The Treatment of Lupus Nephritis
Budapest Nephrology School

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Learning Objectives

1. To be familiar with the important studies of the past 3 decades that examined the management of lupus nephritis.
2. To understand the source of the evidence for cyclophosphamide as the treatment of choice for severe lupus nephritis.
3. To review common pitfalls in the treatment of lupus nephritis
4. An update on recent studies of proliferative and membranous lupus

Treatment of Diffuse Proliferative Lupus Nephritis with Prednisone and Combined Prednisone and Cyclophosphamide

- 50 patients with diffuse proliferative lupus nephritis
- randomized to prednisone alone or with daily oral cyclophosphamide

prednisone →

prednisone + CTX →

Donadio et al, N England J Med 1978

Treatment of Diffuse Proliferative Lupus Nephritis with Prednisone and Combined Prednisone and Cyclophosphamide

Results

- both groups had same degree of improvement over first 6 months
- prednisone-only group had more renal relapses
- the addition of a second agent did not improve the *initial* response rate
- patients with advanced disease ended up on dialysis with either therapy

Donadio et al, N England J Med 1978

Donadio et al: What it Teaches Us Three Decades Later

- it's the corticosteroid that works the fastest
- But don't be lulled into leaving them just on corticosteroids: corticosteroids alone is associated with more relapses and worse renal outcome
- use a second agent, *but you don't have to do this right away*
- patients with a lot of established renal damage don't do well, no matter what

The Important Papers :

Felson; N Engl J Med 1984

- pooled analysis of outcome trials of lupus nephritis
- 8 trials (including Donadio's)
- better outcome with corticosteroids + AZA or corticosteroids + CTX than steroids alone
- *less renal deterioration with AZA compared to CTX*
- *trend to more deaths in the cyclophosphamide groups*

The Important Papers:

Austin; N Engl J Med 1986

Outcome of 5 NIH protocols for lupus nephritis 1969 – 1981

1) High dose oral prednisone 4-8 weeks, with taper;
2) AZA po + low dose prednisone
3) CTX po + low dose prednisone
4) AZA + CTX po + low dose prednisone
5) IV CTX + low dose prednisone

Austin N Engl J Med 1986: Renal Survival

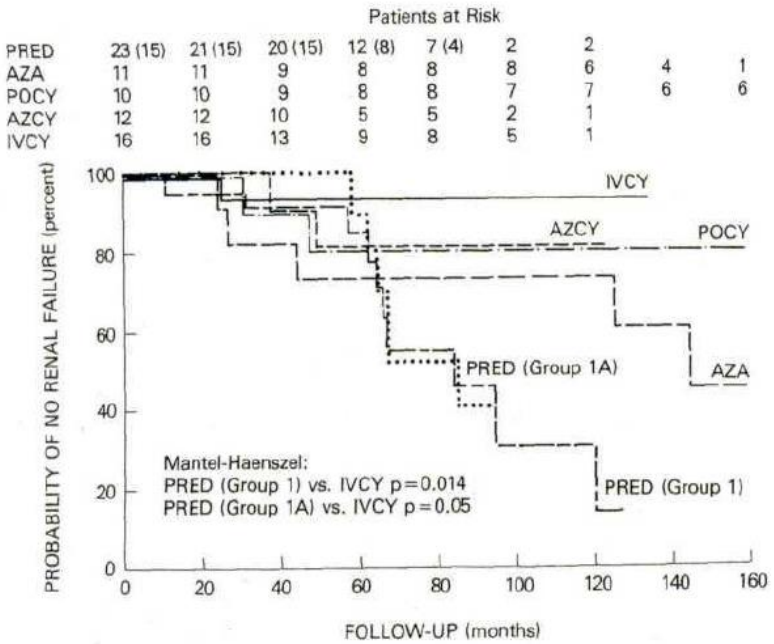


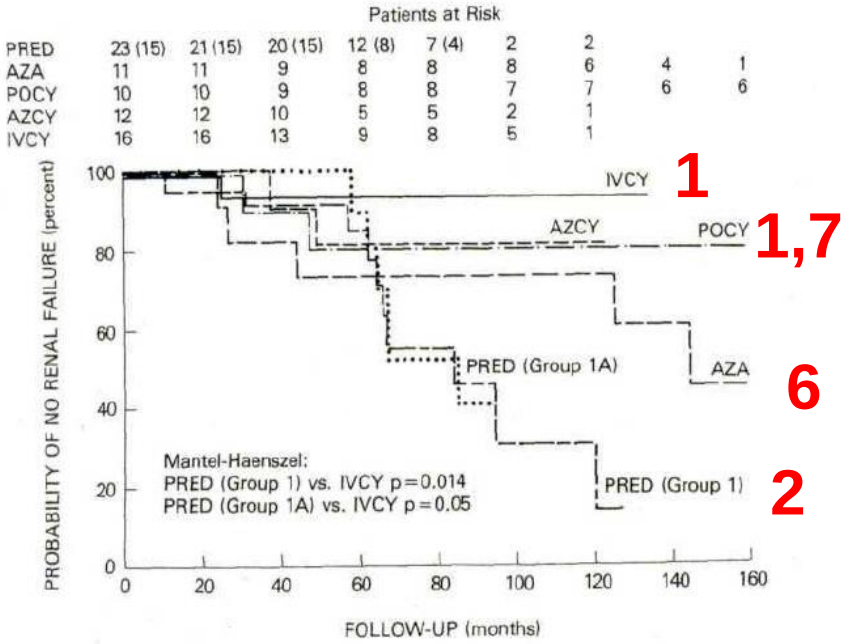
Figure 3. Probability of Maintaining Life-Supporting Renal Function, According to Treatment Group, in 72 High-Risk Patients Identified by the Presence of Chronic Histologic Changes.

PRED denotes prednisone, AZA azathioprine, POCY oral cyclophosphamide, AZCY combined oral azathioprine and cyclophosphamide, and IVCY intravenous cyclophosphamide. Under the heading "Patients at Risk," numbers in parentheses refer to Group 1A. The 95 percent confidence limits at seven years for Groups 1, 1A, and 2 to 5 were 0.73 to 0.23, 0.76 to 0.06, 0.98 to 0.48, 1.00 to 0.55, 1.00 to 0.57, and 1.00 to 0.81, respectively.[23]

Austin N Engl J Med 1986: *The Small Print*

- this was not a contemporaneous study
  - Groups 1*, 2 and 3 – 1969-1976
  - Groups 4,5 – 1973 – 1981
  - *Group 1- in both eras (1 and 1a)
- varying duration of follow-up
- no statistical differences in outcome among IV CTX, AZA/CTX, PO CTX, and AZA

Austin N Engl J Med 1986: Renal Survival



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!

The Influence of this Paper

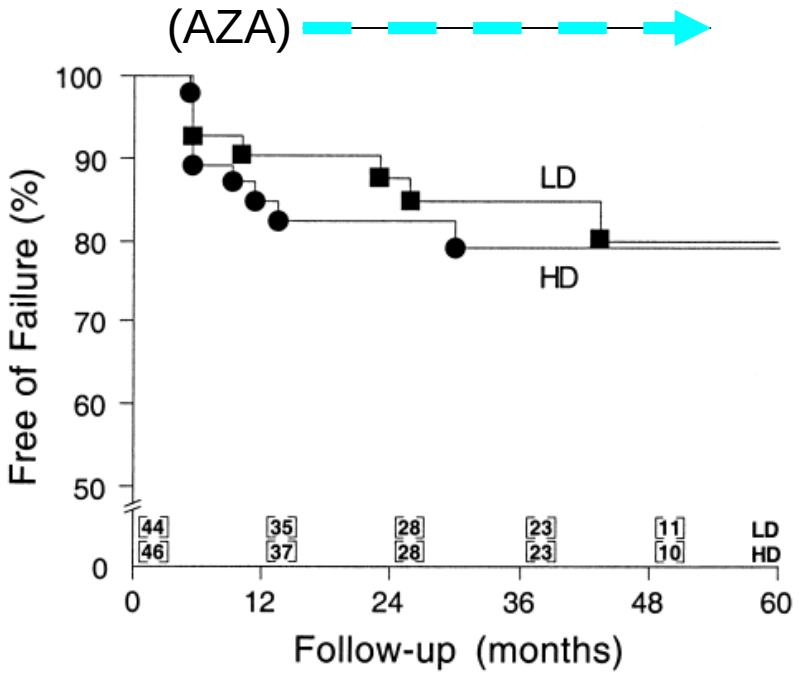
Never has so much practice been influenced by so few patients !

Low Dose versus High Dose Cyclophosphamide

- high dose (monthly pulses X 6) then quarterly pulses X 2

versus

- low dose (500 mg q2weeks X 6) followed by azathioprine
- same renal outcome
- twice as many infections in the high-dose group



Houssiau et al Arthr Rheum 2002

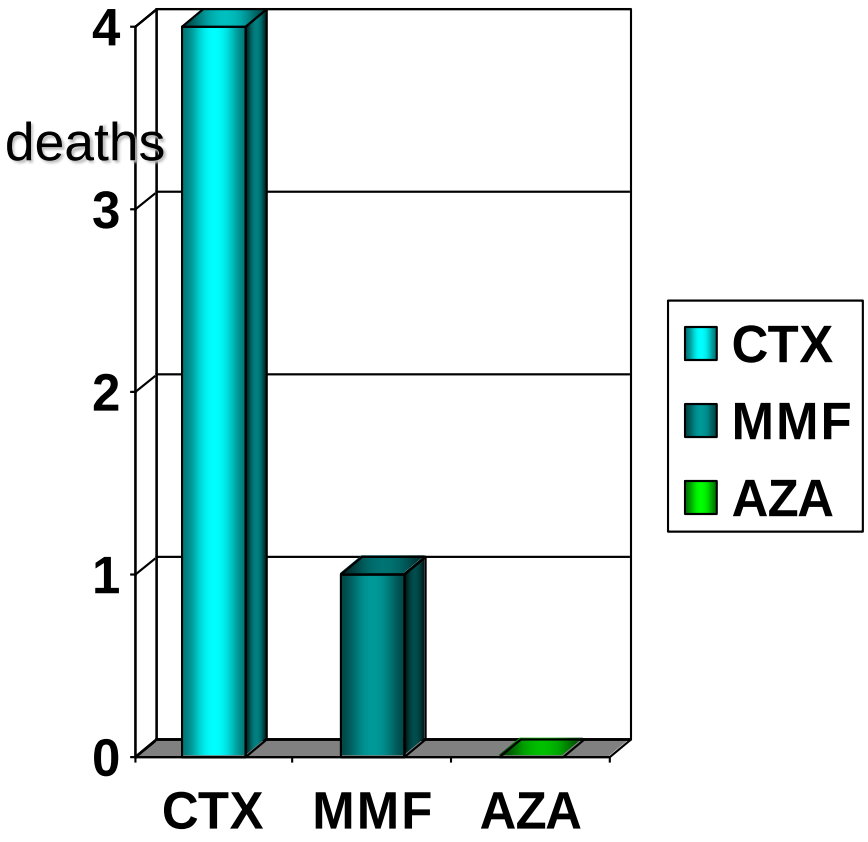
The Important Papers

Contreras; N Engl J Med 2004

- 59 pts (58 with WHO III or IV)
- all received IV CTX “induction” for 3 mos
- then randomized to
  - continued IV CTX q 3 months, *or*
  - azathioprine (AZA), *or*
  - mycophenolate mofetil (MMF)
- stratified by Black or non-Black race

The Important Papers

Contreras; N Engl J Med 2004

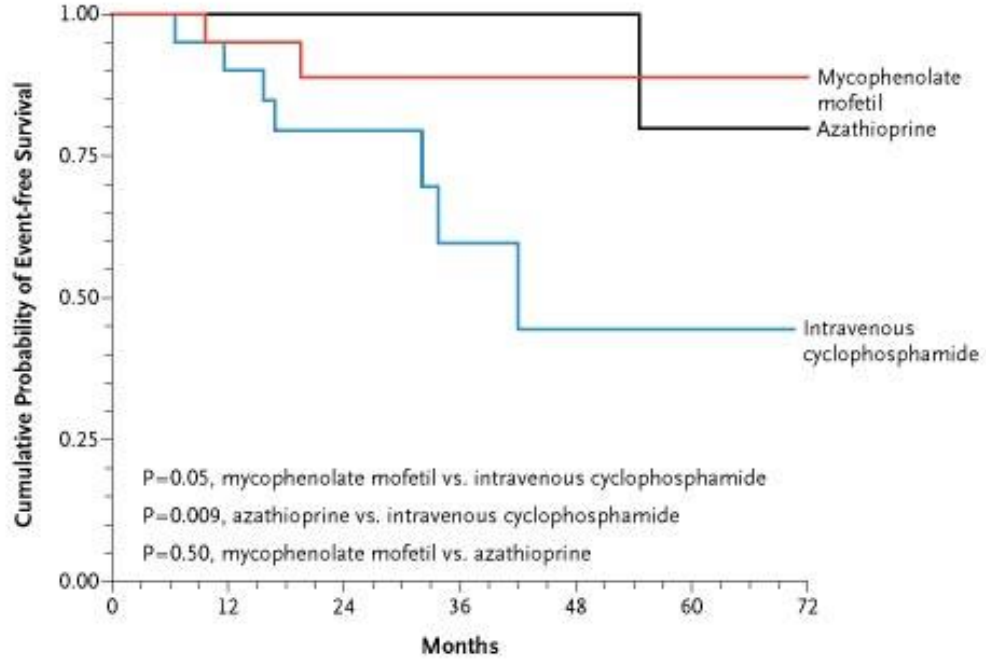


- 4 out of 5 deaths were in the cyclophosphamide group

The Important Papers

Contreras; N Engl J Med 2004

Event-free (death, CRF) survival



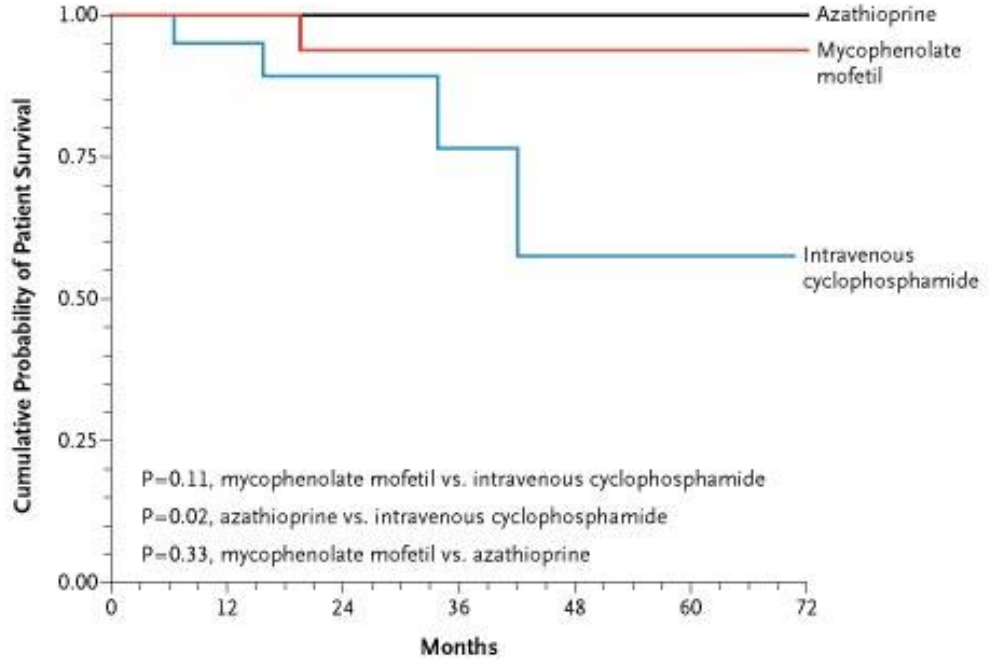
No. at Risk							
Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2

The NEW ENGLAND JOURNAL of MEDICINE

The Important Papers

Contreras; N Engl J Med 2004

Patient Survival



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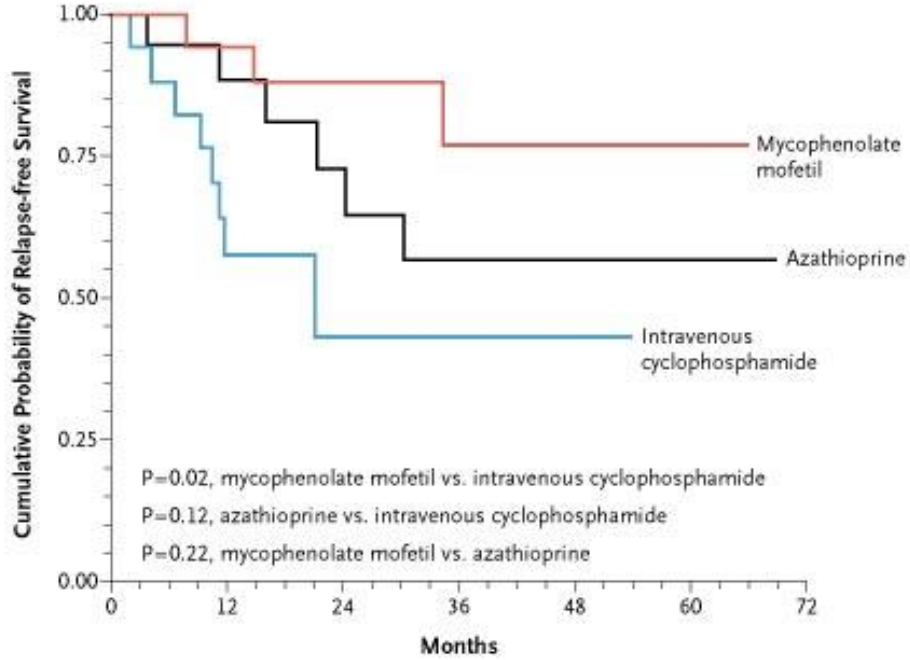
The NEW ENGLAND JOURNAL of MEDICINE

The Important Papers

Contreras; N Engl J Med 2004

Relapse-free survival



No. at Risk							
Azathioprine	19	15	10	6	4	3	1
Intravenous cyclophosphamide	17	10	4	2	2	1	1
Mycophenolate mofetil	19	17	12	8	3	2	1

} **Signal?**

The NEW ENGLAND JOURNAL of MEDICINE

The Important Papers
Contreras; N Engl J Med 2004

- azathioprine and MMF come out well in this study
- tendency for fewest relapses in MMF group, but AZA did well too
- this is Level 1 evidence for reconsideration of the dogma of IV CTX as “standard of therapy” for lupus nephritis
- doesn’t address non-CTX induction therapy

Non-CTX Induction:

Chan N Engl J Med 2000

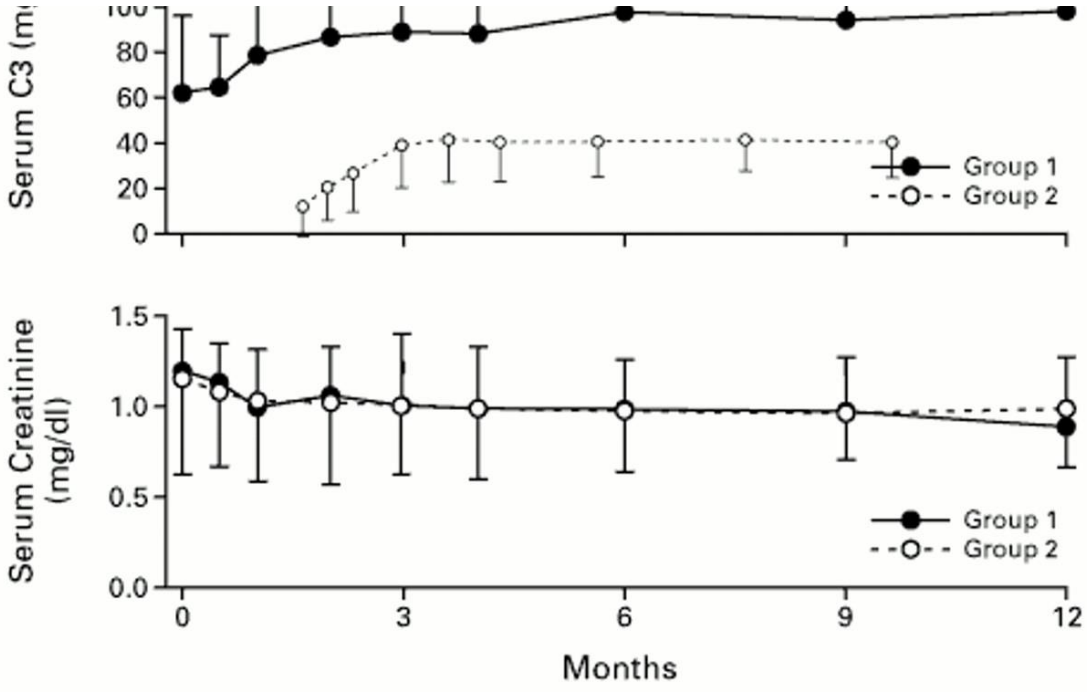
Prednisone +

- MMF 2g/d X 6 m, then 1g/d X 6m

or

- CTX 2.5 mg/kg/d x 6m, then AZA 1.5 mg/kg/d X 6m

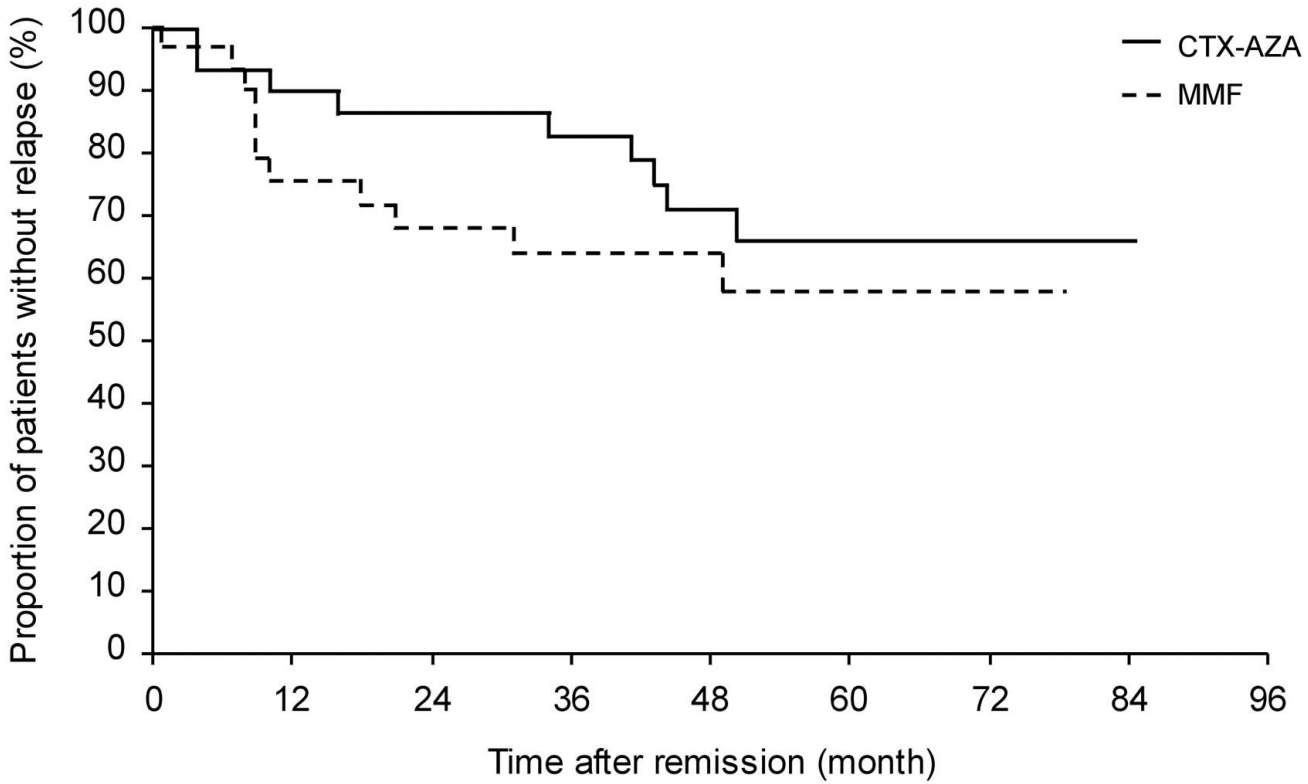
Cyclophosphamide vs MMF Induction



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

Chan et al N Engl J Med 2000

Long-Term Follow-Up MMF vs CTX/AZA



Number of patients	30	27	24	22	15	9	4	CTX-AZA
	32	20	18	14	11	7	4	MMF

Chan, T.-M. et al. J Am Soc Nephrol 2005;16:1076-1084

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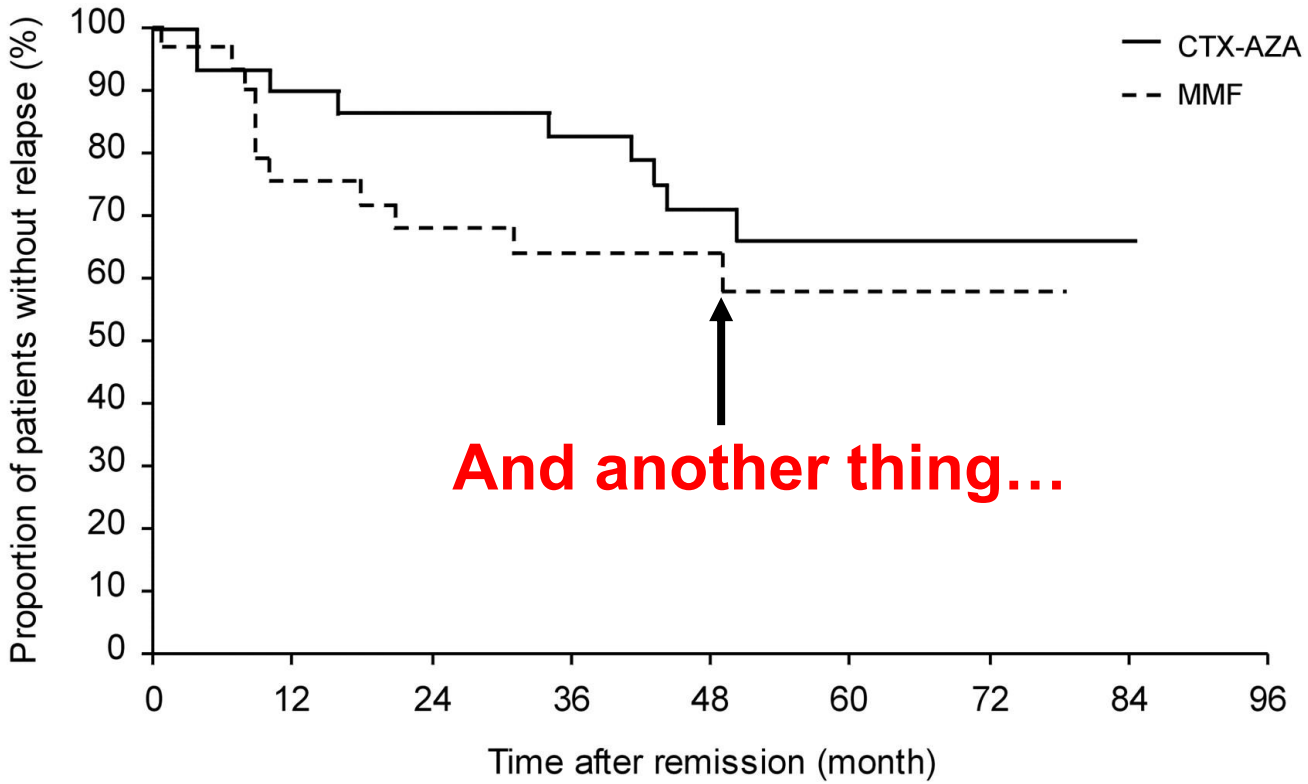
JASN

Long-Term Follow-Up MMF vs CTX/AZA



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Chan, T.-M. et al. J Am Soc Nephrol 2005;16:1076-1084

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JASN

Lupus is a Disease That Relapses

- most studies show about a 40% 4-year relapse rate NO MATTER WHAT IMMUNOSUPPRESSIVE REGIMEN (including pulse cyclosphosphamide)
- a relapse does *not* imply failure of current therapy and mandate a change of immunosuppressive agent
- *(relapse if patient is not taking their medication is certainly not a failure of therapy)*

MMF or Intravenous CTX (Induction) for Lupus Nephritis *(Ginzler et al, N Engl J Med 2005; 353: 2219-28)*

- multicenter, randomized, nonblinded trial of induction Rx for severe active LN
- designed as equivalence trial
  - calculated sample size: 64/ Rx arm
- Hypothesis: MMF has equivalent efficacy with superior toxicity / tolerability profile *vs* IV CTX
- Duration: 24 weeks

Table 3. Adverse Events.*

	Mycophenolate Mofetil (N=83)	Intravenous Cyclophosphamide (N=75)
Severe infections†	1	6
Necrotizing fasciitis	0	1
Gram-negative sepsis	0	1
Pneumonia, lung abscess	1	4
Other infections	3	5
Oral or vaginal candida	4	8
Tinea of skin, nails	1	5
Cellulitis, skin abscess	5	7
Herpes zoster	3	4
Mucocutaneous herpes	1	4
Varicella	0	1
URI, bronchitis, pharyngitis	18	18
Urinary tract infection	5	4
Upper GI symptoms (nausea, vomiting, bloating, epigastric pain)	23	25
Chronic or recurrent episodes	4	10
Diarrhea	15	2
Persistent	3	0
Rectal bleeding	0	3
Lymphopenia (new onset)‡	18	28
Sustained lymphopenia	5	14
Neutropenia§	1	1
Anemia unrelated to SLE	2	2
Menstrual irregularities	8	11
Change in menstrual cycle	8	13
Amenorrhea	0	2
Alopecia unrelated to SLE	0	8
Severe generalized rash	1	0
Urticaria or angioedema	1	0
Duration of therapy (patient-wk)	1738	1350

Ginzler 2005

Table 4. Outcomes during Follow-up after Induction Therapy.*

Event	No. of Events		Relative Risk (95% CI)†	P Value
	Mycophenolate Mofetil	Intravenous Cyclophosphamide		
First renal flare	8	8	0.98 (0.37–2.61)	0.96
Renal failure	4	7	0.53 (0.15–1.81)	0.31
Death	4	8	0.48 (0.15–1.60)	0.24

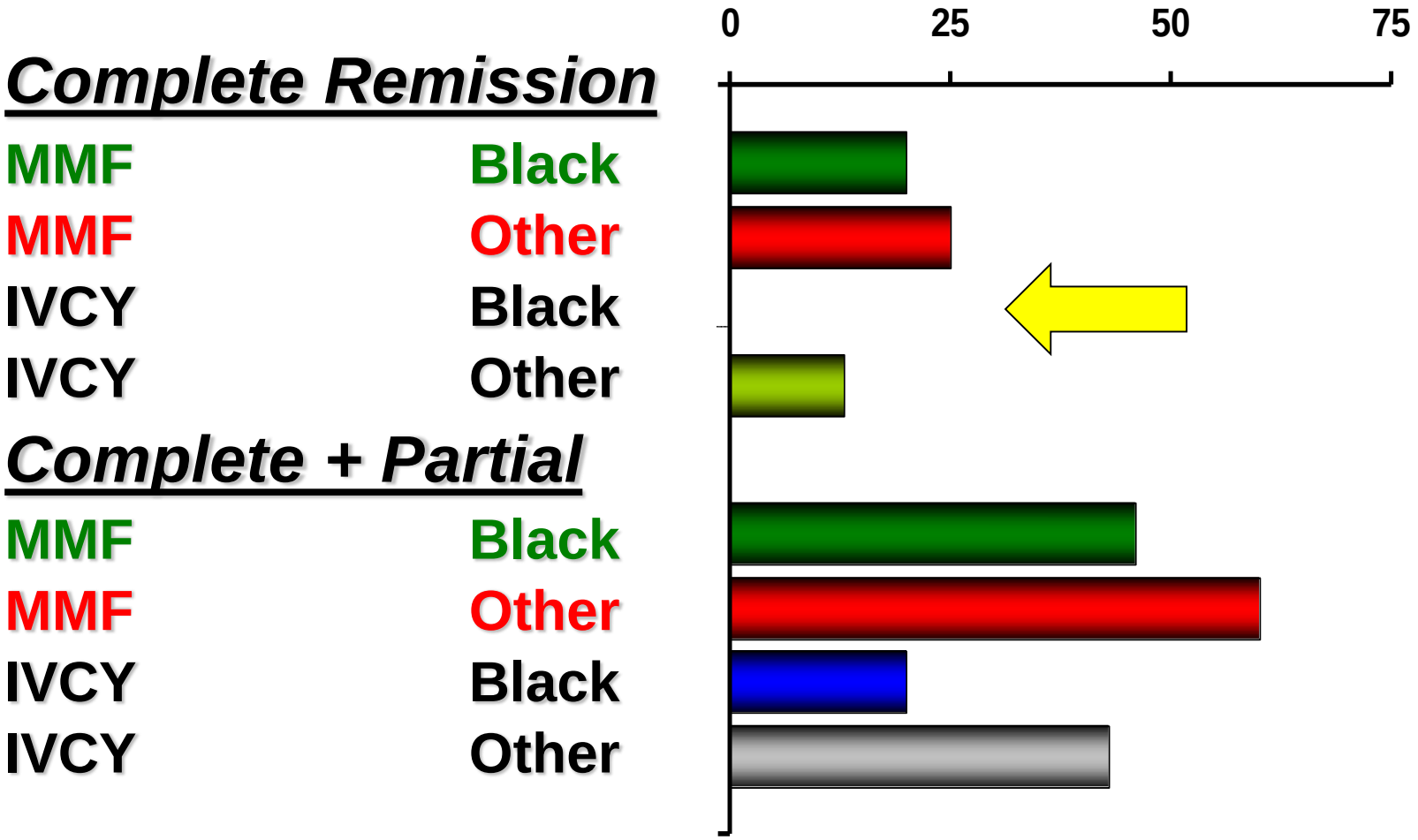
Ginzler 2005

A Recurrent Theme Since 1984…

- more deaths in the cyclophosphamide-treated patients

MMF *vs* IVCY Induction - *24* ***Wk***

Remission Rates: Blacks vs Others



Ginzler 2005

Conclusions to the Study

- MMF was superior to IV CTX in inducing remissions of severe LN
- MMF and IV CTX had similar efficacy in improving renal parameters in pts treated for 24 wks
- MMF was well tolerated (most 2-3g/d) and had less withdrawals and toxicity than CTX
- (My conclusion) MMF is an alternative, and perhaps preferable induction therapy to CTX for severe lupus nephritis

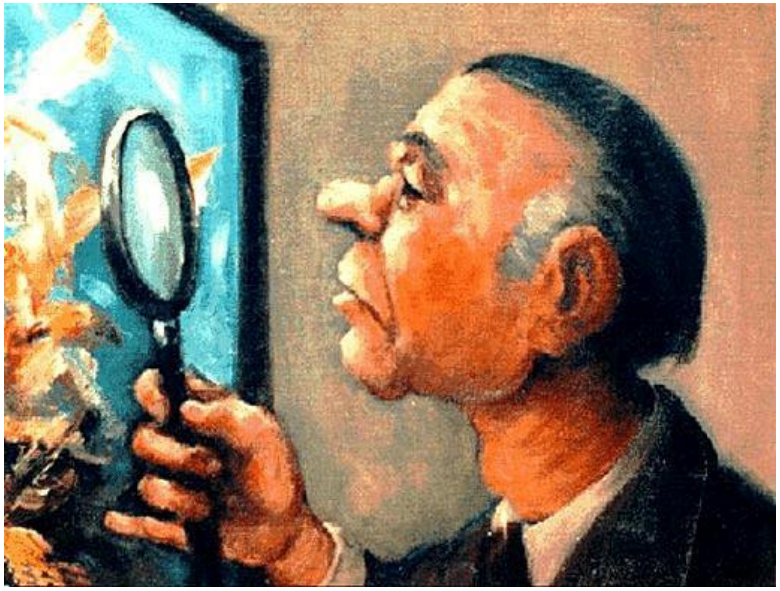
And who knows about azathioprine?

Criticism of the Chan and Ginzler Studies

- Mean serum creatinine was just 1.0 – 1.4 mg/dl

  (88-123 umol/l)

  ie not so bad GFR



Test Question: What was the median serum creatinine in the Austin 1986 NIH report?

1. 1.0 mg/dl
2. 1.8 mg/dl
3. 2.5 mg/dl
4. 5.3 mg/dl

The International MMF vs IV Cyclophosphamide Study *(Appel et al 2009)*

- 370 patients with III/IV/V (16% had V only) nephritis randomized to MMF (median dose 2.6 g/d) vs IV CTX (0.75 g/M^2 X 6 doses)
- mean dose of prednisone 26 mg/d
- primary endpoint: decrease in urine protein/creatinine ratio and stable or improving serum creatinine
- secondary endpoint: complete renal remission, disease activity, safety

Response Rates

Appel et al J Am Soc Nephrol 2009

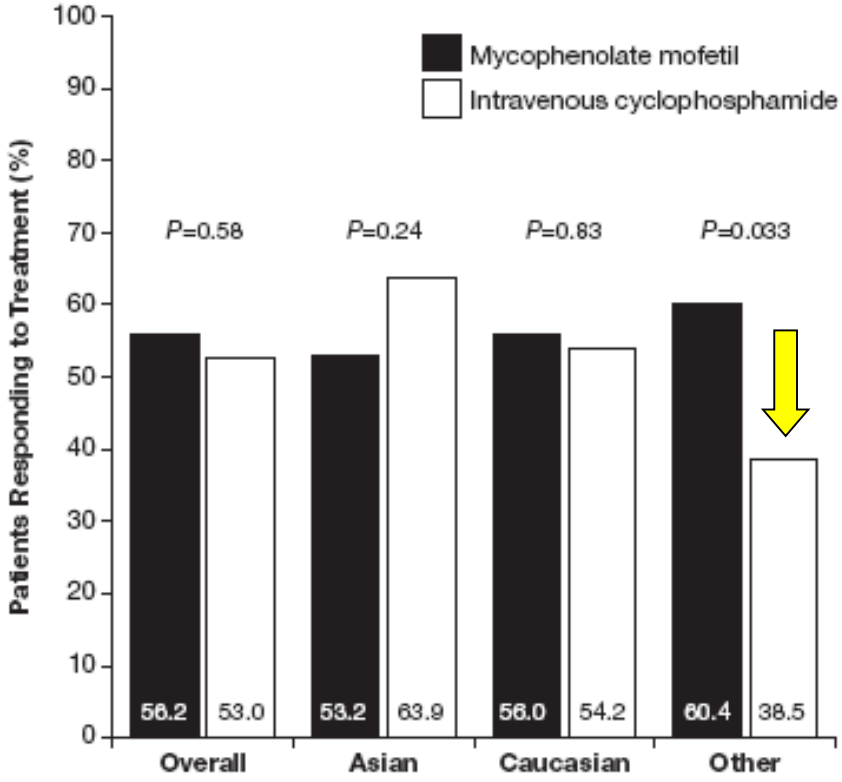


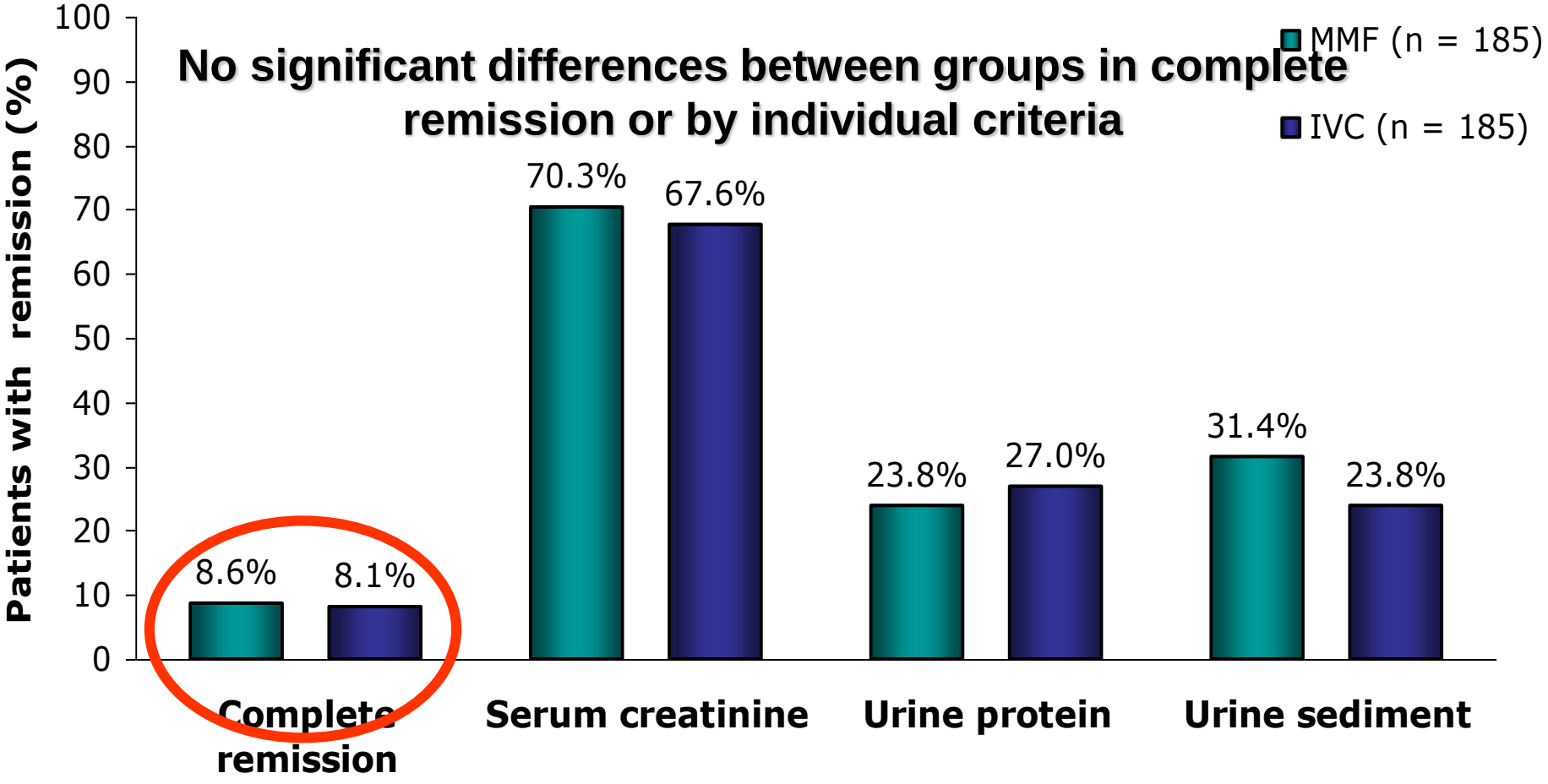
Figure 2. Response rates of study population and by racial group.

The Most Interesting Result to Me

Appel et al J Am Soc Nephrol 2009

- only 8-9% in either group were in complete remission at 24 weeks!

Remission Rates by Renal Criteria



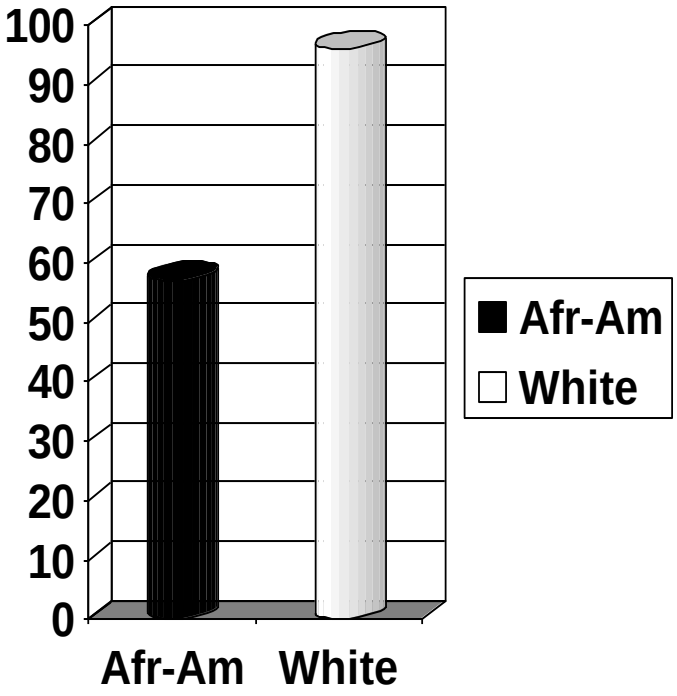
Slide courtesy of G. Appel

The Role of Race in Lupus Nephritis

- review of renal outcome in Glomerular Disease Collaborative Network (Southeastern US)
- 89 patients with diffuse proliferative nephritis were treated with IV CTX for median of 10 months (median cumulative dose 6 g)
- 57% were African Americans

Dooley; Kidney Int 1997

The Role of Race in Lupus Nephritis



- equivalent therapy and BP control A-A vs Whites
- 5 y survival much better in Whites
- 17 / 19 patients reaching ESRD were African-Americans
- 8 of these 17 reached ESRD within 8 months

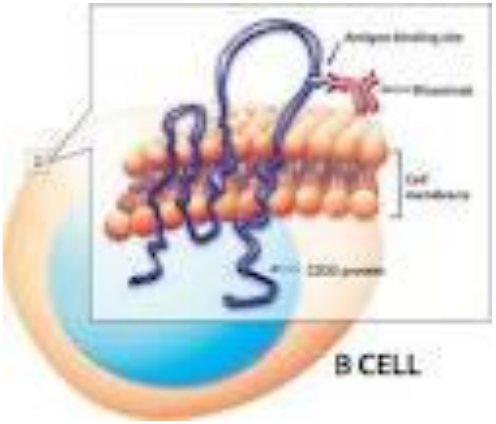
Dooley, Kidney Int 1997

Race and Outcome in Lupus Nephritis

- Caucasian race appears to be “protective” in outcome of lupus nephritis
- this is independent of socioeconomic factors
- must be taken into account when reading the literature and treating your patients
- I think that Southeast Asian patients are also a “high-risk” race with regard to lupus nephritis

So What About Rituximab?

- The more expensive the drug, the better it works, right?



The LUNAR Study

- Rituximab: monoclonal antibody that depletes CD-20 B cells
- uncontrolled studies suggested it worked in refractory lupus
- this study: patients with Class III or IV lupus nephritis
- 144 patients at 52 centers

Rovin et al Arth Rheum 2012

The LUNAR Study

- solumedrol 1000 mg Day 1 and again within 3 days
  - and again with each dose of RTX
- prednisone 0.75 mg/kg/d tapered to < 10 mg/day by week 16 *(fast!)*
- MMF 1.5 g/day up-titrated to 3.0 g/day
- RTX or placebo IV days 1, 15, 168, 182

Rovin et al Arthr Rheum 2012

The LUNAR Study - Results

At 52 weeks:

- no difference in renal endpoints between steroid/MMF/RTX and steroid/MMF/placebo
- this is despite more improvement in lupus serology (anti-DNA antibodies and complements) in the Rituximab group
- sensitivity analysis showed that even taking out microhematuria as an endpoint didn't make a difference

Rovin et al Arthr Rheum 2012

Maintenance Therapy

- continuing therapy with pulse cyclophosphamide as per NIH protocol associated with more infections, deaths along with no improvement in relapse rate
- 2 trials examined maintenance therapy with azathioprine versus MMF

The MAINTAIN Trial

Houssiau et al Ann Rheum Dis 2010

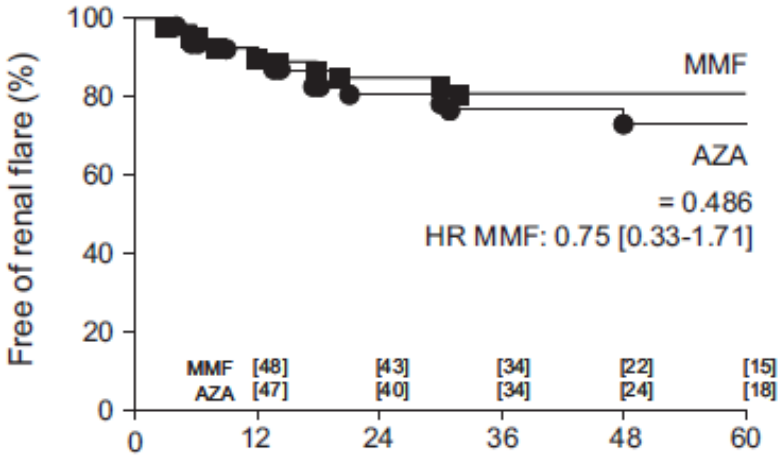
- 105 patients induced with solumedrol and IV cyclophosphamide
- all patients were placed on AZA or MMF after 12 weeks *regardless of remission status*
- target dose 2mg/kg AZA, 2g/day MMF
- very few patients of African-Caribbean descent

The MAINTAIN Trial

Houssiau et al Ann Rheum Dis 2010

- 25% of AZA group had a renal flare compared with 19% of MMF group (p=NS)
- no difference in any outcome such as 24h urine, serum creatinine, ESRD etc
- more cytopenias in AZA group, but not clinically significant
- Authors: AZA may still have an advantage, because safe in pregnancy and a lot cheaper

Figure 1 Trial profile and patient disposition. AZA, azathioprine; GCs, glucocorticoids; ITT, intent to treat.



The ASPREVA Lupus Management Study

Dooley et al N Engl J Med 2011

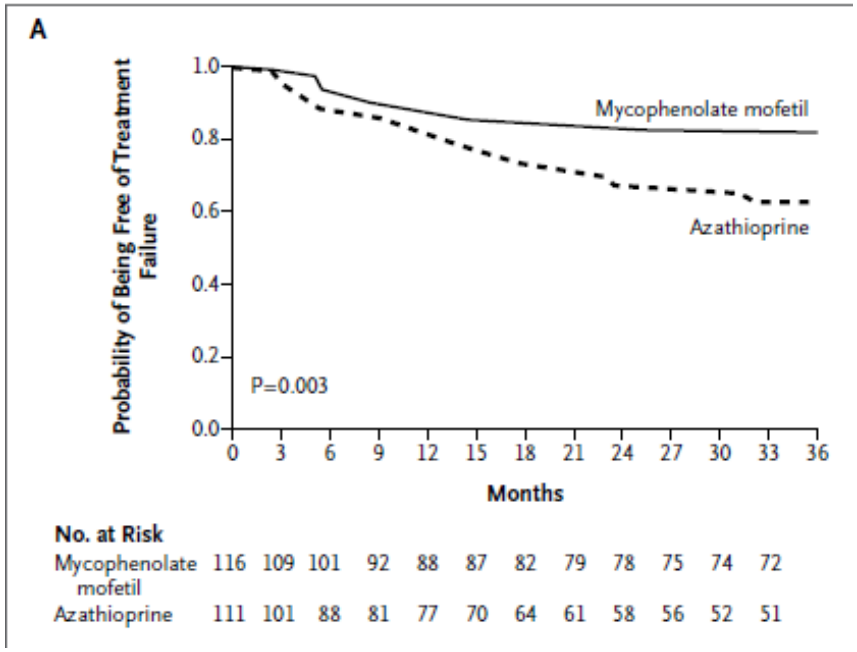
- follow-up to the induction study of IV cyclophosphamide versus MMF
- those who satisfied *response criteria* were re-randomized to azathioprine versus MMF for maintenance
- 227 patients with class III, IV or V nephritis
  - only 127 patients completed the 36 month study
  - main reasons for withdrawal were adverse events and flares

The ASPREVA Lupus Management Study

Dooley et al N Engl J Med 2011

- Hazard ratio 0.44 (95%CI .25 -.77, p=0.003)

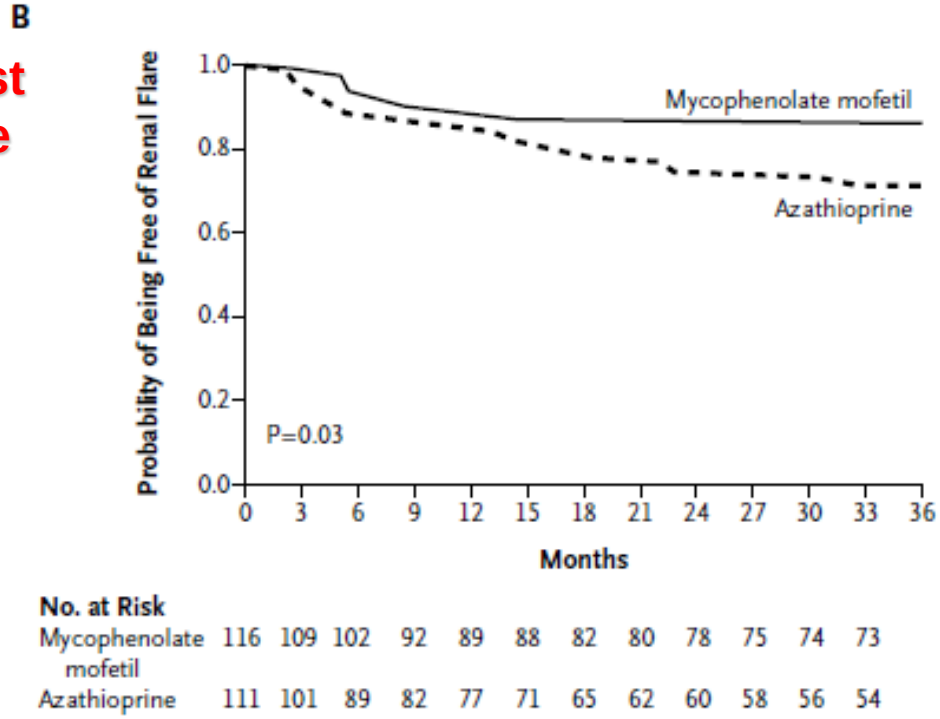
  for MMF for time to treatment failure *(death/ESRD/sustained doubling of s.creatinine/proteinuric/ nephriticflare/immunosuppresi ve rescue therapy)*



The ASPREVA Lupus Management Study

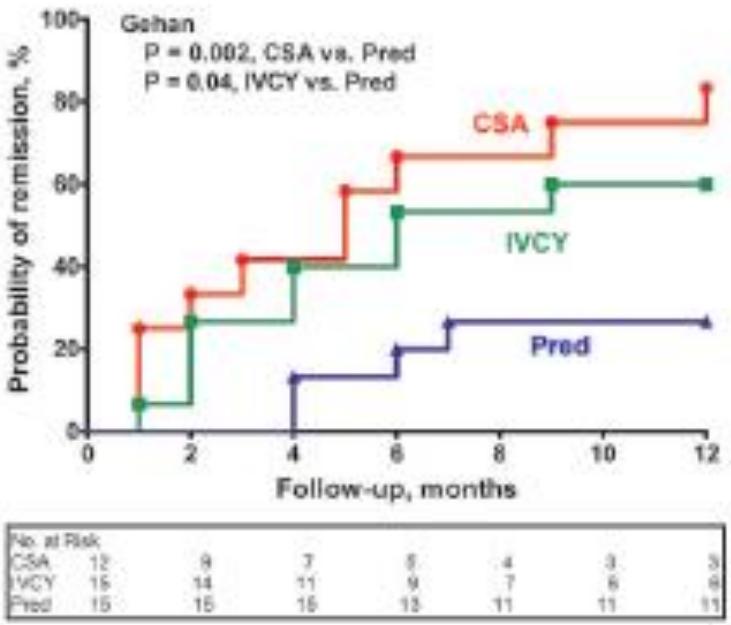
Dooley et al N Engl J Med 2011

Time to First Renal Flare



Lupus Membranous Nephropathy

- 42 patients over 20 years randomized to alt-day prednisone alone, or along with cyclosporine (5 mg/kg) for 11 months, or CTX (0.5-1.0 g/M^2) every other month for 6 doses
- latter 2 groups more likely to obtain remission



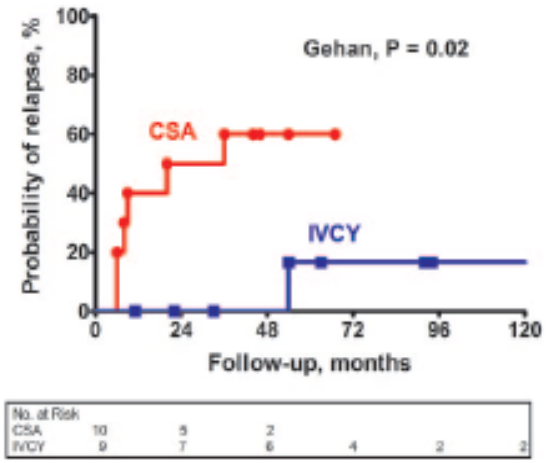
Austin et al J Am Soc Nephrol 2009

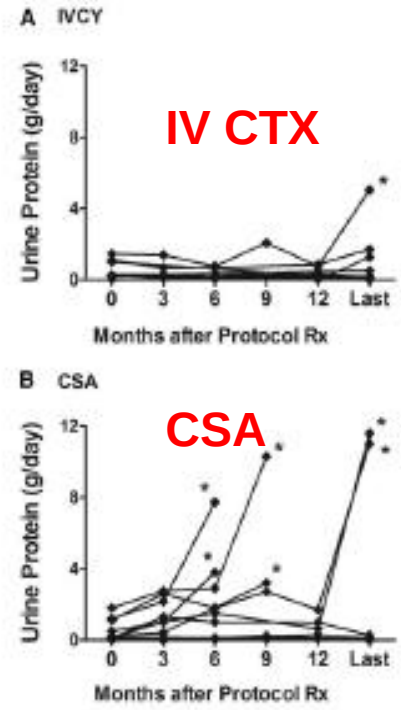
Predictors of Remission

- race (but not on multivariate analysis)
- 24h protein < 5g
- adjunctive therapy with IV CTX or CsA (compared to alternate-day prednisone alone)

Austin et al J Am Soc Nephrol 2009

Relapse More Likely with Cyclosporine After Stopping Therapy





Austin et al J Am Soc Nephrol 2009

My Approach to Lupus Membranous Nephropathy

- subnephrotic proteinuria: use ACE/ARB and observe
- nephrotic-range proteinuria:
  - daily (not alternate-day) prednisone 0.5 mg/kg X 3months
  - if no remission, add low-dose cyclosporine (1-2 mg/kg)
  - the proteinuria may get worse before it gets better
  - may need to stay on low-dose cyclosporine for a long time (years)
- consider stopping oral contraceptives if patient has significant proteinuria

My Approach to Lupus Membranous Nephropathy (continued)

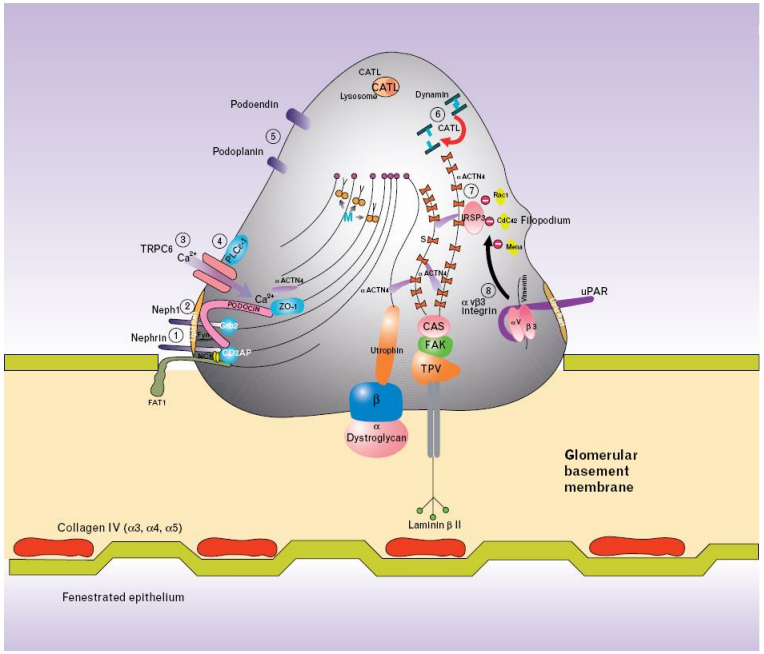
- in mixed proliferative or membranous disease (III/V or IV/V) treat each lesion separately
  - prednisone + another agent for the proliferative lesion
  - cyclosporine or tacrolimus for the membranous lesion (probably works by a non-immunologic mechanism)

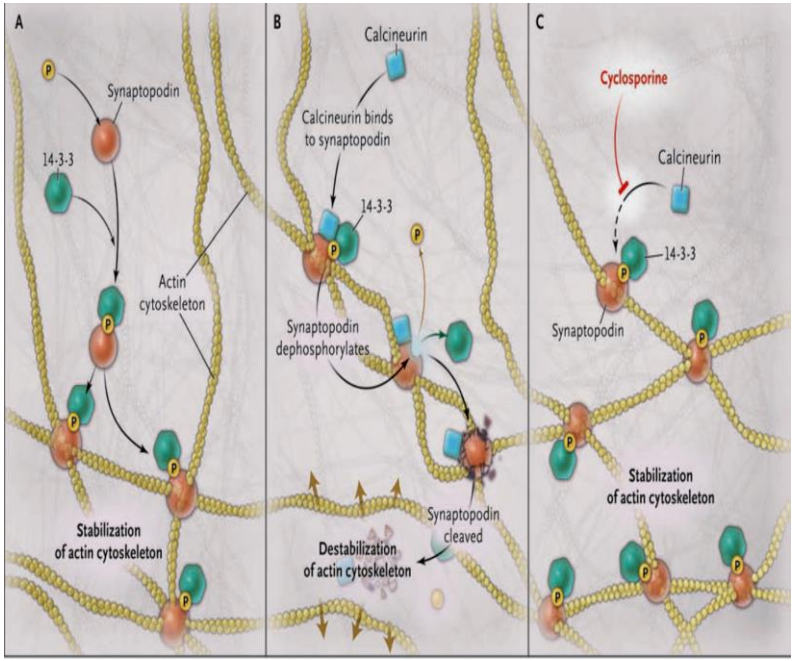
nature medicine

ARTICLES

The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A

Christian Faul[1,2], Mary Donnelly[1,2], Sandra Merscher-Gomez[1,2], Yoon Hee Chang[2,5], Stefan Franz[2,5], Jacqueline Delfgaauw[2,5], Jer-Ming Chang[3], Hoon Young Choi[2], Kirk N Campbell[1,2], Kwanghee Kim[2], Jochen Reiser[1,4] & Peter Mundel[1,2]





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Pitfalls in Management

- 33 yo old Philippina, fever, abnormal liver function tests, lupus serology strongly positive, pancytopenia, creatinine 195 umol/l
- renal biopsy: DPGN
- Rx pulse solumedrol, azathioprine 100 mg od
- also diuretics, antihypertensives

33 year old Philippina:

DAY	Serum Creatinine
1	195 umol/l
2	193 umol/l
3	204 umol/l
4	210 umol/l

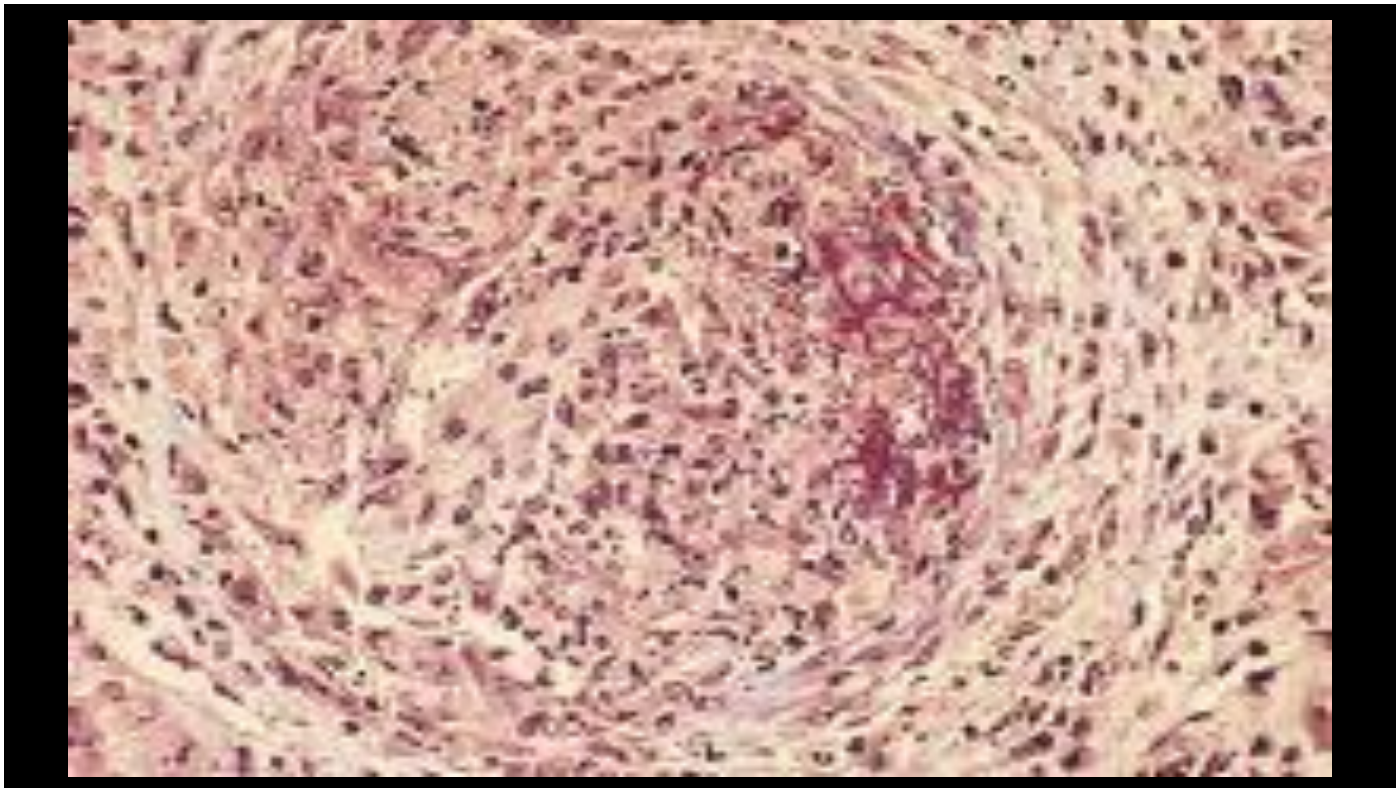
What to Do Now?

- why is the creatinine increasing?
- is this failure of therapy?
- how long does it take for kidneys to heal?

What Happened…

- because of “nonresponse”, given IV cyclophosphamide on Day 5
- severe, prolonged leukopenia
  - Herpes Zoster
  - CMV pneumonitis

How Long Does this Take to Heal?



Pitfalls in Therapy – *Not Waiting for Healing (1)*

- may take weeks for creatinine to improve
- it's the steroid that works the fastest
- often renal indicies get worse before they get better (especially proteinuria)

Pitfalls in Therapy – *Not Waiting for Healing (2)*

- other non-nephritis causes of high creatinine
  - diuretic-induced volume depletion
  - co-trimoxazole for pneumocystis prophylaxis
  - may be component of ATN
- avoid “spiraling empiricism” (the panic factor)
- remember, 8% complete remission at 6 months in the Appel 2009 paper

More Pitfalls in Therapy

- over-treating mild lupus (more than NSAIDs and anti-malarials +/- low-dose corticosteroids)

or

- under-treating severe lupus

Pitfalls in Therapy

- over-treating mild lupus (more than NSAIDs and anti-malarials +/- low-dose corticosteroids)

or

- under-treating severe lupus

Pitfalls in Therapy – *Under-treating Severe Lupus*

- most serious presentations of lupus should be treated with 1 mg/kgBW of prednisone for *2 to 3 months*
- assuming improvement, slow taper *over the next year*
- continue non-prednisone agent (AZA, MMF) *for another year*

Proposed Timeline of Treatment – The UHN Renal/Rheumatology Clinic Protocol

Pitfalls in Management – the high risk renal biopsy

- Scenarios where renal biopsy not usually necessary
  - explosive and obvious presentation of lupus
  - extra-renal manifestations (such as pulmonary hemorrhage) are necessitating intensive therapy anyway

Rational indications for Renal Biopsy

- ongoing proteinuria / hematuria in the face of clinically inactive disease or normalized serology
- increasing or persistently elevated creatinine in face of clinically quiescent disease
- to differentiate renal thrombotic microangiopathy from “classic” lupus nephritis in lupus patient with known anticardiolipin / antiphospholipid antibody

Summary: Treatment of Severe Lupus Nephritis (I)

- aggressive therapy with high dose corticosteroid and a second agent for severe proliferative nephritis
- the corticosteroid will turn off the disease the fastest
- you don't have to rush into the second agent, but do use a second agent
- treatment with corticosteroid for at least one year, the second agent for at least two years
- pulse cyclophosphamide should <u>not</u> be the "standard of practice" for class IV nephritis

Treatment of Lupus Nephritis (II)

- just because a treatment is new and really expensive doesn't mean that it works
- just because a drug is old and cheap doesn't mean that it isn't good (azathioprine)
- expect relapses in about half the patients – it doesn't necessarily mean a change in choice of immunosuppressive agent and can often be managed with a temporary increase in corticosteroid

Treatment of Lupus Nephritis (III)

- MMF may be superior to azathioprine for maintenance therapy, but cost and pregnancy considerations are important here too
- allow time for healing