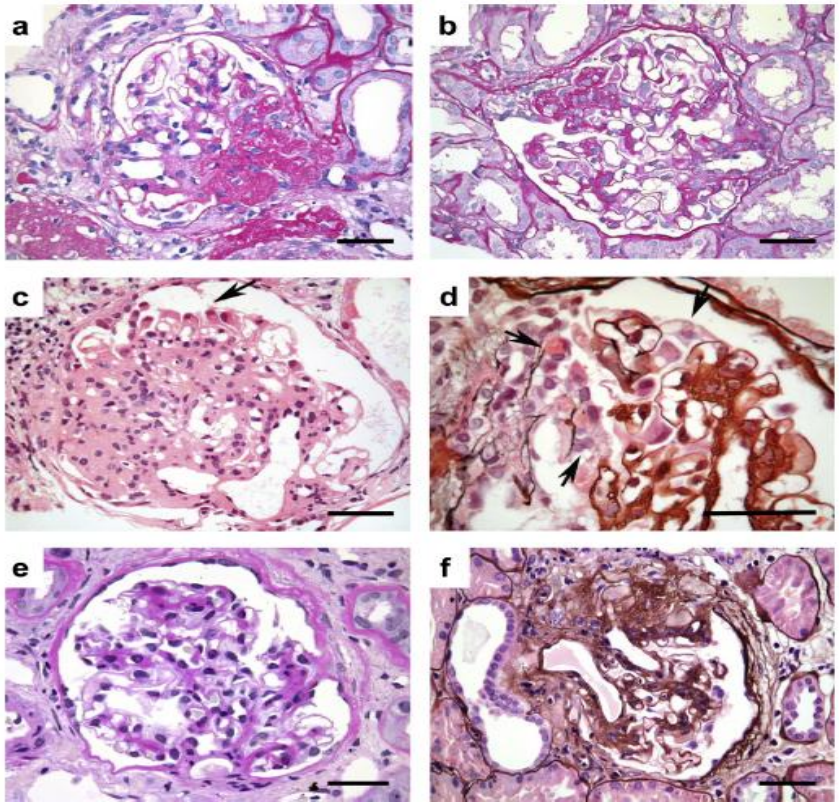
Outcomes in propensity score matched IgAN patients with MST lesions

	RASB	Corticosteroids+RASB	p
M1			
eGFR yearly loss ml/min/y	- 6.1	-1.8	0.001
Final proteinuria < 1 g	57%	80%	0.008

Kidney Int. 2017 Jan;91(1):235-243.

Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy

Shubha S. Bellur[1], Fanny Lepeytre[2], Olga Vorobyeva[1], Stéphan Troyanov[2], H. Terence Cook[3] and Ian S.D. Roberts[1]; on behalf of the International IgA Nephropathy Working Group



(b) Glomerular tip lesion

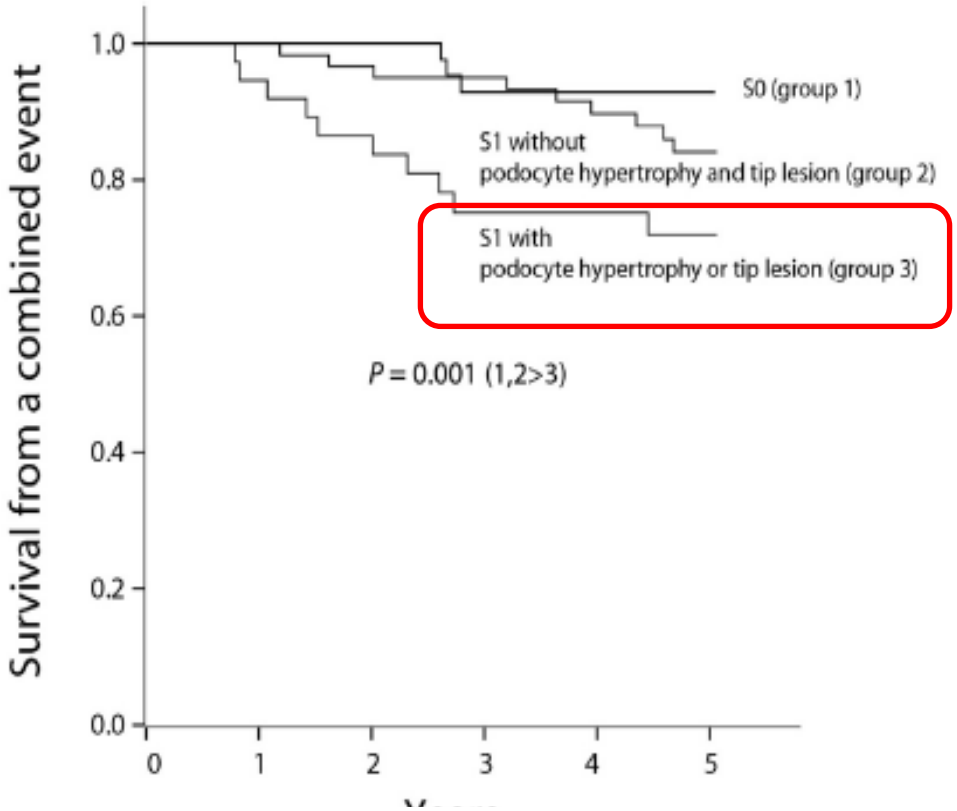
Segmental sclerosis
podocyte hypertrophy

Capsular adhesion

Perihilar segmental sclerosis and hyalinosis

Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy

Shubha S. Bellur[1], Fanny Lepeytre[2], Olga Vor
Ian S.D. Roberts[1]; on behalf of the Internatio



Podocyte hypertrophy or tip lesions are markers of podocyte injury and in untreated patients are associated with

- **proteinuria increase**
- **worse prognosis**

J Nephrol 2016

J Nephrol
DOI 10.1007/s40620-015-0227-8

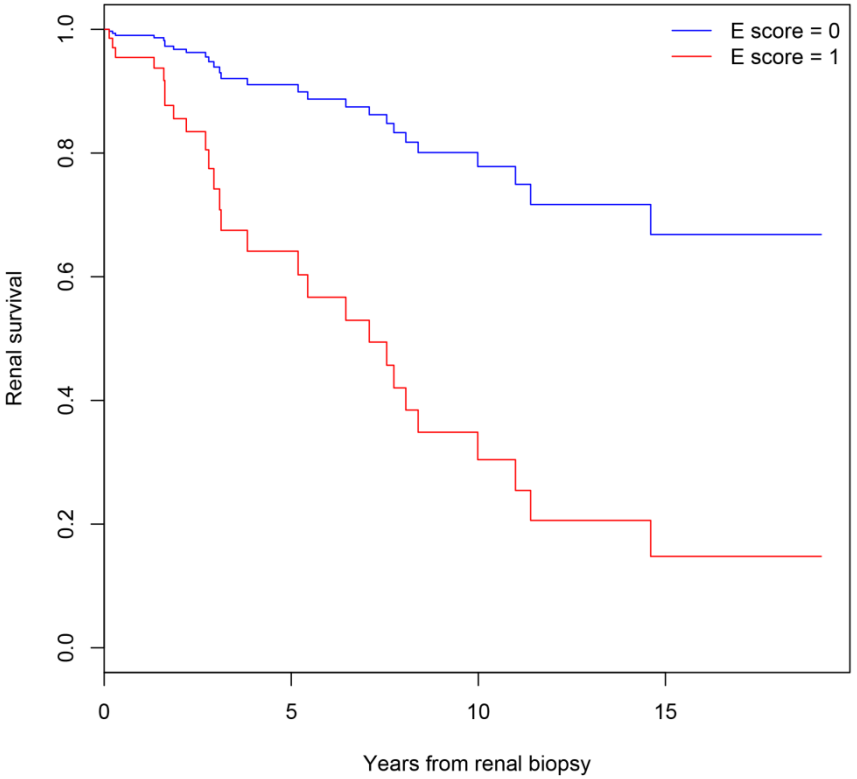
ORIGINAL ARTICLE

Prognostic value of endocapillary hypercellularity in IgA nephropathy patients with no immunosuppression

Aron Chakera[1] · Clare MacEwen[2] · Shubha S. Bellur[3] · La-or Chompuk[3] · Daniel Lunn[4] · Ian S. D. Roberts[3]

In these patients without corticosteroid treatment

E1 score was predictor of worse renal survival. HR 4.75 , p<0.001



CLINICAL RESEARCH www.jasn.org

J Am Soc Nephrol. 2017 Feb;28(2):691-701.

A Multicenter Study of the Predictive Value of Crescents in IgA Nephropathy

Mark Haas,* Jacobien C. Verhave,† Zhi-Hong Liu,‡ Charles E. Alpers,§ Jonathan Barratt,‖ Jan U. Becker,¶ Daniel Cattran,** H. Terence Cook,†† Rosanna Coppo,‡‡ John Feehally,‖ Antonello Pani,§§ Agnieszka Perkowska-Ptasinska,‖‖ Ian S.D. Roberts,¶¶ Maria Fernanda Soares,*** Hernan Trimarchi,††† Suxia Wang,‡‡‡ Yukio Yuzawa,§§§ Hong Zhang,‖‖‖ Stéphan Troyanov,¶¶¶ and Ritsuko Katafuchi****

Pooled data: Oxford, VALIGA, China and Japan cohorts

(3096 patients, 36% with crescents)

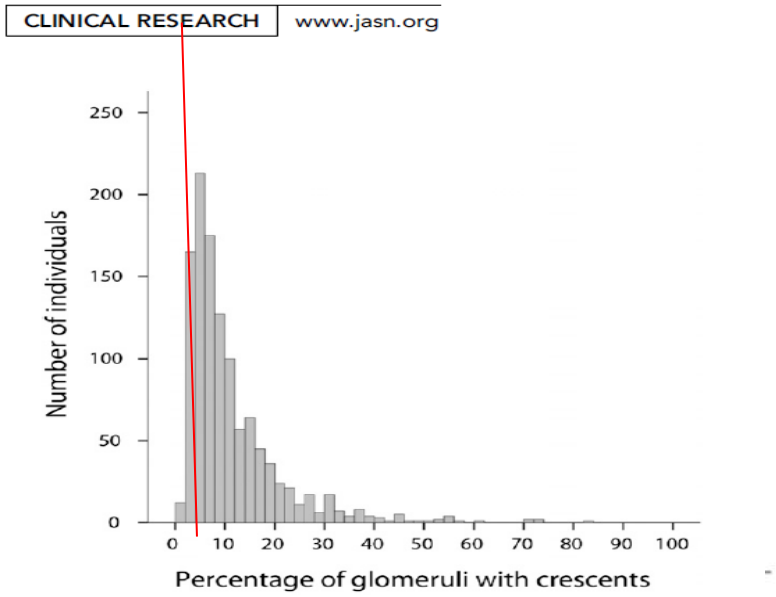
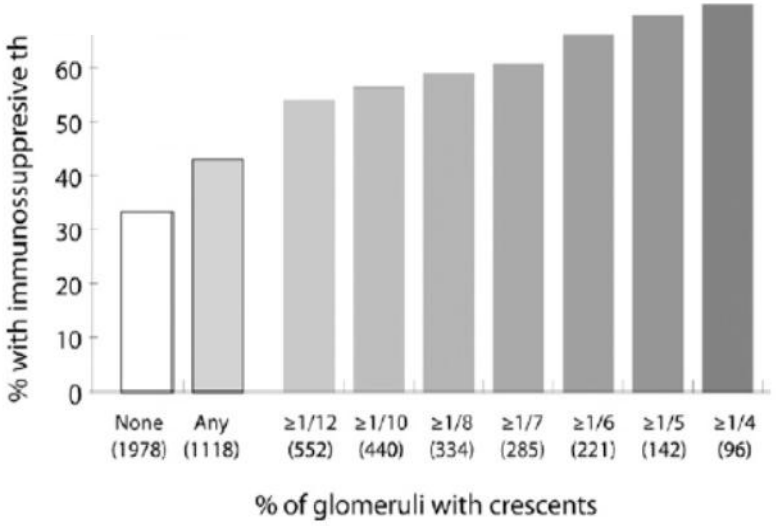
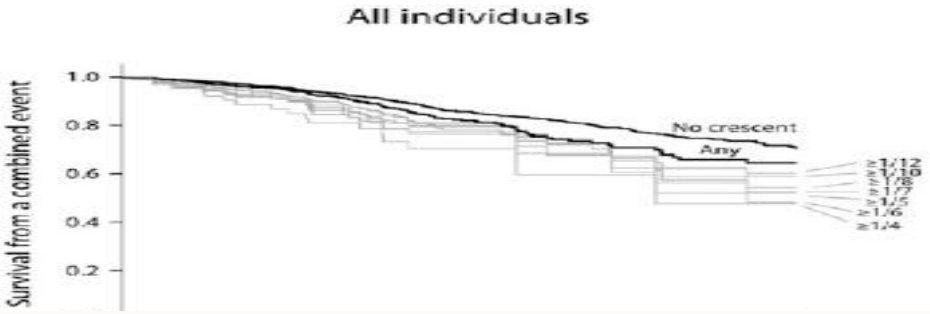


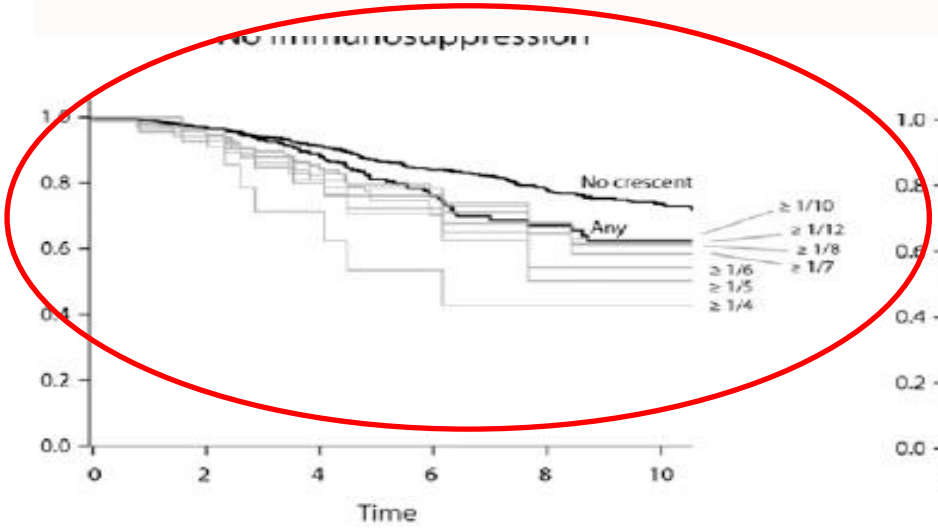
Figure 1. Distribution of the percentage of glomeruli with crescents in biopsies with any crescents. Crescents were present in 1118 (36%) of 3096 total biopsies.

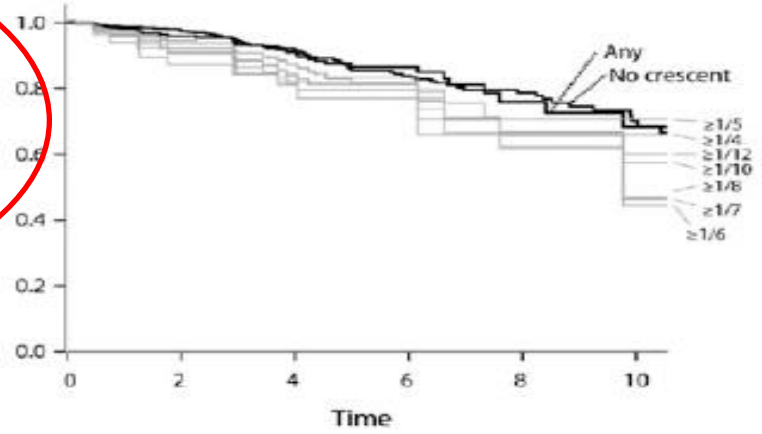


Crescents correlated with E1 and were associated with immunosuppressors.



Crescents were predictive of combined event,
but only in patients not receiving immunosuppressors.





Crescents in >25% had an unfavorable outcome independently from treatment

Kidney Int. 2017 May;91(5):1014-1021.

Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group

Hernán Trimarchi[1], Jonathan Barratt[2], Daniel C. Cattran[3], H. Terence Cook[4], Rosanna Coppo[5], Mark Haas[6], Zhi-Hong Liu[7], Ian S.D. Roberts[8], Yukio Yuzawa[9], Hong Zhang[10] and John Feehally[2] on behalf of the IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society[1]; for Conference Participants[11]

MEST-C :

C0: no crescents

C1 < 25% of glomeruli

C2 25% or more glomeruli with crescents

Is it time to design new RCTs,
looking for personalized teatments of IgAN
considering pathology lesions?

AJKD
Original Investigation
Am J Kidney Dis. 2017;69(6):788-795

Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

Jin-Hua Hou, MD,[1,] Wei-Bo Le, PhD,[1,*] Nan Chen, MD,[2] Wei-Ming Wang, PhD,[2] Zhang-Suo Liu, MD,[3] Dong Liu, PhD,[3] Jiang-Hua Chen, MD,[4] Jiong Tian, PhD,[4] Ping Fu, MD, PhD,[5] Zhang-Xue Hu, MD,[5] Cai-Hong Zeng, PhD,[1] Shao-Shan Liang, MD,[1] Min-Lin Zhou, MD,[1] Hai-Tao Zhang, MD,[1] and Zhi-Hong Liu, MD[1]*

- proteinuria >1.0 g/24 h, eGFR >30 ml/min

Prednisone 0.8-1 /Kg /d 2 mo, tapering 4 mo
vs MMF +

- biopsy within 1 month
- crescents (>10 <50% of glomeruli)
- endocapillary hypercellularity or glomerular necro
- tubular atrophy/interstitial fibrosis <50%

A good example of RCT with new design

- Primary end poi complete remission at 6-12 months (UP undete able Cr ,not >25% baseline).
- Seconda oints: time to remission and cha ctive proliferative lesions on a repeat biopsy.

MMF+ prednisone half doses versus full-dose prednisone did not differ in reducing proteinuria, but fewer adverse events with similar results.

For all patients with IgAN and proteinuria > 0.75 <3.5 g/day:
rigorous supportive care targeting RAS, dysmetabolism and lifestyle

is additional corticosteroid therapy needed?

Addition of corticosteroids to supportive care induces reduction in proteinuria
possible reno-protective effects on the long term (**)
benefits also when GFR < 50 ml/min71.73m2 (*)
increase in adverse events but mostly in cases with impaired renal function (**)

No when
proteinuria 0.75- 1.5 g/day and
negative MEST scores (§)

YES when IgAN is in progression with rapid loss of GFR (**)

YES when risk factors are present (**)

Patients at risk of progression thought to benefit from corticosteroids:
persistent proteinuria > 3 g/day (**)
Persistent proteinuria >1 g/day (*)
proteinuria < 1 g/day with M1 or E1 or S1 with podocytopathy or when C 1- C2 (§)

§ suggestion

* consistent indication

** strong indication

Coppo 2017 JASN

Patients enrolled in all the RCTs were selected only on the basis of persistent proteinuria >1 g/day

histopathology was not considered
(active versus sclerotic lesions)

rapidity of progression over the previous weeks/months was not considered
(fast versus indolent course)

J Am Soc Nephrol 13: 142–148, 2002

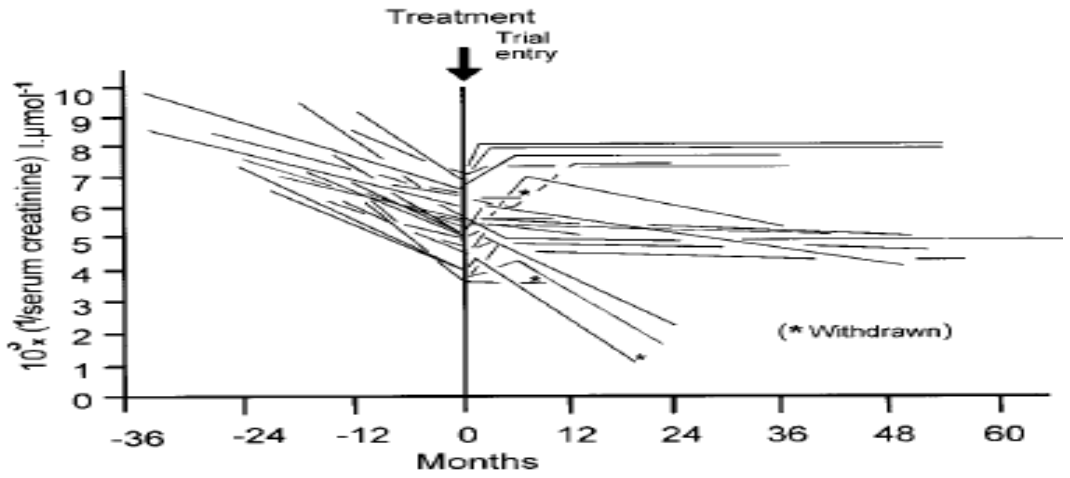
Controlled Prospective Trial of Prednisolone and Cytotoxics in Progressive IgA Nephropathy

FRANCIS W. BALLARDIE* and IAN S. D. ROBERTS‡

sCr > 1.5 mg/dl, worsening e-GFR & expected ESRD in 5 years proteinuria 4-4.8 g/day.

Prednisone for 2 years, cyclophosphamide for 3 months, azathioprine for 2 years

J Am Soc Nephrol 13: 142–148, 2002



Clinical & Experimental Immunology
The Journal of Translational Immunology

Clinical and Experimental Immunology

2016 Nov;186:115-133.

F. M. Rasche,* F. Keller,†
W. G. Rasche,‡ S. Schiekofer,§
A. Boldt,¶ U. Sack¶ and J. Fahnert**

Why, when and how should immunosuppressive therapy considered in patients with immunoglobulin A nephropathy?

Progressive course of IgAN and RPGN-IgAN

Progressive decrease of renal function (ΔGFR > 3 ml/min within 3 months or > 12 ml/min per year or > 10% increase of serum creatinine within 3 months) or refractory high proteinuria > 1 g/day or crescents in renal biopsy

and normal kidney size and eGFR > 10 ml/min

I: CyC pulses with steroid pulse therapy and high dose orally corticosteroid Induction (month 1-2)

M: MPA with low dose prednisolone

Should we in the future continue to expose patients with IgAN to the systemic effects of steroids?

Nephrol Dial Transplant (2014) 0: 1–7
doi: 10.1093/ndt/gfu343

ndt
Nephrology Dialysis Transplantation

Full Review

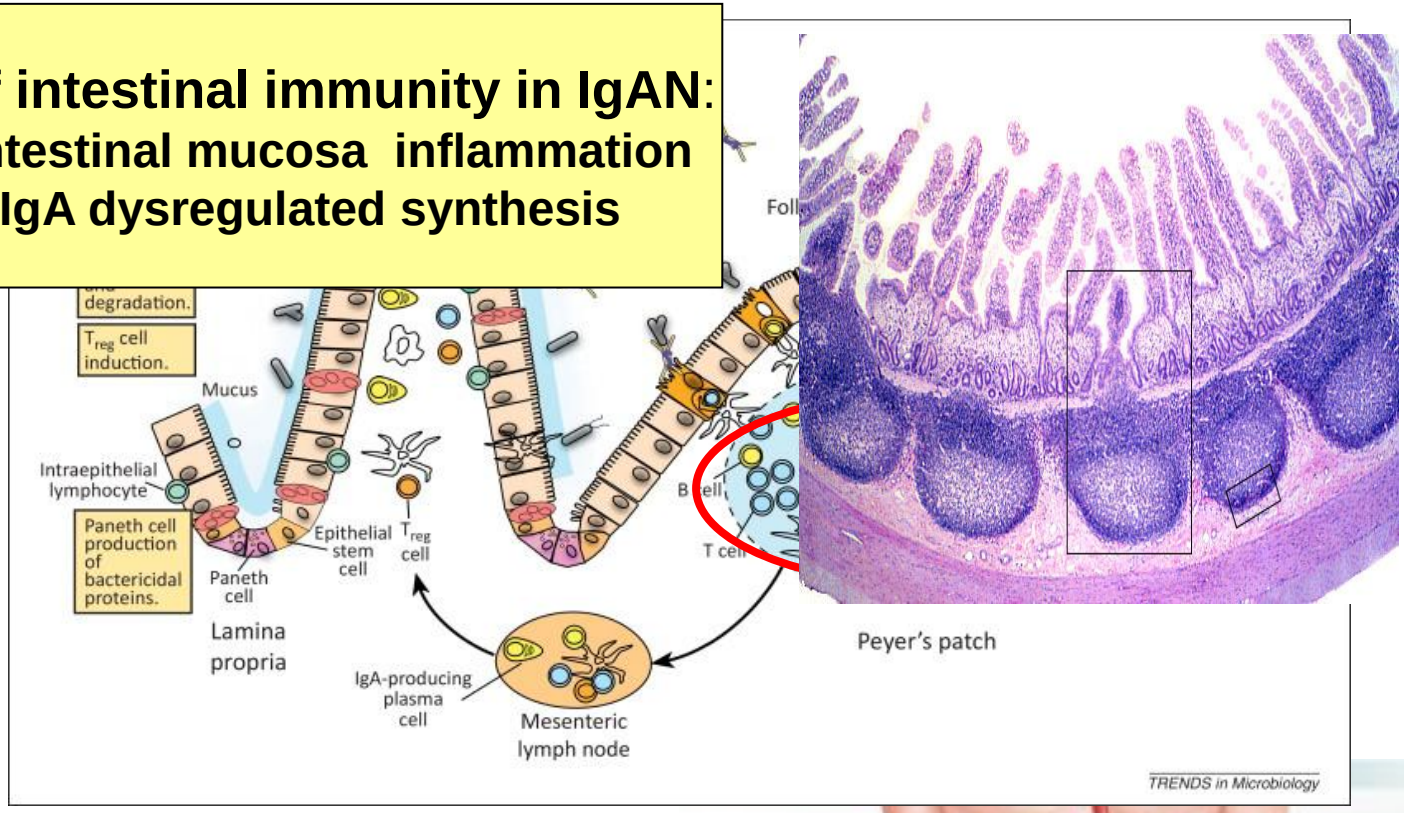
The intestine–renal connection in IgA nephropathy

Rosanna Coppo

Nephrology, Dialysis and Transplantation Unit, University and Hospital Health Agency "Città della Salute e della Scienza di Torino", Regina Margherita Children's Hospital, Turin, Italy

involvement of intestinal mucosal immunity in the pathogenesis of IgAN: focus on the the gut-kidney axis

Activation of intestinal immunity in IgAN: subclinical intestinal mucosa inflammation leading to IgA dysregulated synthesis



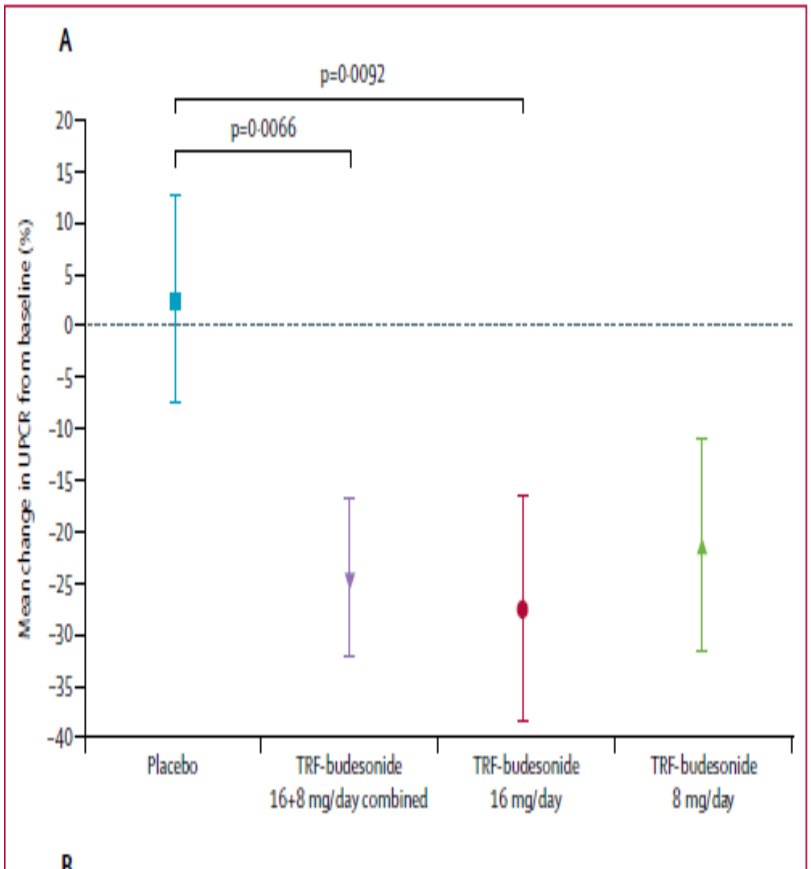
Sites of mucosal B cell induction: lower ileum and ascending colon with high density of Peyer's patches.

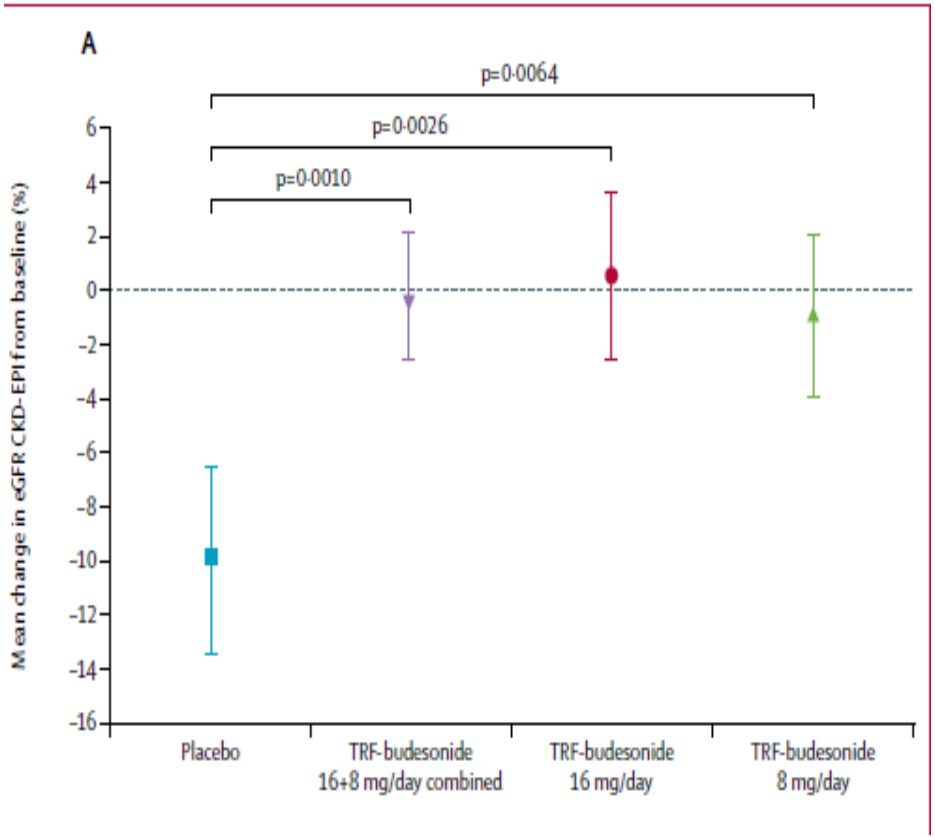
target release formulation of the glucocorticoid budesonide: coated starch capsules for site-specific drug delivery at the ileo-cecal junction

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

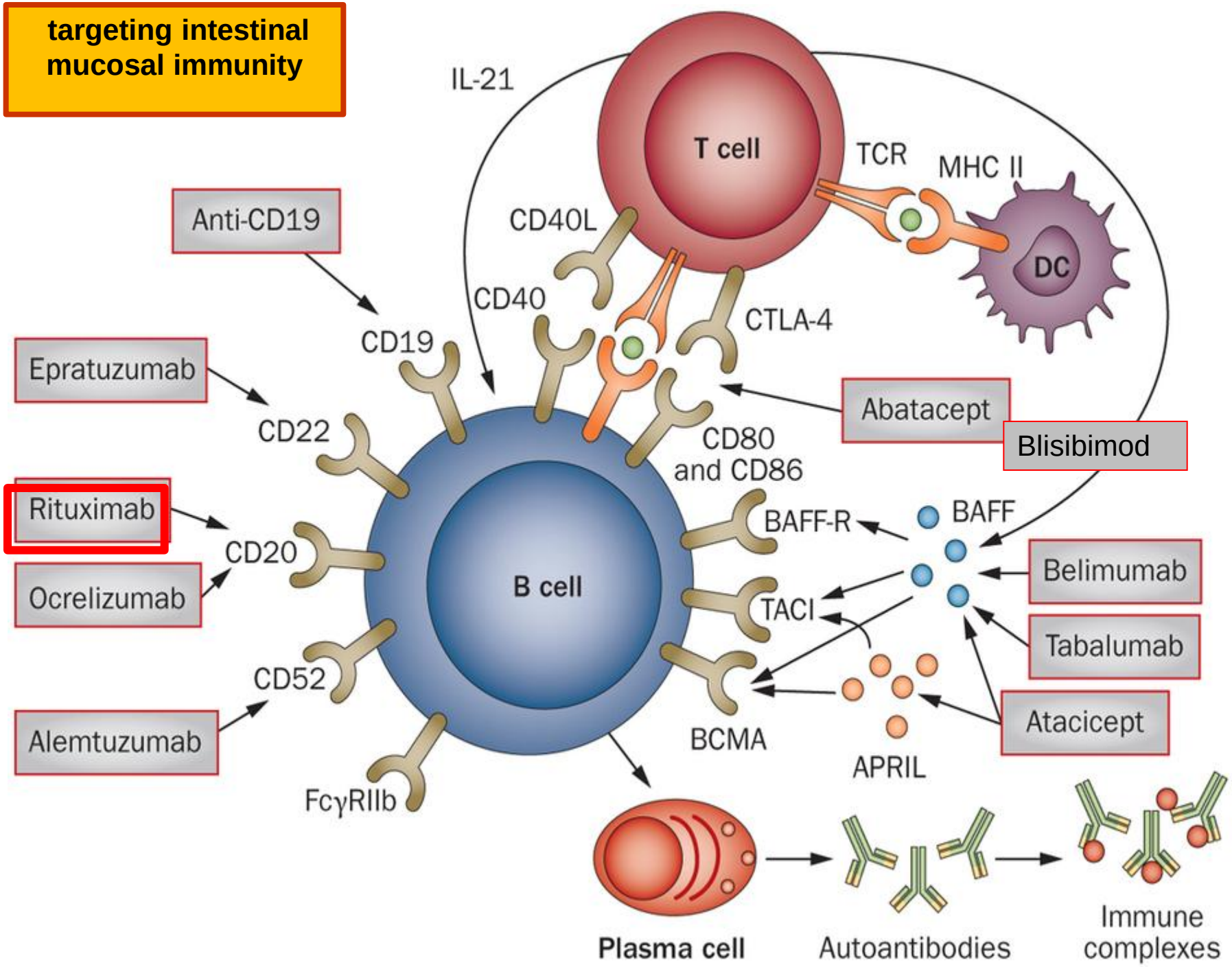
Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

www.thelancet.com **Published online March 28, 2017 http://dx.doi.o**





targeting intestinal mucosal immunity



CLINICAL RESEARCH www.jasn.org J Am Soc Nephrol 28: 1306–1313, 2017.

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

Richard A. Lafayette,* Pietro A. Canetta,† Brad H. Rovin,‡ Gerald B. Appel,† Jan Novak,§ Karl A. Nath,‖ Sanjeev Sethi,¶ James A. Tumlin,** Kshama Mehta,* Marie Hogan,‖ Stephen Erickson,‖ Bruce A. Julian,§†† Nelson Leung,‖ Felicity T. Enders,‡‡ Rhubell Brown,§ Barbora Knoppova,§§§ Stacy Hall,§ and Fernando C. Fervenza‖

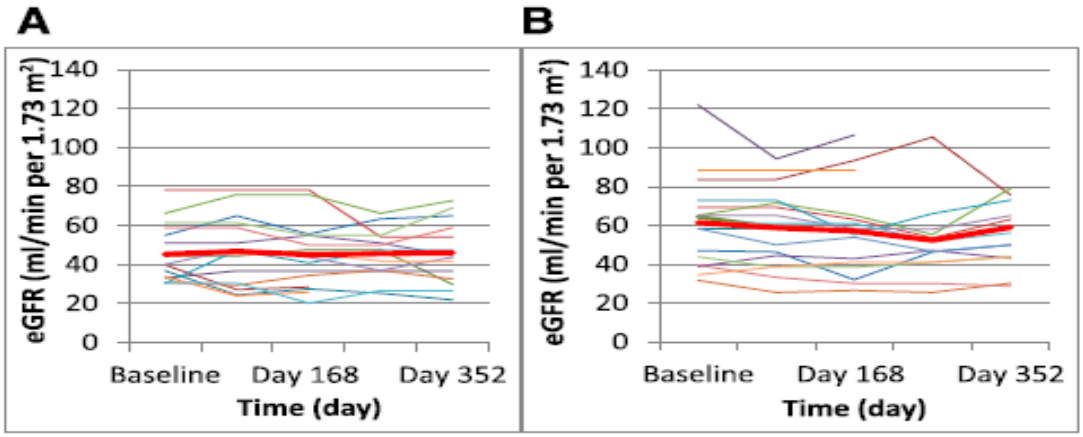


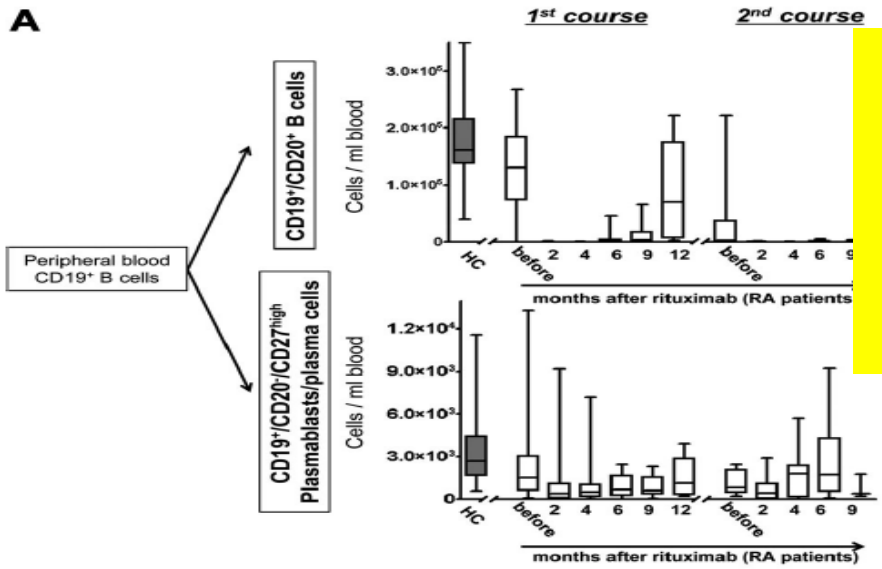
Figure 2. eGFR trends in (A) rituximab versus (B) control groups. The red line represents average data.

failed to show after 1 year any improvement in eGFR, proteinuria, Gd-IgA1 or anti-Gd-IgA1 antibody levels

Steady-state generation of mucosal IgA$^+$ plasmablasts is not abrogated by B-cell depletion therapy with rituximab

Henrik E. Mei,[1,2] Daniela Frölich,[2] Claudia Giesecke,[2] Christoph Loddenkemper,[3] Karin Reiter,[2] Stefanie Schmidt,[1,2] Eugen Feist,[2] Capucine Daridon,[1,2] Hans-Peter Tony,[4] Andreas Radbruch,[1] and Thomas Dörner[1,2]

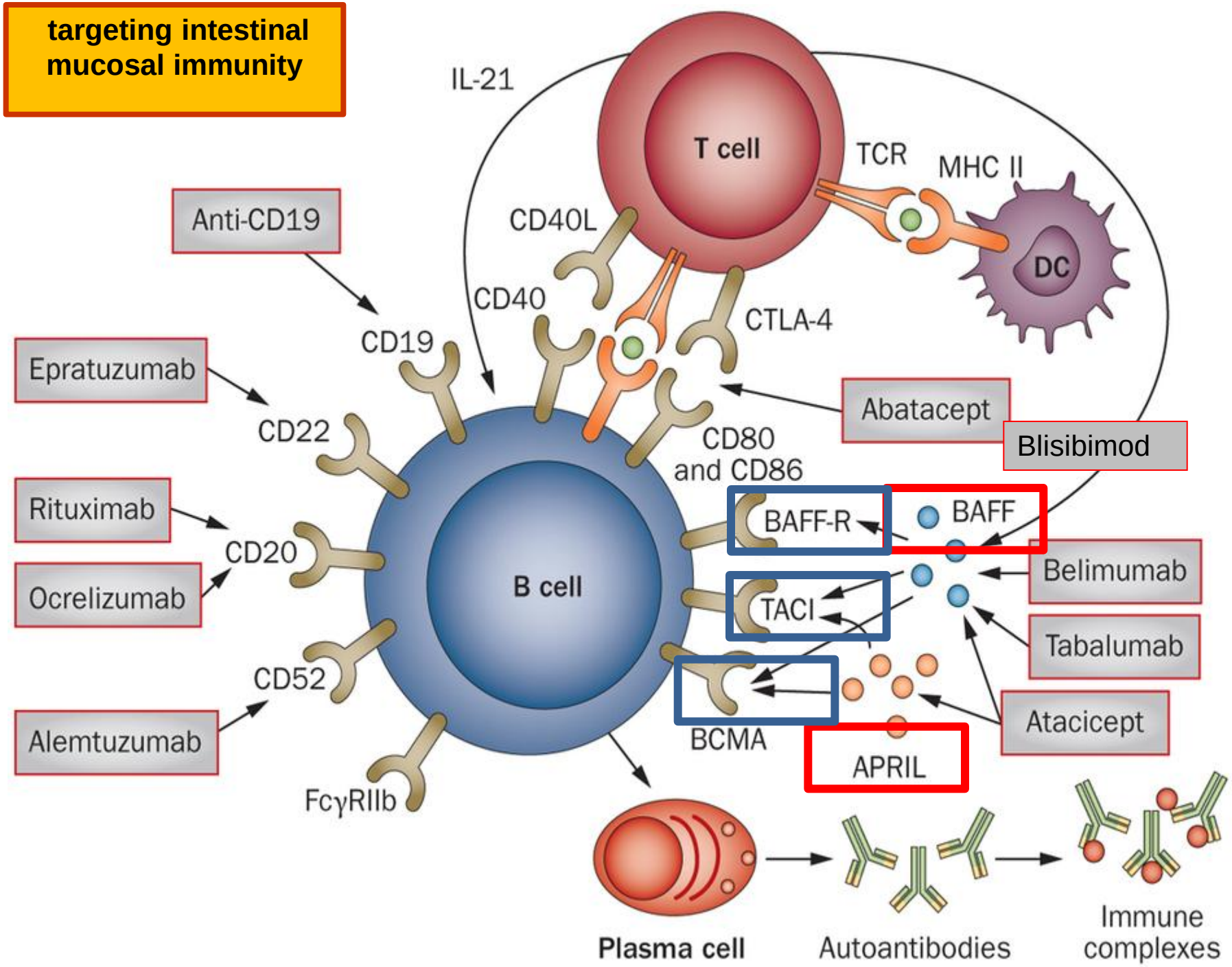
CD20-CD19+ CD27high plasmocytes/plasmoblasts
express IgA, the mucosal cell adhesion molecule β7 integrin
and the mucosal chemokine receptor CCR10



B cells resident in the mucosa are not deleted by Rituximab

Rituximab is not useful in ulcerative colitis

targeting intestinal mucosal immunity



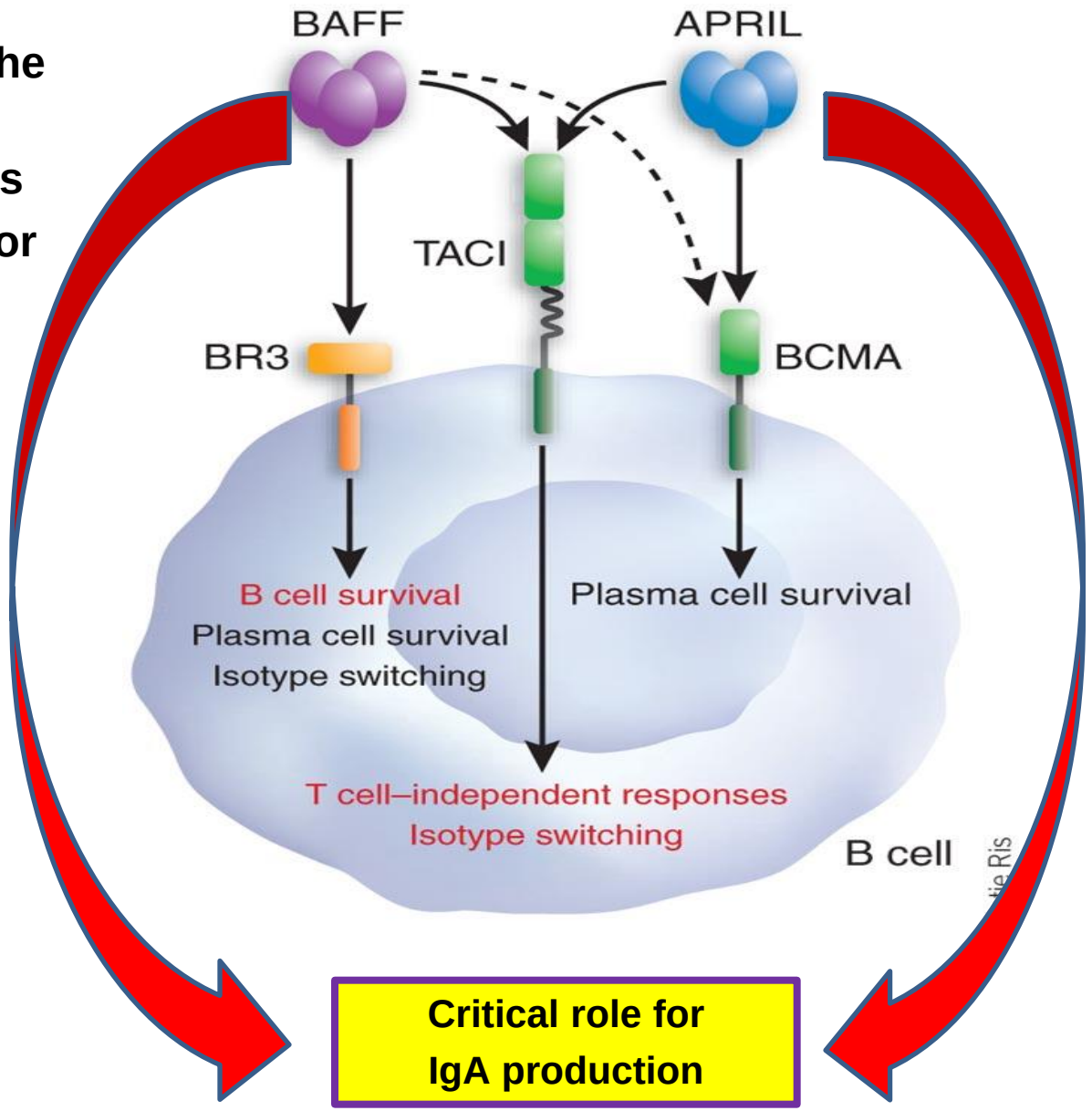
Factors controlling the switch to IgA:

TNF family members

B cell activator factor

BAFF (BlyS)

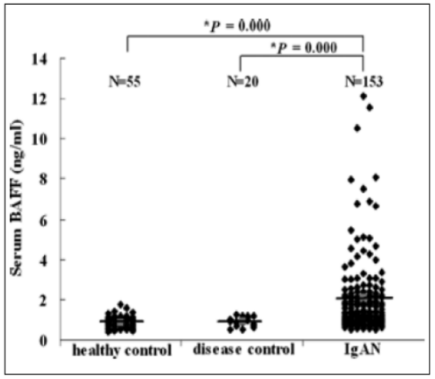
APRIL

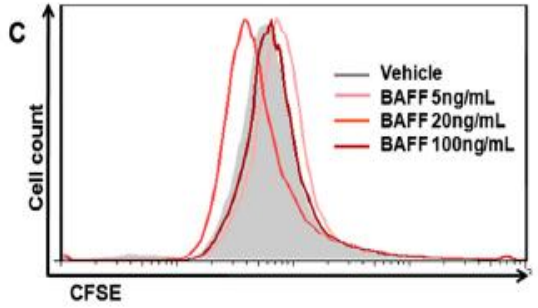


Critical role for IgA production

Clinical data
Experimental evidence

Serum BAFF is increased in IgAN patients

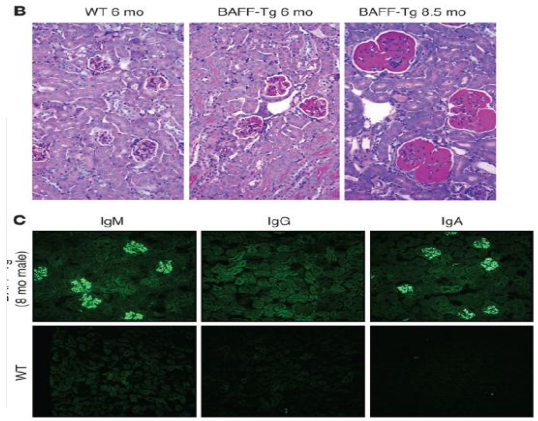


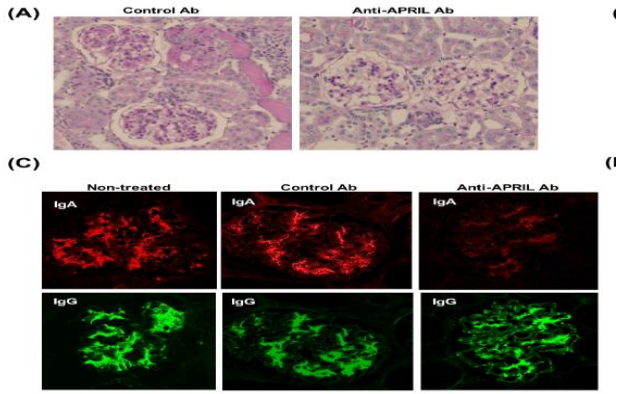


BAFF promotes proliferation of mesangial cells

Mice overexpressing BAFF develop a commensal flora–dependent, IgA-associated nephropathy

Douglas D. McCarthy,[1] Julie Kujawa,[2] Cheryl Wilson,[2] Adrian Papandile,[2] Urjana Poreci,[2] Elisa A. Porfilio,[1] Lesley Ward,[1] Melissa A.E. Lawson,[3] Andrew J. Macpherson,[3] Kathy D. McCoy,[3] York Pei,[4] Lea Novak,[5] Jeannette Y. Lee,[6] Bruce A. Julian,[5] Jan Novak,[5] Ann Ranger,[2] Jennifer L. Gommerman,[1] and Jeffrey L. Browning[2]





PLOS ONE

RESEARCH ARTICLE

Pathogenic Role of a Proliferation-Inducing Ligand (APRIL) in Murine IgA Nephropathy

Yang Gyun Kim[1,2], Montserrat Alvarez[1,3], Hitoshi Suzuki[1], Sachiko Hirose[4], Shozo Izui[5], Yasuhiko Tomino[1], Bertrand Huard[5], Yusuke Suzuki[1]*

Clinical Trials. Gov

NCT02062684

BRIGHT-SC: Blisibimod Response in IgA Nephropathy Following At-Home Treatment by Subcutaneous Administration

Recruiting

Target: BAFF

Interventions

drug: Blisibimod;

drug: Placebo

Phase 2 BRIGHT-SC study of blisibimod in 58 patients with IgAN.
Interim analysis

Patients were treated for up to 2 years, with at least 60 weeks of treatment.

Blisibimod: no change in proteinuria with slight decline
Placebo: increase in proteinuria

Interventions

drug: Atacicept 25 mg

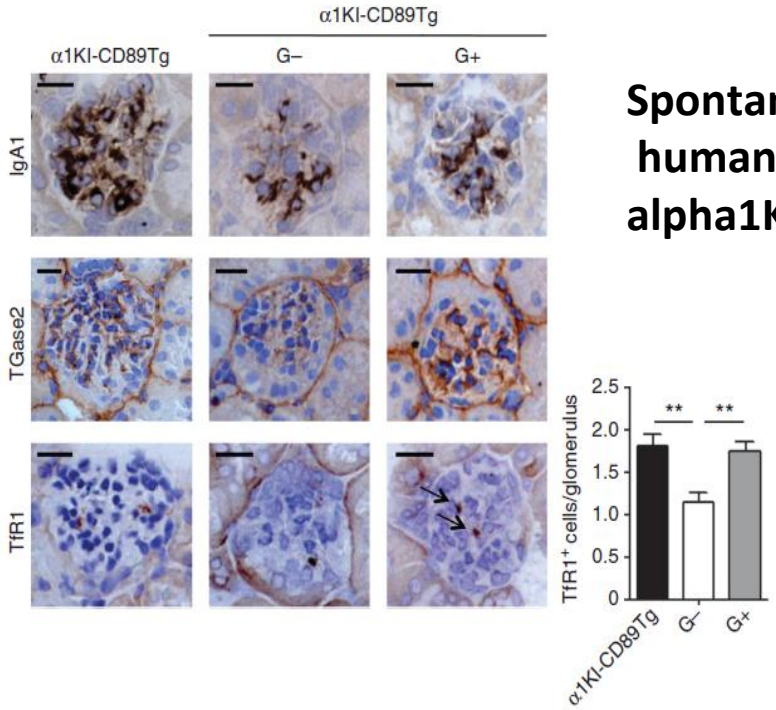
drug: Placebo

Target:TACI

Gluten exacerbates IgA nephropathy in humanized mice through gliadin–CD89 interaction

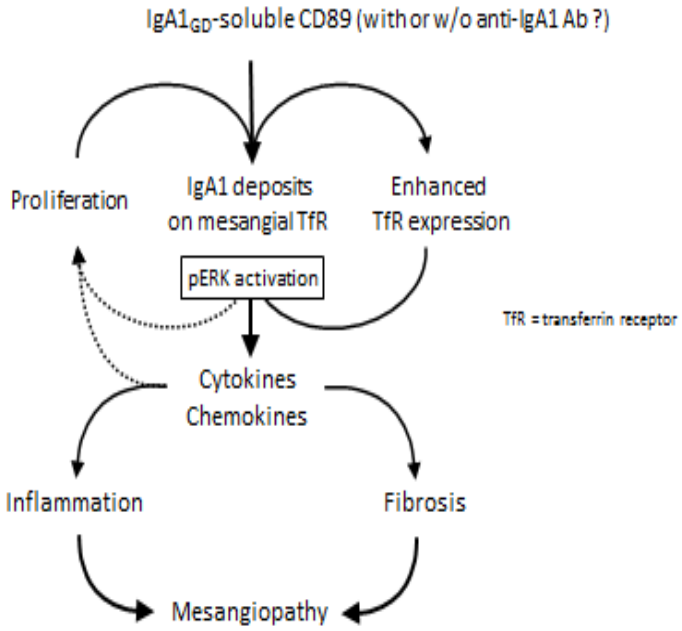
Kidney International (2015) **88**, 276–285

Christina Papista[1,2,3,4], Sebastian Lechner[1,2,3,4], Sanae Ben Mkaddem[1,2,3,4], Marie-Bénédicte LeStang[1,2,3,4], Lilia Abbad[1,2,3,4], Julie Bex-Coudrat[1,2,3,4], Evangéline Pillebout[5], Jonathan M. Chemouny[1,2,3,4], Mathieu Jablonski[6], Martin Flamant[1,2,4,7], Eric Daugas[1,2,3,4,6], François Vrtovsnik[1,2,3,4,6], Minas Yiangou[8], Laureline Berthelot[1,2,3,4,10] and Renato C. Monteiro[1,2,3,4,9,10]



Spontaneous IgAN mouse model expressing human IgA1 and CD89 (double transgenic alpha1KI-CD89Tg mice)

The complexes IgA1-CD89 interact with transferrin 1R (TfR1/CD71) and transglutaminase 2 (TG2)

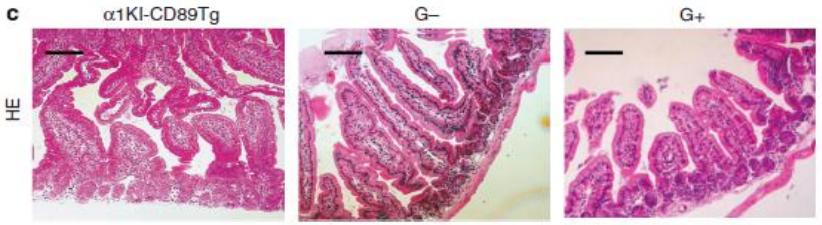


Gluten free diet for 3 generations

reduction in

- IgA1 mesangial deposition
- glomerular inflammatory-cell infiltration
- IgA1–sCD89 complexes in serum and kidney eluates
- hematuria

Gluten diet for 30 days



Intestinal injury
(inflammation and villous atrophy)

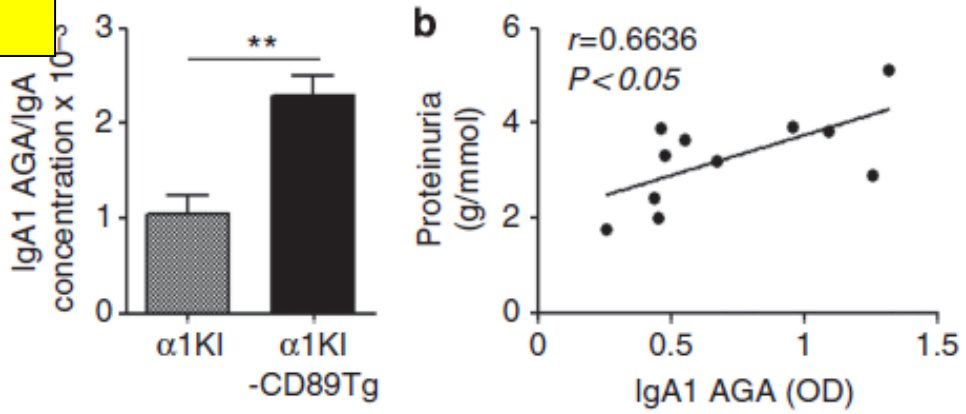
Increase in

- IgA1–sCD89 complexes
- IgA1 mesangial deposition
- IgA1 antigliadin Ab
- correlation with proteinuria

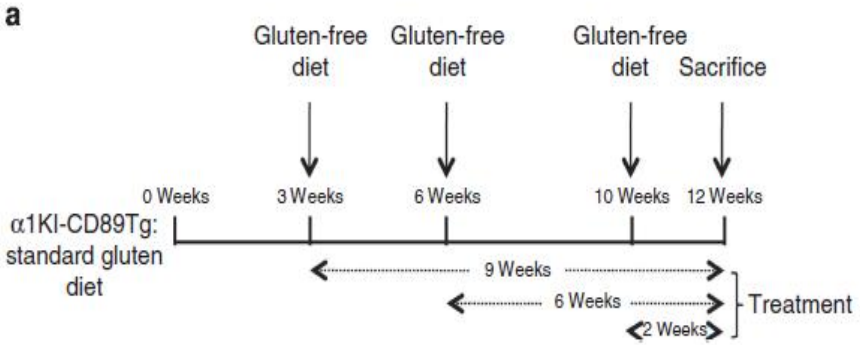
.

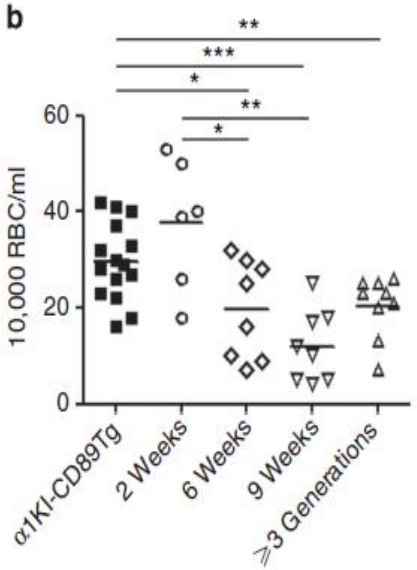
Correlation between anti-gliadin antibodies and proteinuria

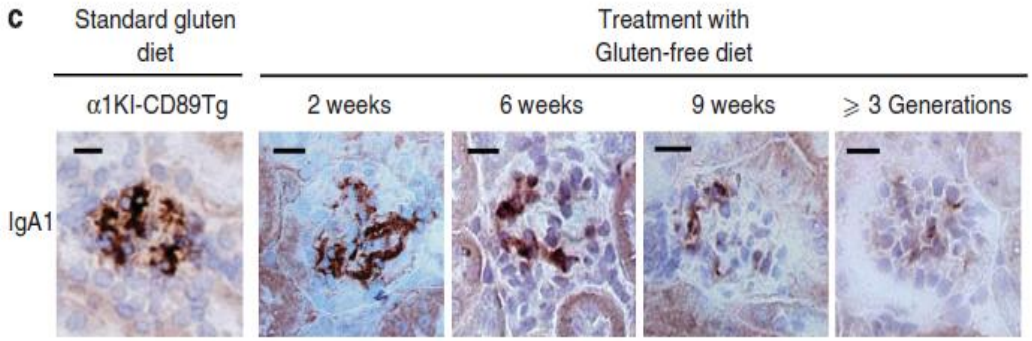
in experimental alpha1KI-CD89 mice on gluten diet

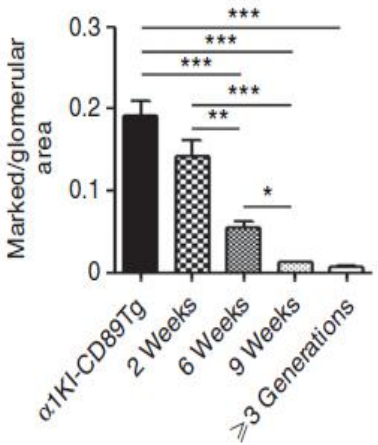


Early gluten-free diet abolishes IgAN development, hematuria and proteinuria in alpha1KI-CD89Tg mice









Gluten-induced experimental IgA glomerulopathy

Coppo R, et al Mazzucco G, Martina G, Roccatello D, Amore A, Novara R, Bargoni A, Piccoli G, Sena LM. Lab Invest.1989 ;60:499-506.

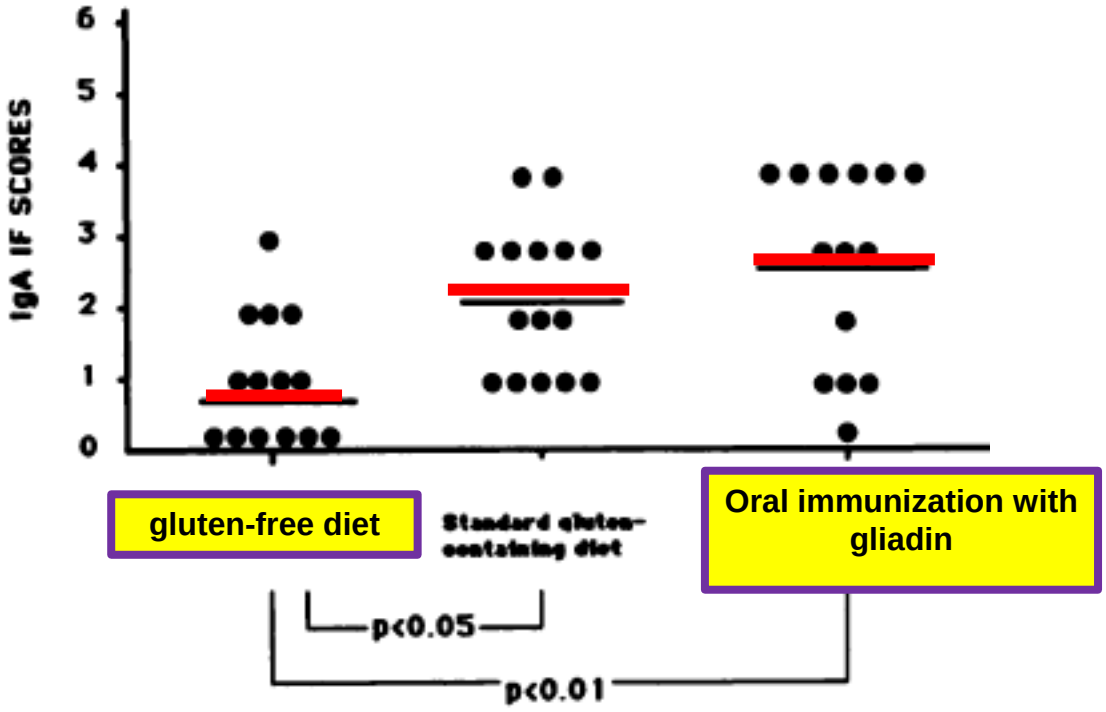


Figure 2. Semiquantitative analysis of IgA immune deposits in BALB/c mice after 14 wk of different diets.

Proc EDTA–ERA (1985) Vol 22

122

MAY GLUTEN-FREE DIET REDUCE THE LEVELS OF IgA IMMUNE COMPLEXES IN PRIMARY IgA NEPHROPATHY?

R Coppo, B Basolo, C Rollino, D Roccatello, G Martina, A Amore, *G Bongiorno, G Piccoli

*University of Turin Nephrology and Dialysis Unit, *Dietetic Service, S Giovanni Hospital, Turin, Italy*

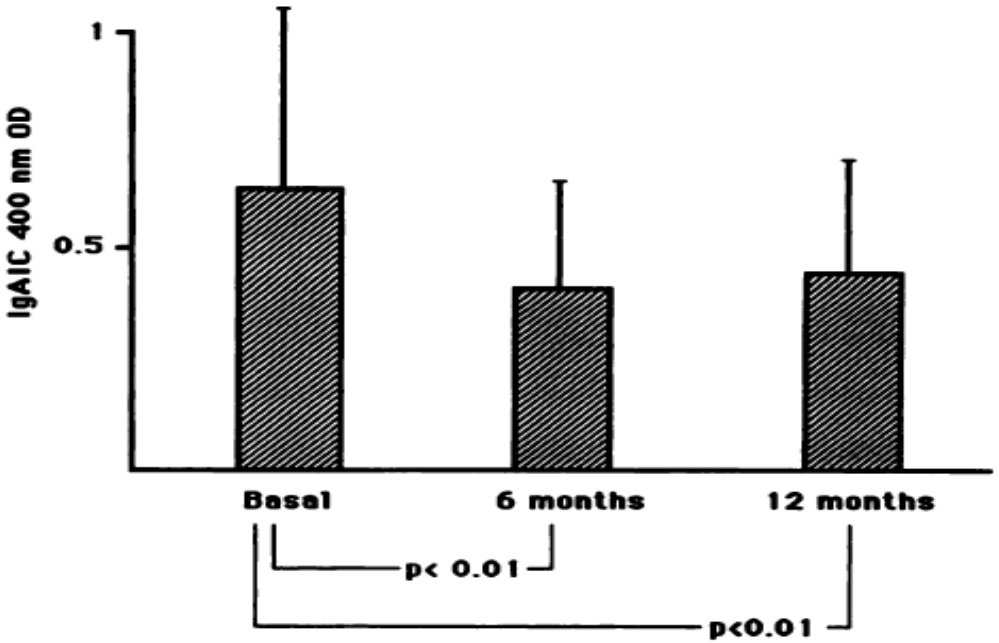
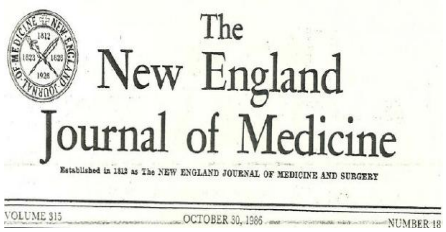


Figure 4. Effects of a gluten-free diet on the levels of IgAIC in IgAGN patients.



NEJM correspondence
Coppo R et al
October 30, 1986

Dietary Antigens and Primary Immunoglobulin A Nephropathy

(J. Am. Soc. Nephrol. 1992; 2:S173–S180)

Clinical Nephrology, Vol. 26 No. 2 – 1986 (pp. 72–82)

Mediterranean diet and primary IgA nephropathy

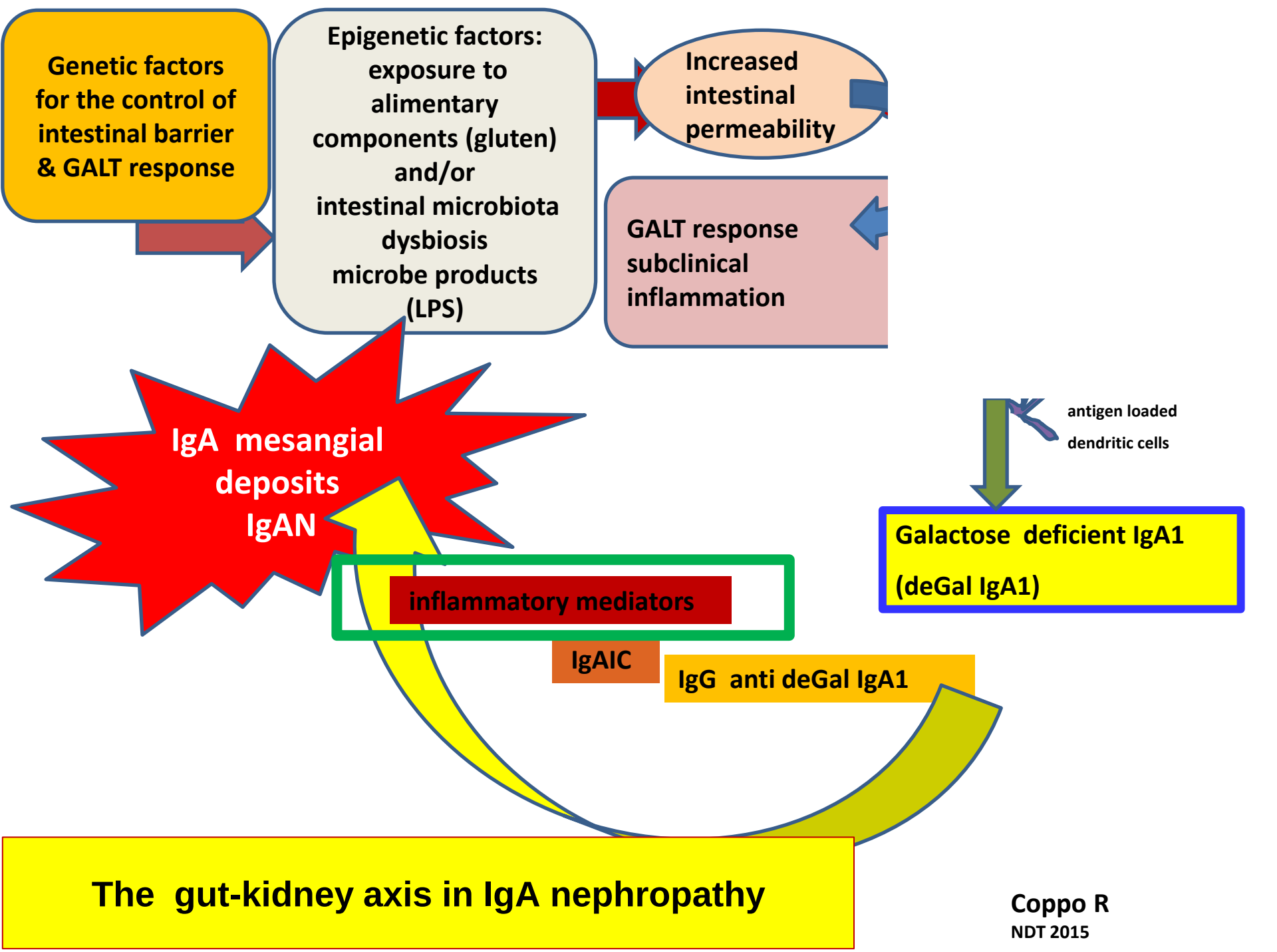
R. Coppo[1], B. Basolo[1], C. Rollino[1], D. Roccatello[1], G. Martina[1], A. Amore[1], G. Bongiorno[2] and G. Piccoli[1]

[1]Medical Nephrology Institute, University of Turin, Division of Nephrology and Dialysis, Nuova Astanteria Martini Hospital, Turin, Italy
[2]Dietetic Division, S. Giovanni Hospital, Turin, Italy

Conclusion of early studies (30 years ago)
to target gluten for treating patients with IgAN

- **Gluten-free diet was of some benefit in our exploratory study (29 patients without evidence of celiac disease) with reduction of proteinuria, but without effect on renal function decline after 4 years.**
- **The gluten-free diet is difficult to be followed without gastrointestinal symptoms**
- **RAS inhibition became an easy therapeutic choice and the diet was abandoned**

Need of a new RCT testing gluten-free diet in IgAN


Genetic factors for the control of intestinal barrier & GALT response
Epigenetic factors: exposure to alimentary components (gluten) and/or intestinal microbiota dysbiosis microbe products (LPS)
Increased intestinal permeability
GALT response subclinical inflammation
IgA mesangial deposits IgAN
antigen loaded dendritic cells
Galactose deficient IgA1 (deGal IgA1)
inflammatory mediators
IgAIC
IgG anti deGal IgA1
The gut-kidney axis in IgA nephropathy
Coppo R
NDT 2015

treat key mediators!

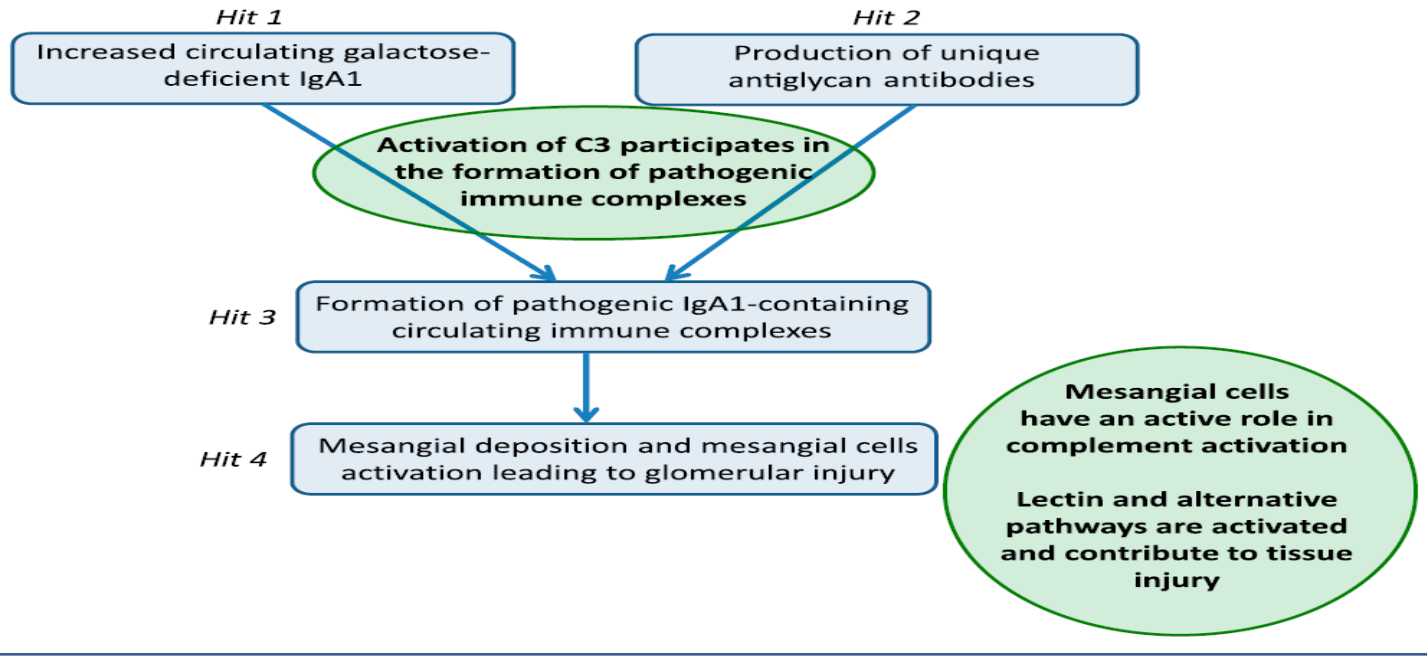
Complement activation in IgAN as a biomarker of activity and progression

BRIEF REVIEW www.jasn.org

J Am Soc Nephrol 26: , 2015.

Current Understanding of the Role of Complement in IgA Nephropathy

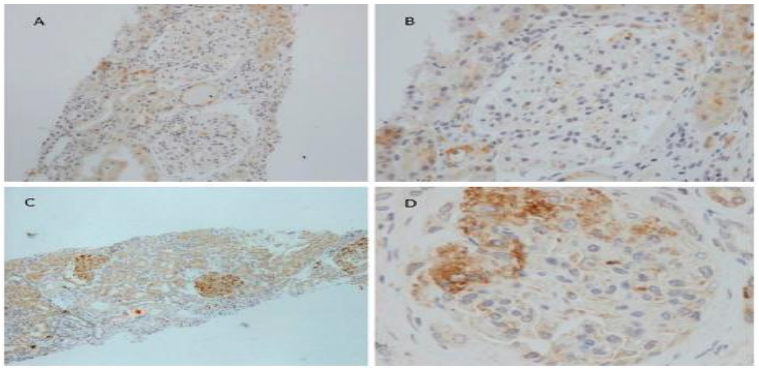
Nicolas Maillard,*† Robert J. Wyatt,‡ Bruce A. Julian,* Krzysztof Kiryluk,§ Ali Gharavi,§ Veronique Fremeaux-Bacchi,‖ and Jan Novak*

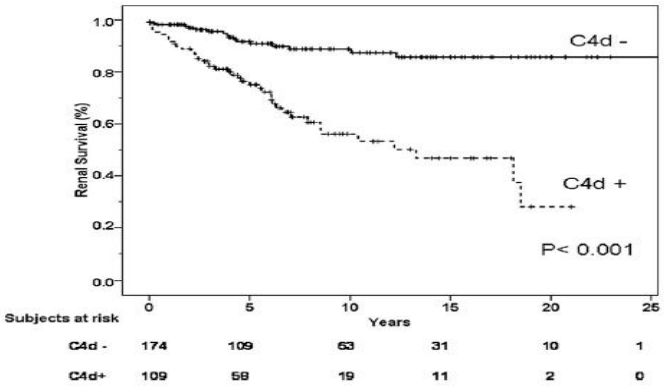


NDT 2014

Association of C4d Deposition with Clinical Outcomes in IgA Nephropathy

Mario Espinosa, Rosa Ortega, Marina Sánchez, Alfons Segarra, Maria Teresa Salcedo, Fayna González, Rafael Camacho, Miguel Angel Valdivia, Rocio Cabrera, Katia López, Fernando Pinedo, Eduardo Gutierrez, Alfonso Valera, Miryam Leon, Maria Angeles Cobo, Rosa Rodriguez, Jose Ballarín, Yolanda Arce, Beatriz García, María Dolores Muñoz, and Manuel Praga for the Spanish Group for the Study of Glomerular Diseases (GLOSEN)





Pediatr Nephrol
DOI 10.1007/s00467-016-3575-2

EDITORIAL

C4d deposits in IgA nephropathy: where does complement activation come from?

Rosanna Coppo [1]

Clin J Am Soc Nephrol 13: 258–264, February, 2018

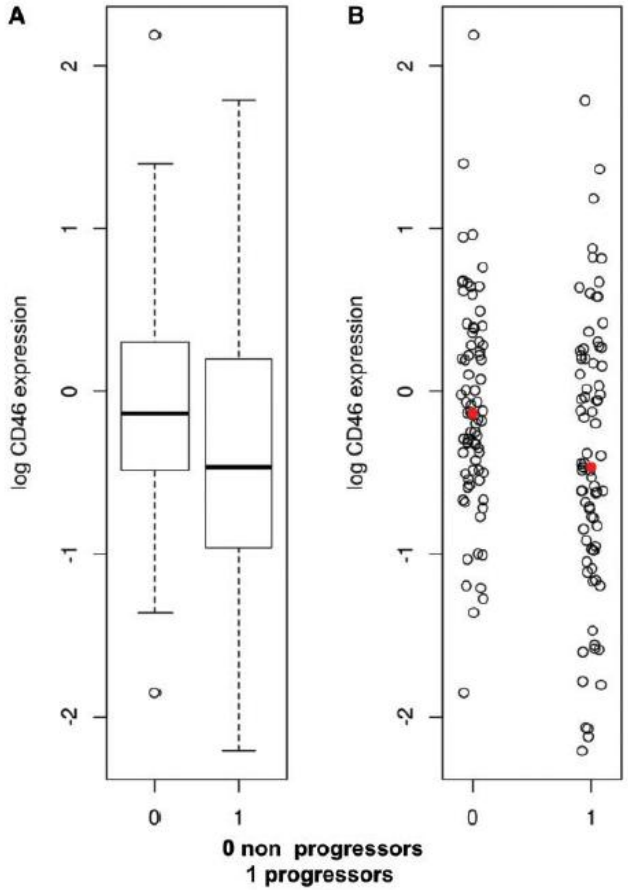
Mesangial C4d Deposits in Early IgA Nephropathy

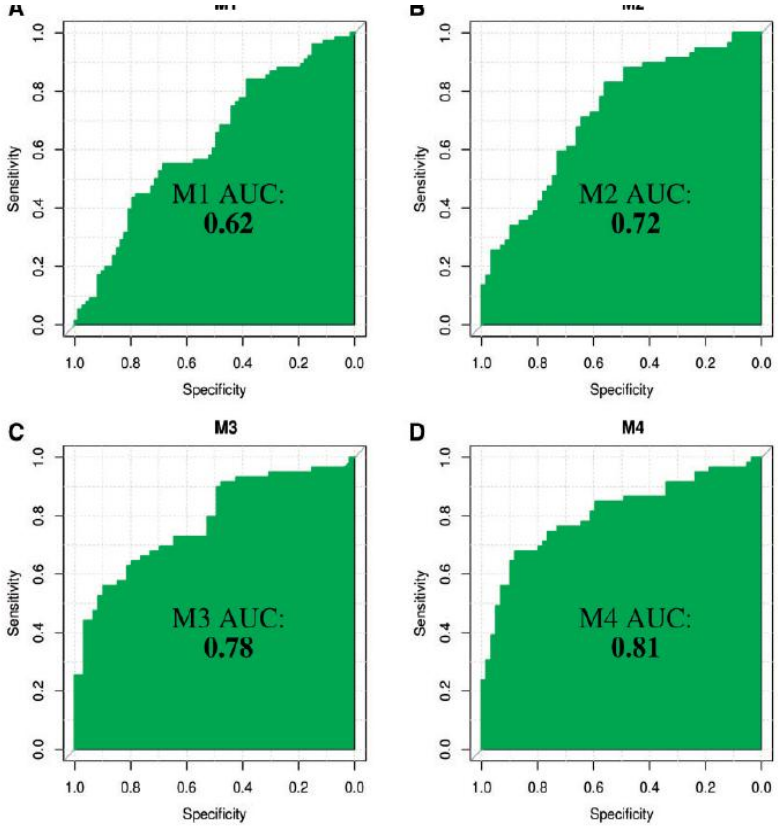
Alfons Segarra,[1] Katheryne Romero,[1] Irene Agraz,[1] Natalia Ramos,[1] Alvaro Madrid,[2] Clara Carnicer,[3] Elias Jatem,[4] Ramón Vilalta,[2] Luis Enrique Lara,[2] Elena Ostos,[4] Naiara Valtierra,[4] Juliana Jaramillo,[1] Karla V. Arredondo,[1] Gema Ariceta,[2] and Cristina Martinez[5]

Nephrol Dial Transplant (2018) 1–10
doi: 10.1093/ndt/gfy064

Defective gene expression of the membrane complement inhibitor CD46 in patients with progressive immunoglobulin A nephropathy

Coppo R et al Immunonephrology Working Group ERA-EDTA Nephrol Dial Transplant. 2018 Apr 9. doi: 10.1093



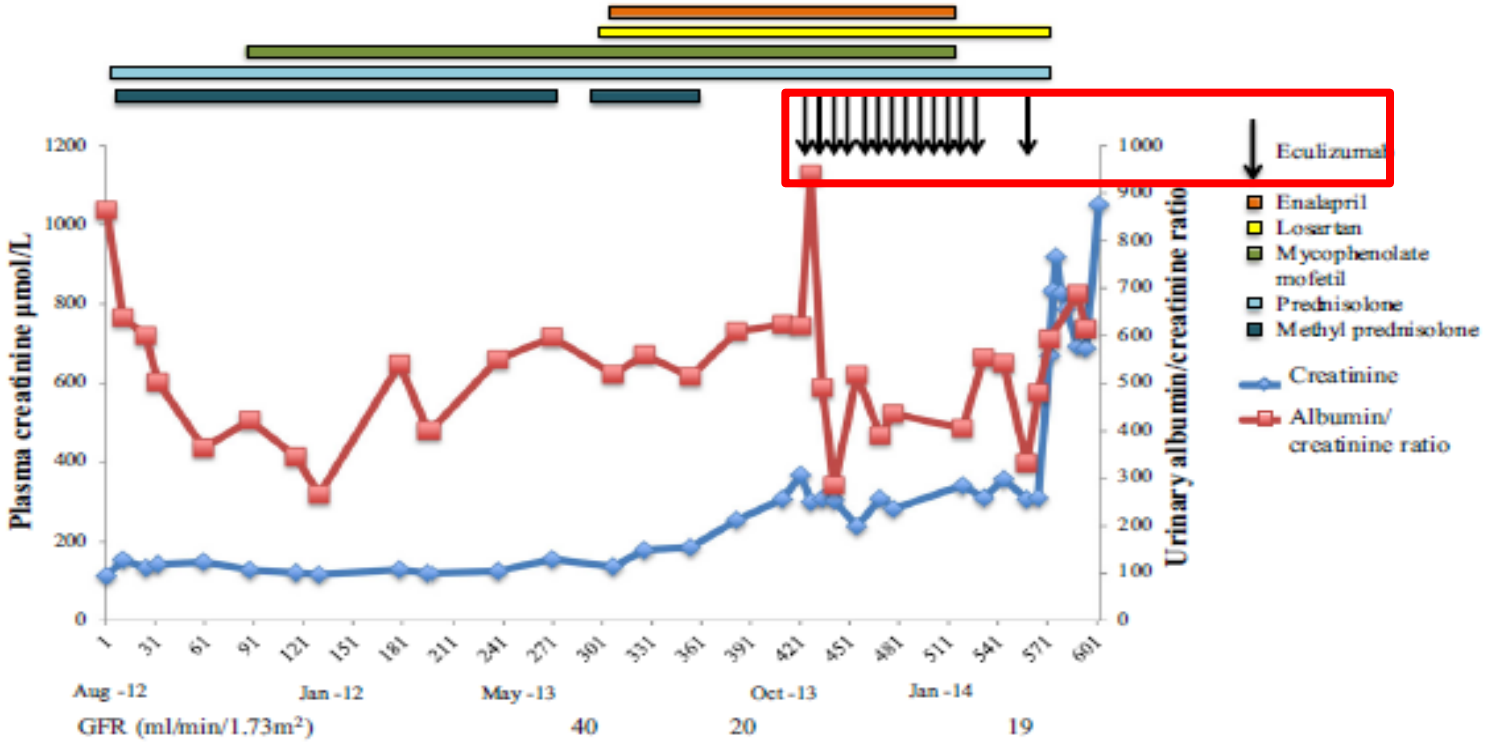


Pediatr Nephrol (2014) 29:2225–2228
DOI 10.1007/s00467-014-2863-y

BRIEF REPORT

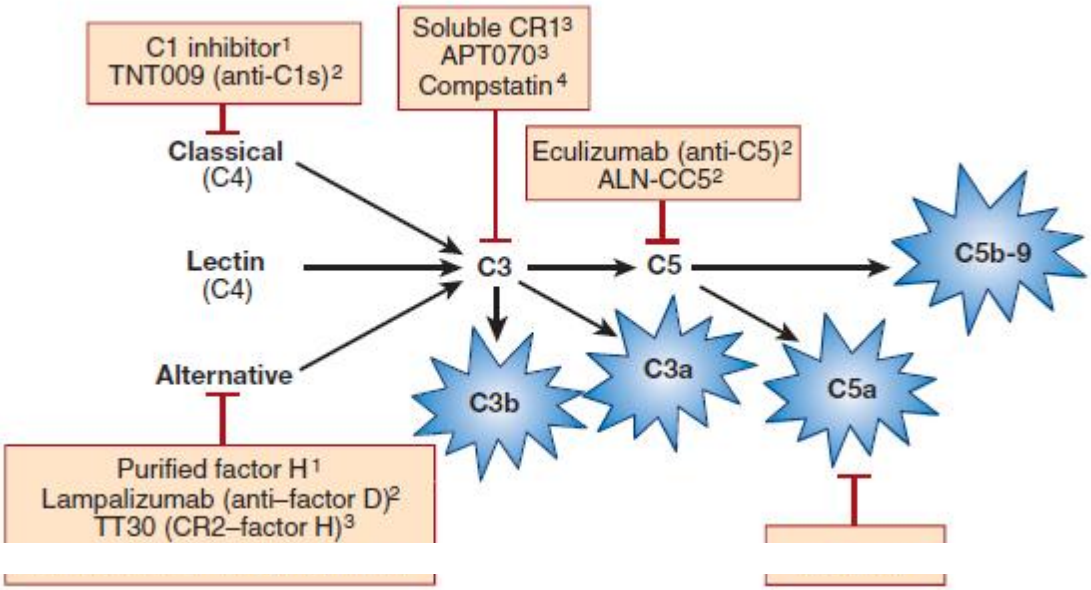
Eculizumab treatment for rescue of renal function in IgA nephropathy

Therese Rosenblad · Johan Rebetz · Martin Johansson · Zivile Békássy · Lisa Sartz · Diana Karpman



Targeting the complement cascade: novel treatments coming down the pike

Joshua M. Thurman[1] and Moglie Le Quintrec[2]



C5A RECEPTOR INHIBITOR AVACOPAN IN IGA NEPHROPATHY STUDY

Annette Bruchfeld Patrick Nachman Samir Parikh Richard Lafayette Antonia Potarca Janet Diehl Lisa LohrShichang Miao Thomas Schall Pirow Bekker

Nephrology Dialysis Transplantation, Volume 32, Issue suppl_3, 1 May 2017, Pages iii82,https://doi.org/10.1093/ndt/gfx129.TO012

Open-label pilot Phase 2 trial in Sweden and the USA

Presented as oral communication at ERA-EDTA 2017 meeting

Some encouraging early results

IgA1 Protease Treatment Reverses Mesangial Deposits and Hematuria in a Model of IgA Nephropathy

Sebastian M. Lechner,*†‡§ Lilia Abbad,*†‡§ Erwan Boedec,*†‡§ Christina Papista,*†‡§ Marie-Bénédicte Le Stang,*†‡§ Christelle Moal,*†‡§ Julien Maillard,*†‡§ Agnès Jamin,*†‡§ Julie Bex-Coudrat,*‡§ Yong Wang,‖ Aiqun Li,‖ Paolo G.V. Martini,‖ Renato C. Monteiro,*†‡§¶ and Laureline Berthelot*†‡§

J Am Soc Nephrol

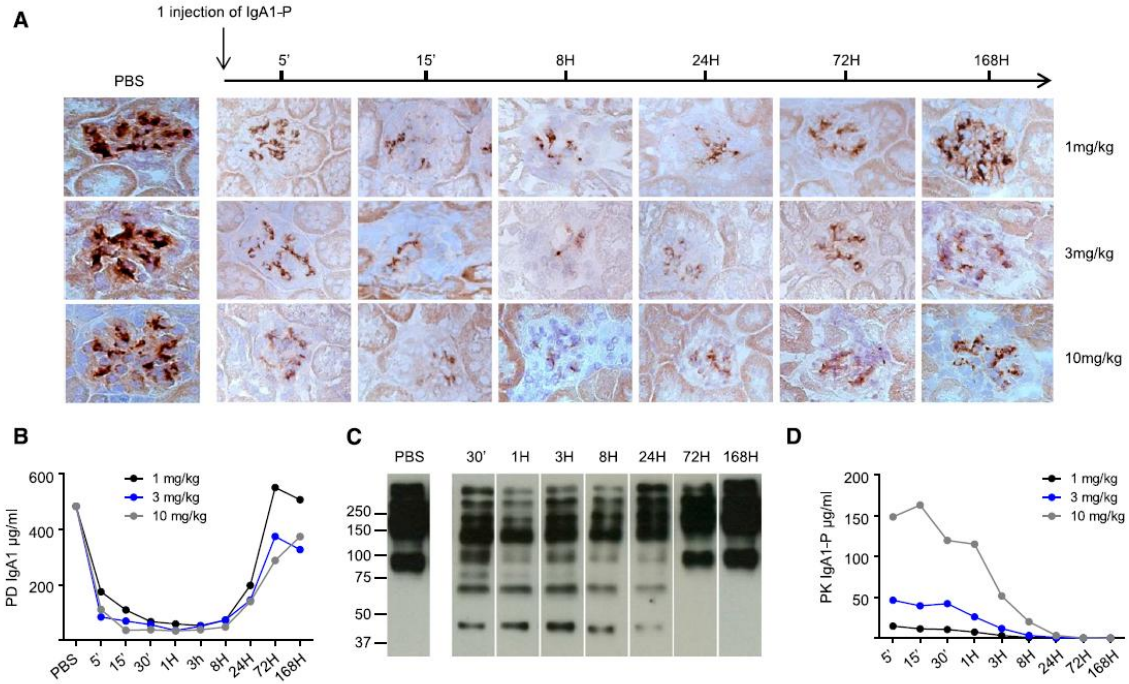
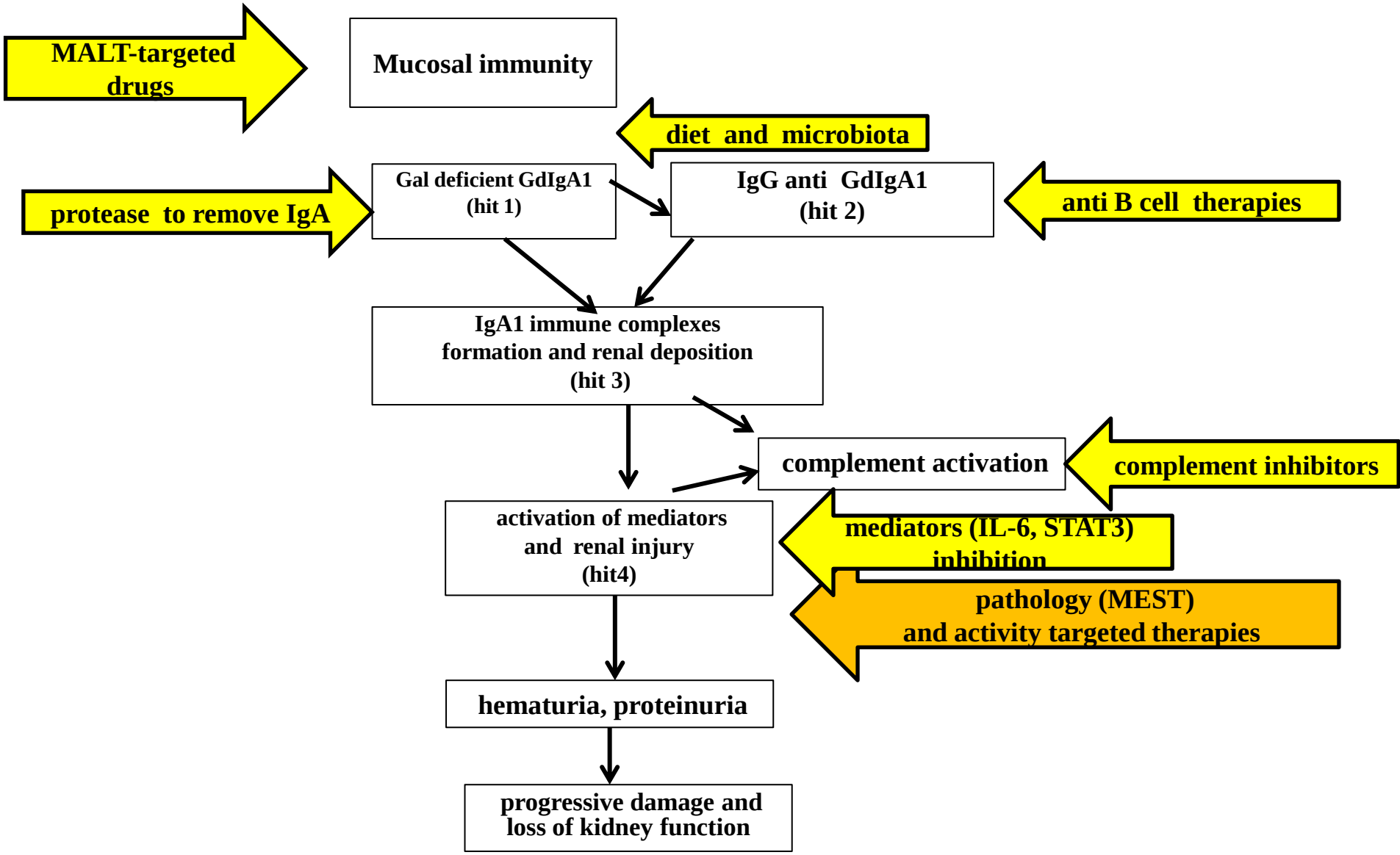


Figure 1. Decrease in serum IgA1 levels and mesangial IgA1 deposits after IgA1-P treatment. (A) IgA1 deposit detection in the mesangium (brown) after IgA1-P IV injection (1, 3, and 10 mg/kg) in α1KI-CD89Tg mice (n=3 mice per group) using immunohistochemistry directed against human IgA on frozen kidney sections. Representative sections. (B) Concentrations of serum IgA1 after IgA1-P injection for each time point of euthanized mice as described in (A). (C) Detection of IgA1 fragments by western blot in serum from mice after 3 mg/kg injection. Representative samples of selected time points. (D) Pharmacokinetics (PK) of IgA1-P in serum of α1KI-CD89Tg mice after IV injection for each time point of euthanized mice as described in (A). PD, pharmacodynamics.


MALT-targeted drugs
Mucosal immunity
diet and microbiota
protease to remove IgA
Gal deficient GdIgA1 (hit 1)
IgG anti GdIgA1 (hit 2)
anti B cell therapies
IgA1 immune complexes formation and renal deposition (hit 3)
complement activation
complement inhibitors
activation of mediators and renal injury (hit4)
mediators (IL-6, STAT3) inhibition
pathology (MEST) and activity targeted therapies
hematuria, proteinuria
progressive damage and loss of kidney function


50 years later

15th International Symposium on IgANephropathy

IIgANN2018

September 27th-29th, 2018 - The Brick Hotel, Buenos Aires, Argentina

5th Anniversary of IgA Nephropathy

The International IgA Nephropathy Network

https://www.iigann2018.com

Merci de votre attention