Evidence based therapy in Lupus Nephritis

Ioannis Griveas, MD, PhD

The treatment of lupus nephritis

evidence. Many opinions about the treatment of lupus nephritis are based on faith rather than valid observation. When faith rather than evidence is used to support clinical decisions, the treatment chosen becomes, like religion, a matter of personal preference.

Lewis EJ. The treatment of lupus nephritis: revisiting Galen. Annals of Internal Medicine 2001;21:296-298

SPECIAL FEATURE

J Am Soc Nephrol 15: 241–250, 2004

The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited

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**Academic Medical Center University of Amsterdam, Amsterdam, The Netherlands; †Columbia University, College of Physicians and Surgeons, New York, New York; ‡Rush Medical College, Chicago, Illinois; §Weill Medical College, Cornell University, New York, New York; ‖University of Washington, Seattle, Washington; ¶Columbia Presbyterian Medical Center, New York, New York; #National Institutes of Health, Bethesda, Maryland; **Leiden University Medical Center, Leiden, The Netherlands; ††Imperial College Medical School, London, United Kingdom; ‡‡San Carlo Borromeo Hospital, Milan, Italy; §§Vanderbilt University, Nashville, Tennessee; ‖‖SUNY Health Science Center, Brooklyn, New York; ¶¶Ohio State University, Columbus, Ohio; ###Georges Pompidou European Hospital, Paris, France; ***St. Vincent's Hospital, Fitzroy, Victoria, Australia; †††University of North Carolina School of Medicine, Chapel Hill, North Carolina; ‡‡‡University Kebangsaan Malaysia, Kuala Lumpur, Malaysia; §§§Necker Hospital, Paris, France; ‖‖‖University of Malaya Medical School, Kuala Lumpur, Malaysia; ¶¶¶Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan; ###Federal University of Sao Paulo, Sao Paulo, Brazil; and ****University of Tsubuka, Ibaraki, Japan*

Table 1. Original World Health Organization (WHO) classification of lupus nephritis (1974)

Class I	Normal glomeruli (by light microscopy, immunofluorescence, and electron microscopy)
Class II	Purely mesangial disease a. Normocellular mesangium by light microscopy but mesangial deposits by immunofluorescence or electron microscopy b. Mesangial hypercellularity with mesangial deposits by immunofluorescence or electron microscopy
Class III	Focal proliferative glomerulonephritis (<50%)
Class IV	Diffuse proliferative glomerulonephritis (≥50%)
Class V	Membranous glomerulonephritis

Table 2. World Health Organization (WHO) morphologic classification of lupus nephritis (modified in 1982)

Class I	Normal glomeruli
	a. Nil (by all techniques)
	b. Normal by light microscopy, but deposits by electron or immunofluorescence microscopy
Class II	Pure mesangial alterations (mesangiopathy)
	a. Mesangial widening and/or mild hypercellularity (+)
	b. Moderate hypercellularity (++)
Class III	Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations)
	a. With "active" necrotizing lesions
	b. With "active" and sclerosing lesions
	c. With sclerosing lesions
Class IV	Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangio-capillary proliferation and/or extensive subendothelial deposits)
	a. Without segmental lesions
	b. With "active" necrotizing lesions
	c. With "active" and sclerosing lesions
	d. With sclerosing lesions
Class V	Diffuse membranous glomerulonephritis
	a. Pure membranous glomerulonephritis
	b. Associated with lesions of class II
	c. Associated with lesions of class III
	d. Associated with lesions of class IV
Class VI	Advanced sclerosing glomerulonephritis

Table 3. International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis**[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis**[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

Prognostic Features in LN

Histological Predictors

- WHO – ISN Histologic Class IV
- Activity and Chronicity Index
- Crescents and Interstitial fibrosis
- Segmental necrotizing lesions

Clinical Predictors

- Hypertension
- Anemia
- High baseline serum creatinine
- Higher baseline proteinuria
- Delay in therapy

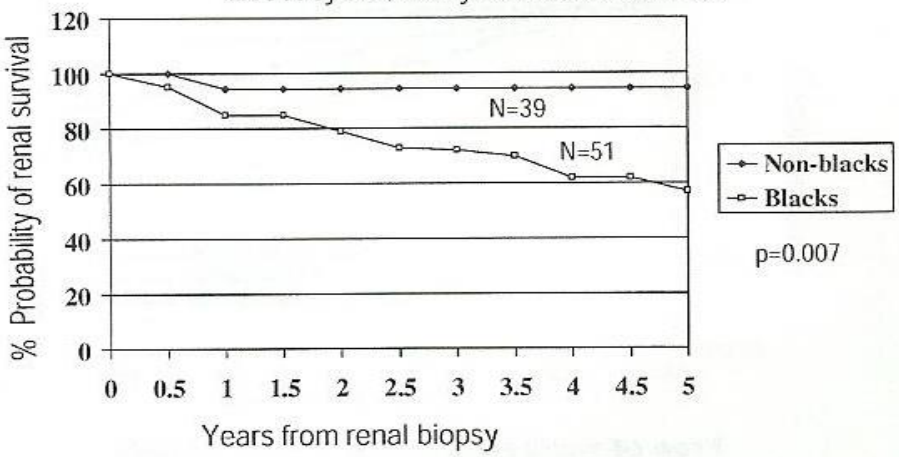
Epidemiologic Predictors

- African American Race
- Low socioeconomic status.

Appel G, Cameron JS in Comprehensive Clinical Nephrology 2007.

Renal Survival for Class IV Lupus Nephritis at the UNC-Chapel Hill

MA Dooley et al, Kidney Int 1997; 51:1188-1195



Prognosis In Proliferative LN: Role of socio-economic status and race

New York City Cohort:

- 129 pts -51 H, 22 AA, 55 C Class III -IV LN
- Predictors (age-adjusted hazard ratio)
  - Hispanic ethnicity (3.7)
  - African – American race (3.1)
  - Living in neighborhood with high poverty (2.9)
  - Government insurance – Medicare (3.2)
  - Elevated Screatinine (4.3)
  - Heavier Proteinuria (3.8)
  - Hypertension (3.2)
  - WHO Class IV vs III (3.3)

Barr,Seliger,Appel et al. NDT 18:2039-46, 2003.

Basic Differences between Segmental Proliferative and Global Proliferative Class IV Lupus Nephritis

G.S. Hill et al, in press 2005

	Segmental Proliferative	Global Proliferative
Involvement of all viable glomeruli	None	74.2% of cases ($p < .0001$)
Membranoproliferative features	None	64.5% of cases ($p < .0001$)
Glomerular Monocyte/Macrophages	Minimal	Prominent
Fibrinoid Necrosis – % affected gl.	Significantly more frequent	Less frequent
Fibrinoid Necrosis in absence of Endocapillary Proliferation	Yes	No
Glomerular IF	Mesangial IF predominates	Capillary IF predominates
Glomerular Subendothelial Deposits	Negative correlation	Positive correlation
Serum CH50 and C3	No correlation	Negative correlation

What Have We Learned about Optimal Induction Therapy for Lupus Nephritis (III through V) from Randomized, Controlled Trials?

William F. Clark and Jessica M. Sontrop
London Health Sciences Centre, and Department of Medicine, University of Western Ontario, London, Canada

Clin J Am Soc Nephrol 3: 895-898, 2008. doi: 10.2215/CJN.00170108

Year Reported	Study	*n*/Design	Entry Serum Creatinine (mg/dl)	Renal Biopsy	% Black	Primary End Point	Follow-up/Outcome
2001	NIH Illei *et al.* (1)	*n* = 82 1. intravenous cyclophosphamide 2. MP 3. combination	1.16	Types III and IV	23	Treatment failure = Suppl I.S. or serum creatinine ×2 or death	Median 132 mo/ intravenous cyclophosphamide + combination < MP
2002	EURO, Houssiau *et al.* (2)	*n* = 90 1. low-dosage intravenous cyclophosphamide-AZA 2. high-dosage intravenous cyclophosphamide	1.15	Type III to V c + d	9	Treatment failure = no primary response or flare or serum creatinine ×2	Median 41 mo/ND + low-dosage < toxic
2005	Chan *et al.* (3)	*n* = 64 1. MMF 2. oral cyclophosphamide-AZA	1.28	Type IV	0	Serial measurement of serum creatinine	Median 63 mo/ND + MMF < toxic
2005	Ginzler *et al.* (4)	*n* = 140 1. MMF 2. intravenous cyclophosphamide	1.07	Types III to V	56	Complete remission: Return to 10% of normal for serum creatinine + urine protein and sediment	6 mo/MMF > intravenous cyclophosphamide + < toxic
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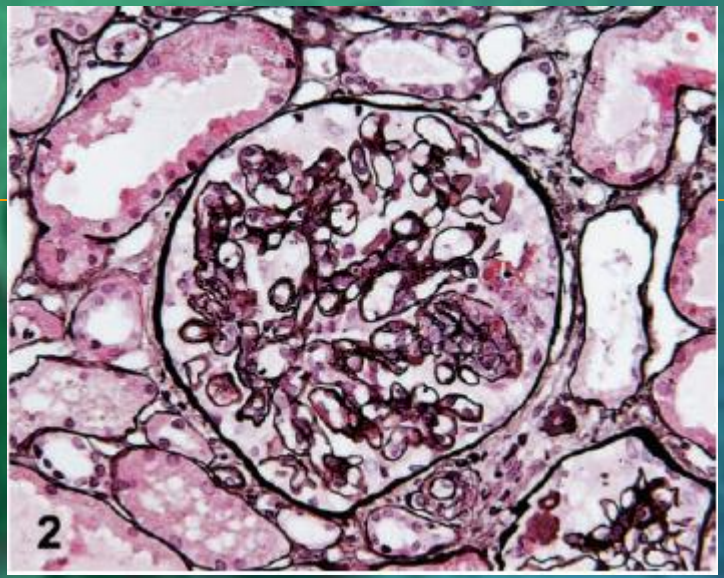

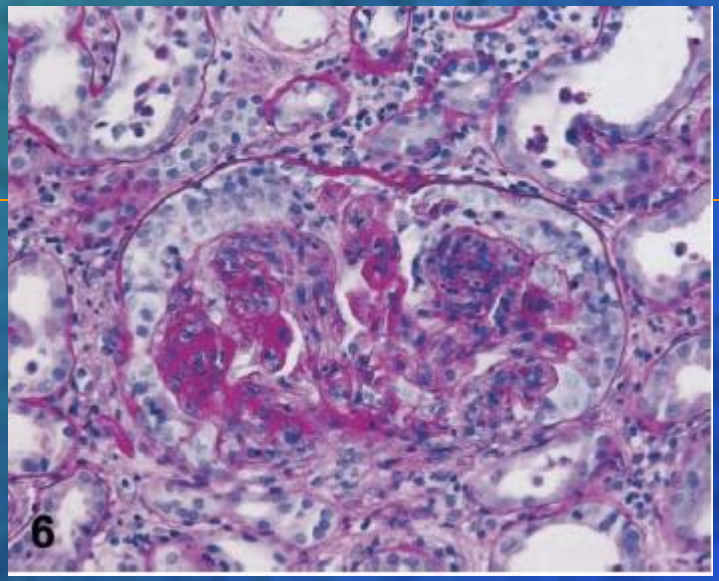

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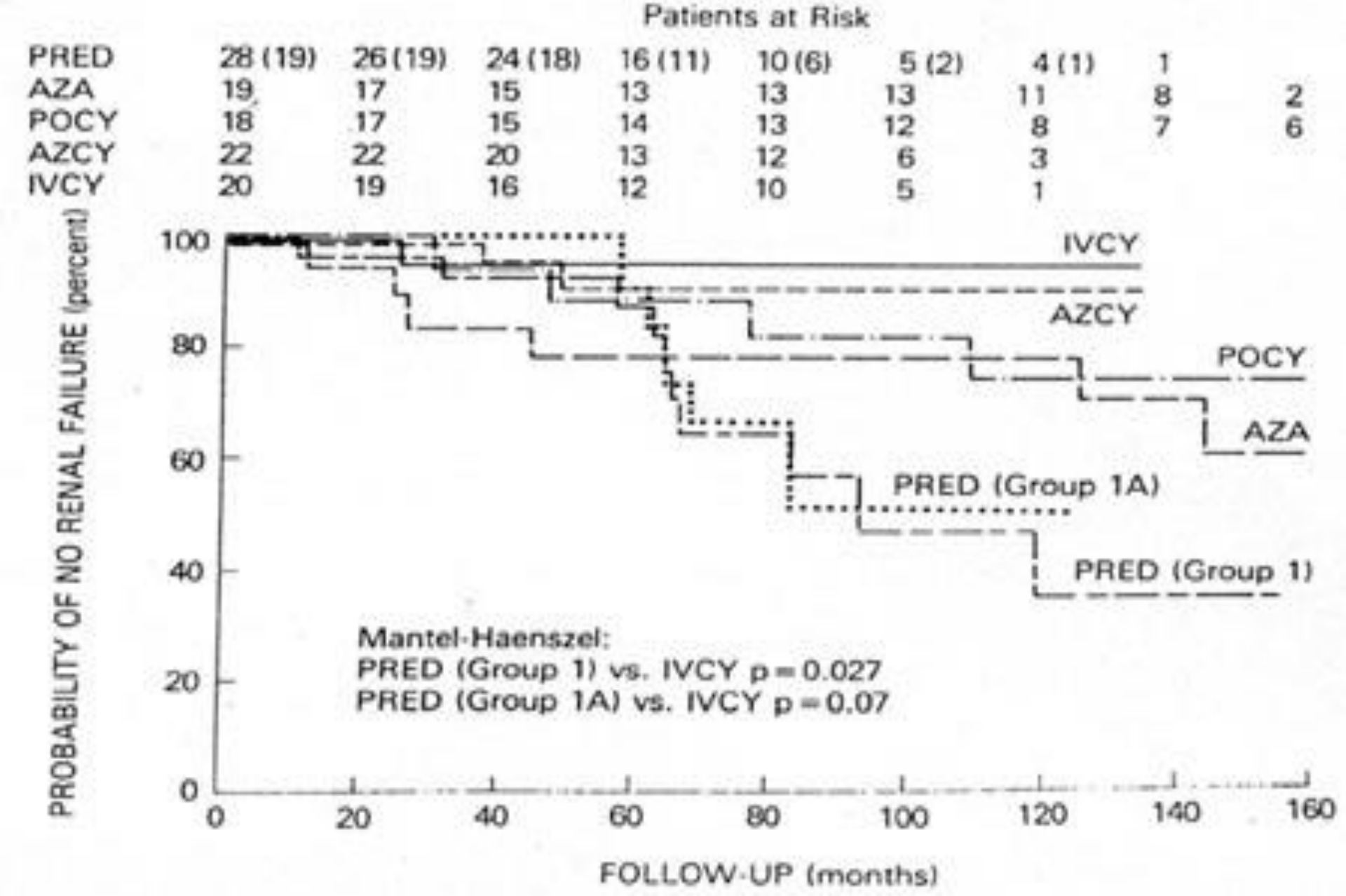
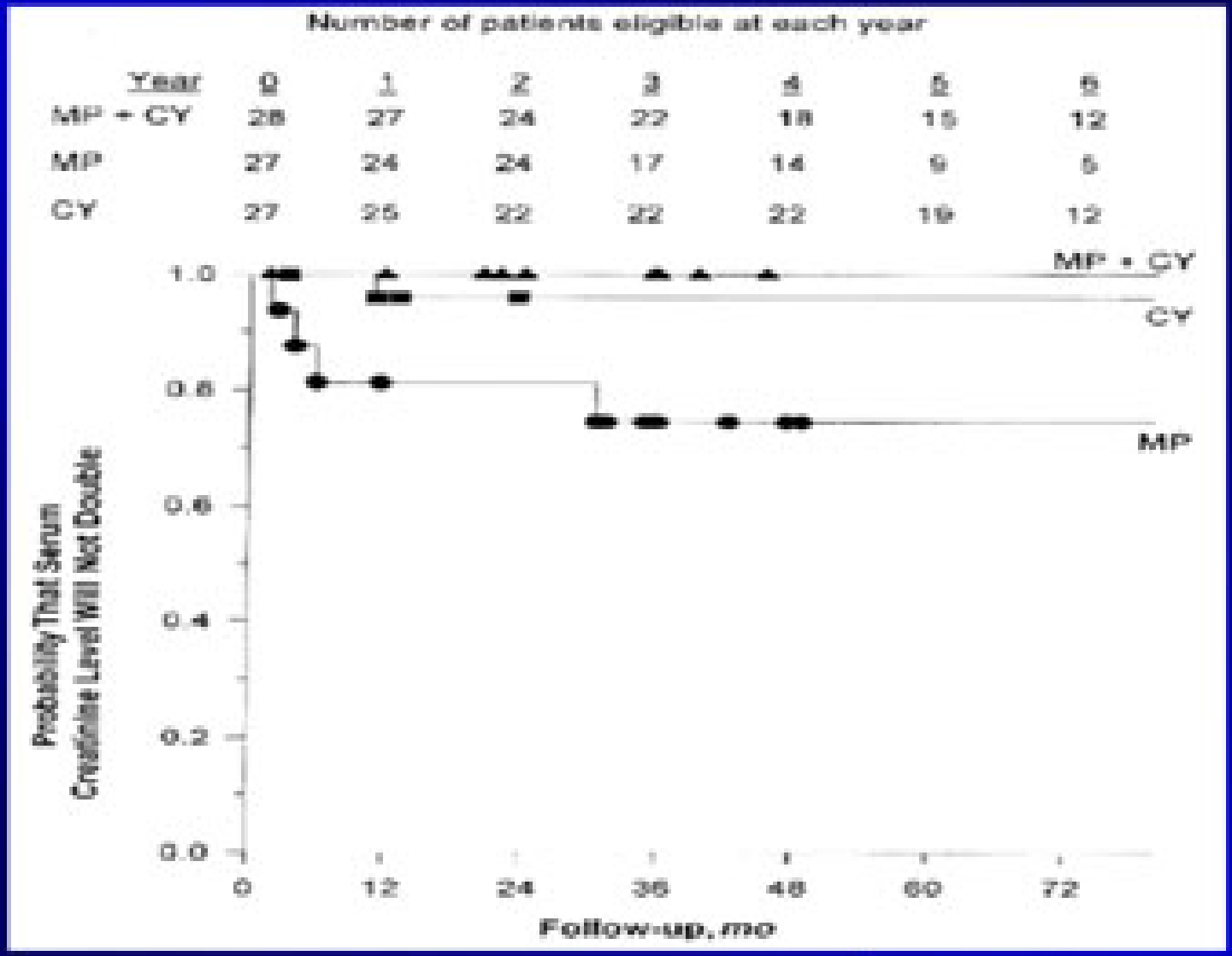
Austin HA III et al N Engl J Med 314,614,1986



Probability that the serum creatinine level would not double during the study period by treatment group



Annals of Internal Medicine

Gourley, M. F. et. al. Ann Intern Med 1996;125:549-557

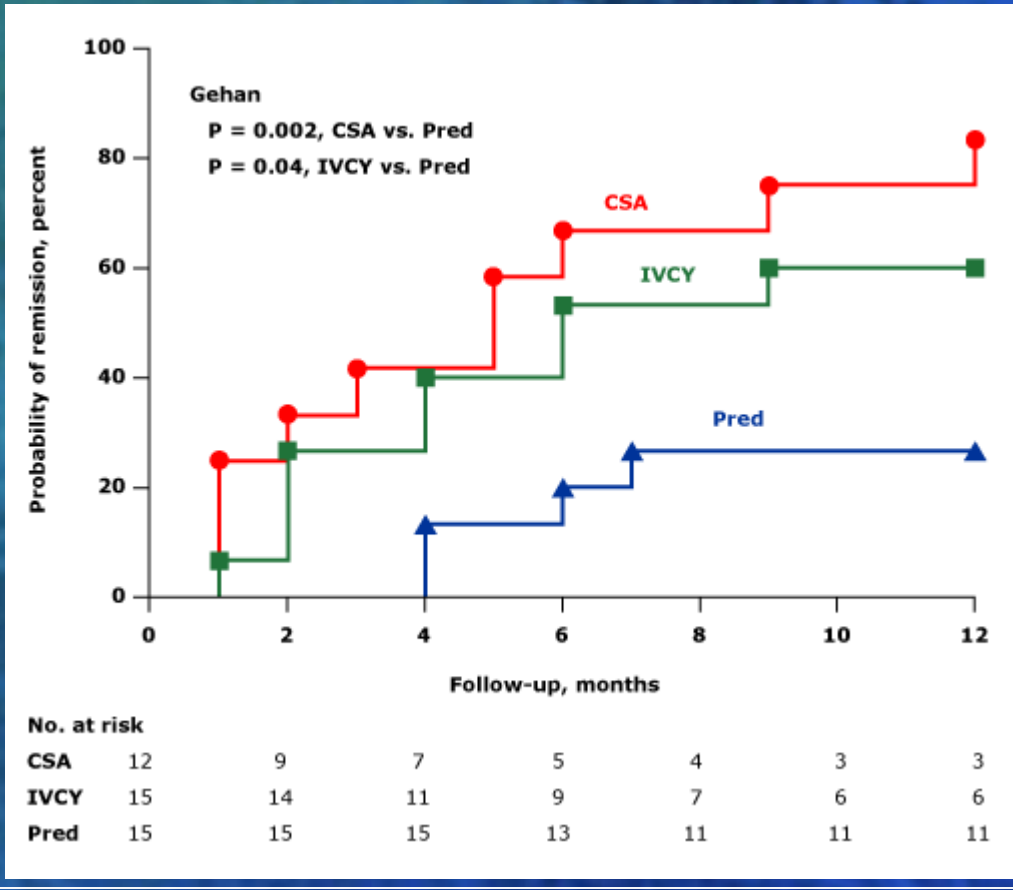
Side-effects, morbidity, comorbidity

Illei GG et al Ann Int Med 135, 248,2001

	Cy	*Combined*	*MP*
Avascular necrosis	36%	31%	30%
Osteoporosis	23%	21%	13%
Amenorrhea	60%	52%	33%
Infection	26%	32%	8%

Cyclophosphamide versus Cyclosporine

42 patients with MN participated in a randomized, controlled trial .



Austin HA, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol. 2009 Apr;20(4):901-11.

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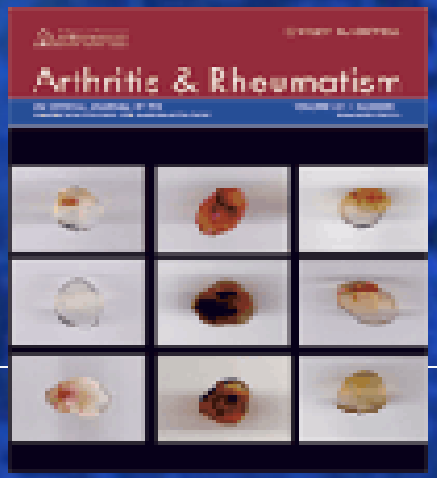


Low-dose versus high-dose i.v. cyclophosphamide

Houssiau et al Arthritis and Rheum. 2002

Induction therapy 1 MP pulse 750mg for 3 days of IV

- **High-dose CYC**
- 8 IV CYC pulses (1g)
- Mean 8.5±1.9 gr

- **Low dose CYC**
- 6 fortnightly CYC 500mg
- Total 3 g

- Azathioprine 2mg/Kg/day from 13th to 30th month.

- Azathioprine 2mg/Kg/day from the 4th to the 30th month.

EURO-LUPUS TRIAL
mean follow-up 41 months

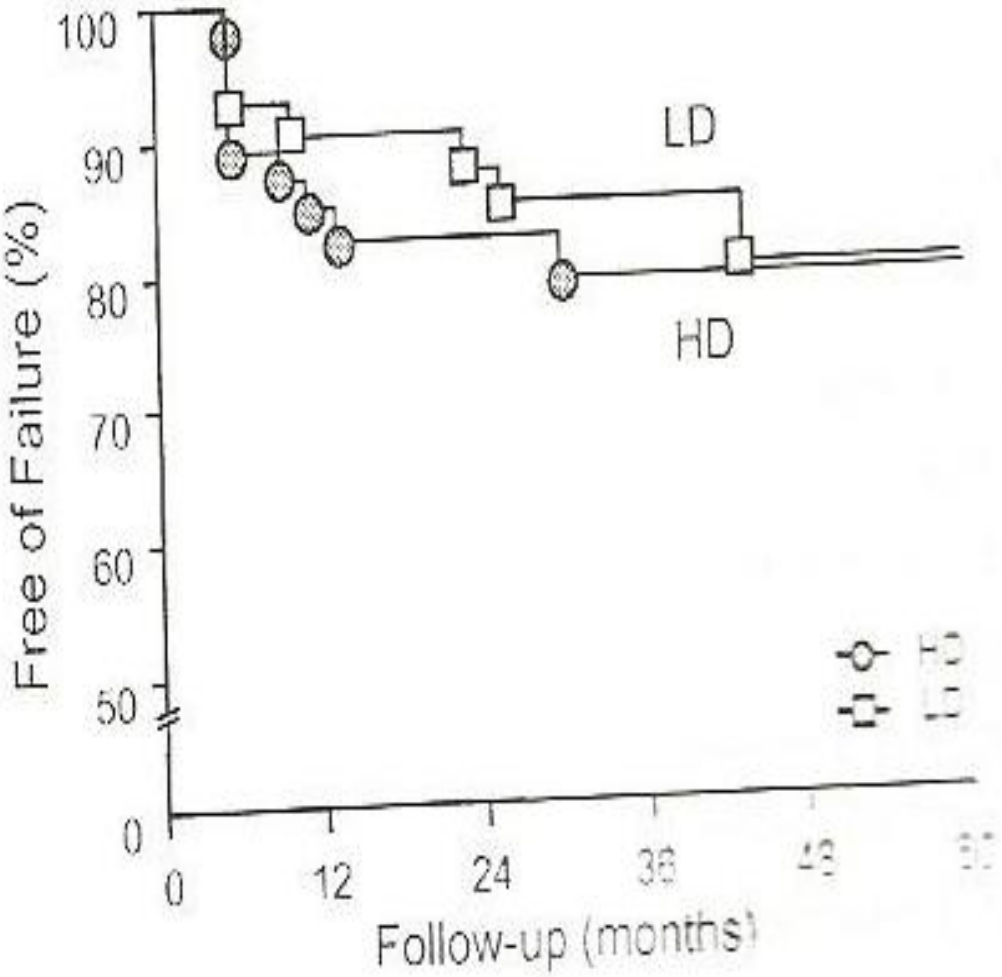
	High-dose CYC 45 pts	Low-dose CYC 44 pts
Renal failure	6.6%	9.0%
Death	0	4.5%
Renal flares	29%	26%
Renal remission	54%	70%
Treatment failure	20%	16%
Severe infection	22%	11%

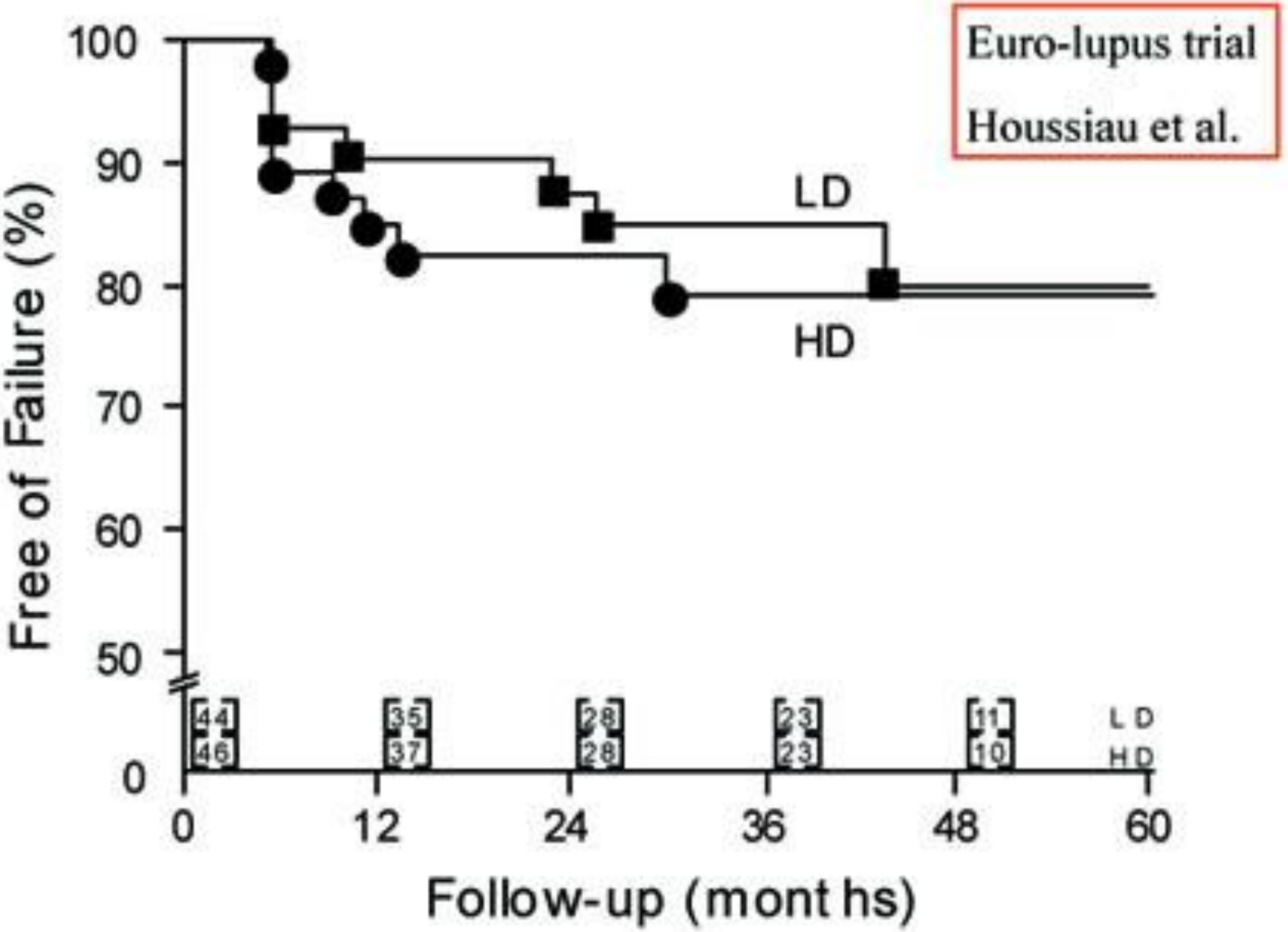
The Euro-Lupus Nephritis Trial

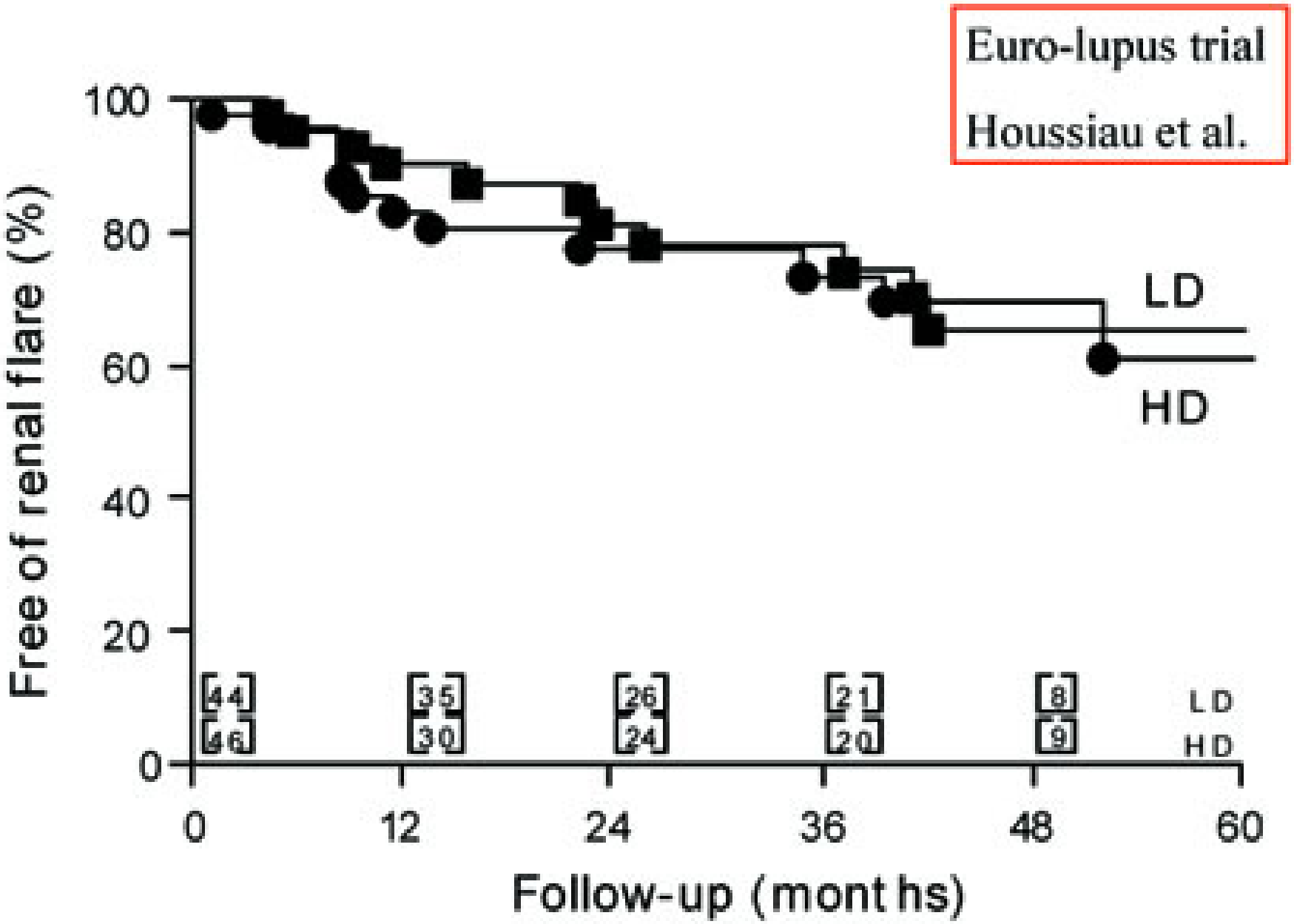
- Multicenter prospecitive trial of 90 LN pts with Proliferative LN (WHO III,IV,Vc-d)
- High dose IVCYT (6 mo IVP + 2 quarterly pulses) vs Low dose IV CYT (IVP q 2 wks x 6 followed by AZA)
- Follow 41 months

Houssiau et al. Arthritis & Rheumatisms 46: 2121-2131, 2002

Euro Lupus Trial Treatment failure

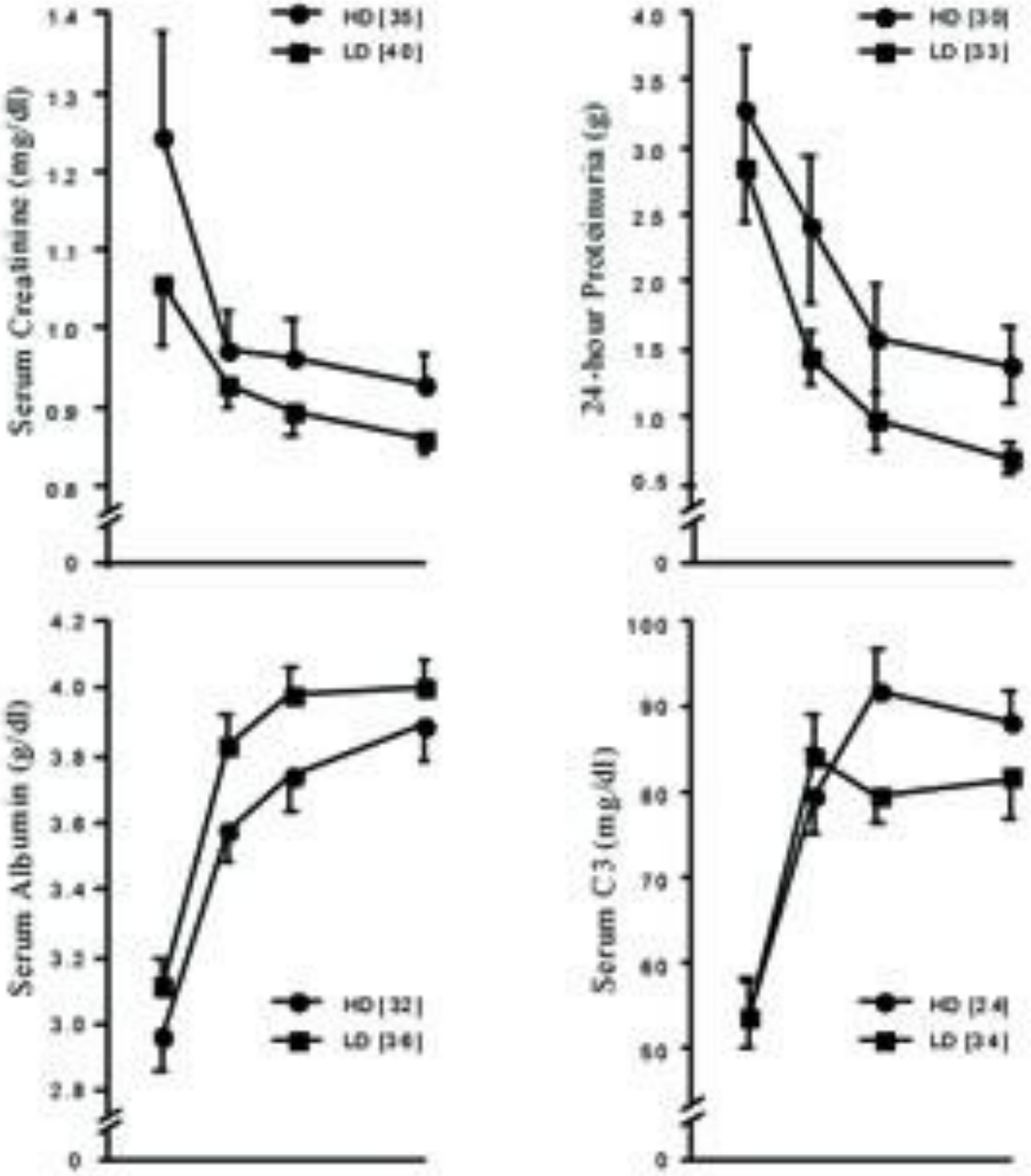



Euro-lupus trial
Houssiau et al.
100
90
80
70
60
50
0
Free of Failure (%)
LD
HD
44
46
35
37
28
28
23
23
11
10
L D
H D
0
12
24
36
48
60
Follow-up (mont hs)


Euro-lupus trial
Houssiau et al.
Free of renal flare (%)
100
80
60
40
20
0
LD
HD
44
46
35
30
26
24
21
20
8
9
LD
HD
0
12
24
36
48
60
Follow-up (months)

Euro-lupus trial

Houssiau et al.



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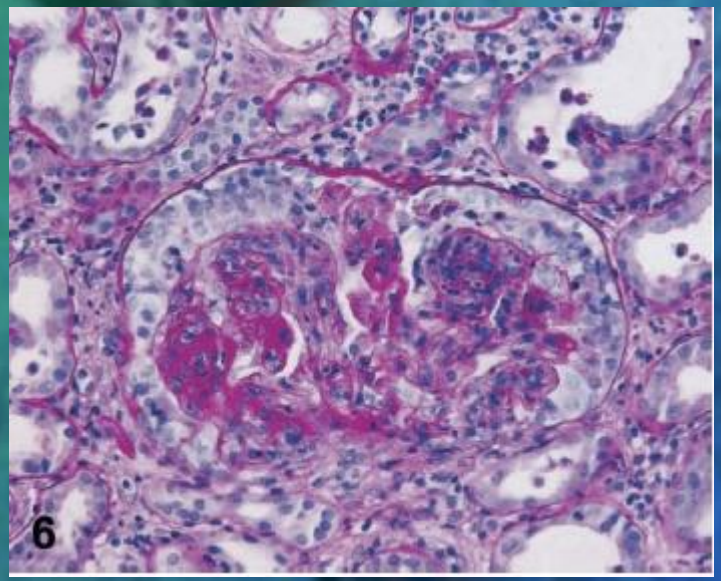
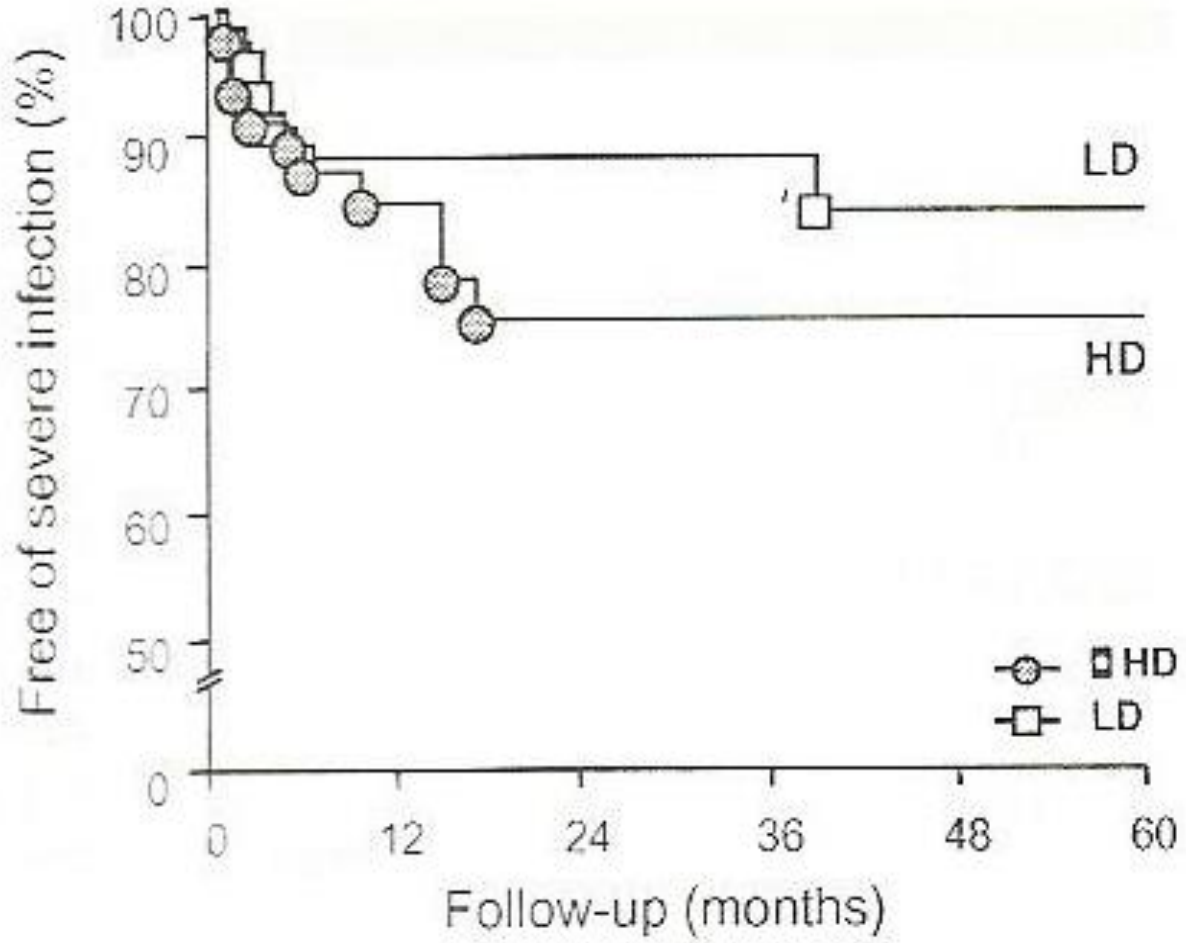


Euro Lupus Trial - Severe infection



UCL

Houssiau *et al.*, Arthritis Rheum, 2002

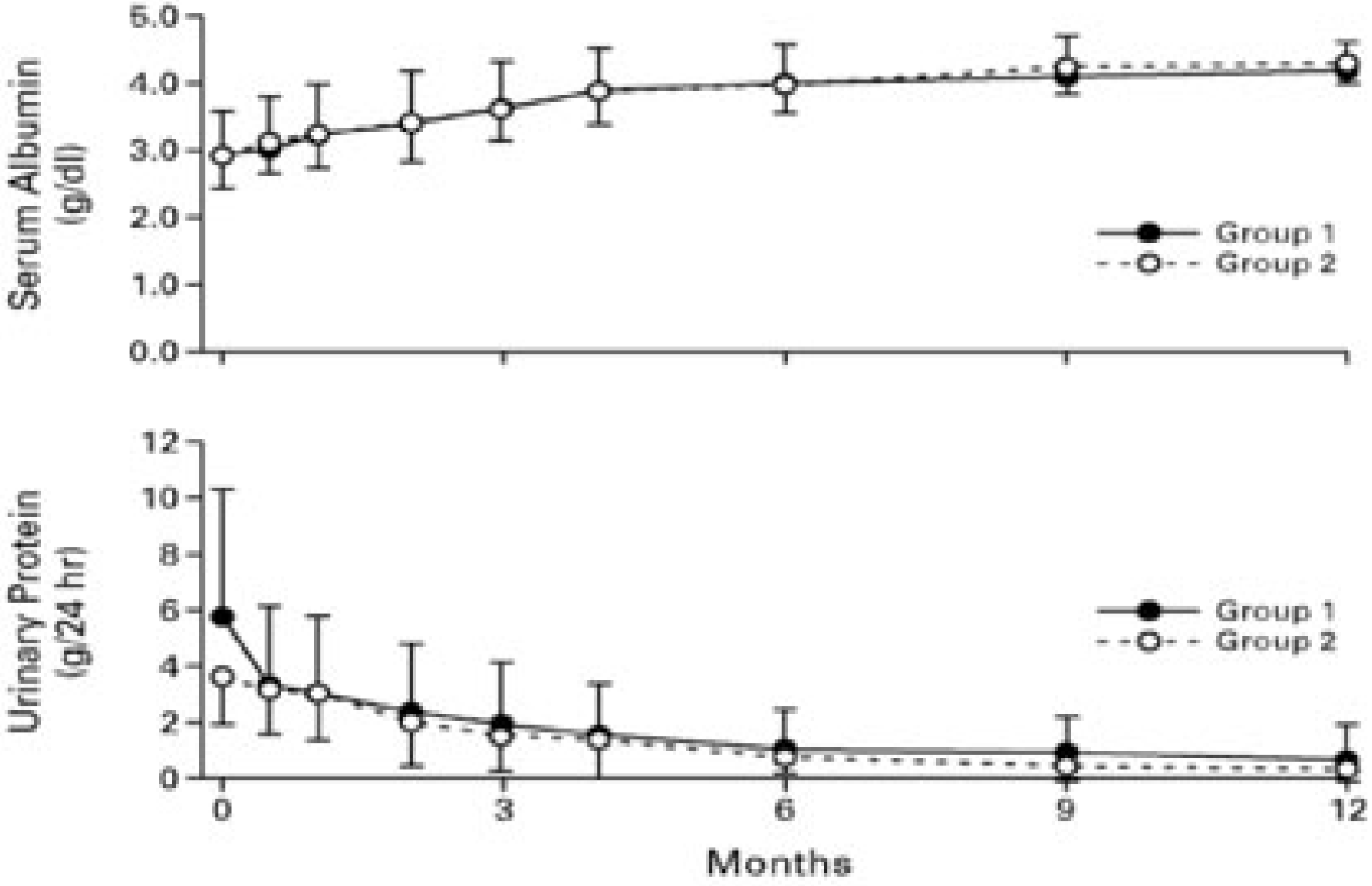
Diffuse proliferative SLE nephritis

MMF (2g/day for 6 mo ,
then 1g/day for 6 other mo)

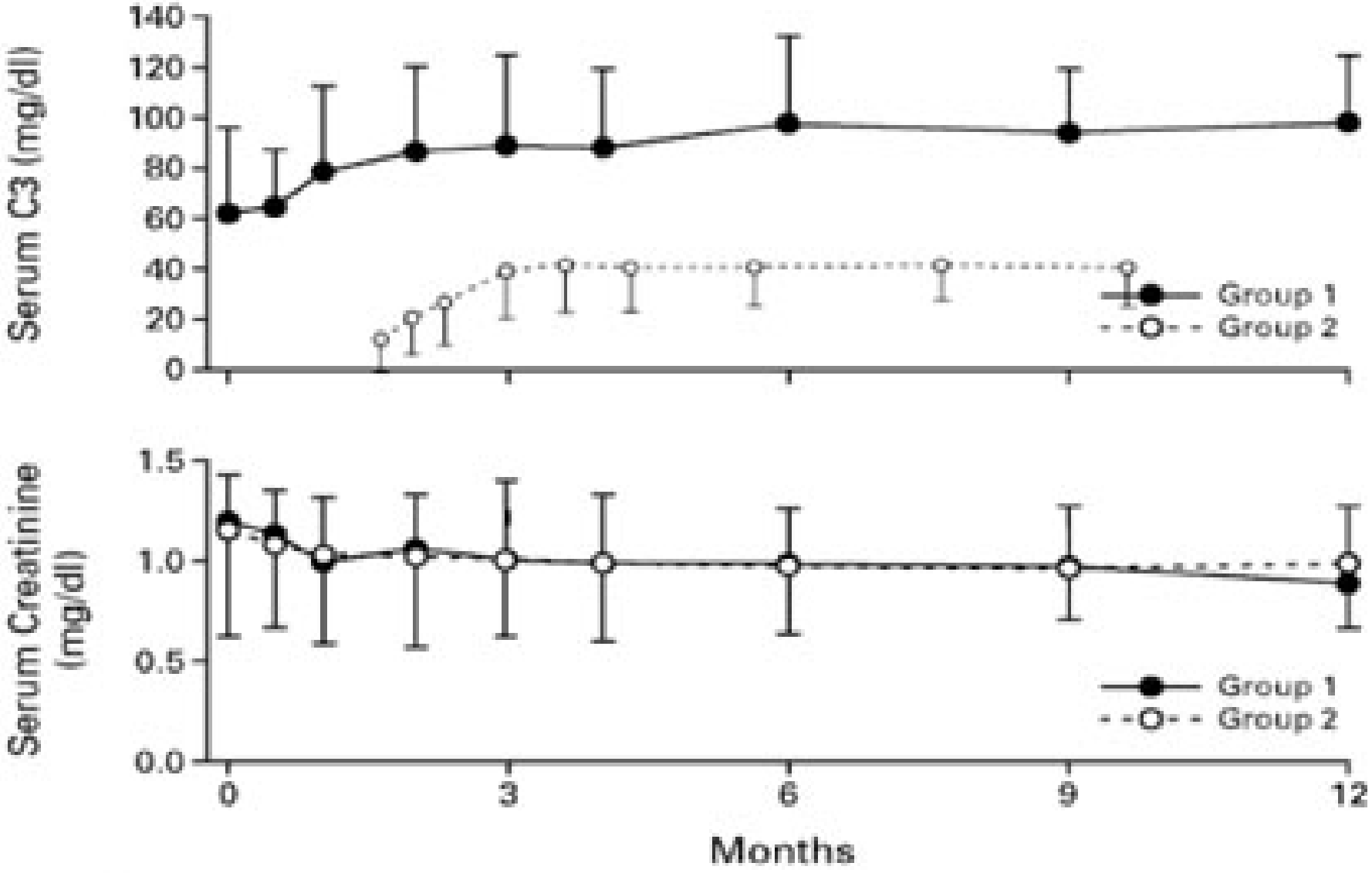
vs

Cyclophosphamide for 6 m and
AZA for other 6 mo

Chan TM et al N Engl J Med 343,1156,2000



No. of Patients					
Group 1	21	20	20	20	17
Group 2	21	20	20	17	16



No. of Patients					
Group 1	21	20	20	20	17
Group 2	21	20	20	17	16

Adverse effects

(Chan TM et al , NEJM 343,1156, 2000)

	MMF	*Cy/Aza*
Relapses	15%	11%
Leukopenia	0	10%
Amenorrhea	0	23%
Infection	19%	33%
Death	0	10%

Long-term (63 months) follow-up
Chan T JASN 16,1076,2005

	MMF	Cyc-Aza	P
Patients	33	31	
ESRD/death	0	4	0.062
Double creat.	2	3	
Relapse	9	11	
Infections	4 (12.5%)	12 (40%)	0.013

The NEW ENGLAND JOURNAL of MEDICINE

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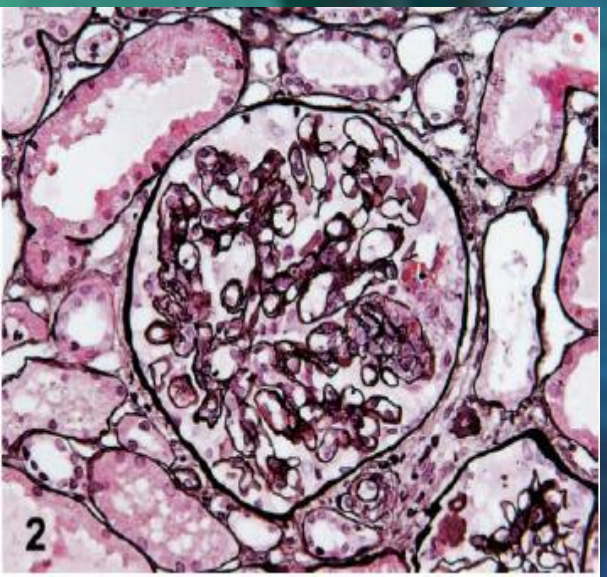
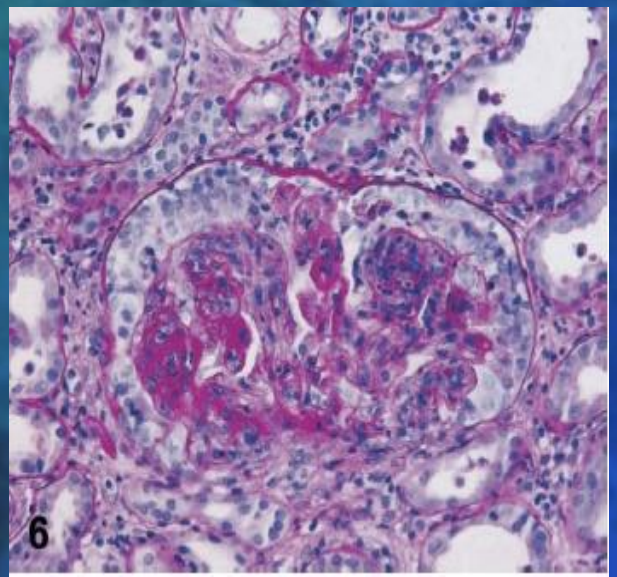
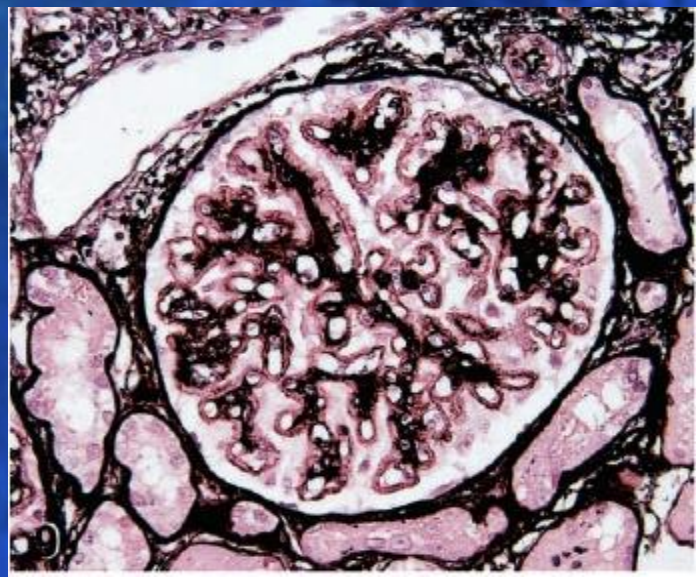
2005	Ginzler *et al.* (4)	*n* = 140 1. MMF 2. intravenous cyclophosphamide	1.07	Types III to V	56	Complete remission: Return to 10% of normal for serum creatinine + urine protein and sediment	6 mo/MMF > intravenous cyclophosphamide + < toxic







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2007	ALMS, Appel *et al.* (5)	*n* = 370 1. MMF 2. intravenous cyclophosphamide	0.88	Types III to V	12	Response: Increased urinary protein/ creatinine + decreased or stable serum creatinine	6 mo/ND + MMF > toxic

Mycophenolate Mofetil for Induction Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis

Michael Walsh,*† Matthew James,* David Jayne,‡ Marcello Tonelli,§‖¶ Braden J. Manns,*†¶ and Brenda R. Hemmelgarn*†

*Departments of *Medicine and †Community Health Sciences, University of Calgary, Calgary, and Departments of §Medicine and ‖Critical Care, University of Alberta, and ¶Institute of Health Economics, Edmonton, Alberta, Canada; and ‡Renal Unit, Addenbrooke's Hospital, Cambridge, United Kingdom*

Table 1. Characteristics of RCT included for meta-analysis of the RR for failure to induce remission (complete or partial)[a]

Study	Jadad Score	Year	Follow-Up (mo)	MMF					CYC				
				Dosage (g/d)	Patients (*n*)	Pure Class V	Treatment Failures	Deaths/ ESRD	Dosage	Patients (*n*)	Pure Class V	Treatment Failures	Deaths/ ESRD
Flores-Suarez and Villa (19)	2	2004	12	NR	10	3	4	0/0	NR	10	0	8	3/0
Ong *et al.* (14)	3	2005	6	2	19	0	8	0/1	0.75 to 1 g/m^2 intravenously	25	0	12	0/0
Ginzler *et al.* (13)	3	2005	6	3	71	14	34	0/0	0.75 to 1 g/m^2 intravenously	69	13	48	0/2
								4/4[b]					8/7[b]
Chan *et al.* (18)	2	2005	12	2	33	0	1	0/0	2.5 mg/kg orally	31	0	2	0/2
			63[b]					0/0[b]					2/2[b]

[a]CYC, cyclophosphamide; MMF, mycophenolate mofetil; NR, not reported; RCT, randomized, controlled trial; RR, relative risk.
[b]Extended follow-up.

Clin J Am Soc Nephrol 2: 968-975, 2007. doi: 10.2215/CJN.01200307

Lupus (2005) 14, 65–71
www.lupus-journal.com

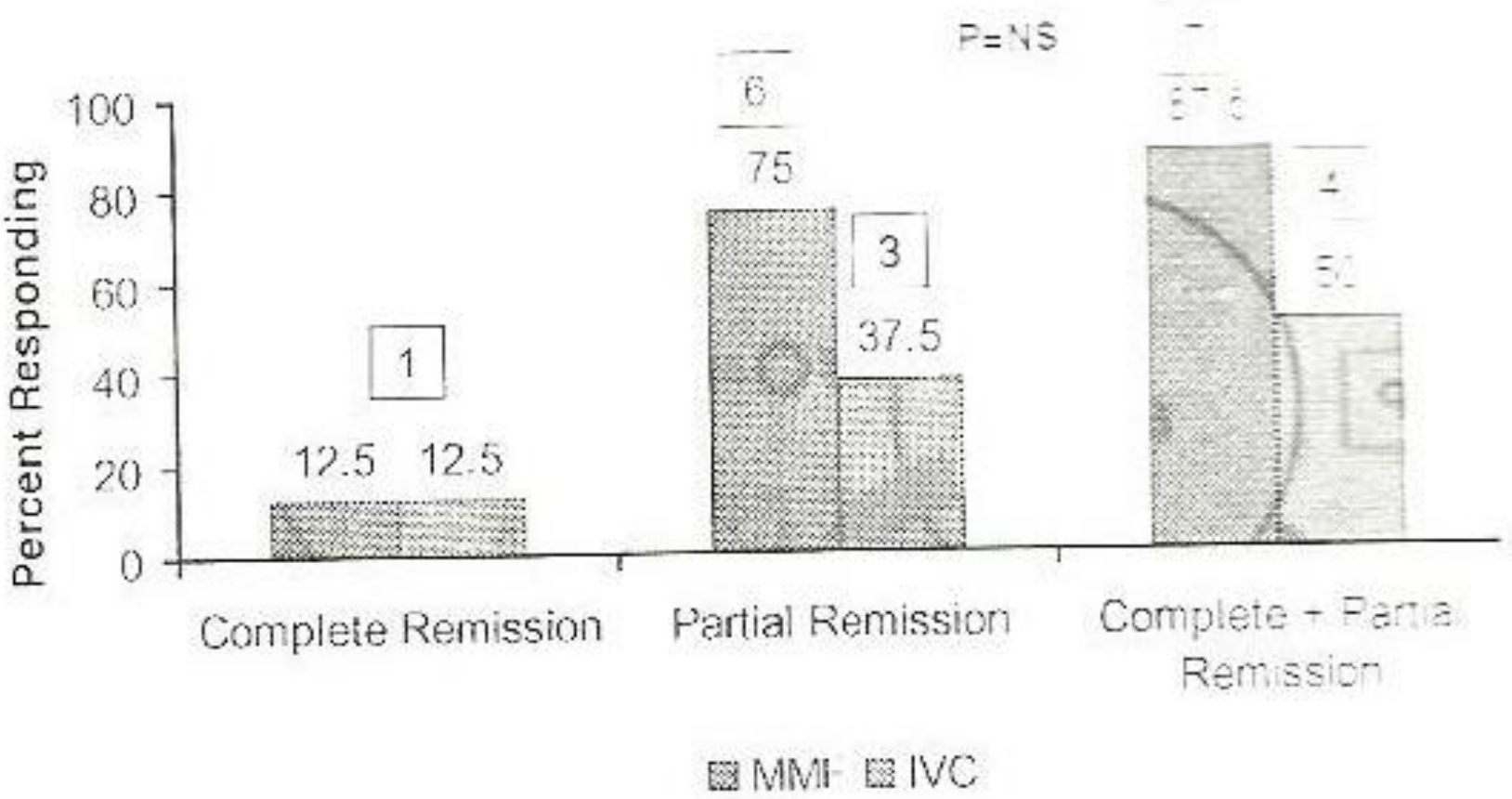
Membranous lupus nephritis

HA Austin[1] and GG Illei[2]*
[1]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, USA; and [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, USA

Table 2 Treatment options and recommendations for membranous lupus nephritis

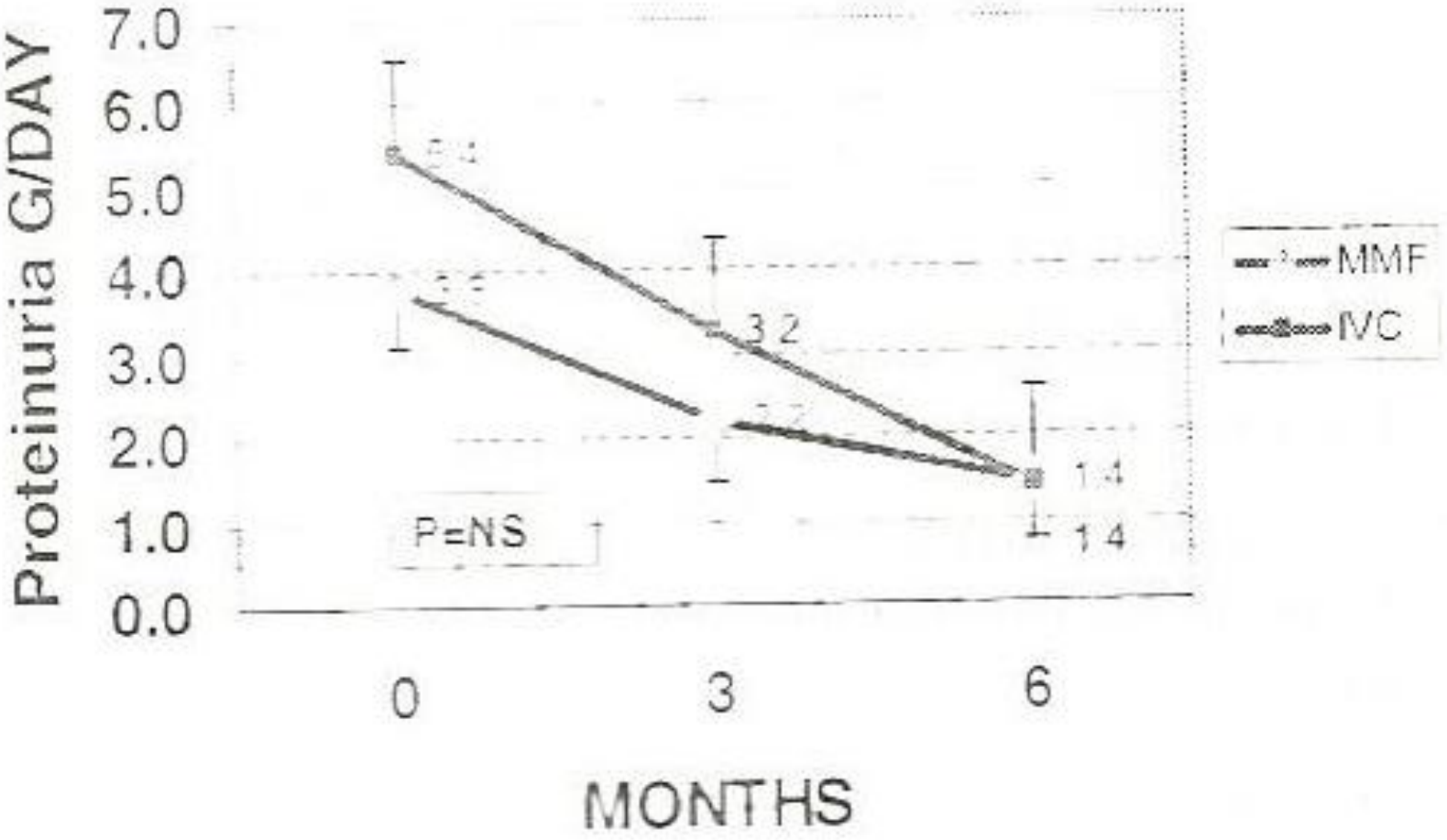
Treatment	*Membranous LN*	*Mixed membranous and proliferative LN*
Immunosuppressive		
Non-nephrotic proteinuria	Directed by extrarenal manifestations	
Nephrotic proteinuria	1) First line: high-dose alternate day prednisone (e.g., 1–2 mg/kg) for two months; taper to ~0.25 mg/kg alternate days within three to four months 2) Optional: • Pulse cyclophosphamide, ≤1 g/m^2 every one to three months • Cyclosporine, ≤5 mg/kg/day • Azathioprine 2 mg/kg • Pulse methylprednisolone, alternating with cyclophosphamide (or chlorambucil): pulse methylprednisolone, 1 g/day for three days followed by 27 days of prednisone (0.5 mg/kg/day) alternating with 30 days of cyclophosphamide 2 mg/kg/day (or chlorambucil 3–6 mg/m^2/day); three cycles of each therapy over a six-month period • Oral cyclophosphamide, 2 mg/kg/day	Treat as the proliferative component
Background	• Angiotensin antagonists for renoprotection and to minimize proteinuria • Tight control of hypertension • Control of hyperlipidemia • Control other cardiovascular risk factors (obesity, smoking, consider aspirin, if high titer anticardiolipin antibodies are present)	

Remission Rates in LMN
MMF (n=8) vs. IVC (n=8)



Radhakrishnan, Ginzler, Appel ASN Abs. 2005

Evolution of Proteinuria

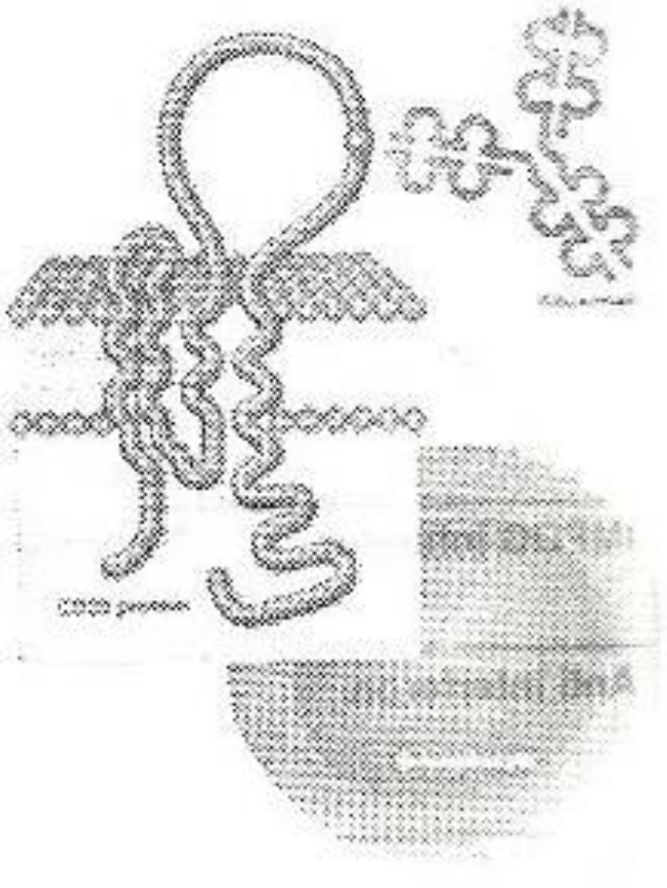


Radhakrishnan

Rituximab: Anti-CD20 Monoclonal Antibody

Rituximab - FDA approved for the treatment of relapsed or refractory, CD20-positive B-cell NH Lymphomas and Rheumatoid Arthritis

- Chimeric murine/human monoclonal antibody
- Used in many glomerular diseases in uncontrolled trials
- Over 300 SLE pts treated in uncontrolled trials



Protocol for the LN Assessment with Rituximab (LUNAR) Study

- Randomized , double blind, placebo-controlled 52 week trial of efficacy and safety of RTX in ISN III/IV LN
- 140 pts w LN randomized to MMF 3g/d + pbo vs MMF 3g/d + RTX. Protocol steroid taper.
- End-point complete or partial response.
- Secondary EP time to response, reduction extra-renal disease, decrease in anti-dsDNAab.
- All 140 patients randomized by 12/07.

Appel et al. ASN 2006

G. Appel's Treatment of DPLN

- In past Standard NIH Rx - monthly IV pulse Cytoxan + IV pulse solumedrol x 6 mo with q 3 mo follow up doses (Effective but Toxic)

- Pts at high risk for further Cytoxan – Eurolupus protocol - IV cytoxan 500 mg q 2wks x 6 doses then AZA or MMF

- Black Pts and those at high risk for progression – IV cytoxan + IV solumedrol induction x 6 mo with MMF or AZA follow (Miami Trial)

- MMF 2-3g/day x 6 mo Ginzler-Appel Study - ALMS

Sequential therapies for proliferative lupus nephritis

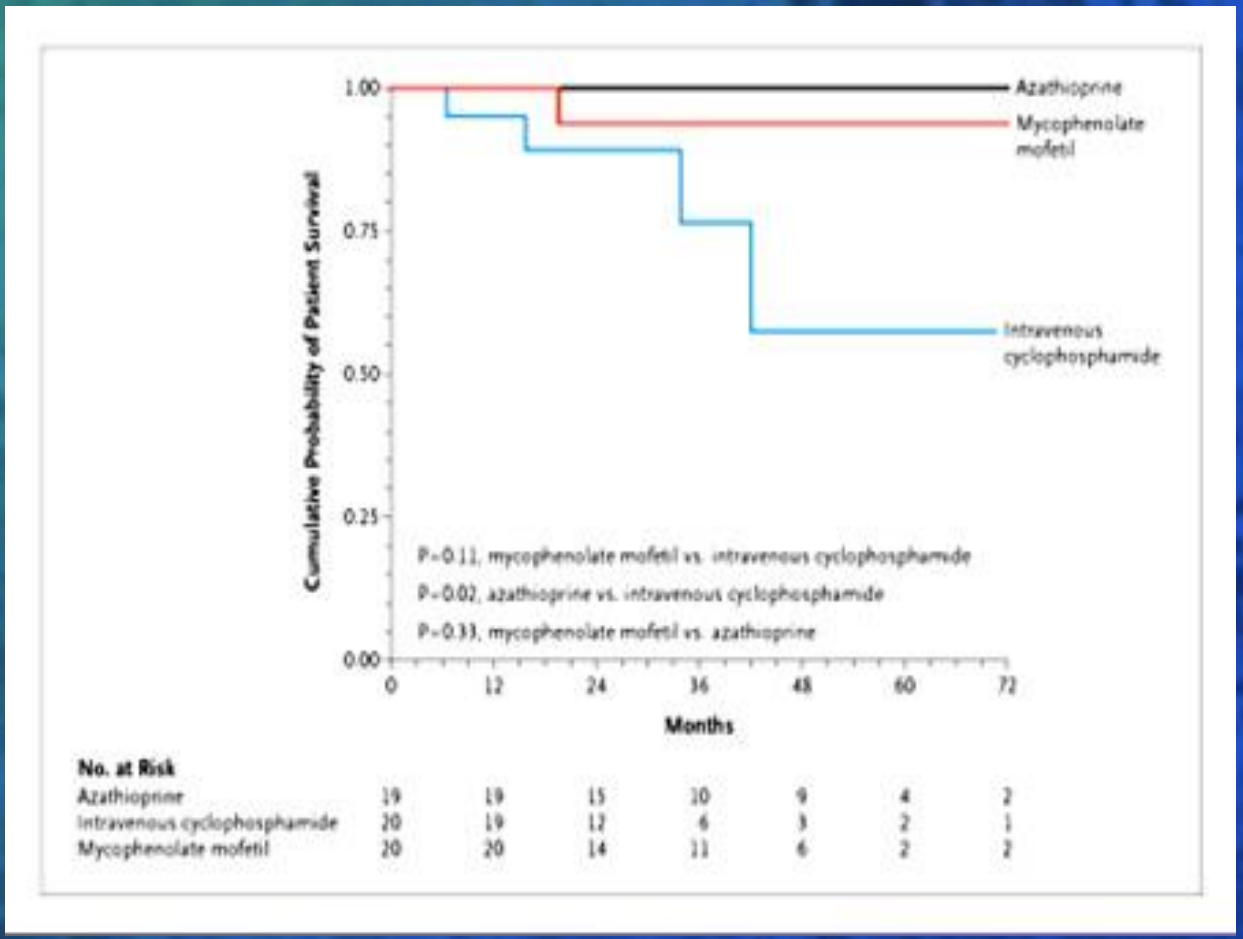
Contreras et al N Engl J Med 350,971, 2004

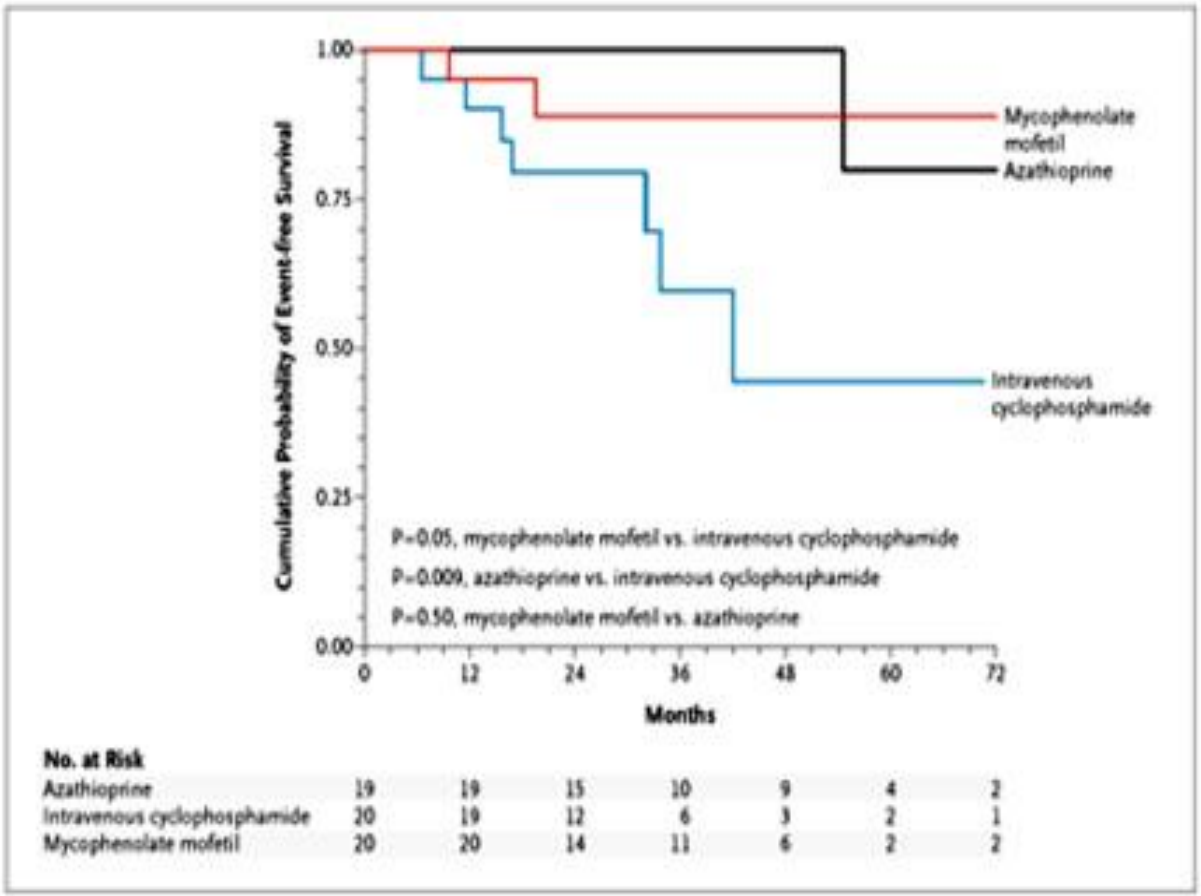
Induction therapy

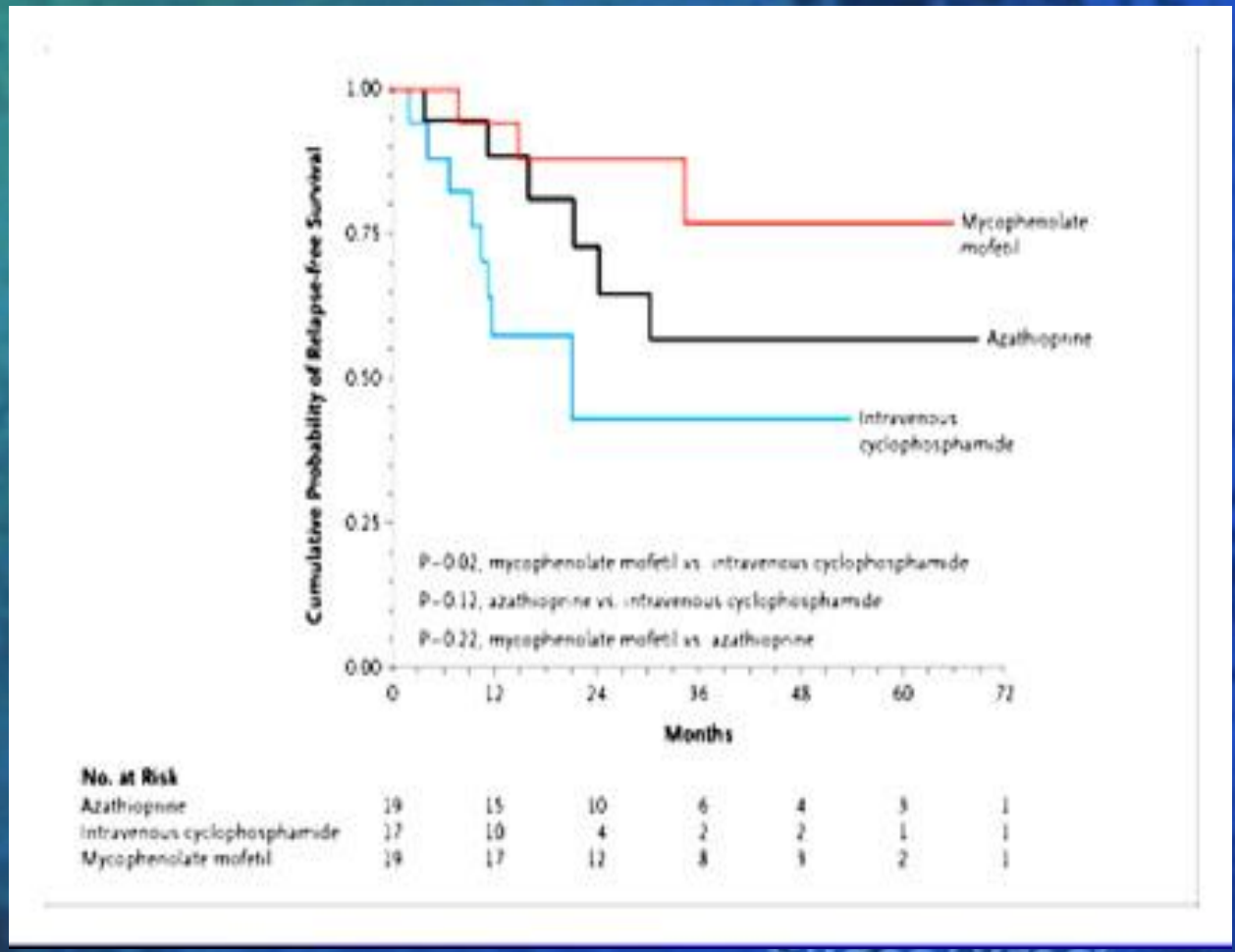
7 monthly iv Cyclophosphamide pulses + prednisone

Maintenance (Randomized)

- Cyclophosphamide pulses every 3 months (20 pts)
- Azathioprine 0.5-4mg/Kg/day (19 pts)
- Mycophenolate mofetil 0.5-3g/day (20 pts)







Maintenance therapy

MMF compared with AZA following induction with either CYC or MMF for 6 months.

No significant differences.

Chan TM, Tse KC, Tang CS, Mok MY, Li FK. Long term study of MMF as continuous induction and maintance treatment for diffuse proliferatve lupus nephritis . J Am Soc Nephrol 2005; 16:1076-1084

Maintenance therapy

MMF did not increase the rate of death, ESRD, renal relapse comparing with AZA.

Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis (MAINTAIN)

Aspreva Lupus Management Study, maintenance therapy (ALMNS)

Zhu B, Chen N, Lin Y, et al. MMF in induction and maintenance therapy of severe lupus nephritis: a meta analysis of randomized controlled trials. Nephrol Dial Transplant 2007;22:1933-1942

Azathioprine

87 European pts with biopsy proven nephritis (8 class IIIVc and 79 class IV-Vd) and mean CCI: 65 mil/min.

The results are limited by the exclusion of pts with severe renal impairment (rarity of crescents), 70% Caucasian and short duration of trial.

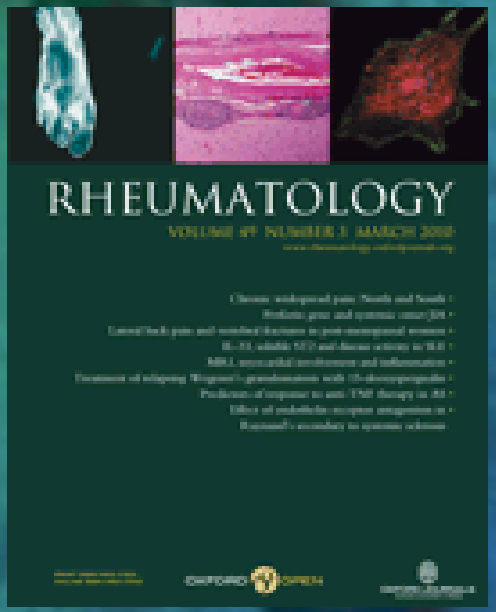
CYC is superior to AZA as induction.

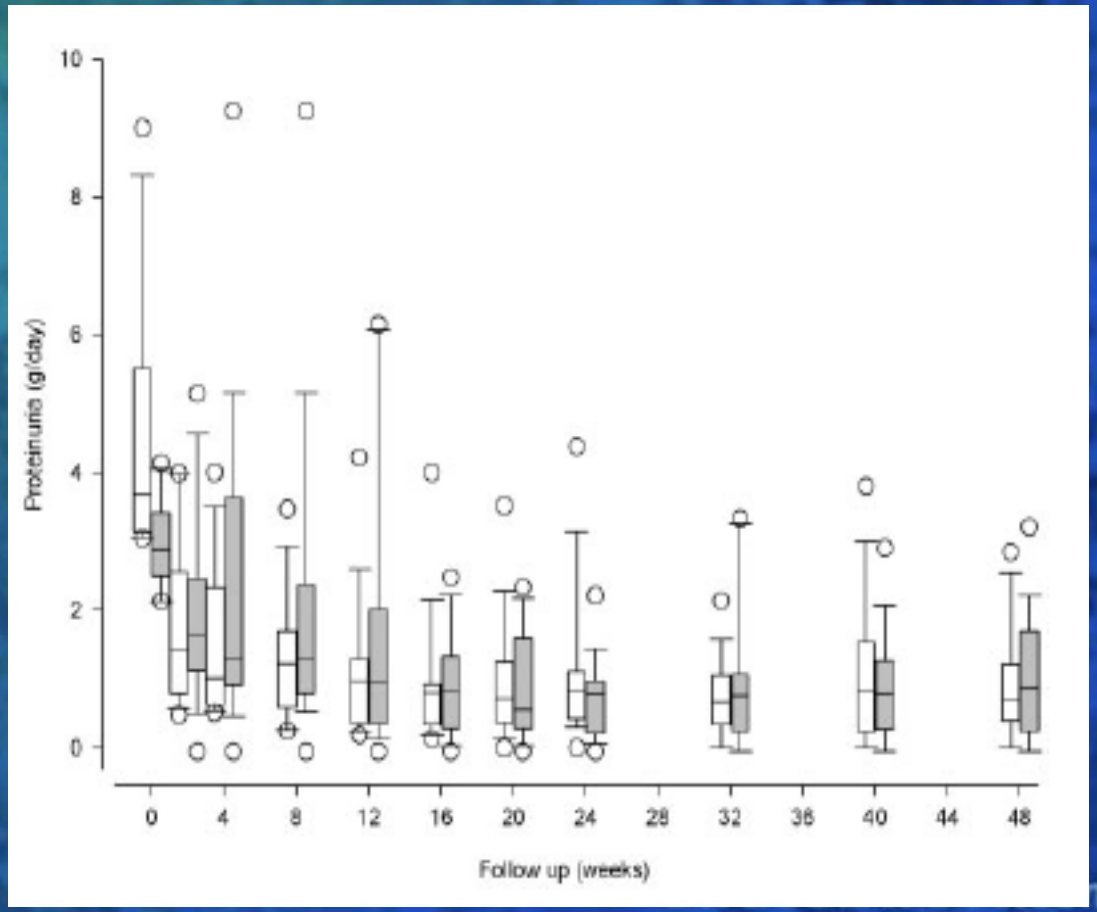
Grootscholten C, Bajema IM, Florquin S, et al. Azathioprine/methyprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized control trial. Kidney Int 2006;70:732-742.

Rheumatology 2008;47:1678–1681
Advance Access publication 27 August 2008
doi:10.1093/rheumatology/ken335

Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis

C.-C. Szeto[1], B. C.-H. Kwan[1], F. M.-M. Lai[2], L.-S. Tam[1], E. K.-M. Li[1], K.-M. Chow[1], W. Gang[1] and P. K.-T. Li[1]



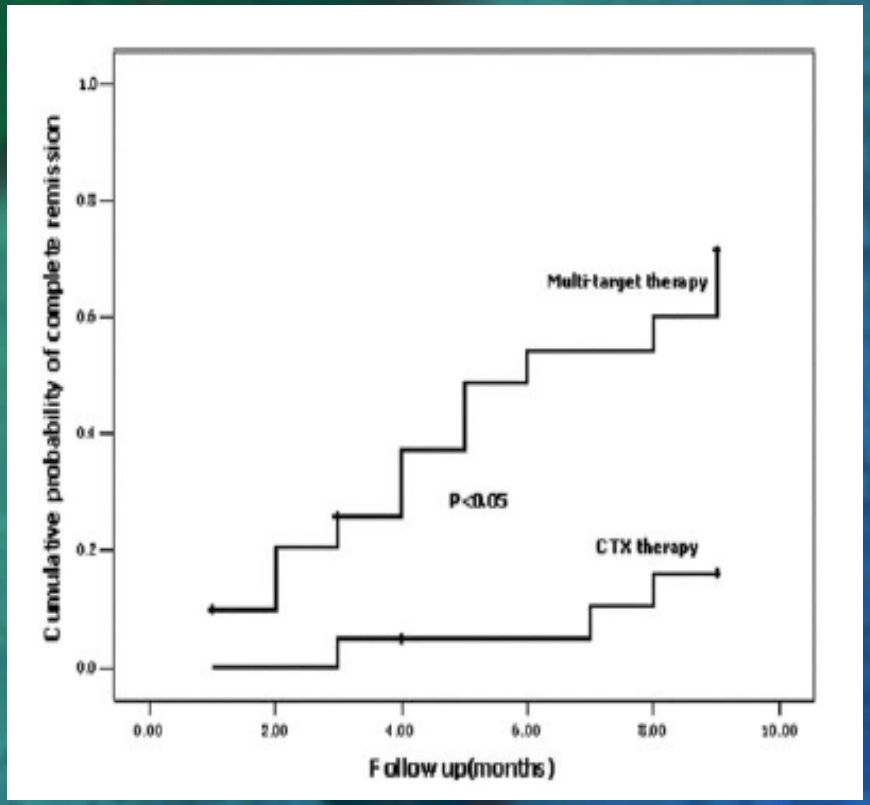


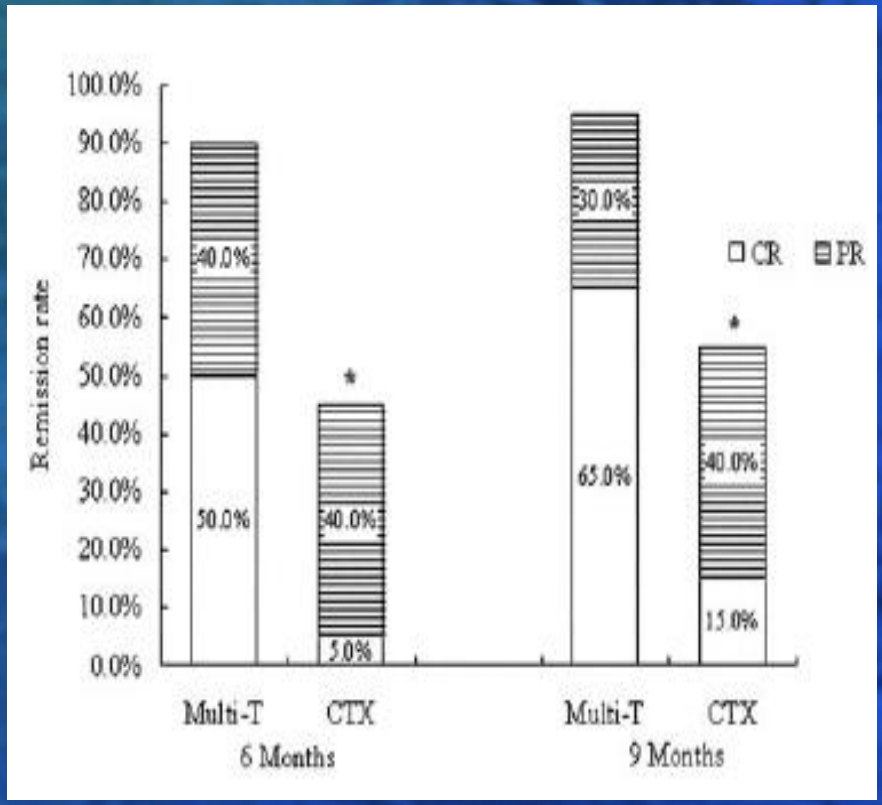
CLINICAL RESEARCH www.jasn.org

Successful Treatment of Class V+IV Lupus Nephritis with Multitarget Therapy

Hao Bao, Zhi-Hong Liu, Hong-Lang Xie, Wei-Xin Hu, Hai-Tao Zhang, and Lei-Shi Li

Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China





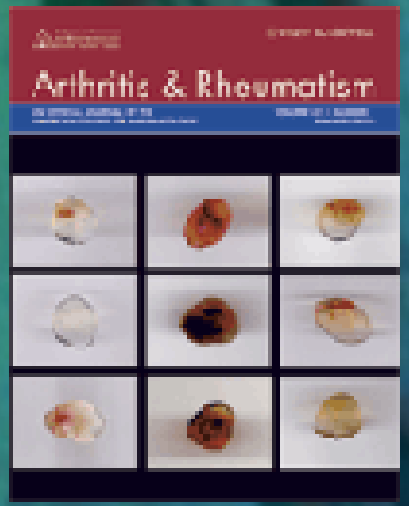
J Am Soc Nephrol 19: 2001–2010, 2008

ARTHRITIS & RHEUMATISM
Vol. 54, No. 9, September 2006, pp 2970–2982
DOI 10.1002/art.22046

Long-Term Comparison of Rituximab Treatment for Refractory Systemic Lupus Erythematosus and Vasculitis

Remission, Relapse, and Re-treatment

K. G. C. Smith,[1] R. B. Jones,[2] S. M. Burns,[2] and D. R. W. Jayne[1]



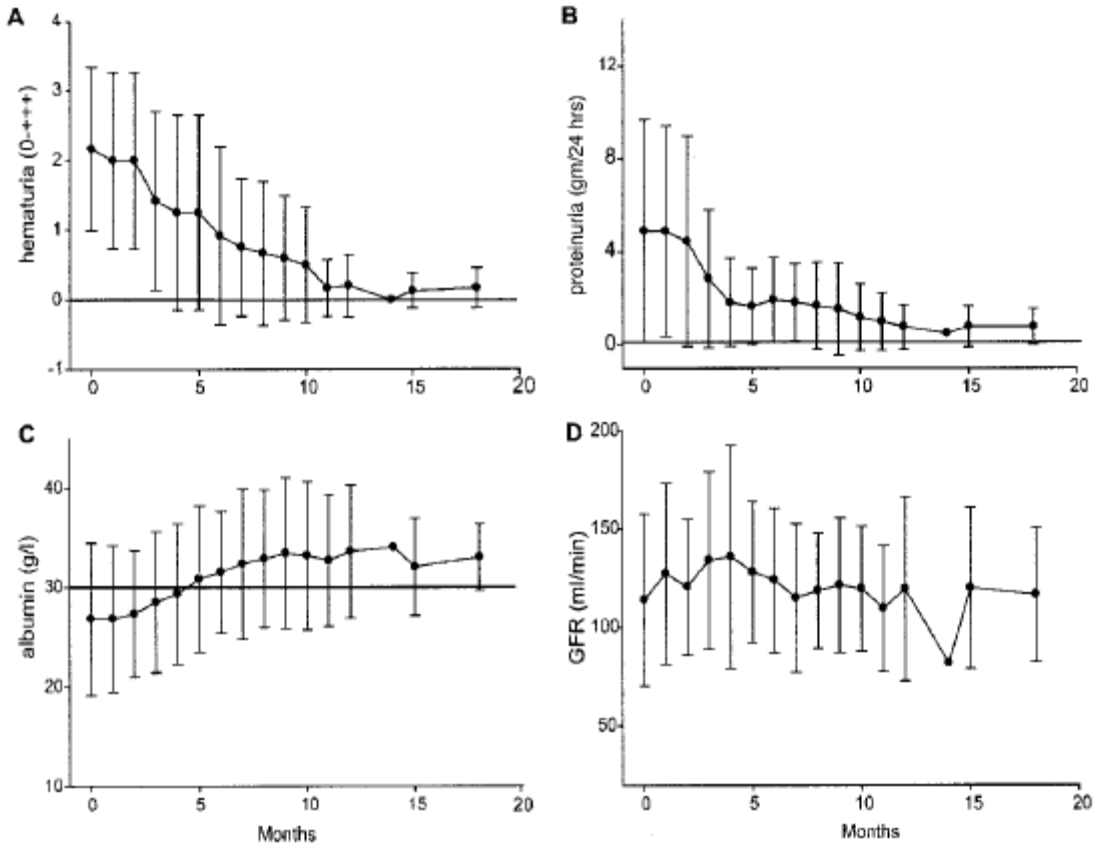


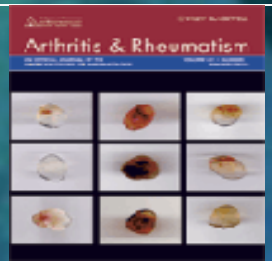
Figure 2. Response to rituximab in patients with lupus nephritis. **A**, Hematuria. **B**, Proteinuria. **C**, Serum albumin. **D**, Glomerular filtration rate (GFR), as calculated using the Cockcroft-Gault equation. The horizontal lines represent the upper limit of normal in **A** and **B** and the lower limit of normal in **C**. Values are the mean ± 1 SD.

Rituximab

The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial tested the efficacy and safety of rituximab versus placebo in patients with moderately-to-severely active extrarenal SLE.

No differences were noted between placebo and rituximab in the primary and secondary end points.

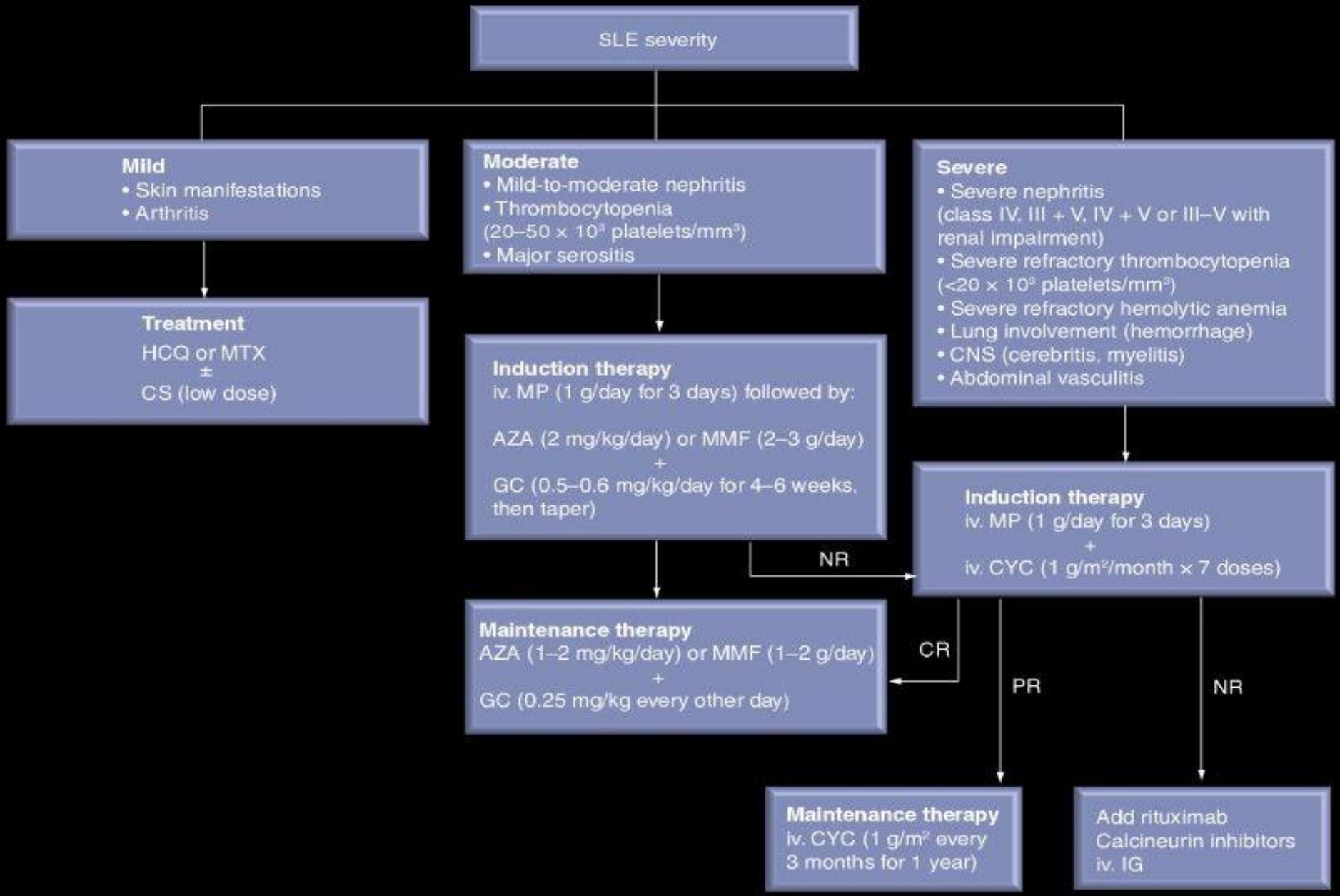
Efficacy in lupus nephritis in 2 RCTs (EXPLORER and Lupus Nephritis Research).



JT Merrill , C Neuwelt , DJ Wallace, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010 ;62(1):222-33.

Conclusions: Pilot Study of Rituximab

- Safe
- Not all patients showed B Cell depletion
- In depleters, lupus parameters appeared to improve
- ADNA titers did not change

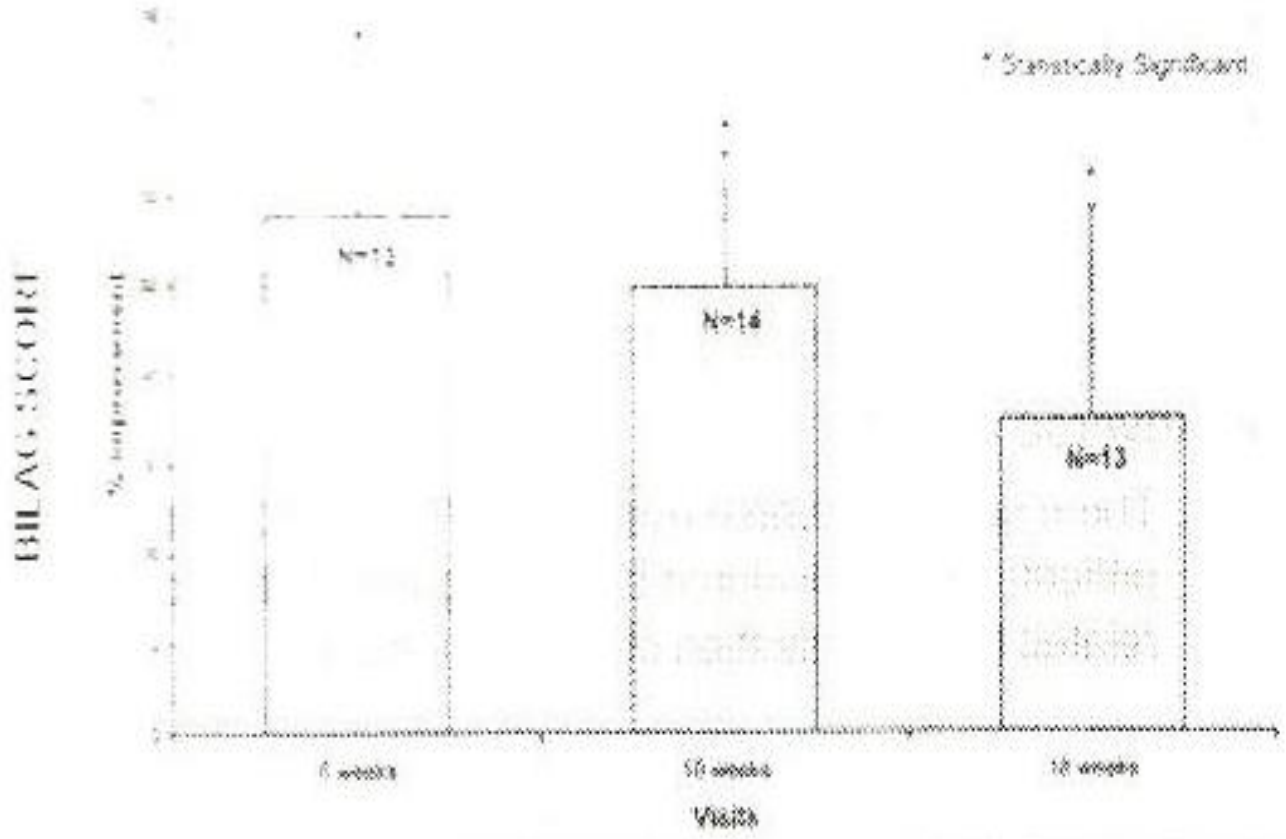


Cyclophosphamide

…All who drink of this remedy recover in a short time except those whom it does not help, who all die. Therefore it is obvious that it fails in incurable cases…

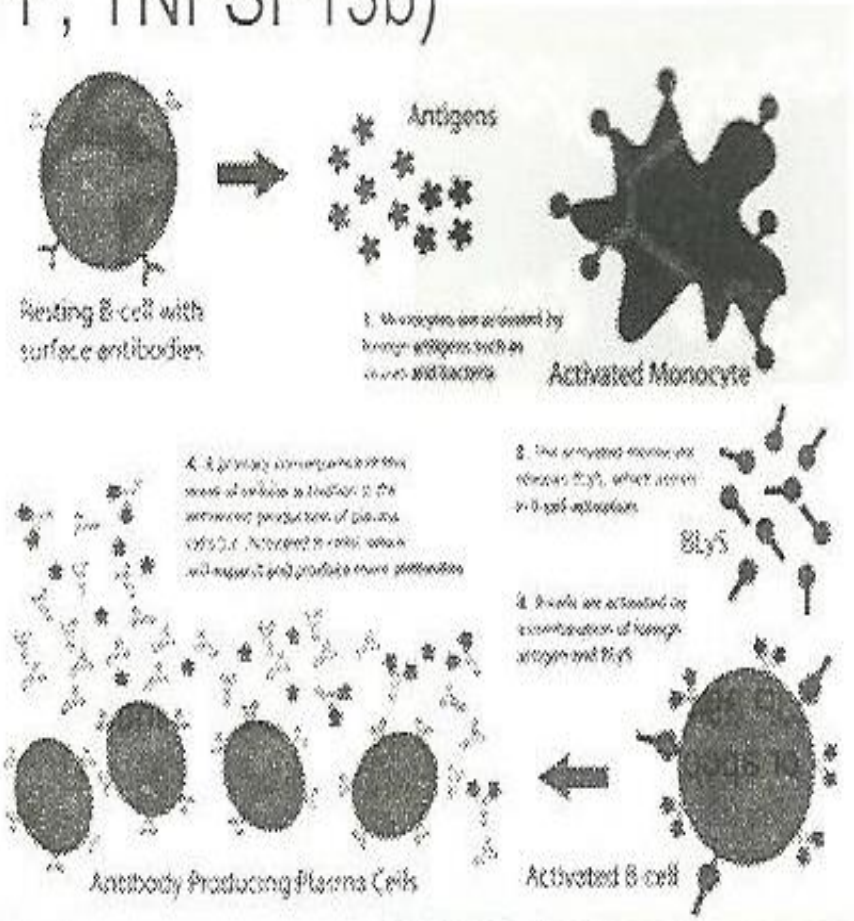
Strauss MB. Commentary. Milbank Memorial Fund Quarterly. 1969;67:80.

Epratuzumab: anti CD22 antibody
Pilot study in mod. active SLE (n=14)



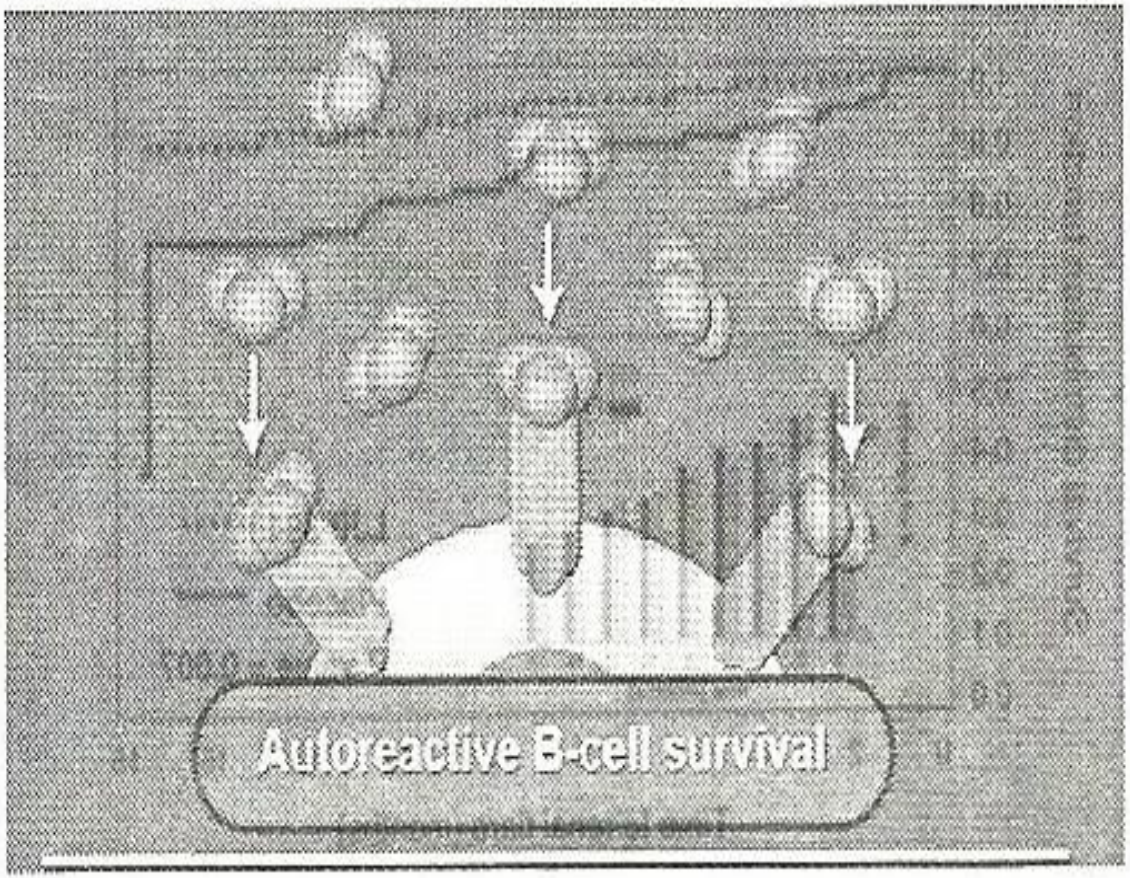
Dorner T., Arthritis Res Ther. 2006;8(3):R74.

B-Lymphocyte Survival factor (BAFF; TNFSF13b)

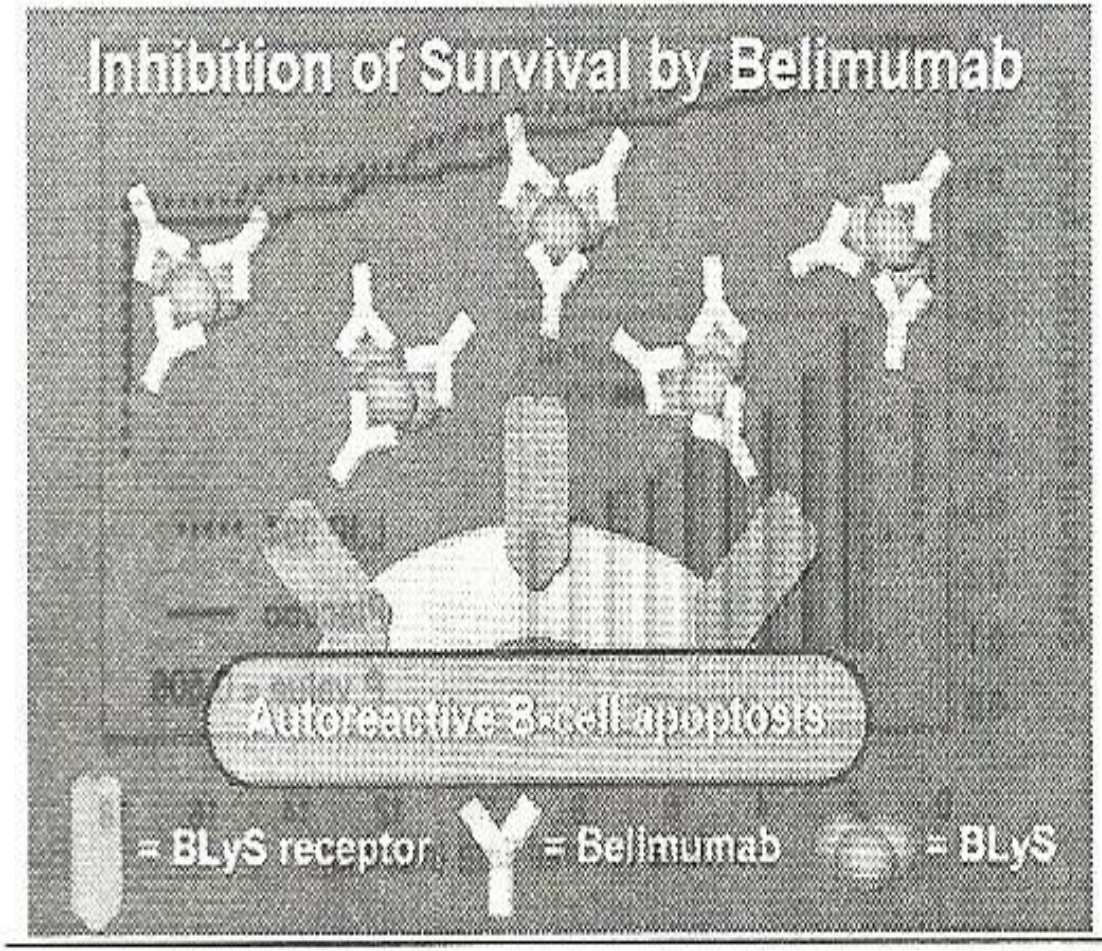


www.hgsi.com/

BLyS in Autoimmune Diseases



Belimumab: BLyS



www.hgsi.com

Belimumab (Lymphostat-B)
BLyS Antagonist

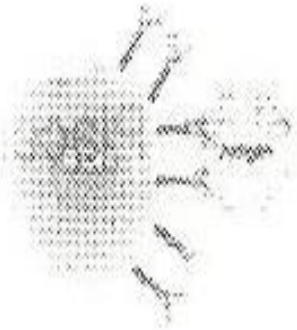
Phase 2 study completed in active SLE(n=449):

- Decreased anti-dsDNA autoantibodies
- Decrease in B-cell subsets
- Increased C4 complement
- Reduced risk of SLE flares
- Decreased SLE disease activity (SELENA SLEDAI and Physician's Global Assessment
- Improved quality of life
- Reduced need for steroid increase

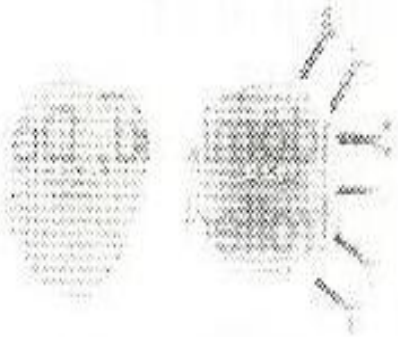
EULAR 2006

Induction of B Cell Tolerance

B cell activation

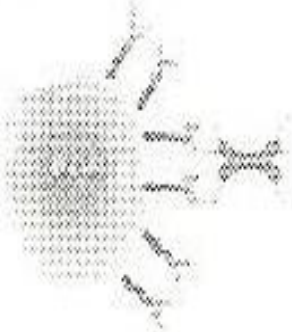


Signal 1 - Ag cross-links Ab



Signal 2 - T cell contacts B cell

B cell tolerance



Signal 1 - Toleragen cross-links Ab

Lack of Signal 2 results in anergy or cell death

Proliferative LN (I)

ACE inhibitors and ARBS, <130/80 mmHg (Grade 1B).

Mild focal proliferative LN (defined as less than 25 percent of the glomeruli affected on light microscopy and no necrotizing lesions or crescent formation, normal blood pressure and serum creatinine, and subnephrotic proteinuria), suggest a trial of glucocorticoids alone (Grade 2C).

60 mg/day for one week, tapered to 30 mg every other day for a total of three months.
Goals of therapy are loss of hematuria and reduced proteinuria.
Patients who do not respond or who progress are treated as if they have diffuse proliferative LN.

Proliferative-Diffuse LN (II)

Moderate to severe focal proliferative or diffuse proliferative LN, recommend initiation glucocorticoids given with either iv cyclophosphamide or oral mycophenolate mofetil (MMF) (Grade 1A).

The choice between iv cyclophosphamide or oral MMF depends upon the clinical features (eg, MMF is preferred in blacks and Hispanics) and upon patient preference (eg, a young woman may want to avoid the potential ovarian toxicity of cyclophosphamide).

Proliferative-Diffuse LN (III)

iv. cyclophosphamide in patients with more severe disease (eg, substantial elevation in serum creatinine and/or crescents on renal biopsy) (Grade 1B)-short course regimen.

MMF-based regimen is chosen, suggest the regimen in the ALMS trial.

Severe active disease (eg, acute renal failure, florid crescentic glomerulonephritis, severe extrarenal disease), glucocorticoid therapy be initiated with intravenous pulse methylprednisolone (500 to 1000 mg given over 30 minutes daily for three days) to induce a rapid immunosuppressive effect since a response to intravenous cyclophosphamide is not seen for 10 to 14 days (Grade 1B).

Proliferative-Diffuse LN (IV)

Maintenance — at least 18 to 24 months or longer (Grade 1B). Recommend azathioprine or MMF over cyclophosphamide for maintenance therapy (Grade 1B).

The maintenance regimen depends upon the initial induction therapy: For patients who received iv. cyclophosphamide induction therapy, the preferred regimen is azathioprine (2 mg/kg per day to a maximum of 150 to 200 mg/day) (Grade 1C).

For patients who receive MMF as induction therapy, recommend MMF should be continued as maintenance therapy at a dose of 1000 to 2000 g/day. Low-dose oral prednisone at a dose of 0.05 to 0.20 mg/kg per day is continued in all patients receiving maintenance therapy.

Membranous (I)

10-20% -mainly proteinouria with normal renal function.

ACE inhibitors and ARBS, <130/80 mmHg (Grade 1B).

Immunosuppressive therapy

- nephrotic syndrome and/or rising creatinine, or membranous lesions that are associated with focal or diffuse proliferative changes.
- pure membranous LN who do NOT show a decline in proteinuria to less than 3.5 g/day with angiotensin inhibition and rigorous control of blood pressure, or who have a rising serum creatinine (Grade 1B).

Membranous (II)

Recommend prednisone and either intravenous cyclophosphamide or cyclosporine (NIH trial) (Grade 1B).

Relapsing or resistant disease — In the NIH trial, relapse of proteinuria occurred in 20 percent of patients treated with cyclophosphamide and 60 percent of those treated with cyclosporine.

Membranous (III)

Among patients who do not respond to initial therapy with cyclosporine, recommend treatment with cyclophosphamide (Grade 1B).

Among patients who respond to but relapse after initial treatment cyclosporine, either intravenous cyclophosphamide or a repeat course of cyclosporine may be used.

Among the infrequent patients who do not respond to or relapse after initial intravenous cyclophosphamide therapy, suggest a trial of cyclosporine (Grade 2C).

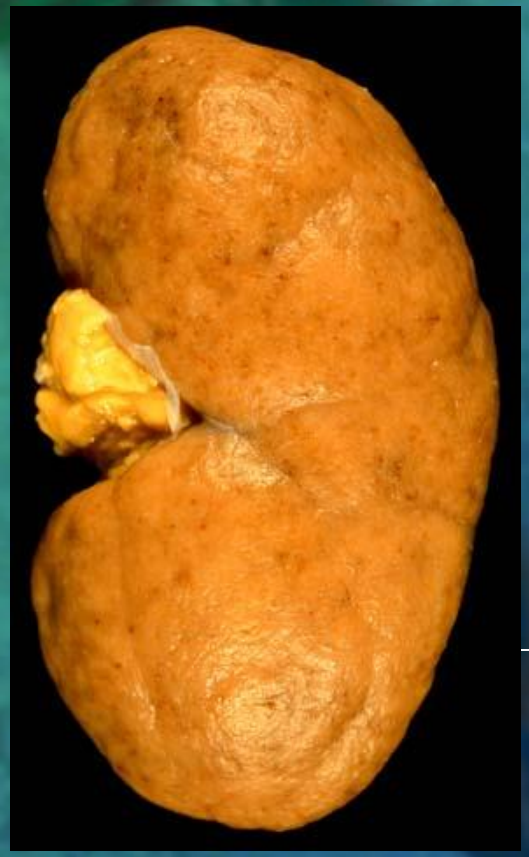
Conclusions

In proliferative lupus nephritis, MMF reasonable alternative as an induction therapy for moderate to moderately severe disease.

AZA in mild disease

Minutolo R, Bellizzi V, Cioffi M et al. Postdialytic rebound of serum Phosphorus : Pathogenetic and clinical insights . J Am Soc Nephrol 2002; 13:1046-1054

…No matter how important are new discoveries and methods , they cannot be considered to have reached fulfillment until generally applied to sick…



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