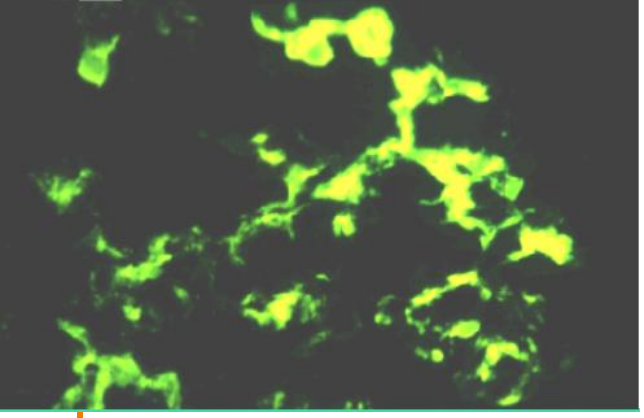
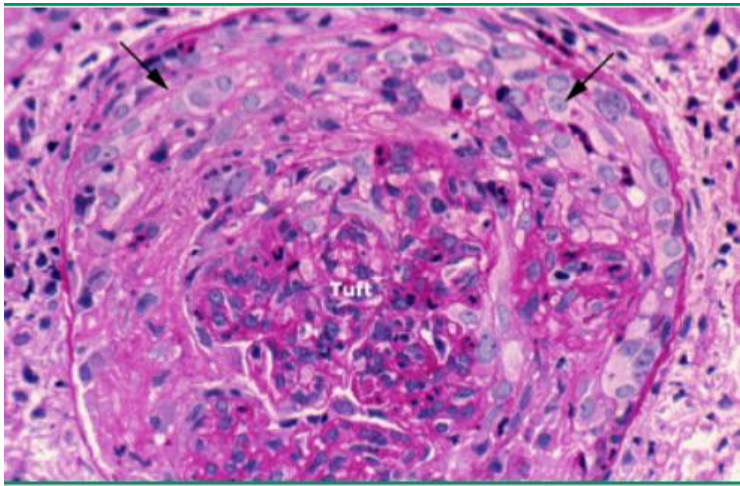


Impact of the Crescents on the Prognosis of IgA nephropathy

Shahrzad Ossareh- M.D.

HCK- IUMS



Introduction

- Immunoglobulin A nephropathy is the most prevalent primary glomerular disease, particularly in the Asia-Pacific region.
- Up to 30% of all people with IgA nephropathy will eventually develop end-stage kidney disease (ESKD)
- Decreased kidney function, persistent proteinuria, and hypertension are the strongest risk factors.

http://www.kidney-international.org

see commentary on page 477

The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Daniel C. Cattran[1,†], Rosanna Coppo[2,†], H. Terence Cook[3,†], John Feehally[4,†], Ian S.D. Roberts[5,†], Stéphan Troyanov[6,†], Charles E. Alpers[7], Alessandro Amore[2], Jonathan Barratt[4], Francois Berthoux[8], Stephen Bonsib[9], Jan A. Bruijn[10], Vivette D'Agati[11], Giuseppe D'Amico[12], Steven Emancipator[13], Francesco Emma[14], Franco Ferrario[15], Fernando C. Fervenza[16], Sandrine Florquin[17], Agnes Fogo[18], Colin C. Geddes[19], Hermann-Josef Groene[20], Mark Haas[21], Andrew M. Herzenberg[22], Prue A. Hill[23], Ronald J. Hogg[24], Stephen I. Hsu[25], J. Charles Jennette[26], Kensuke Joh[27], Bruce A. Julian[28], Tetsuya Kawamura[29], Fernand M. Lai[30], Chi Bon Leung[31], Lei-Shi Li[32], Philip K.T. Li[31], Zhi-Hong Liu[32], Bruce Mackinnon[19], Sergio Mezzano[33], F. Paolo Schena[34], Yasuhiko Tomino[35], Patrick D. Walker[36], Haiyan Wang[37], Jan J. Weening[38], Nori Yoshikawa[39] and Hong Zhang[37,*]

IgA nephropathy is the most common glomerular disease worldwide, yet there is no international consensus for its pathological or clinical classification. Here a new classification for IgA nephropathy is presented by an international consensus working group. The goal of this new system was to identify specific pathological features that more accurately predict risk of progression of renal disease in IgA follow-up. The value of crescents was not addressed due to their low prevalence in the enrolled cohort.

Kidney International (2009) **76,** 534–545; doi:10.1038/ki.2009.243; published online 1 July 2009

KEYWORDS: glomerulonephritis; IgA nephropathy; Oxford classification; pathology; renal failure

Table 8 | Recommended elements in renal biopsy report for a case of IgA nephropathy

Detailed description of the features present on

- Light microscopy
- Immunohistochemistry
- Electron microscopy

Summary of four key pathological features

- Mesangial score $\leqslant$0.5 (M0) or $>$0.5 (M1)
- Segmental glomerulosclerosis absent (S0) or present (S1)
- Endocapillary hypercellularity absent (E0) or present (E1)
- Tubular atrophy/interstitial fibrosis $\leqslant$25% (T0), 26–50% (T1), or $>$50% (T2)

Total number of glomeruli

Number of glomeruli with endocapillary hypercellularity, extracapillary proliferation, global glomerulosclerosis, and segmental glomerulosclerosis

The study cohort of 265 cases (206 adult and 59 children) of IgA nephropathy from China, Japan, France, Italy, UK, US, Canada, Chile

Cattran D. Kidney International (2009) 76, 534

Further retrospective cohort studies have confirmed that …

- In biopsy specimens with a minimum of 8 glomeruli, mesangial hypercellularity (M), segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T) lesions predict clinical outcome.

- Patients whose biopsy specimens were scored E1 were more likely to receive immunosuppressive therapy, most frequently corticosteroids, and patients with E lesions had an improved outcome if treated with corticosteroids.

Inclusion criteria.

- Biopsy-proven IgAN (defined by the predominant mesangial deposition of IgA)
  - Initial eGFR >30 ml/min per 1.73 m^2 ,
  - Initial proteinuria >0.5 g per 24 h in adults and >0.5 g per 24 h per 1.73 m2 in
  - At least 12 months of F/U
- Therapy was not considered

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] and Agnieszka Perkowska-Ptasinska[8], on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group[8]

[1]City of the Health and the Science of Turin Health Agency, Regina Margherita Children's Hospital, Turin, Italy; [2]Hôpital du Sacré-Coeur de Montréal, Montreal, Canada; [3]Oxford University Hospitals, Oxford, UK; [4]Unversity Health Network, Toronto General Hospital, Toronto, Canada; [5]Imperial College, Hammersmith Hospital, London, UK and [6]University Hospitals of Leicester, Leicester, UK

The Oxford Classification of IgA Nephropathy (IgAN) identified mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T) as independent predictors of outcome. Whether it applies to individuals excluded from the original study and how therapy influences the predictive value of pathology remain uncertain. The VALIGA study examined 1147 patients from 13 European countries that encompassed the whole spectrum of IgAN. Over a median follow-up of 4.7 years, 86% received renin–angiotensin system blockade and 42% glucocorticoid/immunosuppressive drugs. M, S, and T lesions classification in a large European cohort of IgAN patients across the whole spectrum of the disease. The independent predictive value of pathology MEST score is reduced by glucocorticoid/immunosuppressive therapy.

Kidney International (2014) **86,** 828–836; doi:10.1038/ki.2014.63; published online 2 April 2014

KEYWORDS: glomerular diseases; IgA nephropathy; progression of chronic renal failure; proteinuria; renal pathology; risk factors

IgA nephropathy (IgAN) is the most common glomerulonephritis in the world, being particularly frequent in Asia,

VALIGA cohort (1147 patients)

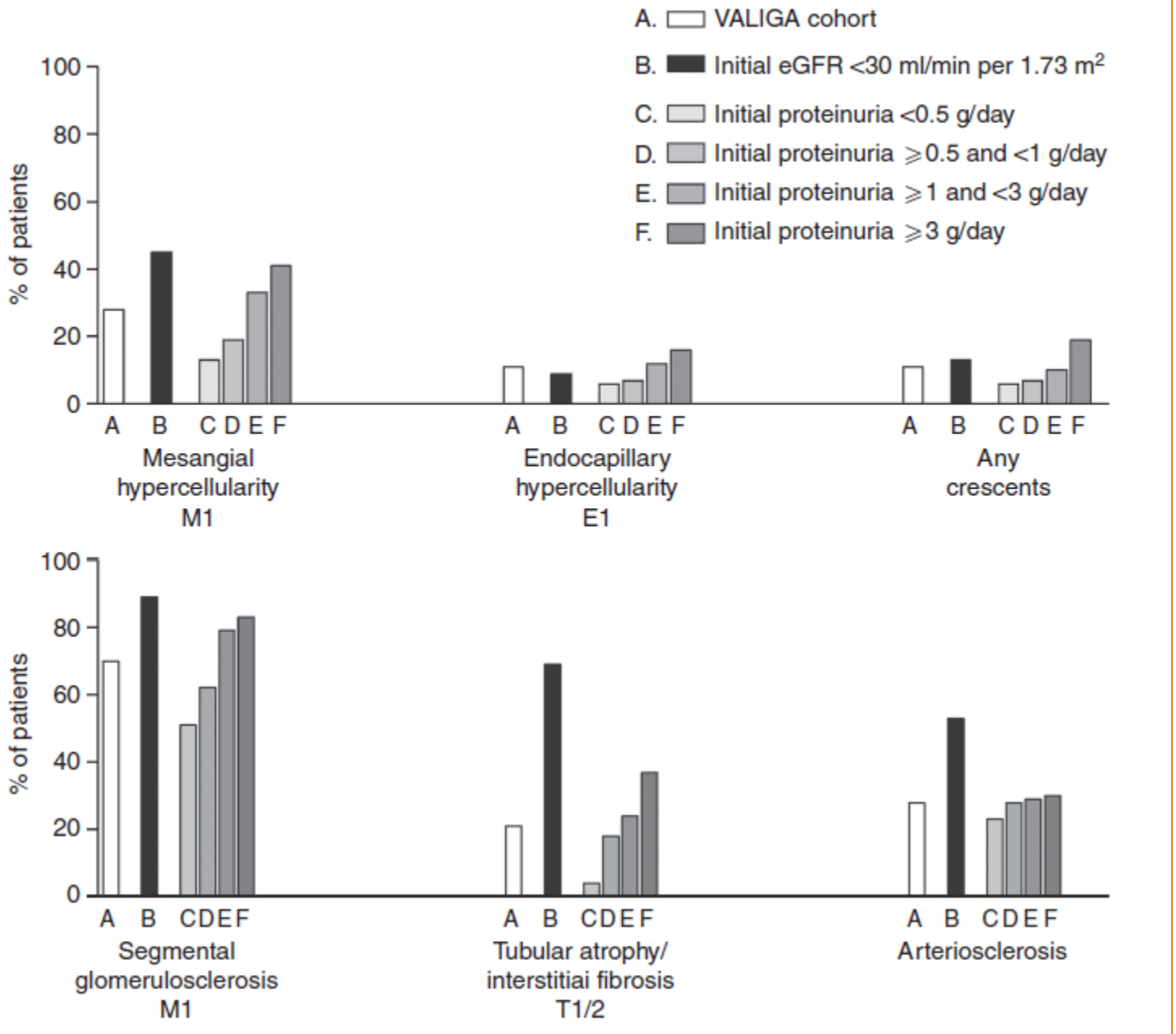


Table 3 | Correlations between pathological features and outcomes

Rate of renal function decline			Survival from renal failure or 50% drop in eGFR	
	Univariate (ml/min per 1.73 m^2/year)	Multivariate ß (s.d.)[a]	Univariate hazard ratio (95% CI)	Multivariate hazard ratio (95% CI)[a]
Mesangial proliferation				
M0	−1.29 ± 7.49		1	1
M1	−3.02 ± 7.32	−0.9 (0.5)	2.3 (1.7–3.0)	1.3 (0.9–1.7)
	$P<0.001$	$P=0.04$	$P<0.001$	$P=0.12$
Segmental glomerulosclerosis				
S0	−1.15 ± 5.46		1	1
S1	−2.03 ± 8.18	−0.1 (0.5)	4.1 (2.6–6.5)	1.8 (1.1–2.9)
	$P=0.03$	$P=0.85$	$P<0.001$	$P=0.02$
Tubular atrophy/interstitial fibrosis				
T0	−1.36 ± 7.29		1	1
T1–2	−3.28 ± 7.97	−1.4 (0.6)	5.6 (4.2–7.5)	2.6 (1.8–3.6)
	$P<0.001$	$P=0.01$	$P<0.001$	<0.001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
Mesangial score >0.5 (M1), any endocapillary hypercellularity (E1), any segmental sclerosis (S1), tubular atrophy, and interstitial fibrosis (T1 and T2).
[a]Multivariate models are adjusted for initial eGFR, follow-up blood pressure, and proteinuria.

The exception was the E lesion,

- which did not predict any of the outcomes when addressing the entire cohort.
- E lesion was not predictive in the subgroup that did not receive immunosuppression, as it was in the original study

Table 1 | Summary of studies correlating Oxford MEST parameters with clinical outcomes in IgA nephropathy (minimum cohort size: 99 patients)

Study	Center	No. of patients	End point	Univariate analysis	Multivariate analysis	IS bias
Cattran *et al.*[1] (Oxford), 2009	Multicenter global	265 (206 A, 59 C)	Rate of eGFR decrease, ESRD, or	M, S, T	S, T	Yes
			≥50% eGFR decrease	M, S, T	M, T	
Katafuchi *et al.*,[6] 2011	Single center, Japan	702 C	ESRD	MET	MET	Yes
Herzenberg *et al.*,[7] 2011	Multicenter, United States and Canada	187 (143 A, 44 C)	Rate of eGFR decrease	Not done	E, S, T	Yes
El Karoui *et al.*,[8] 2012	Single center, France	128 A	ESRD or doubling of SCr; rate of eGFR decrease	None	M, E, S, T	No
Shi *et al.*,[9] 2011	Single center, China	410	ESRD	M, S, T	S, T	Yes
Alamartine *et al.*,[10] 2011	Single center, France	183	ESRD or doubling of Scr	E, S, T	None	Yes
Edström Halling *et al.*,[12] 2012	Single center, Sweden	99 C	ESRD or ≥50% eGFR decrease	M, E, T	None	Yes
Shima *et al.*,[13] 2012	Single center, Japan	161 C	Rate of eGFR decrease	M, E, T	M, T	Yes
Le *et al.*,[15] 2012	Multicenter, China	218 C	eGFR decrease (doubling Scr) or ESRD	S, T	T	Yes
				S, T	T	
Zeng *et al.*,[17] 2012	Multicenter, China	1026 A	Rate of eGFR decrease, ESRD, or	M, S, T	M, T	Yes
			≥50% eGFR decrease	M, S, T	M, T	
Kang *et al.*,[18] 2012	Single center, South Korea	197 A	ESRD or ≥50% eGFR decrease	T	T	Yes
Gutierrez *et al.*,[20] 2012	Single center, Spain	141 A	eGFR decrease (doubling Scr), ESRD	T	T	Yes
				S	S	
Nasri *et al.*,[22] 2012	Multicenter, Iran	102 A	Scr	ST	Not done	Yes
Coppo *et al.*,[23] 2014, VALIGA	Multicenter, Europe	1147 (973 A, 174 C)	ESRD or ≥50% eGFR decrease, rate of eGFR decrease	M, S, T	S, T	Yes
				M, S, T	S, T	
Espinosa *et al.*,[24] 2014	Multicenter, Spain	283 (A + C)	ESRD	M, S, T	S, T	Yes
Moriyama *et al.*,[25] 2014	Single center, Japan	1012 A	eGFR decrease or ESRD	T	None	Yes
Park *et al.*,[26] 2014	Multicenter, South Korea	500 A	ESRD or doubling of Scr	M, T	T	Yes
Chakera *et al.*,[27] 2016	Multicenter, Australia, United Kingdom	156 A	ESRD or eGFR decrease >5 ml/min per year	E, T	E	No
Hou *et al.*,[28] [e-pub ahead of print]	Multicenter, China	176 A	Proteinuria	Not done	Not done	Yes

A, adults; C, children; E, endocapillary proliferation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IS, immunosuppression; IS bias, inherent bias due to nonrandomized use of immunosuppressive therapy in study cohort; M, mesangial proliferation; S, glomerulosclerosis; Scr, serum creatinine; T, tubular atrophy.

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]

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Since the Oxford Classification of IgA nephropathy (IgAN) was published in 2009, MEST scores have been increasingly used in clinical practice. Further retrospective cohort

Kidney International (2017) **91,** 1014–1021; http://dx.doi.org/10.1016/j.kint.2017.02.003

KEYWORDS: chronic kidney disease; glomerulonephritis; IgA nephropathy; proteinuria

Limitations of the original Oxford

- Only 265 adults and children,
- Only those of white European and North American and East Asian ethnicities.
- Typical slowly progressive IgAN
- Excluded those with an eGFR<30 ml/min/1.73 m^2

Pooled cohort of 3096 patients

- Assembled from 4 retrospective studies Oxford and VALIGA and 2 large Asian databases, 1 from China and another from Japan.
- The working subgroup studied relationships between the proportion of glomeruli containing cellular or fibrocellular crescents and the rate of renal function decline and survival of a 50% decline in renal function or ESRD (combined event), while adjusting for covariates used in the original Oxford study.

Table 2 | Recommendations for updating the Oxford Classification of IgAN

- We recommend no changes to the published criteria for biopsy adequacy in cases of IgAN. A minimum of 8 glomeruli is required.
- We recommend that MEST criteria continue to be applied to cases of IgAN.
- We confirm the predictive value of M, S, and T.
- We confirm the predictive value of E in patients not treated with immunosuppression.
- We recommend that a C score be added to the MEST score in all cases of IgAN to indicate the frequency of cellular and/or fibrocellular crescents.
  C0 (no crescents) or
  C1 (crescent in a least 1 glomerulus) or
  C2 (crescents in at least 25% of glomeruli)
- We recommend no change in the definition of S1, but adding text to indicate whether there are podocytopathic features.
- We recommend that MEST criteria are not yet applied to cases of Henoch-Schönlein purpura nephritis (IgA vasculitis).

C, crescent; E, endocapillary cellularity; IgAN, IgA nephropathy; M, mesangial hypercellularity; S, segmental sclerosis; T, interstitial fibrosis/tubular atrophy.

Timarchi H. Kidney Int (2017) 91, 1014-21

The added value of crescents on Oxford classification score in risk stratification of ESKD in patients with IgAN

- 115 patients with IgAN (76% male, mean age: 37±13 years, mean serum creatinine: 4.0±4.3 mg/dl and mean proteinuria: 3.4±2.5 g/24 hours) were followed for 43±29 months.

- MEST score was defined according to Oxford classification (M0/M1, E0/E1, S0/S1).

- To increase the power of the study, T was defined as T0≤25% and T1> 25%.

The added value of crescents on Oxford classification score in risk stratification of ESKD in patients with IgAN

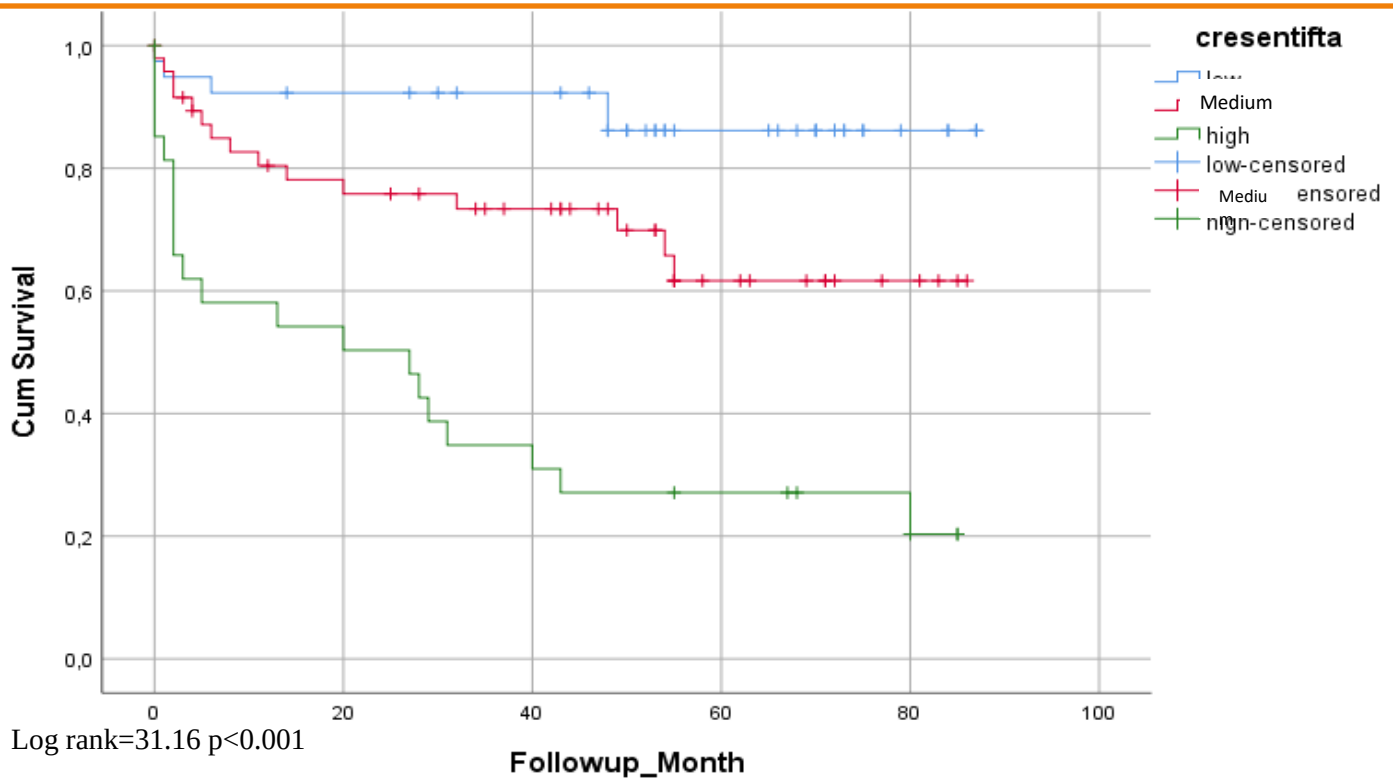
- Crescents were defined as:
  - C0: absence and C1: at least one crescents in biopsy.
- Additionally in sensitivity analysis, the risk of ESKD was estimated at different cut-off levels of at least 10%, 20% and 30% crescents

	Total No.115	ESKD (40, 35%)
C1	46 (40%)	21 (46% of C1)
C>30%	11 (9.5%)	7 (66% of C30)
T1	57 (49%)	34 (60% of T1)
T1+C1	27 (23%)	20 (78% of T1+C1)

Pathologic predictors of ESKD in adjusted model

	ESKD (%)	Univariate analyses HR (95% CI)	P-value	Multivariate analyses HR (95% CI)	P-value
C1+M1	25	0.93 (0.27.-3.20)	0.908	0.63 (0.23-1.14)	0.067
C1+E1	30	1.36 (0.53-3.48)	0.520	0.68 (0.26-1.81)	0.450
C1+S1	44	2.22 (1.00-4.95)	0.51	1.30 (0.49-3.45)	0.591
C1+T1	74	9.20 (3.43-24.63)	<0.0001	**6.54** (1.75-24.34)	**0.004**
C30%+T1	75	12.54 (3.80-41.30)	<0.0001	**7.95** (2.05-30.75)	**0.003**

Impact of presence or absence of combination of C and T in progression of ESKD with Kaplan–Meier plots.



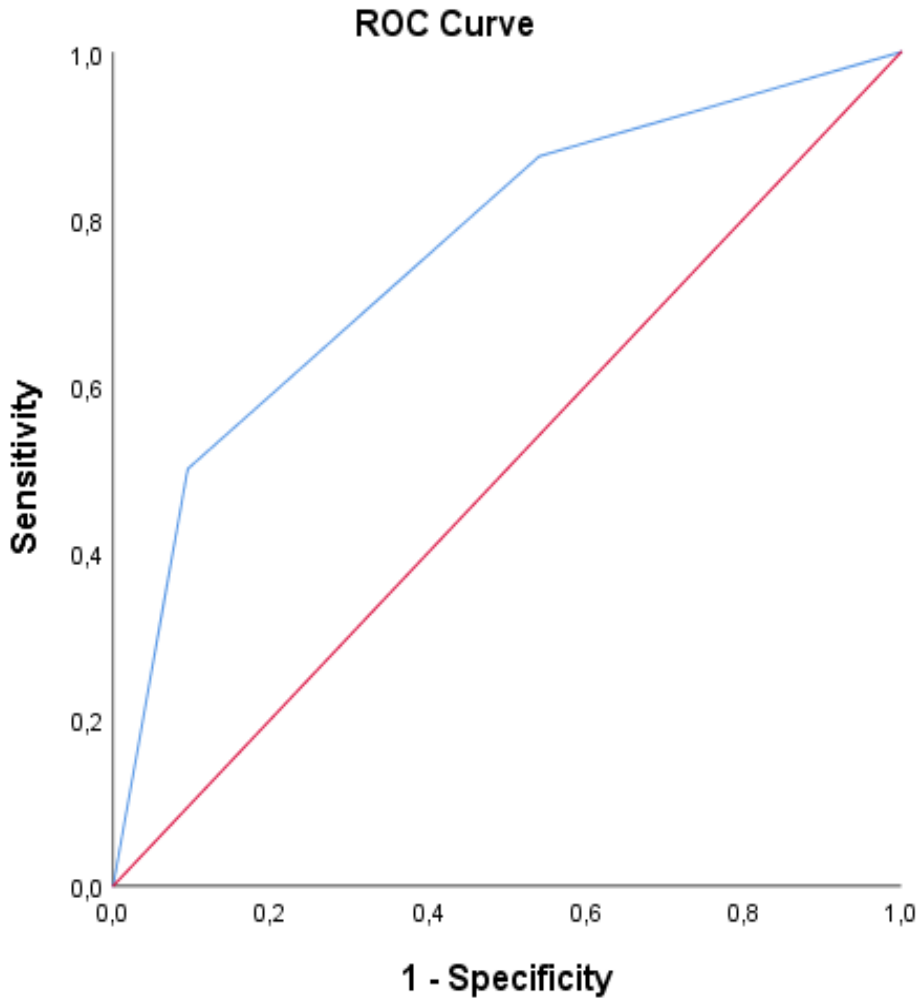
Log rank=31.16 p<0.001

	Mean survival time (months) (95% CI)
Low risk	78,08 (70.50-85.66)
Medium risk	61.64 (51.48-71-81)
High risk	32.30 (19.29-45.31)
Overall	60.63 (53.93-67.32)

Low risk: C0+T0. Medium risk: C1+T0 or C0+T1. High risk: C1+T1.

C1: at least one cellular or fibrocellular crescents. T1: tubular atrophy and interstitial fibrosis>25%.

Receiver-operating characteristic curves (estimated for evaluating the capacity of discrimination of the risk to predict ESKD with presence of C1+T1 in model. C-Statistic of 0.76 (95% CI: 0.67-0.85)



Univariate and multivariate analyses of baseline clinical and laboratory predictors of ESKD

	Univariate analyses HR 95% CI	P-value	Multivariate analyses HR 95% CI	P-value
Age (year)	0.99 (0.97-1.01)	0.587	0.99(0.96-1.03)	0.965
Sex (male)	0.63 (0.29-1.37)	0.246	0.78 (0.36-1.78)	0.569
Weight (kg)	0.99 (0.96-1.02)	0.603	0.98 (0.94-1.03)	0.608
S Cr(mg/dl)	1.20 (1.14-1.26)	<0.0001	1.22 (1.12-1.29)	**<0.0001**
U protein (g/24h)	1.00 (1.00-1.00)	0.623	1.00 (1.00-1.00)	**0.057**
Hypertension	2.71 (1.37-5.33)	0.004	1.69 (0.94-3.06)	0.316
M1	0.58 (024.-1.39)	0.224	2.26 (0.91-5.64)	0.079
E1	1.65 (0.80-3.38)	0.171	0.68 (0.26-1.81)	0.450
S1	1.71 (0.88-3.32)	0.111	0.69 (0.33-1.45)	0.021
T1	7.20 (3.01-17.18)	<0.0001	6.95 (2.20-22.02)	**0.01**
C1	2.13 (1.14-3.97)	0.017	1.02 (0.39-2.63)	0.96
C1 (10%)	1.94 (0.99-3.82)	0.055	0.631 (0.25-1.58)	0.325
C1 (20%)	2.77 (1.21-6.29)	0.015	1.41 (0.51-3.90)	0.501
C1(30%)	3.37 (1.48-7.68)	0.004	3.56 (1.15-11.00)	**0.027**

http://www.kidney-international.org

Treatment of IgA nephropathy

J Barratt[1] and J Feehally[1]

[1]*The John Walls Renal Unit, Department of Infection, Immunity and Inflammation, Leicester General Hospital, University of Leicester, Leicester, UK*

IgA nephropathy (IgAN) is an important cause of progressive kidney disease with 25–30% of patients developing end-stage renal disease within 20 years of diagnosis. There is still no treatment to modify mesangial IgA deposition and available treatments are those extrapolated from the management of other patterns of chronic glomerulonephritis. There remains no consensus on the use of immunosuppressive agents for treatment of progressive IgAN and this is compounded by the relative lack in IgAN of randomized controlled trials relevant to current clinical practice. Patients with recurrent macroscopic hematuria or isolated microscopic hematuria and proteinuria <1 g/24 h require no specific treatment. Those with nephrotic syndrome and minimal change on renal biopsy should be managed as for minimal change nephropathy. There is no evidence to support the use of corticosteroids for nephrotic IgAN outside this group of patients. Patients presenting with acute renal failure require evaluation to distinguish acute tubular necrosis, which

Immunoglobulin A nephropathy (IgAN) is the most common pattern of idiopathic glomerulonephritis in all countries where renal biopsy is widely practiced. It is an important cause of end-stage renal disease (ESRD) at all ages, and therefore treatment strategies to reduce the risk of IgAN progressing to ESRD would have substantial health benefit. There are, however, few well-designed randomized controlled trials (RCTs) to inform the treatment of this condition. The reason for this is in part the slow rate of progression of IgAN, making it necessary to study large numbers of patients for prolonged periods of time to determine the efficacy of any therapeutic intervention. Another consequence of the slowly progressive nature of IgAN is that for many of the trials now published patient recruitment occurred at a time when the management of progressive glomerular disease was less clearly defined than it is now.

In this review, we will critically evaluate the available evidence on the treatment of IgAN, especially focusing

mini review

http://www.kidney-international.org

Treatment of IgA nephropathy

J Barratt[1] and J Feehally[1]

[1]*The John Walls Renal Unit, Department of Infection, Immunity and Inflammation, Leicester General Hospital, University of Leicester, Leicester, UK*

Table 1 | Treatment recommendations for IgAN according to clinical features

Clinical presentation	Recommended treatment
Recurrent macroscopic hematuria with preserved renal function	No specific treatment – no role for antibiotics or tonsillectomy
Proteinuria <1 g/24 h ± microscopic hematuria	No specific treatment
Proteinuria >1 g/24 h ± microscopic hematuria	Combined renin–angiotensin blockade with ACE inhibitor and ARB
Acute renal failure	
Acute tubular necrosis	Supportive measures
Crescentic IgAN (with little or no chronic damage)	
Induction (~8 weeks)	Prednisolone 0.5–1 mg/kg/day Cyclophosphamide 2 mg/kg/day
Maintenance	Prednisolone in reducing dosage Azathioprine 2.5 mg/kg/day
Nephrotic syndrome	
With minimal change on light microscopy	Prednisolone 0.5–1 mg/kg/day for up to 8 weeks
With structural glomerular changes	No specific treatment
Hypertension	Target BP 125/75 mm Hg if proteinuria >1 g/24 h ACE inhibitors/ARB first choice agents

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; IgAN, IgA nephropathy.

There are limited data concerning the effectiveness of cytotoxic agents in adults with progressive IgA nephropathy

Nephrol Dial Transplant (1995) 10: 2054–2059

Nephrology
Dialysis
Transplantation

Original Article

Report on intensive treatment of extracapillary glomerulonephritis with focus on crescentic IgA nephropathy

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[1]Divisione di Nefrologia e Dialisi dell'Ospedale G. Bosco, and [2]Istituto di Nefrourologia Università di Torino; [3]Divisione di Nefrologia e Dialisi dell'Ospedale Infantile Regina Margherita, Torino, Italy

Abstract

Purpose and design of study. In this retrospective analysis the effects of combined treatment with steroid pulses, cyclophosphamide and plasma exchange on six crescentic IgA glomerulonephritis (IgAGN) patients, selected on a histological basis, were examined. The histological criteria included involvement of more than 40% of glomeruli by cellular crescents. The effects of this treatment were compared to those observed in three untreated crescentic IgAGN patients and 12 treated patients who had extracapillary glomerulonephritis of different origins, i.e. ANCA-associated systemic or renal-limited vasculitis. All patients, except the three crescentic untreated IgAGN patients, received the same 2-month treatment according to a standardized protocol: steroid boli 15 mg/kg methylpredniso-

Introduction

Crescentic glomerulonephritis with a rapidly progressive course can result from deposition of antiglomerular basement membrane antibody, immune complexes or yet undefined mechanisms involving cell mediated processes, via inflammatory effector cells and sensitized lymphocytes. Despite several advances in understanding glomerular immune injury (reviewed in [1]), therapy remains largely empirical. Prognosis of crescentic GN has generally improved over time, but no disease-specific therapy has been clearly shown to be definitely beneficial. In addition, the currently available data have been collected or analysed without considering several variables which affect outcome, including the relative balance between active phlogistic

Nephrol Dial Transplant (1995) 10: 2054–2059

Nephrology
Dialysis
Transplantation

Original Article

Report on intensive treatment of extracapillary glomerulonephritis with focus on crescentic IgA nephropathy

- Methylprednisolone 15mg/kg IV for 3 days→
- Prednisone oral (1 mg/kg/day for 4 weeks, 0.75 mg/kg/day for 4 more weeks), →
- Cyclophosphamide oral 2.5 mg/kg/day for 8 weeks &
- Plasma exchange.

Purpose and design of study. In this retrospective ana-

- After this 2-month course of therapy, substantial clinical improvement was observed in both IgAGN and vasculitis patients.
- However, a second biopsy revealed that florid crescents persisted in IgAGN patients and, unlike the vasculitis group, during the long-term the initial clinical amelioration disappeared in one-half of the treated IgAGN cases.
- Nevertheless, even in the progressive cases, intensive treatment seemed to substantially delay the onset of dialysis

ing the relative balance between active phlogistic

J Am Soc Nephrol 13: 142–148, 2002

Controlled Prospective Trial of Prednisolone and Cytotoxics in Progressive IgA Nephropathy

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Abstract. In a single-center, multiple-referral source study, 38 patients with progressive IgA nephropathy and controlled hypertension were randomized to treatment with prednisolone and cytotoxic agents, to therapy with low-dose cyclophosphamide then azathioprine, and to control groups. The follow-up period lasted 2 to 6 yr. Renal survival, as assessed by Kaplan-Meier analysis annually to 5 yr, showed significant preservation of function from 3 yr in the treatment group and 82, 82, 72, and 72% for 2, 3, 4, and 5 yr, respectively, compared with 68, 47, 26, and 6% in controls. Rate of loss of renal function, evaluated objectively by least-squares analyses of reciprocal serum creatinine, was reduced—and in one-third of the patients, arrested—during immunosuppressive treatment. Proteinuria, present in all patients at the time of entry into the trial, was reduced by treatment from 12 mo, compared with pretreatment levels or controls; erythrocyturia was reduced from 6 mo. Histologic activity and chronicity indexes were determined in renal biopsies performed at trial entry. Multivariate analysis demonstrated that mesangial cell proliferation and matrix scores were highest in those patients with more rapidly progressive disease. No morphologic variable or residual renal function predicted response to immunosuppressive therapy at entry. Mean arterial pressures did not differ significantly between treatment and control groups. There was thus no explanation other than treatment for the improved outcome in patients who received immunosuppressive therapy. Morbidity attributable to treatment or to renal failure occurred in both groups; an audit showed that benefits of therapy outweighed expected or minor side effects of drugs in this population at risk of end-stage renal failure. Patients selected for moderately progressive IgA nephropathy benefit from treatment with prednisolone and cytotoxic agents; results are consistent with modulation of systemic immune response or nephritic injury, thus explaining improved outcome, and indicate that this therapy has an acceptably low risk of side effects.

Randomization of 38 patients with progressive IgAN

A- control group (no immunosuppression

B- Prednisolone 40 mg/d (red. to 10 mg/d by 2 yr) +

Cyclophosphamide 1.5 mg/kg per day (adjusted down to the nearest 50 mg) for the initial 3 mo, then

azathioprine at the same dose continued for a minimum of 2 yr (up to 6 yrs)

Duration of follow-up was 2 -6 yr, with the low-dose immunosuppressive treatment unaltered, unless the patient reached ESKD

Ballardie FW. J Am Soc Nephrol. 2002;13(1):142

Randomization of 38 patients with progressive IgAN

A- contro

B- Predniso

Cyclophospha ed down to the nearest 50 mg) for the initial 3 mo, then

azathioprine at the same dose continued for a minimum of 2 yr (up to 6 yrs)

- impaired renal function,
- hypertension,
- absence of macroscopic hematuria,
- heavy proteinuria.

Duration of follow-up was 2 -6 yr, with the low-dose immunosuppressive treatment unaltered, unless the patient reached ESKD

Ballardie FW. J Am Soc Nephrol. 2002;13(1):142

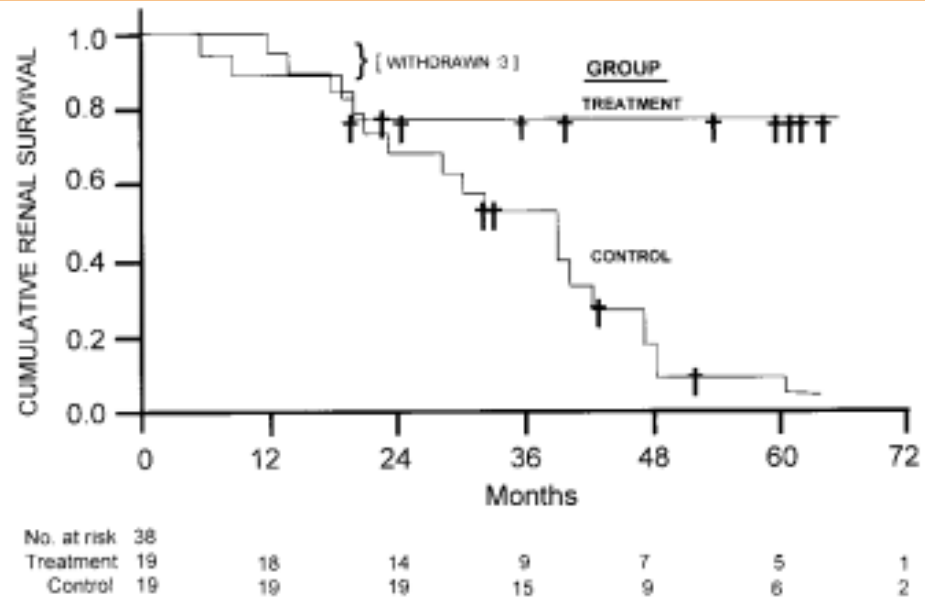

Figure 1. Kaplan-Meier survival functions for progressive IgA-related nephropathy for treatment and control groups. Preservation of function was significant after 2 yr ($P = 0.006$, log rank; $P = 0.036$, Tarone-Ware; †, censored—*i.e.*, not incurring event).

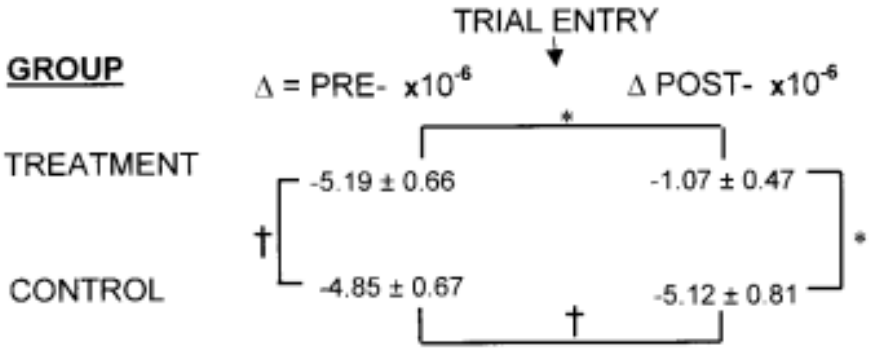

Figure 2. Rate of decline of renal function before and after trial entry for treatment and control groups. The mean rate of decline was reduced more than fourfold in the treatment group (mean ± SEM; *, $P < 0.005$, t test; †, P = NS; units are Δ = L · μmol^{-1} · d^{-1}). End-stage failure in 5 yr implies renal function loss, $\Delta \geq -4.9 \times 10^{-6}$ L · μmol^{-1} · d^{-1}).

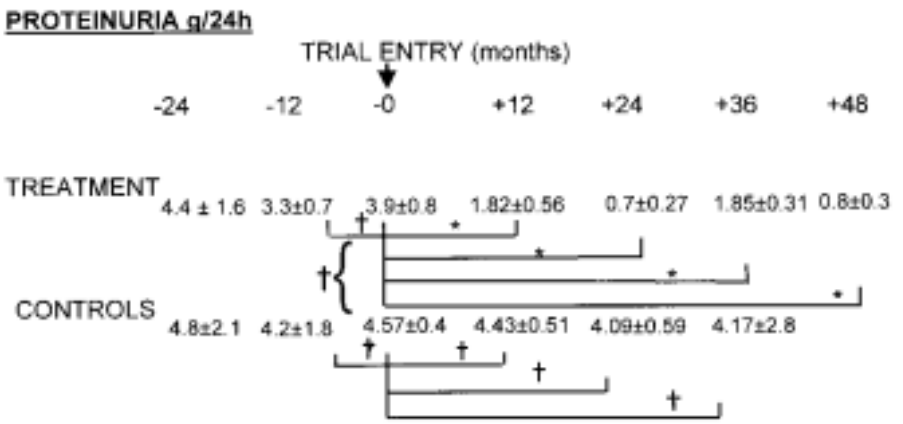

Figure 4. Trial proteinuria data. Significant reductions in the treatment group were consistent from 12 mo after trial entry (mean ± SEM; *, $P < 0.02$; †, P = NS; Wilcoxon-Mann-Whitney test).

Ballardie FW. J Am Soc Nephrol. 2002;13(1):142

STOP- IgAN trial

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*

ABSTRACT

BACKGROUND

The outcomes of immunosuppressive therapy, when added to supportive care, in patients with IgA nephropathy are uncertain.

METHODS

We conducted a multicenter, open-label, randomized, controlled trial with a two-group, parallel, group-sequential design. During a 6-month run-in phase, supportive care (in particular, blockade of the renin–angiotensin system) was adjusted on the basis of proteinuria. Patients who had persistent proteinuria with urinary protein excretion of at least 0.75 g per day were randomly assigned to receive supportive care alone (supportive-care group) or supportive care plus immunosuppressive therapy (immunosuppression group) for 3 years. The primary end points in hierarchical order were full clinical remission at the end of the trial (protein-to-creatinine ratio <0.2 [with both protein and creatinine measured in grams] and a decrease in the estimated glomerular filtration rate [eGFR] of <5 ml per minute per 1.73 m^2 of body-surface area from baseline) and a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2 at the end of the trial. The primary end

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*A complete list of participating centers and investigators in the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Rauen and Eitner contributed equally to this article.

Randomization

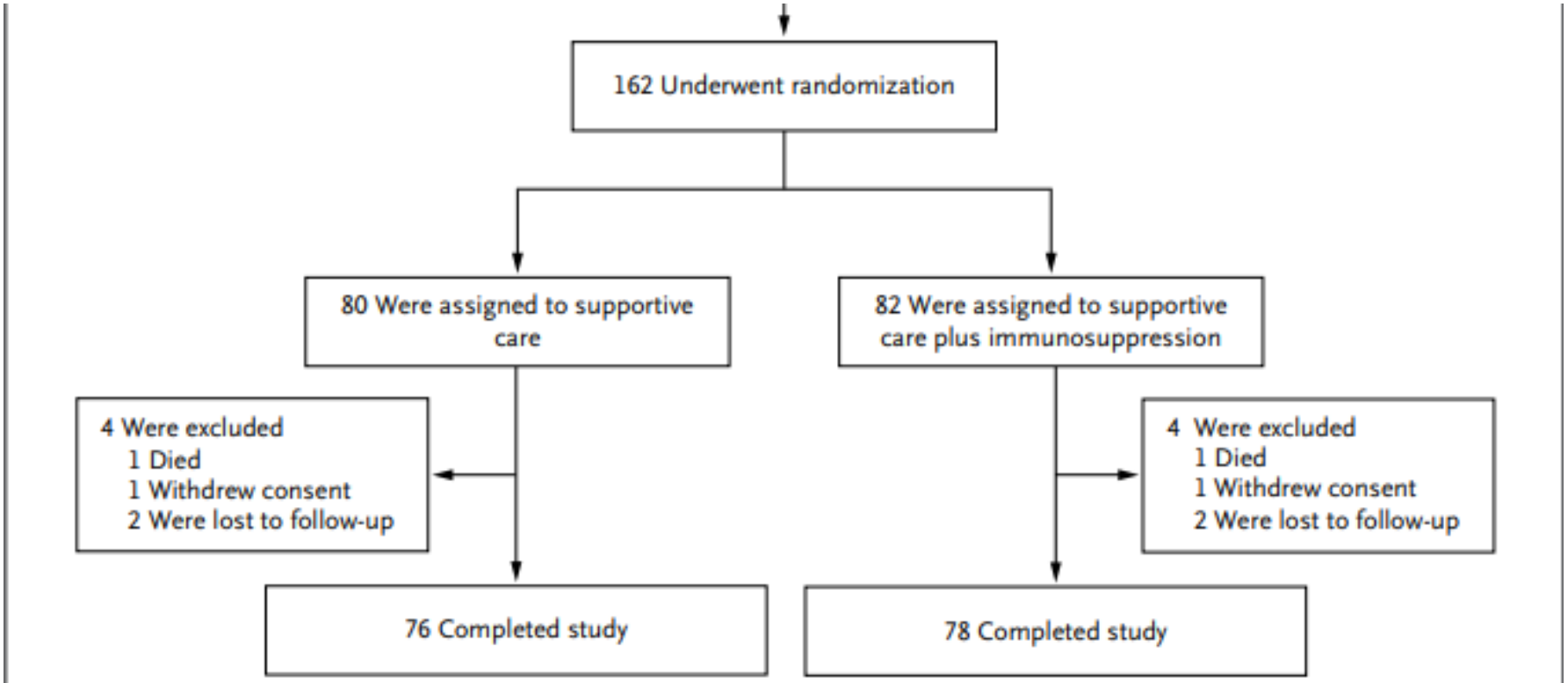
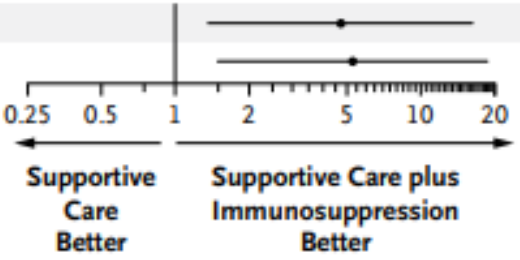


Figure 1. Eligibility, Enrollment, and Randomization.

A total of 379 patients with IgA nephropathy were screened for eligibility, of whom 337 entered the 6-month run-in phase, during which all patients received supportive care. Among the 309 patients who completed this phase, 165 still had proteinuria with urinary protein excretion rates of 0.75 to less than 3.5 g per day, and 106 had proteinuria with urinary protein excretion rates below 0.75 g per day. Among the latter 106 patients, 12 had an increase in urinary protein excretion rates to at least 0.75 g per day during further follow-up. Thus, 177 patients were eligible for the subsequent 3-year randomized trial phase, of whom 162 consented to participate in this phase and were randomly assigned to either continue supportive care or receive supportive care plus immunosuppressive therapy.

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

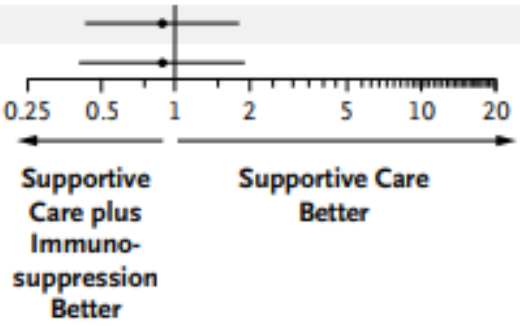


Figure 2. Primary End Points.

Panel A shows the first primary end point: full clinical remission at the end of the 3-year trial phase (protein-to-creatinine ratio <0.2 [with both protein and creatinine measured in grams] and a decrease in the estimated glomerular filtration rate [eGFR] of <5 ml per minute per 1.73 m^2 of body-surface area from baseline). Panel B shows the second primary end point: a decrease in the eGFR of at least 15 ml per minute per 1.73 m^2 during the trial phase. A subgroup analysis was performed for both end points with the use of a full-analysis set and an available-case analysis set. In the full-analysis set, missing values in all events in all patients who underwent randomization were substituted by the worst clinical case (i.e., no clinical remission and decrease in the eGFR of at least 15 ml per minute per 1.73 m^2); in the available-case analysis set, only documented events among patients with available data were included in the analysis.

- Despite the significant, though moderate, effects on proteinuria, we did not observe a significant effect of immunosuppressive therapy on a decrease in the eGFR over the 3 year study period either on the basis of the primary end point of an eGFR decrease of 15 ml/min/1.73 m^2 or more from the baseline eGFR or on the basis of various secondary eGFR end points.

ELSEVIER

Kidney International

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clinical trial

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

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

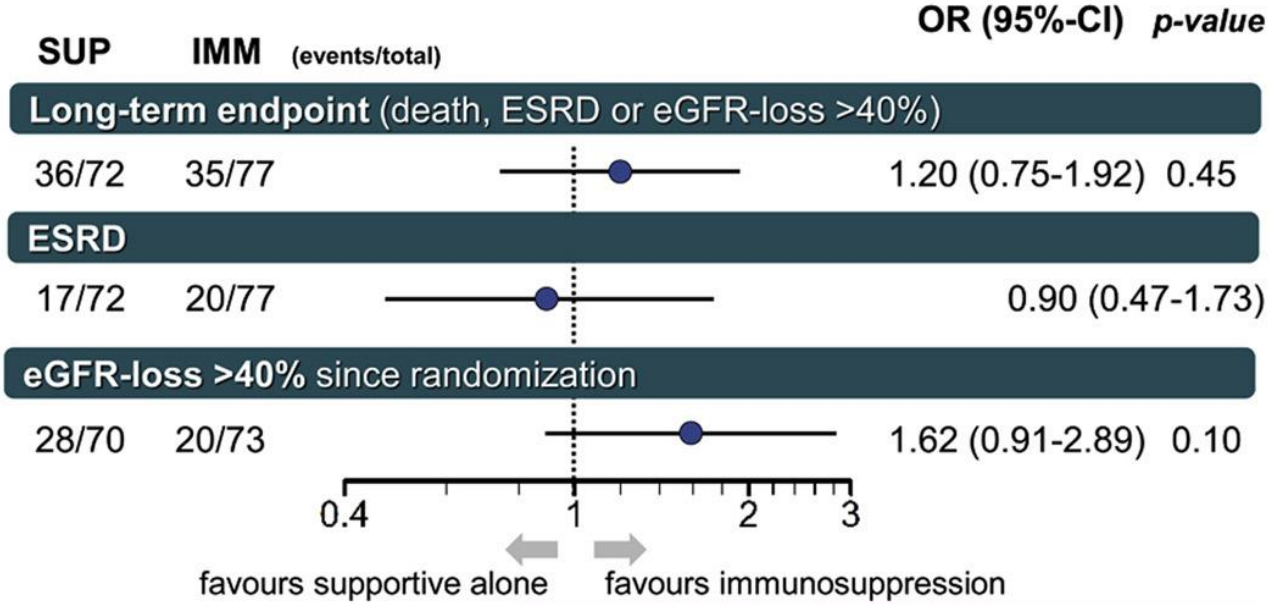
After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy.

Randomized 3-year trial phase

Supportive care alone

Supportive care plus immuno-suppression

Passive follow-up after end of randomized trial (up to 10 years)



CONCLUSION:

Within the limitations of a retrospective study, over a follow-up of up to 10 years, IgAN patients did not benefit from additional immuno-suppression on top of supportive care measures.

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Rauen *et al.* 2020

Occurrence of the primary endpoint since randomization in patient groups stratified by GFR and proteinuria at baseline

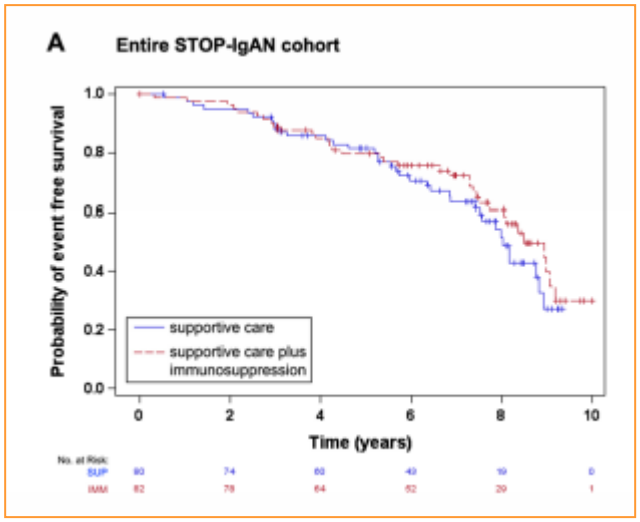
Baseline-Proteinuria Baseline eGFR	<1.5 g per day (N=77)	≥1.5 g per day (N=72)
≥60 ml/min per 1.73 m² (N=101)	**17**	**21**
• Supportive (N=50)	11	10
• Immunosuppression (N=51)	6	11
<60 ml/min per 1.73 m² (N=48)	**12**	**21**
• Supportive (N=22)	7	8
• Immunosuppression (N=26)	5	13

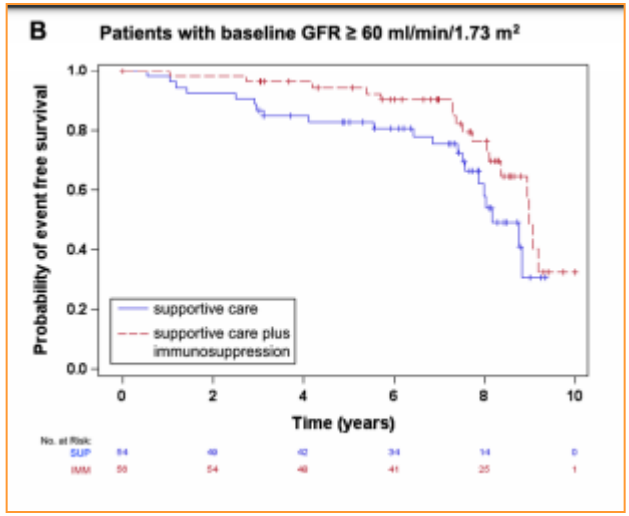
Table 2: **Occurrence of secondary endpoints since randomization** (based on the analysis of available cases at the end of the long-term observation)

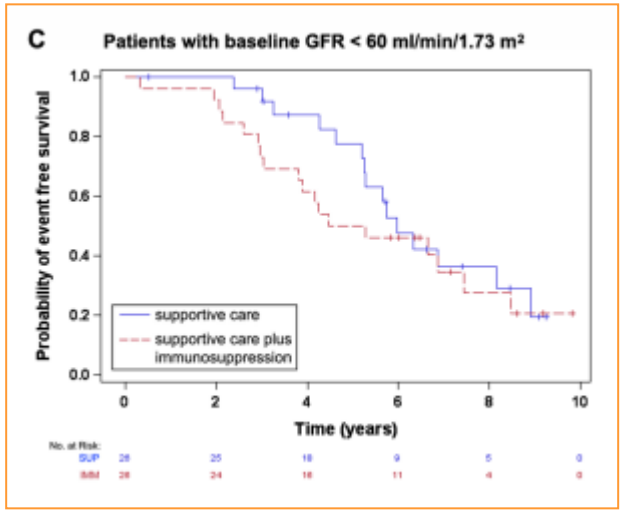
	Supportive care		Supportive care plus immunosuppression				
	available	n (%)	available	n (%)	HR	95% CI	*p* value
All-cause death	72	2 (2.8)	77	3 (3.9)	0.71	0.12 to 4.32	0.71
Onset of ESRD	72	17 (23.6)	77	20 (26.0)	0.90	0.47 to 1.73	0.74
GFR loss >40%*	70	28 (40.0)	73	20 (27.4)	1.62	0.91 to 2.89	0.10
GFR loss >30%*	70	38 (54.3)	73	29 (39.7)	1.28	0.78 to 2.08	0.33

	available	mean	SD	available	mean	SD	*p* value
Annual eGFR change since randomization (ml/min per 1.73 m²)	80	-2.68	1.99	79	-2.36	2.19	0.46
Annual eGFR change after the randomized trial phase (ml/min per 1.73 m²)	70	-3.15	2.44	71	-2.86	3.47	0.28
Protein/creatinine ratio at the end of observation (g/g)	30	1.29	1.34	33	1.28	2.49	0.99
Proteinuria at the end of observation (g/day)**	37	1.44	1.00	37	1.23	1.27	0.43

ESRD, end-stage renal disease; HR, hazard ratio; CI, confidence interval; (*) = as compared to baseline eGFR; (**) = in some patients proteinuria was available in "g/g creatinine", whereas in others it was available in "g/day"


A
Entire STOP-IgAN cohort
Probability of event free survival
1.0
0.8
0.6
0.4
0.2
0.0
supportive care
supportive care plus immunosuppression
0
2
4
6
8
10
Time (years)
No. at Risk:
SUP 80 74 60 49 19 0
IMM 82 78 64 52 29 1


B
Patients with baseline GFR ≥ 60 ml/min/1.73 m²
Probability of event free survival
1.0
0.8
0.6
0.4
0.2
0.0
supportive care
supportive care plus immunosuppression
0
2
4
6
8
10
Time (years)
No. at Risk:
SUP 64 49 42 34 14 0
IMM 59 54 46 41 25 1


C
Patients with baseline GFR < 60 ml/min/1.73 m²
Probability of event free survival
1.0
0.8
0.6
0.4
0.2
0.0
supportive care
supportive care plus immunosuppression
0
2
4
6
8
10
Time (years)
No. at Risk:
SUP 26 25 18 9 5 0
IMM 26 24 16 11 4 0

JAMA | Original Investigation

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

eGFR : 20-120 mL/min & proteinuria> 1 g/d

0.6 to 0.8mg/kg/d of oral methylpred. or placebo) for 2 mo, tapered by 8 mg/d each month, totally 6 to 8 mo.

RESULTS After randomization of 262 participants (mean age, 38.6 [SD, 11.1] years; 96 [37%] women; eGFR, 59.4 mL/min/1.73 m^2; urine protein excretion, 2.40 g/d) and 2.1 years' median follow-up, recruitment was discontinued because of excess serious adverse events. Serious events occurred in 20 participants (14.7%) in the methylprednisolone group vs 4 (3.2%) in the placebo group (P = .001; risk difference, 11.5% [95% CI, 4.8%-18.2%]), mostly due to excess serious infections (11 [8.1%] vs 0; risk difference, 8.1% [95% CI, 3.5%-13.9%]; P < .001), including 2 deaths. The primary renal outcome occurred in 8 participants (5.9%) in the methylprednisolone group vs 20 (15.9%) in the placebo group (hazard ratio, 0.37 [95% CI, 0.17-0.85]; risk difference, 10.0% [95% CI, 2.5%-17.9%]; P = .02).

CONCLUSIONS AND RELEVANCE Among patients with IgA nephropathy and proteinuria of 1 g/d or greater, oral methylprednisolone was associated with an increased risk of serious adverse events, primarily infections. Although the results were consistent with potential renal benefit, definitive conclusions about treatment benefit cannot be made, owing to early termination of the trial.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01560052

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

Table 3. Effects of Corticosteroids on Prespecified Primary and Secondary Outcomes

Outcome	Methylprednisolone (n = 136)	Placebo (n = 126)	Absolute Difference (95%CI)	*P* Value[a]
Primary outcome, No. (%)				
40% eGFR decrease, ESKD, or death due to kidney failure	8 (5.9)	20 (15.9)	10.0 (2.5 to 17.9)	.02
Protocol-specified secondary outcomes				
40% eGFR decrease, ESKD, or all-cause death, No. (%)	10 (7.4)	20 (15.9)	8.5 (0.7 to 16.6)	.03
50% eGFR decrease, ESKD, or all-cause death, No. (%)	10 (7.4)	15 (11.9)	4.6 (2.7 to 12.1)	.29
40% eGFR decrease, No. (%)	7 (5.1)	16 (12.7)	7.6 (0.6 to 15.0)	.05
50% eGFR decrease, No. (%)	7 (5.1)	11 (8.7)	3.6 (2.8 to 10.3)	.33
ESKD or death due to kidney failure, No. (%)[b]	4 (2.9)	10 (7.9)	5.0 (0.7 to 11.3)	.10
Death due to any cause, No. (%)	2 (1.5)	1 (0.8)	0.7 (−0.3 to 0.4 to)	>.99
Rate of eGFR decline using all visits, mean (95% CI), mL/min/1.73 m^{2}[c]	−1.79 (−4.74 to 1.16)	−6.95 (−10.68 to −3.21)	5.15(0.42 to 9.89)	.03
Rate of eGFR decline excluding values on high-exposure treatment, mean (95% CI), mL/min/1.73 m^{2}[d]	−0.11 (−2.52 to 2.30)	−6.38 (−8.93 to −3.82)	6.27 (2.77 to 9.76)	<.001
Rate of eGFR decline excluding values on treatment, mean (95% CI), mL/min/1.73 m^{2}[b,e]	−1.64 (−3.33 to 0.05)	−5.64 (−7.86 to −3.41)	4.00 (1.22 to 6.78)	.005

Key Points

Question Do corticosteroids safely prevent loss of kidney function in patients with IgA nephropathy receiving optimal supportive therapy?

Findings This randomized clinical trial that included 262 participants was stopped early (after 28 of the 335 planned events) due to a significantly increased risk of serious adverse events with oral methylprednisolone vs placebo (14.7% vs 3.2%, primarily excess infections); at that point, the primary efficacy outcome favored methylprednisolone (5.9% vs 15.9%).

Meaning Oral corticosteroid therapy was associated with an increased risk of serious adverse events; the effect on kidney outcomes remains uncertain due to the limited number of events.

Addition of Azathioprine to Corticosteroids Does Not Benefit Patients with IgA Nephropathy

Claudio Pozzi,*† Simeone Andrulli,* Antonello Pani,‡ Patrizia Scaini,§ Lucia Del Vecchio,* Giambattista Fogazzi,‖ Bruno Vogt,¶ Vincenzo De Cristofaro,** Landino Allegri,†† Lino Cirami,‡‡ Aldo Deni Procaccini,§§ and Francesco Locatelli*

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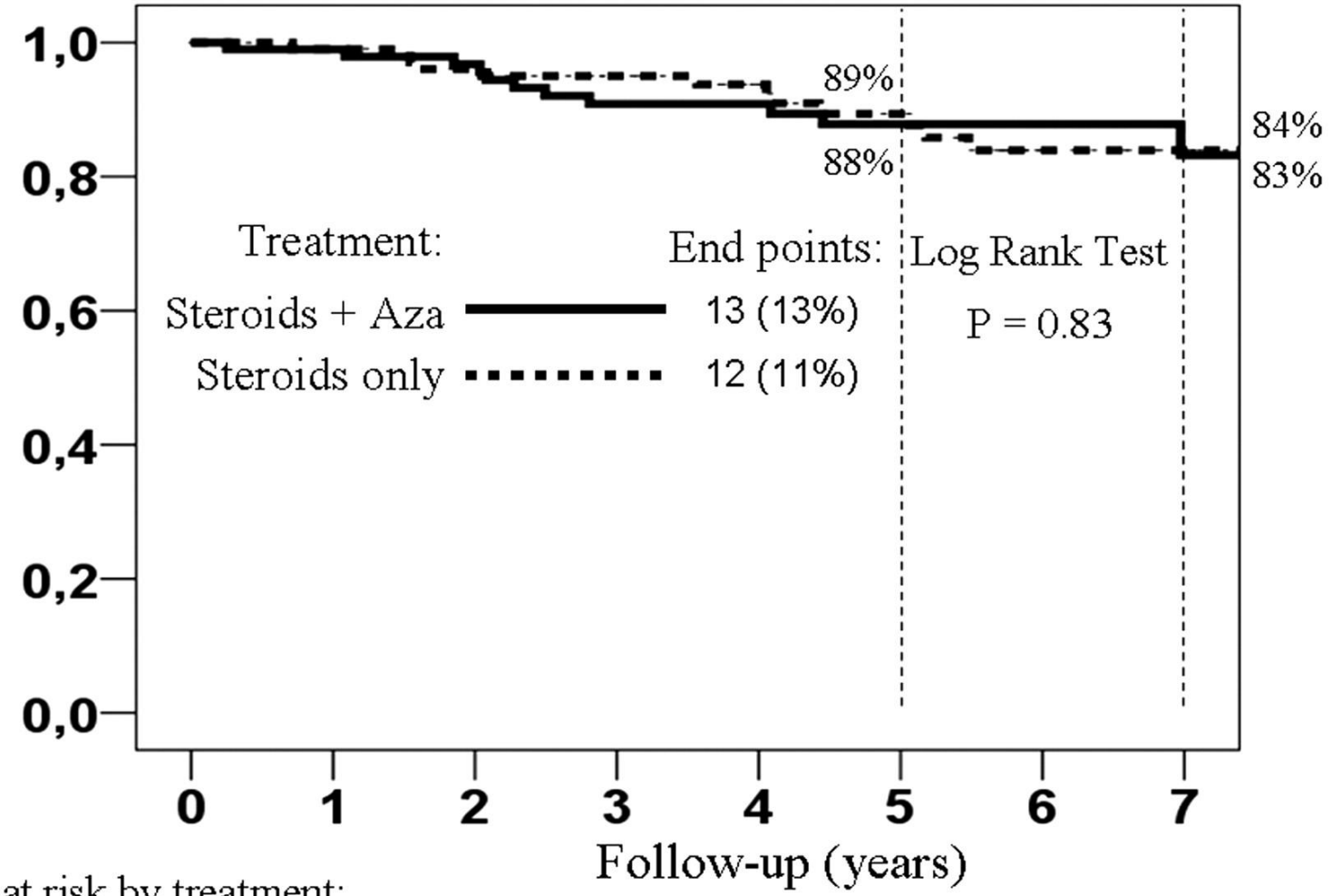
ABSTRACT

The optimal treatment for IgA nephropathy (IgAN) remains unknown. Some patients respond to corticosteroids, suggesting that more aggressive treatment may provide additional benefit. We performed a randomized, multicenter, controlled trial to determine whether adding azathioprine to steroids improves renal outcome. We randomly assigned 207 IgAN patients with creatinine ≤2.0 mg/dl and proteinuria ≥1.0 g/d to either (*1*) a 3-day pulse of methylprednisolone in months 1, 3, and 5 in addition to both oral prednisone 0.5 mg/kg every other day and azathioprine 1.5 mg/kg per day for 6 months ($n = 101$, group 1) or (*2*) steroids alone on the same schedule ($n = 106$, group 2). The primary outcome was renal survival (time to 50% increase in plasma creatinine from baseline); secondary outcomes were changes in proteinuria over time and safety. After a median follow-up of 4.9 years, the primary endpoint occurred in 13 patients in group 1 (12.9%, 95% CI 7.5 to 20.9%) and 12 patients in group 2 (11.3%, CI 6.5 to 18.9%) ($P = 0.83$). Five-year cumulative renal survival was similar between groups (88 *versus* 89%; $P = 0.83$). Multivariate Cox regression analysis revealed that female gender, systolic BP, number of antihypertensive drugs, ACE inhibitor use, and proteinuria during follow-up predicted the risk of reaching the primary endpoint. Treatment significantly decreased proteinuria from 2.00 to 1.07 g/d during follow-up ($P < 0.001$) on average, with no difference between groups. Treatment-related adverse events were more frequent among those receiving azathioprine. In summary, adding low-dose azathioprine to corticosteroids for 6 months does not provide additional benefit to patients with IgAN and may increase the risk for adverse events.

J Am Soc Nephrol 21: 1783–1790, 2010. doi: 10.1681/ASN.2010010117

Renal survival is similar in the 2 treatment groups



Patients at risk by treatment:

Steroids+Aza	101	90	84	74	65	47	35	17
Steroids	106	101	93	82	67	53	31	19

Claudio Pozzi et al. JASN 2010;21:1783-1790

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]

ABSTRACT

The role of immunosuppression in IgA nephropathy (IgAN) is controversial. In the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) Trial, 162 patients with IgAN and proteinuria >0.75 g/d after 6 months of optimized supportive care were randomized into two groups: continued supportive care or additional immunosuppression (GFR≥60 ml/min per 1.73 m^2: 6-month corticosteroid monotherapy; GFR=30–59 ml/min per 1.73 m^2: cyclophosphamide for 3 months followed by azathioprine plus oral prednisolone). Coprimary end points were full clinical remission and GFR loss ≥15 ml/min per 1.73 m^2 during the 3-year trial phase. In this secondary intention to treat analysis, we separately analyzed data from each immunosuppression subgroup and the corresponding patients on supportive care. Full clinical remission occurred in 11 (20%) patients receiving corticosteroid monotherapy and three (6%) patients on supportive care (odds ratio, 5.31; 95% confidence interval, 1.07 to 26.36; P=0.02), but the rate did not differ between patients receiving immunosuppressive combination and controls on supportive care (11% versus 4%, respectively; P=0.30). The end point of GFR loss ≥15 ml/min per 1.73 m^2 did not differ between groups. Only corticosteroid monotherapy transiently reduced proteinuria at 12 months. Severe infections, impaired glucose tolerance, and/or weight gain in the first year were more frequent with either immunosuppressive regimen than with supportive care. In conclusion, only corticosteroid monotherapy induced disease remission in a minority of patients who had IgAN with relatively well preserved GFR and persistent proteinuria. Neither immunosuppressive regimen prevented GFR loss, and both associated with substantial adverse events.

J Am Soc Nephrol 29: 317–325, 2018. doi: https://doi.org/10.1681/ASN.2017060713

J Am Soc Nephrol 29: 317–325, 2018

Randomization

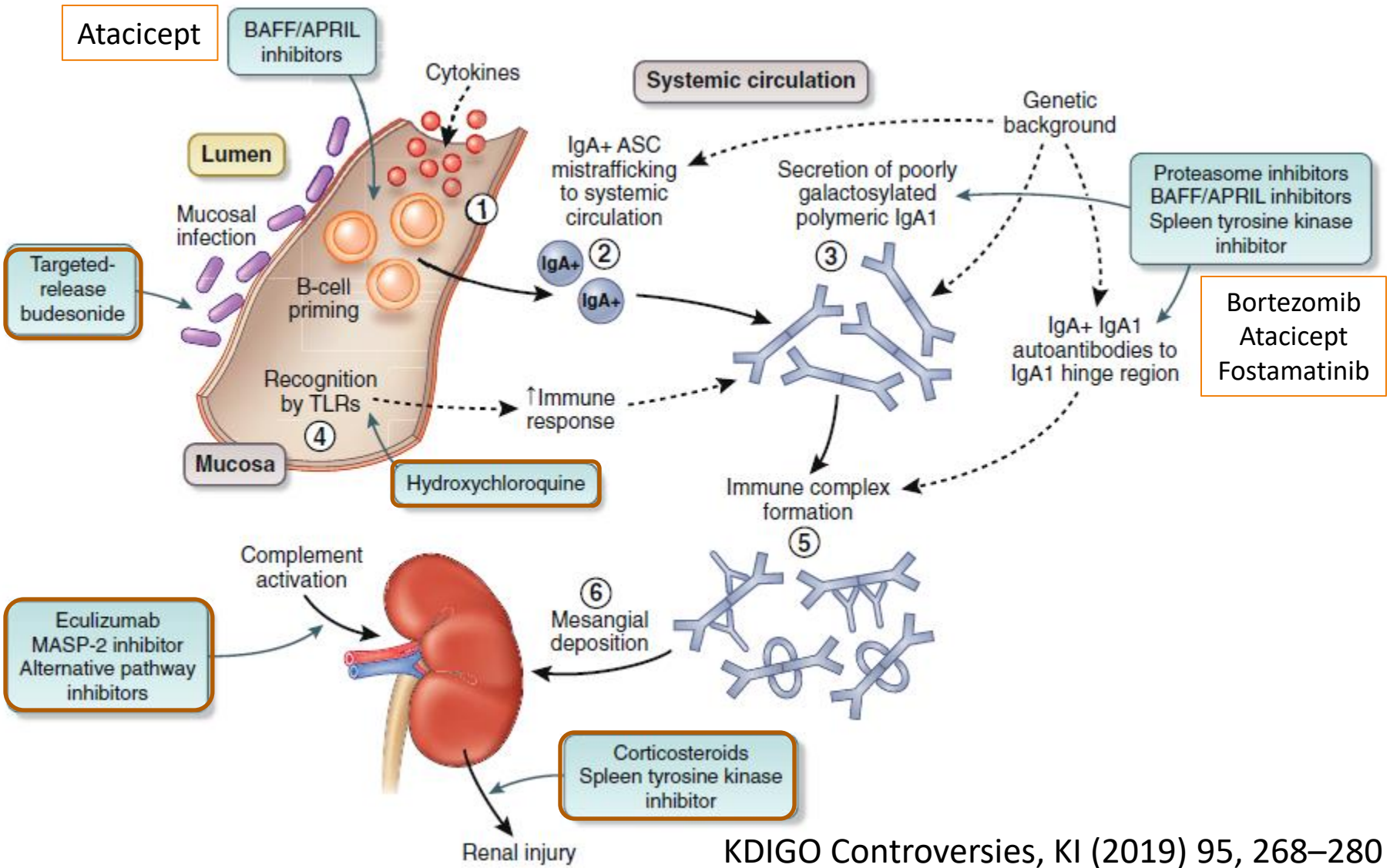
Table 1. Baseline characteristics of randomized patients in the two GFR arms

Characteristic	High-GFR Arm (109, >60 ml/min/1.73 ^{2})		Low-GFR Arm (53, 30-59 ml/min/	
	Supportive Care, *n*=54	Corticosteroid Monotherapy, *n*=55	Supportive Care, *n*=26	Immunsuppressive Combination, *n*=27
Women, %	13	24	31	26
Smoker, %	19	20	12	11
Age, yr	45.6±11.9	41.7±13.3	46.0±14.0	45.1±12.8
Body mass index, kg/m^2	28.0±4.7	27.3±5.0	29.9±6.2	26.6±5.2
BP, mm Hg				
Systolic	127±8.4	124±10.2	125±8.7	126±8.7
Diastolic	79±7.7	77±6.7	78±5.3	78±7.6
Serum creatinine, mg/dl	1.4±0.5	1.3±0.4	2.0±0.6	2.2±0.7
GFR, ml/min per 1.73 m^2	88.2±28.6	94.2±32.2	49.9±17.5	42.4±11.4
Daily urinary protein excretion, g/d	1.6±0.7	1.6±0.8	1.7±0.7	2.0±0.8
Urinary protein-to-creatinine ratio, g/g	0.9±0.5	0.9±0.5	1.1±0.6	1.5±0.7
Cholesterol, mg/dl	196±46	194±42	183±25	193±53

Significance Statement

In the STOP-IgAN trial patients with IgA nephropathy (IgAN) did not benefit from immunosuppression added to comprehensive supportive care. In this *post-hoc* sub-group analysis, patients with a baseline eGFR ≥60 ml/min per 1.73 m^2 were more likely to achieve full clinical remission under corticosteroid monotherapy than with supportive care, whereas patients with a baseline eGFR 30-59 ml/min per 1.73 m^2 treated with combination immunosuppression had similar rates of clinical remission as supportive care. GFR-loss rates did not differ between treatment regimens. Severe infections, impaired glucose tolerance and/or weight gain were more frequent with corticosteroids or combination immunosuppression than with supportive care. Potential benefits from corticosteroid monotherapy in IgAN with preserved kidney function must be balanced against increased adverse events; alternative therapeutic approaches to IgAN are needed.

Proposed pathogenesis of IgA nephropathy (IgAN) and potential therapeutic targets



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CLINICAL RESEARCH www.jasn.org

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

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ABSTRACT

IgA nephropathy frequently leads to progressive CKD. Although interest surrounds use of immunosuppressive agents added to standard therapy, several recent studies have questioned efficacy of these agents. Depleting antibody–producing B cells potentially offers a new therapy. In this open label, multicenter study conducted over 1-year follow-up, we randomized 34 adult patients with biopsy–proven IgA nephropathy and proteinuria >1 g/d, maintained on angiotensin–converting enzyme inhibitors or angiotensin receptor blockers with well controlled BP and eGFR<90 ml/min per 1.73 m^2, to receive standard therapy or rituximab with standard therapy. Primary outcome measures included change in proteinuria and change in eGFR. Median baseline serum creatinine level (range) was 1.4 (0.8–2.4) mg/dl, and proteinuria was 2.1 (0.6–5.3) g/d. Treatment with rituximab depleted B cells and was well tolerated. eGFR did not change in either group. Rituximab did not alter the level of proteinuria compared with that at baseline or in the control group; three patients in each group had ≥50% reduction in level of proteinuria. Serum levels of galactose-deficient IgA1 or antibodies against galactose-deficient IgA1 did not change. In this trial, rituximab therapy did not significantly improve renal function or proteinuria assessed over 1 year. Although rituximab effectively depleted B cells, it failed to reduce serum levels of galactose-deficient IgA1 and antigalactose–deficient IgA1 antibodies. Lack of efficacy of rituximab, at least at this stage and severity of IgA nephropathy, may reflect a failure of rituximab to reduce levels of specific antibodies assigned salient pathogenetic roles in IgA nephropathy.

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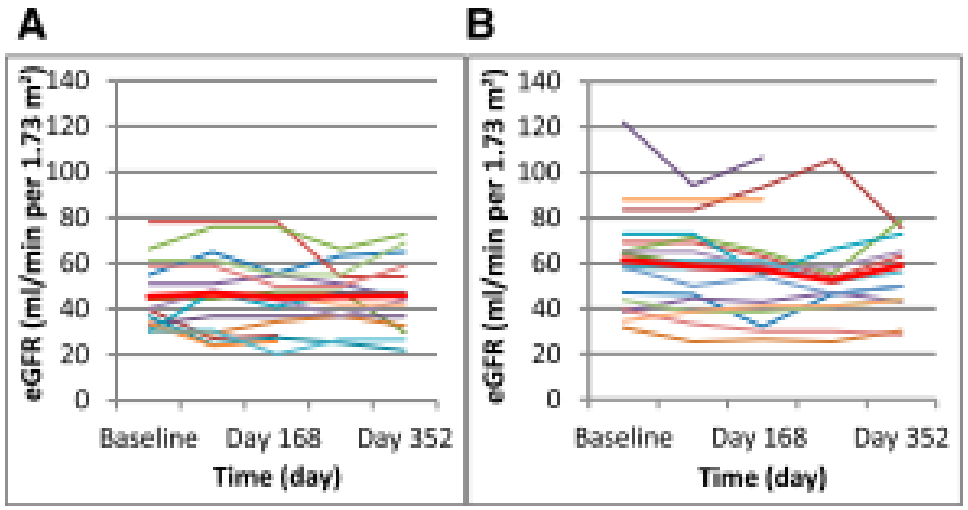

Figure 2. eGFR trends in (A) rituximab versus (B) control groups. The red line represents average data.

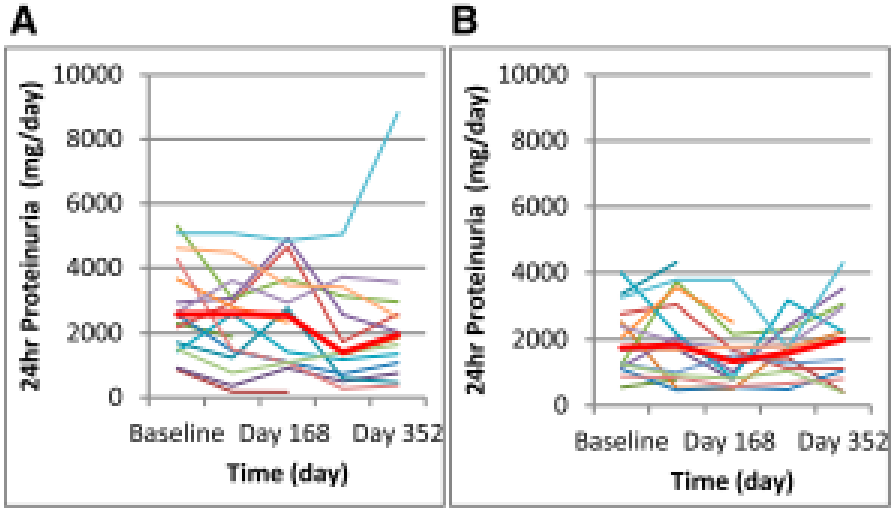

Figure 3. Proteinuria trends in (A) rituximab versus (B) control groups. The red line represents median data.

Rituximab therapy for IgA nephropathy

Jürgen Floege

As IgA nephropathy (IgAN) is considered to result in part from autoimmune processes, B-cell depletion using rituximab might be a plausible therapy. However, a small randomized, controlled trial in patients at risk of progressive IgAN reports that this therapy failed to reduce proteinuria over 1 year and was associated with more adverse events per patient.

Refers to Lafayette R. A. *et al.* A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2016060640 (2016)

IgA nephropathy (IgAN) is considered to be the most common type of glomerulonephritis worldwide. The disease is characterized by IgA deposits, in particular undergalactosylated IgA, in the glomerular mesangium[1] (FIG. 1). Most patients exhibit co-deposits of IgG, IgM and/or complement component C3. Increased levels of undergalactosylated IgA1 are found in the circulation of patients with IgAN, and IgG or IgA autoantibodies bind to this galactose-deficient IgA1 to form immune complexes, which then apparently deposit in the mesangium[2]. These events form the basis by which IgAN is considered to be an immune-mediated, possibly autoimmune dis-

system (RAS) blockers[4]. About 30% of patients in both study groups had received corticosteroid therapy at least 3 months before entering the trial. Patients were randomly assigned to either continue on standard care, which included a minimum of 3 g of fish oil per day ($n = 17$), or to receive an additional 1 g rituximab at weeks 0, 2, 26 and 28 ($n = 17$). 15 patients in the control group and 14 patients on rituximab completed the 12 month trial. Primary outcome measures were change in proteinuria and estimated (e)GFR from baseline. At 12 months neither eGFR nor proteinuria were significantly different from baseline in either group. Importantly, protein-

the control group (61 ml/min/1.73 m^2) than in the rituximab group (40 ml/min/1.73 m^2). Similarly, baseline proteinuria tended to be higher among patients assigned to rituximab (2.6 g per day versus 1.7 g per d, respectively). Patients in the control group were on average 10 years younger than those on rituximab. Despite randomization, the possibility exists that patients with more advanced renal disease were assigned to the rituximab group, and that such patients might be less responsive to B-cell depletion than patients with earlier stages of the disease. However, it is important to note that histological changes, in particular tubulointerstitial fibrosis, did not follow the above trend and rather were very comparable between the two groups.

Second, despite highly effective depletion of B cells with rituximab, the fact that neither circulating levels of galactose-deficient IgA1 nor IgG autoantibodies to this particular IgA1 were reduced at 6 months or 12 months comes as a major surprise. This finding is in striking contrast to other autoimmune renal diseases, in particular membranous glomerulonephritis, in which autoantibodies to the phospholipase A2 receptor rapidly fall after rituximab and indeed predict proteinuria responses and outcome[5]. Of course one might argue that autoantibody-producing plasma cells are CD20 negative and are thus not targeted by rituximab unlike plasma cell precursors, which are depleted by the antibody. But why then would autoantibody-producing plasma cells in patients with membranous glomerulo-

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BRIEF REPORT

Eculizumab treatment for rescue of renal function in IgA nephropathy

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Abstract
Background Immunoglobulin A (IgA) nephropathy is a chronic glomerulonephritis with excessive glomerular deposition of IgA1, C3 and C5b-9, which may lead to renal failure. *Case Diagnosis/Treatment* We describe the clinical course of an adolescent with rapidly progressive disease leading to renal failure in spite of immunosuppressive treatment. Due to refractory disease the patient was treated with eculizumab (anti-C5) for 3 months in

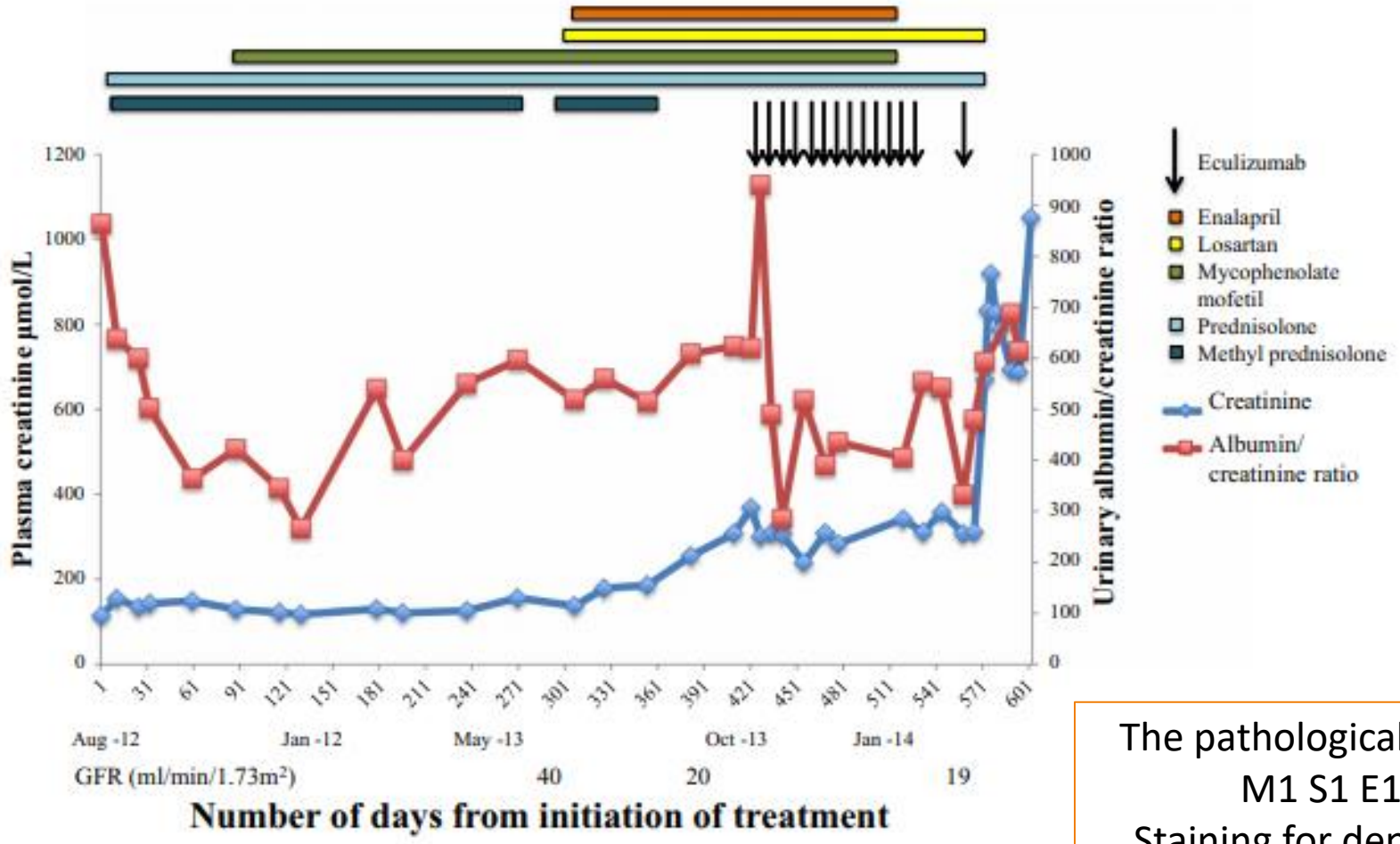
Introduction

Immunoglobulin A (IgA) nephropathy is the most common form of chronic glomerulonephritis worldwide. Patients typically present in the second or third decade of life with continuous asymptomatic microscopic hematuria interspersed by recurrent episodes of macroscopic hematuria and proteinuria in association with upper respiratory tract or gastrointestinal in-

Case report

- A 16 yr old adolescent with rapidly progressive IgAN leading to renal failure in spite of immunosuppressive treatment.
- Proteinuria 7.5 grams/d
- Due to refractory disease the patient was treated with eculizumab (anti-C5) for 3 months in an attempt to rescue renal function.
- Treatment led to clinical improvement with stabilization of the glomerular filtration rate and reduced proteinuria.
- Discontinuation of treatment led to a rapid deterioration of renal function.
- This was followed by a single dose of eculizumab, which again reduced creatinine levels temporarily

Clinical Course



The pathological score was M1 S1 E1 T2.
Staining for deposition of C5b-9 revealed prominent glomerular C5b-9 staining

Conclusions

1. IgAN, as the leading type of GN in many parts of the world, with about 30% ESKD during 20 yrs, has no definite immunosuppressive treatment till now.
2. Crescents clearly worsen the prognosis of IgAN.
3. The only immunosuppressive protocol clinical trials are on **Progressive** (reduced GFR, severe proteinuria) and **not Crescentic IgAN**
4. Multicenter studies in our country and the region are suggested,

Thank You