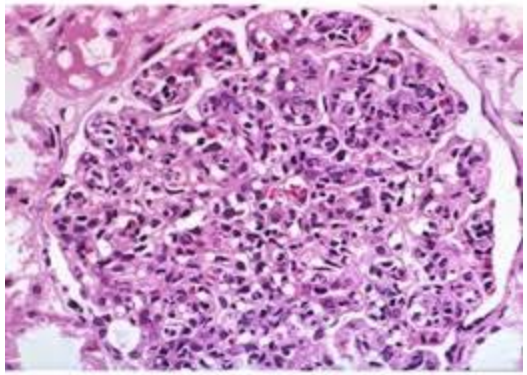

The Treatment of Lupus Nephritis

3rd GCC Organ Transplant and Nephrology Congress

Joanne Bargman MD FRCPC

Staff Nephrologist and Co-Director

Combined Renal-Rheumatology Lupus Clinic,
University Health Network Toronto

The Email I Receive Too Often

**"I have a patient with Class IV lupus nephritis who is on MMF *for 3 months* and still has proteinuria.
Should I give her rituximab?"**

What's The Problem?

1. There is no mention of the corticosteroid therapy, like it doesn't matter.
2. Three months is too early to conclude that the treatment doesn't work.
3. Do we know that the patient is taking their medicine?

"I have a patient with Class IV lupus nephritis who is on MMF *for 3 months* and still has proteinuria.
Should I give her rituximab?"

What I Want You to Know in 20 Minutes

1. It takes a lot longer for resolution of proteinuria and hematuria than is appreciated (this is NOT minimal lesion disease)
2. Corticosteroids remain the mainstay of therapy in 2017 – the choice of the second agent is not as crucial as everyone thinks
3. Use antimalarial agents
4. “Resistant” lupus is usually due to non-adherence

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

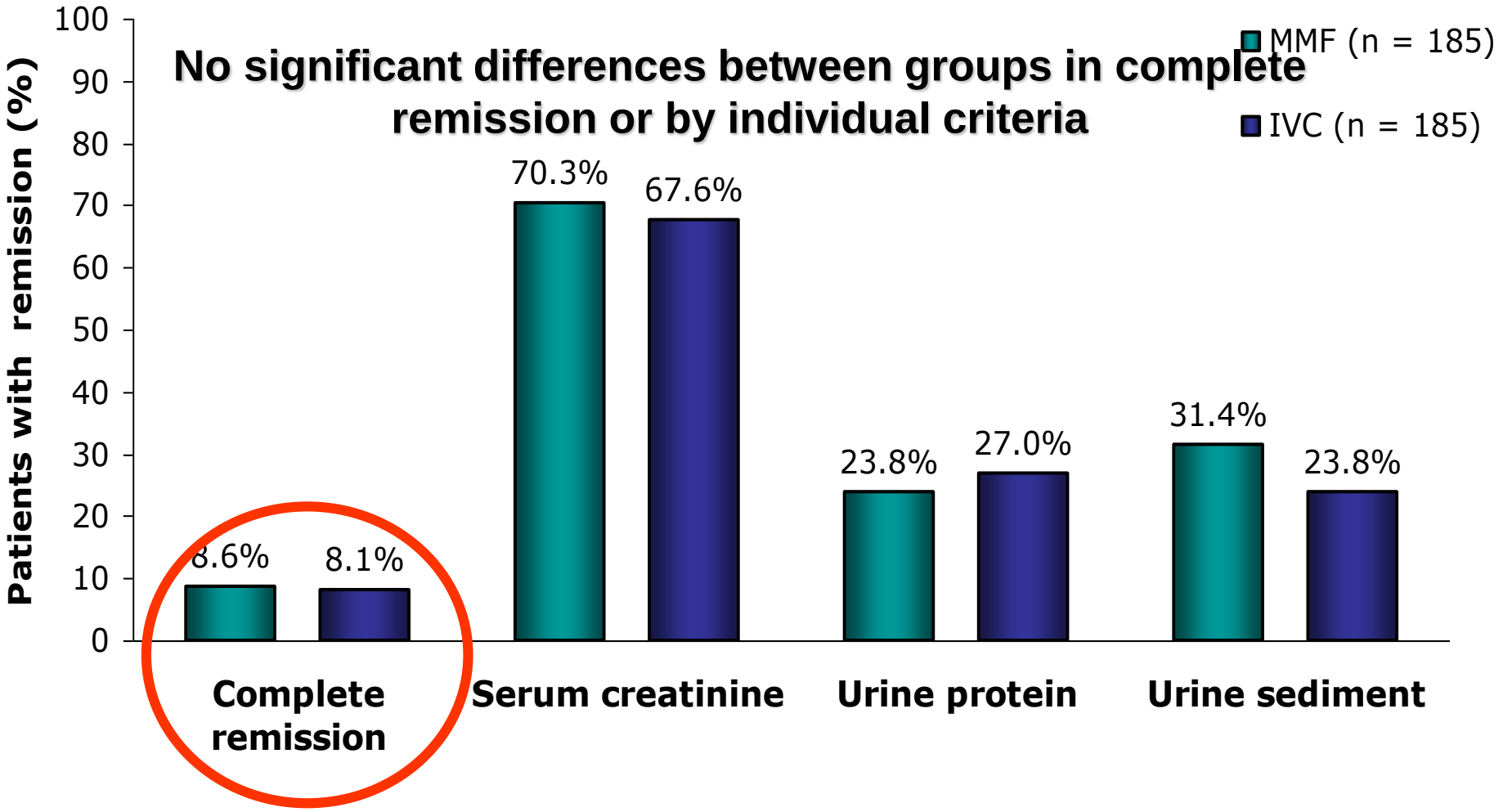
- 370 patients with lupus nephritis randomized to MMF vs IV CTX
- mean dose of prednisone 26 mg/d
- primary endpoint: decrease in urine protein/creatinine ratio and stable or improving serum creatinine
- secondary endpoint: complete renal remission, disease activity, safety

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 Lesson from Primary Membranous Nephropathy

- there is a lag between disappearance of the causative antibody and resolution of proteinuria
- when antibody levels reach zero, there is still 2-3 g/day of proteinuria
- this is compatible with *residual structural deficits in the absence of immunologic activity*

Beck and Salant, Kidney Int 2010

Lag Between Disappearance of Antibody and Resolution of Proteinuria (Primary Membranous Nephropathy)

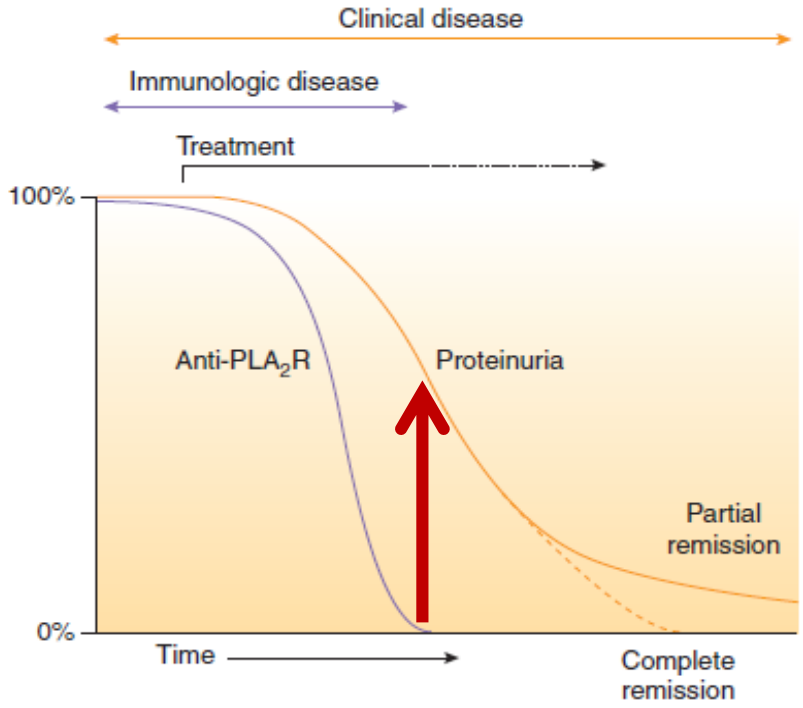
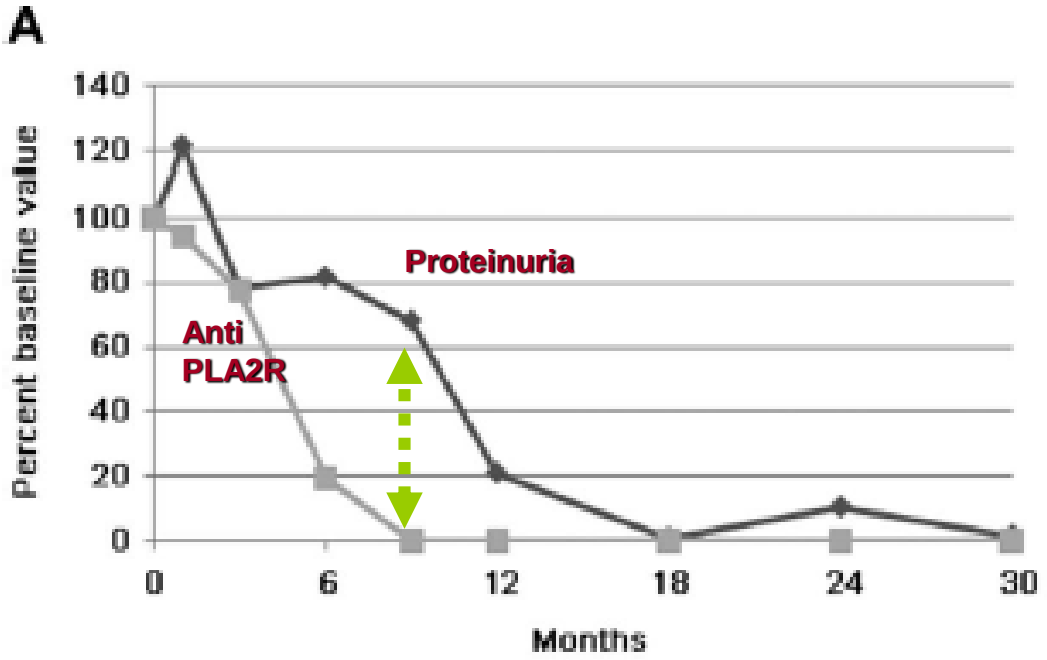


Figure 1 | Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA2R) in idiopathic membranous nephropathy.

Beck and Salant
Kidney Int 2010

Lag Between Disappearance of Antibody and Improvement in Proteinuria: Rituximab



Beck et al J Am Soc Nephrol 2011

Probably the Same Phenomenon in Lupus Membranous

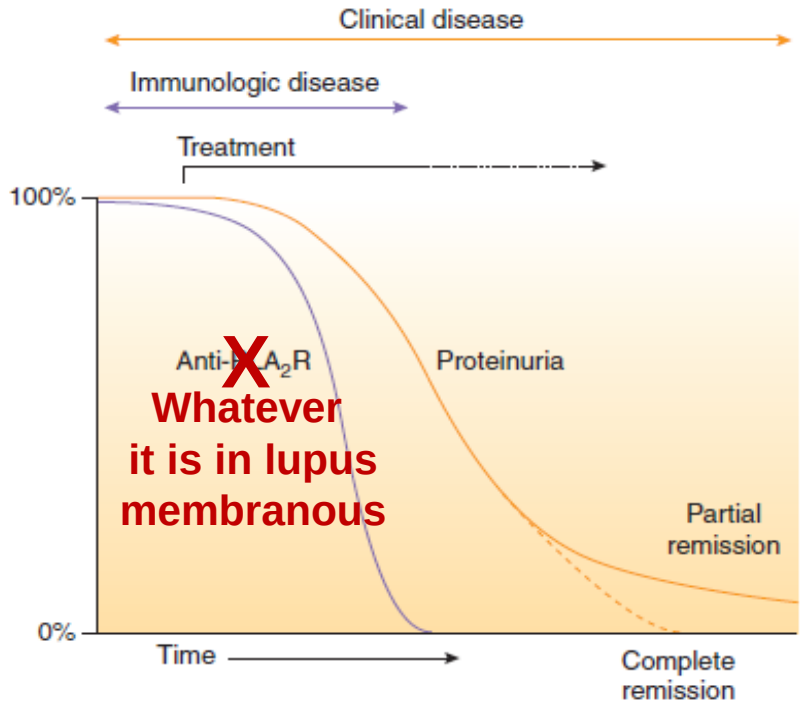
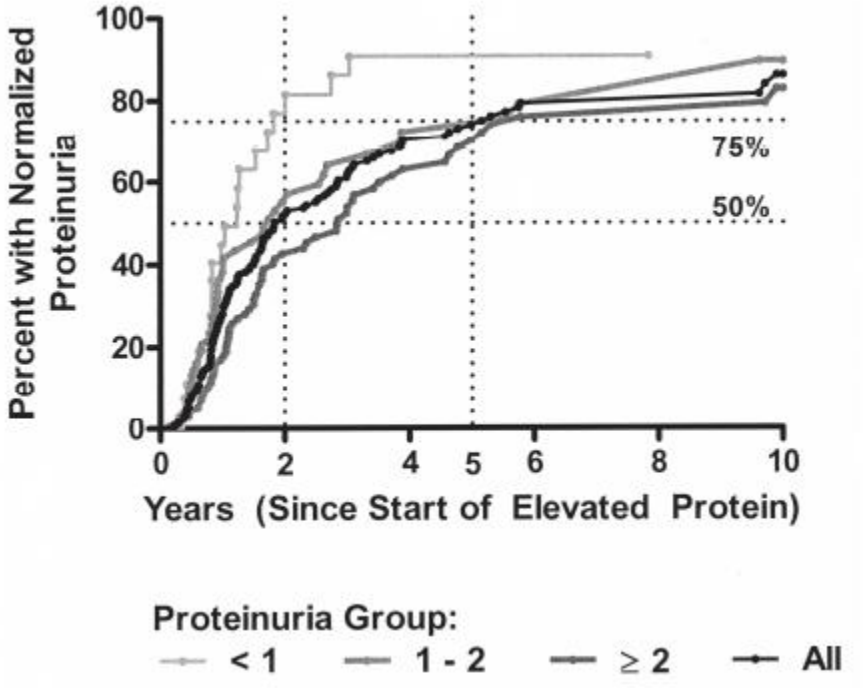


Figure 1 | Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA2R) in idiopathic membranous nephropathy.

The lag time to resolution of proteinuria

- we shouldn't be continuing intensive immunosuppression or escalating immunosuppression for ongoing proteinuria or hematuria
- "*Abwarten und tee trinken*"

The Toronto Cohort: It Takes a Long Time for Proteinuria to Improve

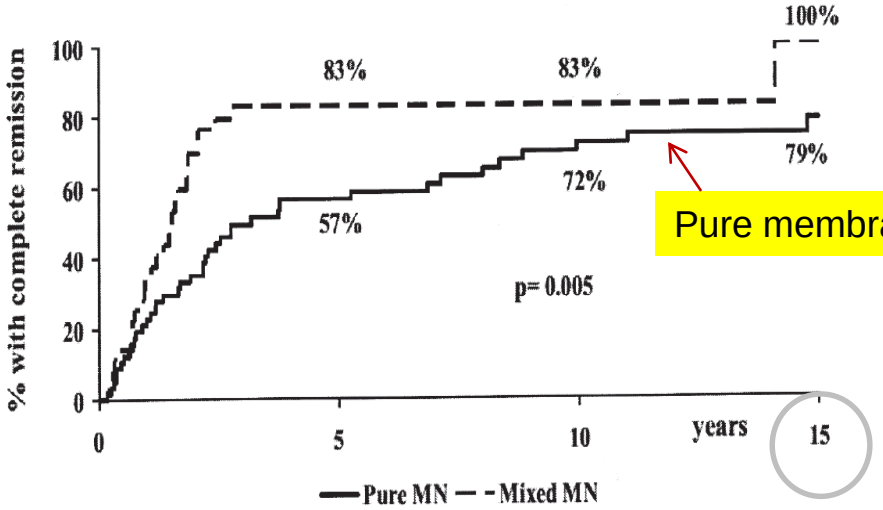


Touma J Rheum 2014

Editorial

Resolution of Proteinuria in Lupus Nephritis: Hurry Up and Wait

Bargman and Avila Casado J Rheum 2014



Pure membranous lupus

Moroni et al Semin Arthritis Rheum 2012

Lupus Nephritis: When to Change Treatment (KDIGO)

- 2 important points about waiting, buried in the rationale:

Duration of Therapy

Few patients reach complete remission by 6 months, and kidney biopsies after 6 months of initial therapy have shown that, while active inflammation tends to improve, complete resolution of pathologic changes is unusual [39, 57-59]. Consistent with this finding, clinical improvement in class III/IV LN continues well beyond 6 months and into the maintenance phase of therapy [18, 21-23, 29, 60]. Decisions to alter therapy should not be based on urine sediment alone. A

Immunosuppression should be continued for patients who achieve only a partial remission. However, the strategy of trying to convert a partial remission to a complete remission by increasing corticosteroids or using alternative immunosuppressive agents is not supported by evidence.

What I Want You to Know in 20 Minutes

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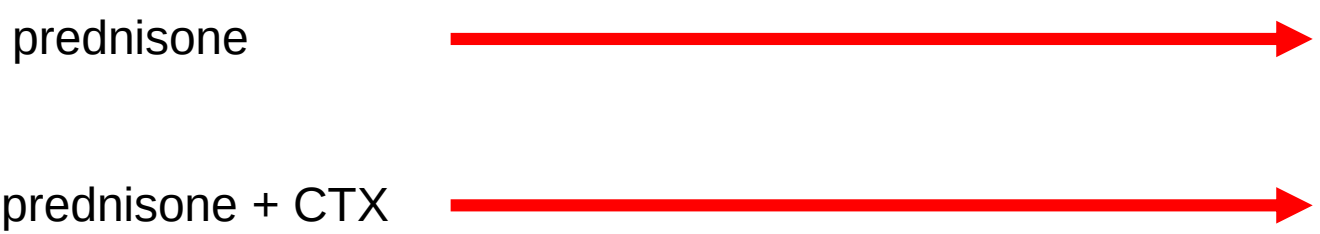
Treatment of Diffuse Proliferative Lupus Nephritis with Prednisone and Combined Prednisone and Cyclophosphamide

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



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

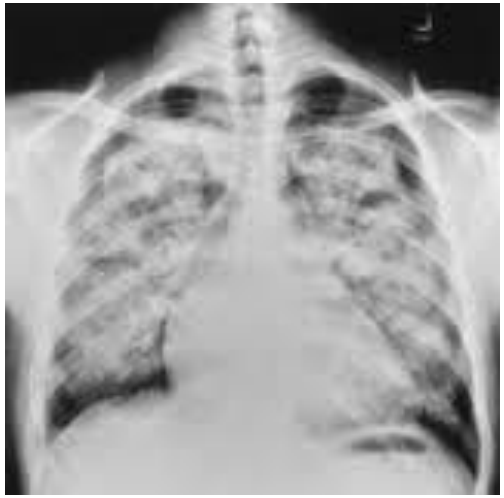
- it's the corticosteroid that works the fastest
- But don't be lulled into leaving them just on corticosteroids: corticosteroids alone is associated with more relapses and worse renal outcome
- use a second agent, *but you don't have to do this right away*
- patients with a lot of established renal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

The Importance of Corticosteroids

- the steroid brings the disease under control the fastest

Prednisone

- Patients need urgent prednisone the most in order to turn off the inflammation
- 1 mg/kg X at least 6 weeks, with a s-l-o-w taper
- IV pulse steroid is indicated for organ-threatening emergencies (rapidly progressive renal failure, cerebritis, pulmonary hemorrhage)



The Importance of Corticosteroids

- this isn't asthma
- for severe lupus nephritis, the current standard of therapy is prednisone 1 mg/kg body weight X 6 weeks minimum
- slow taper (to zero or to some lower dose) over 12 months *or longer*
  - some patients may never get off steroids
- nephrologists are more focused on the "second agent" than the corticosteroid

KDIGO Guidelines for treatment of lupus nephritis

12.3: 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*).

Kidney Int Suppl 2012; 2: 143-153

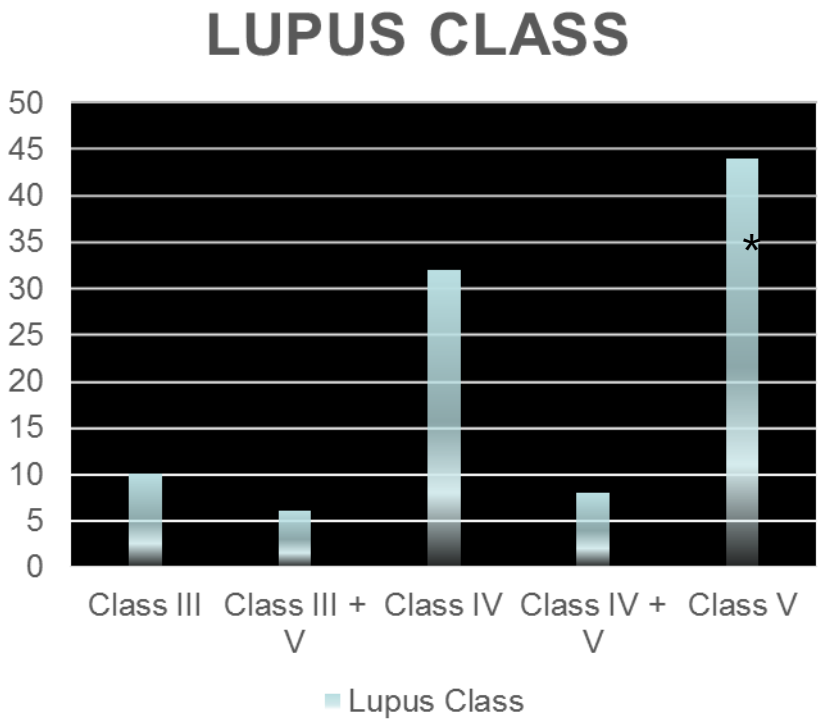
Rituximab and pulse corticosteroid followed by MMF

- Protocol
  - rituximab 1 g IV on days 1 and 15
  - methylprednisolone 500 mg IV on days 1 and 15
  - MMF 500 mg bid titrated up to 1500 mg bid

Condon Ann Rheum Dis 2013

Rituximab and pulse corticosteroid followed by MMF

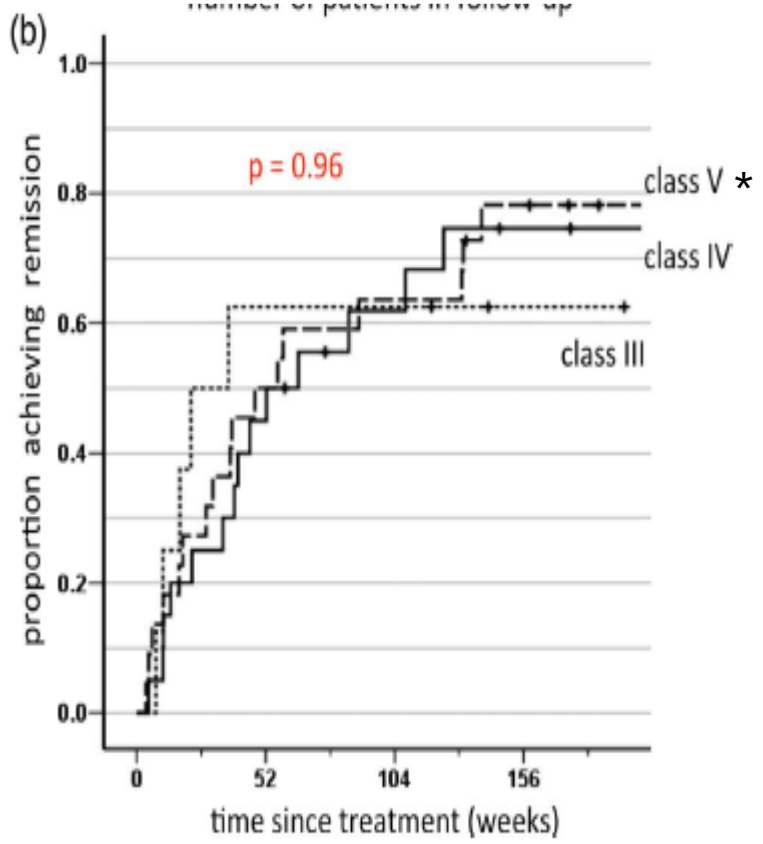
- There was over-representation of membranous (class V) nephritis compared to other cohorts



Condon Ann Rheum Dis 2013

Rituximab and pulse corticosteroid followed by MMF

- the time to complete remission was more or less independent of histological class
- Class III always lags behind (my impression)
- Note again: it takes a long time to achieve complete remission



The Second Agent

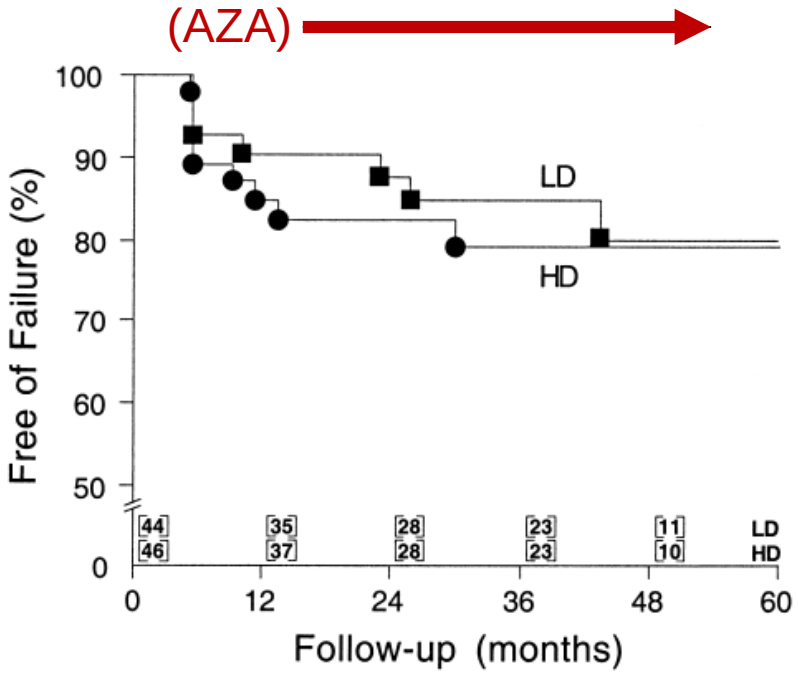
- Too much attention is focussed on this
- MMF may be better than azathioprine, but if the patient is intolerant of MMF, then azathioprine or daily oral cyclphosphamide may be reasonable second choices
- If the patient is likely to become pregnant, or can't afford MMF, azathioprine is a good second choice
- I save IV cyclophosphamide for patients I don't trust to take tablets at home
- I don't give IV cyclophosphamide to patients with decreased GFR because it is too unpredictable

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
- did AZA do all the work in the low-dose group?



Houssiau et al Arthr Rheum 2002

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Antimalarial Drugs

- the probability of a patient with lupus receiving an antimalarial is decreased (odds ratio 0.51) if their primary lupus doctor is a nephrologist instead of a rheumatologist
- randomized, controlled trials and other studies have shown that use of antimalarials is associated with
  - decreased frequency of lupus flares, including renal flares
  - diminished damage accrual
  - safe in pregnancy
  - decreased thrombosis risk

Antimalarial Use Associates with Protection from Atherosclerosis in Lupus Patients

- study of carotid intima-medial thickness in long-term lupus patients
- the absence of plaque was associated with
  - more prednisone use (!)
  - hydroxychoroquine

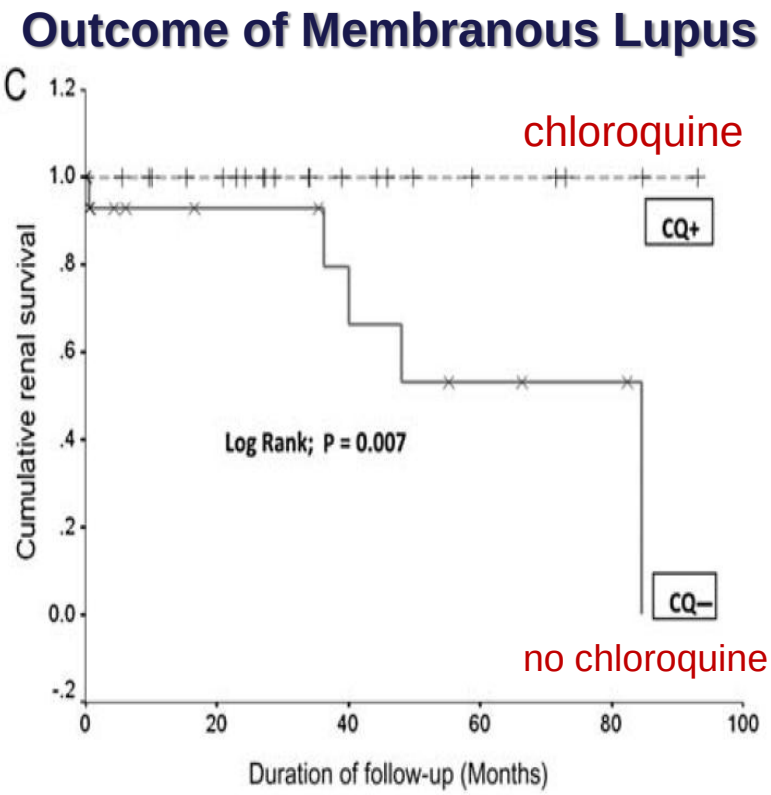
	No plaque	plaque	P value
% using prednisone	93%	85%	.09
Avg daily dose	12 mg	7 mg	**.002**
% using antimalarial	82%	63%	**.003**

Roman et al N Engl J Med 2003

Anti-Malarials

What you need to remember about antimalarials:

- *it's all good*
  - reduced flares, including renal flares
  - damage index, including vascular disease
  - reduced thrombosis
  - may also apply to lupus membranous



Okpechi et al Nephrol Dial Transplant 2012

For further information…

REVIEWS

The role of antimalarial agents in the treatment of SLE and lupus nephritis

Senq-J Lee, Earl Silverman and Joanne M. Bargman

Nature Reviews Nephrology 2011

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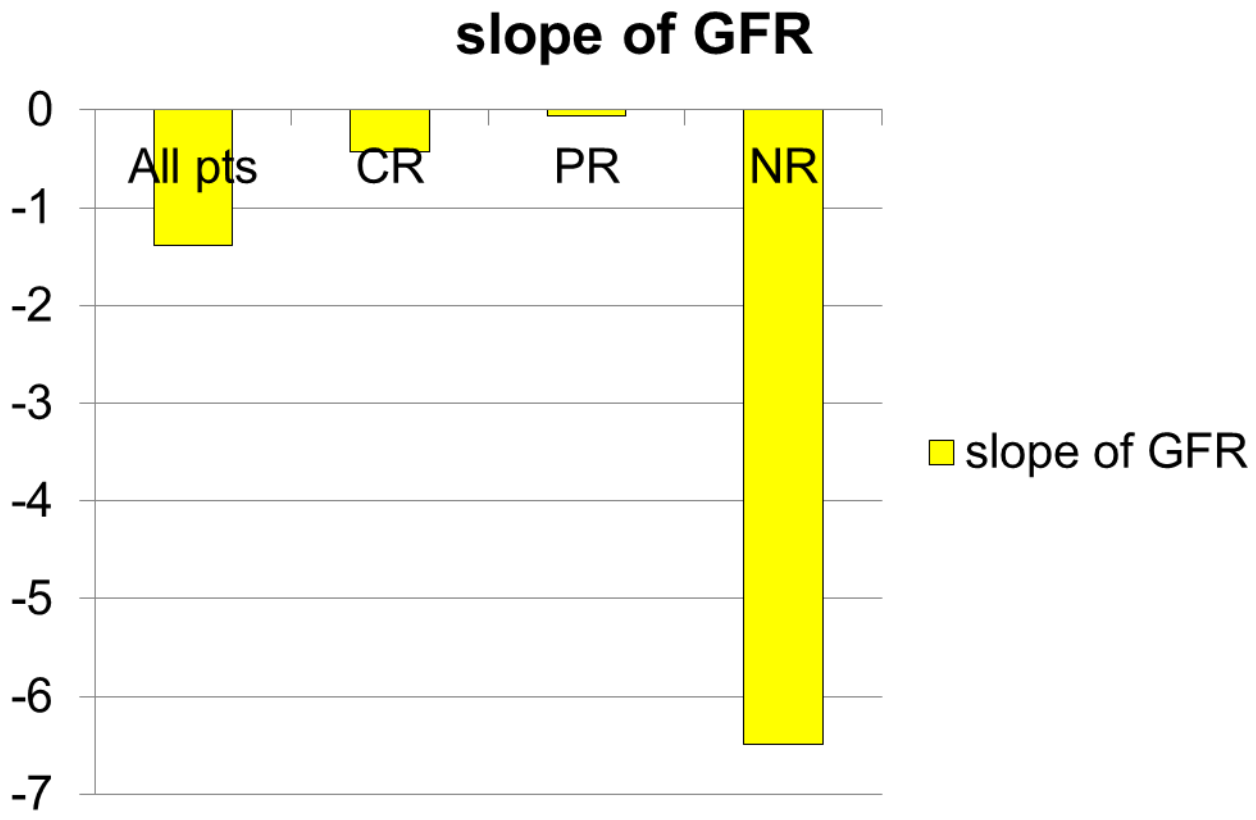
How Do the Guidelines Define Resistance?

- **ACR**: give it 6 months
  - if patient on CTX, change to MMF (or vice versa) and re-pulse with corticosteroids
  - can consider rituximab (no consensus reached)
  - not enthusiastic about calcineurin inhibitors
- **EULAR**: same as above

Resistant Lupus Nephritis

- for increasing creatinine and/or proteinuria, a repeat renal biopsy may help to distinguish from superimposed scarring (ungraded)
- if still active disease, consider an alternative agent (ungraded)
- consider use of IVIG, rituximab or calcineurin inhibitors (2D)

Lack of Remission is Associated with Poor Renal Outcome



Reich Kidney Int 2011

My Quabble (bigger than a quibble)

- one of the major causes for “nonresponse” is not addressed: non-adherence to therapy
  - think of this if serology is not improving and hemoglobin is not increasing
  - think of this if patient doesn’t look Cushingoid
  - think of this if patient can’t immediately tell you how many prednisone tablets they take every day

What to Do About Non-Adherence

- diagnosis
  - pill counts
  - calls to the pharmacy
  - quizzing the patient (but they will lie)
  - drug levels (MMF, calcineurin inhibitors)
- *minimize the number of pills*
- changing behaviour: I wish I knew

What to Do About Non-Adherence

- patients don’t know that lupus is a potentially fatal disease (unless you tell them)
- if you prescribe prednisone and they develop acne, they may just stop it

Compared to cancer

- patients undergoing chemo know that their hair will fall out, mucositis, etc. but it is *life-saving therapy*
- how many patients know this about lupus?

What to Do About Non-Adherence

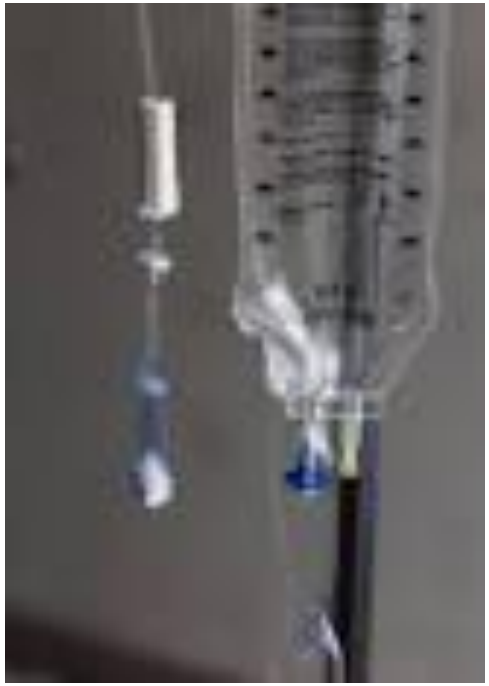
Minimize the Number of Pills

- 22 year old, previously well, severe lupus nephritis
- The most important medicine they should be adherent to is prednisone +/- a second agent
- BUT they are also prescribed
  - proton pump inhibitor
  - co-trimoxazole for PJP prophylaxis
  - calcium and vitamin D
  - bisphosphonate
  - statin for increased lipids
  - ACE-inhibitor or ARB for “proteinuria”
- approximately 24 tablets/day

Is it any surprise that they stop taking all their medicines?

Parenteral Therapy May Help

- Examples: intravenous methylprednisolone, cyclophosphamide, rituximab + pulse steroid
- at least you know if the patient got the drug (or didn’t show up)



Conclusions: Four Important Points About Lupus Nephritis

1. It takes much longer for resolution of proteinuria or hematuria than is appreciated (and it may never resolve)
2. Corticosteroids (high dose and for a long time) and a second agent remain the cornerstones of therapy
3. Don’t forget to use antimalarial drugs
4. The main cause of “resistant” lupus is that the patient isn’t taking their medicine, and this is much more common than you think