

Common Mistakes in the Management of Lupus Nephritis

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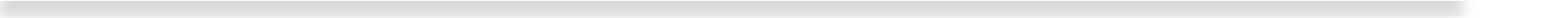
University Health Network

Professor of Medicine

University of Toronto

Disclosures

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- Consultant and Speaker, GSK (Canada)
 - Consultant, Roche Pharmaceuticals
- 
- A thin grey horizontal bar is located at the bottom of the slide.

Learning Objectives

- To discuss the downstream effect of polypharmacy on adherence and outcome in patients with lupus.
- To revisit the role of calcineurin inhibitors in the treatment of lupus nephritis.
- To understand the dissociation between immunologic remission and remission of proteinuria in lupus nephritis.
- To understand the role of antimalarial therapy in lupus and its underuse by non-rheumatologists.

The Renal-Rheumatology Lupus Clinic

- Toronto is a vibrant multicultural city with large numbers of people from Africa, the Caribbean, Southeast and East Asia
- We see a LOT of lupus!
- I co-established the University Health Network Combined Renal-Rheumatology Lupus Clinic 25 years ago with Dr. Paul Fortin, and then with Dr. Jorge Sanchez-Guerrero
- We follow hundreds of lupus patients



Toronto Caribbean Carnival AKA Caribana Festival

How I Got to Thinking About This

- I'm not a trials person
- I'm not an immunologist
- However, when you have extensive exposure over many years you may become "expert"
- I noticed a pattern of errors being repeated by those who managed just the occasional lupus patient
- No one was talking about this!



This Was the First Iteration:

AJKD

Narrative Review

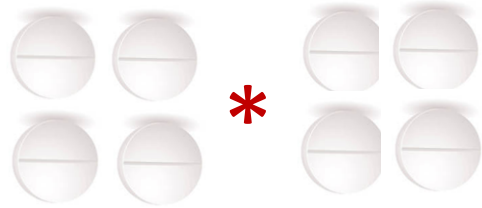
Ten Common Mistakes in the Management of Lupus Nephritis

*Bhadran Bose, MBBS, FRACP,¹ Earl D. Silverman, MD, FRCPC,² and
Joanne M. Bargman, MD, FRCPC¹*

True Story!

- 20 year old marginalized woman with lupus
- No-show to clinic for 18 months
- Presents to hospital with severe lupus flare, managed with pulse corticosteroids and MMF
- Good response to therapy, discharged to our renal-rheumatology lupus clinic for follow-up
- Upon reviewing her hospital course, I came to the discharge medications...

Discharge Medications: Prednisone 20 mg bid



Discharge Medications: + Myfortic 1080 mg
bid



Discharge Medications: +
Hydroxychloroquine 400 mg daily



Discharge Medications: + Ramipril 2.5 mg daily (“to reduce proteinuria”)



Discharge Medications: + Atorvastatin 40 mg daily



Discharge Medications: + Folic Acid 5mg



Discharge Medications: Ferrous Gluconate 300 mg



Discharge Medications: Septra



Discharge Medications: + B12



She Was
Discharged on
> 30 Pills/Day!



So What Happened?

- No-show for our appointment (*more on no-shows later...*)
- Presented to another hospital with an acute event one month later (?PE) and died

Mistake: Too Many Medications

- Pick your medical battles
- The majority of people with lupus are young and not used to taking pills
- The literature shows that the more medications prescribed, the lower the adherence
- We have sometimes prescribed just *one 50 mg tablet of prednisone* daily and nothing else





It's Worth
Saying Again:
Pick Your
Battles



Mistake: Insufficient Attention to 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 over 6-12 months (currently under debate)
- doctors are more focused on the “second agent” than the corticosteroid

The steroid brings the disease under control the fastest

The Importance of Corticosteroids



Mistake: Bad Renal Disease Needs a “Bad” Drug (Cyclophosphamide)

- Even when nephrologists and rheumatologists routinely use MMF induction, if the renal biopsy shows crescents, or the patient has severe AKI, they use cyclophosphamide instead or something expensive



The Buckley's Mixture Hypothesis

- Because it tastes so bad, it must work well
- Cyclophosphamide has so many side effects, it *must* be better



Got a cough?
Trade it for a gag.
Post your disgusted
face online 📷

It tastes awful.
It works.

Use as Directed.

▲ Advertisement

The advertisement features a bottle of Buckley's Cough Mixture on the left. The bottle is dark brown with a blue cap and a white label that reads 'Buckley's COUGH Mixture' and 'COUGH SUPPRESSANT'. To the right of the bottle, the text reads: 'Got a cough? Trade it for a gag. Post your disgusted face online 📷'. Below this, there are two lines of text: 'It tastes awful. ' and 'It works. '. At the bottom left of the advertisement, it says 'Use as Directed.' and at the bottom center, there is a small triangle icon followed by the word 'Advertisement'.

And Another Problem with Cyclophosphamide in Lupus Nephritis

- IV cyclophosphamide can lead to severe and unpredictable leukopenia in patients with decreased kidney function
- Once you've given the bolus cyclophosphamide, you're stuck with the results

Mistake: Because Azathioprine is Old, It Must Not Very Good

- This is the “hydrochlorothiazide” philosophy
- Azathioprine appears to be inferior to MMF in some trials, but it’s not 100% versus 0%
- There are situations where it may be appropriate, especially compared to taking nothing at all

When I Use Azathioprine

- Cost
- GI intolerance to MMF or Myfortic
- Patient keeps forgetting the second dose of MMF or Myfortic
 - *(taking a bid drug once a day is worse than taking a “weaker” once-a-day drug once a day)*
- Significant possibility of the patient becoming pregnant

Corollary Mistake:
If a Drug is New
and/or Expensive, it
Must be Better



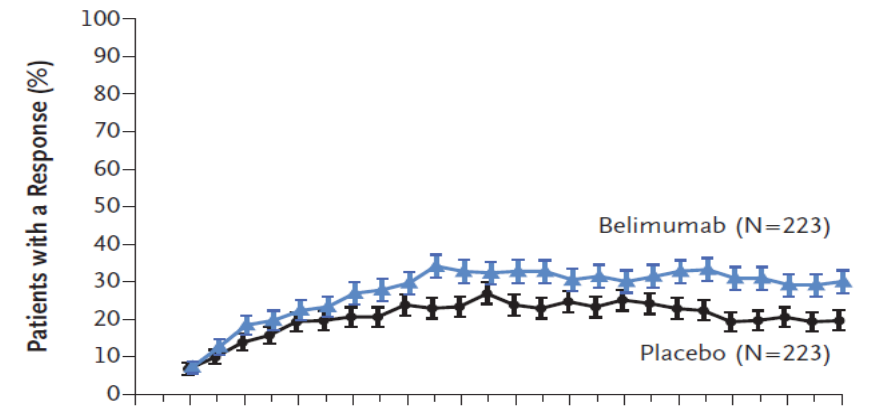
Belimumab



What I like about this study:

- 2 year follow-up
- urinary sediment was not an endpoint
- decent amount of corticosteroid was allowed

C CRR over Time



ORIGINAL ARTICLE

Two-Year, Randomized, Controlled Trial
of Belimumab in Lupus Nephritis

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

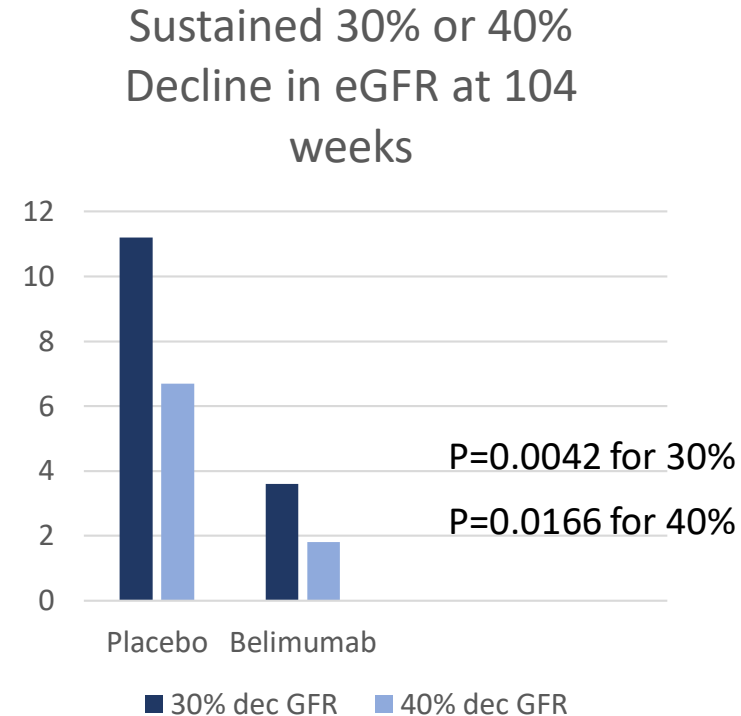
However, some “fine print”:

- Still a high number of non-responders in both groups
- In patients who were induced with cyclophosphamide – azathioprine (Euro-lupus) there was no difference +/- belimumab
- Little effect in those of African-Caribbean descent

Post-Hoc Analysis of the Belimumab Study


Rovin Kidney Int 2022

- Add-on belimumab not effective in nephrotic patients or those with membranous lupus
- But overall there was better preservation of GFR in those with add-on belimumab at 2 years





So What to Do with Belimumab?

- I note that colleagues want to use it when patients have heavy proteinuria that isn't getting better quickly
- This may be the subset of patients where belimumab doesn't work
- My impression is that it helps in patients with “grumbling” lupus not responding to low dose immunosuppression

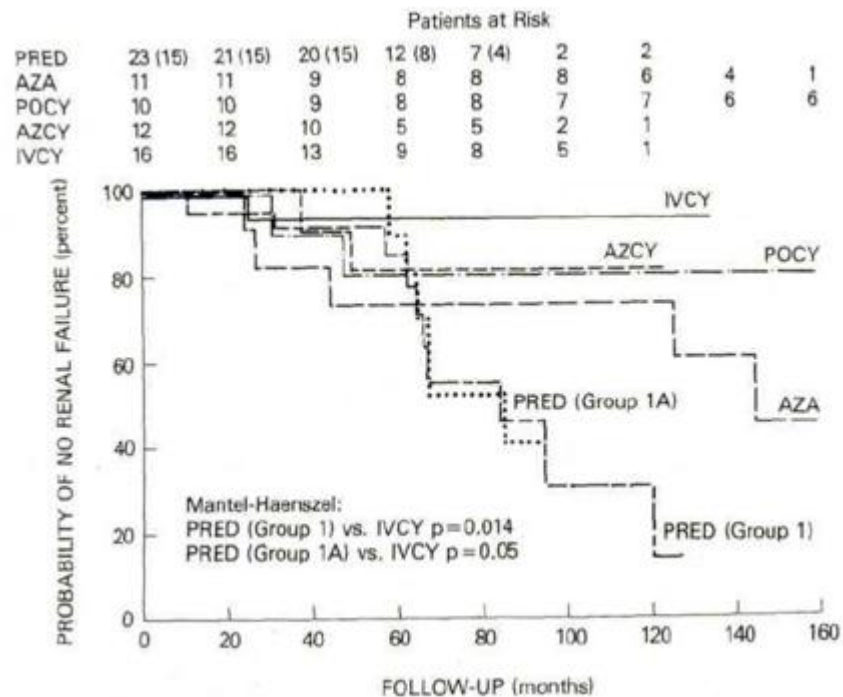


Mistake: Do Calcineurin
Inhibitors Even Treat Lupus
Nephritis?



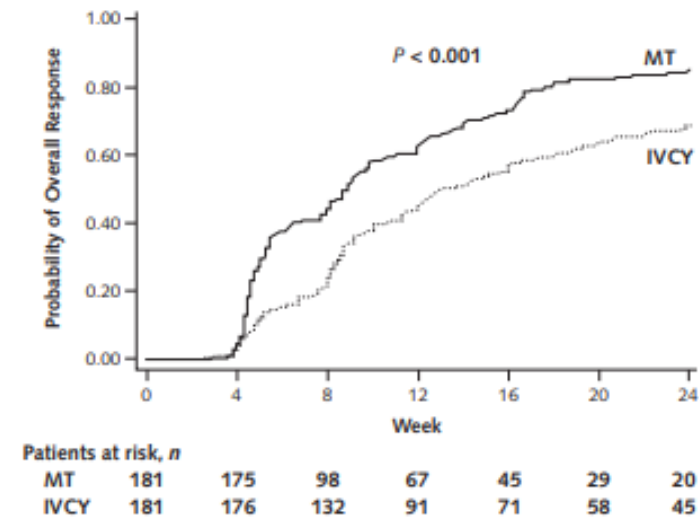
How the “Cool Kids” Treated Lupus Nephritis

1980's: NIH protocol of IV Cyclophosphamide



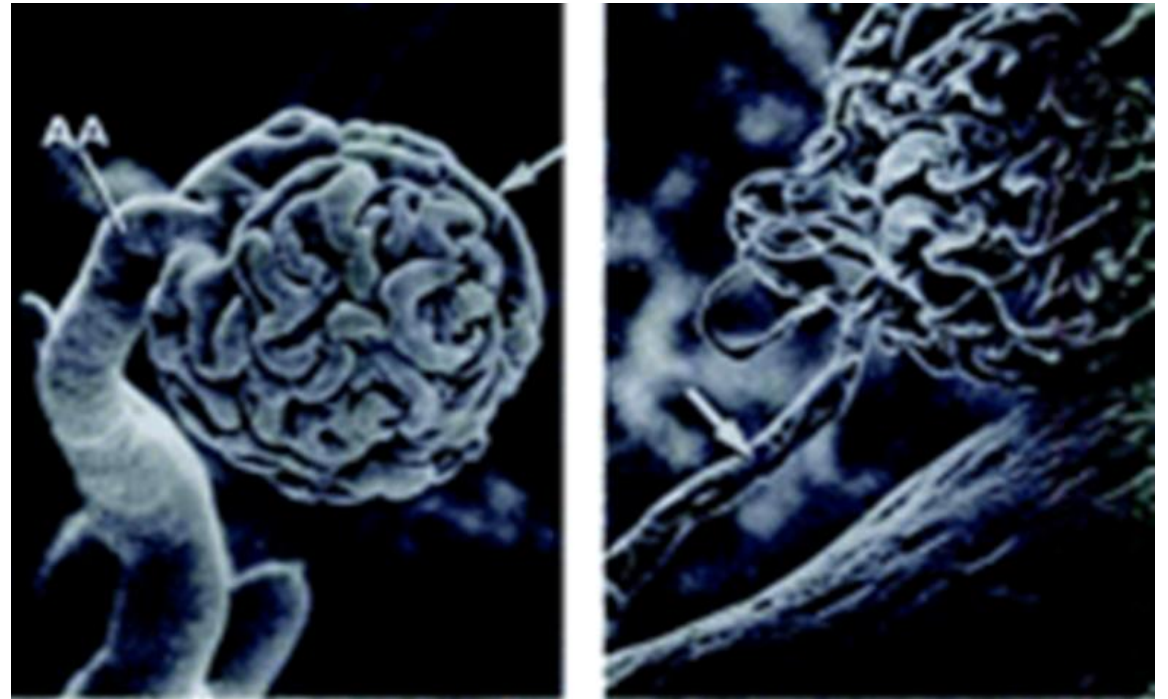
2000's: Multitarget Therapy

Figure 3. Probability of achieving overall remission (complete remission and partial remission) in patients treated with the MT regimen or IVCY.



Calcineurin Inhibitors Reduce Proteinuria by *Non-Immunologic* Mechanisms

- Afferent arteriolar vasoconstriction leads to decreased filtration pressure across the glomerulus
- CNIs also stabilize the actin cytoskeleton of the glomerular podocytes



Elzinga Transplantation 1987

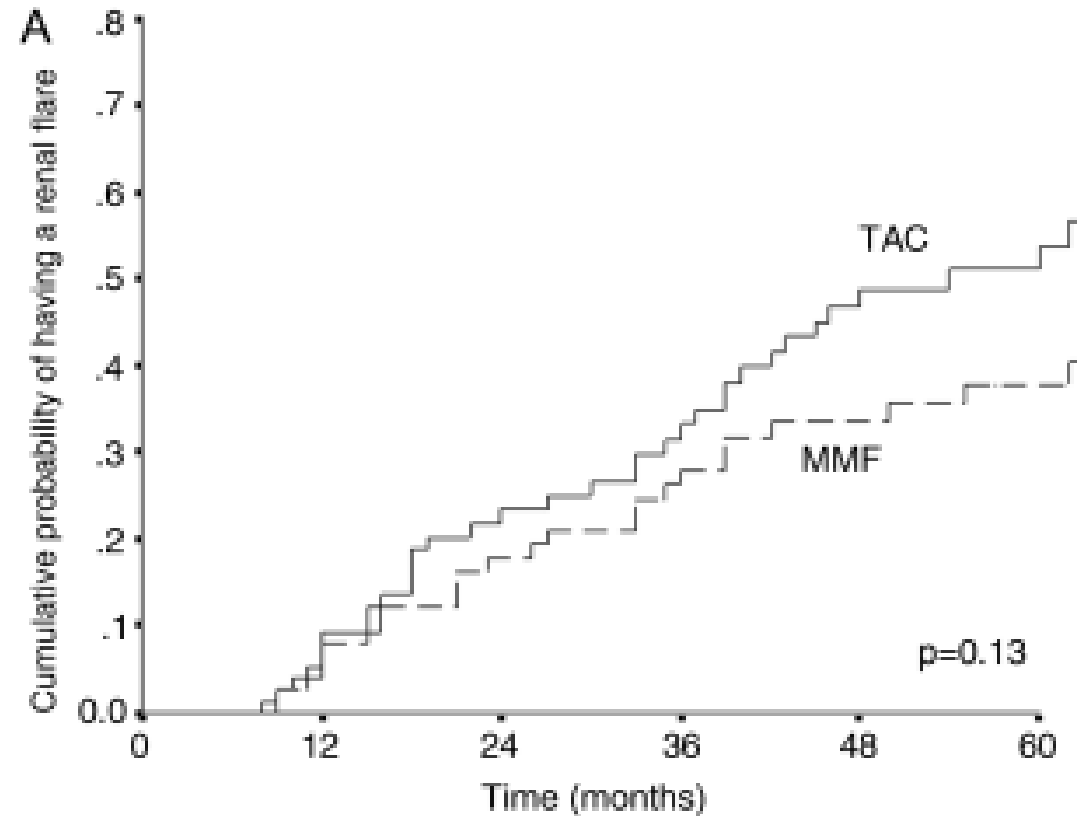
Tacrolimus vs MMF for Induction Therapy of Lupus Nephritis

Mok Ann Rheum Dis 2014

- 150 patients randomized to prednisolone 0.6 mg/kg/day X 6 weeks with either tacrolimus (.06 – 0.1 mg/kg/day) or MMF (2-3 g/day) for 6 months
 - No difference in complete remission rate at 6 months
- No difference in composite outcome of decline in GFR, stage 4/5 CKD or death between tacrolimus or MMF group, but MMF group had improvement in CrCl
- More renal flares in the tacrolimus group in long-term follow-up

Cumulative Probability of Renal Flare

Tacrolimus vs MMF for Induction Therapy of Lupus Nephritis: Increased Risk of Renal Flare with Tacrolimus
Mok Ann Rheum Dis 2014



Multitarget Therapy for Induction Therapy of Lupus Nephritis

Liu Ann Intern Med 2015

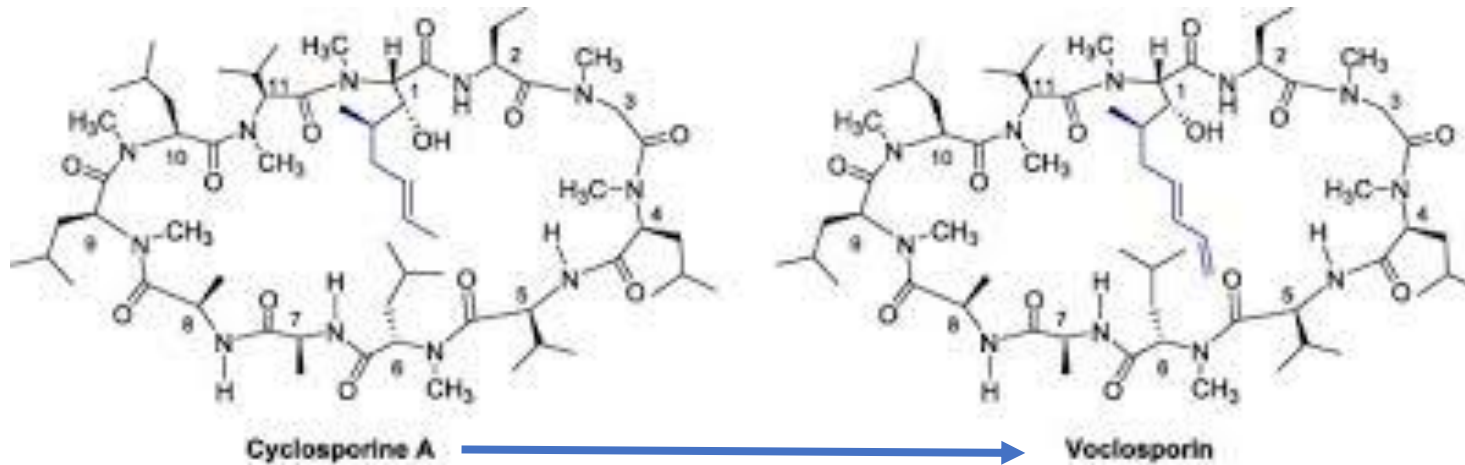
- Biopsy-proven lupus nephritis, Classes III, IV, V, III + V, IV + V
- Proteinuria of at least 1.5 g/day
- Serum creatinine 3 mg/dl or less
- Intravenous MP 500 mg/day X 3 days, then oral prednisone .6 mg/kg/day for 4 weeks, followed by taper for both groups
 - “Multitarget” group: MMF 500 mg bid + tacrolimus 2 mg bid
 - Other group: IV cyclophosphamide 750 mg/m² (.5 to 1.0 g/m²) every 4 weeks X 6 doses

Multitarget Therapy for Induction Therapy of Lupus Nephritis

Liu Ann Intern Med 2015

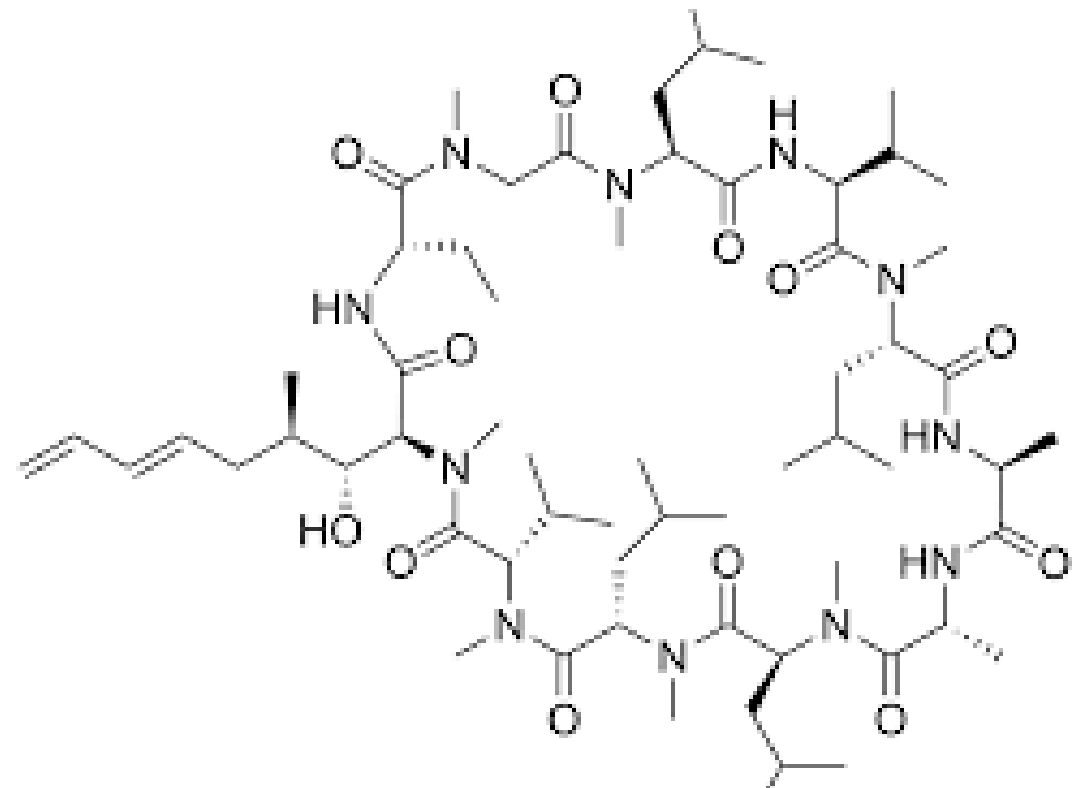
- 368 patients enrolled
- Median follow-up 11.9 weeks (!!!) in multitarget group and 6.6 weeks (!!!) in the IVCY group
- Multitarget group had greater reduction in urine protein (3.38 g vs 2.68 g)
- NO difference in renal function

The Hot New(ish) Calcineurin Inhibitor



Advantages of Voclosporin

- No need to monitor drug levels
- Fewer adverse effects on lipid and glucose metabolism compared to other CNIs

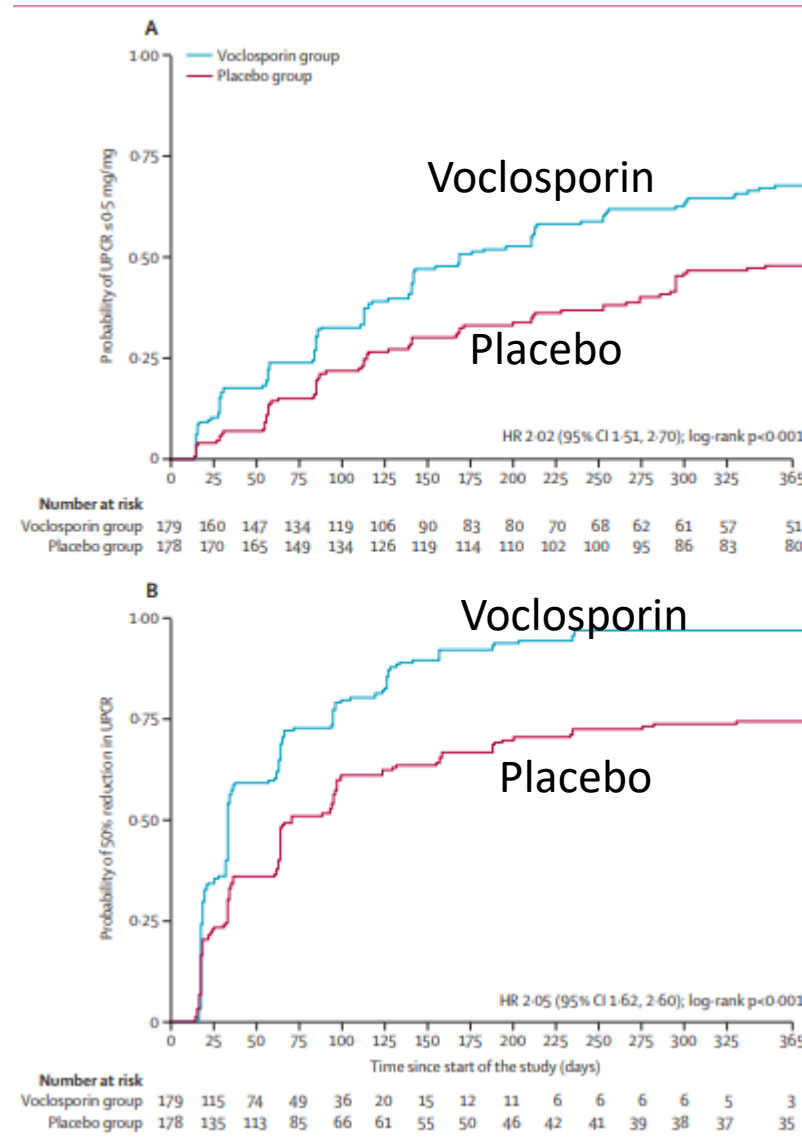


The Voclosporin Study that Sealed the Deal

Rovin et al Lancet 2021: 397: 2070-80

- RCT across 27 countries
- Class 3/4/5 lupus nephritis in a biopsy within the last 2 years
- Active nephritis
- GFR > 45 ml/min
- Everyone got intravenous methylprednisolone 250 or 500 mg Days 1 and 2 followed by prednisone 20-25 mg with rapid taper; everyone received MMF 1 g BID
- Study group: voclosporin 23.7 mg bid X 52 weeks versus placebo

The Positive Results were Driven by *Proteinuria*



U PCR < 0.5 mg/mg

50 % reduction in U PCR

Rovin Lancet 2021

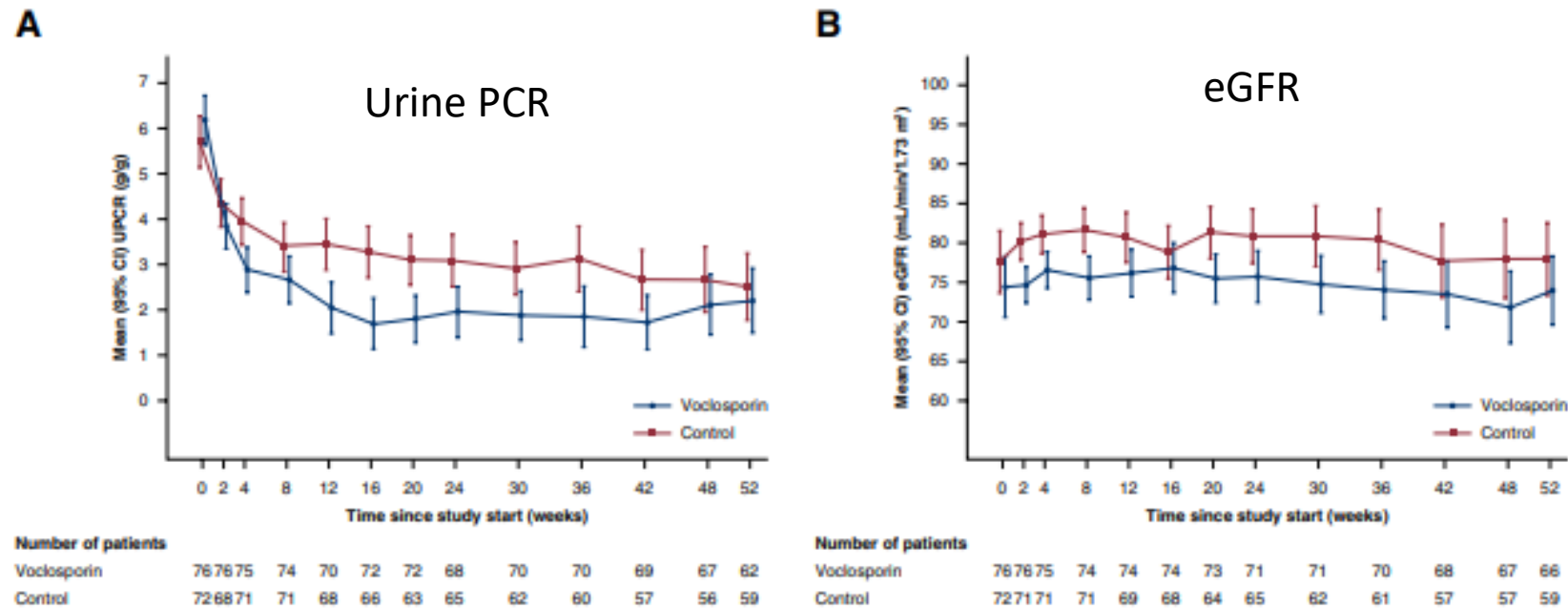
Post-Hoc Analysis of AURORA 1
*Menn-Josephy Clin J Am Soc
Nephrol 2024*

- If “success” of AURORA was driven by reduction in proteinuria, what about in the subgroup of patients with more proteinuria?
- This cohort: baseline UPCr > 3g/g and active class III or IV LN +/- Class V



Again: Greater Reduction in the Heavier Proteinuric Group with Voclosporin, but No Difference in GFR or Serology

Menn-Josephy Clin J Am Soc Nephrol 2024



So Voclosporin was a “Positive” Study

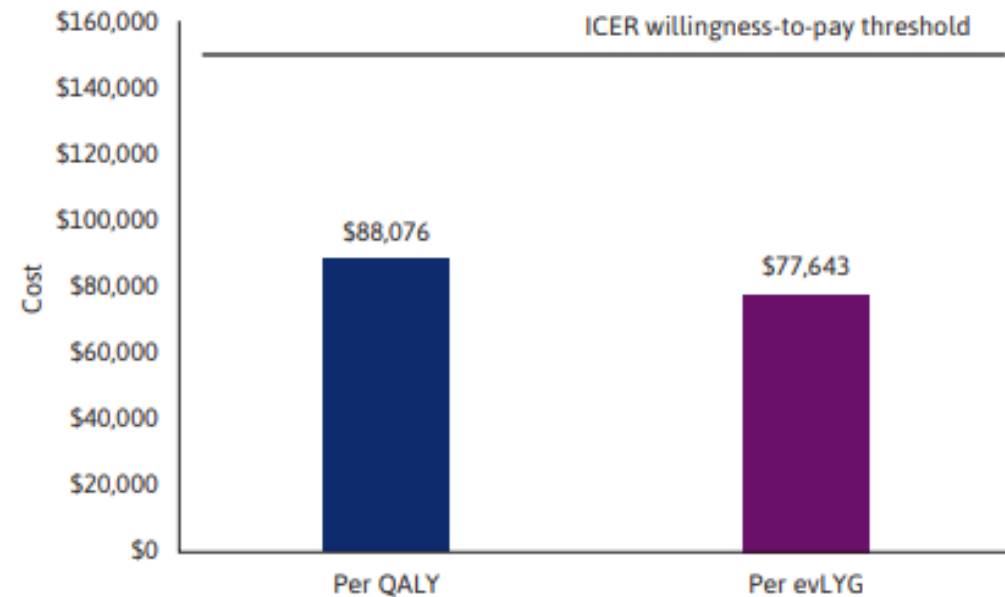
- What was positive?
 - GFR? **NO**
 - Lupus serology? **NO**
 - SLEDAI? **NO**



Incremental Cost-Effectiveness of Voclosporin for Lupus Nephritis

Kennedy JMCP.org 2024

- Analysis purports to show that voclosporin is cost-effective in an American model
- Previous analysis suggested QALY was \$149,260 USD
- Some authors of the analysis declared potential conflicts of interest with stock in the parent company



Okay, So CNI's May Drive Down Proteinuria on a Non-Immunologic Basis: Maybe That's Still Good?

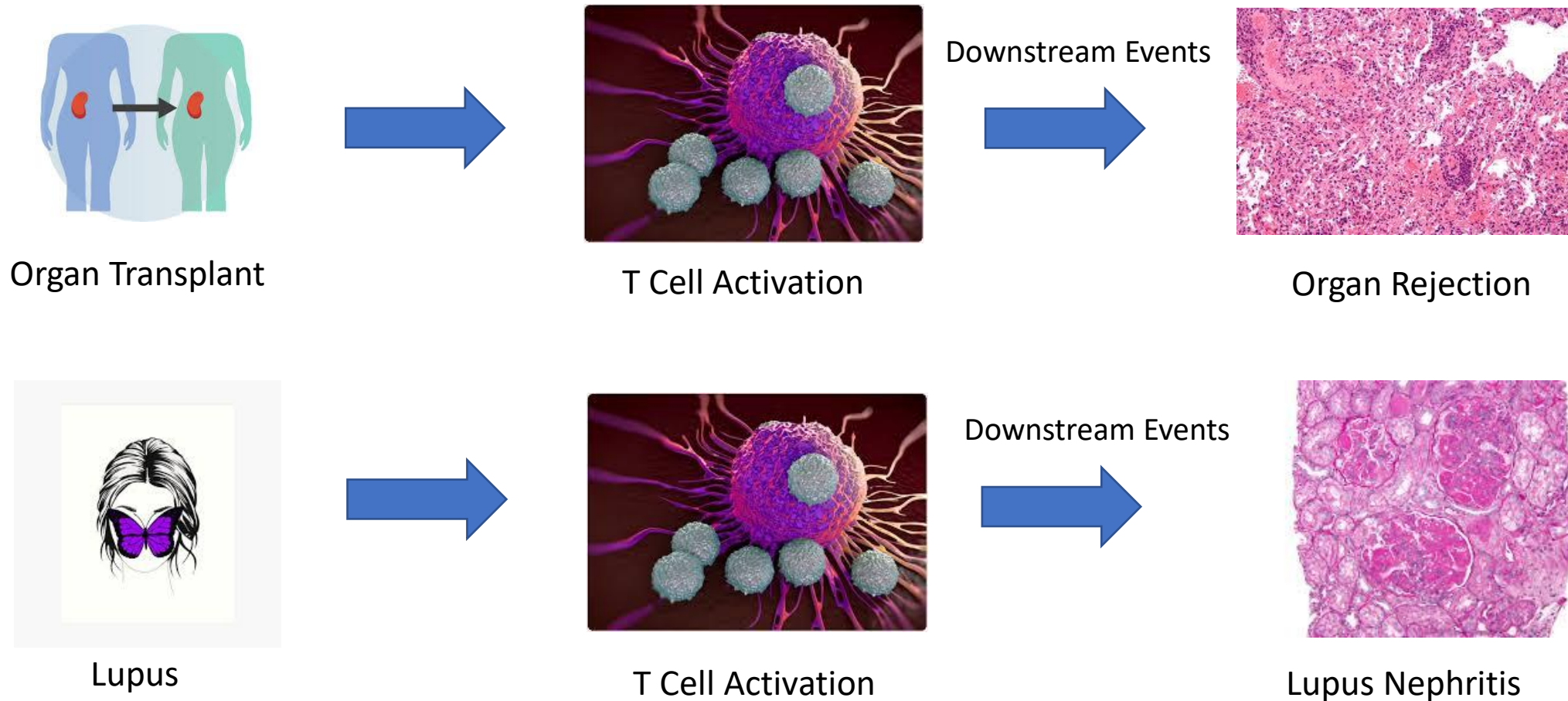
- I don't know
- Studies showing association of more proteinuria with worse outcomes heavily confounded by *non-response* and/or *non-adherence* and/or by *fixed damage*
 - all of these would be associated with worse kidney outcome
- Doesn't necessarily imply that driving down proteinuria will lead to better kidney outcomes

You May Argue: Calcineurin Inhibitors Are Immunosuppressive So They Should Work in Lupus

- These drugs block T cell activation and downstream events (cytokine and B cell proliferation)
- They are the mainstay of anti-rejection therapy for organ transplantation
- So wouldn't they work immunologically for lupus nephritis?



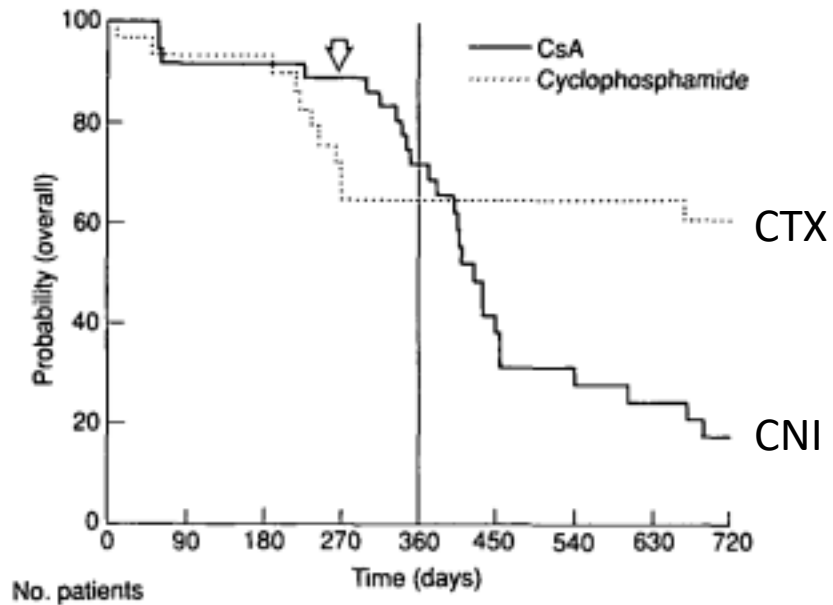
Is What's Good for Rejection Good for Lupus?



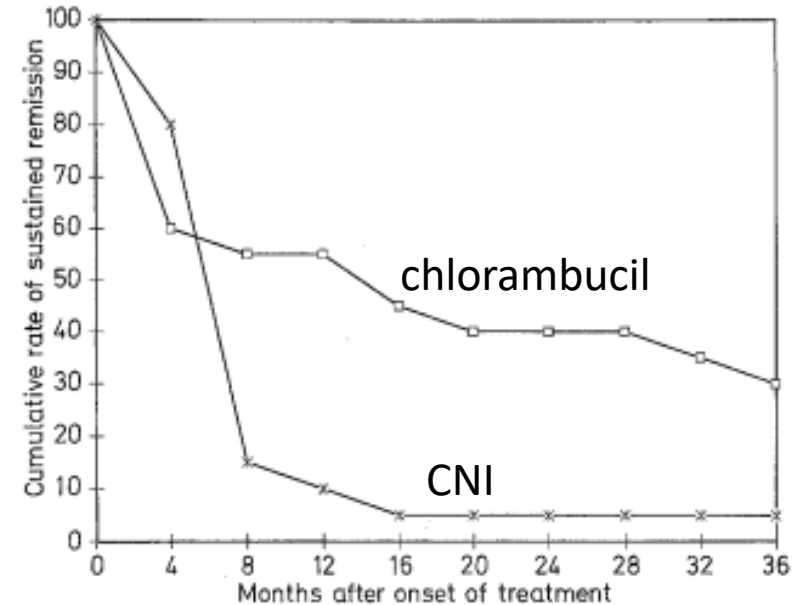
Idiopathic Nephrotic Syndrome: High Rate of Relapse When CNIs Are Stopped

Ponticelli Neph Dial Transpl 1993; Niaudet Pediatr Nephrol 1992

Idiopathic Nephrotic Syndrome



Pediatric Nephrotic Syndrome

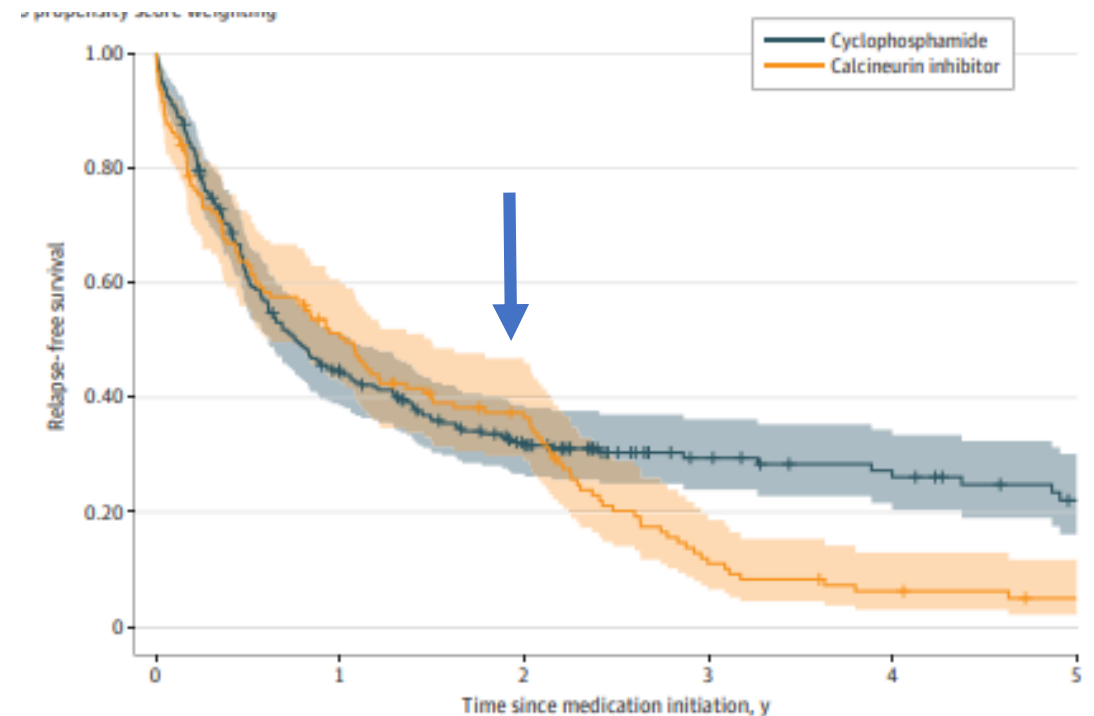


Probability of Remaining Free of Relapse

Comparative Efficacy in Childhood Nephrotic Syndrome

Robinson JAMA Pediatrics 2025

- Target trial emulation
- Children with steroid-sensitive nephrotic syndrome
- 252 children received cyclophosphamide and 131 CNIs
- Relapses more common in the CNI group compared to cyclophosphamide
- About 60% of children relapsed while on CNI and *almost all relapsed once CNI withdrawn*



A Mistake?

Calcineurin Inhibitors in Lupus Nephritis

- They are recommended in the latest guidelines
- I wonder if this might change in the next decade with studies that don't just focus on reduction of proteinuria as a positive outcome
- These agents may be eclipsed by those focusing on B cell dysregulation

Mistake: Not Using 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



We Need to Keep Antimalarial Drugs on the Radar

- 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
 - reduction in neonatal lupus
 - decreased thrombosis risk

Mistake: Using the Urinalysis as a Response Index

- The American College of Rheumatology Advisory Panel (comprised mainly of rheumatologists and internists !) used number of red cells and red cell casts as an index of flare or response
- I think number of cells or casts on a slide depends on how long you spin the urine, and how hard you re-suspend the pellet
- also, mesangial proliferative (Class II) lupus may have RBC casts in the urine but is associated with excellent long-term kidney outcome

A Phone Call/Email I get Too Often



I have a patient with lupus nephritis who I treated with MMF and isn't getting better. Should I use Rituximab?

Mistake: Escalating Therapy Because of Persistent Proteinuria

- This isn't minimal lesion disease
- The occasional patient will have resolution of proteinuria quickly, but in the majority of patients it takes longer than you think
- Sometimes the proteinuria gets worse before it gets better



Lessons We Have to Learn from Primary Membranous Nephropathy

- there is a lag between disappearance of the putative 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

Primary Membranous Nephropathy: Resolution of Proteinuria Lags Behind Immunologic Remission
Beck and Salant Kidney Int 2010

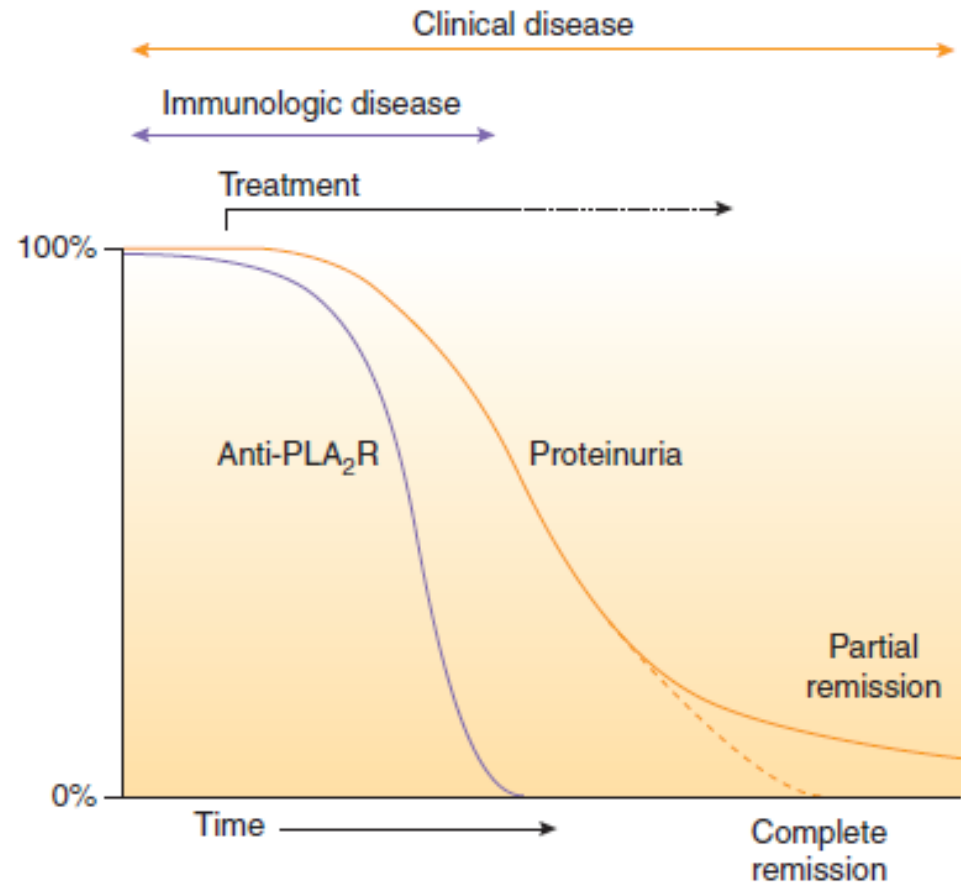
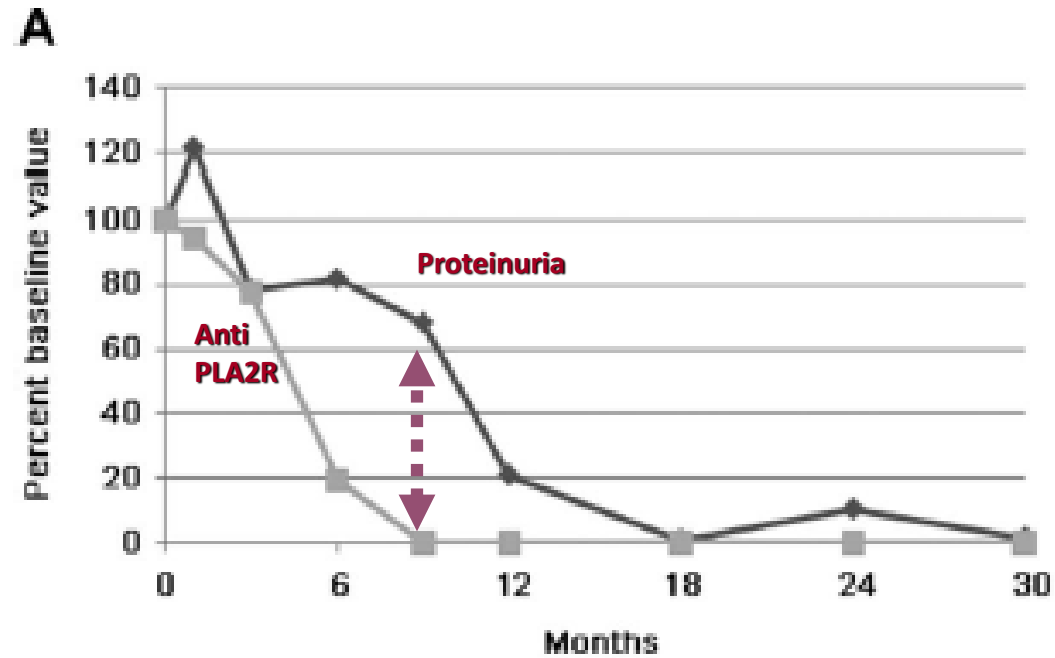


Figure 1 | Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA₂R) in idiopathic membranous nephropathy.

Lag Between Disappearance of Antibody and Improvement in Proteinuria: Rituximab



Probably the Same Phenomenon in Lupus Nephritis

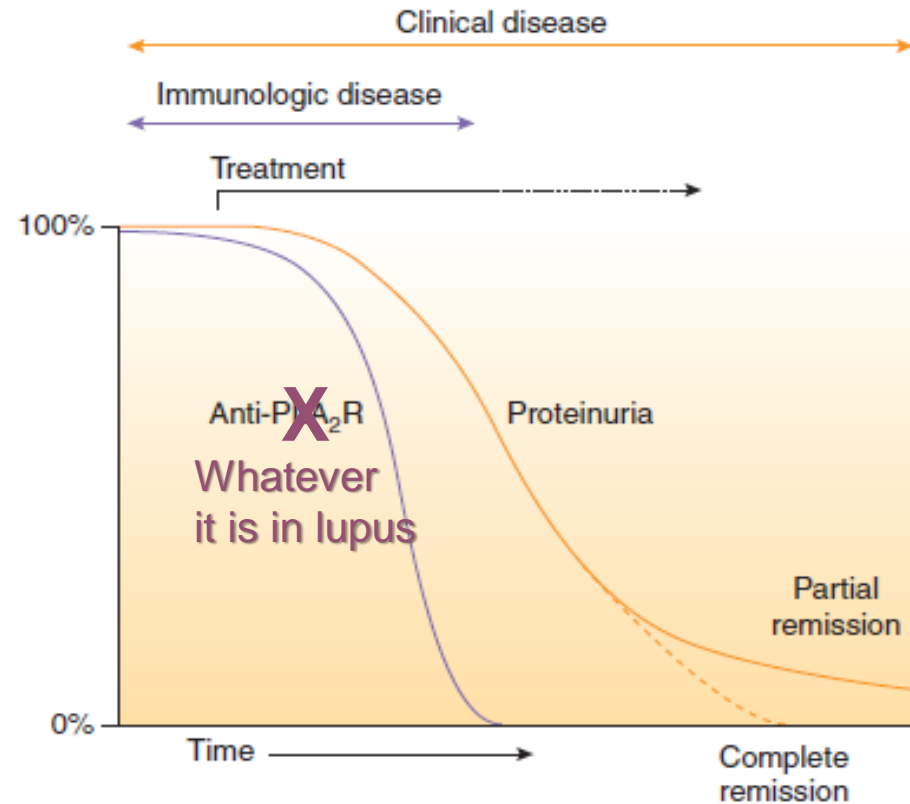
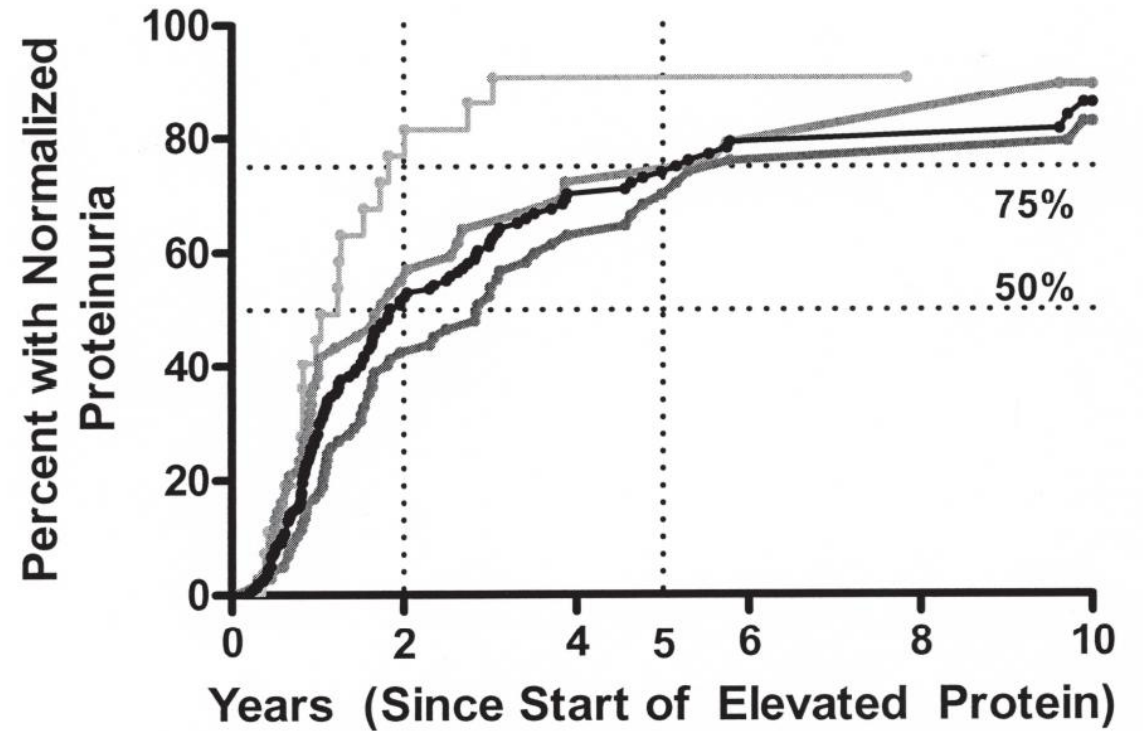


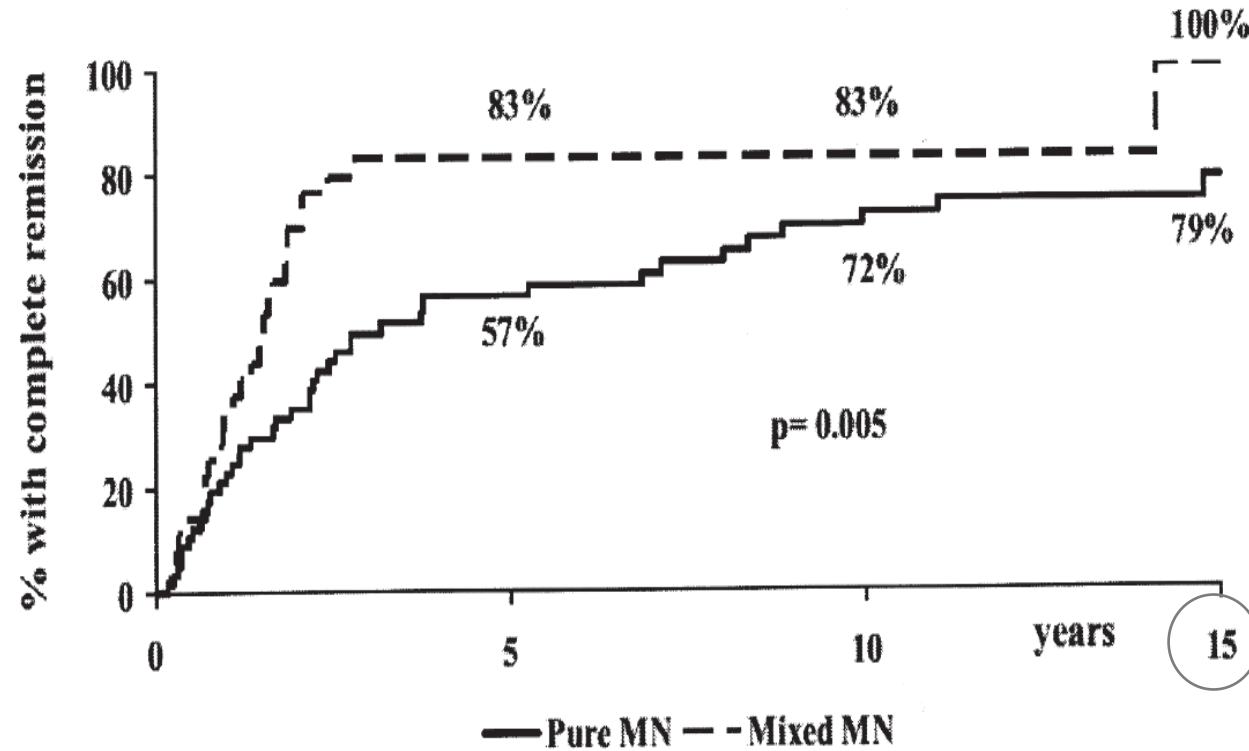
Figure 1 | Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA₂R) in Lupus nephritis.
~~idiopathic membranous nephropathy.~~

Mistake: It Takes A Lot Longer from Proteinuria to Resolve than You Think: The Toronto Lupus Cohort

Touma J Rheum 2014



Timeline for Resolution of Proteinuria in Lupus Nephritis (Italy)



||| *Abwarten
und Tee
Trinken*



There is No Magic Bullet in Lupus Nephritis...

- Most bad outcomes in lupus are the result of nonadherence to therapy
- However, there are rare lupus patients who are adherent but who have terrible disease
- As of 2026, there are no miracle treatments for lupus
 - just because a new medicine is \$175k/QALY, doesn't mean it's going to help



Remember What Galen Said

*Everything works in mild
disease, and nothing
works
in severe disease*



Mistake: Forgetting About Nonadherence as the Commonest Cause of Treatment Failure

- the cruel joke of lupus is affecting young, predominantly female patients and having the principal medication lead to profound physical changes
- medication adherence is hard enough in young people without adding on the side effects of lupus drugs
- I think non-adherence is much higher than we imagine



Mistake: Resistant Lupus Nephritis (2012)

- “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)”



Why Was KDIGO Wrong?



- the major causes for “nonresponse” is not addressed in the 2012 guidelines: 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

If You Nag Long Enough...

| | |
|---|---|
| 1 | <ul style="list-style-type: none">• Verify adherence (check mycophenolic level if on MMF/check infusion records if on CYC) |
| 2 | <ul style="list-style-type: none">• Repeat biopsy if concern for chronicity or other diagnosis (e.g., TMA) |
| 3 | <ul style="list-style-type: none">• Switch from MMF to CYC or vice versa |
| 4 | <ul style="list-style-type: none">• Consider regimen with combined MMF/CNI “multi-target” therapy <i>or</i>• Addition of rituximab <i>or</i>• Consider prolonged course of i.v. pulse CYC |
| 5 | <ul style="list-style-type: none">• Consider i.v. Ig <i>or</i> plasmapheresis (especially in setting of concomitant TMA or refractory APS) though there is minimal evidence outside of case reports |

New KDIGO Recommendations 2021

How to Increase Adherence

- I don't know!
- many patients are not told that lupus is a life-threatening disease
- I tell them that it is like being diagnosed with cancer
 - they are going to go through a bad phase with physical changes but will come out the other end in better shape

Mistake: The Unnecessary or High-Risk Renal Biopsy (I)

- Patient presents with explosive lupus, elevated creatinine, blood and protein in the urine
 - why do they need a renal biopsy at that time?
 - you know what the diagnosis is
 - it's probably a high-risk biopsy too (high blood pressure, elevated creatinine)



The Unnecessary or High-Risk Renal Biopsy (II)

- or the patient presents with severe extra-renal lupus that mandates intensive immunosuppressive therapy anyway
- what is the rationale for doing a kidney biopsy at that point?



When *Should* a Lupus Patient Have a Kidney Biopsy?

- A kidney biopsy is probably more informative around a decision to *decrease* immunotherapy
 - worsening proteinuria in the face of otherwise-improving lupus
(but don't forget the mistake – depending too much on the urinary findings)
 - rising creatinine in the face of otherwise-improving lupus
- To rule out other causes of renal involvement
 - thrombotic microangiopathy if patient anti-phospholipid antibody positive
(although biopsy often too high-risk)
 - other suspect medications, or co-morbid disease like diabetes

Mistake: Forgetting to Address Pregnancy

- 17 year old high school student develops lupus and diffuse proliferative nephritis
- Elevated creatinine, 4g proteinuria
- treated with high dose corticosteroids and MMF
- attends follow-up clinic looking ecstatic:

“Doctor! I’m so excited! I’m going to have a baby!”

Forgetting to Address Pregnancy



Forgetting to Address Pregnancy

- the patient may not know that pregnancy during a lupus flare is high-risk, *unless you tell her*
- additional risk of teratogenic medications
 - Cyclophosphamide
 - MMF
 - ACE-inhibitors, ARBs



Summary: Mistakes in the Treatment of Lupus Nephritis

1. Corticosteroids are still important.
2. Anti-malarial drugs are very helpful, and under-used by non-rheumatologists.
3. Calcineurin inhibitors may reduce proteinuria on a non-immunologic basis, but that doesn't mean they are treating lupus nephritis.
4. Just because a drug is old and cheap doesn't mean it doesn't work.
5. Just because a drug is new and expensive doesn't mean it's better.

Summary: Mistakes in the Treatment of Lupus Nephritis

6. Nonadherence is the commonest cause of “treatment resistance” or failure. Minimize drugs!
7. If a patient doesn’t show up to clinic, they have stopped taking their medicine.
8. You don’t have to do a renal biopsy in the face of an obvious diagnosis, especially if it is high-risk.
9. Don’t forget to counsel about pregnancy *before* it happens.

Ευχαριστώ πολύ

Thank You

