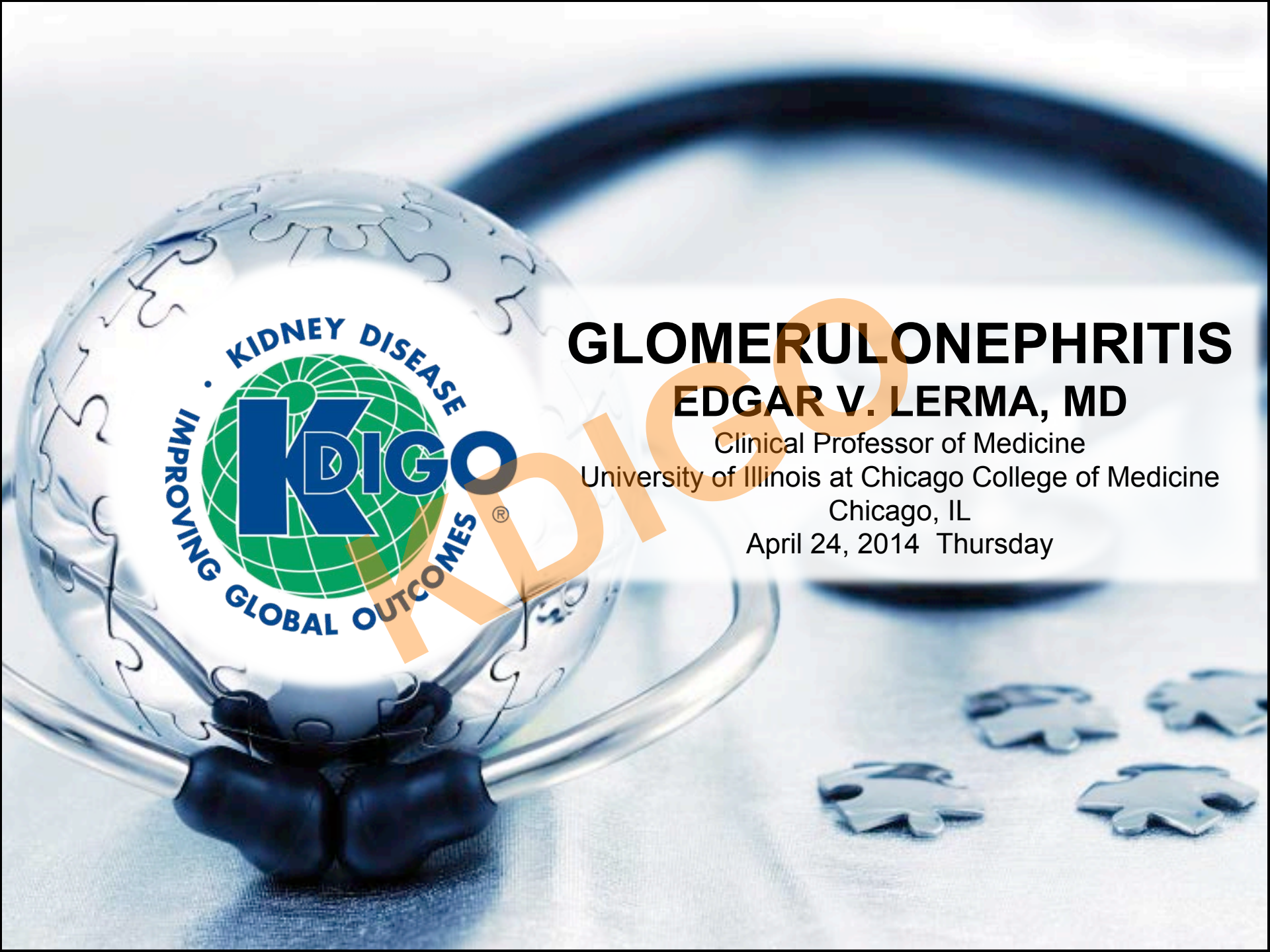


GLOMERULONEPHRITIS

EDGAR V. LERMA, MD
Clinical Professor of Medicine
University of Illinois at Chicago College of Medicine
Chicago, IL

April 24, 2014 Thursday

The KDIGO App is downloadable!

Michelle Josephson
ITF North America Leader

Joel Topf
Leader, KDIGO App Workgroup

W. James Chon
KDIGO App Workgroup

Edgar Lerma
KDIGO App Workgroup

Powered by visiblehealth

Table 1. Nomenclature and Description for Ratings of Recommendation Statement Strength and Quality of Evidence

Rating Strength of Recommendation

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

Rating Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Note: Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

[a]The additional category "Not Graded" was used, typically to provide guidance based on common sense or when the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

CLINICAL RELEVANCE OF RATING GUIDELINE RECOMMENDATIONS

LEVEL1	**WE RECOMMEND**	**Most patients should receive the recommended course of action**
LEVEL 2	**WE SUGGEST**	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them.
NOT GRADED		Usually provides guidance based on common sense or where the issue does not allow adequate application of evidence

QUALITY OF SUPPORTING EVIDENCE

A 1A (STRONGEST)

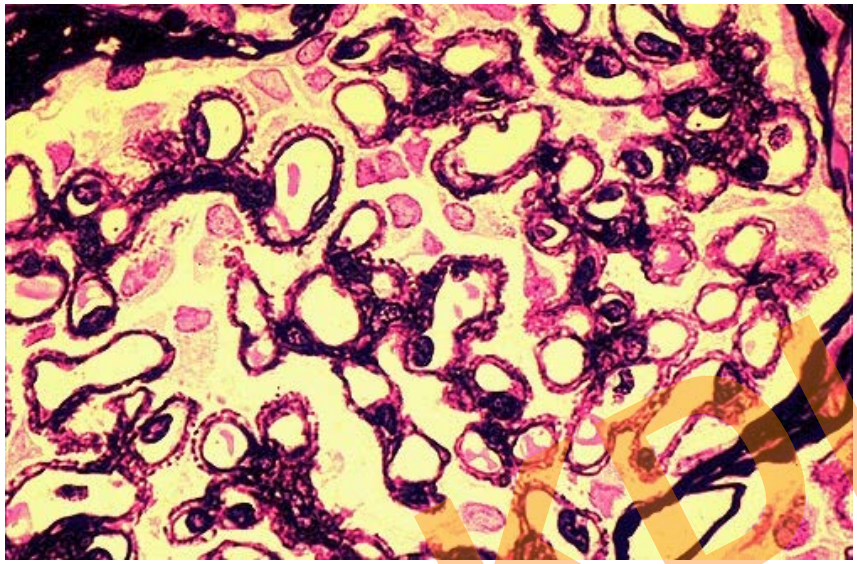
B

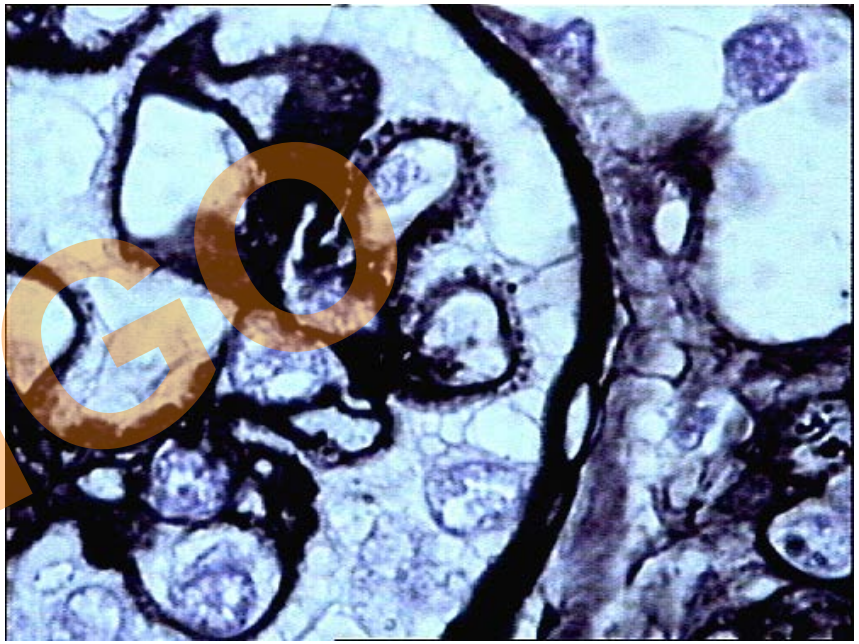
C

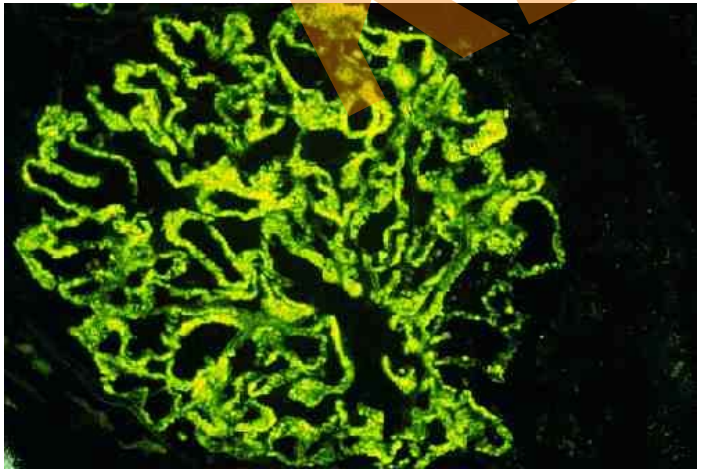
D 2D (WEAKEST)

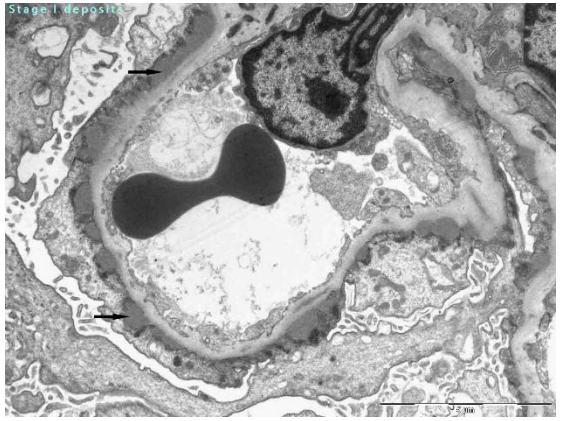
MEMBRANOUS NEPHROPATHY

MEMBRANOUS NEPHROPATHY









MEMBRANOUS NEPHROPATHY EVALUATION

7.1.1. Perform appropriate investigations to exclude **SECONDARY CAUSES** in all cases of biopsy proven MN. **(NOT GRADED)**

Table 12 | Reported causes of secondary MN (% in adults)

Cause	China Zeng *et al.*[196] (*n*=390)	Japan Abe *et al.*[191] (*n*=137)	France Cahen *et al.*[192] (*n*=82)	Finland Honkanen[197] (*n*=82)	United States Ehrenreich *et al.*[198] (*n*=167)
IMN	31.8	65.0	79.3	69.8	62.3
Secondary MN	68.2	35.0	20.7	30.2	37.7
Autoimmune diseases	50.0	25.5	6.1	17.7	7.2
Infections	12.0	5.1	2.5		2.4
Tumors	3.1	1.5	4.9	2.1	1.8
Drugs or toxins	3.1	2.2	6.1	10.4	4.2

IMN, idiopathic membranous nephropathy; MN, membranous nephropathy.

Abe *et al.*, Cahen *et al.*, and Ehrenreich *et al.* also reported diabetes as a secondary cause of MN, accounting for 0.7%, 1.2%, and 16.8% of secondary MN cases, respectively. Reprinted from Zeng CH, Chen HM, Wang RS *et al.* Etiology and clinical characteristics of membranous nephropathy in Chinese patients. *Am J Kidney Dis* 2008; 52: 691–698 with permission from National Kidney Foundation;[196] accessed http://www.ajkd.org/article/S0272-6386(08)01058-5/fulltext.

Table 13 | Reported causes of secondary MN

Autoimmune	Infections
Autoimmune diseases	Hepatitis B
Systemic lupus erythematosus	Hepatitis C
Rheumatoid arthritis	Human immunodeficiency virus
Mixed connective tissue disease	Malaria
Dermatomyositis	Schistosomiasis
Ankylosing spondylitis	Filariasis
Systemic sclerosis	Syphilis
Myasthenia gravis	Enterococcal endocarditis
Bullous pemphigoid	Hydatid disease
Autoimmune thyroid disease	Leprosy
Sjögren's syndrome	
Temporal arteritis	
Crohn's disease	
Graft-versus-host disease	

Malignancies	
Carcinomas	*Noncarcinomas*
Lung	Hodgkin's lymphoma
Esophageal	Non-Hodgkin's lymphoma
Colon	Leukemia (chronic lymphocytic leukemia)
Breast	Mesothelioma
Stomach	Melanoma
Renal	Wilm's tumor
Ovary	Hepatic adenoma
Prostate	Angiolymphatic hyperplasia
Oropharynx	Schwannoma
	Neuroblastoma
	Adrenal ganglioneuroma

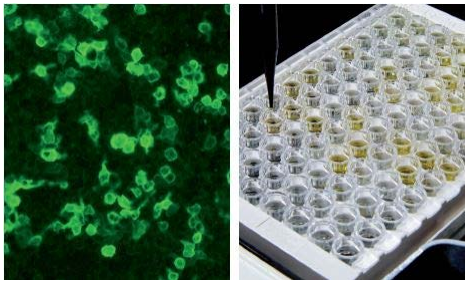
Drugs/Toxins	Miscellaneous
Gold	Diabetes mellitus (association or cause?)
Penicillamine	Sarcoidosis
Bucillamine	Sickle cell disease
Mercury compounds	Polycystic kidney disease
Captopril	α1-antitrypsin deficiency
Probenicid	Weber-Christian disease
Trimethadione	Primary biliary cirrhosis
Nonsteroidal anti-inflammatory drugs	Systemic mastocytosis
Cyclooxygenase-2 inhibitors	Guillain-Barre syndrome
Clopidogrel	Urticarial vasculitis
Lithium	Hemolytic-uremic syndrome
Formaldehyde	Dermatitis herpetiformis
Hydrocarbons	Myelodysplasia

- **Distinguishing secondary MN from IMN is very important**, since the therapy in the former must be directed at the underlying cause and some of the treatments for IMN are potentially toxic both to the patient and the kidney.

- The recognition of the underlying disorder responsible for MN has **important implications for PROGNOSIS and THERAPY**.
- MN is typically a **disease of adults** (fewer than 3% of cases are found in children).
- IMN is often a **‘‘diagnosis of exclusion’’.**

Anti-PLA2R

- A recent study has shown that about 70–80% of IMN patients exhibit **circulating antibodies of IgG4 subtype against a conformation-dependent epitope in the M-type phospholipase A2 receptor**.
- Such autoantibodies appear to be **absent or very uncommon in patients with secondary MN.**
- The **IgG4 subclass** dominates in the **deposits of IMN**, while IgG1, IgG2, and/or IgG3 dominate in secondary forms of MN.



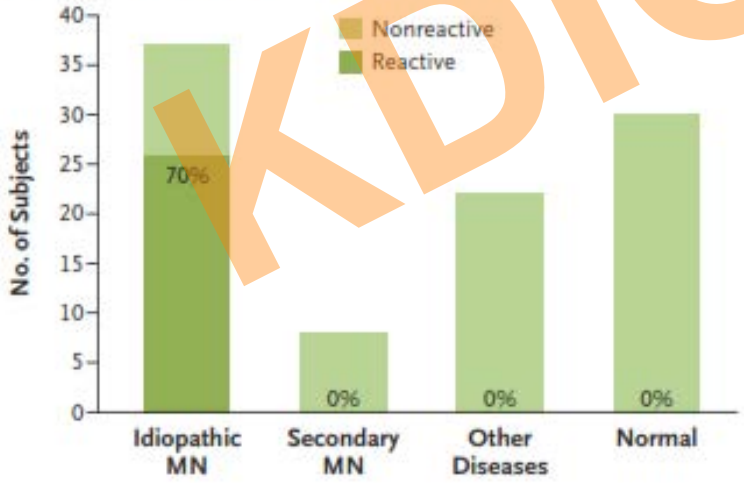
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2009 VOL. 361 NO. 1

M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.

B Reactivity to the 185-kD Protein



No. of Subjects				
Reactive serum	26	0	0	0
Nonreactive serum	11	8	22	30

- 75% SENSITIVITY
- 100% SPECIFICITY

MEMBRANOUS NEPHROPATHY
SELECTION OF CANDIDATES FOR TREATMENT WITH IMMUNOSUPPRESSIVE AGENTS

7.2.1: We recommend that initial therapy be started **ONLY IN PATIENTS WITH NEPHROTIC SYNDROME** AND when at least one of the following conditions is met:

- **Urinary protein excretion persistently exceeds 4 g/d** AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and anti-proteinuric therapy (see during an observation period of **at least 6 months**; **(1B)**
- the presence of **severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (1C)**
- **SCr has risen by 30% or more** within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min/1.73 m2 AND this change is not explained by superimposed complications. **(2C)**

NATURAL HISTORY OF MN
RULE OF THIRDS

- **SPONTANEOUS REMISSION**
  20-30%
- **PERSISTENT PROTEINURIA** 30-40%
- **PROGRESSION TO RENAL FAILURE** 20-30%

NATURAL HISTORY OF MN
RULE OF THIRDS

- **SPONTANEOUS REMISSION**
  20-30%
  - Reasonable to delay specific therapy for at least 6 months utilizing supportive therapy, incl. RAS blockade
- **PERSISTENT PROTEINURIA** 30-40%
  - Related complications: infections, thromboembolic events, accelerated CV disease
- **PROGRESSION TO RENAL FAILURE** 20-30%

The Natural History of the Non-Nephrotic Membranous Nephropathy Patient

Michelle A. Hladunewich, Stephan Troyanov, Jennifer Calafati, and Daniel C. Cattran, for the Metropolitan Toronto Glomerulonephritis Registry

University Health Network, University of Toronto, Toronto, Ontario, Canada

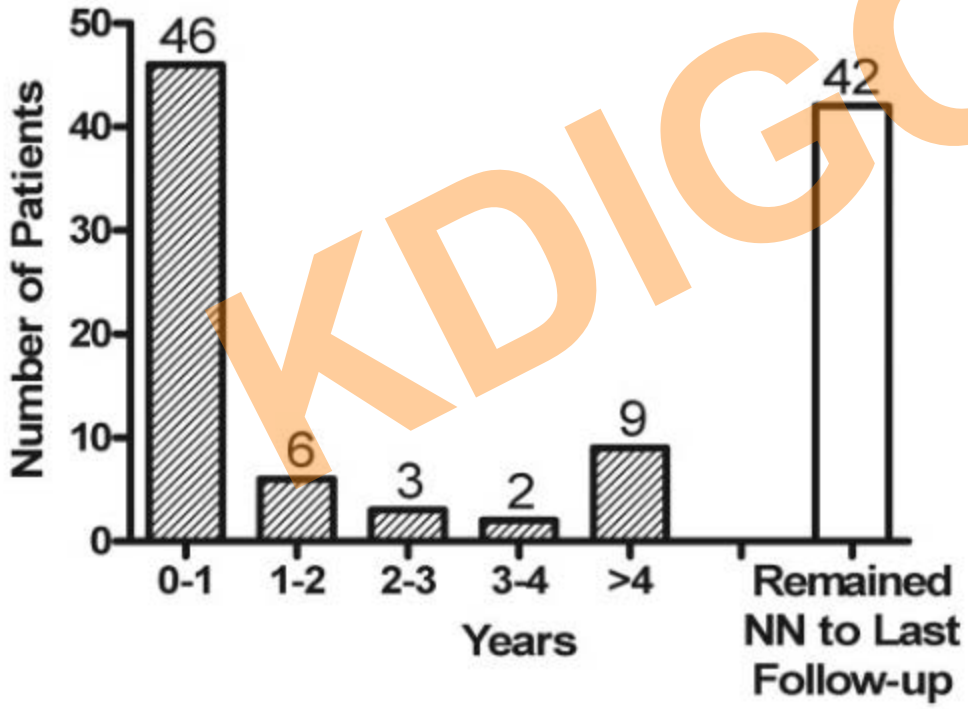


Figure 2. Time (years) for progression from non-nephrotic to nephrotic range proteinuria.

Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy

Natalia Polanco,* Elena Gutiérrez,* Adelardo Covarsí,† Francisco Ariza,‡ Agustín Carreño,§ Ana Vigil,‖ José Baltar,¶ Gema Fernández-Fresnedo,** Carmen Martín,†† Salvador Pons,‡‡ Dolores Lorenzo,§§ Carmen Bernis,‖‖ Pilar Arrizabalaga,¶¶ Gema Fernández-Juárez,*** Vicente Barrio,*** Milagros Sierra,††† Ines Castellanos,† Mario Espinosa,‡ Francisco Rivera,§ Aniana Oliet,‖ Francisco Fernández-Vega,¶ and Manuel Praga* for the Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología

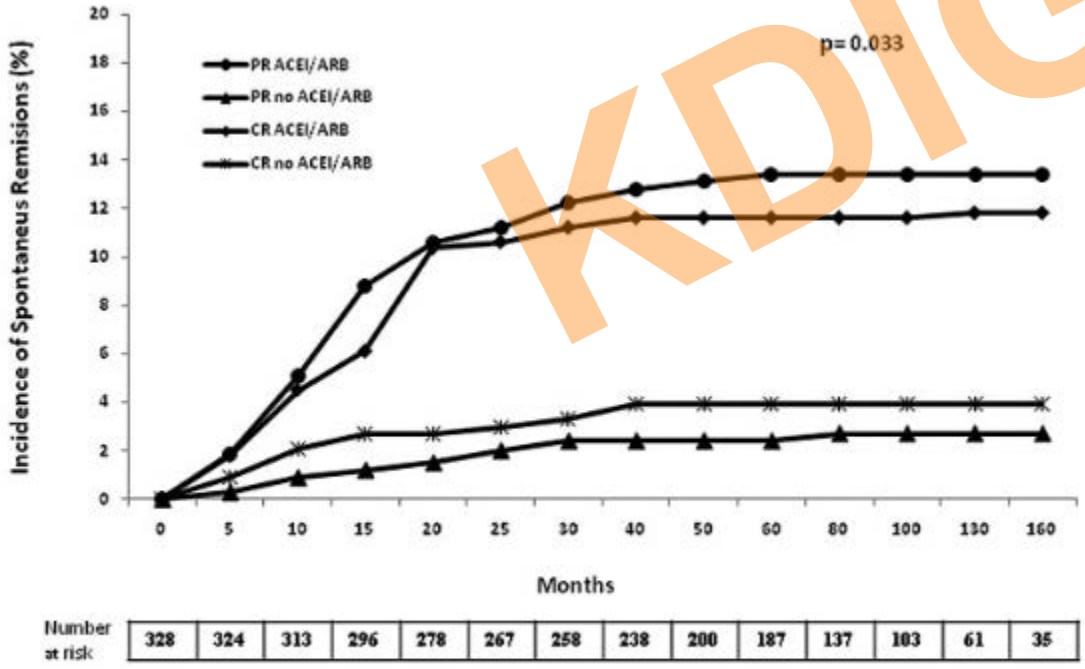


Figure 2. Probability of SR in patients treated with ACEIs/ARBs and in patients who did not receive this treatment.

SPONTANEOUS REMISSION IS COMMON among patients with nephrotic syndrome resulting from MN and carries a **FAVORABLE LONG-TERM OUTCOME** with a **LOW INCIDENCE OF RELAPSE.**

A **decrease in proteinuria > 50%** from baseline during the 1st year **PREDICTS SPONTANEOUS REMISSION.**

Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy

Natalia Polanco,* Elena Gutiérrez,* Adelardo Covarsí,† Francisco Ariza,‡ Agustín Carreño,§ Ana Vigil,‖ José Baltar,¶ Gema Fernández-Fresnedo,** Carmen Martín,†† Salvador Pons,‡‡ Dolores Lorenzo,§§ Carmen Bernis,‖‖ Pilar Arrizabalaga,¶¶ Gema Fernández-Juárez,*** Vicente Barrio,*** Milagros Sierra,††† Ines Castellanos,† Mario Espinosa,‡ Francisco Rivera,§ Aniana Oliet,‖ Francisco Fernández-Vega,¶ and Manuel Praga* for the Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología

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Table 3. Results of univariate and multivariate analyses of independent prognostic factors for the appearance of SR

Factor	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio for SR (95% CI)	*P* Value	Hazard Ratio for SR (95% CI	*P* Value
Female gender	1.8 (1.10 to 3)	0.008	1.45 (0.68 to 3.10)	0.33
Baseline serum creatinine (mg/dl)	0.35 (0.18 to 0.66)	<0.001	0.40 (0.19 to 0.85)	0.018
Baseline proteinuria (g/24 h)	0.92 (0.86 to 0.98)	<0.003	0.85 (0.77 to 0.94)	<0.002
Proteinuria decrease >50% in the first year of follow-up	7.08 (3.59 to 13.9)	<0.0001	12.6 (5.2 to 30.5)	<0.0001
ACEI/ARB treatment	2 (1.1 to 3.5)	0.009	2.36 (1.09 to 5.12)	0.029

Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy

Natalia Polanco,* Elena Gutiérrez,* Adelardo Covarsí,† Francisco Ariza,‡ Agustín Carreño,§ Ana Vigil,‖ José Baltar,¶ Gema Fernández-Fresnedo,** Carmen Martín,†† Salvador Pons,‡‡ Dolores Lorenzo,§§ Carmen Bernis,‖‖ Pilar Arrizabalaga,¶¶ Gema Fernández-Juárez,*** Vicente Barrio,*** Milagros Sierra,††† Ines Castellanos,† Mario Espinosa,‡ Francisco Rivera,§ Aniana Oliet,‖ Francisco Fernández-Vega,¶ and Manuel Praga* for the Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología

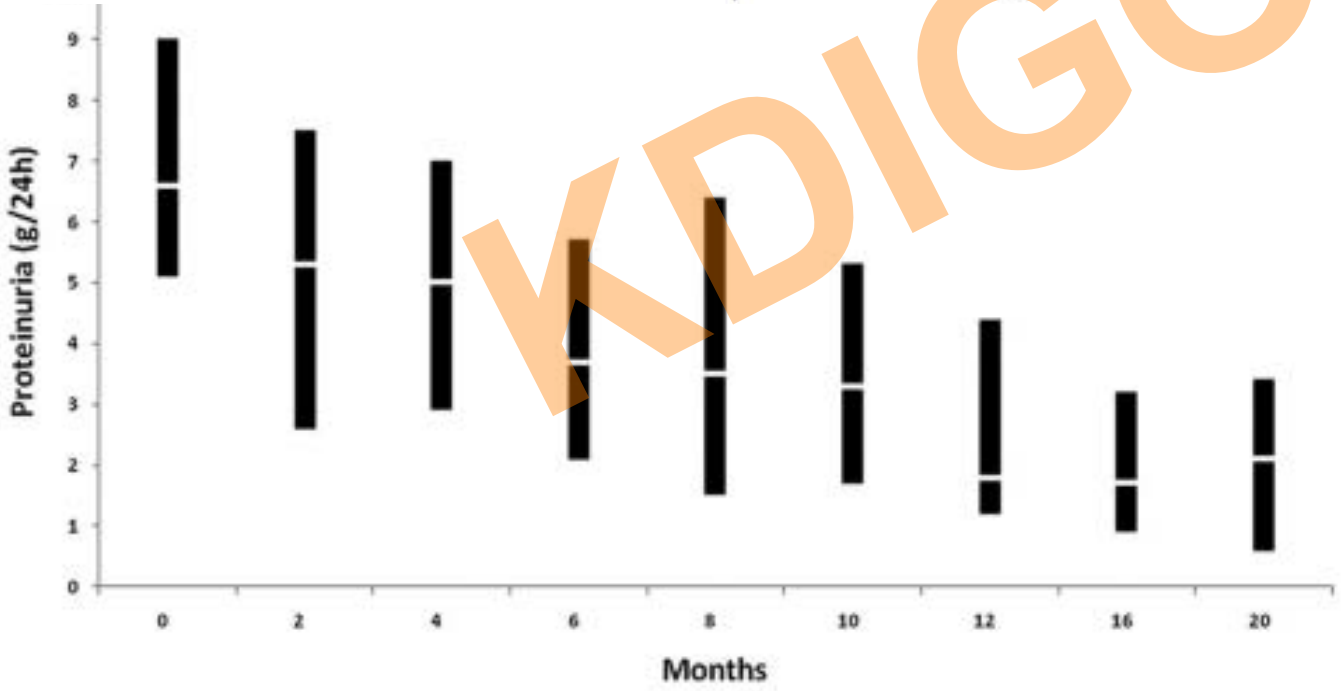


Figure 1. Evolution of proteinuria in patients with SR. The line within the box denotes the median and the box spans the interquartile range (25th to 75th percentiles).

- The **LIKELIHOOD OF SPONTANEOUS REMISSION AND PROGRESSION** is dependent upon:
- Age
- **Gender**
- Degree of proteinuria
- Kidney function at presentation

Nephrol Dial Transplant (2008) 23: 2247–2253
doi: 10.1093/ndt/gfm919
Advance Access publication 8 January 2008

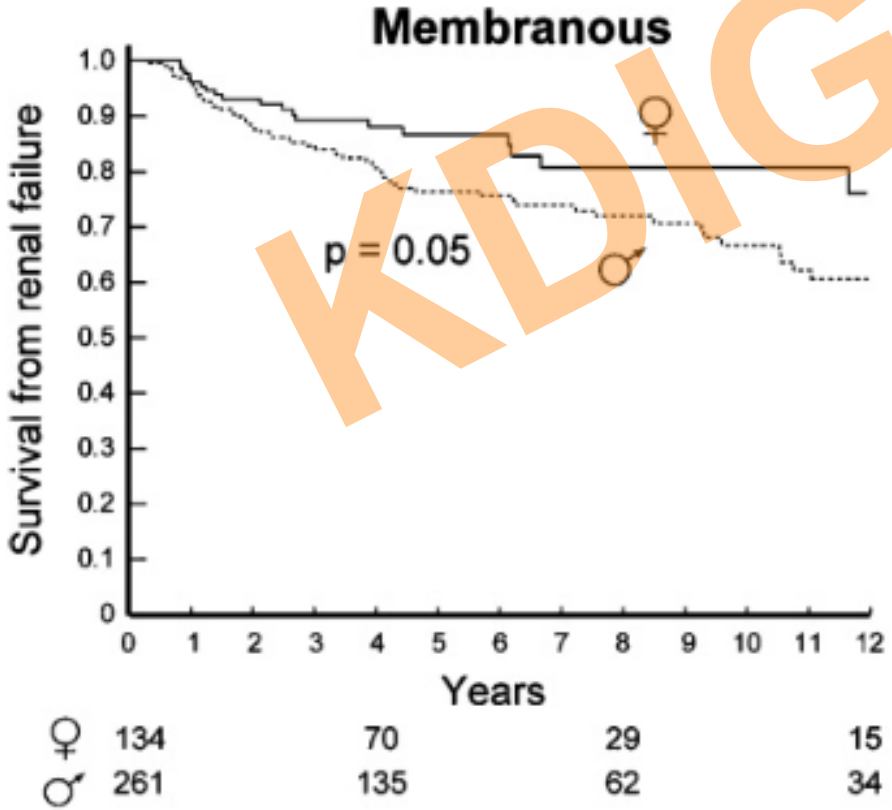
NDT
Nephrology Dialysis Transplantation

Original Article

The impact of sex in primary glomerulonephritis

Daniel C. Cattran, Heather N. Reich, Heather J. Beanlands, Judith A. Miller, James W. Scholey and Stéphan Troyanov for the Genes, Gender and Glomerulonephritis Group

Department of Nephrology, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada



- The **LIKELIHOOD OF SPONTANEOUS REMISSION AND PROGRESSION** is dependent upon:
- Age
- Gender
- **Degree of proteinuria**
- **Kidney function at presentation**

Frontiers in Nephrology

Management of Membranous Nephropathy: When and What for Treatment

Daniel Cattran

Toronto General Research Institute, University Health Network, Toronto General Hospital, Toronto, Ontario, Canada

188–1194, 2005. doi: 10.1681/ASN.2005010028

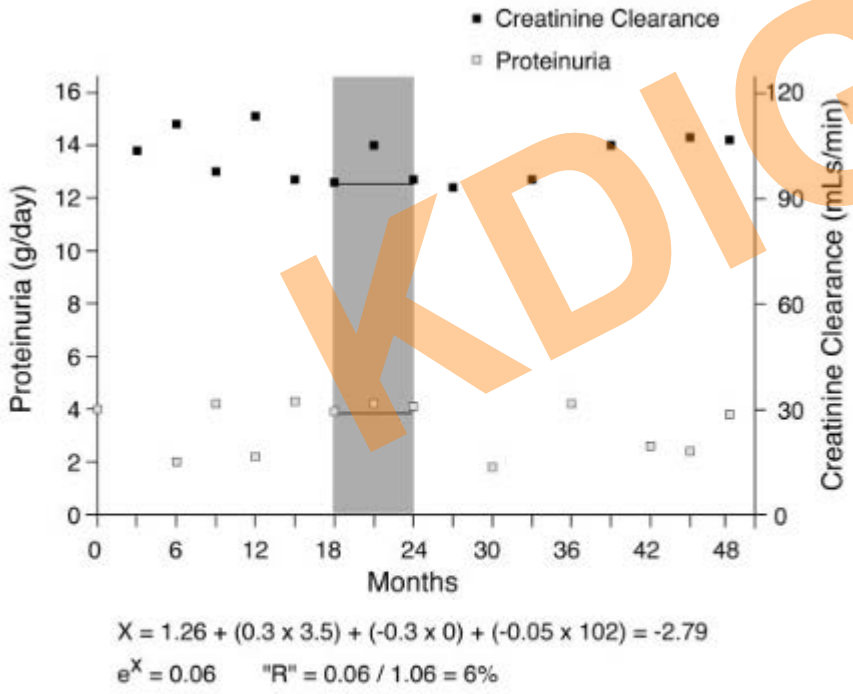


Figure 1. Predicting risk of renal disease progression. The algorithm uses a time frame of 6 mo (bar) and the initial and change in creatinine clearance over this period plus the minimum persistent proteinuria value to calculate the "R" (risk) value.

MEMBRANOUS NEPHROPATHY
SELECTION OF CANDIDATES FOR TREATMENT WITH IMMUNOSUPPRESSIVE AGENTS

Table 1: Risk stratification in membranous nephropathy

Risk stratification	Proteinuria	Creatinine clearance	Follow-up	Risk of developing chronic kidney disease over 5 years	Recommended treatment
Low risk	<4 g/day	Remains normal	6 months	<8% over 5 years	Nondisease-specific treatment
Moderate risk	4–8 g/day	Normal or near normal	6 months	50%	Nondisease specific then disease-specific therapy if not better in 6 months
High risk	>8 g/day	Below normal or decreases during the observation period	3 months	75%	Diseasespecific therapy in addition to non-disease specific

MEMBRANOUS NEPHROPATHY
SELECTION OF CANDIDATES FOR TREATMENT WITH IMMUNOSUPPRESSIVE AGENTS

7.2.2: DO NOT USE immunosuppressive therapy in patients with **a SCr persistently > 3.5 mg/dl (or an eGFR < 30 ml/min per 1.73 m2)** AND **reduction of kidney size** on ultrasound (e.g., < 8 cm in length) OR those with concomitant severe or potentially life-threatening infections. **(NOT GRADED)**

- There is **no agreed definition of the "point of no return"** in the evolution of IMN after which the risks of immunosuppressive drugs become unacceptable and futile.
  - severe tubular interstitial fibrosis, tubular atrophy, and glomerular obsolescence on biopsy, accompanied by
  - persistent elevation of SCr > 3.5 mg/dl (or eGFR < 30 ml/min per 1.73 m2), and
  - reduction in kidney size on ultrasound.

MEMBRANOUS NEPHROPATHY
INITIAL TREATMENT

7.3.1: We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of ORAL and IV **CORTICOSTEROIDS**, and ORAL **ALKYLATING AGENTS.** **(1B)**

7.3.2: We suggest using **CYCLOPHOSPHAMIDE** rather than chlorambucil for initial therapy. **(2B)**

A Randomized, Controlled Trial of Steroids and Cyclophosphamide in Adults with Nephrotic Syndrome Caused by Idiopathic Membranous Nephropathy

Vivekanand Jha,* Anirban Ganguli,* Tarun K. Saha,* Harbir S. Kohli,* Kamal Sud,* Krishan L. Gupta,* Kusum Joshi,† and Vinay Sakhuja*

*Departments of *Nephrology and †Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

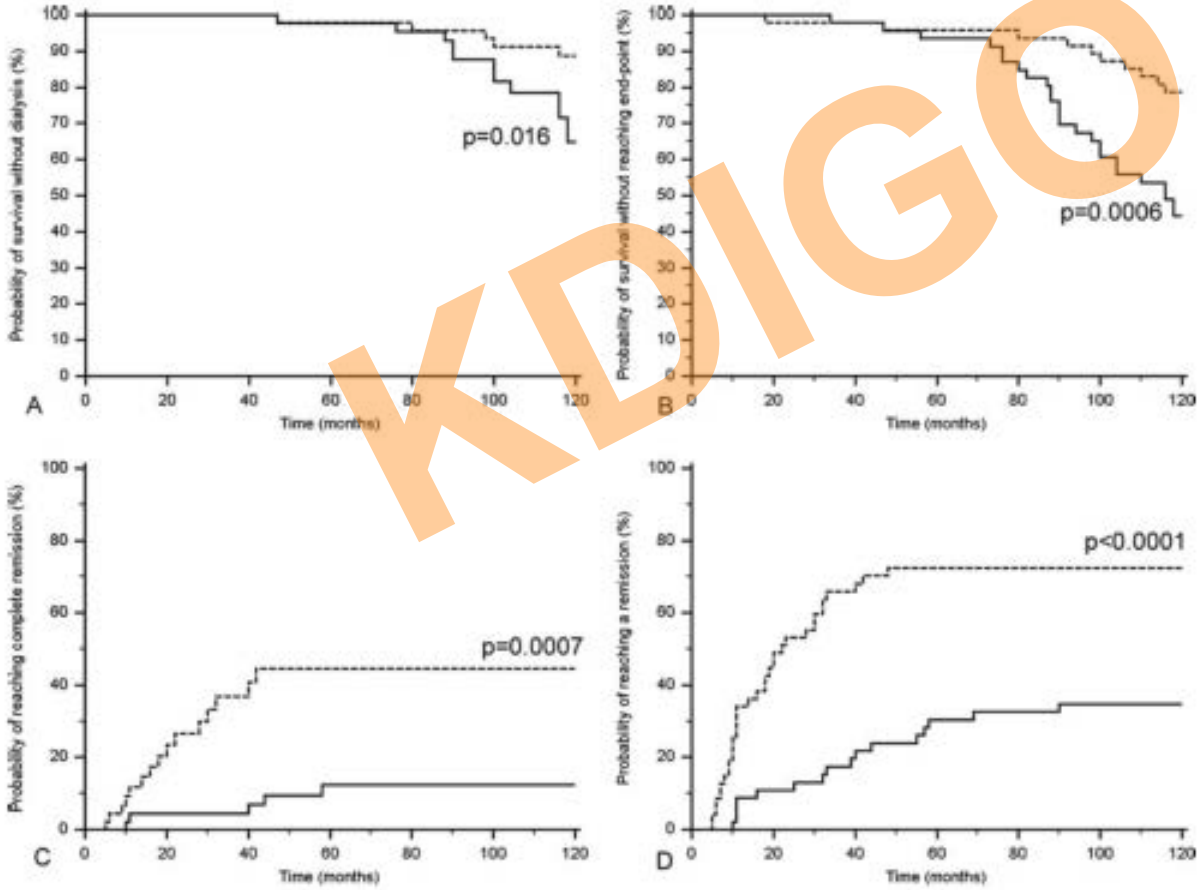


Figure 1. Kaplan-Meier plots showing probabilities of dialysis-free survival (A), survival without reaching either end point (B), complete remission (C), and complete or partial remission (D). Solid line, group 1; dashed line, group 2.

A Randomized, Controlled Trial of Steroids and Cyclophosphamide in Adults with Nephrotic Syndrome Caused by Idiopathic Membranous Nephropathy

Vivekanand Jha,* Anirban Ganguli,* Tarun K. Saha,* Harbir S. Kohli,* Kamal Sud,* Krishan L. Gupta,* Kusum Joshi,† and Vinay Sakhuja*

*Departments of *Nephrology and †Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

- Untreated IMN with nephrotic syndrome is associated with a **HIGH RISK OF DETERIORATION of renal function**.
- A **6-month regimen of CYCLOPHOSPHAMIDE and STEROIDS** induces remissions in a high proportion, arrests progression of renal insufficiency, and improves quality of life.

Table 15 | Cyclical corticosteroid/alkylating-agent therapy for IMN (the "Ponticelli Regimen")

Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methyprednisolone (0.5 mg/kg/d) for 27 days
Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days[a]
Month 3: Repeat Month 1
Month 4: Repeat Month 2
Month 5: Repeat Month 1
Month 6: Repeat Month 2

IMN, idiopathic membranous nephropathy.

[a]Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If total leukocyte count falls to $<3500/mm^3$, then hold chlorambucil or cyclophosphamide until recovery to $>4000/mm^3$.

Table 16 | Risks and benefits of the cyclical corticosteroid/alkylating-agent regimen in IMN

Risks	Benefits
Enhanced risk of opportunistic infection	Prevention of CKD and ESRD
Reactivation of viral hepatitis	Avoidance of complications of nephrotic syndrome (thrombosis, accelerated atherogenesis)
Alopecia	Prolongation of life; improved quality of life
Gonadal damage (aspermatogenesis, ovulation failure)	
Hemorrhagic cystitis (cyclophosphamide only)	
Neoplasia (myelodysplastic syndrome, acute myelogenous leukemia	
Transitional cell carcinoma of the bladder, ureter or pelvis	
Toxic hepatitis	

CKD, chronic kidney disease; ESRD, end-stage renal disease; MN, membranous nephropathy.

Table 17 | Contraindications to the use of the cyclical corticosteroid/alkylating-agent regimen in IMN

Untreated infection (HIV, hepatitis B and C, tuberculosis, fungal infection, etc.)
Neoplasia (lung, skin [except squamous cell]), breast, colon, etc.
Urinary retention
Inability to comply with monitoring
Pre-existing leukopenia (<4000 leukocytes/mm^3)
SCr >3.5 mg/dl (>309 μmol/l)

HIV, human immunodeficiency virus; MN, membranous nephropathy; SCr, serum creatinine.

Kidney International, Vol. 48 (1995), pp. 1600–1604

A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy

CLAUDIO PONTICELLI, PIETRO ZUCCHELLI, PATRIZIA PASSERINI, BRUNO CESANA, FRANCESCO LOCATELLI, SONIA PASQUALI, MAURO SASDELLI, BRUNO REDAELLI, CLAUDIO GRASSI, CLAUDIO POZZI, DANIELA BIZZARRI, and GIOVANNI BANFI

Division of Nephrology and Dialysis, IRCCS, Ospedale Maggiore Milano, Ospedale Malpighi Bologna, Ospedale Civile Lecco, Ospedale Civile Arezzo, Ospedale San Gerardo dei Tintori Monza, and Ospedale Predabissi Melegnano, Italy

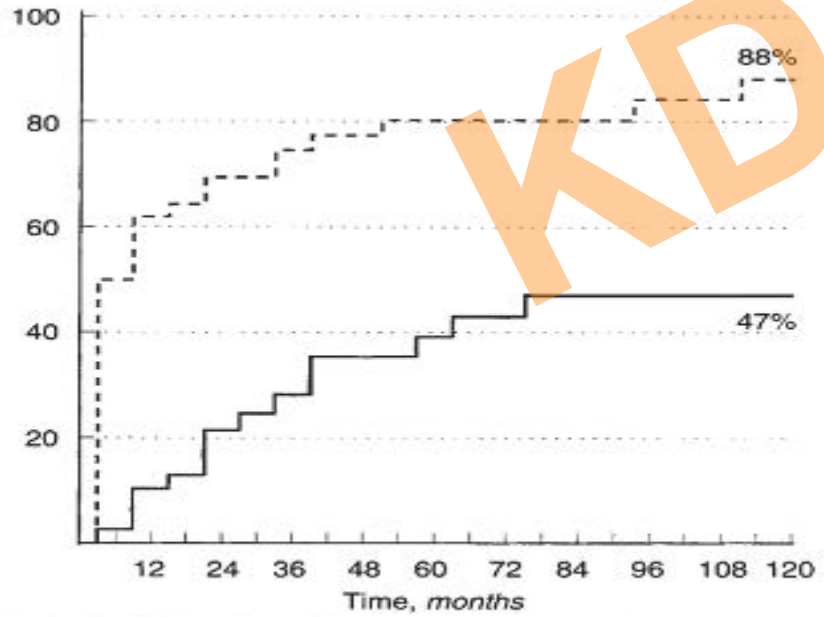


Fig. 3. *Probability of complete or partial remission of the nephrotic syndrome as a first event in the treated group (- - -) and in control group (——).* The difference between the two curves is statistically significant ($P = 0.0000$).

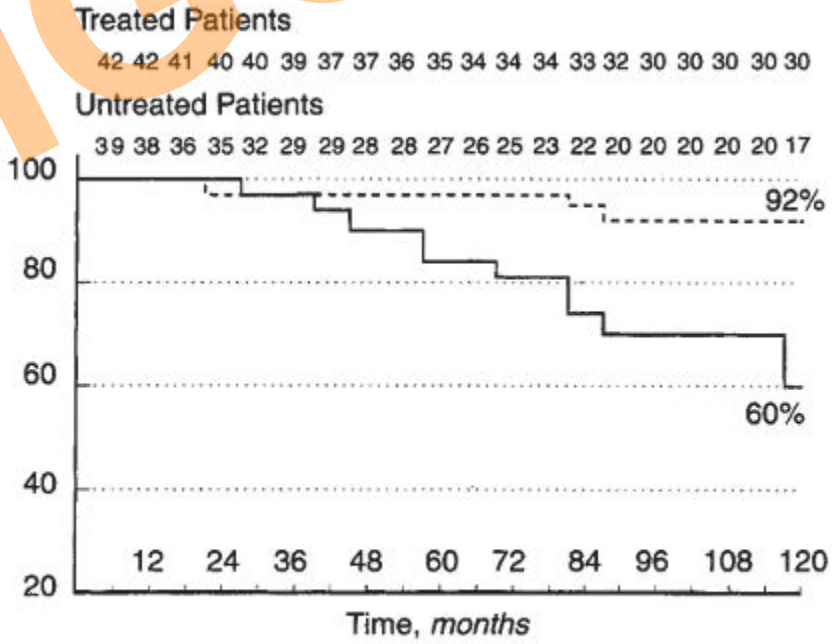


Fig. 1. *Cumulative probability of survival without dialysis in patients who received treatment (- - -) and in untreated controls (——).* The difference is significant ($P = 0.0038$).

Q J Med 1998; **91**:359–366

Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency

A.J.W. BRANTEN, L.J.M. REICHERT, R.A.P. KOENE and J.F.M. WETZELS

From the Department of Medicine, Division of Nephrology, University Hospital Nijmegen, Nijmegen, The Netherlands

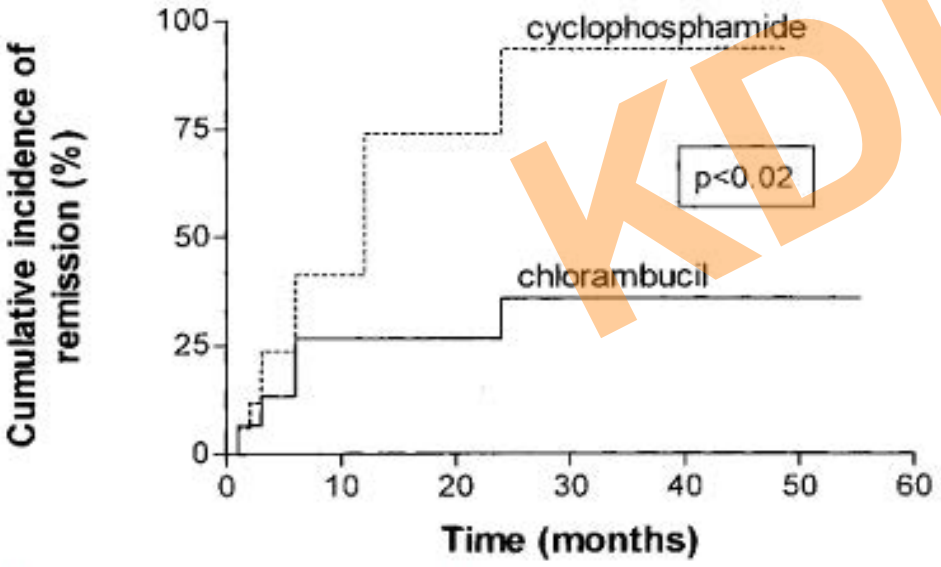


Figure 1. Cumulative incidence of partial remissions of proteinuria (i.e. proteinuria <2 g/10 mmol creatinine) in patients treated with either chlorambucil or cyclophosphamide.

- **RENAL FUNCTION IMPROVED** in both groups but was SHORTLIVED IN THE CHLORAMBUCIL group.
- **REMISSIONS OF PROTEINURIA** occurred MORE FREQUENTLY after CYCLOPHOSPHAMIDE treatment.
- **PO CYCLOPHOSPHAMIDE WAS BETTER TOLERATED.**

- Cyclophosphamide has a more favorable side-effect profile compared to chlorambucil.

MEMBRANOUS NEPHROPATHY
INITIAL TREATMENT

7.3.3: We recommend patients **be managed conservatively for at least 6 months** following the completion of this regimen before being considered a **TREATMENT FAILURE** if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present. **(1C)**

MEMBRANOUS NEPHROPATHY
INITIAL TREATMENT

Table 14 | Definitions of complete and partial remission in IMN

Complete Remission: Urinary protein excretion <0.3 g/d (uPCR <300 mg/g or <30 mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration, and a normal SCr.

Partial Remission: Urinary protein excretion <3.5 g/d (uPCR <3500 mg/g or <350 mg/mmol) ***and*** a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of the serum albumin concentration and stable SCr.

MN, membranous nephropathy; uPCR, urine protein:creatinine ratio.
See also Chapter 1.
Based on previously published information, Jha *et al.* and Passerini *et al.*[204,205]

Treatment-induced REMISSIONS are associated with an IMPROVED PROGNOSIS.

REMISSION	10-year survival free of kidney failure (%)	Rate of decline in CrCl (mL/min/year)
COMPLETE Remission	100	- 1.5
PARTIAL Remission	90	- 1.5
NO Remission	50	-2.0

PREDICTORS OF REMISSION

- Treatment with **RAS BLOCKADE**
- **50% DECLINE OF PROTEINURIA** from baseline during 1st year of follow-up
- Hypertension
- Histologic evidence: Interstitial fibrosis and tubular atrophy
- Persistently elevated Urinary C5b-9
- Elevated Urinary low or high molecular weight proteins (β2-macroglobulin and IgG)

*STAGING OF MN by histologic criteria has **LIMITED UTILITY** for prediction of outcomes or response to therapy for IMN.*

MEMBRANOUS NEPHROPATHY
INITIAL TREATMENT

7.3.4: Perform a **REPEAT KIDNEY BIOPSY** only if the patient has **rapidly deteriorating kidney function** (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria (> 15 g/d). **(NOT GRADED)**

7.3.5: ADJUST THE DOSE of cyclophosphamide or chlorambucil according to the **age of the patient** and **eGFR**. **(NOT GRADED)**

MEMBRANOUS NEPHROPATHY
INITIAL TREATMENT

7.3.6: We suggest that **CONTINUOUS DAILY (NONCYCLICAL)** use of oral alkylating agents may also be effective, but can be associated with **GREATER RISK OF TOXICITY**, particularly when administered for 46 months. **(2C)**

Table 17 | Contraindications to the use of the cyclical corticosteroid/alkylating-agent regimen in IMN

Untreated infection (HIV, hepatitis B and C, tuberculosis, fungal infection, etc.)
Neoplasia (lung, skin [except squamous cell]), breast, colon, etc.
Urinary retention
Inability to comply with monitoring
Pre-existing leukopenia (<4000 leukocytes/mm^3)
SCr >3.5 mg/dl (>309 μmol/l)

HIV, human immunodeficiency virus; MN, membranous nephropathy; SCr, serum creatinine.

MEMBRANOUS NEPHROPATHY
ALTERNATIVE REGIMENS FOR INITIAL THERAPY: CNI THERAPY

7.4.1: We recommend that **CYCLOSPORINE** or **TACROLIMUS** be used for a period of at least 6 months in patients who meet the criteria for initial therapy, but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen. **(1C)**

MEMBRANOUS NEPHROPATHY
ALTERNATIVE REGIMENS FOR INITIAL THERAPY: CNI THERAPY

7.4.2: We suggest that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. **(2C)**

7.4.3: We suggest that the **dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage**, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months. **(2C)**

MEMBRANOUS NEPHROPATHY
ALTERNATIVE REGIMENS FOR INITIAL THERAPY: CNI THERAPY

7.4.4: We suggest that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr (> 20%) during therapy. **(NOT GRADED)**

WHY CNIs ARE NOT THE 1st OPTION

- Although EFFECTIVE IN INDUCING REMISSION, one limitation with CNIs is a **HIGH RELAPSE RATE**
  - Relapse may be decreased **BY PROLONGING TREATMENT DURATION TO 1 YEAR**

Kidney International, Vol. 59 (2001), pp. 1484–1490

Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial

Daniel C. Cattran, Gerald B. Appel, Lee A. Hebert, Lawrence G. Hunsicker, Marc A. Pohl, Wendy E. Hoy, Douglas R. Maxwell, and Cheryl L. Kunis, for the North American Nephrotic Syndrome Study Group

Department of Medicine, University of Toronto, Toronto, Ontario, Canada; Departments of Medicine, Columbia Presbyterian Medical Center, New York, New York, Ohio State University, Columbus, Ohio, University of Iowa Hospitals, Iowa City, Iowa, Cleveland Clinic Foundation, Cleveland, Ohio, Lovelace Medical Foundation, Albuquerque, New Mexico, and Indiana University School of Medicine, Indianapolis, Indiana, USA

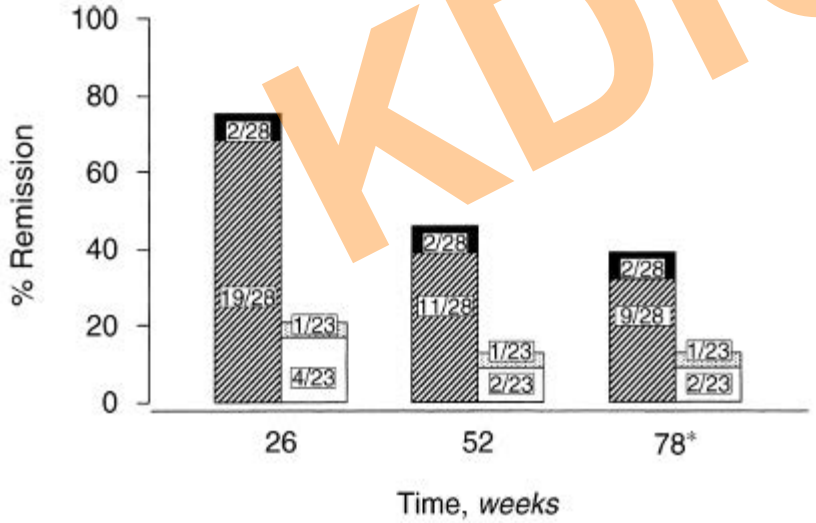


Fig. 1. Remissions in proteinuria in the cyclosporine patients [(▨) partial, (■) complete] compared with the placebo-treated [(▩) complete, (□) partial] at different time points of the study. At week 26, $P = 0.001$; at week 52, $P = 0.004$; and week 78, $P = 0.007$. Early stops (*) were assessed at the last follow-up.

Tacrolimus monotherapy in membranous nephropathy: A randomized controlled trial

M Praga[1], V Barrio[2], G Fernández Juárez[2] and J Luño[3], For the GRUPO ESPAÑOL DE ESTUDIO DE LA NEFROPATÍA MEMBRANOSA (Members of the Group listed at the end of the paper)

[1]Hospital 12 de Octubre, Madrid, Spain; [2]Fundación Hospital Alcorcón, Alcorcón, Madrid, Spain and [3]Hospital Gregorio Marañón, Madrid, Spain

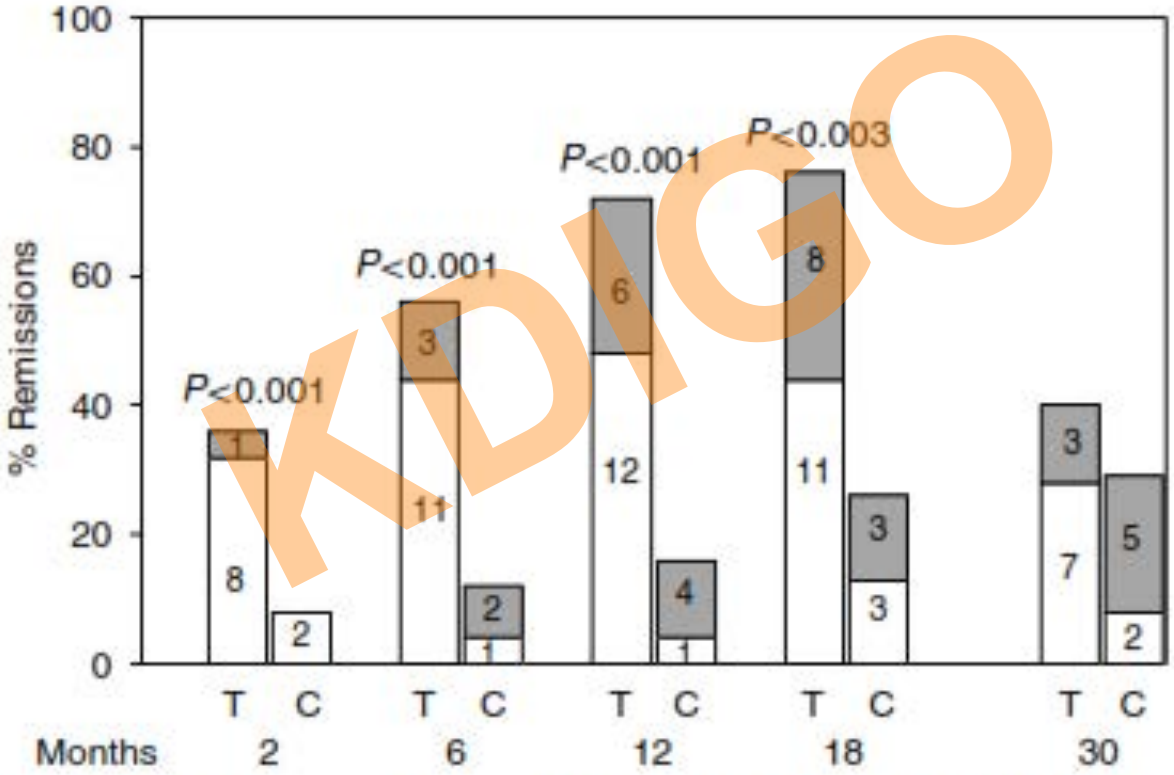
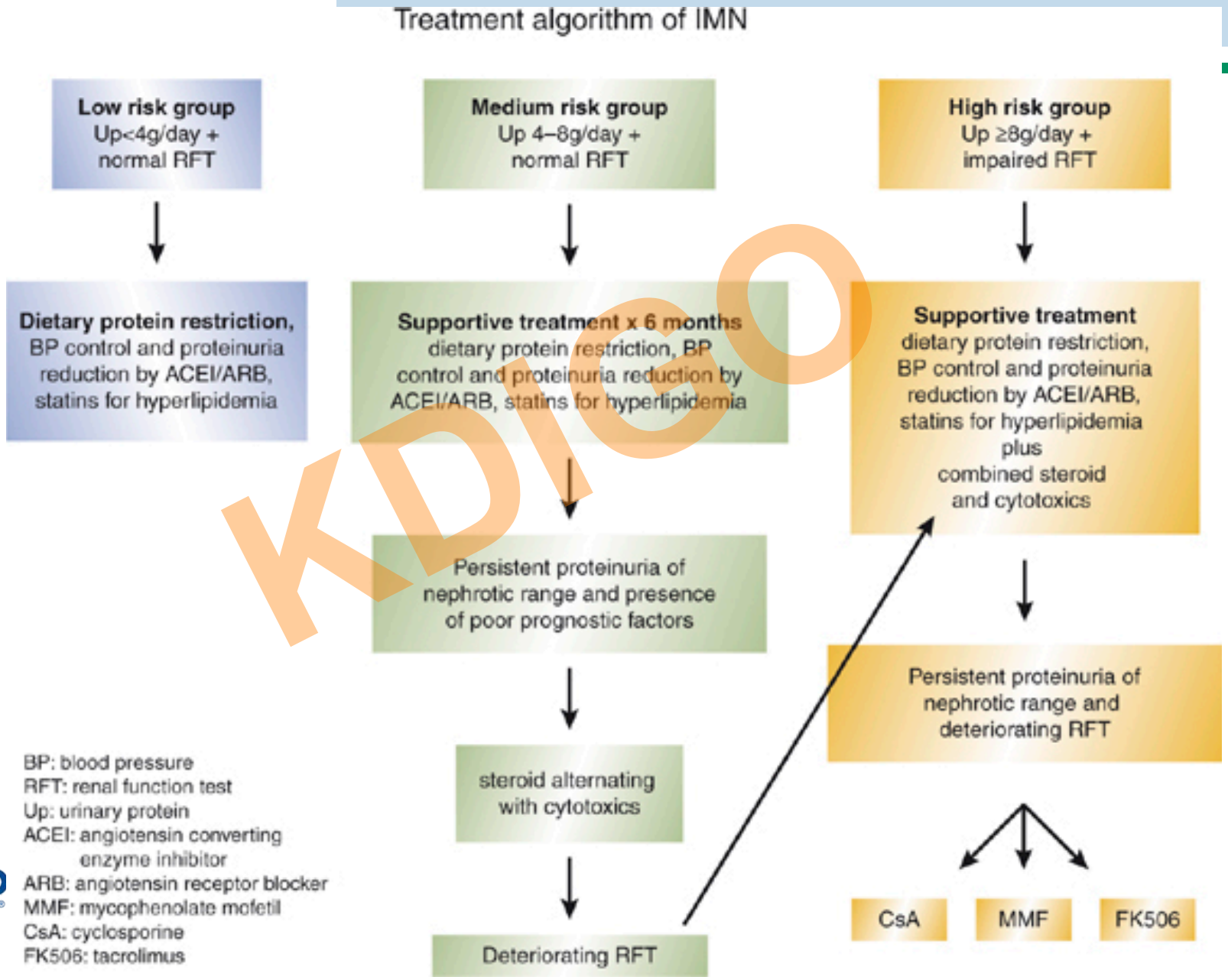


Figure 3 | Percentage of complete (grey) and partial (white) remissions in the tacrolimus (T) and in the control (C) group. Numbers within columns indicate the total number of patients in CR or PR in both groups.

MEMBRANOUS NEPHROPATHY



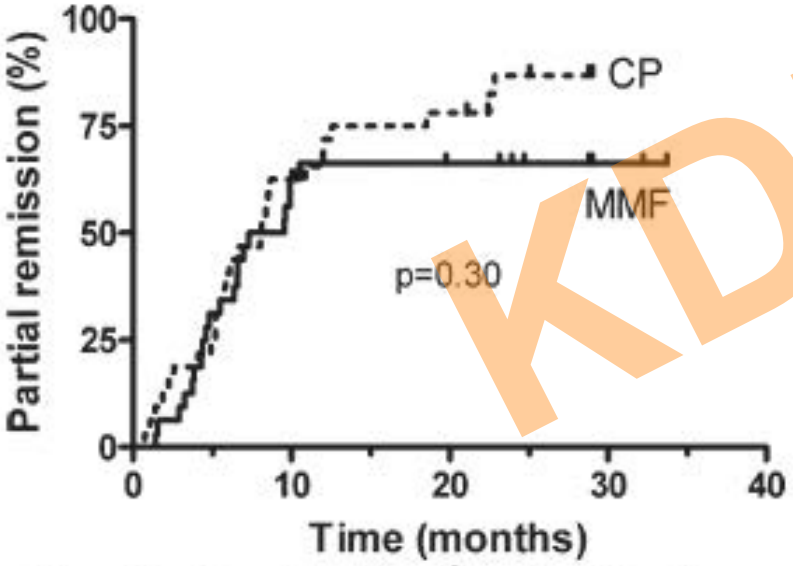
MEMBRANOUS NEPHROPATHY
REGIMENS NOT RECOMMENDED OR SUGGESTED FOR INITIAL THERAPY

7.5.1: We recommend that **CORTICOSTEROID MONOTHERAPY** not be used for initial therapy of IMN. **(1B)**

7.5.2: We suggest that **MONOTHERAPY WITH MMF** not be used for initial therapy of IMN. **(2C)**

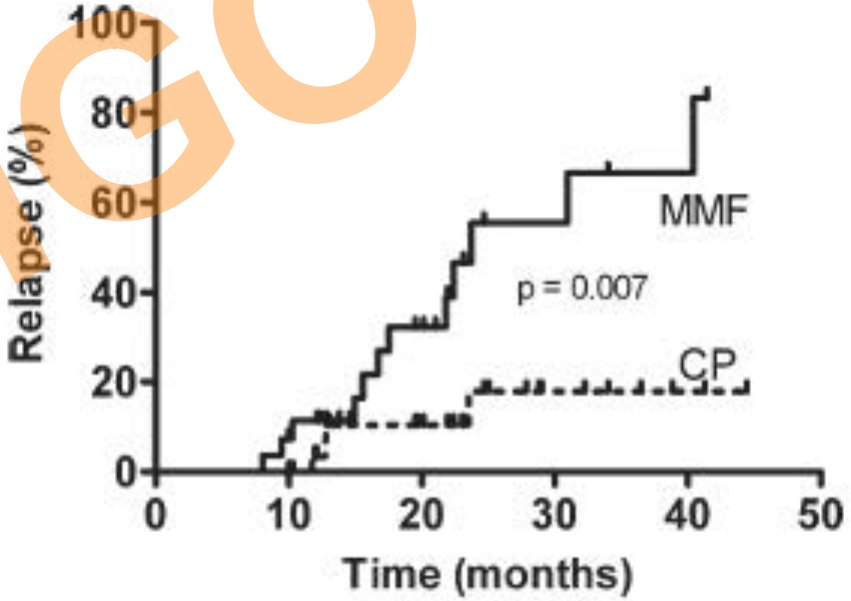
Mycophenolate Mofetil in Idiopathic Membranous Nephropathy: A Clinical Trial With Comparison to a Historic Control Group Treated With Cyclophosphamide

Amanda J. Branten, MD, PhD,[1] Peggy W. du Buf-Vereijken, MD, PhD,[1,2] Marc Vervloet, MD,[3] and Jack F. Wetzels, MD, PhD[1]



CP	32	25	13	9	8	4	1	1
MMF	32	23	14	9	8	5	3	1

Figure 1. Cumulative incidence of partial remission of proteinuria in patients treated with mycophenolate mofetil (MMF) or cyclophosphamide (CP). Numbers of patients at risk are indicated.



CP	32	32	19	7	3
MMF	27	26	13	5	3

Figure 2. Cumulative incidence of relapses in patients treated with mycophenolate mofetil (MMF) or cyclophosphamide (CP). Numbers of patients at risk are indicated.

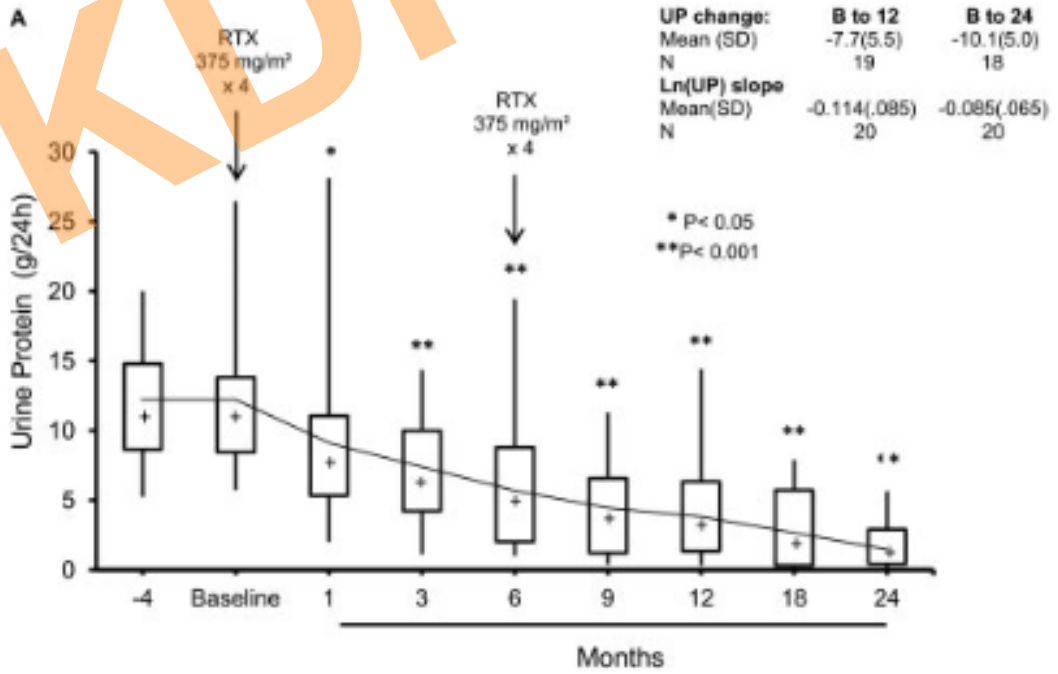
MMF vs CYCLOPHOSPHAMIDE in IMN

- MMF reduced proteinuria
- MMF improved renal function
- Complication rates similar
- MMF had **HIGHER RELAPSE RATE**
- MMF was **NOT AS EFFECTIVE** as Cyclophosphamide

Rituximab Therapy in Idiopathic Membranous Nephropathy: A 2-Year Study

Fernando C. Fervenza,* Roshini S. Abraham,† Stephen B. Erickson,* Maria Valentina Irazabal,* Alfonso Eirin,* Ulrich Specks,‡ Patrick H. Nachman,§ Eric J. Bergstralh,‖ Nelson Leung,* Fernando G. Cosio,* Marie C. Hogan,* John J. Dillon,* LaTonya J. Hickson,* Xujian Li,‖ and Daniel C. Cattran,¶ for the Mayo Nephrology Collaborative Group

*Division of Nephrology and Hypertension, †Division of Clinical Biochemistry and Immunology, Department of Laboratory Medicine and Pathology, ‡Division of Pulmonary and Critical Care, and ‖Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; §Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ¶Department of Nephrology, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada



Drug Design, Development and Therapy

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CASE REPORT

Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel

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Purpose: A synthetic adrenocorticotropin (ACTH) analog has shown efficacy in Europe as primary and secondary therapy for nephrotic syndrome, but there is no published experience using the natural, highly purified ACTH gel formulation, available in the United States, for nephrotic syndrome. We therefore investigated the use of ACTH gel for nephrotic syndrome in the United States.

Patients and methods: Twenty-one patients with nephrotic syndrome treated with ACTH gel outside of research settings in the United States, with initiation of therapy by December 31, 2009, allowing a minimum 6 months follow-up. We defined complete remission as stable renal function with proteinuria falling to <500 mg/day, and partial remission as stable renal function

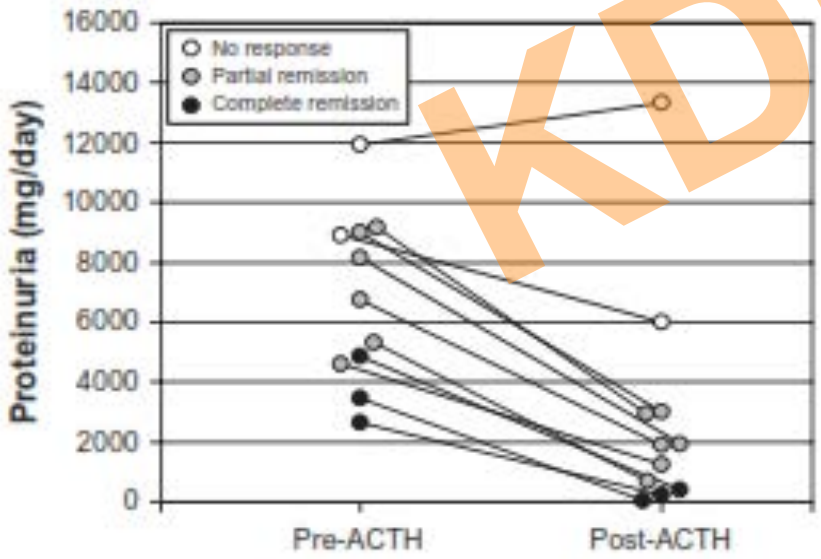

Figure 1 Changes in proteinuria with ACTH gel therapy in 11 patients with nephrotic syndrome due to membranous nephropathy.
Abbreviation: ACTH, adrenocorticotropin.

Table 2: Drug-specific treatment

Regimen	Protocol	Advantages	Disadvantages	Comment	Reference
Steroid alone			Not beneficial		[14,15]
Steroid with chlorambucil	A 3-day course of IG methylprednisolone followed by prednisone (0.4–0.5 mg/kg/day) for 1 month alternating with 1 month of chlorambucil (0.2 mg/kg/day) for a total treatment period of 6 months	After 5 years of follow-up, renal function had deteriorated in about 50% of the control group, but only in 10% of the treated patients	Not widely used in the United States because of bone marrow suppression		[16]
Cyclophosphamide, with low-dose prednisone	Cyclophosphamide (1.5–2.0 mg/kg/day) with prednisone (0.5 mg/kg/day) for 3–6 months	Comparable results to steroid with chlorambucil	Side effects leading to stop therapy in only 10% cases	First-line treatment	[17,18]
Cyclosporine	3.5–5 mg/kg/day (trough levels of 150–225 mg)	70% of patients show occasional complete or partial remission	Prolonged courses (1–2 years) may produce more permanent remission	The best-studied alternative to steroid–cytotoxic drug therapy	[19,20]
Tacrolimus	Tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper	Decreases proteinurea in MN	Patients have significant relapse rate		[21,22]
Mycophenolatemofetil	With steroids in a dose of 2 g/day for a year		Limited data	Third alternative in the treatment	[23]
Anti-B cell monoclonal antibody	Four weekly infusions	Proteinuria was significantly reduced and renal function stabilized 1 year later	Limited data		[24]
Adrenocorticotropic hormone		Comparably to a combined regimen of steroids and alkylating agents	Limited data		[25]

MEMBRANOUS NEPHROPATHY
RESISTANT TO RECOMMENDED INITIAL THERAPY

7.6.1: We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a **CNI**. (2C)

7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an **ALKYLATING AGENT/ STEROID**-based therapy. (2C)

MEMBRANOUS NEPHROPATHY
RELAPSES OF NEPHROTIC SYNDROME

7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by **REINSTITUTION OF THE SAME THERAPY** that resulted in the initial remission. **(2D)**

7.7.2: We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy, the regimen be **REPEATED ONLY ONCE** for treatment of a relapse. **(2B)**

MEMBRANOUS NEPHROPATHY
PROPHYLACTIC ANTICOAGULATION

7.9.1: We suggest that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin (< 2.5 g/dl) and additional risks for thrombosis, be considered for **prophylactic anticoagulant therapy,** using ORAL **WARFARIN**. **(2C)**

CJASN ePress. Published on November 10, 2011 as doi: 10.2215/CJN.04250511

Venous Thromboembolism in Patients with Membranous Nephropathy

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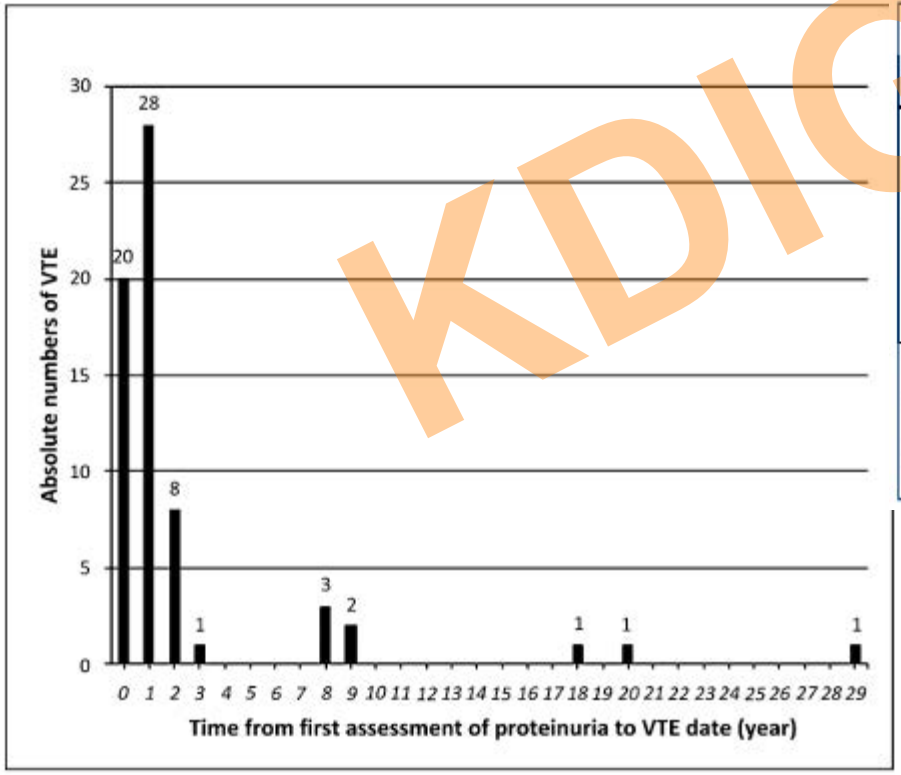


Table 4. Adjusted risk of VTE by the level of serum albumin in 732 patients with available data

Serum Albumin (g/dl)	*N*	Patients with VTE	Odds Ratio	95% Confidence Interval	*P* Value[a]
Reference range ≥3.0[b]	219		1.00		
2.8 to <3.0	66	3	1.41	0.34, 5.87	0.64
2.6 to <2.8	74	2	2.17	0.63, 7.46	0.22
2.4 to <2.6	72	4	2.05	0.59, 7.12	0.26
2.2 to <2.4	77	1	1.31	0.31, 5.62	0.72
2.0 to <2.2	82	8	4.32	1.46, 12.77	0.01
<2.0	142	15	3.56	1.28, 9.88	0.02
<2.8 versus ≥2.8	447/285		2.53	1.17, 5.47	0.02

[a]Logistic regression model with incremental values of serum albumin, adjusted for age at biopsy, sex, 24-hour proteinuria (g/d), immunosuppressive therapy, and registry site.

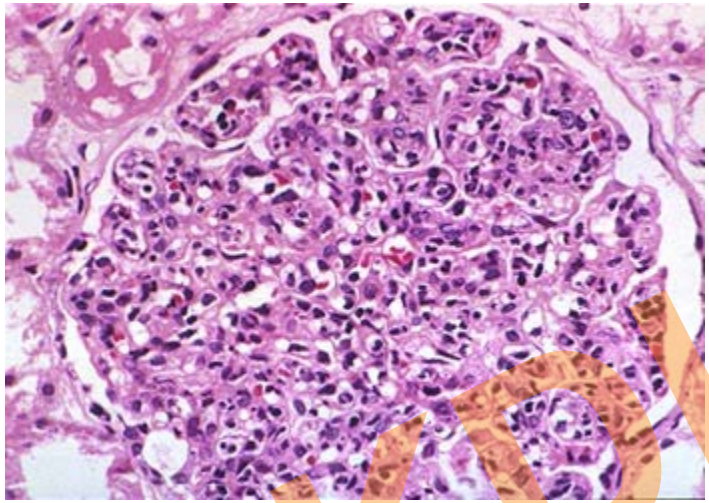
[b]Logistic regression model with serum albumin as a dichotomous variable. The serum albumin cut-point of 2.8 g/dl was determined from the incremental model (by 0.2 g/dl) reported in this table, with threshold for effect noted for values <2.8 g/dl. Adjusted for age at biopsy, sex, 24-hour proteinuria (g/d), immunosuppressive therapy, and registry site.

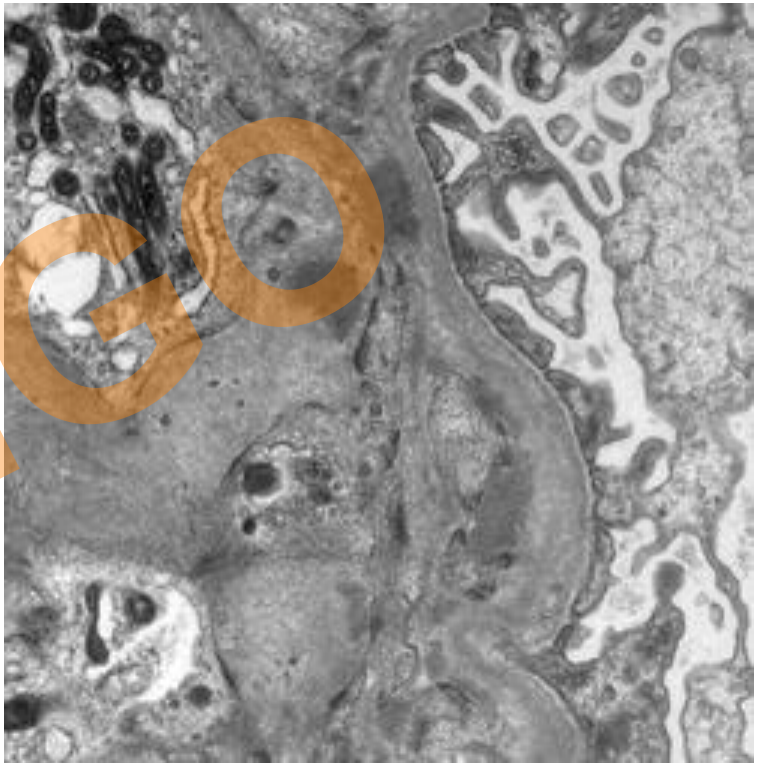
Figure 2. | Distribution of venous thromboembolic event (VTE) during the observation time.

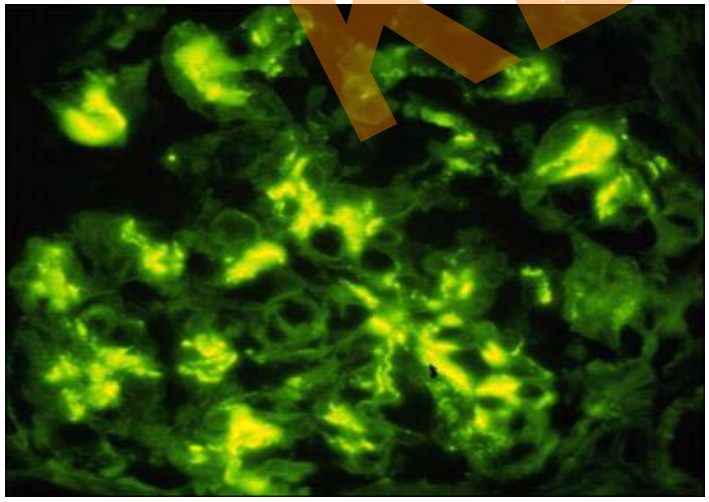
- There is very low–quality evidence to suggest the use of prophylactic anticoagulation with warfarin in patients with IMN and severe nephrotic syndrome.
- Based on Markov modeling of anticipated benefits and risks derived from observational studies, prophylactic anticoagulation might be considered when the **serum albumin concentration is < 2.0–2.5 g/dl** with one or more of the following:
  - proteinuria > 10 g/d
  - BMI > 35 kg/m2
  - prior history of thromboembolism
  - family history of thromboembolism with documented genetic predisposition
  - NYHA class III or IV congestive heart failure
  - recent abdominal or orthopedic surgery
  - prolonged immobilization.

IMMUNOGLOBULIN A NEPHROPATHY

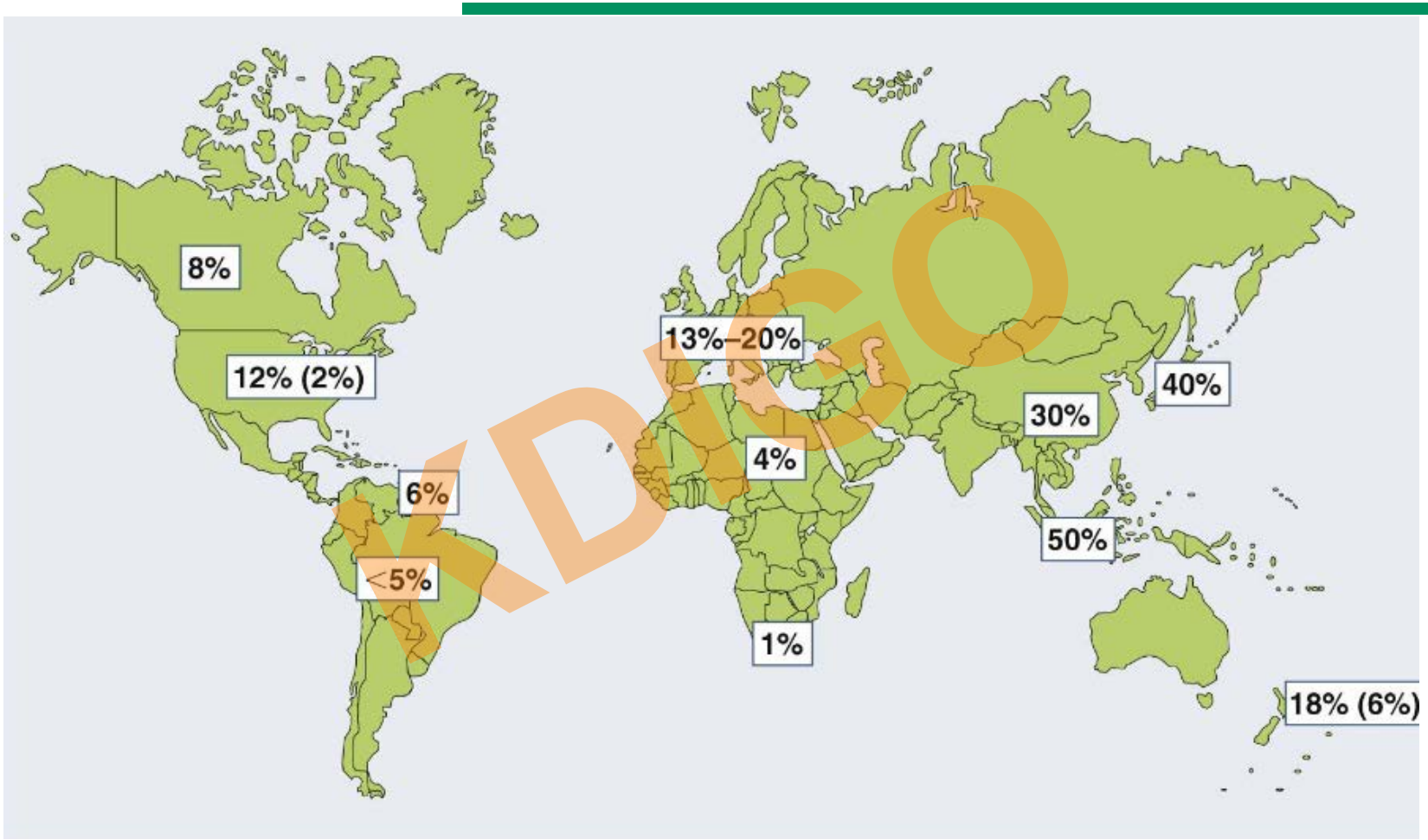
IMMUNOGLOBULIN A NEPHROPATHY







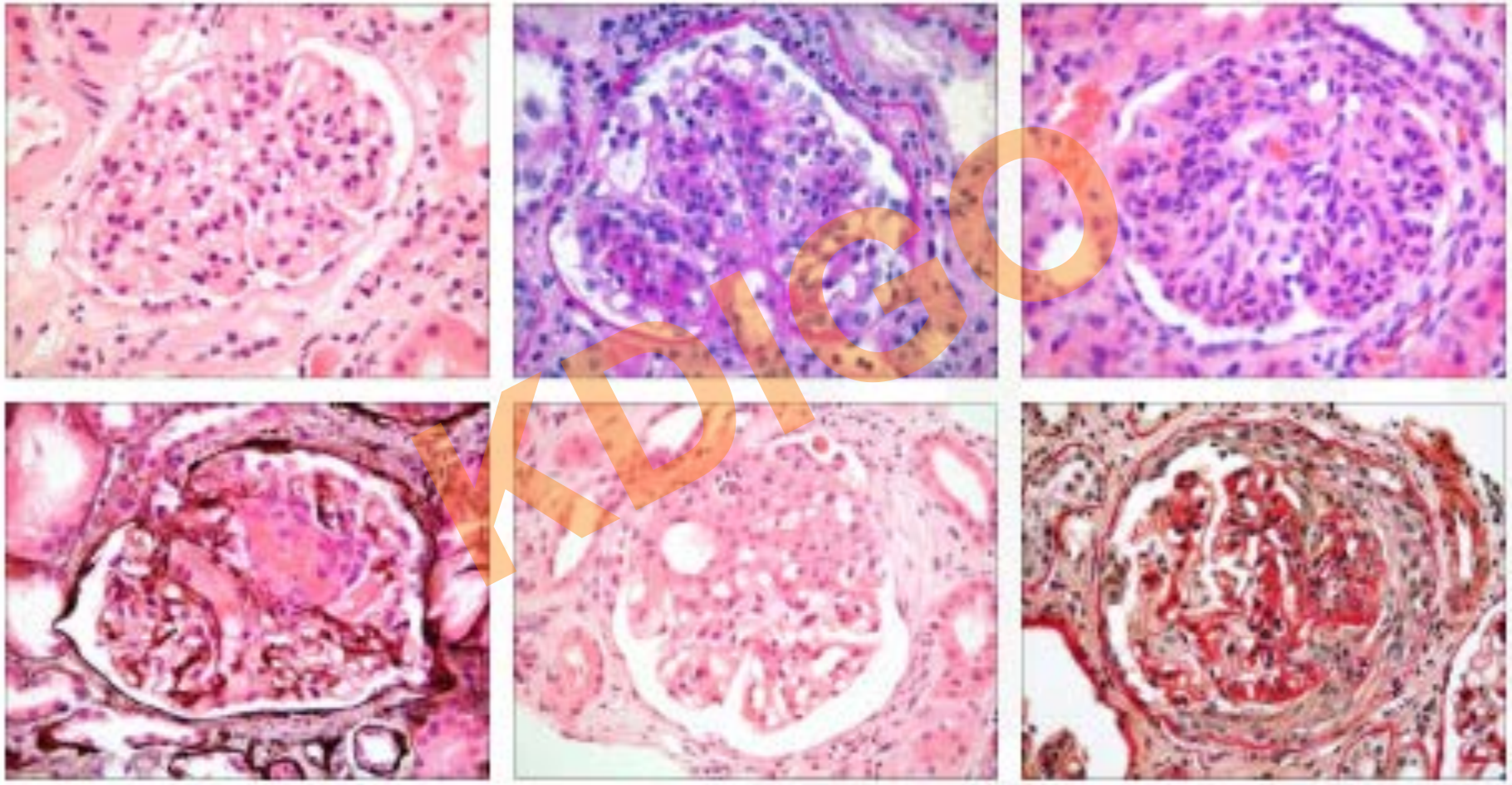
IgA Nephropathy is the MOST COMMON GLOMERULONEPHRITIS in the world.



- RARE in African Americans
- COMMON in Native Americans
- **EVEN WITH LOW PROGRESSION RATE, its HIGH PREVALENCE results in <u>10-20%</u> <u>contribution to ESKD</u>.**

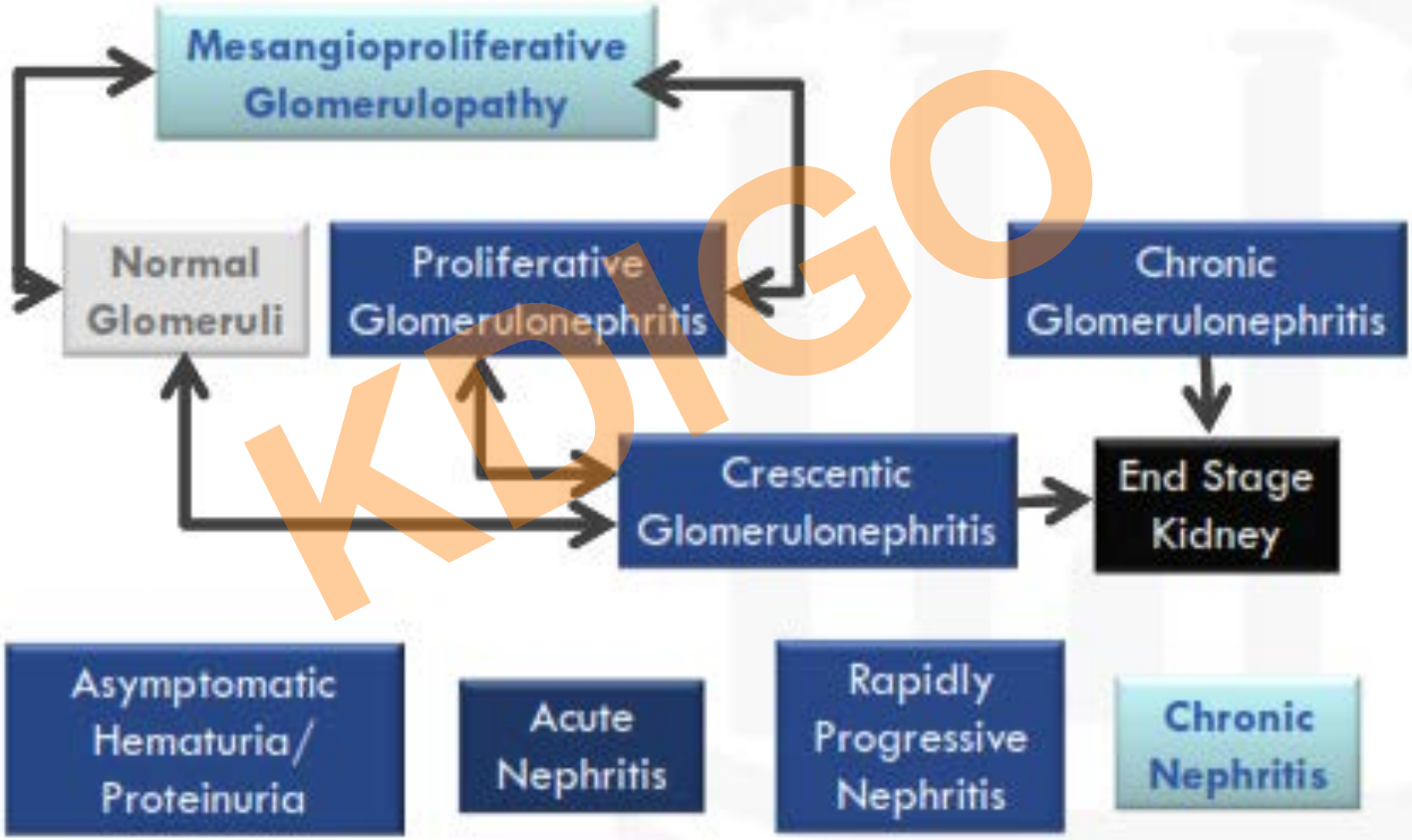
	ALL BIOPSIES (%)	GN BIOPSIES (%)
USA	5	10
ASIA	30	40
EUROPE	15	20

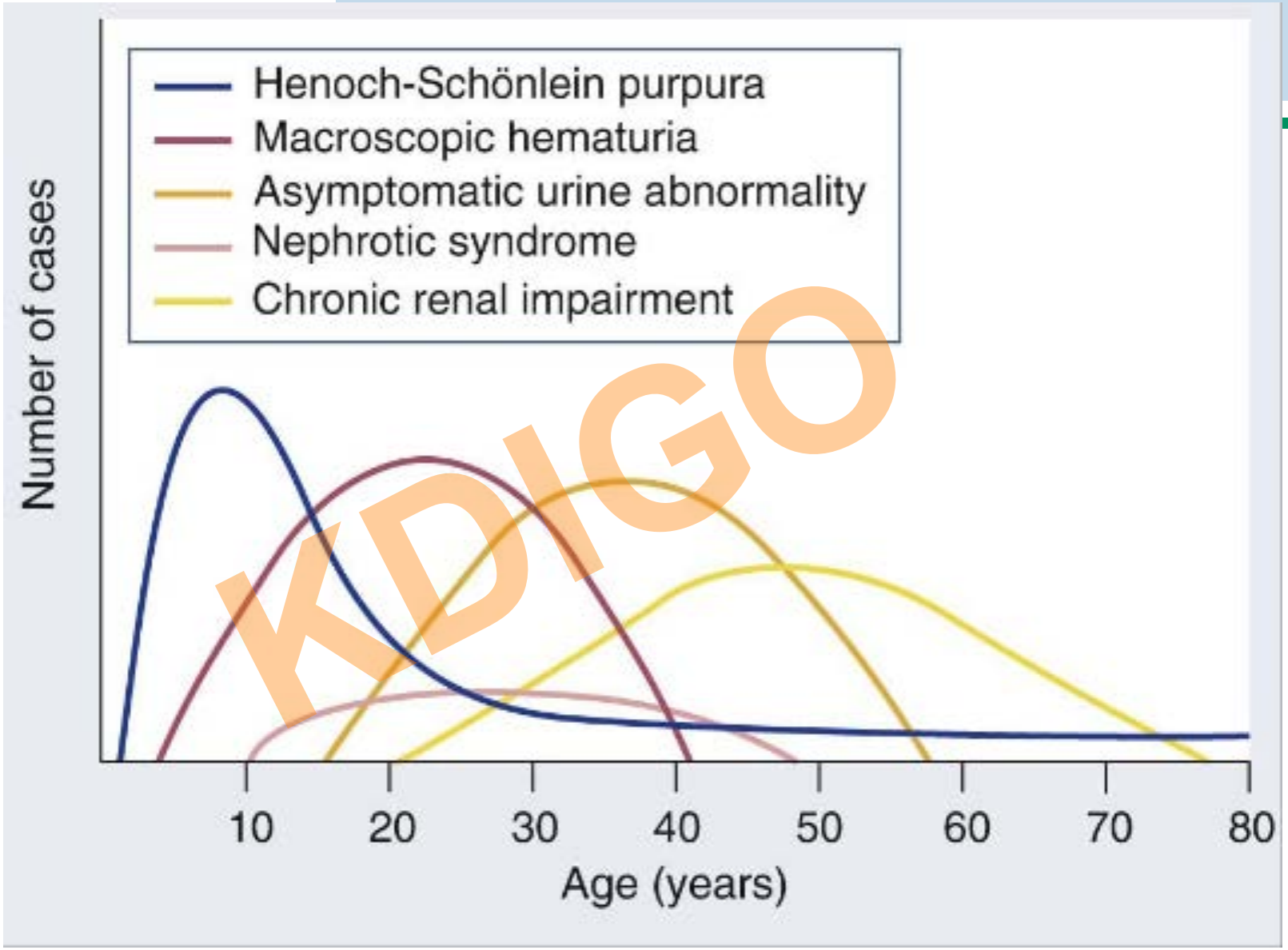
IgA Nephropathy is Morphologically Heterogeneous



Roberts SD et al. Kidney Int 76:546-56, 2009

Light Microscopic Morphology




Henoch-Schönlein purpura
Macroscopic hematuria
Asymptomatic urine abnormality
Nephrotic syndrome
Chronic renal impairment
Number of cases
10
20
30
40
50
60
70
80
Age (years)

IMMUNOGLOBULIN A NEPHROPATHY
INITIAL EVALUATION

10.1.1: Assess all patients with biopsy-proven IgAN for **SECONDARY CAUSES of IgAN**. **(NOT GRADED)**

DISEASES REPORTED IN ASSOCIATION WITH IgA NEPHROPATHY

DISEASE	COMMON	REPORTED	RARE
RHEUMATIC and AUTOIMMUNE DISEASE	• Ankylosing spondylitis • Rheumatoid arthritis • Reactive arthritis • Uveitis	• Behcet's syndrome • Takayasu's arthritis • Myasthenia gravis	
GASTROINTESTINAL DISEASE	Celiac disease	Ulcerative colitis	
HEPATIC DISEASE	• Alcoholic liver disease • Non-alcoholic cirrhosis • Schistosomal liver disease		
LUNG DISEASE	Sarcoid		
SKIN DISEASE	Dermatitis herpetiformis		
MALIGNANCY		IgA monoclonal gammopathy	
INFECTION	• HIV • HBV	Brucellosis	
MISCELLANEOUS		Wiskott-Aldrich syndrome	

IMMUNOGLOBULIN A NEPHROPATHY
INITIAL EVALUATION

10.1.2: Assess the **risk of progression** in all cases by evaluation of **proteinuria, blood pressure, and eGFR** at the time of diagnosis and during follow-up. **(NOT GRADED)**

IMMUNOGLOBULIN A NEPHROPATHY PROGNOSTIC IMPLICATIONS (?)

- **DEGREE OF PROTEINURIA**: 1.0 vs 0.5 g/d
- **DEGREE OF BP CONTROL**
  - 130/80 for proteinuria 0.3 g/d
  - 125/75 mm Hg for proteinuria 1 g/d
- **OXFORD Pathology Classification**

IMMUNOGLOBULIN A NEPHROPATHY
INITIAL EVALUATION

10.1.3: Pathological features may be used to assess prognosis. **(NOT GRADED)**

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,*]

Table 7 | Definitions of pathological variables used in the classification of IgA nephropathy

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 >8 Mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0 ⩽0.5 M1 >0.5[a]
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 – present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0–25% – T0 26–50% – T1 >50% – T2

[a]Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

Nephrol Dial Transplant (2002) 17: 1197–1203

Nephrology Dialysis Transplantation

Original Article

Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy

James V. Donadio[1], Erik J. Bergstralh[2], Joseph P. Grande[3] and Diana M. Rademcher[2]

[1]Division of Nephrology, Department of Internal Medicine, [2]Section of Biostatistics and [3]Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic and Foundation, Rochester, MN, USA

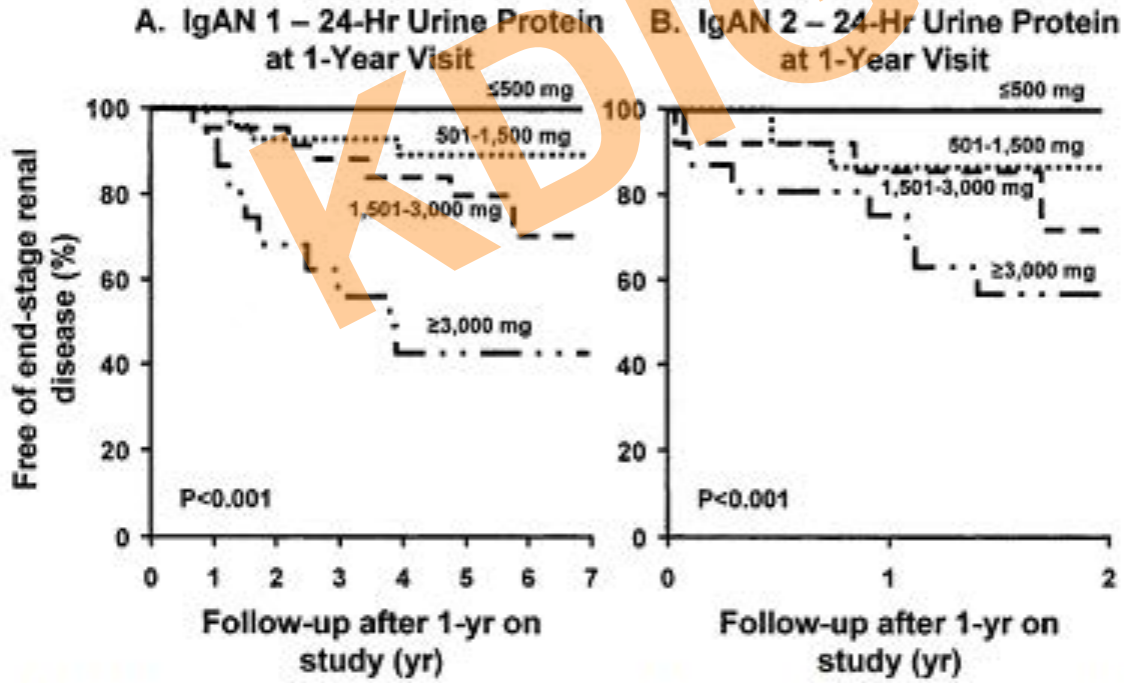


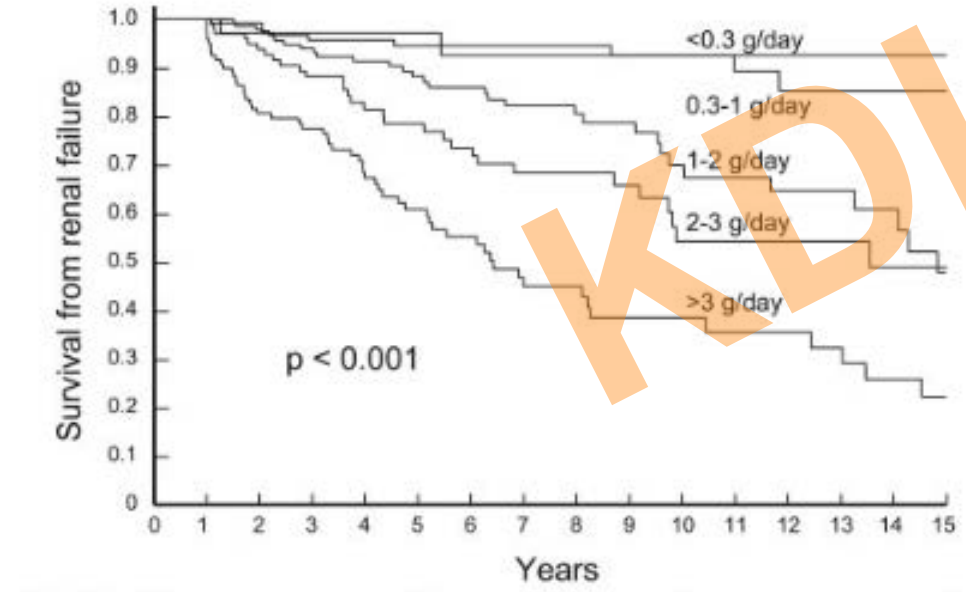
Fig. 1. 24-h UP levels at 1 year were significantly associated with subsequent ESRD after 1 year on study in (A) IgAN 1 ($P<0.001$, linear trend) and (B) IgAN 2 ($P<0.001$, linear trend).

CLINICAL RESEARCH www.jasn.org

Remission of Proteinuria Improves Prognosis in IgA Nephropathy

Heather N. Reich,* Stéphan Troyanov,† James W. Scholey,* and Daniel C. Cattran,* for the Toronto Glomerulonephritis Registry

*Division of Nephrology, University Health Network, University of Toronto, Toronto, Ontario, and †Department of Medicine, Division of Nephrology, Hôpital du Sacré-Coeur de Montréal, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada



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

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

- **Rate of decline of function increased with the amount of proteinuria.**
- Those with **sustained proteinuria ≥ 3 gms/day lost renal function 25-FOLD FASTER** than those with < 1 gm/day
- Those who presented with ≥ 3 gms/day who **achieved proteinuria < 1 gm/day had a SIMILAR COURSE** to those who had < 1gm/day throughout and **fared far better than those who never achieved it**
- **NO EVIDENCE in IgAN that decreasing proteinuria < 1 gm/day in adults gives additional benefit**

IMMUNOGLOBULIN A NEPHROPATHY
PROGNOSTIC MARKERS AT PRESENTATION

CLINICAL	HISTOPATHOLOGIC
POOR PROGNOSIS	
• **HYPERTENSION** • **RENAL IMPAIRMENT** • **SEVERITY OF PROTEINURIA** • Hyperuricemia • Gross Obesity • Duration of preceding symptoms • Increasing age	• Mesangial hypercellularity • Endocapillary proliferation • Segmental glomerulosclerosis • Tubular atrophy • Interstitial fibrosis • CAPILLARY LOOP IgA DEPOSITS *- Specific to IgA Nephropathy* • Crescents (Controversial)
GOOD PROGNOSIS	
Recurrent macroscopic hematuria	
NO IMPACT ON PROGNOSIS	
• Gender • Serum IgA level	• Intensity of IgA deposits

RECURRENT MACROSCOPIC HEMATURIA IN IgAN

- Most frequent in **CHILDREN**
- Associated with URT or GIT infection; flank or loin pain is common
- **Nephrotic syndrome and Hypertension are <u>UNCOMMON</u>**
- **PROLONGED REMISSIONS OF CLINICAL SIGNS**
- Associated with **GOOD PROGNOSIS**

ASYMPTOMATIC HEMATURIA/ PROTEINURIA

- **PERSISTENT MICROSCOPIC HEMATURIA**
- **<u>HYPERTENSION MORE COMMON</u>**
- **IMPAIRMENT OF RENAL FUNCTION** may be apparent on presentation
- **REMISSION IS UNCOMMON**

IMMUNOGLOBULIN A NEPHROPATHY
ANTIPROTEINURIC AND ANTIHYPERTENSIVE THERAPY

10.2.1: We recommend **long-term ACE-I or ARB** treatment when **proteinuria is > 1 g/d**, with up-titration of the drug depending on blood pressure. **(1B)**

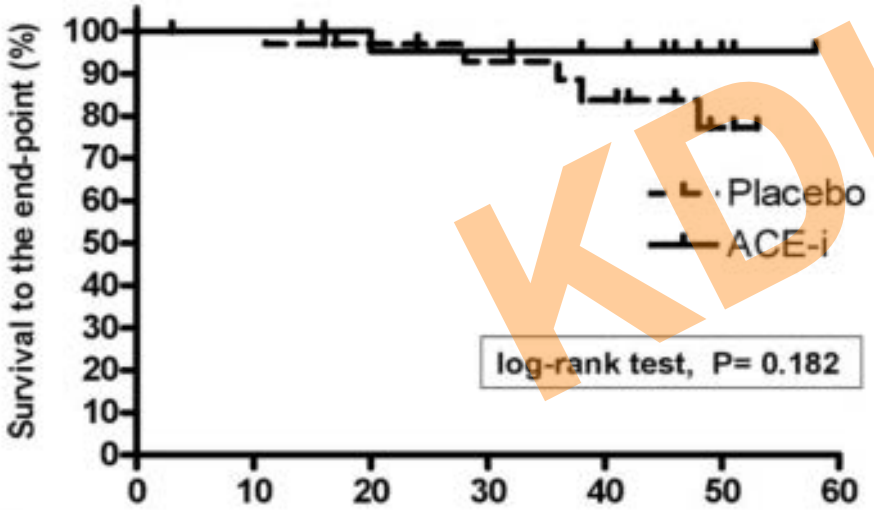
10.2.3: We suggest the **ACE-I or ARB** be titrated upwards as far as tolerated **to achieve proteinuria < 1 g/d. (2C)**

10.2.4: In IgAN, use blood pressure treatment goals of **< 130/80 mmHg** in patients with **proteinuria < 1 g/d,** and **< 125/75 mmHg** when **initial proteinuria is > 1 g/d. (NOT GRADED)**

IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

Rosanna Coppo,* Licia Peruzzi,* Alessandro Amore,* Antonio Piccoli,† Pierre Cochat,‡ Rosario Stone,§ Martin Kirschstein,‖ and Tommy Linné;¶ on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

*Nephrology, Dialysis and Transplantation, Pediatric Nephrology School, Regina Margherita University Hospital, Turin, Italy; †Department of Medical and Surgical Sciences, Nephrology Clinic, University of Padua, Padua, Italy; ‡Departement de Pediatrie, Hopital Edouard-Herriot, Lyon, France; §Unidade de Nefrologia, Serviço de Pediatria, Hospital de Santa Maria, Lisboa, Portugal; ‖Klinik für Kinder- und Jugendmedizin des Allgemeines Krankenhaus, Celle, Germany; and ¶Department of Women and Child Health, Karolinska Universitaet, Stockholm, Sweden



Subjects at risk

ACEI	32	23	20	17	15	8
PLACEBO	34	32	26	23	16	6

Figure 3. Survival without end point of 30% reduction of baseline CrCl in IgAN patients receiving ACE-I or placebo (Kaplan-Meier estimates, log rank, $P = 0.180$).

- Placebo-controlled, double blind RCT of ACE-I
- 66 patients randomly assigned
- **Primary outcome** was progression of of kidney disease, i.e., > 30% decrease in CrCl
- **Secondary outcomes**: endpoint > 30% decrease in CrCl, worsening of proteinuria, proteinuria partial/ total remission

Combination Therapy of Prednisone and ACE Inhibitor Versus ACE-Inhibitor Therapy Alone in Patients With IgA Nephropathy: A Randomized Controlled Trial

Jicheng Lv, MD,[1,2] Hong Zhang, MD, PhD,[1,2] Yuqing Chen, MD,[1,2] Guangtao Li, MD,[1,2] Lei Jiang, MD,[1,2] Ajay K. Singh, MB, FRCP,[3] and Haiyan Wang, MD[1,2]

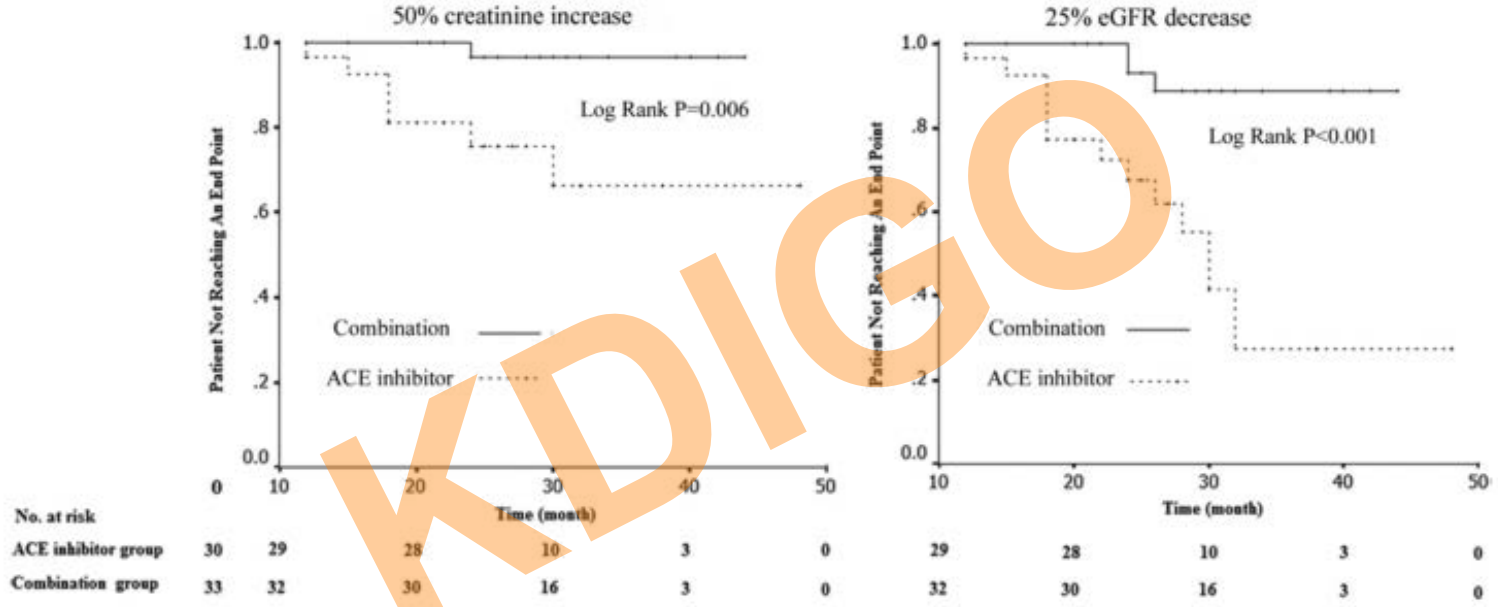


Figure 2. Kidney survival estimated on the basis of an increase up to 50% greater than baseline serum creatinine level and a decrease of 25% in estimated glomerular filtration rate (eGFR). Abbreviation: ACE, angiotensin-converting enzyme.

Conclusions: Our results suggest that the addition of steroid to ACE-inhibitor therapy provided additional benefit compared with an ACE inhibitor alone. However, this was a pilot study with a small number of participants achieving the end points, and thus further validation is necessary.

Am J Kidney Dis 53:26-32.

Nephrol Dial Transplant (2009) 24: 156–160
doi: 10.1093/ndt/gfn454
Advance Access publication 6 August 2008

NDT
Nephrology Dialysis Transplantation

Original Article

Combined treatment with renin–angiotensin system blockers and polyunsaturated fatty acids in proteinuric IgA nephropathy: a randomized controlled trial

Pietro Manuel Ferraro[1], Gian Franco Ferraccioli[2], Giovanni Gambaro[3], Pierluigi Fulignati[1] and Stefano Costanzi[1]

[1]Department of Nephrology, [2]Department of Rheumatology, Catholic University of the Sacred Heart, Rome and [3]Department of Nephrology, University Hospital of Verona, Verona, Italy

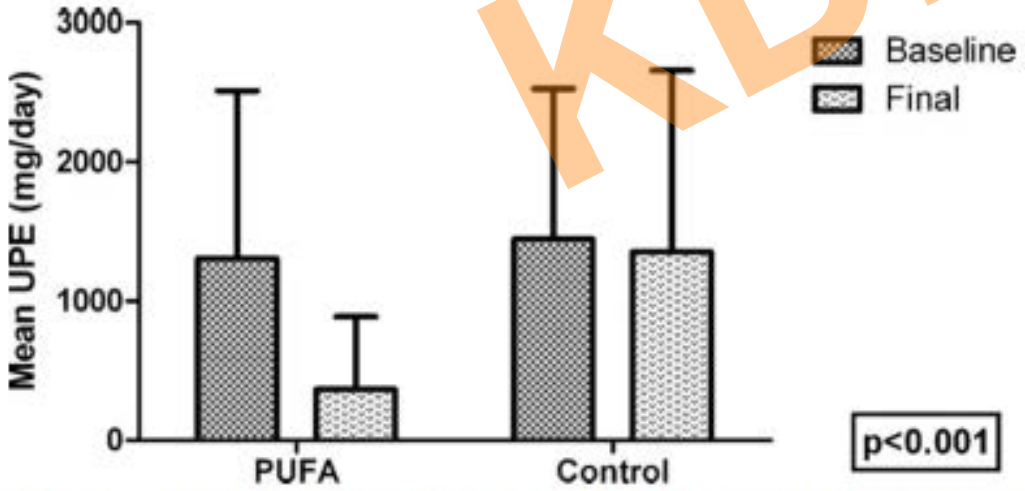


Fig. 1. Proteinuria at 6 months. UPE, urinary protein excretion; PUFA, polyunsaturated fatty acids.

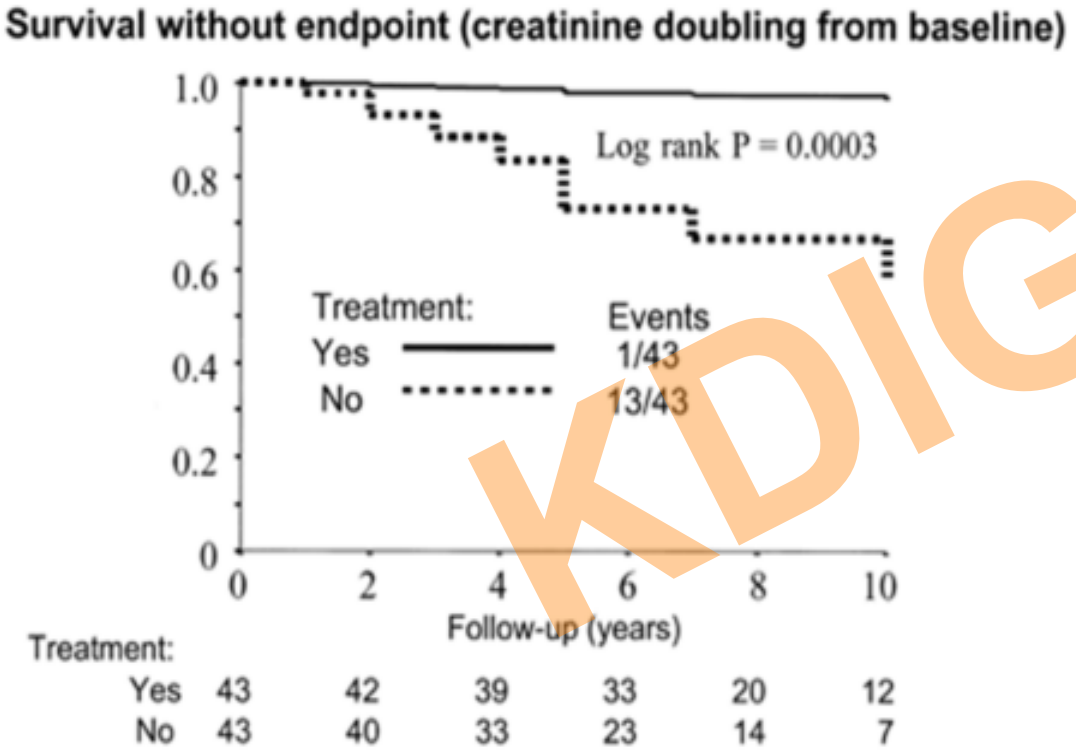
- PUFA associated with RASB reduced proteinuria in patients with IgAN more than RASB alone.
- **It appears that ACE-I enhance the effects of PUFA.**

IMMUNOGLOBULIN A NEPHROPATHY
CORTICOSTEROIDS

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 m2**, receive a 6-month course of **CORTICOSTEROID** therapy. **(2C)**

2 Important studies showed benefit of ACE-I + Corticosteroids

Pozzi et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. The Lancet, Volume 353, Issue 9156, Pages 883 - 887, 13 March 1999



A 6-month course of steroid treatment **protected against deterioration in renal function** in IgA nephropathy with **no notable adverse effects during follow-up**. An increase in urinary protein excretion could be a marker indicating the need for a second course of steroid therapy.

Nephrol Dial Transplant (2009) 24: 3694–3701
doi: 10.1093/ndt/gfp356
Advance Access publication 23 July 2009

Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy

Carlo Manno, Diletta Domenica Torres, Michele Rossini, Francesco Pesce and Francesco Paolo Schena

Renal, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

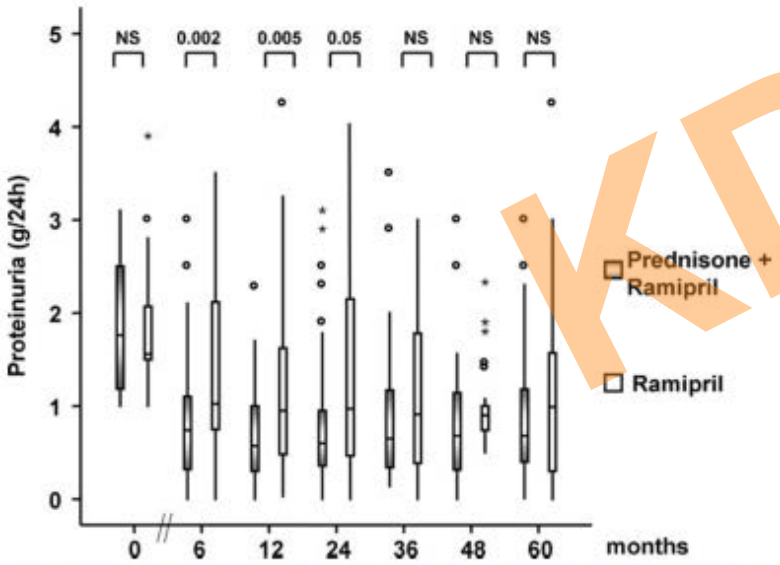


Fig. 3. Median urinary protein excretion was significantly lower in the prednisone plus ramipril group compared with the ramipril alone group at 6 months, at 1 and 2 years. The boxes indicate median and interquartile ranges. The lines at the ends of the boxes show the distance to the largest and smallest observed values that are <1.5 box lengths from either end. Circles and asterisks indicate values that are distant from 1.5 to 3 times and >3 times, respectively, the length of the box starting from its upper limit. NS, not significant.

- The combination of **CORTICOSTEROIDS and RAMIPRIL** may provide **ADDITIONAL BENEFITS** compared with Ramipril alone in **PREVENTING THE PROGRESSION OF RENAL DISEASE** in proteinuric IgAN patients in the long-term follow up.

IMMUNOGLOBULIN A NEPHROPATHY
CORTICOSTEROIDS

Table 26 | Corticosteroid regimens in patients with IgAN

References	Pozzi C *et al.*[509]	Manno C *et al.*[510]; Lv J *et al.*[511]
Regimen	i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months	6-month regime of oral prednisone[a] starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

IgAN, immunoglobulin A nephropathy.
[a]Prednisone and prednisolone are equivalent and can be used interchangeably with the same dosing regimen.

MAIN LIMITATION: Subjects with IgAN and eGFR < 50 mL/min were EXCLUDED from these trials

Controlled, Prospective Trial of Steroid Treatment in IgA Nephropathy: A Limitation of Low-Dose Prednisolone Therapy

Ritsuko Katafuchi, MD, Kiyoshi Ikeda, MD, Tohru Mizumasa, MD, Hiroshi Tanaka, MD, Takashi Ando, MD, Tetsuro Yanase, MD, Kohsuke Masutani, MD, Michiaki Kubo, MD, and Satoru Fujimi, MD

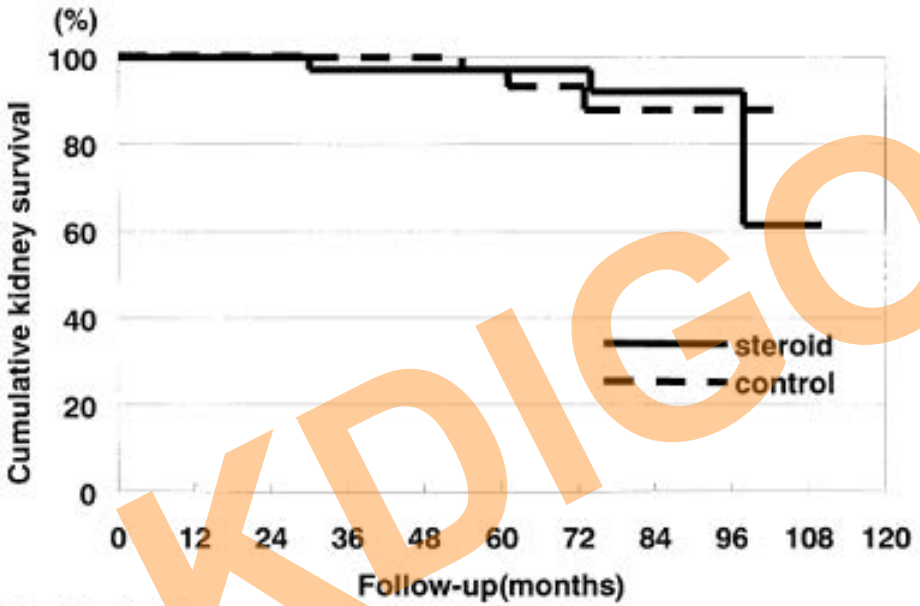


Fig 2. Kidney survival curves in the steroid and control groups show no significant difference in cumulative kidney survival between the two groups.

Low dose corticosteroids (20 mgs/day tapered to 5 mgs/day by 2 years) **HAD ANTIPROTEINURIC EFFECT** but **COULD NOT IMPROVE KIDNEY SURVIVVAL.**

Corticosteroid Therapy in IgA Nephropathy

Jicheng Lv,* Damin Xu,* Vlado Perkovic,† Xinxin Ma,* David W. Johnson,‡§ Mark Woodward,†‖ Adeera Levin,¶ Hong Zhang,* and Haiyan Wang,* for the TESTING Study Group

*Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China; †George Institute for Global Health, University of Sydney, Sydney, Australia; ‡Department of Renal Medicine, Princess Alexandra Hospital, Brisbane, Australia; §School of Medicine, University of Queensland, Brisbane, Australia; ‖Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; and ¶Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

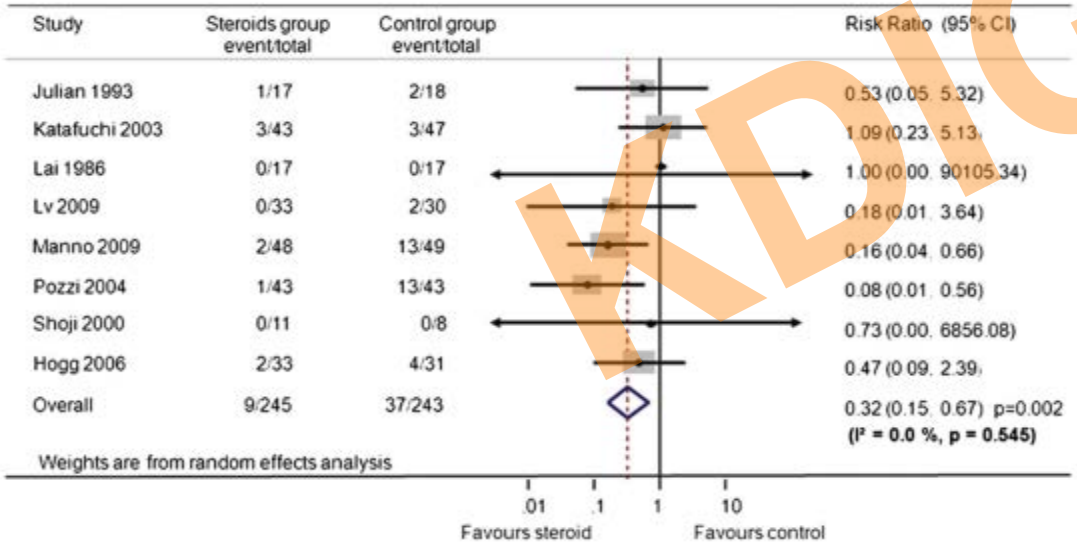


Figure 2. Effect of steroids on composite renal endpoint (ESRD or doubling of serum creatinine or halving of GFR) in patients with IgA nephropathy. Boxes and horizontal lines represent relative risk and 95% CI, respectively, for each trial. Size of boxes is proportional to weight of that trial result. Diamonds represent the 95% CI for pooled estimates of effect and are centered on pooled relative risk. Dotted lines on the center of the diamonds represent pooled relative risk. Solid lines represent that the relative risk is 1.

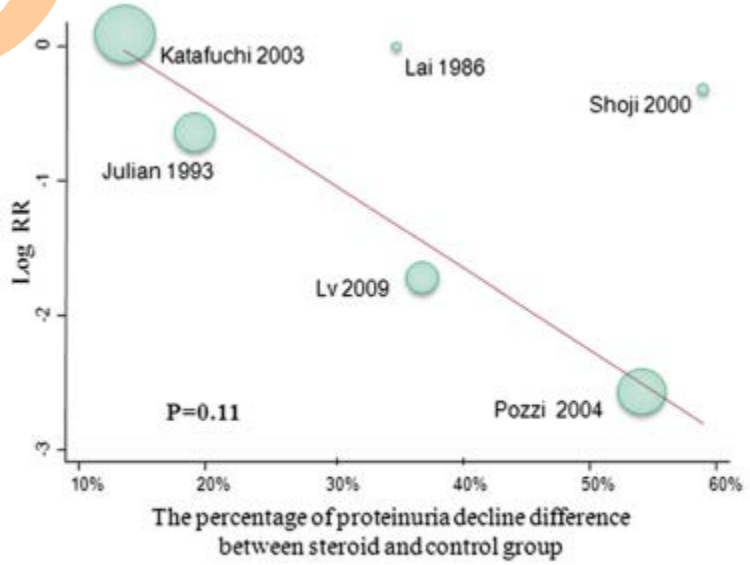


Figure 5. Meta-regression for the association of RR for composite renal endpoint and proteinuria reduction.

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Corticosteroid Therapy in IgA Nephropathy

Jicheng Lv,* Damin Xu,* Vlado Perkovic,† Xinxin Ma,* David W. Johnson,‡§ Mark Woodward,†‖ Adeera Levin,¶ Hong Zhang,* and Haiyan Wang,* for the TESTING Study Group

*Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China; †George Institute for Global Health, University of Sydney, Sydney, Australia; ‡Department of Renal Medicine, Princess Alexandra Hospital, Brisbane, Australia; §School of Medicine, University of Queensland, Brisbane, Australia; ‖Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; and ¶Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

- **Relatively HIGH-DOSE and SHORT-TERM STEROID THERAPY** (prednisone 30 mg/d or high-dose pulse IV methylprednisolone for 1year) produced **SIGNIFICANT RENAL PROTECTION**, whereas low-dose, long-term steroid use did not.
- Steroid therapy was associated with a **55% HIGHER RISK FOR ADVERSE EVENTS**.
- **The quality of included studies was low, thereby limiting the generalizability of the results.**
- The authors concluded that **although steroids appeared to provide renal protection in patients with IgAN there was a significant increased risk for adverse events**. They also recommended that defining the efficacy and safety of steroids in IgAN requires a *high-quality trial with a large sample size.*

IgA Nephropathy: A Disease in Search of a Large-Scale Clinical Trial to Reliably Inform Practice

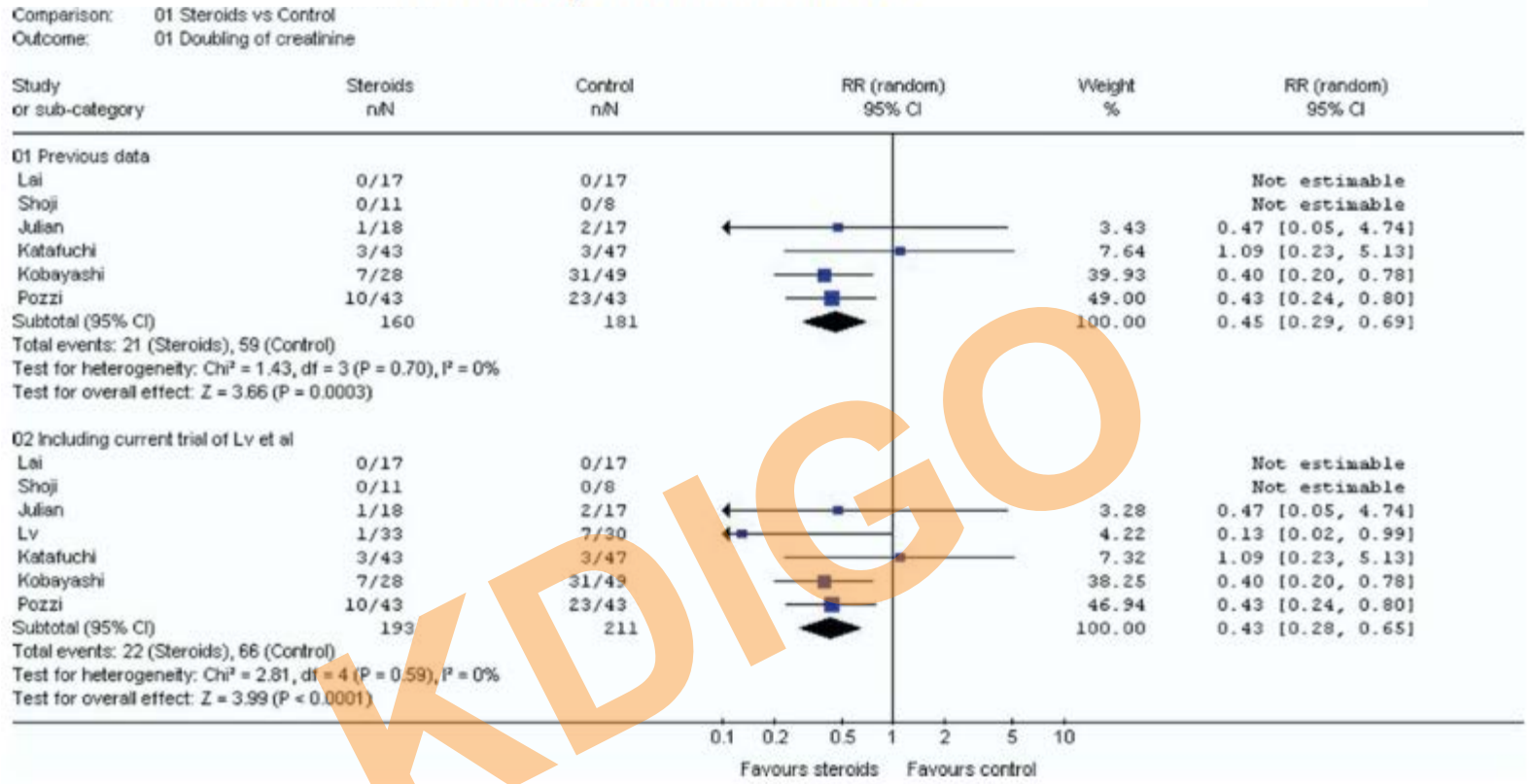


Figure 1. Effect of corticosteroids versus comparator treatments on doubling of creatinine in patients with IgA nephropathy.

CORTICOSTEROIDS REDUCED DOUBLING OF SERUM CREATININE (Strippoli et al, Am J Kidney Dis 2009)

(85% of the weight was contributed by 2 studies: Pozzi et al, Lancet 1999 and Kobayashi et al, Nephron 1996, both of which lacked optimal antiproteinuric and antihypertensive therapy based on contemporary studies.

IMMUNOGLOBULIN A NEPHROPATHY
IMMUNOSUPPRESSIVE AGENTS

- Cyclophosphamide
- Azathioprine
- MMF
- Cyclosporine

IMMUNOGLOBULIN A NEPHROPATHY
IMMUNOSUPPRESSIVE AGENTS

10.4.1: We suggest **NOT TREATING** with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients **(unless there is crescentic IgAN with rapidly deteriorating kidney function).** **(2D)**

IMMUNOGLOBULIN A NEPHROPATHY
IMMUNOSUPPRESSIVE AGENTS

10.4.2: We suggest **NOT USING immunosuppressive therapy** in patients with GFR < 30 ml/min per 1.73 m2 **unless there is crescentic IgAN with rapidly deteriorating kidney function**. **(2C)**

10.4.3: We suggest **NOT USING MMF** in IgAN. **(2C)**

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‡
*Department of Nephrology, Royal Infirmary and University, Manchester, United Kingdom; and ‡Department of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom.

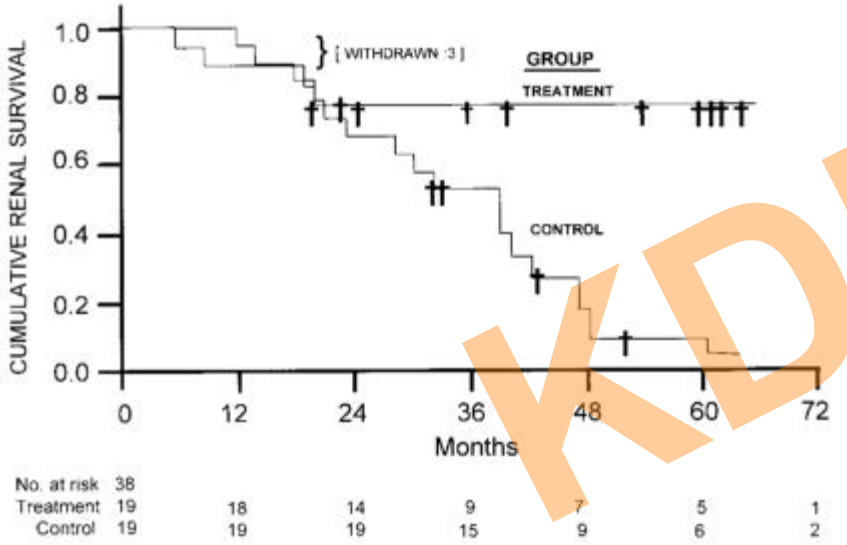


Figure 1. Kaplan-Meier survival functions for progressive IgA-related nephropathy for treatment and control groups. Preservation of function was significant after 2 yr ($P = 0.006$, log rank; $P = 0.036$, Tarone-Ware; †, censored—*i.e.*, not incurring event).

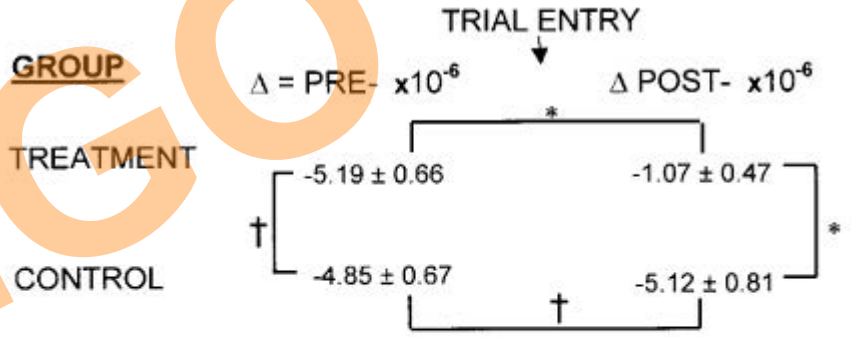


Figure 2. Rate of decline of renal function before and after trial entry for treatment and control groups. The mean rate of decline was reduced more than fourfold in the treatment group (mean ± SEM; *, $P < 0.005$, *t* test; †, P = NS; units are Δ = L · μmol^{-1} · d^{-1}). End-stage failure in 5 yr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

Patients selected for moderately progressive IgAN benefit from treatment with prednisolone and cytotoxic agents.

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‡
*Department of Nephrology, Royal Infirmary and University, Manchester, United Kingdom; and ‡Department of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom.

Corticosteroids combined with cyclophosphamide followed by several years of azathioprine in patients with serum creatinine 2-3 mgs/dL plus a 15% rise within the previous year.

The active treatment group had a much greater renal survival (**72% 5-year survival** vs 6% in control group).

- ***There was NO steroid monotherapy arm***
- ***Use of RASB was NOT detailed but these agents could not be initiated after the start of the trial***
- ***The follow-up BP was higher than recommended by current guidelines.***

Harmankaya O, et al. Efficacy of immunosuppressive therapy in IgA nephropathy presenting with isolated hematuria. Int Urol Nephrol. 2002;33(1):167-71.

- **Early treatment with prednisolone and azathioprine appears to be beneficial** in preventing the progression of immunologic renal injury and in improving histopathological features in **IgAN patients with isolated hematuria**.

However, the patients enrolled have an excellent prognosis and there is consensus that they should not have received immunosuppression.

CLINICAL RESEARCH www.jasn.org

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*

*Departments of Nephrology and Dialysis, Ospedale A. Manzoni, Lecco, Italy; †Ospedale E. Bassini, Cinisello Balsamo, Milan, Italy; ‡Ospedale G. Brotzu, Cagliari, Italy; §Spedali Civili, Brescia, Italy; ‖Ospedale Maggiore IRCCS, Milan, Italy; ¶University Hospital of Vaudois, Lausanne, Switzerland; **Ospedale di Sondrio, Sondrio, Italy; ††Ospedale Universitario, Parma, Italy; ‡‡Ospedale Careggi, Florence, Italy; and §§Ospedale Universitario, Foggia, Italy

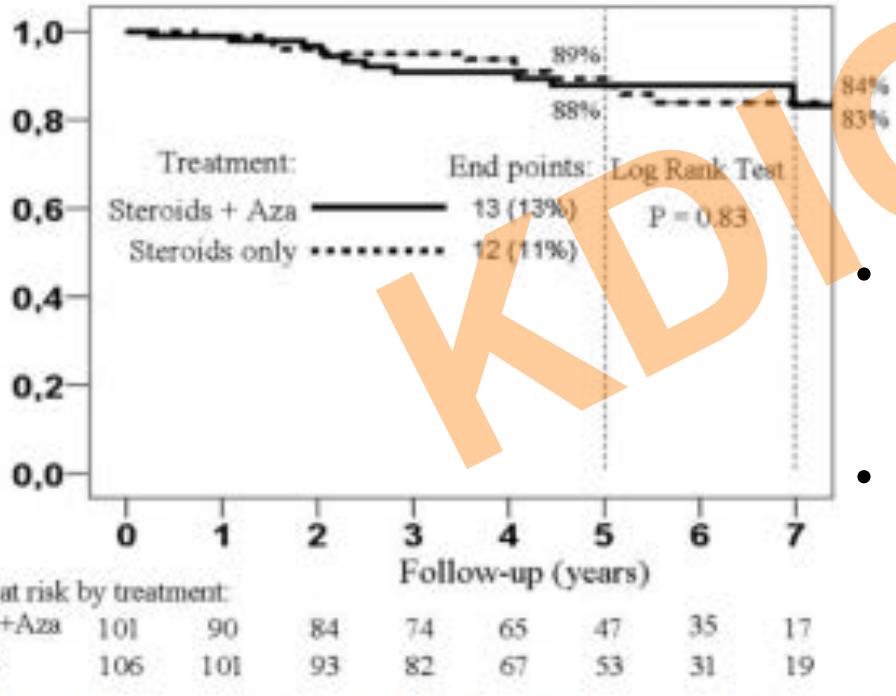


Figure 2. Renal survival is similar in the two treatment groups. Kaplan-Meier renal survival curves were estimated on the basis of the time to a 50% increase in plasma creatinine levels ($P = 0.83$, log-rank test).

- Treatment **significantly decreased proteinuria** from 2.00 to 1.07 gms/ day during follow up ($p < 0.001$) on average, with no difference between groups.
- Treatment related **adverse events** were more frequent among those receiving azathioprine.
- **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.**

Steroid Treatment for Severe Childhood IgA Nephropathy: A Randomized, Controlled Trial

Norishige Yoshikawa,* Masataka Honda,† Kazumoto Iijima,‡ Midori Awazu,§ Shinzaburou Hattori,‖ Koichi Nakanishi,* and Hiroshi Ito;§ for the Japanese Pediatric IgA Nephropathy Treatment Study Group

*Department of Pediatrics, Wakayama Medical University, Wakayama; †Tokyo Metropolitan Hachiouji Children's Hospital, Tokyo; ‡Department of Nephrology, National Center for Child Health and Development, Tokyo; §Department of Pediatrics, Keio University School of Medicine, Keio; and ‖Kumamoto University School of Medicine, Kumamoto, Japan

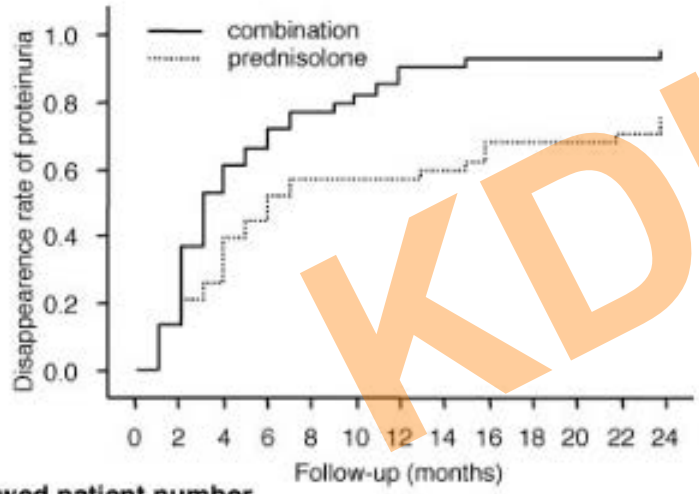


Figure 2. Disappearance of proteinuria as defined by urinary protein excretion <0.1 g/m² per d.

2 YEAR **COMBINATION OF PREDNISOLONE/ AZATHIOPRINE/ WARFARIN/ DIPYRIDAMOLE** vs PREDNISOLONE alone

- There was **COMPLETE REMISSION OF PROTEINURIA in 92%** in the combination group (vs 74% in the prednisolone alone group
- GFR remained normal in all children
- **It may be difficult to justify an intense immunosuppression in children on the basis of a relatively soft endpoint.**

Kidney International, Vol. 65 (2004), pp. 1842–1849

Mycophenolate mofetil in IgA nephropathy: Results of a 3-year prospective placebo-controlled randomized study

BART D. MAES, RAYMOND OYEN, KATHLEEN CLAES, PIETER EVENEPOEL, DIRK KUYPERS, JOHAN VANWALLEGHEM, BOUDEWIJN VAN DAMME, and YVES F. CH. VANRENTERGHEM

Department of Medicine, Division of Nephrology, University Hospital Gasthuisberg, Leuven, Belgium; Department of Radiology and Department of Pathology, University Hospital Gasthuisberg, Leuven, Belgium

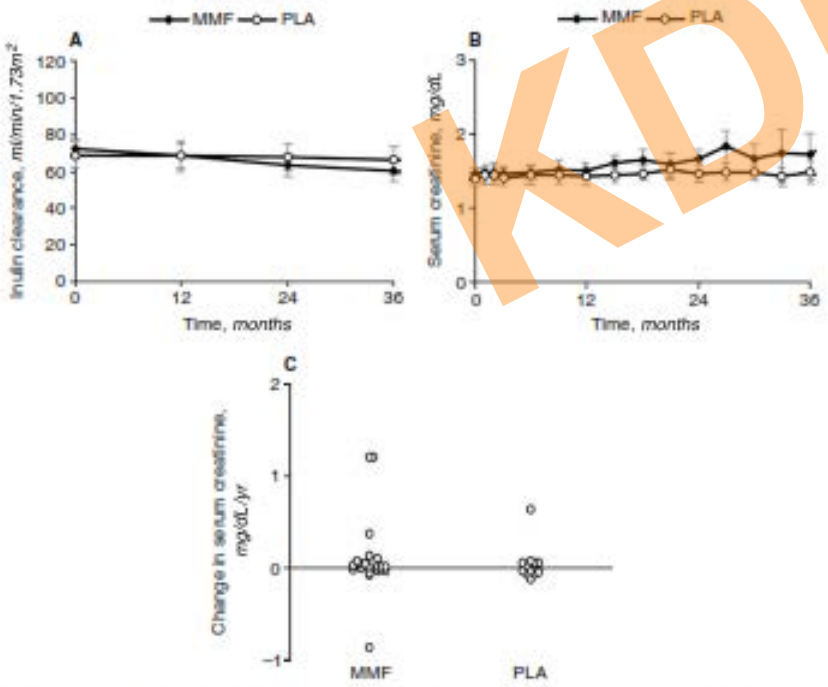


Fig. 2. Inulin clearance (A) (mean ± SEM), serum creatinine (B) (mean ± SEM) and annualized rate of change in serum creatinine (C) in patients with IgA nephropathy (IgAN) treated with mycophenolate mofetil (MMF) or placebo (PLA).

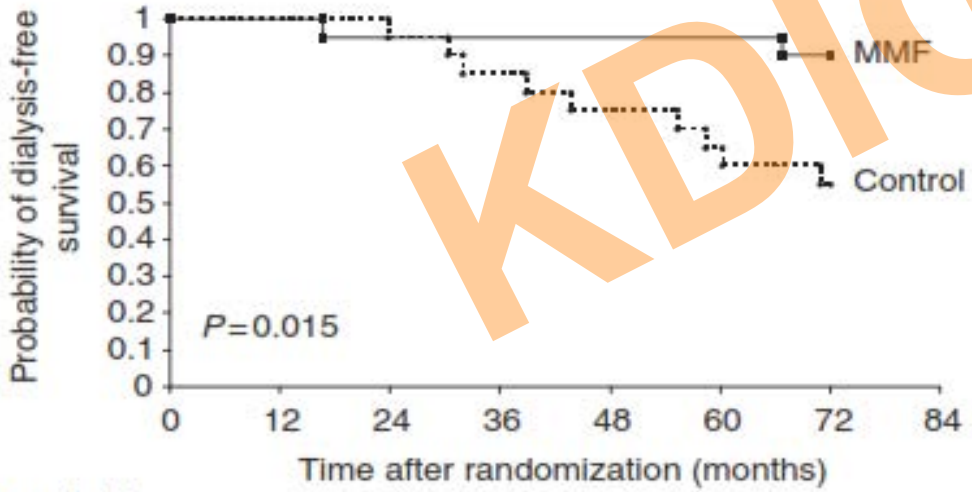
MMF 2 gms/day for 3 years vs. Placebo (34 patients with average initial inulin clearance 70 mL/min/1.73 m2 and proteinuria 1.8 gms/day)

- **NO DIFFERENCE IN PROTEINURIA REDUCTION or PRESERVATION OF GFR** was observed.

Long-term study of mycophenolate mofetil treatment in IgA nephropathy

Sydney C.W. Tang[1,2], Anthony W.C. Tang[2], Sunny S.H. Wong[2], Joseph C.K. Leung[1], Yiu Wing Ho[2] and Kar Neng Lai[1]

[1]Nephrology Division, Department of Medicine, The University of Hong Kong and Queen Mary Hospital, Hong Kong, China and [2]Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong, China



Number at risk							
MMF group:	20	20	19	19	19	19	18
Ctl group:	20	20	19	17	15	13	11

Figure 1 | Kaplan–Meier analysis of overall renal survival of 40 IgAN subjects over the 6-year follow-up period. Ctl, control; MMF, mycophenolate mofetil.

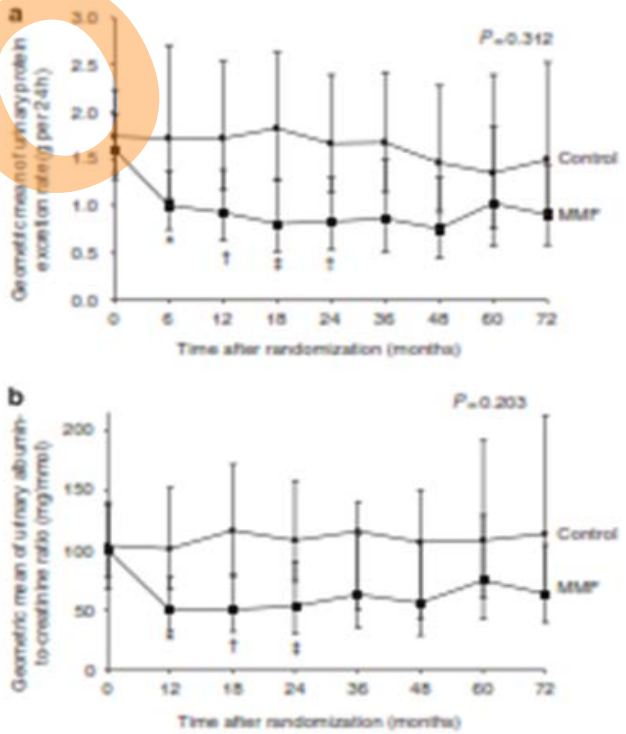


Figure 3 | Proteinuria change from baseline to study end. (**a**) Changes in urinary protein excretion during follow-up. The geometric mean values, with 95% confidence intervals, are shown. *$P = 0.019$, †$P = 0.023$, ‡$P = 0.007$ versus the control group at the corresponding time point. (**b**) Changes in urinary albumin-to-creatinine ratio during follow-up. The geometric mean values, with 95% confidence intervals, are shown. *$P = 0.019$, †$P = 0.006$, ‡$P = 0.027$ versus the control group at the corresponding time point.

http://www.kidney-international.org original article

Long-term study of mycophenolate mofetil treatment in IgA nephropathy

Sydney C.W. Tang[1,2], Anthony W.C. Tang[2], Sunny S.H. Wong[2], Joseph C.K. Leung[1], Yiu Wing Ho[2] and Kar Neng Lai[1]

[1]Nephrology Division, Department of Medicine, The University of Hong Kong and Queen Mary Hospital, Hong Kong, China and [2]Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong, China

40 patients with mean initial GFR 72 mL/min/1.73 m2 and mean proteinuria 1.8 gms/day

- **SIGNIFICANT REDUCTION IN PROTEINURIA** at 18 months with MMF given for 6 months vs controls (2005 study)
- 6 year follow-up: **RENAL SURVIVAL BENEFIT (2010 study)**

The ANTI-PROTEINURIC EFFECT DISAPPEARED after nearly 2 years.

Nephrol Dial Transplant (2005) 20: 2139–2145
doi:10.1093/ndt/gfh974
Advance Access publication 19 July 2005

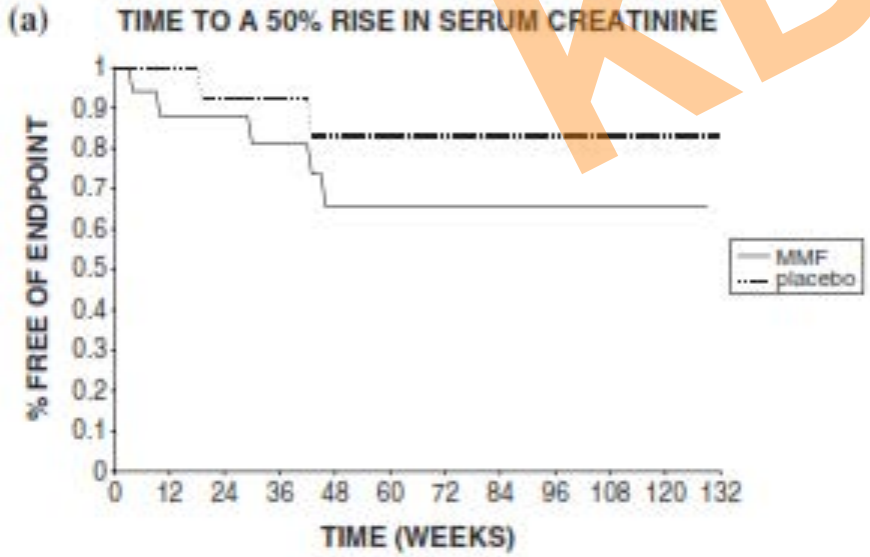
Nephrology
Dialysis
Transplantation

Original Article

Mycophenolate mofetil (MMF) *vs* placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial

Gershon Frisch, Julie Lin, Jordan Rosenstock, Glen Markowitz, Vivette D'Agati, Jai Radhakrishnan, Dean Preddie, John Crew, Anthony Valeri and Gerald Appel

Division of Clinical Nephrology, New York Presbyterian Hospital, Columbia University, New York, NY, USA



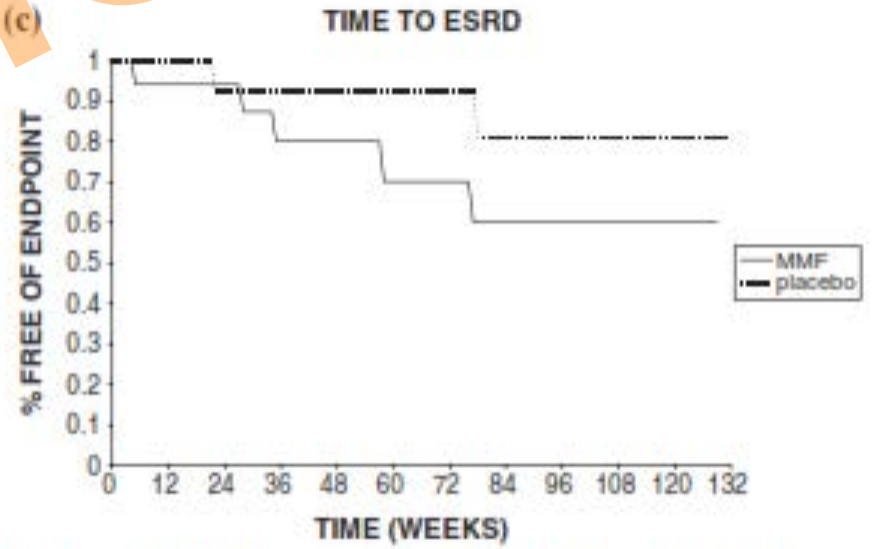


Fig. 1. Kaplan–Meier survival to outcomes. Log rank significance for a 50% increase in SCr = 0.31 (**a**), a 0.5 mg/dl increase in SCr = 0.19 (**b**) and for ESRD = 0.26 (**c**).

Nephrol Dial Transplant (2005) 20: 2139–2145
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Original Article

Nephrology Dialysis Transplantation

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Division of Clinical Nephrology, New York Presbyterian Hospital, Columbia University, New York, NY, USA

1 year regimen of MMF 2 gms/day vs Placebo (32 patients with initial GFR 40 mL/min/1.73 m2 and proteinuria 2.7 gms/day)

- **NO BENEFITS over 24 months** was seen in patients who received MMF in this **high-risk group** probably reflecting the advanced stage of disease in the population studied.
- **MMF IS PROBABLY NOT EFFECTIVE in patients with IgAN who already have moderate renal insufficiency.**

IMMUNOGLOBULIN A NEPHROPATHY
OTHER TREATMENTS

FISH OIL TREATMENT

10.5.1.1: We suggest using fish oil in the treatment of IgAN with **persistent proteinuria > 1 g/d**, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). **(2D)**

A CONTROLLED TRIAL OF FISH OIL IN IgA NEPHROPATHY

JAMES V. DONADIO, JR., M.D., ERIK J. BERGSTRALH, M.S., KENNETH P. OFFORD, M.S.,
DOROTHY C. SPENCER, AND KEITH E. HOLLEY, M.D., FOR THE MAYO NEPHROLOGY COLLABORATIVE GROUP*

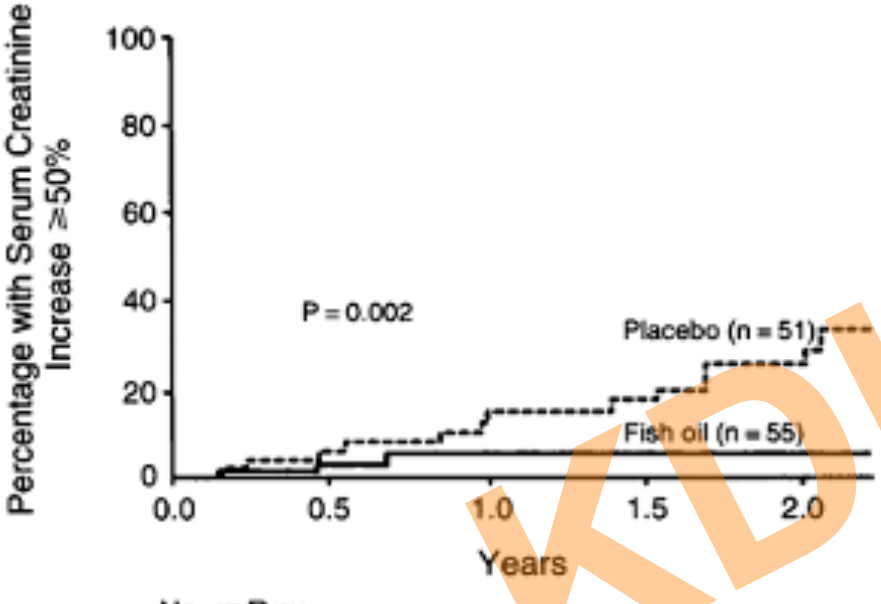


Figure 1. Cumulative Percentage of Patients with IgA Nephropathy Treated with Fish Oil or Placebo Whose Serum Creatinine Increased by 50 Percent or More during the Two-Year Treatment Period.

The figure stops at 2.2 years. Note that five patients (two in the fish-oil group and three in the placebo group) were treated for 2.3 years; one of them (in the placebo group) reached the serum creatinine end point at that time. Events are clustered near the times of follow-up visits. In the placebo group, 33 percent of the patients had an increase in serum creatinine of ≥50 percent by 2.2 years, as compared with 6 percent in the fish-oil group.

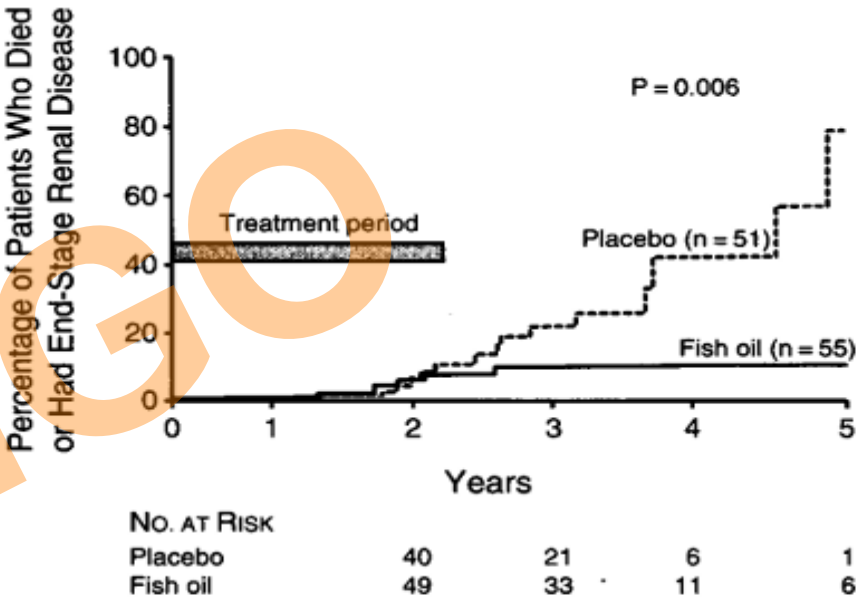


Figure 2. Cumulative Percentage of Patients with IgA Nephropathy Treated with Fish Oil or Placebo Who Had End-Stage Renal Disease or Died during or after the Two-Year Treatment Period.

All the patients in the fish-oil group and 10 patients in the placebo group received fish oil from year 2 onward.

In patients with IgAN, treatment with fish oil for 2 years **retards the rate at which renal function is lost.**

IMMUNOGLOBULIN A NEPHROPATHY
OTHER TREATMENTS

ANTIPLATELET AGENTS

10.5.2.1: We suggest **NOT** using antiplatelet agents to treat IgAN. **(2C)**

DIPYRIDAMOLE, Trimetazidine and Dilazep were the 3 moist commonly used antiplatelet agents in studies.

- ***SUBOPTIMAL QUALITY of individual controlled trials***
- ***Most studies DID NOT ASSESS the true outcome of renal death***
- ***Long-term follow up studies yielded DIFFERENT RESULTS***

The EFFECT OF ANTIPLATELET AGENTS ALONE could not be discerned because patient received other concomitant therapies.

- Walker RG, et al. The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole and warfarin: a two-year prospective trial. Clin Nephrol. 1990 Sep; 34(3):103-7.

  *This study supports the observation that treatment of IgA nephropathy with **cyclophosphamide, dipyridamole and warfarin is associated with a reduction of urinary protein excretion** but a significant effect on preservation of renal function, at least as determined by serum creatinine values, could not be confirmed over this two-year study.*

- Woo KT, et al. Dipyridamole and low-dose warfarin without cyclophosphamide in the management of IgA nephropathy. Kidney International (2000) 57, 348–349.

  *While we agree that cyclophosphamide cannot be recommended, we suggest that there is **available evidence to support the use of dipyridamole and low-dose warfarin**. This regimen has been shown to be safe and its use as long-term therapy in patients with IgA nephropathy with poor prognostic indices can slow the rate of decline in renal function and progression to ESRD.*

IMMUNOGLOBULIN A NEPHROPATHY
OTHER TREATMENTS

TONSILLECTOMY

10.5.3.1: We suggest that tonsillectomy **NOT BE PERFORMED** for IgAN. **(2C)**

TONSILLECTOMY FOR IgAN
WHY IT MAKES SENSE?

IgA1 Molecules Produced by Tonsillar Lymphocytes Are Under–*O*-Glycosylated in IgA Nephropathy

Akeyo Horie, MD, Yoshiyuki Hiki, MD, PhD, Hiroko Odani, PhD, Yoshinari Yasuda, MD, PhD, Mami Takahashi, Masashi Kato, MD, PhD, Hitoo Iwase, MD, PhD, Yutaka Kobayashi, MD, PhD, Izumi Nakashima, MD, PhD, and Kenji Maeda, MD, PhD

- Tonsillar lymphocytes from patients with IgAN synthesize excessive amounts of under-glycosylated IgA_1, some of which "spills" into the circulation
- IgA in glomerular deposits resemble IgA synthesized in the tonsils
- Tonsillar stimulation (ultra short wave) causes deterioration of urinary findings in IgAN
- Tonsillectomy possibly decreases hematuria and proteinuria

  ? effect on ESKD

TONSILLECTOMY FOR IgAN
WHAT DOES THE LITERATURE SAY?

Tonsillectomy and Steroid Pulse Therapy Significantly Impact on Clinical Remission in Patients With IgA Nephropathy

Osamu Hotta, MD, Mariko Miyazaki, MD, Takashi Furuta, MD, Sachiko Tomioka, MD, Shigemi Chiba, MD, Ikuo Horigome, MD, Keishi Abe, MD, and Yoshio Taguma, MD

• We conducted a retrospective investigation of renal outcome in 329 patients with immunoglobulin A (IgA) nephropathy with an observation period longer than 36 months (82.3 ± 38.2 months) in our renal unit between 1977 and 1995. Clinical remission, renal progression, and the impact of covariates were estimated by Kaplan-Meier analysis and a Cox regression model. In 157 of 329 patients (48%), disappearance of urinary abnormalities (clinical remission) was obtained. None of these 157 patients showed progressive deterioration, defined as a 50% increase in serum creatinine (Scr) level from baseline, during the observation period. Conversely, in patients without clinical remission, the Kaplan-Meier estimate of probability of progressive deterioration was 21% ± 5% at 10 years. In the multivariate Cox regression model with 13 independent covariates, initial Scr level, histological score, tonsillectomy, and high-dose methylprednisolone therapy had a significant impact on clinical remission, whereas proteinuria, age, sex, levels of hematuria, blood pressure, conventional steroid therapy, angiotensin-converting enzyme inhibitor therapy, and cyclophosphamide therapy had no significant effect. These findings indicate that interventions aimed at achieving clinical remission have provided encouraging results applicable to managing patients with IgA nephropathy.

- Improved urinary protein excretion and hematuria, **BUT NO EFFECT ON LONG-TERM SURVIVAL**

TONSILLECTOMY FOR IgAN
WWHAT DOES THE LITERATURE SAY?

Kidney International, Vol. 63 (2003), pp. 1861–1867

The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy

YUANSHENG XIE, SHINICHI NISHI, MITSUHIRO UENO, NAOFUMI IMAI, MINORU SAKATSUME, ICHIEI NARITA, YASUSHI SUZUKI, KOUHEI AKAZAWA, HISAKI SHIMADA, MASAAKI ARAKAWA, and FUMITAKE GEJYO

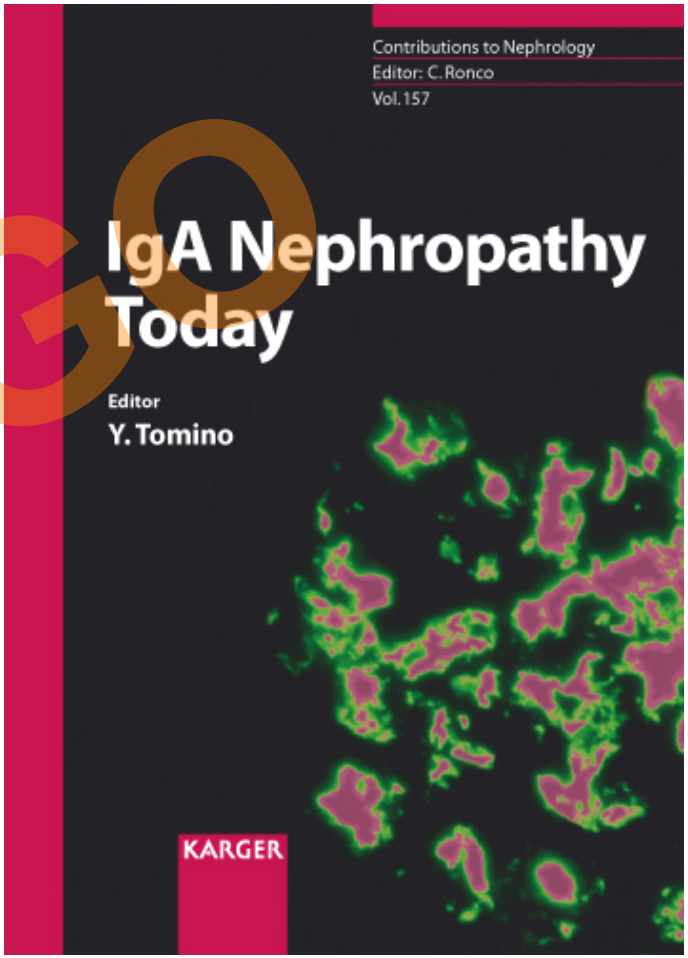
Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Saiseikai Niigata Daini Hospital, Niigata, Japan; Department of Medical Informatics, Niigata University Medical Hospital, Niigata, Japan; Internal Medicine, Niigata Prefectural Central Hospital, Jyoetsu, Japan; and Department of Health & Social Welfare and Bureau of Hospital Administration, Niigata Prefectural Government, Niigata, Japan

- **Improved 20-year outcome in treatment group (90%)** vs non-treatment group (64%)

TONSILLECTOMY FOR IgAN
WHAT DOES THE LITERATURE SAY?

Suwabe at al. Tonsillectomy and corticosteroid therapy with concomitant methylprednisolone pulse therapy for IgA nephropathy. Contrib Nephrol. 2007;157:99-103.

- **Improved (in 2 years) in all** but 5 patients: **hematuria improved; proteinuria decreased** (65% of pre-treatment values)
- **But IS THE EFFECT DUE TO CONCOMITANT GLUCOCORTICOIDS or is it a POPULATION-SPECIFIC ISSUE?**



IMMUNOGLOBULIN A NEPHROPATHY ATYPICAL FORMS

MCD with MESANGIAL IgA DEPOSITS

10.6.1.1: We recommend treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. **(2B)**

IMMUNOGLOBULIN A NEPHROPATHY ATYPICAL FORMS

AKI ASSOCIATED WITH MACROSCOPIC HEMATURIA

10.6.2.1: Perform a **REPEAT KIDNEY BIOPSY** in IgAN patients with AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. **(NOT GRADED)**

10.6.2.2: We suggest general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing **only ATN and intratubular erythrocyte casts.** **(2C)**

IMMUNOGLOBULIN A NEPHROPATHY ATYPICAL FORMS

CRESCENTIC IgAN

10.6.3.1: Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. **(NOT GRADED)**

10.6.3.2: We suggest the use of **STEROIDS** and **CYCLOPHOSPHAMIDE** in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis. **(2D)**

3 observational studies conclude that IMMUNOSUPPRESSION IS POTENTIALLY USEFUL.

Tang Z, et al. Idiopathic IgA nephropathy with diffuse crescent formation. Am J Nephrol. 2002 Sep-Dec;22(5-6):480-6.

- The patients with crescentic IgAN mostly show rapidly progressive nephritis associated with more severe pathological changes including glomerular, tubular interstitial and vascular lesions than in patients with general IgAN.
- The infiltrates in glomeruli may contribute to the crescentic formation, and the intensive immune suppressing treatment is useful to improve renal damage in patients with diffuse crescentic IgAN.

Nephrol Dial Transplant (2003) 18: 1321–1329
DOI: 10.1093/ndt/gfg081

Nephrology Dialysis Transplantation

Original Article

Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide

James A. Tumlin[1], Verachai Lohavichan[1] and Randy Hennigar[2]

[1]Division of Nephrology and [2]Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA

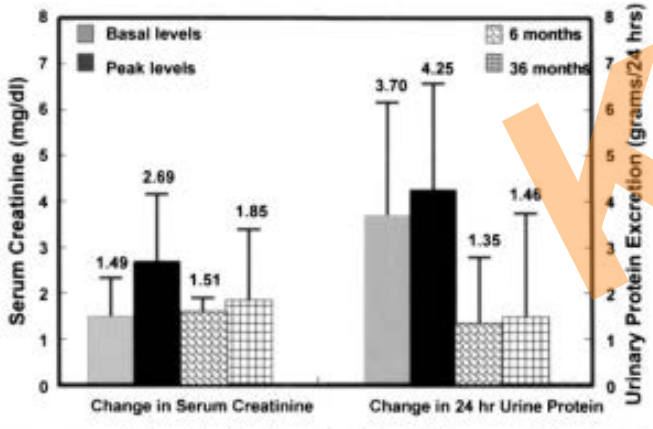


Fig. 1. Steroids and cyclophosphamide stabilizes renal function in patients with crescentic/proliferative IgA nephropathy. Serum creatinine and 24-h proteinuria levels were averaged for all patients at baseline and after 6 and 36 months of follow-up. Serum Cr increased significantly ($P < 0.03$) to a maximum of 2.65 mg/dl, falling to 1.51 mg/dl after 6 months of cyclophosphamide. After 36 months, serum creatinine was 1.72 mg/dl and significantly ($P < 0.04$) lower than peak levels. Proteinuria at baseline was 3.70 g/24 h, increasing to a peak of 4.25 g/24 h. After 6 and 36 months of follow-up, proteinuria was reduced to 1.35 and 1.46 g of protein per 24 h. Data are presented as means ± SD.

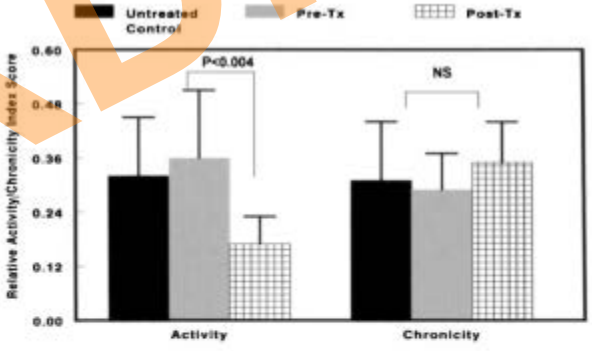


Fig. 4. Steroids and cyclophosphamide reduce glomerular activity and minimize cortical scarring. A modified NIH SLE histological activity/chronicity index was applied to baseline renal biopsies in the treatment group and historical controls. There were no significant differences in the average activity and chronicity scores between the two groups. After 6 months of cyclophosphamide, the mean activity score in the treatment group was significantly lower than pre-treatment levels ($P < 0.004$). Mean chronicity scores were not significantly different between baseline levels in the treatment group or baseline levels among the historical controls. Data are presented as means ± SD.

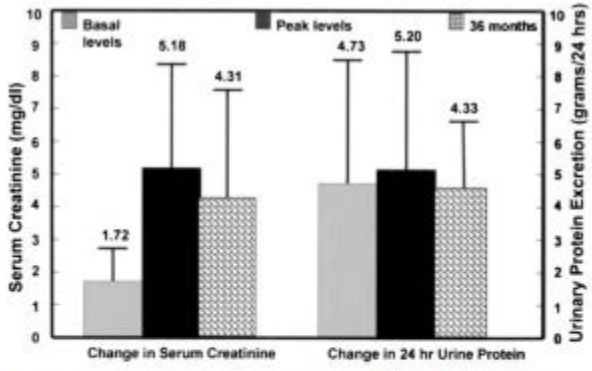


Fig. 5. Progressive renal insufficiency and nephrotic-range proteinuria in untreated crescentic/proliferative IgA nephropathy. Serum creatinine and 24-h proteinuria levels were averaged for 12 patients with crescentic proliferative IgA nephropathy who did not receive immunosuppressive therapy at baseline and after 6 and 36 months of follow-up. Serum Cr increased significantly ($P < 0.03$) from 1.72 to a maximum of 5.18 mg/dl, falling to 4.31 mg/dl after 36 months of follow-up. Proteinuria was 4.73 g/24 h at baseline, remaining in the nephrotic range (4.33 g/24 h) after 36 months of follow-up. Data are presented as means ± SD.

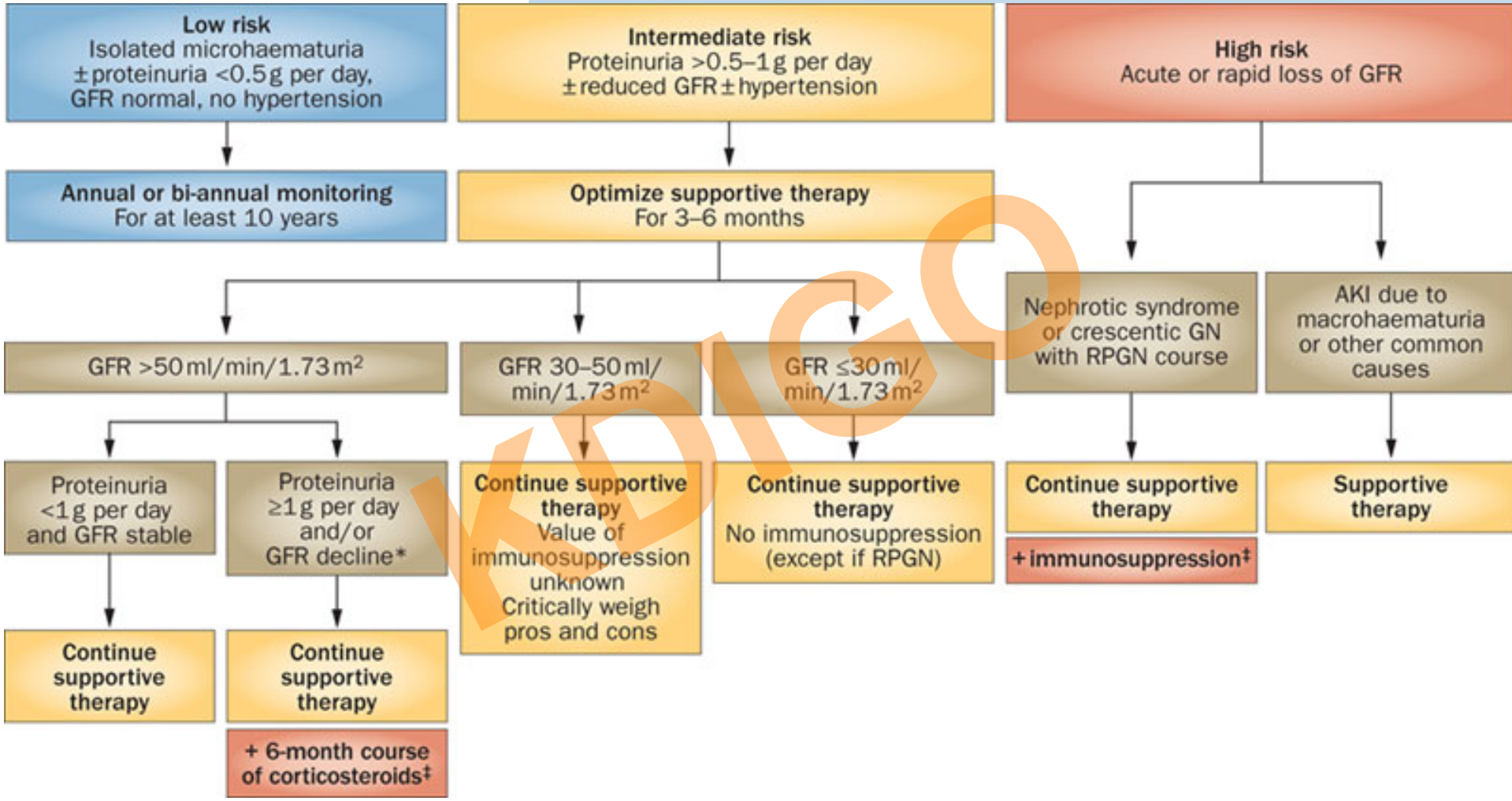
CRESCENTIC IgAN

- N = 12 with **CRESCENTIC, PROLIFERATIVE IgA**
- Pulse Methylprednisolone x 3 days, then monthly IV Cylophosphamide x 6 months
- **REPEAT KIDNEY BIOPSY:** Elimination of endocapillary proliferation, cellular crescents and karyorrhexis in all patients after 6 months

Pankhurst T, et al. Vasculitic IgA nephropathy: prognosis and outcome. Nephron Clin Pract. 2009;112(1):c16-24.

- **Presenting renal function, blood pressure** and **chronic damage in the biopsy** are important prognostic factors in vasculitic IgA nephropathy.
- **Immunosuppression is advocated** in some patients.

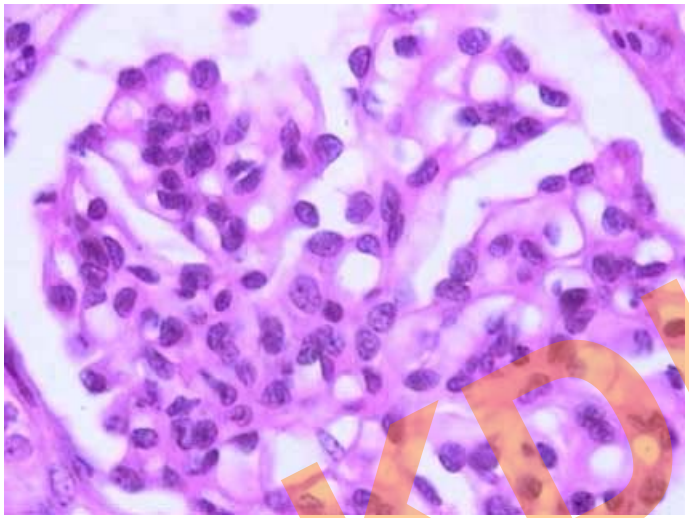
IMMUNOGLOBULIN A NEPHROPATHY

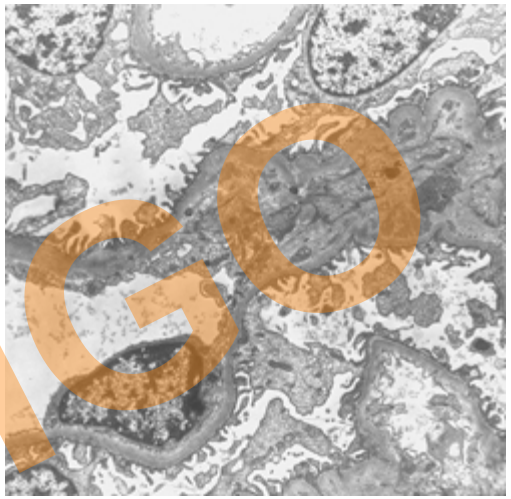


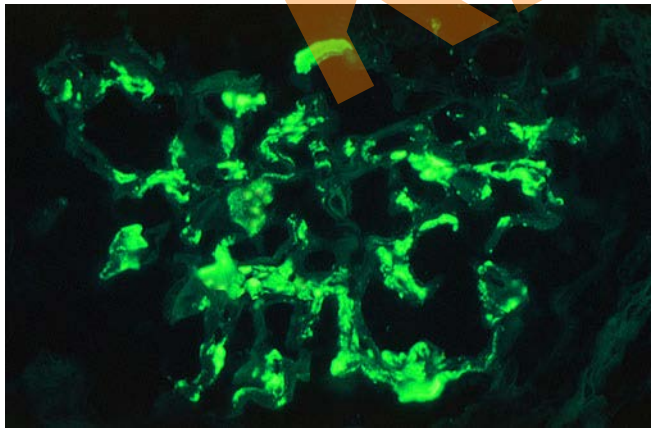
Kidney Disease: Improving Global Outcomes

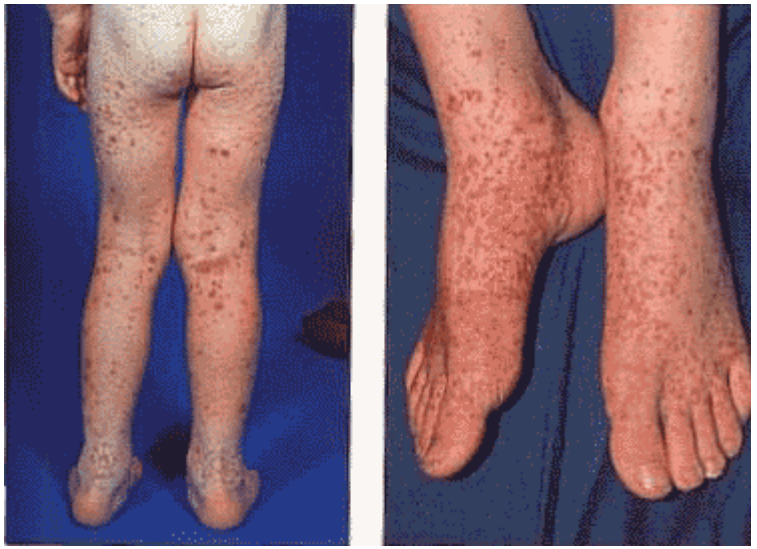
HENOCH-SCHŐNLEIN PURPURA NEPHRITIS

HENOCH-SCHŐNLEIN PURPURA NEPHRITIS









HENOCH-SCHŐNLEIN PURPURA NEPHRITIS TREATMENT

11.4.1: We suggest that HSP nephritis in adults be treated the same as in children. **(2D)**

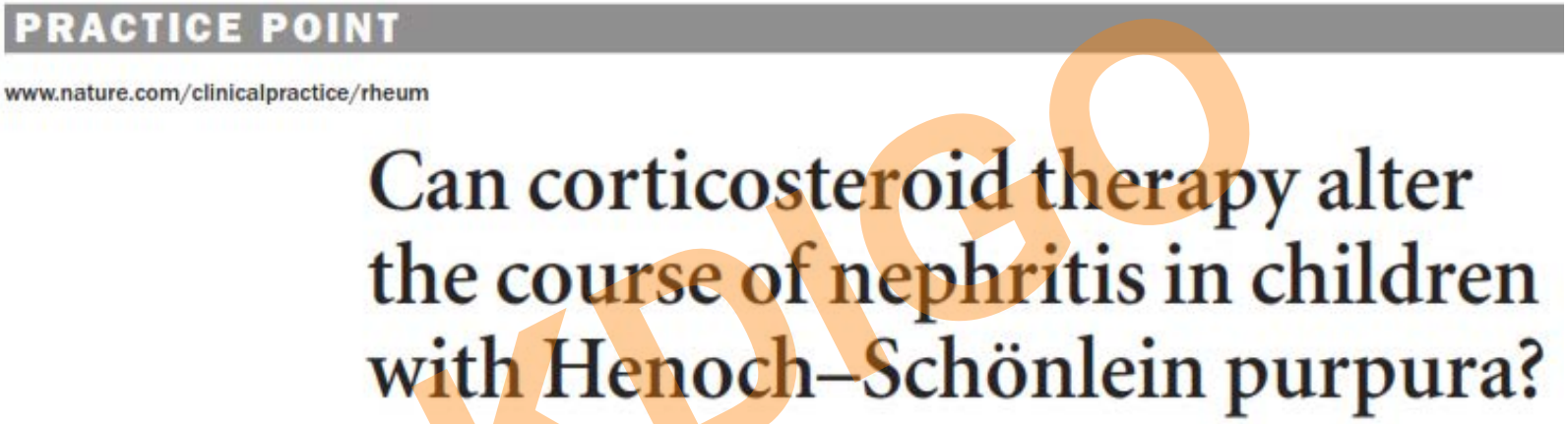
11.1.1: We suggest that children with HSP nephritis and **persistent proteinuria > 0.5–1 g/d per 1.73 m2**, are treated with **ACE-I or ARBs**. **(2D)**

11.1.2: We suggest that children with **persistent proteinuria > 1 g/d per 1.73 m2**, after a trial of ACE-I or ARBs, and **GFR > 50 ml/min per 1.73 m2**, be treated the same as for IgAN with a 6-month course of **CORTICOSTEROID therapy**. **(2D)**

11.2.1: We suggest that children with **crescentic HSP** with nephrotic syndrome and/or deteriorating kidney function are **treated the same as for crescentic IgAN. (2D)**

11.3.1: We recommend **NOT USING CORTICOSTEROIDS** to prevent HSP nephritis. **(1B)**

Ronkainen et al. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2006 Aug;149(2): 241-7.


PRACTICE POINT

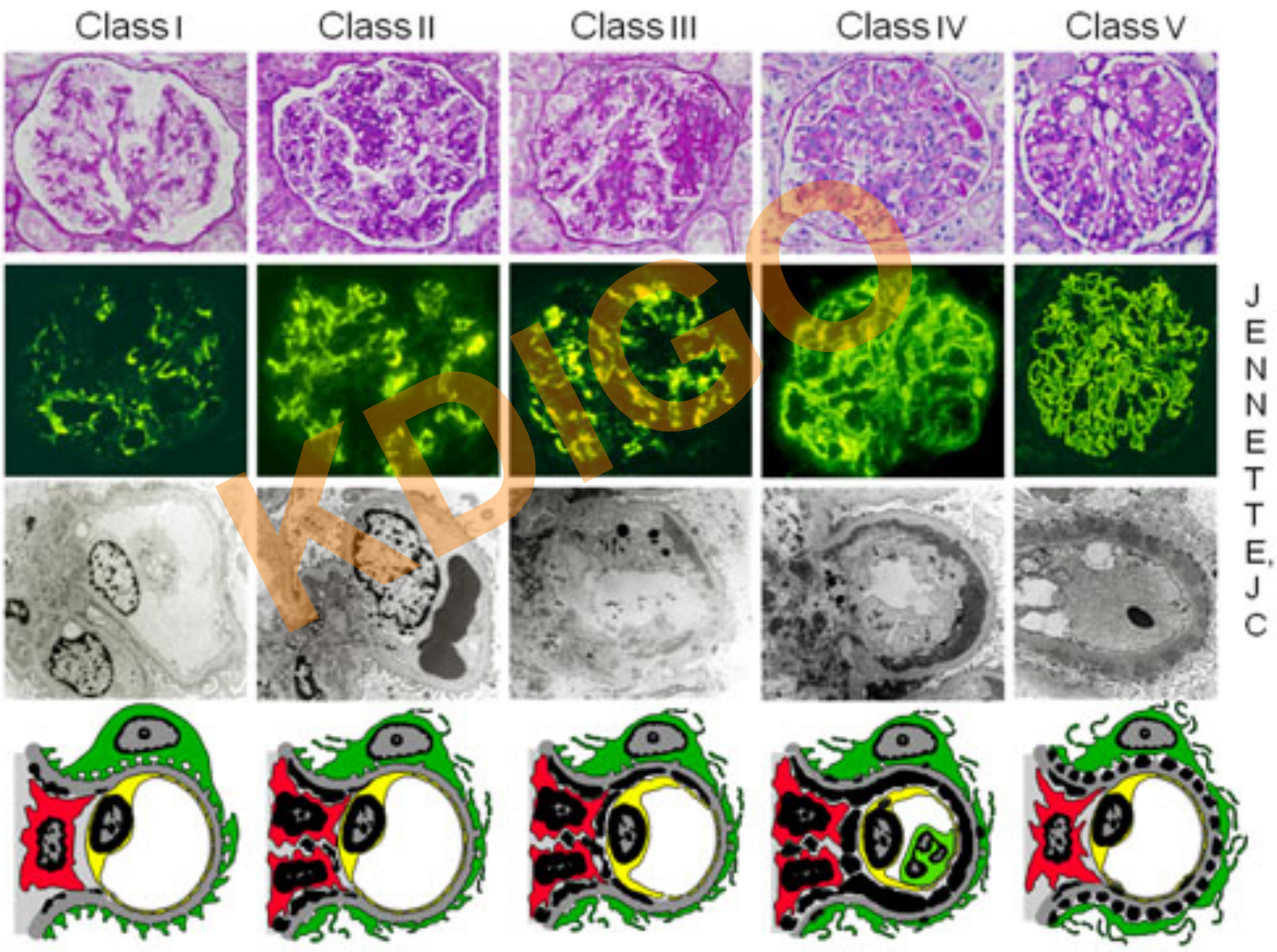
www.nature.com/clinicalpractice/rheum

Can corticosteroid therapy alter the course of nephritis in children with Henoch–Schönlein purpura?

Compared with placebo, **EARLY PREDNISONE THERAPY** controlled extra-renal symptoms more effectively and reduced the severity of nephritis, although **IT DID NOT PREVENT THE DEVELOPMENT OF RENAL INVOLVEMENT**

LUPUS NEPHRITIS

LUPUS NEPHRITIS



ISN/ RPS 2002 CONSENSUS CONFERENCE ON THE CLASSIFICATION OF LUPUS GLOMERULONEPHRITIS

Class I: Minimal mesangial lupus nephritis
Class II: Mesangial proliferative lupus nephritis
Class III: Focal lupus nephritis[a]
Class IV: Diffuse segmental (IV-S) or global (IV-G) lupus nephritis[b]
Class V: Membranous lupus nephritis[c]
Class VI: Advanced sclerosing lupus nephritis
Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis and other vascular lesions
[a]Indicate the proportion of glomeruli with active and with sclerotic lesions
[b]Indicate the proportion of glomerli with fibrinoid necrosis and cellular crescents
[c]Class V may occur in combination with class III or IV, in which case both will be diagnosed

LUPUS NEPHRITIS
CLASS I LN (MINIMAL-MESANGIAL LN)

12.1.1: We suggest that patients with class I LN be **treated as dictated by the extra-renal clinical manifestations** of lupus. **(2D)**

LUPUS NEPHRITIS
CLASS I LN (MINIMAL-MESANGIAL LN)

Table 2

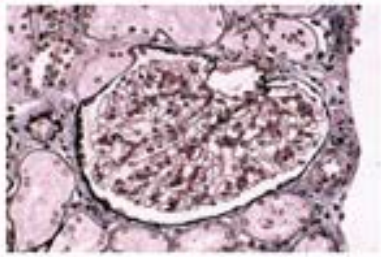
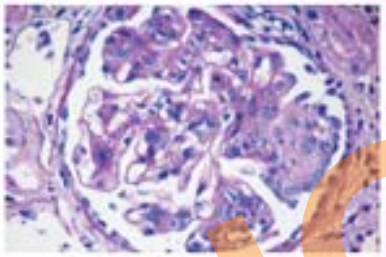
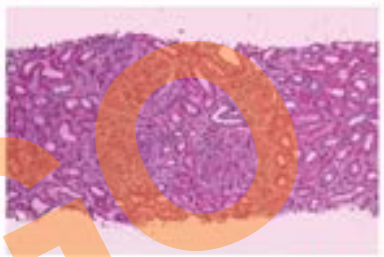
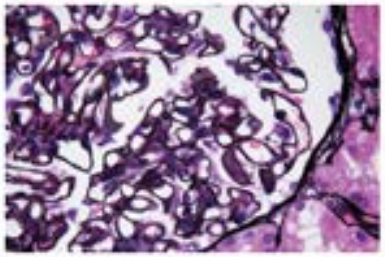
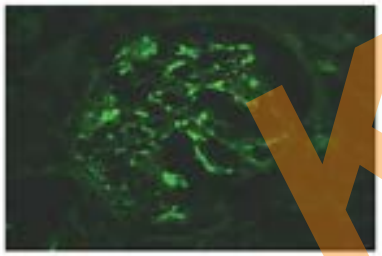
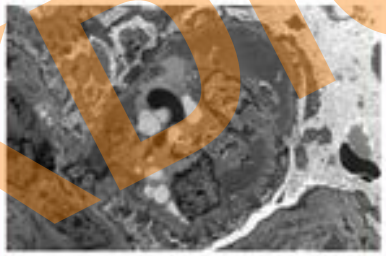
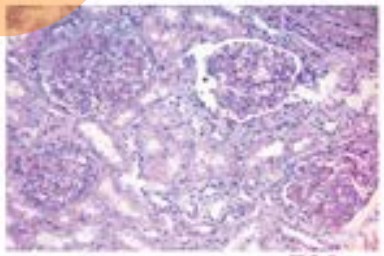
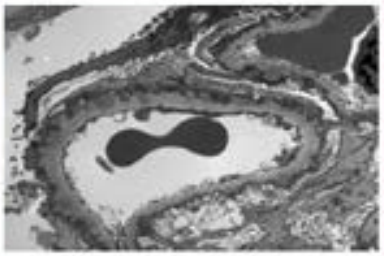
ACR CRITERIA FOR DIAGNOSIS OF SLE

Condition	Description
Malar rash	A "butterfly rash" of flat or raised fixed erythema tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging associated with scarring
Photosensitivity	A reaction to sunlight causing rash that may last for several weeks after brief sun exposure
Oral ulcers	Often painless oral or nasopharyngeal ulceration
Arthritis	Nonerosive arthritis tenderness, swelling, or effusion involving 2 or more peripheral joints
Serositis	Pleuritis (chest pain on inspiration) or pericarditis; note that premature coronary artery disease is associated with inflammatory conditions like SLE
Renal disorder	Persistent proteinuria
Neurologic disorder	Seizures or psychosis in the absence of offending drugs or known metabolic derangements
Hematologic disorder	Leucopenia (often an early sign), hemolytic anemia, lymphopenia, thrombocytopenia in the absence of offending drugs
Immunologic disorder	Positive LE cell preparation, anti-DNA, anti-Sm, or false positive serologic test for syphilis
Antinuclear antibody	An abnormal titer of antinuclear antibody at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

ACR= American College of Rheumatology; LE = lupus erythematosus; SLE = systemic lupus erythematosus.
Adapted from references 3, 4, and 7.

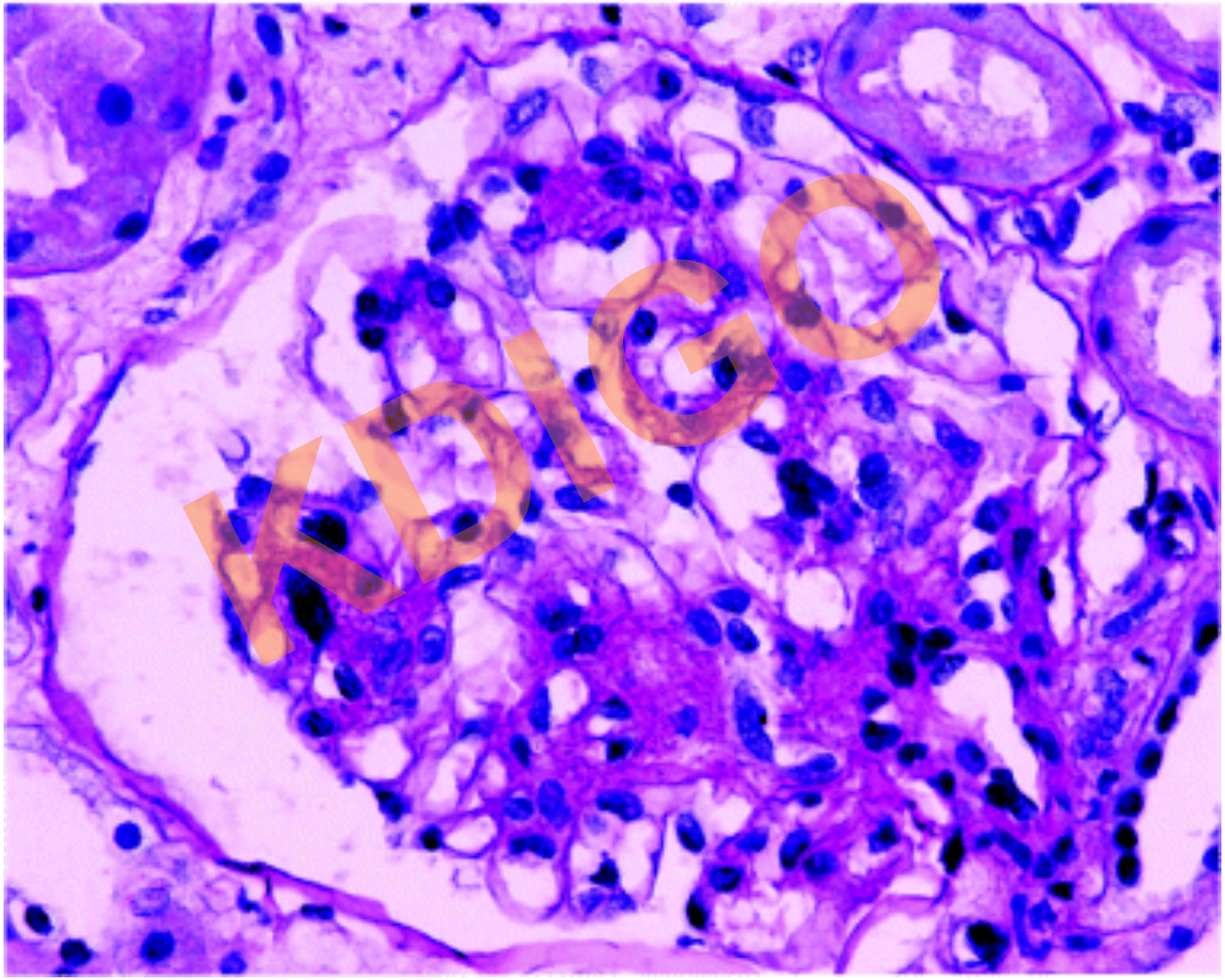
LUPUS NEPHRITIS
CLASS II LN (MESANGIAL-PROLIFERATIVE LN)

TABLE: INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY (ISN/RPS) 2003 CLASSIFICATION OF LUPUS NEPHRITIS (CLASSES II-V)

Class II	Class III	Class IV	Class V
Mesangial proliferative LN	Focal LN	Diffuse LN	Membranous LN
		 IV-G	
		 IV-S	
The glomeruli show mesangial proliferation with mesangial immune deposits by IF (lower panel) and EM. Isolated subepithelial or subendothelial deposits may be present by IF or EM.	Active or inactive segmental or global endocapillary or crescentic GN involving less than 50% of all glomeruli. Segmental is defined as a lesion that involves less than half of the glomerular tuft.	Active or inactive segmental or global lesions in > 50% of all glomeruli. The glomerular lesions are classified as global (G) when > 50% of the involved glomeruli have global lesions (upper panel), and as segmental (S) when > 50% of the involved glomeruli have segmental lesions (lower panel).	Global or segmental subepithelial immune deposits, usually with mesangial alterations. Class V LN may occur in combination with Class III or IV LN.

LN = Lupus Nephritis; IF = Immunofluorescence; EM = Electron Microscopy

LUPUS NEPHRITIS
CLASS II LN (MESANGIAL-PROLIFERATIVE LN)

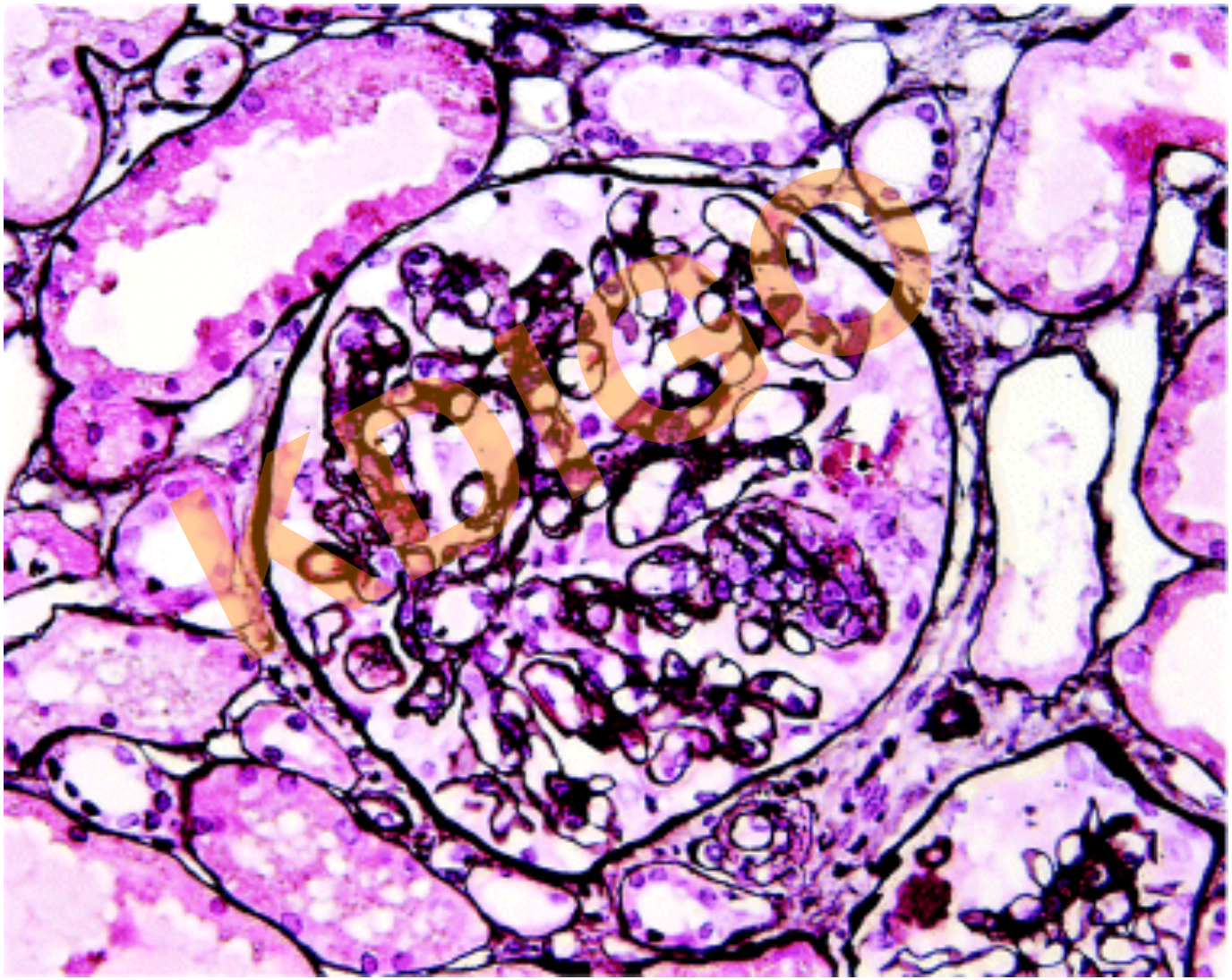


LUPUS NEPHRITIS
CLASS II LN (MESANGIAL-PROLIFERATIVE LN)

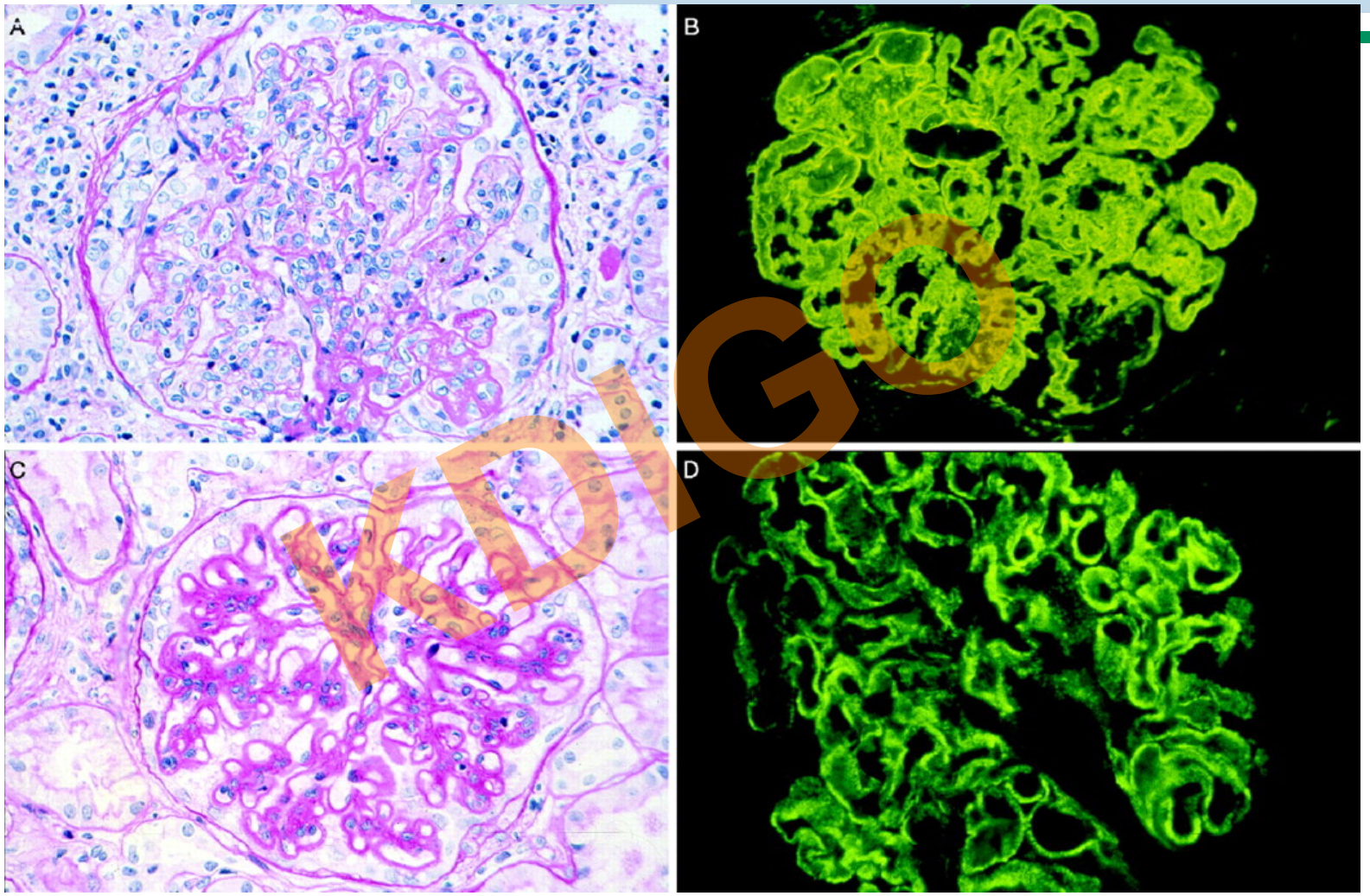
12.2.1: Treat patients with class II LN and **proteinuria < 1 g/d** as dictated by the extra-renal clinical manifestations of lupus. **(2D)**

12.2.2: We suggest that class II LN with **proteinuria > 3 g/d** be treated with **CORTICOSTEROIDS** or **CNIs** as described for MCD. **(2D)**

LUPUS NEPHRITIS
CLASS III LN (FOCAL LN)

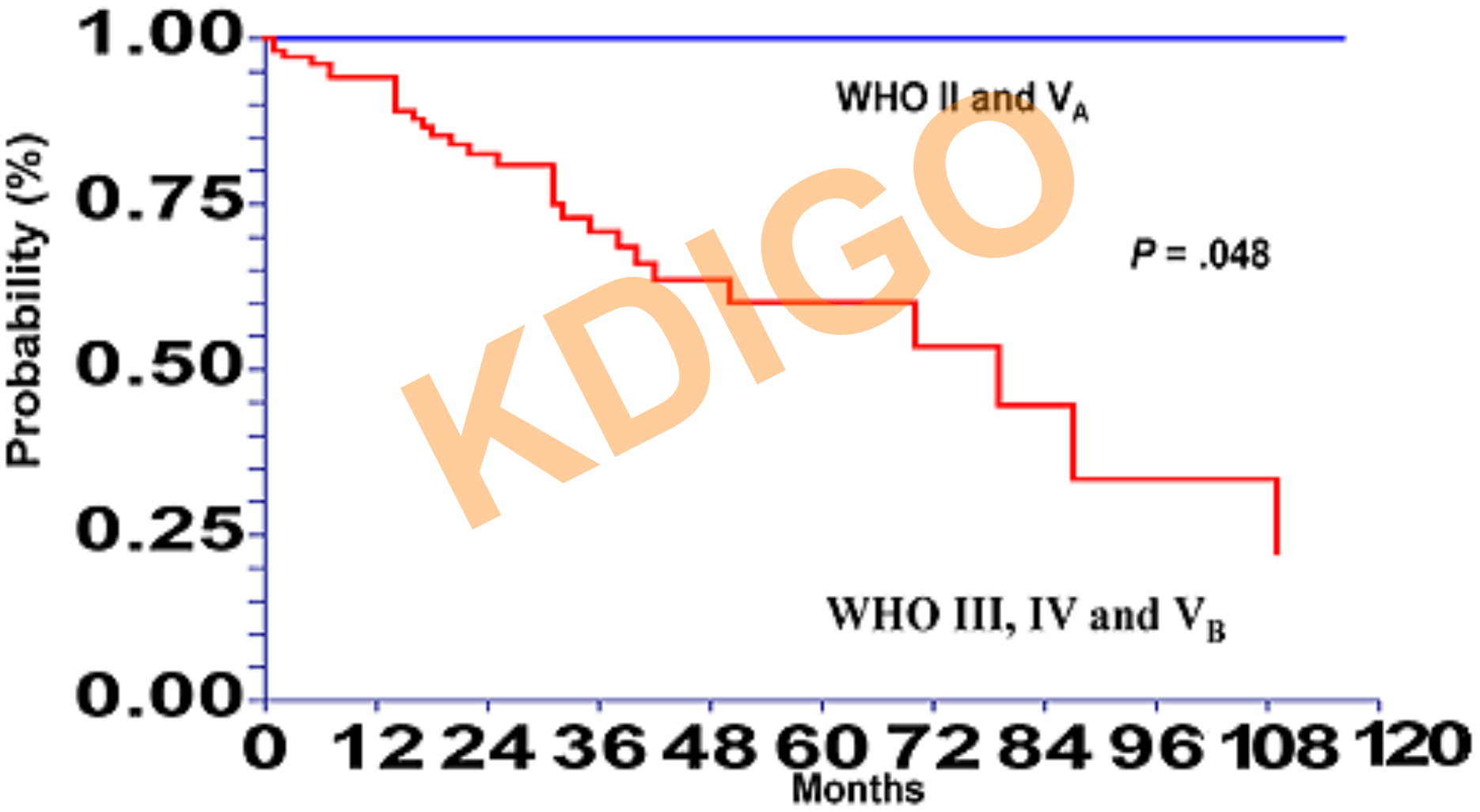


LUPUS NEPHRITIS
CLASS IV LN (DIFFUSE LN)



CAMERON J S JASN 1999;10:413-424

Survival (not doubling serum creatinine, ESRD or death) of 122 Lupus Nephritis Patients as a Function of the WHO Classification



Lupus Nephritis: Indices of Activity and Chronicity

Activity *
Glomeruli
- Hypercellularity
- Karyorrhesis or fibrinoid necrosis
- Cellular crescents **
- Wire loops **
- Leukocyte infiltration

Tubule/Interstitium
- Mononuclear cell infiltration

Chronicity *
Glomerulosclerosis
- Segmental
- Mesangial
- Global

Fibrous crescent
Interstitial fibrosis
Tubule atrophy

* Score 0-3 for each item, ** Multiply by 2 Activity Index

Pollak et al. J Lab Clin Med. 1964;63:537.

Multivariate Analyses: Factors Associated with Increased Risk of Chronic Renal Failure

Not Amenable to Change

- Male gender
- Black race
- Age < 24 years
- Crescents >/= 50 %
- Chronicity index >/= 1

Amenable to change

- Rx with prednisone only
- Initial high SCr (> 1.2 - 2.0 mg/dL
- Nephrotic syndrome
- Hypertension
- Noncompliant patient
- Hematocrit </= 26%

Berden. Kidney International. 1997;52:538.

Treatment options for Lupus Nephritis

Controlled Studies

- Plasmapheresis
- Steroids
- Cyclophosphamide
- Azathioprine
- Mycophenolate mofetil

Uncontrolled Studies

- Chlorambucil
- Nitrogen mustard
- Methotrexate
- Adenosine analogues
- Total lymphoid irradiation
- Monoclonal antibodies
- Cyclosporine A
- Thromboxane inhibitors
- Ancrod venom
- IV gamma globulin
- Marrow ablation/reconstitution

LUPUS NEPHRITIS

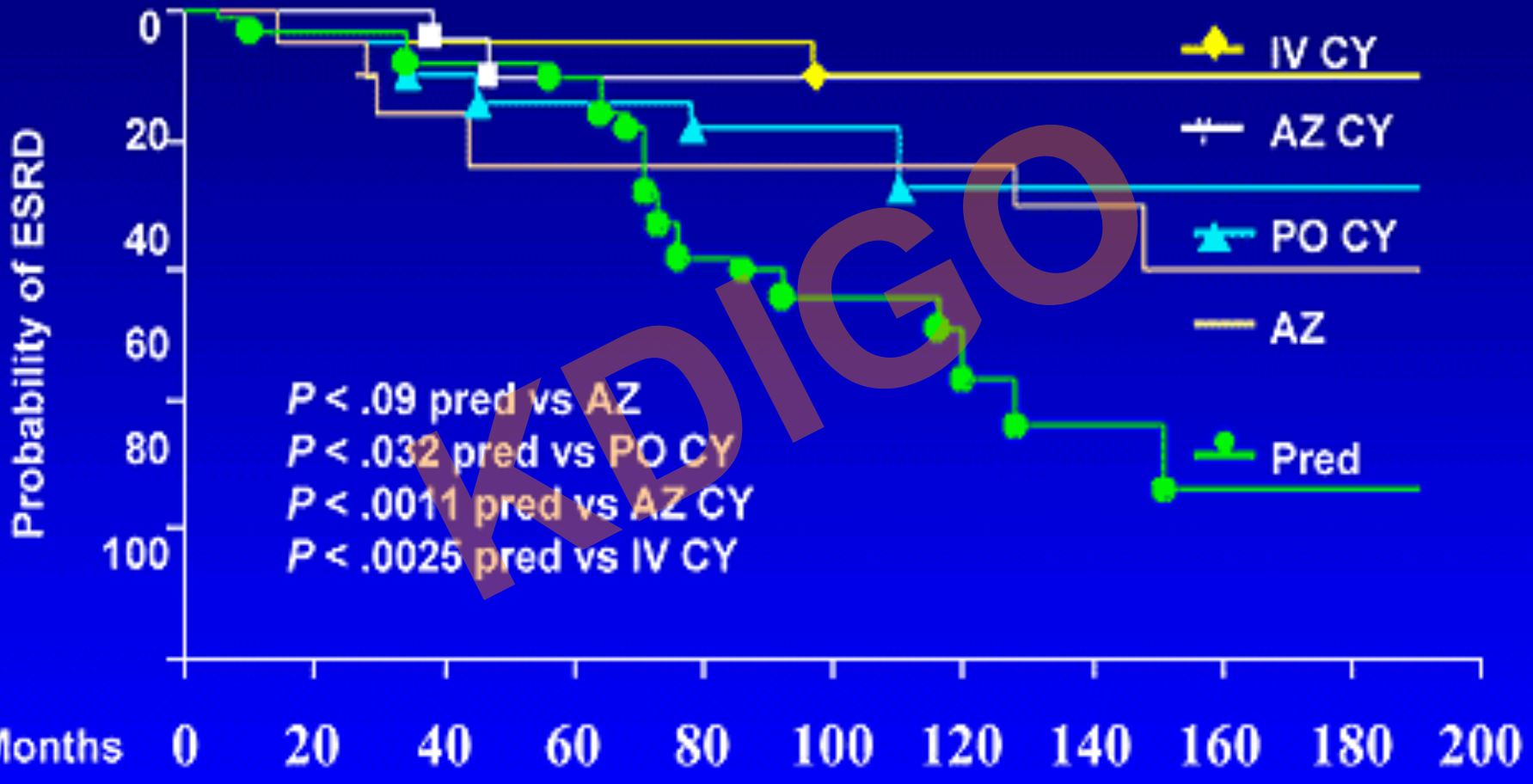
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)

INITIAL THERAPY

12.3.1: We recommend initial therapy with **CORTICOSTEROIDS (1A),** combined with either **CYCLOPHOSPHAMIDE (1B)** or **MMF (1B).**

12.3.2: We suggest that, if patients have **WORSENING LN** (rising SCr, worsening proteinuria) **during the first 3 months of treatment,** a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. **(2D)**

Long term preservation of renal function in 111 patients with Lupus Nephritis



Steinberg and Steinberg. Arthritis Rheum. 1991;34:945.

LUPUS NEPHRITIS
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)
INITIAL THERAPY

Table 28 | Regimens for initial therapy in class III/class IV LN

Regimen	A. NIH	B. Euro-Lupus	C. Oral cyclophosphamide	D. MMF
Cyclophosphamide	i.v. cyclophosphamide 0.5–1 g/m^2; monthly for 6 months	i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months	Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months	—
MMF	—	—	—	MMF up to 3 g/d for 6 months
Benefit shown by RCT in proliferative LN	Yes	Yes	Yes	Yes
Benefit shown by RCT in severe proliferative LN	Yes	Untested	Untested	Untested
Comments	Effective in whites, blacks, Hispanics, Chinese	Effective in whites. Untested in blacks, Hispanics, Chinese	Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide	Effective in whites, blacks, Hispanics, Chinese; high cost

LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomized controlled trial.
All regimens include corticosteroids:

- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to clinical response.
- i.v. methylprednisolone is sometimes added initially for severe disease.

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

Gerald B. Appel,* Gabriel Contreras,† Mary Anne Dooley,‡ Ellen M. Ginzler,§ David Isenberg,‖ David Jayne,¶ Lei-Shi Li,** Eduardo Mysler,†† Jorge Sánchez-Guerrero,‡‡ Neil Solomons,§§ David Wofsy,‖‖ and the Aspreva Lupus Management Study Group

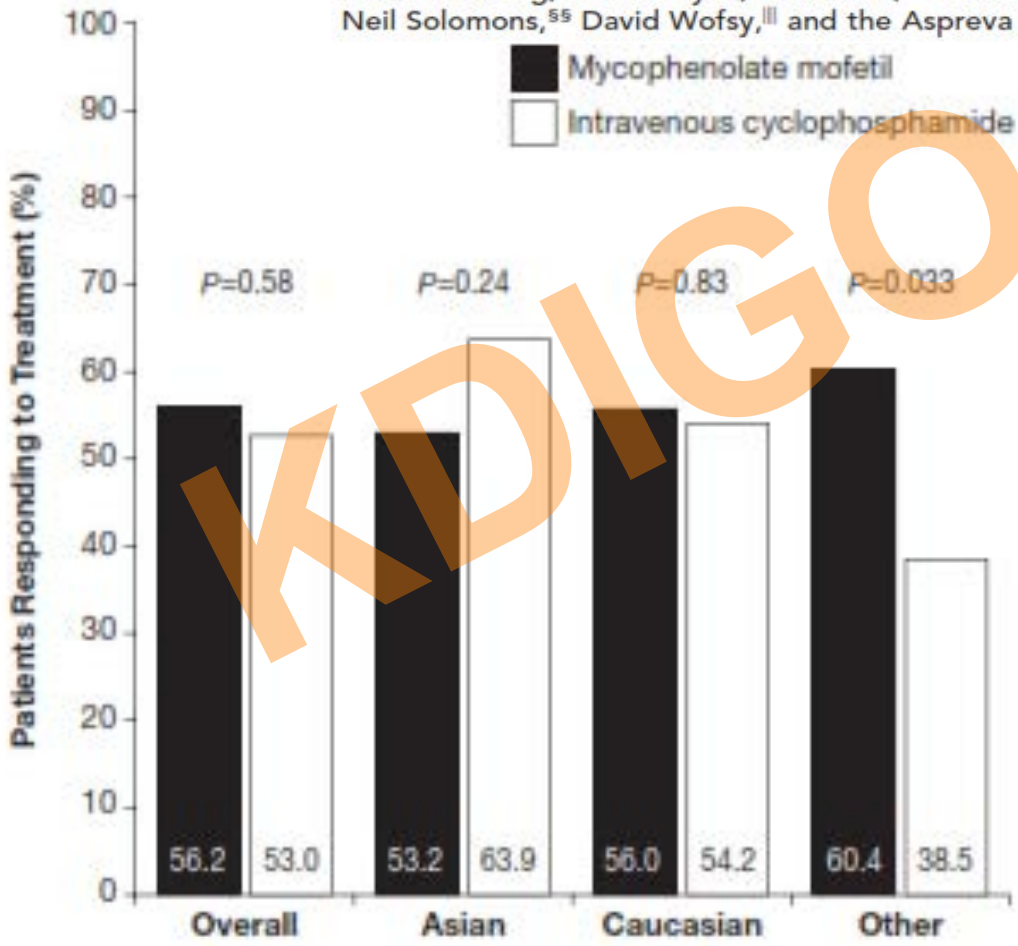


Figure 2. Response rates of study population and by racial group.

LUPUS NEPHRITIS

CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN) MAINTENANCE THERAPY

12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with **AZATHIOPRINE** (1.5–2.5 mg/kg/d) or **MMF** (1–2 g/d in divided doses), and low-dose ORAL **CORTICOSTEROIDS** (≤ 10 mg/d prednisone equivalent). **(1B)**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2004 VOL. 350 NO. 10

Sequential Therapies for Proliferative Lupus Nephritis

Gabriel Contreras, M.D., M.P.H., Victoriano Pardo, M.D., Baudouin Leclercq, M.D., Oliver Lenz, M.D., Elaine Tozman. M.D.. Patricia O'Nan. R.N.. and David Roth. M.D.

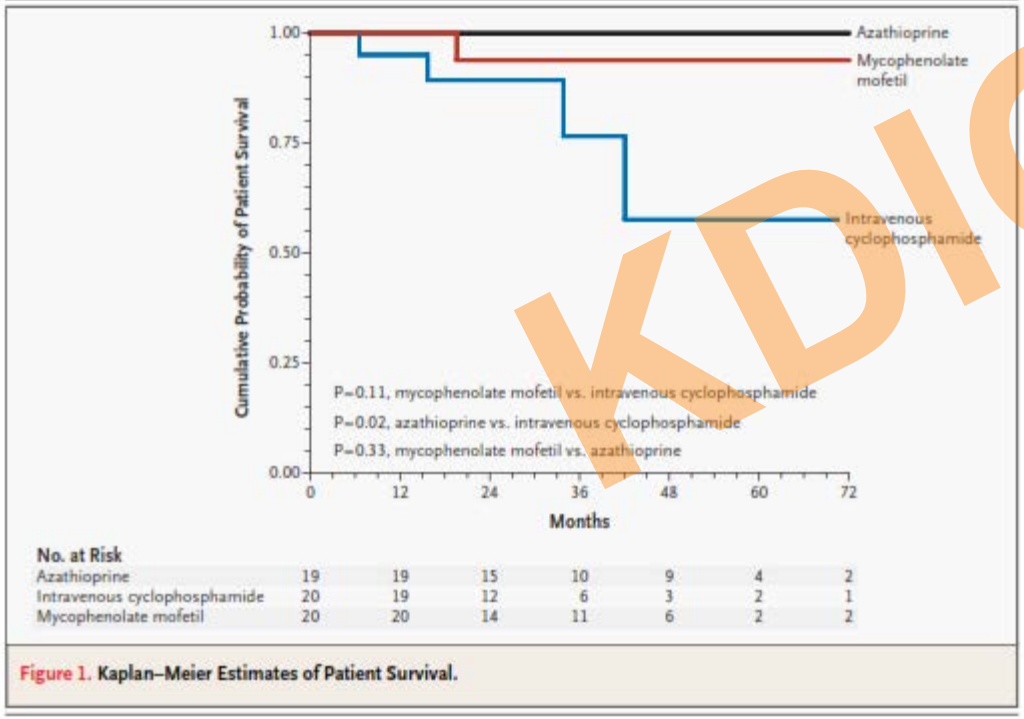


Figure 1. Kaplan–Meier Estimates of Patient Survival.

CONCLUSIONS

For patients with proliferative lupus nephritis, short-term therapy with intravenous cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine appears to be more efficacious and safer than long-term therapy with intravenous cyclophosphamide.

The NEW ENGLAND JOURNAL of MEDICINE

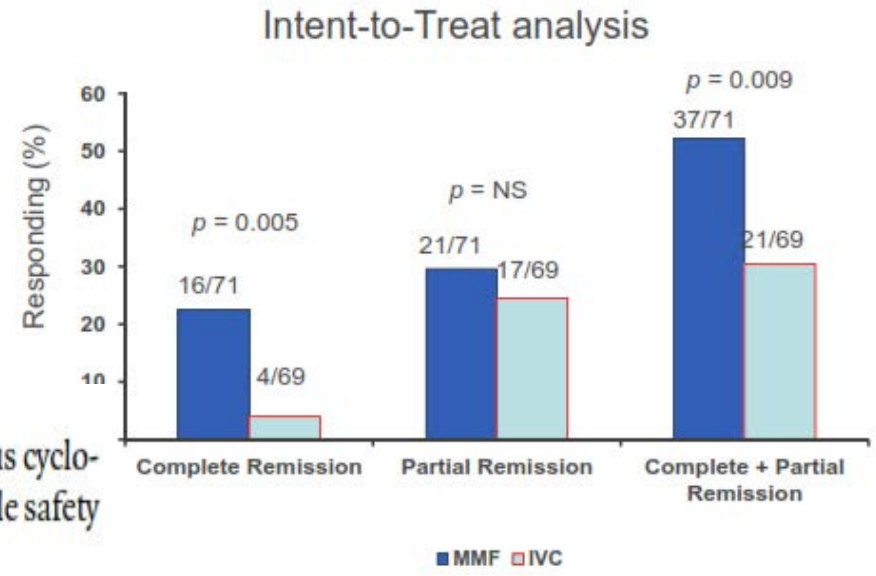
ESTABLISHED IN 1812 NOVEMBER 24, 2005 VOL. 353 NO. 21

Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzler, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

Remission rates: MMF vs IVC

- Open label RCT between IV Cyclophosphamide vs MMF
- Adults and children from age 13
- 140 patients entered



CONCLUSIONS

In this 24-week trial, mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.

Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial

Frédéric A Houssiau,[1] David D' Cruz,[2] Shirish Sangle,[2] Philippe Remy,[3] Carlos Vasconcelos,[4] Radmila Petrovic,[5] Christoph Fiehn,[6] Enrique de Ramon Garrido,[7] Inge-Magrethe Gilboe,[8] Maria Tektonidou,[9] Daniel Blockmans,[10] Isabelle Ravelingien,[11] Véronique le Guern,[12] Geneviève Depresseux,[1] Loïc Guillevin,[12] Ricard Cervera,[13] the MAINTAIN Nephritis Trial Group

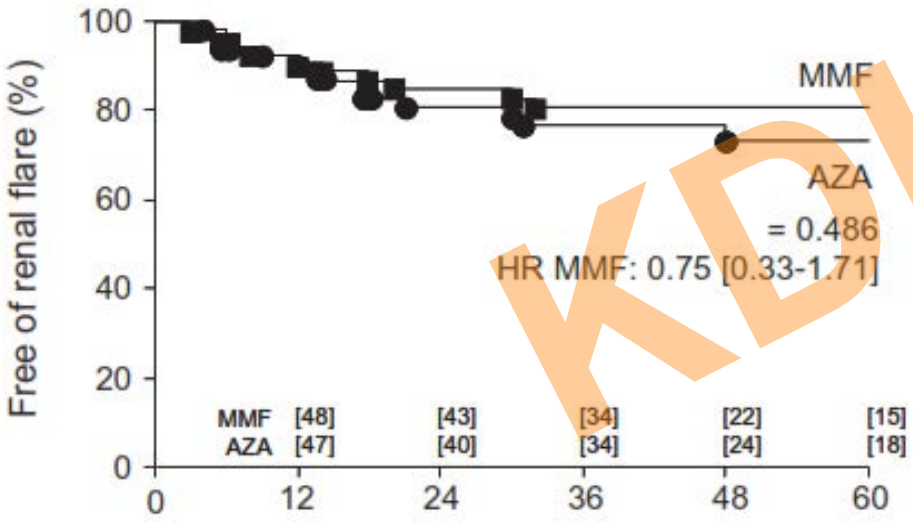


Figure 2 Kaplan–Meier probability analysis of renal flare. Patients were allocated to the 'GC/intravenous CY/AZA' group (circles) or the 'GC/intravenous CY/MMF' group (squares) by randomisation. Survival curves were statistically tested with the log rank test. Data are HR (95% CI). Numbers shown along the abscissa are the number of patients at risk in each group. Analyses were by intent to treat. Time point of reference for follow-up is from baseline. AZA, azathioprine; CY, cyclophosphamide; GCs, glucocorticoids; MMF, mycophenolate mofetil.

- Evidence **supporting the use of AZA as maintenance therapy** is from this trial, in which AZA was comparable to MMF after induction therapy with Euro-Lupus dosing of IV cyclophosphamide.
- **Preferential use of AZA** over MMF as maintenance therapy **should be limited to whites with less severe renal disease** at presentation who have been continued on prednisone, akin to the patients treated in the Euro-Lupus trials.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

Subgroup	MMF	Azathioprine
	no. of events/total no. of patients (incidence rate)	
All patients	19/116 (7.4)	36/111 (17.3)
Induction treatment		
IV cyclophosphamide	6/54 (4.7)	15/53 (14.5)
MMF	13/62 (10.1)	21/58 (20.1)
Region		
Asia	5/37 (5.5)	8/35 (12.1)
Latin America	5/25 (10.2)	16/35 (23.2)
USA and Canada	3/22 (6.4)	8/25 (18.4)
Rest of world	6/32 (8.7)	4/16 (13.6)
Race		
White	9/48 (9.4)	18/51 (18.7)
Black	2/12 (7.0)	6/11 (34.3)
Asian	6/39 (6.5)	9/37 (12.8)
Other	2/17 (5.3)	3/12 (12.6)

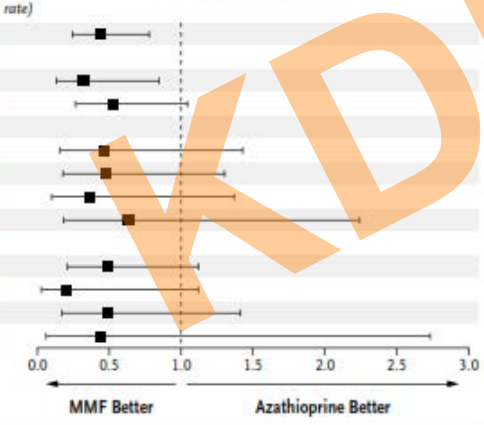
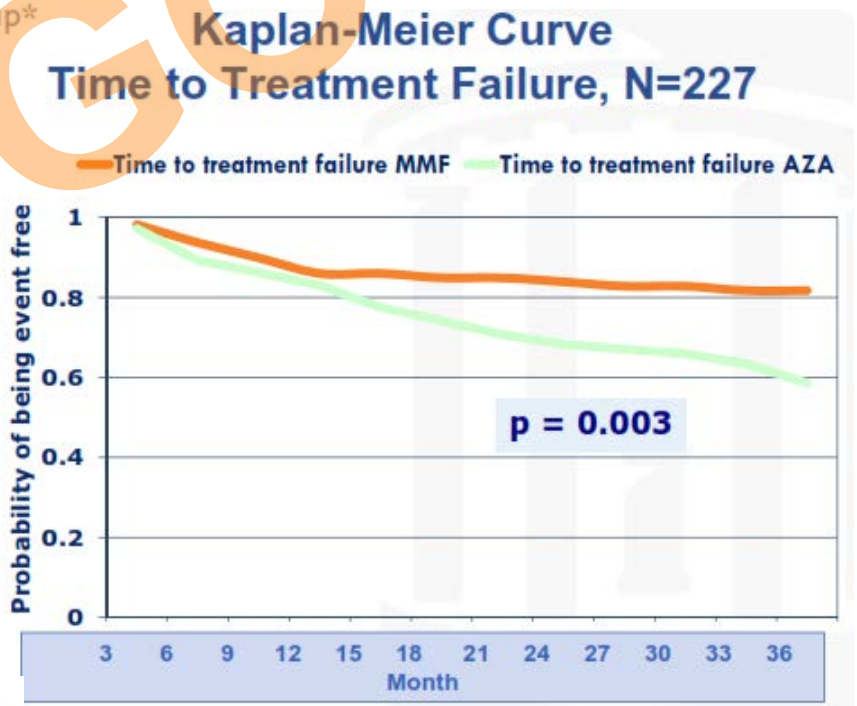


Figure 3. Risk of Treatment Failure in Subgroups of Patients.
The incidence rate is the number of events per 100 person-years. The hazard ratio was derived from a Cox model, with treatment as the only factor, according to subgroup. "Rest of world" includes Europe (40 patients), South Africa (5 patients), and Australia (3 patients). IV denotes intravenous, and MMF mycophenolate mofetil.



CONCLUSIONS

Mycophenolate mofetil was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who had a response to induction therapy. (Funded by Vifor Pharma [formerly Aspreva]; ALMS ClinicalTrials.gov number, NCT00377637.)

- The **ALMS (Aspreva Lupus Management Study) extension phase** results lend **strong support to using MMF** rather than azathioprine **for maintenance therapy,** particularly if steroids are to be tapered and stopped during the maintenance phase.

Indeed, the ACR guideline explicitly spells out this difference by recommending as maintenance options ***MMF alone*** *or* ***azathioprine with steroids.***

- **MMF is SUPERIOR to AZA in MAINTAINING RENAL RESPONSE and PREVENTING RELAPSE** in subjects with active LN who respondedto induction therapy with either MMF or IV Cyclophosphamide
- **FAILURE RATE** was 32% in the AZA Group vs 16% in the MMF Group (p = 0.005)
- **COMPLETION RATE at 3 years** was 49% for AZA and 63% for MMF
- SUPERIORITY OF MMF WAS CONSISTENT <u>regardless of induction treatment, race or region</u>
- SUPERIORITY OF MMF WAS CONFIRMED by <u>consistent results in secondary endpoints</u>

LUPUS NEPHRITIS
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)
MAINTENANCE THERAPY

12.4.2: We suggest that **CNIs** with low-dose **CORTICOSTEROIDS** be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. **(2C)**

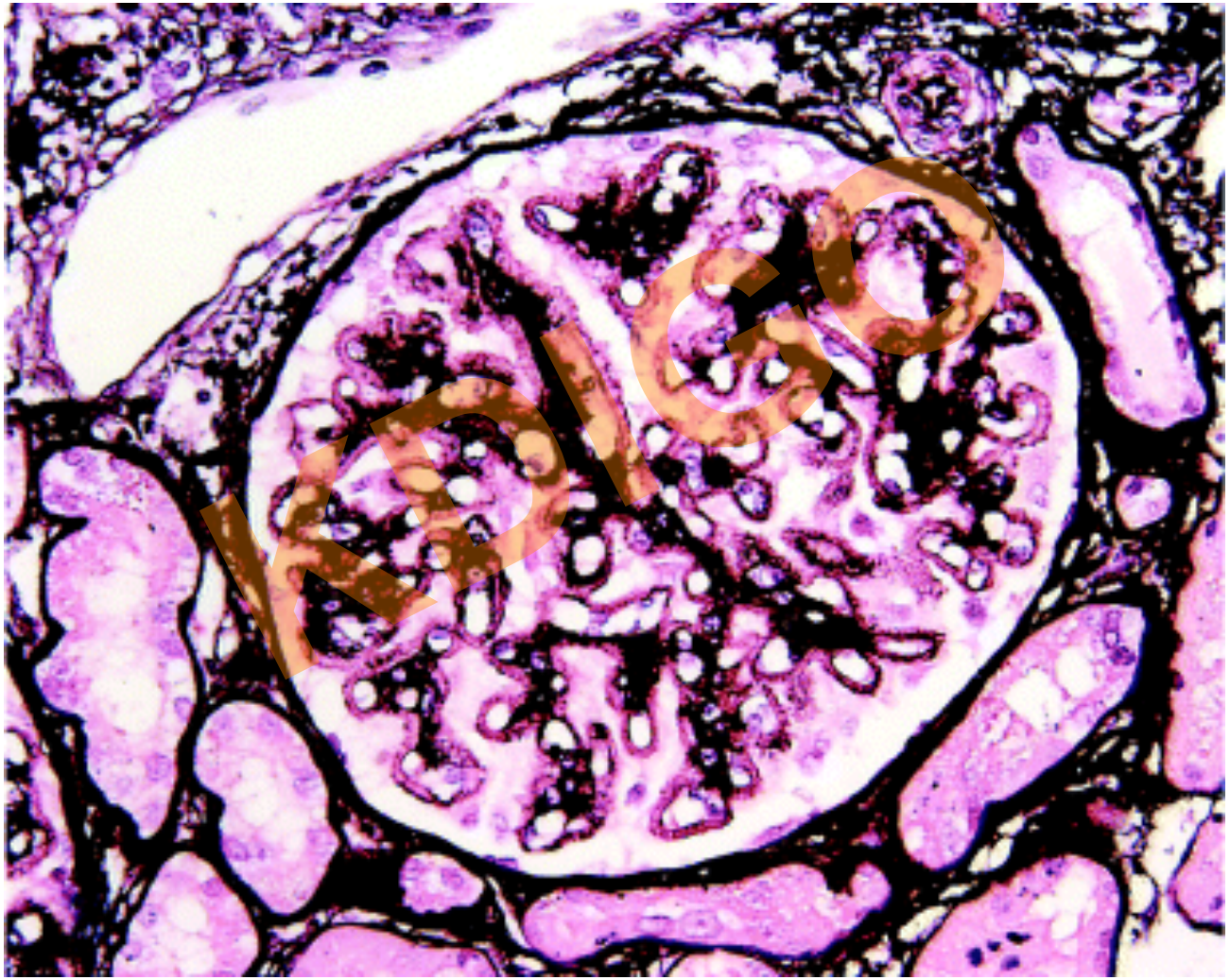
12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be **CONTINUED FOR AT LEAST 1 YEAR** before consideration is given to tapering the immunosuppression. **(2D)**

LUPUS NEPHRITIS
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)
MAINTENANCE THERAPY

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. **(NOT GRADED)**

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. **(2D)**

LUPUS NEPHRITIS
CLASS V LN (MEMBRANOUS LN)



LUPUS NEPHRITIS
CLASS V LN (MEMBRANOUS LN)

WHY IS IT IMPORTANT TO TREAT CLASS V LN (MEMBRANOUS LN)?

- CKD occurs in up to 20% of patients
- ESKD in 12% of these patients after 7-10 years
- Composite endpoint of death or ESKD
  - 14% at 5 years
  - 28% at 10 years
- Unlike IMN, **spontaneous remission of heavy proteinuria DOES NOT OCCUR often**
- Complications of heavy proteinuria
  - Atherosclerosis and CVD
  - Predisposition to clotting

LUPUS NEPHRITIS
CLASS V LN (MEMBRANOUS LN)

12.5.1: We recommend that patients with class V LN, **normal kidney function**, and **non–nephrotic-range proteinuria** be treated with **antiproteinuric and antihypertensive medications**, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. **(2D)**

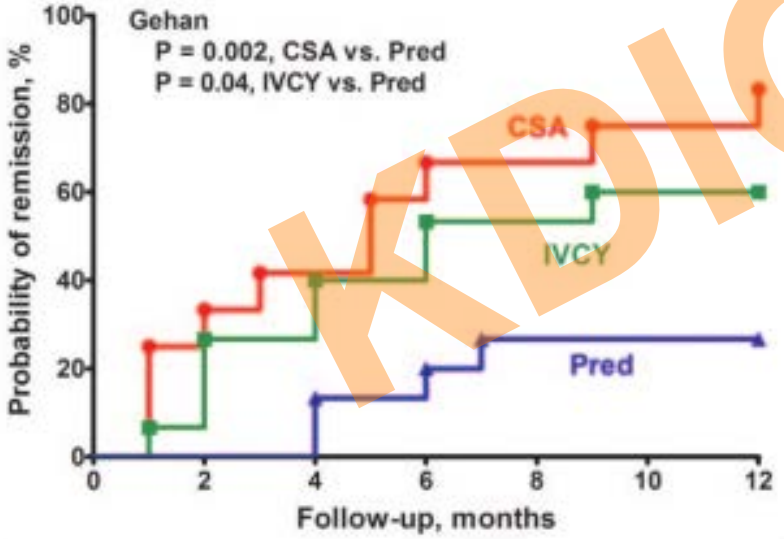
LUPUS NEPHRITIS
CLASS V LN (MEMBRANOUS LN)

12.5.2: We suggest that patients with pure class V LN and **persistent nephrotic proteinuria** be treated with **CORTICOSTEROIDS** plus an additional immunosuppressive agent: **CYCLOPHOSPHAMIDE** **(2C),** or **CNI** **(2C),** or **MMF** **(2D),** or **AZATHIOPRINE** **(2D).**

Randomized, Controlled Trial of Prednisone, Cyclophosphamide, and Cyclosporine in Lupus Membranous Nephropathy

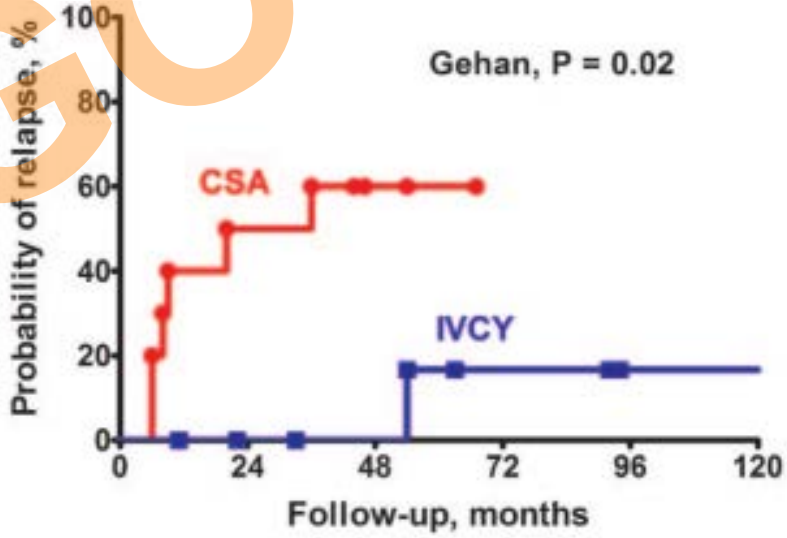
Howard A. Austin, III,* Gabor G. Illei,†‡ Michelle J. Braun,* and James E. Balow*

*National Institute of Diabetes and Digestive and Kidney Diseases, †National Institute of Arthritis and Musculoskeletal and Skin Diseases, and ‡National Institute of Dental and Craniofacial Disorders, National Institutes of Health, Bethesda, Maryland



No. at Risk							
CSA	12	9	7	5	4	3	3
IVCY	15	14	11	9	7	6	6
Pred	15	15	15	13	11	11	11

Figure 1. Cumulative probability of remission of proteinuria during the 12-mo protocol treatment period by treatment group. No patients were lost to follow-up or censored during this period. PRED, prednisone alone.



No. at Risk						
CSA	10	5	2			
IVCY	9	7	6	4	2	2

Figure 3. Cumulative probability of relapse of nephrotic syndrome after completion of protocol treatment with IVCY *versus* CSA. Follow-up begins at the end of the 12-mo protocol treatment period. Patients were censored when they were lost to follow-up.

BIOLOGICS (?)

- No decrease in proportion of patients with LN progressing to ESKD
- ≈ 50% of LN patients achieve Complete/ Partial remission with treatment over 6 months
  - Many patients do not achieve Complete remission following induction therapy.
- No decrease in death rates in LN patients in the last decade

Biologic Therapy for Lupus Nephritis: The time has come.

- **DIRECT B CELL TARGETING** treatments (B cell depletion)
  - Anti-CD20: **Rituximab (EXPLORER 2010/ LUNAR 2012)** , Ocreluzimab
  - Anti-CD22: Epratuzumab
- **INDIRECT B CELL TARGETING** treatments (Targeting C-cell survival molecule Blys)
  - ANTI-BLys: Belimumab
  - Anti-Blys/April: Atacicept
- **BLOCK CO-STUIMULATION INTERACTIONS** between T and B cells
  - Anti-CD40L: BG9566, IDEC-131

LUPUS NEPHRITIS
GENERAL TREATMENT

12.6.1: We suggest that all patients with LN of any class are treated with **HYDROXYCHLOROQUINE**(maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. **(2C)**

LUPUS NEPHRITIS
CLASS VI LN (ADVANCED SCLEROSIS LN)

12.7.1: We recommend that patients with class VI LN be treated with **CORTICOSTEROIDS and IMMUNOSUPPRESSIVES** only as dictated by the extra-renal manifestations of systemic lupus. **(2D)**

LUPUS NEPHRITIS

Table 29 | Criteria for the diagnosis and classification of relapses of LN

Mild kidney relapse	Moderate kidney relapse	Severe kidney relapse
Increase in glomerular hematuria from <5 to >15 RBC/hpf, with ≥2 acanthocytes/hpf *and/or* recurrence of ≥1 RBC cast, WBC cast (no infection), or both	If baseline creatinine is: <2.0 mg/dl [<177 μmol/l], an increase of 0.20–1.0 mg/dl [17.7–88.4 μmol/l] ⩾2.0 mg/dl [⩾177 μmol/l], an increase of 0.40–1.5 mg/dl [35.4–132.6 μmol/l] *and/or* If baseline uPCR is: <500 mg/g [<50 mg/mmol], an increase to ⩾1000 mg/g [⩾100 mg/mmol] 500–1000 mg/g [50–100 mg/mmol], an increase to ⩾2000 mg/g [⩾200 mg/mmol], but less than absolute increase of <5000 mg/g [<500 mg/mmol] >1000 mg/g [>100 mg/mmol], an increase of ⩾2-fold with absolute uPCR <5000 mg/g [<500 mg/mmol]	If baseline creatinine is: <2 mg/dl [<177 μmol/l], an increase of >1.0 mg/dl [>88.4 μmol/l] ⩾2 mg/dl [⩾177 μmol/l], an increase of >1.5 mg/dl [>132.6 μmol/l] *and/or* an absolute increase of uPCR >5000 mg/g [>500 mg/mmol]

hpf, high-power field; LN, lupus nephritis; RBC, red blood cell; uPCR, urine protein:creatinine ratio; WBC, white blood cell.
Adapted from Lahita RG, Tsokos GT, Buyon JP, Koike T (eds). Systemic Lupus Erythematosus, 5th edn. Rovin BH, Stillman IE. Chapter 42: Kidney. Elsevier: Waltham, MA, 2011, pp 769–814 with permission from Elsevier.[687]

LUPUS NEPHRITIS
RELAPSE

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. **(2B)**

LUPUS NEPHRITIS
RELAPSE

12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide-based initial regimen be used. **(2B)**

LUPUS NEPHRITIS
RELAPSE

12.8.2: Consider a **REPEAT KIDNEY BIOPSY** during relapse if there is suspicion that the **histologic class of LN has changed**, or there is **uncertainty whether a rising SCr and/or worsening proteinuria** represents disease activity or chronicity. **(NOT GRADED)**

LUPUS NEPHRITIS RESISTANT DISEASE

12.9.1: In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a **repeat kidney biopsy to distinguish active LN from scarring**. **(NOT GRADED)**

12.9.2: Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the **alternative initial treatment regimens**. **(NOT GRADED)**

LUPUS NEPHRITIS
RESISTANT DISEASE

12.9.3: We suggest that **NON-RESPONDERS** who have failed more than one of the recommended initial regimens may be considered for treatment with **RITUXIMAB, IV IMMUNOGLOBULIN, or CNIs**. **(2D)**

SYSTEMIC LUPUS and THROMBOTIC MICROANGIOPATHY

12.10.1: We suggest that the **ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)** involving the kidney in systemic lupus patients, with or without LN, be treated by **ANTICOAGULATION** (target [INR] 2–3). **(2D)**

12.10.2: We suggest that patients with systemic lupus and **THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)** receive **PLASMA EXCHANGE** as for patients with TTP without systemic lupus. **(2D)**

SYSTEMIC LUPUS AND PREGNANCY

12.11.1: We suggest that women be counseled **TO DELAY PREGNANCY** until a complete remission of LN has been achieved. **(2D)**

12.11.2: We recommend that **cyclophosphamide, MMF, ACE-I, and ARBs NOT BE USED** during pregnancy. **(1A)**

12.11.3: We suggest that **HYDROXYCHLOROQUINE be continued** during pregnancy. **(2B)**

SYSTEMIC LUPUS AND PREGNANCY

12.11.4: We recommend that LN patients who become pregnant while being treated with MMF be **switched to AZATHIOPRINE**. **(1B)**

12.11.5: We recommend that, if LN patients relapse during pregnancy, they receive treatment with **CORTICOSTEROIDS** and, depending on the severity of the relapse, **AZATHIOPRINE**. **(1B)**

SYSTEMIC LUPUS AND PREGNANCY

12.11.6: If pregnant patients are receiving corticosteroids or azathioprine, we suggest that these drugs **not be tapered during pregnancy or for at least 3 months after delivery**. **(2D)**

12.11.7: We suggest administration of low-dose **ASPIRIN** during pregnancy to **decrease the risk of fetal loss**. **(2C)**

- If you would like a copy of my unabridged slide presentation (KDIGO Glomerulonephritis) kindly Email me at nephron0@gmail.com

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ThankYou
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Tack
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Xie
Gra
Dankie
Kruthagnathalu
Arigatou
Dhonnobaad
Asante
Dhanyavad
Khopjai
Gomapsupnida
Terima
Danke
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Shukriya
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