4ο ΔΙΑΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗ ΡΕΥΜΑΤΟΛΟΓΙΑ 2022-24

ΠΡΟΓΡΑΜΜΑ 6ου ΚΥΚΛΟΥ
Σάββατο 17 Δεκεμβρίου 2022
ΣΥΣΤΗΜΑΤΙΚΕΣ ΡΕΥΜΑΤΙΚΕΣ ΠΑΘΗΣΕΙΣ Ι (ΣΕΛ - ΑΝΤΙΦΩΣΦΟΛΙΠΙΔΙΚΟ ΣΥΝΔΡΟΜΟ)

ΘΕΡΑΠΕΙΑ ΝΕΦΡΙΤΙΔΑΣ ΣΕΛ

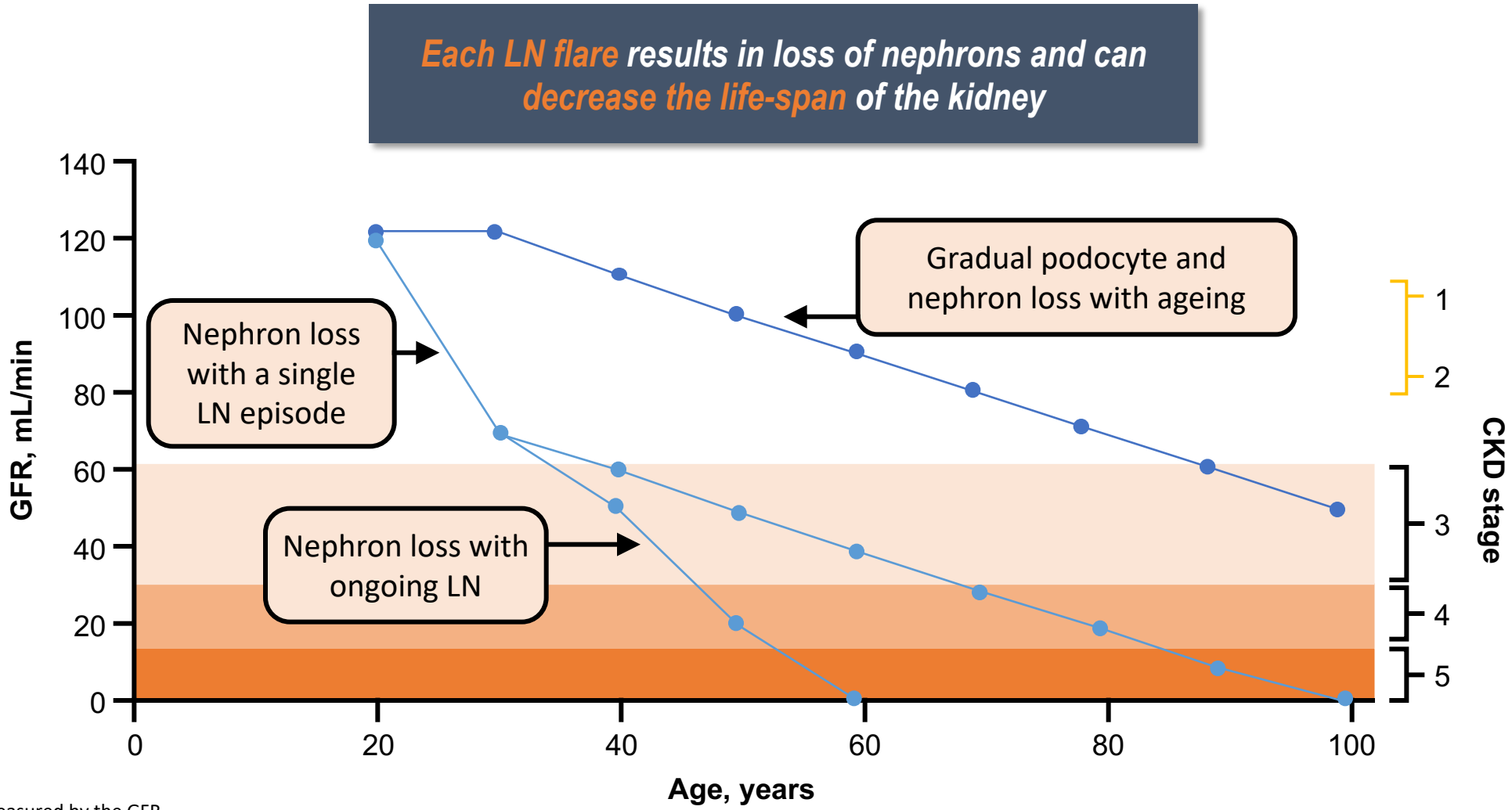
ΔΗΜΗΤΡΙΟΣ Τ ΜΠΟΥΜΠΑΣ

ΕΚΠΑ –ΠΓΝ ΑΤΤΙΚΟΝ ΚΑΙ ΙΙΒΕΑΑ

ΕΚΠΑΙΔΕΥΤΙΚΟΙ ΣΤΟΧΟΙ

- Περίπτωση
- Στόχοι θεραπείας και χρονικός ορίζοντας επίτευξης
- **Εξειδίκευση αναλογα με τον ιστολογικό τύπο και τη βαρύτητα**
- Γενικός αλγόριθμος θεραπειας
- Περιπτωσεις ασθενών
- Σημαντικες λεπτομερεις και πιθανές αστοχίες
- Κυρια σημεία
- Ερωτησεις πολλαπλης επιλογής

Early diagnosis and treatment of lupus nephritis reduces the risk of ESKD[a]



[a] Kidney function measured by the GFR.

CKD = chronic kidney disease; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; LN = lupus nephritis.

Anders HJ, et al. Nat Rev Dis Primers 2020;6:1–25.

Case: Severe or mild? To biopsy or not ? How to treat?

Remember: Rx may modify the clinical presentation of severe LN.

- 16 yo male (60kg) with *active SLE*: SLEDAI 10
- *Active Serology*: low C3 and C4, anti-DNA positive at low titer.
- Normal Cr, albumin and HCT
- UA: *trace protein (300 mg/dL), 5-10 RBCs in the urine (dysmorphic?),* no cellular casts!

- Treated with hydroxychloroquine and prednisone 20 mg/day
- Referred to you 4 weeks later

- Now SLEDAI is now 4 (rash, serology). *UA: trace protein and hematuria*

High or low risk for LN? Would you biopsy him or not and why?

What do you think the renal biopsy will show

ow would you treat?

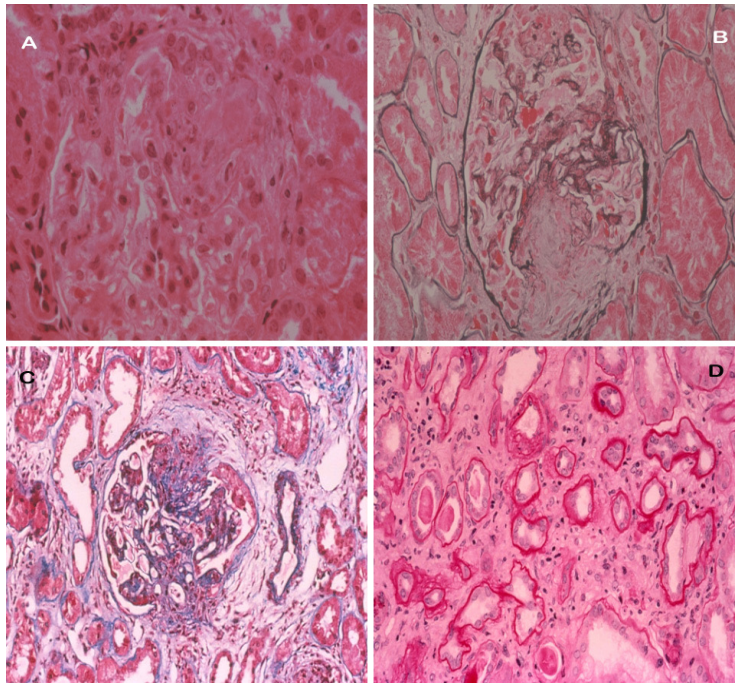
Case 1 Continued

- A closer look at a “fresh” urine sediment showed glomerular hematuria with 20-40 RBCs and cellular casts?

- Would you biopsy?

Essential studies and what to look for in the report

- ***Always light microscopy: H@E; PAS (Silver):basement membrane ; Trichrome (scarring).***
- ***Electron microscopy useful especially for early proliferative disease (subendothelial deposits)***
- ***Immunofluorescence-not absolutely necessary if typical lupus***
- ***Make sure specimen is adequate (at least 7-8 glomeruli) and then look for these two things which are the stronger components in the activity and the chronicity index !!!***

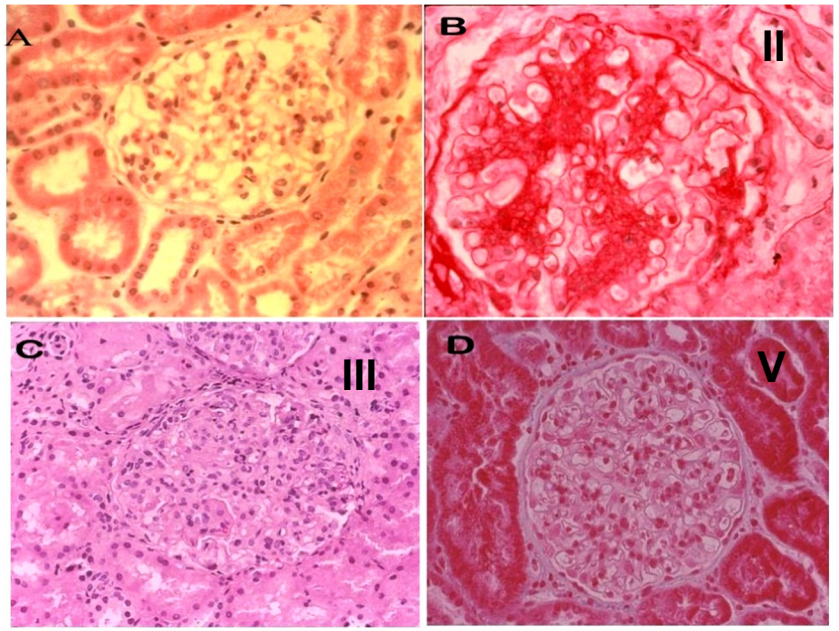


- Activity (fibrinoid necrosis/crescents)
- Chronicity (tubular atrophy/interstitial fibrosis)

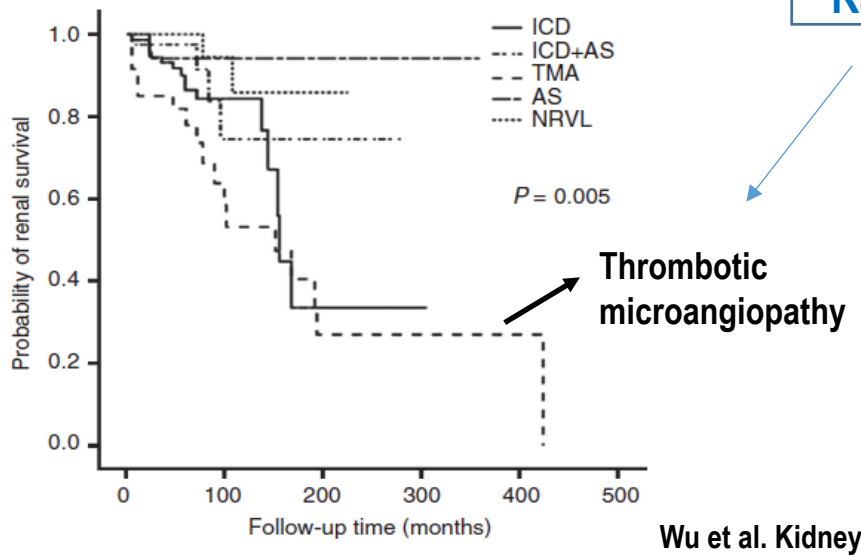
EULAR :Pathological assessment of the kidney biopsy

- **International Society of Nephrology/Renal Pathology Society 2003 classification** [class I → VI] **(Grade: C)**

- **Pathology report;**
  1. **Acute glomerular lesions («activity»)**
  2. **Chronic glomerular lesions («chronicity»)**
  3. ***Tubulo-interstitial lesions (acute/chronic)***
  4. **Vascular bed lesions (associated with aPL) (Grade: A/C)**

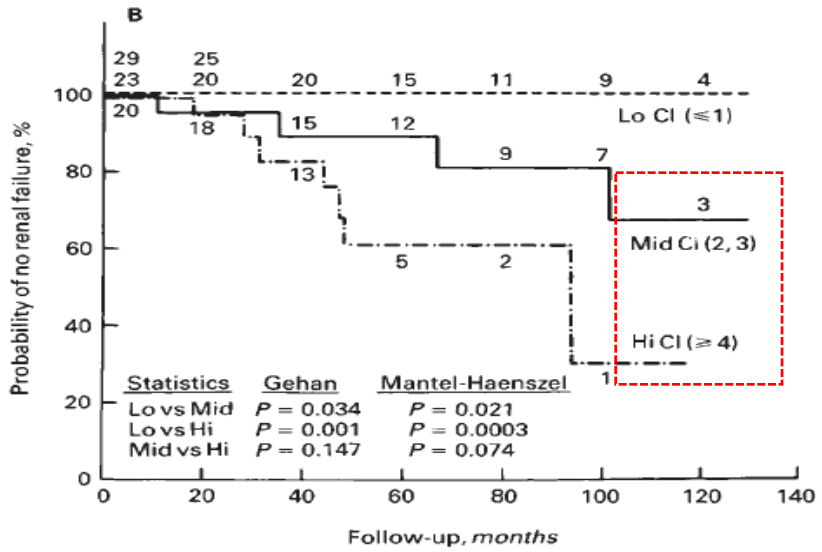


Rare



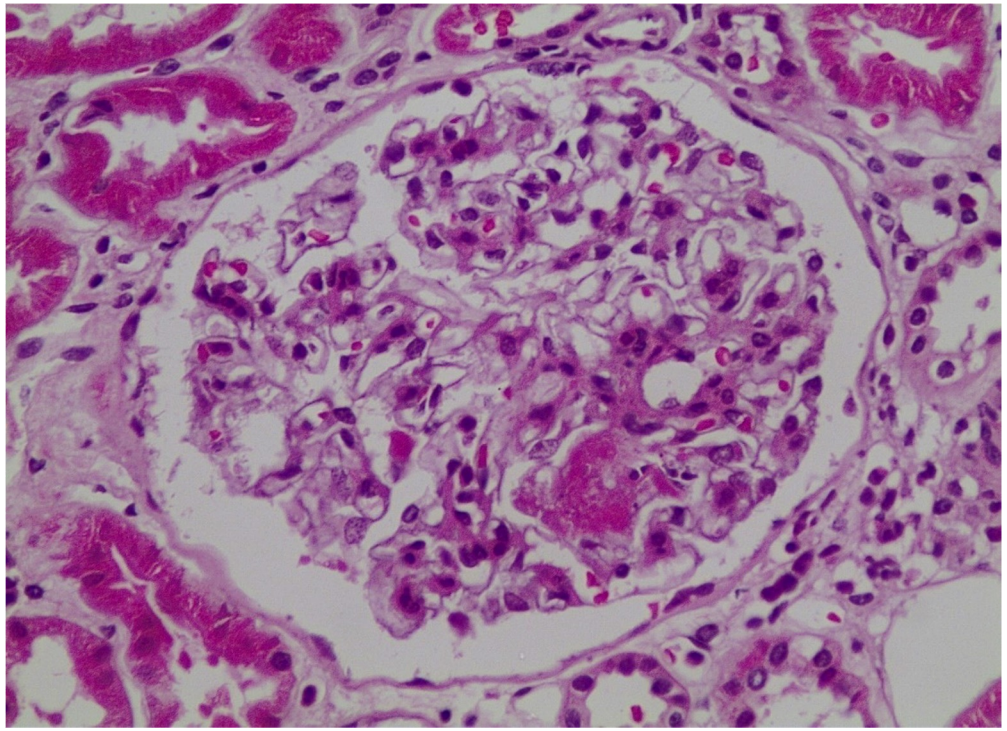
Thrombotic microangiopathy

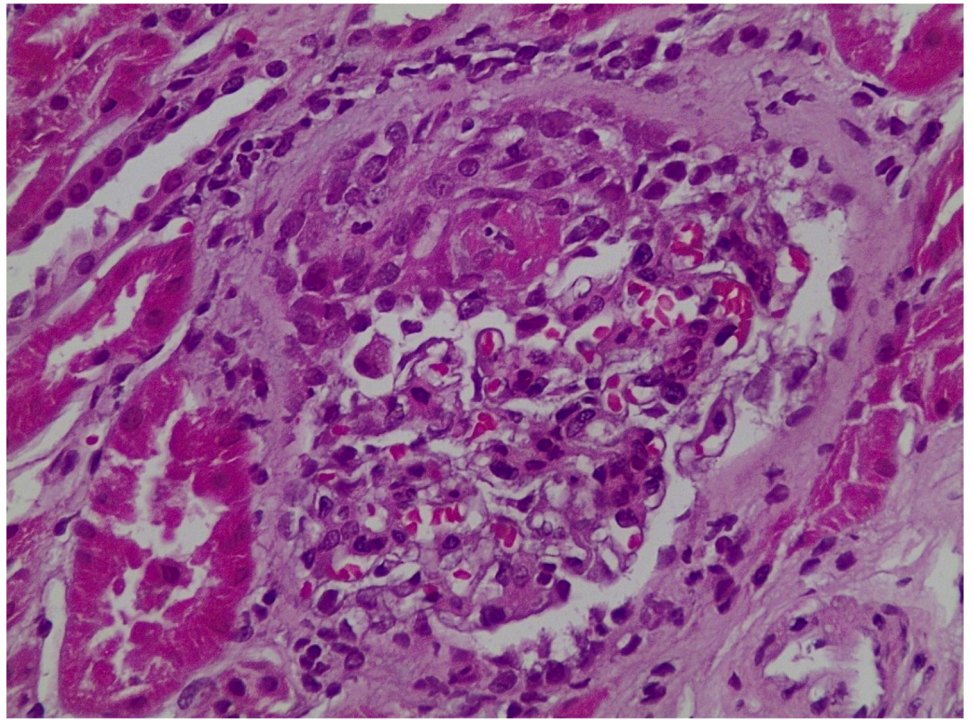
Wu et al. Kidney Int. 2013

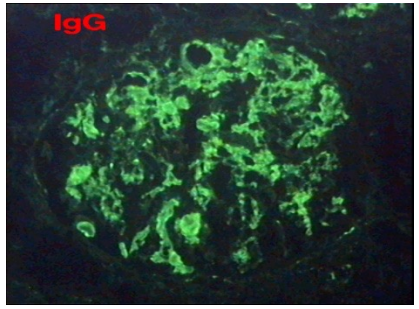


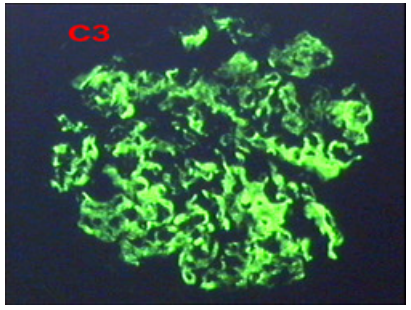
Case: Biopsy report

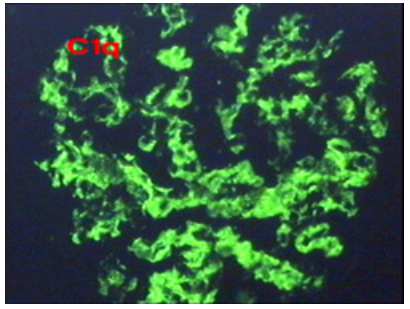
Focal proliferative Class III; early crescents AI 7 CI 0); full house granular membranous immune deposits











Case Continued

- Did this change your management?
- For us, it did in a major way!!!
- 3 pulses of IV-MP and started MMF with 20 mg/prednisone for 4 weeks to be tapered in 3 months to 5 mg /day
- More rigorous monitoring

Take home message in LN : Do not ignore isolated hematuria . Clinical presentation may fool you!!!

Isolated hematuria and renal biopsy: the nephrologists view

➢ *Isolated hematuria IS NOT an indication for biopsy unless*

- **Family history** of renal disease
- Suspicion for **systemic disease**

•In the case of SLE higher index of suspicion if active serology and active lupus

Rahman P[1], Gladman DD, Ibanez D, Urowitz MB. Significance of isolated hematuria and isolated pyuria in systemic lupus erythematosus. Lupus. 2001;10(6):418-23

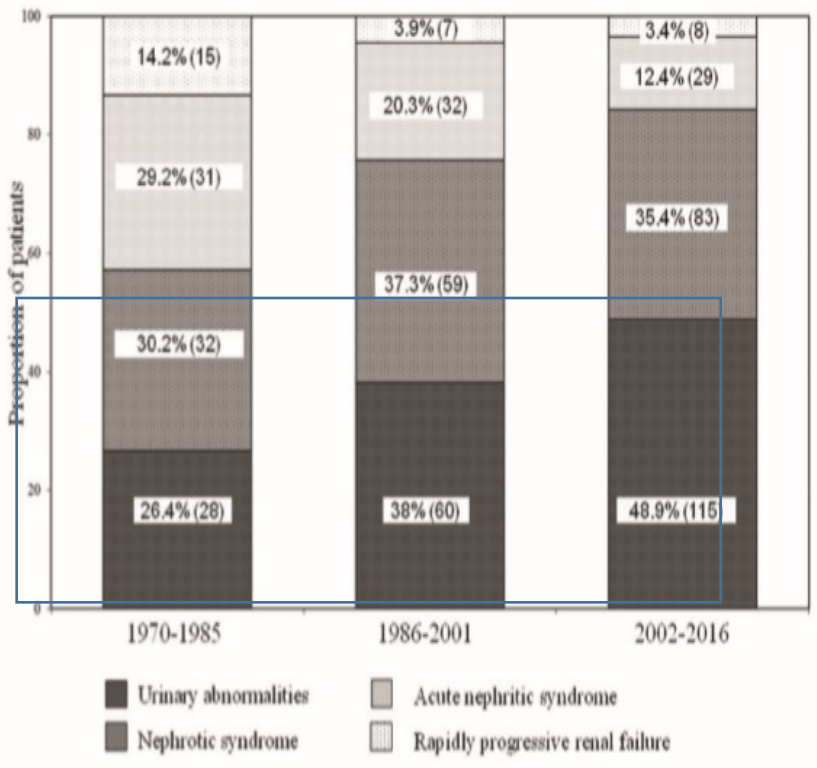
Lupus nephritis is an evolving dynamic process

Earlier biopsies better prognosis (1970-2016

To cite: Moroni G, Vercelloni PG, Quaglini S, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2017-212732

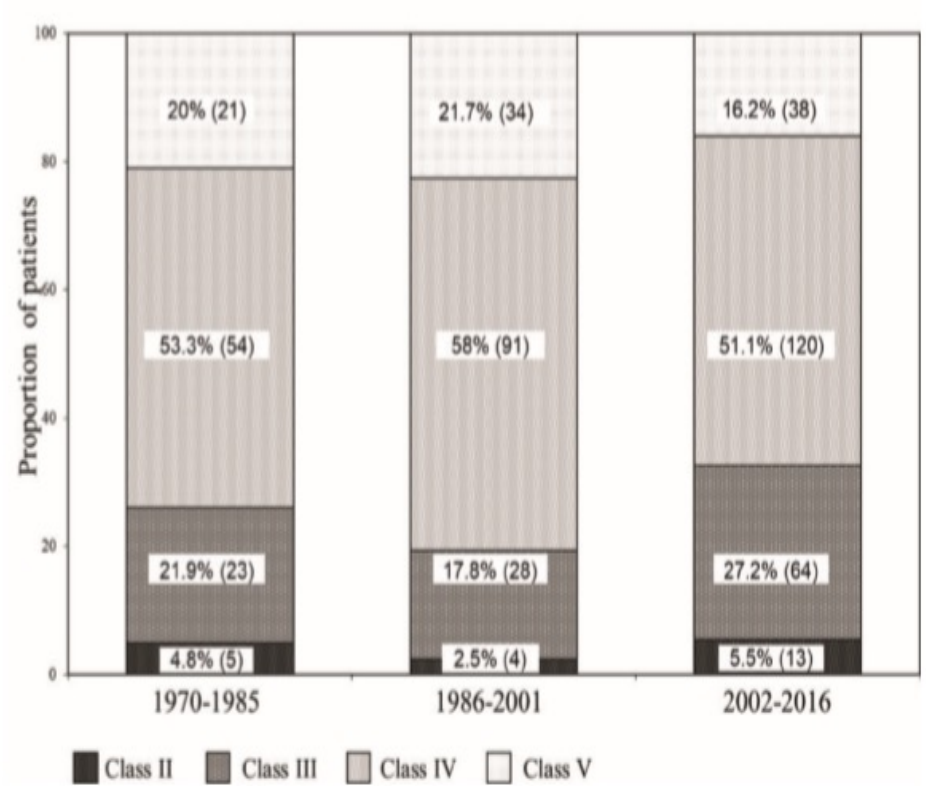
Survival without ESRD rose from 80% to 90% at 20 years
Males, HTN, no maintenance immunosuppression, increased Cr, high AI and CI: predictors of ESRD

Renal insufficiency at presentation decreased and isolated urinary abnormalities increased



No changes in histological class and activity index but chronicity index decreased

B



Hematuria vs proteinuria in diagnosis and monitoring/prognosis

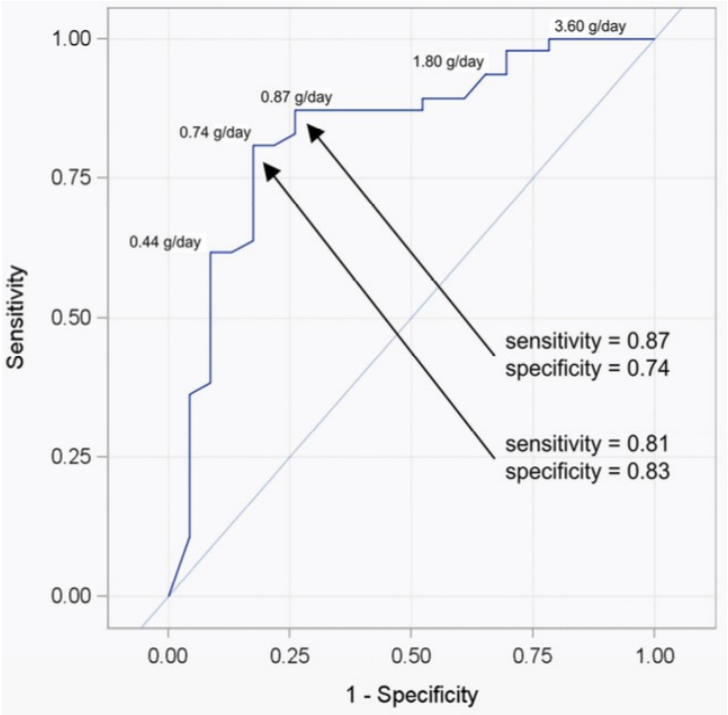
- **Hematuria is valuable and sensitive marker of renal activity!!! BUT**

  -Not a good prognostic marker

- **Not all definitions of remission include inactive sediment**

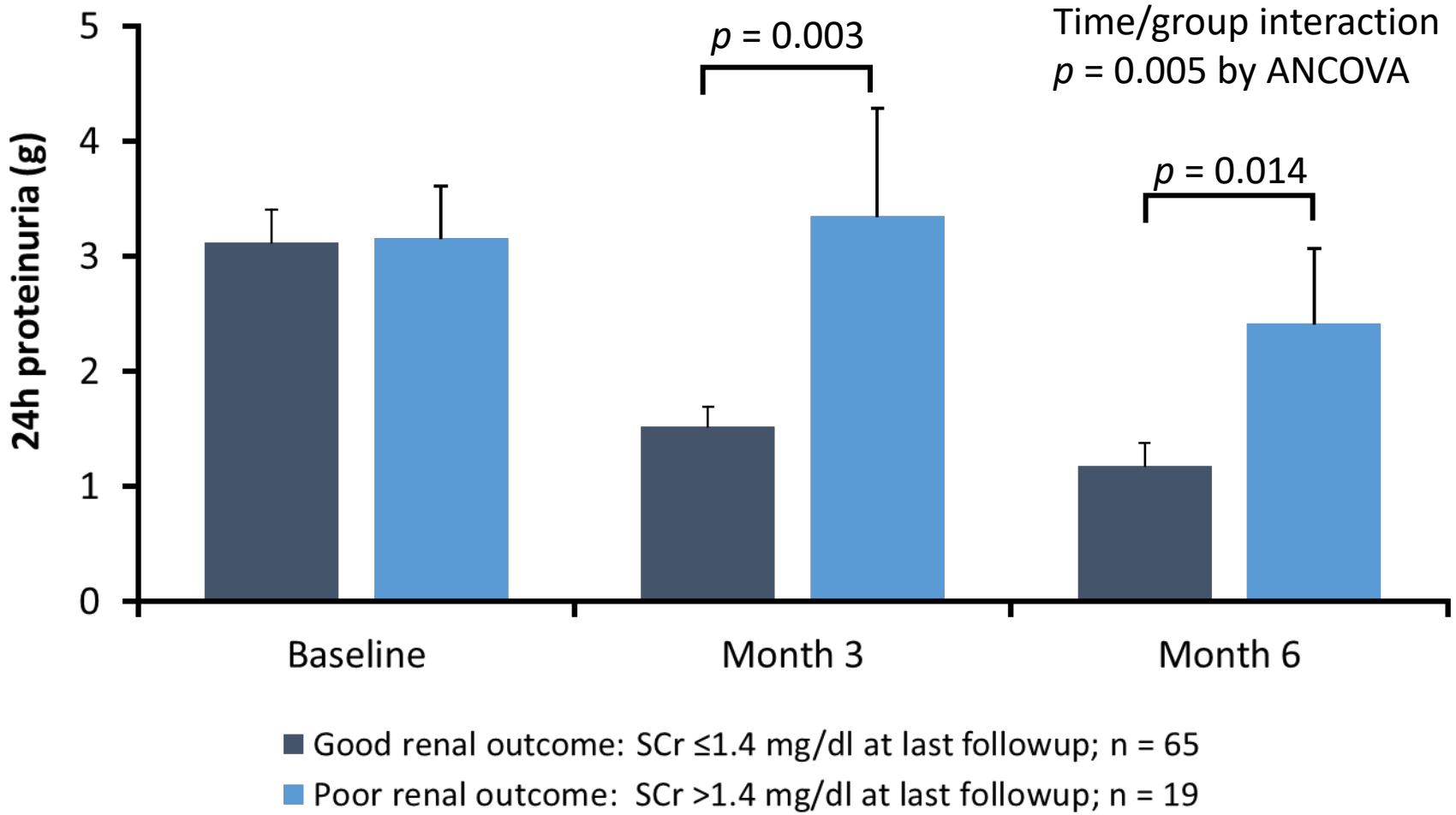
- **Proteinuria a better prognostic marker**

- **Proteinuria less than 700 mg 12 mon after treatment is a good prognostic marker**



Dall'Era M *et al*. *Arthritis Rheumatol* 2015; Epub ahead of print

Early (3 to 6 months) response (i.e. ≥50% reduction in UPCR) predicts favorable long-term (>10 years) outcome



Houssiau FA *et al*. *Ann Rheum Dis* 2010; 69: 61

Therapeutic goals in lupus nephritis

✓ **First 3 months**	➔	any improvement (25%) in UPCR, stable GFR ±10%
✓ **6 months**	➔	reduction by ≥50% in UPCR
✓ **12 months**	➔	<0.8–1 g/24hr UPCR (or, at least ≥50% in UPCR)
✓ **24 months**	➔	<0.5 g/24hr

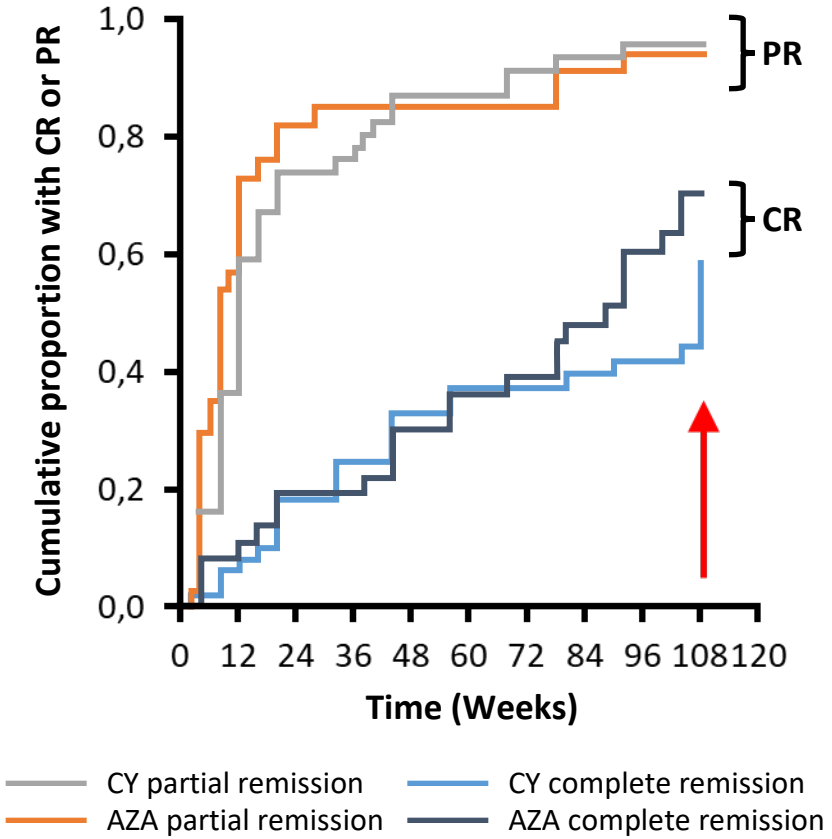
Targets not achieved? Worsening of nephritis? Mod/severe relapse?

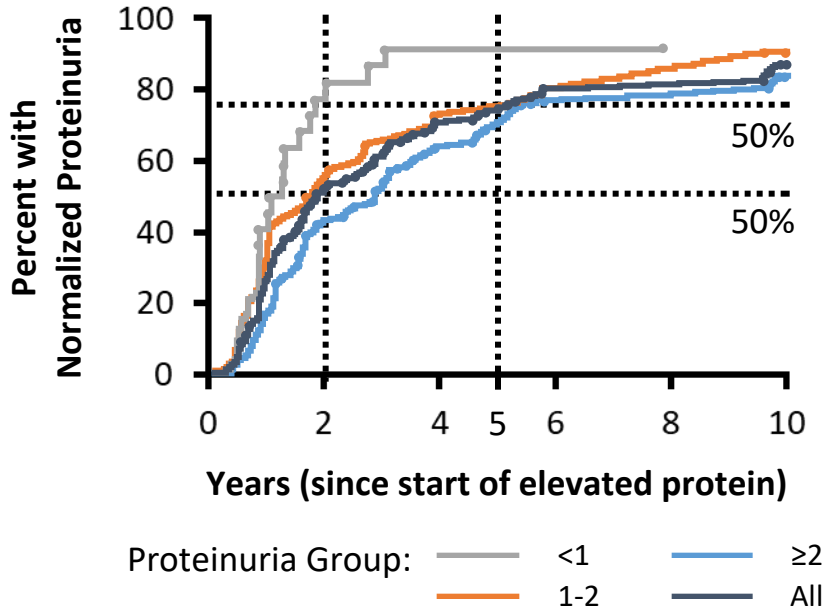
Consider **repeat kidney biopsy**
(activity vs. chronicity)

- Switch MMF ⟷ CYC
- High-dose IV-CYC
- Rituximab
- Comb MMF + CNI

Fanouriakis A, Bertsias G. *EMJ Nephrol*. 2015; 3: 83-89; Dall' Era M, et al. *Arthritis Rheumatol*. 2015; 67: 1305-13

The higher the level of baseline proteinuria, the longer it takes to clear





Kaplan-Meier curve for time to recovery from proteinuria in all patients and in 3 groups

Resolution of proteinuria (UPCR <0.5):

- ✓ 28% within 1 year
- ✓ **52% within 2 years**
- ✓ another 22% within 5 years

Grootscholten C, et al. *Kidney Int*. 2006; 70:732-42
Touma Z, et al. *J Rheumatol*. 2014; 41:688

Take home messages

- **Identify patients at higher risk to develop nephritis** and look for renal disease especially when active by urinalysis
- **Do not underestimate hematuria-especially if active serology and extrarenal lupus**
- **LN is a dynamic**: be aware of evolvement into more severe form while awaiting
- ***Low threshold for renal biopsy. If you think about it, just do it (***unless contraindicated)
- ***Look for crescents/fibrinoid necrosis and tubular atrophy and interstitial fibrosis***
- **Stratify** according to severity (histologic and clinical factors) and treat accordingly
- **Targets of therapy** now defined
- **Proteinuria** is a good prognostic factor -if below 0.7 mg/dl- irrespective of hematuria
- **Hematuria/active urine sediment** reliable ***indicators for activity and flare*** *but not for prognosis*

TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Mild					
1st line	HCQ	GC PO/IM			
Refractory	HCQ	GC PO/IM	MTX/AZA		
Moderate					
1st line	HCQ	GC PO/IV	MTX/AZA	CNI	MMF
Refractory	HCQ	GC PO/IV	BEL	CNI	MMF
Severe					
1st line	HCQ	GC PO/IV	MMF	CYC	
Refractory	HCQ	GC PO/IV	CYC	RTX	

Adjunct:

Sun protection
Vaccinations
Exercise
No smoking
Body weight
Blood pressure
Lipids
Glucose

Antiplatelets
Anticoagulants
(in aPL-positive patients)

TARGET:

Remission:
SLEDAI = 0;
HCQ; No GC

Low Disease Activity
SLEDAI <=4; HCQ - Prednisone <= 7.5 mg/d
Immunosuppresives (in stable doses – well tolerated)

Landmark Trials in Lupus Nephritis

Pollak
- Classify LN by biopsy
- Long vs. short course steroids

1964

Austin
- NIH trial
- Cytotoxics vs. steroids

1986

Boumpas
- CYC + steroids vs. steroids alone

1992

Gourley
- Steroids vs. CYC vs. combo

1996

Chan
- MMF + steroids vs. CYC +
- steroids

2000

Houssaiu
- EuroLupus
- Low vs. High dose CYC

2002

Appel
- ALMS
- MMF vs. CYC (induction)

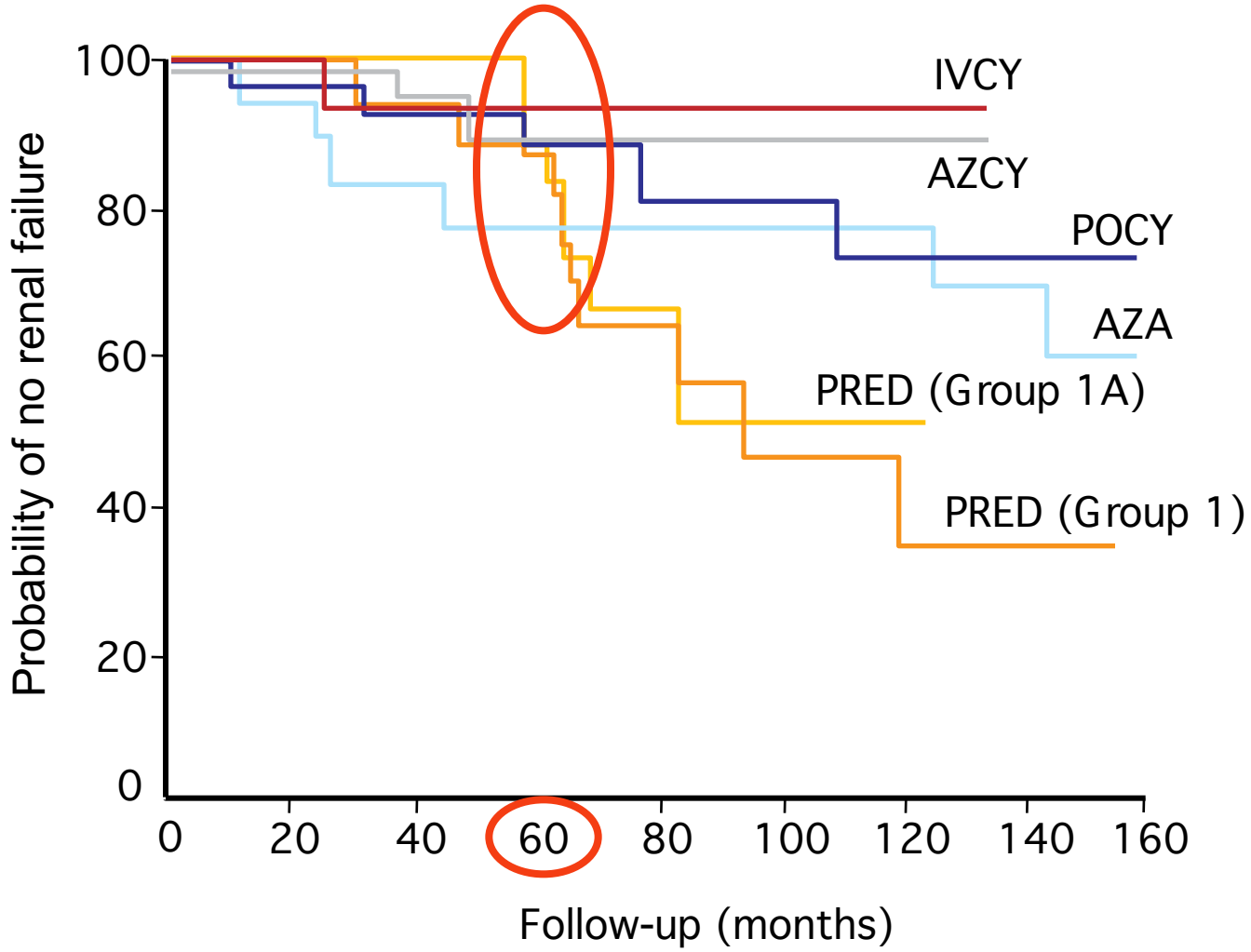
2009

Dooley
- ALMS
- MMF vs. CYC (maintenance)

2011

@DiMiRenalMD @Landmark_Neph

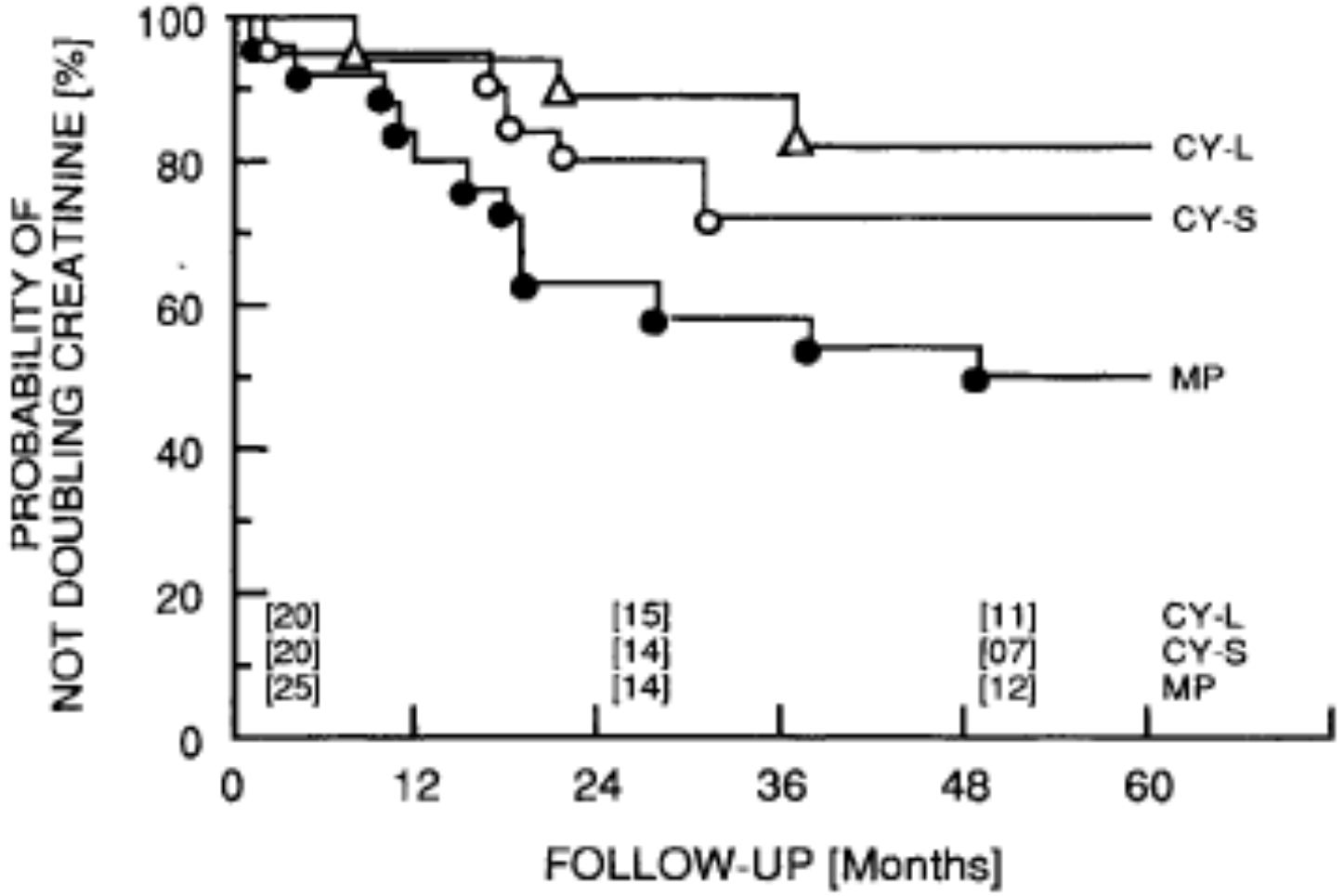
Immunosuppressive therapy in LN improves outcomes
The need for long-term follow-up



WHAT IS THE HIDDEN MESSAGE IN THIS SLIDE?

Austin HA *et al*. *NEJM* 1986; 314: 614.

Almost half of patients with severe LN may be overtreated



Boumpas DT, et al. *Lancet*. 1992 Sep 26;340(8822):741-5.

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

JASN

G.B. Appel, et al. Aspreva Lupus Management Study Group **20:** 1103–1112, 2009

Age 12-75 yo (n = 370) with SLE and biopsy proven LN

- LN class III, IV-S, IV-G, V, III+V, or IV+V
- ≥2 g/day proteinuria for class III or V histology
- 88 centers, 20 countries
- Age ~62 yr
- ~85% Female
- ~40% White

Exclusion: (90 of 460 considered did not meet inclusion)

- On Dialysis >2 wk
- Renal txp
- Malignancy / lymphoprolif dz
- HIV or severe viral dz w/in 3 mo

Power estimates assumed 70% response rated → 358 patients needed for 15% difference

Intervention

Mycophenolate mofetil (n = 185)

500 mg BID ×1 week
1000 mg BID ×1 week
1500 mg BID thereafter (if tolerated)

Cyclophosphamide (n = 185)

0.75 g/m² x1
0.5-1 g/m² x1-5

Control

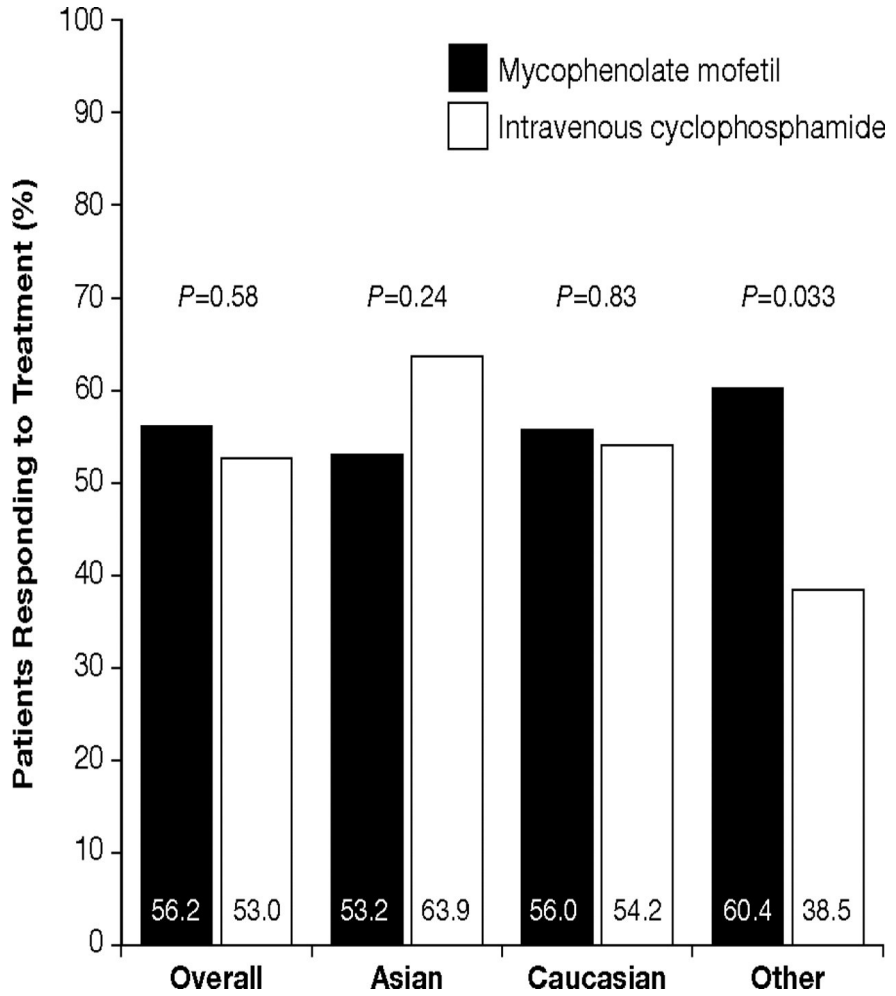
Prednisone tapered over 24 wk; ~50 mg /d to 10-20 mg/d by 24 wk

T: Type, of study - RCT, prospective, **open label**, parallel-group, multi-center **T**: Type, of question - Therapy

U P/Cr <3 or ↓50% + stable S Cr	56 %	=	53 %	P = 0.58
Subgroups -AA -Hispanic	 **60.4 %** **60.9 %**	 OR 2.4 OR 2.5	 38.5 % 38.8 %	 **P = 0.03** **P = 0.01**
W/drawal 2/2 AE	13%	=	7.2%	P = 0.07
Serious AE	27.7 %	=	22.8%	NS

Author's Conclusions: We did not detect significant differences between the MMF and IVC groups with regard to rates of adverse events, serious adverse events, or infections. The study did not meet its primary objective of showing that MMF was superior to IVC as induction treatment for lupus nephritis.

F: Follow up	-	24 wk
R: Randomization	-	Yes, stratified by race and biopsy class
I: Intention to treat	-	Yes
S: Similar at baseline	-	Yes
B: Blinding	-	**NO**, argued different safety profiles of each medication would lead to unblinding
E: Equal treatment	-	Not discussed
S: Source (funding)	-	Not discussed



Recent randomized controlled trials in LN

TRIAL	Response Criteria	Study drug	Placebo	Results
	Results at one year			
LUNAR	UPCR <0.5 ser creat <15%, <5 RBC	30.6	26.4	*Failure*
NOBILITY CRR	UPCR <0.5 ser creat <15%, <10 RBC	34.9%	22.6%	*Failure*
NOBILITY ORR	UPCR <0.5 ser creat <15%,	55.6%	35.5%	Success
AURA III Success	UPCR<0.5 GFR ≥60ml/min	40.8%	22.5%	Success
BLISS-LN success	UPCR<0.7, eGFR <20% and ≥60ml/min	46.6%	35.4%	Success

Rushing into novel therapies from the beginning - i.e., as part of the initiation?
What have we learned from past experience ?

When using rituximab to treat lupus nephritis does the speed, duration, or degree of B-cell depletion matter?

CJASN
Clinical Journal of American Society of Nephrology

LUNAR study: Rituximab in Lupus Nephritis

MMF, methylprednisone and…

4 doses placebo

72 patients

4 doses rituximab

68 patients

Rituximab patients were then sorted based on the peripheral B-cell (CD19) response

Complete depletion of CD19 cells (0 cells/μl)

by 365 days

78%

53 patients

Incomplete depletion of CD19 cells (> 0 cells/μL)

by 365 days

22%

15 patients

Complete response at 78 weeks

Urine protein:creatine ratio < 0.5 with a normal serum creatinine

47%

25 patients

5.8

odds ratio

Complete response at 78 weeks

13%

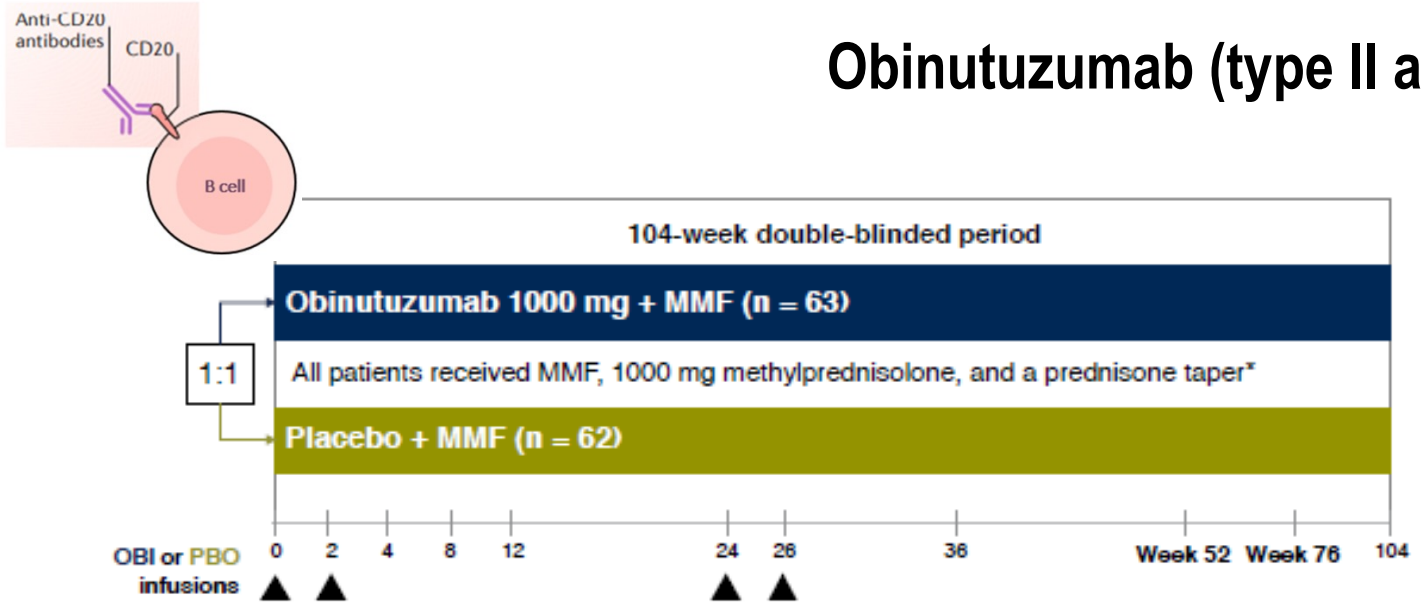
2 patients

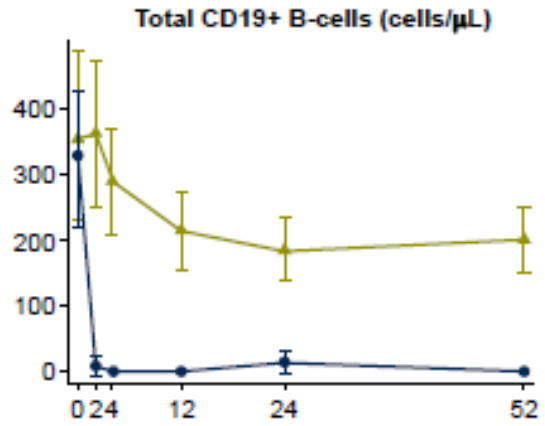
Conclusions When administering rituximab to treat lupus nephritis, complete elimination of CD-19 cells was associated with a higher rate of complete remission.

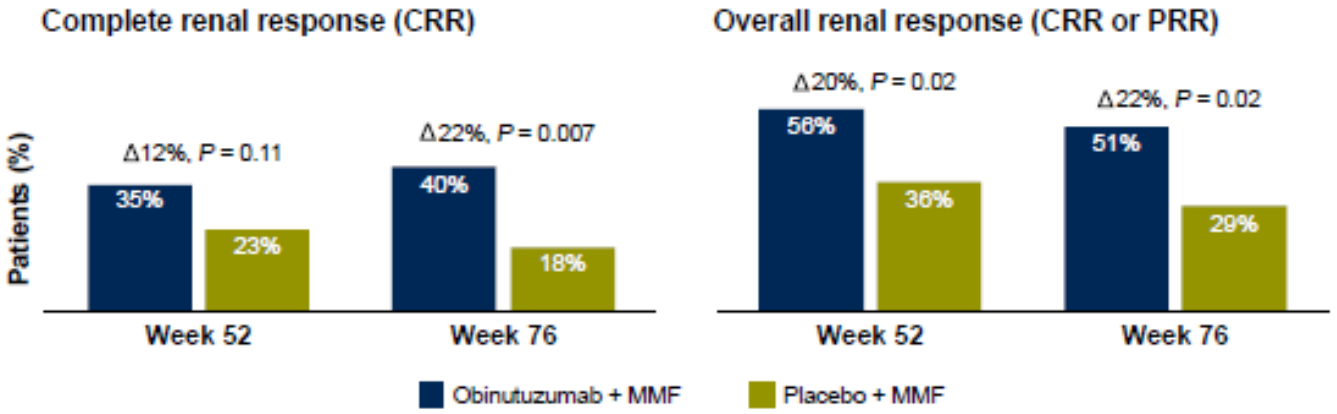
L. Michelle Gomez Mendez, Matthew D. Cascino, Jay Garg, Tamiko R. Katsumoto, Paul Brakeman, Maria Dall'Era, R. John Looney, Brad Rovin, Leonard Dragone, and Paul Brunetta. ***Peripheral Blood B-cell Depletion after Rituximab and Complete Response in Lupus Nephritis***.
CJASN doi: 10.2215/CJN.01070118

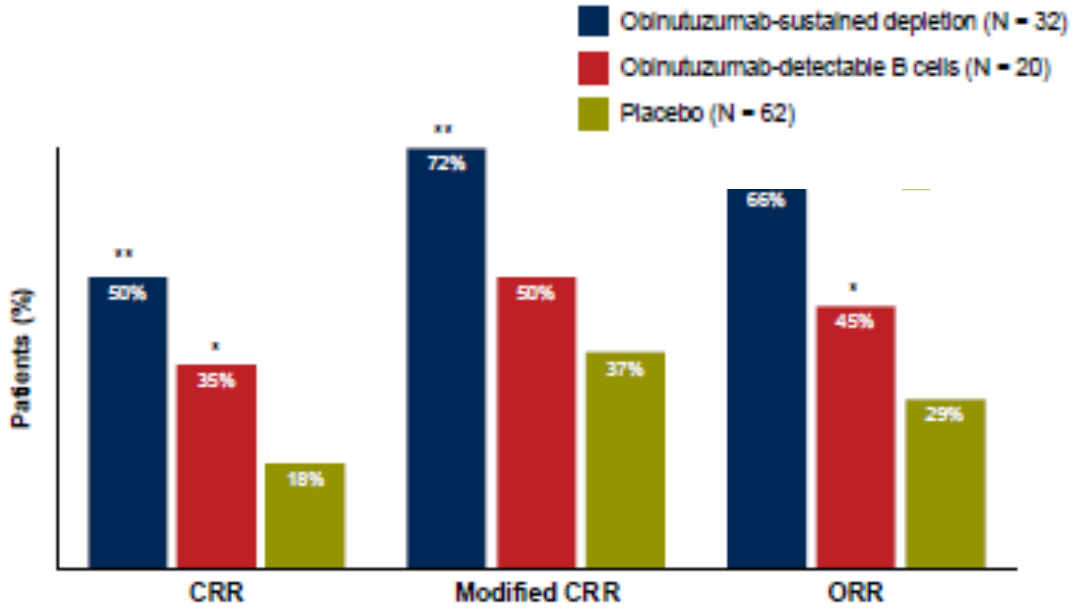
B-depletion

Obinutuzumab (type II anti-CD20)



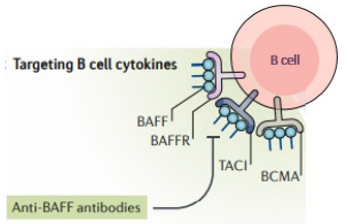






Furie R, et al. *Arthritis Rheumatol.* 2020; 72 (suppl 10).

Belimumab



Renal response definition 104 weeks:

1) UPCr <0.7 2) eGFR >60ml/min or <20% drop in eGFR from baseline 3) No rescue therapy

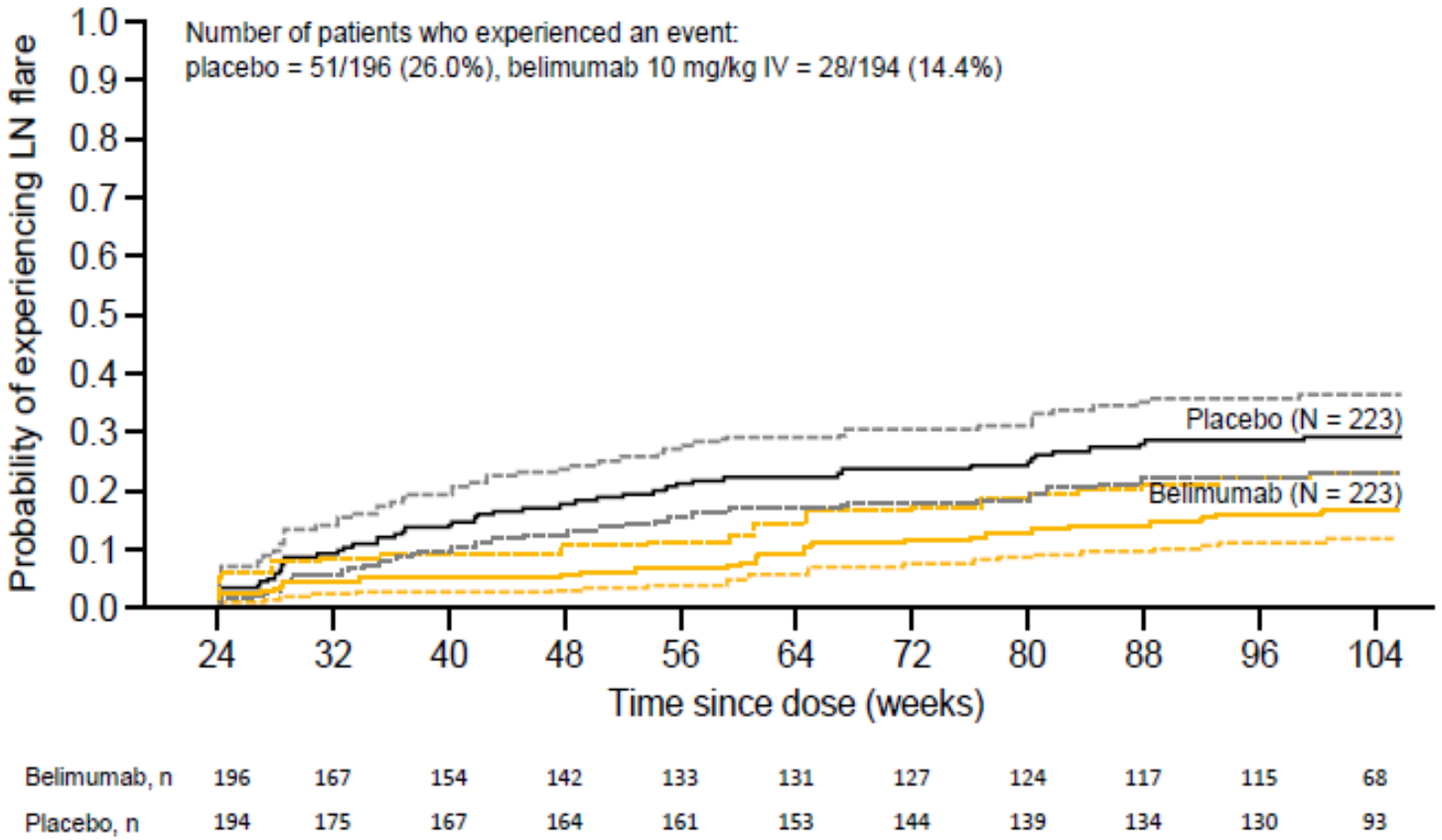
Does addition of belimumab to standard therapy improve kidney outcomes in lupus nephritis?

#NephJC

Methods and Cohort		Intervention		Renal response	Complete Renal Response
Multicentre, double-blind RCT, n=448		Placebo	Study duration = 104 weeks	32%	20%
Lupus Nephritis Class III to V	GFR >30 ml/min/1.73 m^2	versus		OR 1.6 95% CI 1.0 to 2.3 p = 0.03	OR 1.7 95% CI 1.1 to 2.7 p = 0.02
Mean age 33.4±10.6 yrs Females: 88%	50% Asian 30% White 14% Black	Belimumab		43%	30%

Furie R, *et al. N Engl J Med*. 2020 Sep 17;383(12):1117-1128.

Post hoc ανάλυση της BLISS-LN: Το belimumab μείωσε τον κίνδυνο νεφρικής έξαρσης σε σύγκριση με τη συνήθη θεραπεία μόνο



Patients on belimumab had a

55%

Reduced risk of LN flare vs patients who received standard therapy alone (*P* = 0.0008)

Hazard ratio = 0.45 (95% CI: 0.28–0.72)

"Multitargeted therapy": superior efficacy compared to IV-CY for induction treatment of LN"

3 MPP 0.5/each and prednisone 0.6 mg/kg/day

	Multitargeted Tacr. 4mg- MMF1g day 181 pts	Monthly iv CYC 0.75g/m2 181 pts
Serum creat mg/dl	0.78	0.82
Proteinuria g/day	3.44	3.68
GFR ≥30,<60 ml/min	17.7%	18.8%
Class V	17%	20.4%
After 24 weeks		
Complete response	**45.9%**	**25.6%**
Total response	**83.5%**	**63%**
Median time response	**8.9 weeks**	**13 weeks**
Adverse events	**50.3%**	**52.5%**

Follow-up Zhang H JASN 2017

At 18months: *Those on multitarget induction therapy continued to receive multitarget therapy (tacrolimus, 2–3 mg/d; mycophenolate mofetil, 0.50–0.75 g/d; prednisone, 10 mg/d); those on IV-CY induction azathioprine (2 mg/kg per day) plus prednisone (10 mg/d).*

Multitarget vs Cy: Renal flares 5.5 vs 7.62% P: ns

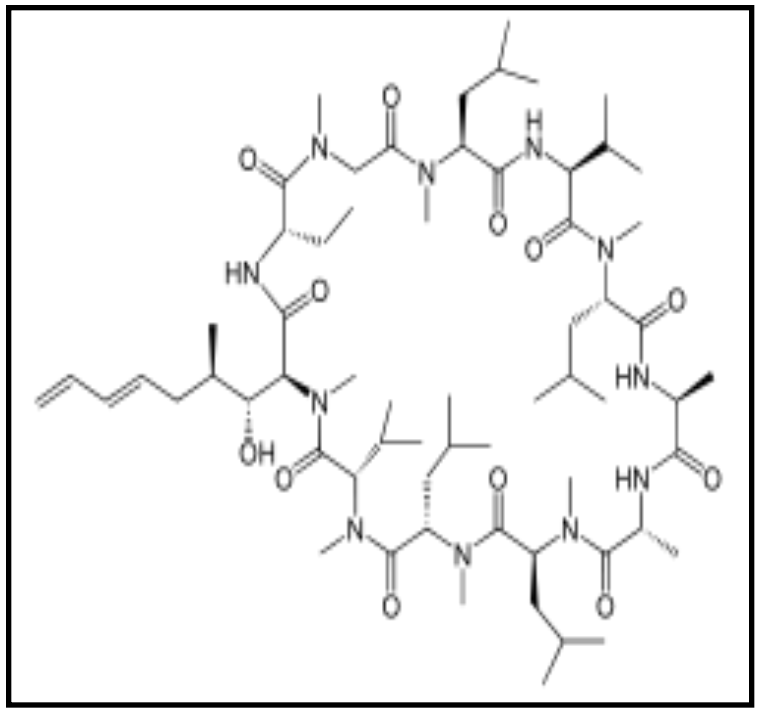
Adverse events 6.4 vs 44.4% (p=0.01), withdrawal rate 1.7 vs 8.9% P= 0.02

Liu Z, *et al. Ann Intern Med*. 2015 Jan 6;162(1):18-26; Zhang H, *et al. J Am Soc Nephrol*. 2017 Dec;28(12):3671-3678.

A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis

Rovin BD Kidney Int 2019

Voclosporin



More potent and less toxic than other CNIs

13 times as potent as cyclosporin and has a predictable dose response potentially *eliminating the need for therapeutic drug monitoring*.

In animals, significantly **less renal toxicity.**

Rovin BH, *et al. Kidney Int.* 2019 Jan;95(1):219-231.

AURA-LV Urinary Protein Reduction in active LN Voclosporin: 265 pts

Randomized, phase II Double-blind Study of –
Voclosporin (23.7 mg BID, or 39.5 mg BID) + 2gMMF+ corticosteroids vs Placebo.

Forced steroid tapering
From MP 1g + prednisone 25mg/day, to 5mg week 8, to 2.5 week 12

	Low dose	High dose	Placebo	P
PRIMARY ENDPOINT at 24 weeks				
Complete Remission	**49%**	**40%**	**24%**	**0.001**
Partial Remission	**68%**	**72%**	**48%**	**0.007**
SECONDARY ENDPOINT				
Time to CR weeks	19.7	23.4	Not achiev.	0.001
Time to PR weeks	4.1	4.4	6.6	0.002
SLEDAI Reduction	-6.3	-7.1	-4.5	0.03
Reduction in UPCR mg/mg	-3.769	-2.792	-2.216	0.001

More serious adverse events in voclosporin groups, more deaths in low dose voclosporin

AURORA PHASE 3 STUDY DEMONSTRATES VOCLOSPORIN 23.7 mg BID+ MMF 2 g/day and steroids, significantly superior over placebo in LN

Arriens C. Ann Rheum Dis 2020

- **357 pts,** 88% female, median age of 31 and 33% of Hispanic/Latino ethnicity.

Renal response at 52 weeks (UPCR of ≤ 0.5 mg/mg, eGFR ≥ 60 mL/min):

40.8% for VCS vs 22.5% for controls (OR: 2.65; p< 0.001).

-Hispanic/Latino (VCS 38.6% and control 18.6%, p=0.0062, OR 3.45) - non-Hispanic/Latino patients (VCS 41.8% vs control 24.6%, p=0.0045,OR 2.29).

Secondary endpoints: RR at 24 weeks, partial renal response (PRR) at 24 and 52 weeks, time to achieve UPCR ≤ 0.5, and time to 50% reduction in UPCR.

SAEs: 20.8% VCS vs 21.3% placebo; Infection :VCS 10.1% vs 11.2% placebo.

No significant decrease at week 52 in eGFR or increase in BP, lipids, or glucose in the VCS arm.

Arriens C, et al Ann Rheum Dis. 2020;**79:**172-173.

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

LANCET 2021

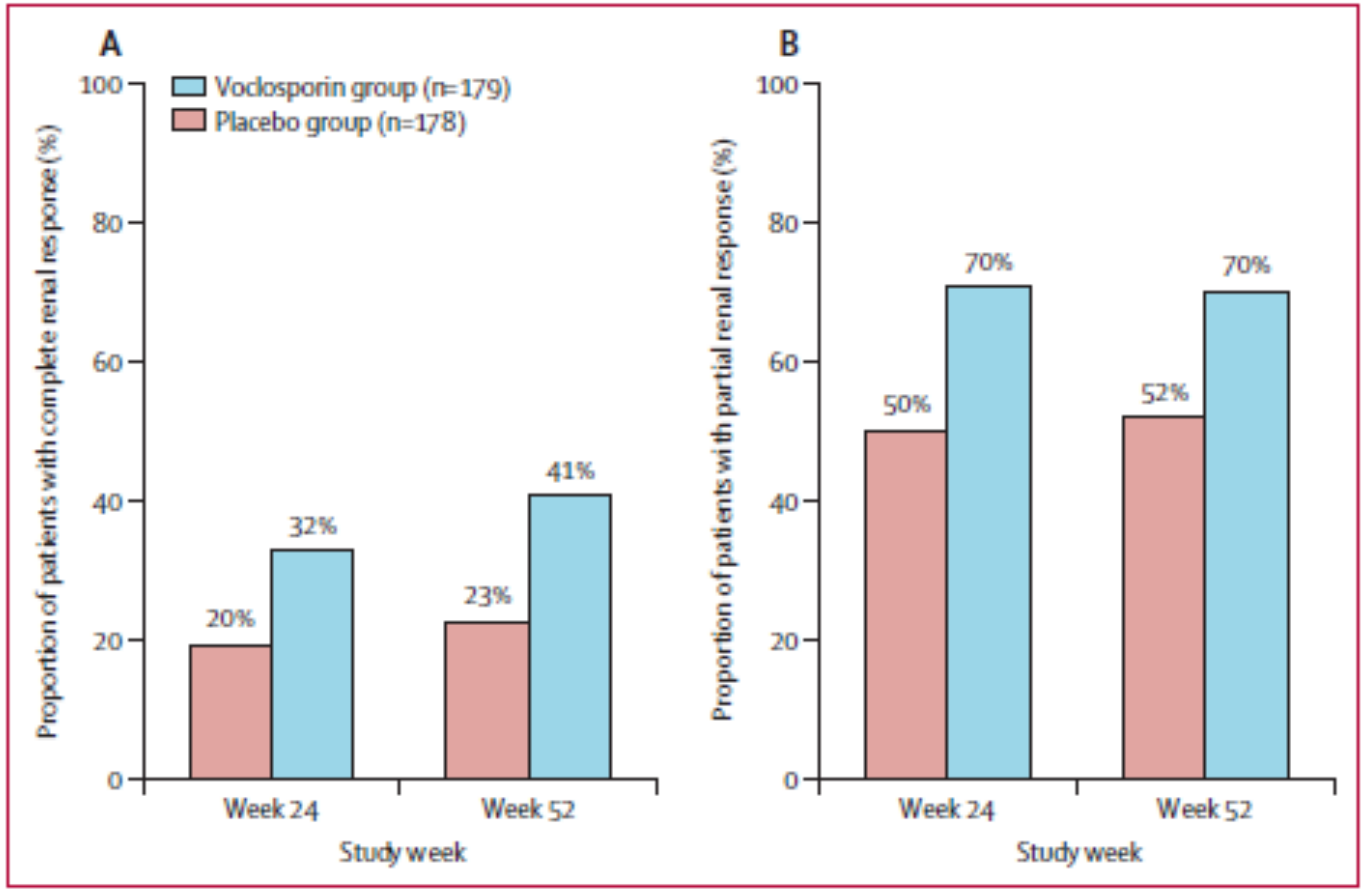


Figure 2: Complete and partial renal response endpoints (intention-to-treat population)

Interpretation Voclosporin in combination with MMF and low-dose steroids led to a clinically and statistically superior complete renal response rate versus MMF and low-dose steroids alone, with a comparable safety profile. This finding is an important advancement in the treatment of patients with active lupus nephritis.

Induction and Maintenance Immunosuppression Treatment of Proliferative LN: A Network Meta-analysis of Randomized Trials *Palmer SC, Am J Kidney Dis 2017*

Compared to IV cyclophosphamide, the most effective treatments to induce remission were:

- combined MMF and calcineurin inhibitor, - calcineurin inhibitors,

- MMF while conferring similar or lower treatment toxicity

NB. Chronic renal failure, high chronicity index at renal biopsy and uncontrolled arterial hypertension are contraindications to calcineurin inhibitors

We can't rush to conclusions based on proteinuria as the reduction of proteinuria comes from an additional "mechanical" effect (stabilization of the cytoskeleton of the podocytes) that may overestimate the effect on the control of renal activity

Palmer SC, *et al. Am J Kidney Dis.* 2017 Sep;70(3):324-336.

The **2019 Update of the joint EULAR/EDTA recommendations for the management of lupus nephritis.**
Fanouriakis A et al Ann Rheum Dis. 2020

Initial treatment

4.6 To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months.

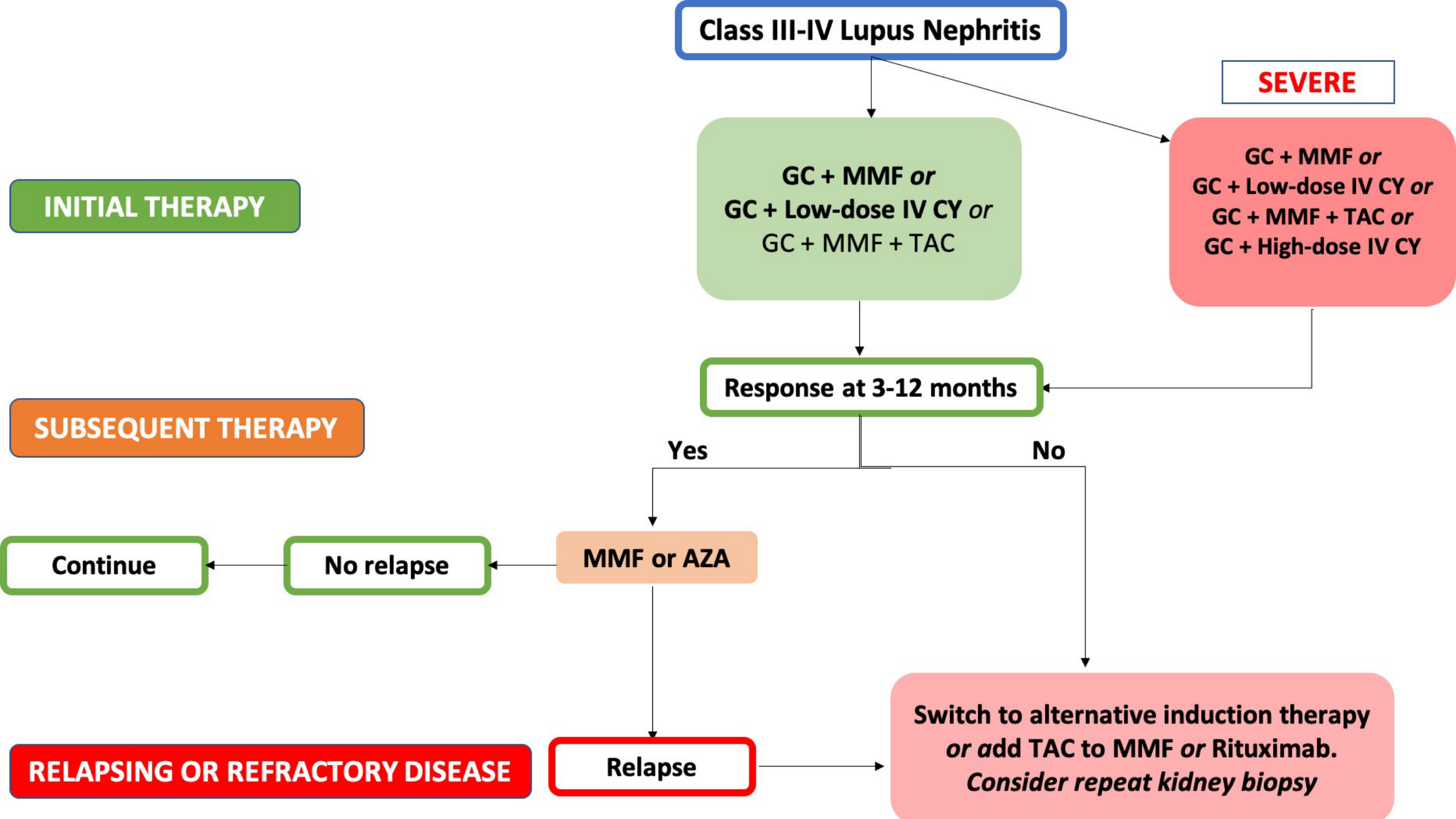
4.3 For class III or IV (±V) LN, MMF (target dose: 2 to 3 g/day, or MPA at equivalent dose) or low-dose intravenous CY (500 mg every 2 weeks for a total of 6 doses) in combination with glucocorticoids.

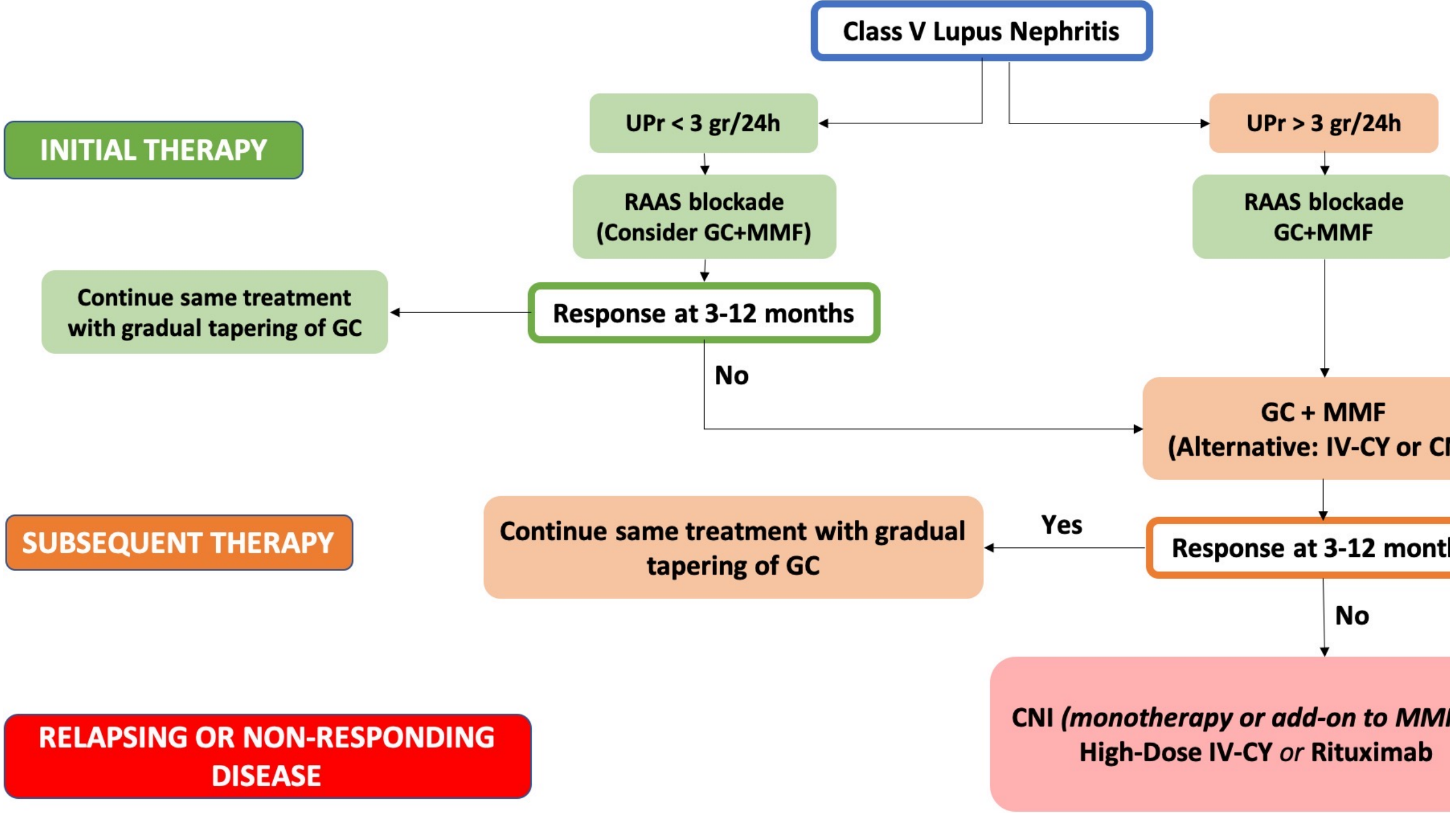
4.5 Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4, but high-dose iv CY (0.5–0.75 g/m2 monthly for 6 months) can also be considered.

4.4 Combination of MMF (target dose: 1 to 2 g/day) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria.

4.5 Belimumab, when added to standard-of-care (including MMF or CY), may gradually reduce proteinuria and the risk for kidney flares.

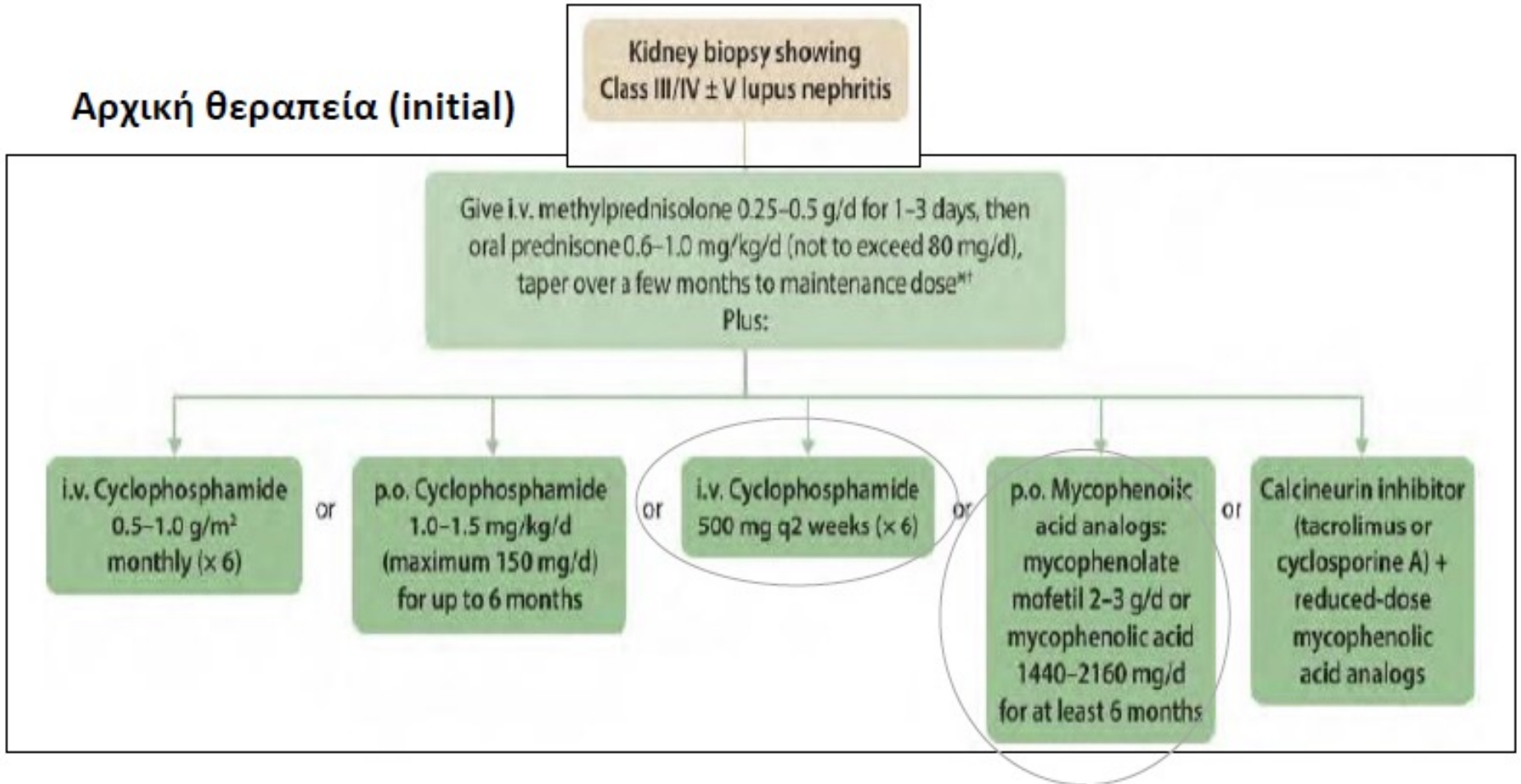
Fanouriakis A, *et al. Ann Rheum Dis*. 2020;79(6):713-723.


Class III-IV Lupus Nephritis
SEVERE
INITIAL THERAPY
GC + MMF or
GC + Low-dose IV CY or
GC + MMF + TAC
GC + MMF or
GC + Low-dose IV CY or
GC + MMF + TAC or
GC + High-dose IV CY
Response at 3-12 months
SUBSEQUENT THERAPY
Yes
No
Continue
No relapse
MMF or AZA
RELAPSING OR REFRACTORY DISEASE
Relapse
Switch to alternative induction therapy
or add TAC to MMF or Rituximab.
Consider repeat kidney biopsy


Class V Lupus Nephritis
INITIAL THERAPY
UPr < 3 gr/24h
UPr > 3 gr/24h
RAAS blockade
(Consider GC+MMF)
RAAS blockade
GC+MMF
Continue same treatment
with gradual tapering of GC
Response at 3-12 months
No
GC + MMF
(Alternative: IV-CY or CI
SUBSEQUENT THERAPY
Continue same treatment with gradual
tapering of GC
Yes
Response at 3-12 montl
No
RELAPSING OR NON-RESPONDING
DISEASE
CNI (monotherapy or add-on to MMI
High-Dose IV-CY or Rituximab

Θεραπεία υπερπλαστικών μορφών νεφρίτιδας λύκου (KDIGO 2021)

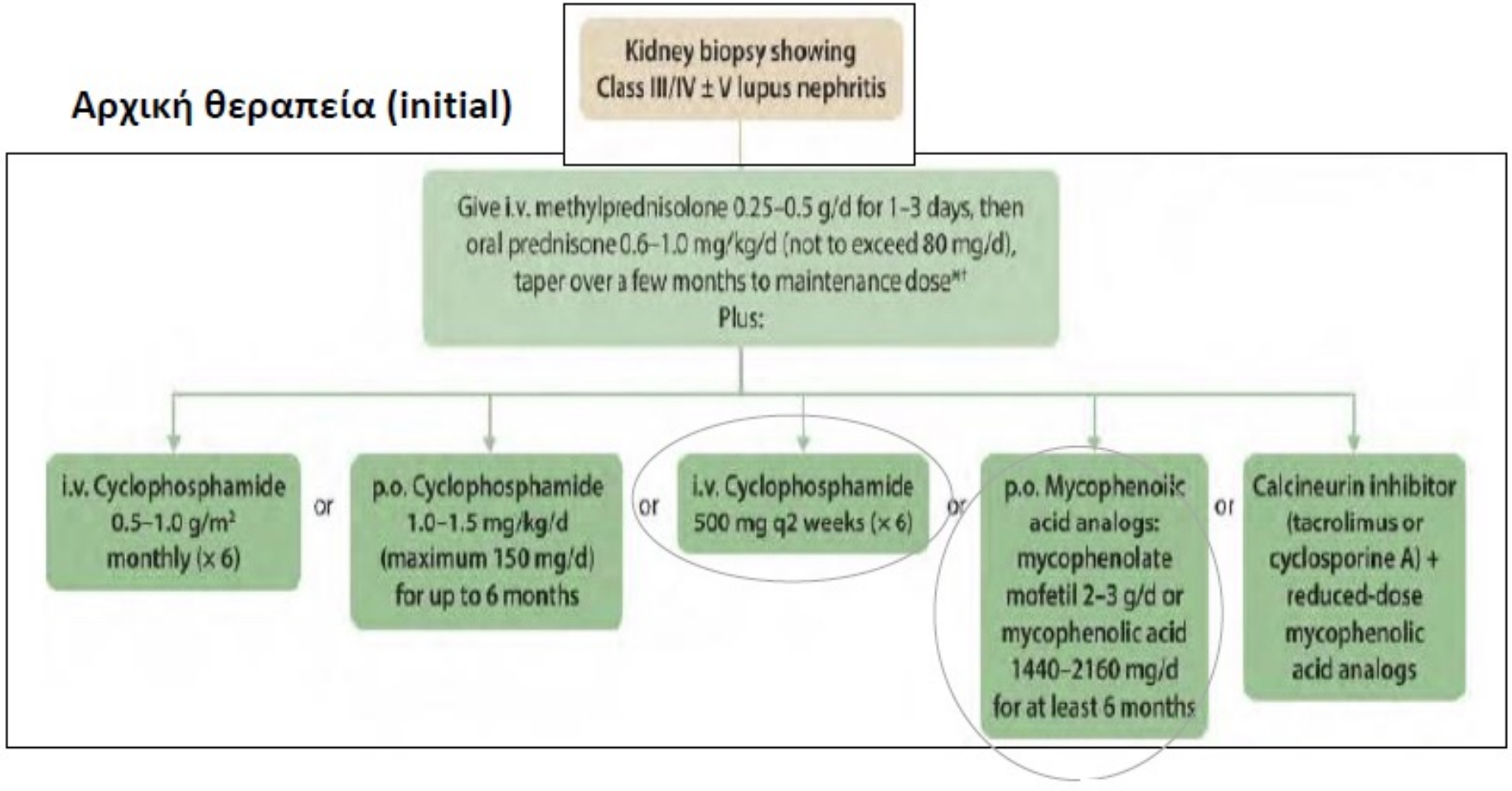
Αρχική θεραπεία (initial)



Kidney International (2021) **100**, S1–S276

Θεραπεία υπερπλαστικών μορφών νεφρίτιδας λύκου (KDIGO 2021)

Αρχική θεραπεία (initial)



Kidney International (2021) **100**, S1–S276

Case study: lupus nephritis in a young biologist

- **SB is a 22-year-old biology student**
- **Prior to her final exams, she presented with symptoms of SLE**
  - **Low complement**
  - **Anti-dsDNA positive**
  - **Non-renal SLEDAI score 8**
- **Glomerular haematuria, trace proteinuria**

Biopsy or not?

- **Biopsy: focal proliferative nephritis high activity index (16), low chronicity (1), fibrinoid necrosis, few crescents**

Treatment

- **IV methylprednisolone x3 doses, then 0.5 mg/d prednisone plus immunosuppressive**
- **IV cyclophosphamide or MMF? Both slow onset of action and risk for failure at least 30% in 5 years**
- **Treatment goals: minimise steroid exposure, reduce risk of flare, and protect the kidneys**

Would you add Benlysta▼ (belimumab)?

dsDNA = double-stranded DNA; IV = intravenous; MMF = mycophenolate mofetil;
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

Personal communication from Professor Boumpas.

Risk stratification in lupus nephritis: adverse prognostic factors → more aggressive therapies

- Nephrotic-range proteinuria
- Reduced GFR or rapidly-progressive GN
- Uncontrolled hypertension
- Class IV, or mixed (class V + III/IV) nephritis
- High-risk histological features
  - *High activity [NIH AI] > 11, high chronicity [NIH CI] > 3,*
  - *Combination of AI > 10 & CI > 2*
  - *Cellular crescents, fibrinoid necrosis*

Increased risk for progression into chronic renal failure or ESKD

High-risk histological features
Activity (fibrinoid necrosis, crescents)
Chronicity (interstitial fibrosis, tubular atrophy)

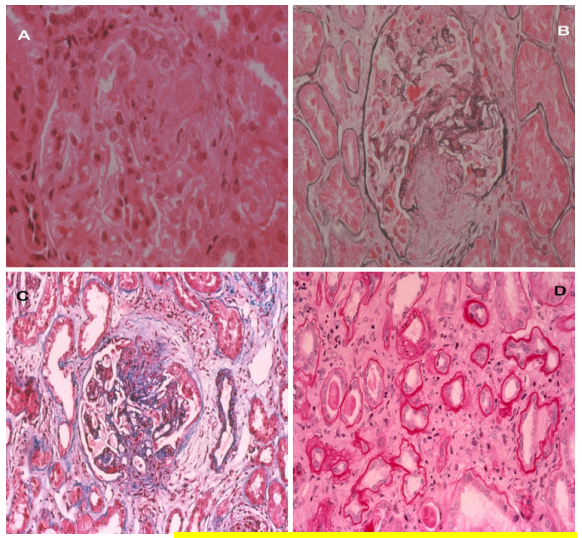


Photo Courtesy of D Boumpas from Bertsias G and Boumpas D. Nat Rev in Rheumatol 2008;4:464–472.

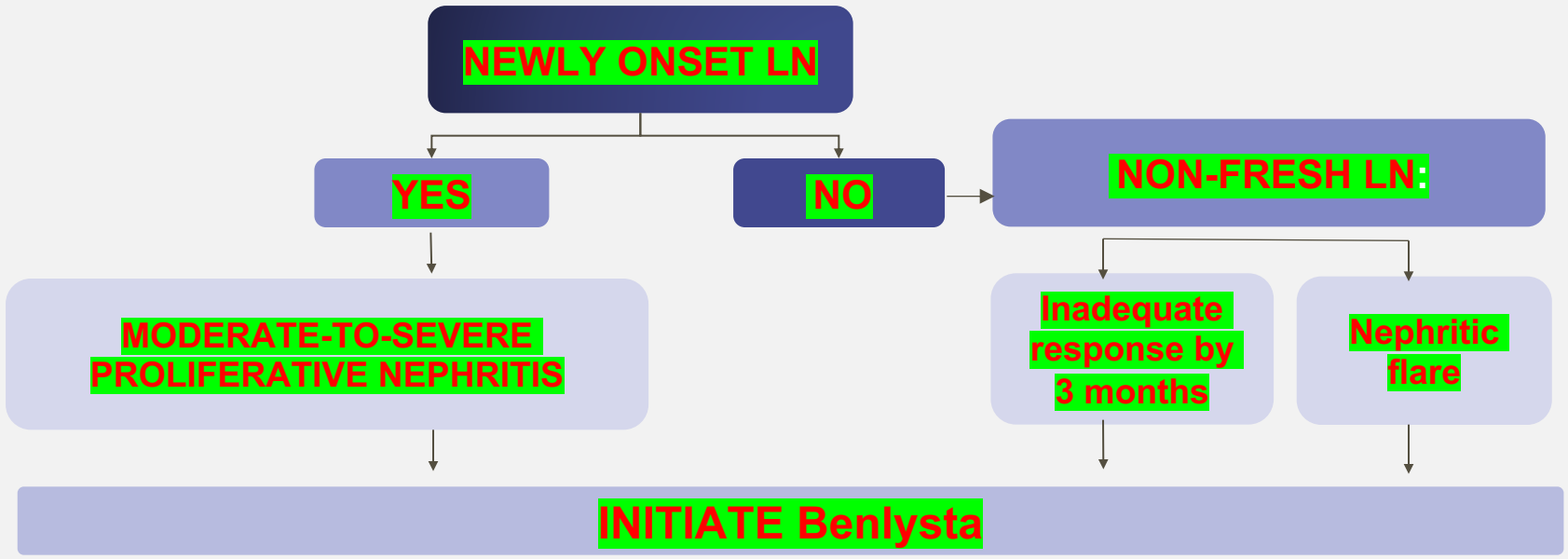
AI = activity index; CI = chronicity index; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; GN = glomerulonephritis; NIH = National Institutes of Health.

Fanouriakis A, et al. Ann Rheum Dis 2021;80:14–25.

Balancing overtreating vs. undertreating: Potential use of Benlysta for lupus nephritis[1,2]

Benlysta label for lupus nephritis[2]

"Add on to standard immunosuppressive therapy in active lupus nephritis"



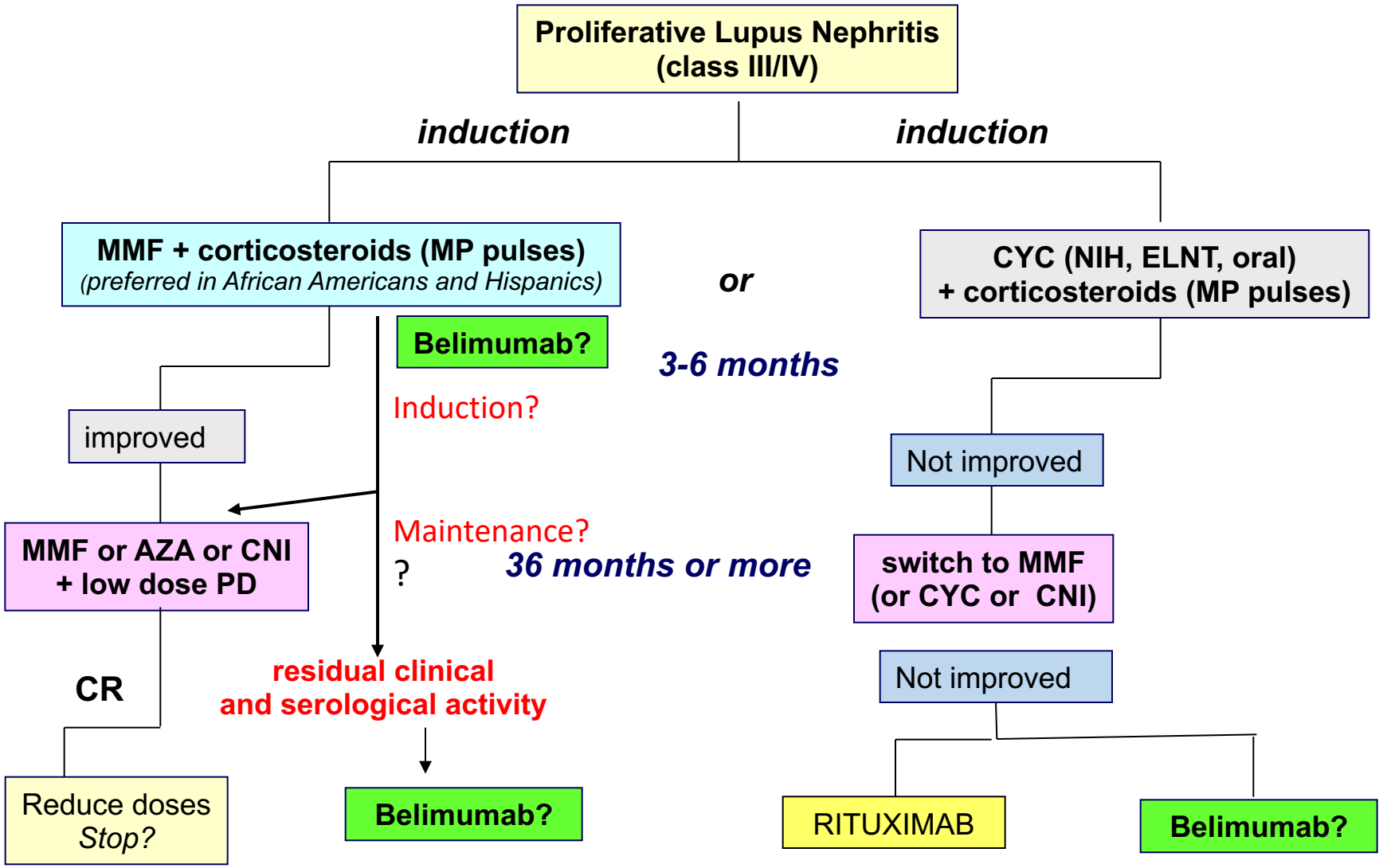
Activity index > 5 and at least one of the following: a) chronicity index > 2; or b) proteinuria > 3 gm/24h; or c) increase in creatinine > 20%
**** Inadequate response: no decrease in UPCR by at least 25% and no return of GFR to normal GFR ± 10%**

GFR = glomerular filtration rate;

UPCR = urine protein:creatinine ratio.

1. Kostopoulou M, et al. Ann Rheum Dis 2022;81:753–775;
2. Benlysta (belimumab) SmPC. May 2021.
3.Boumpas D, Boletis I, Betrsias G, Fanouriakis A, Liapis, Marinaki S et et at Lupus nephritis Workshop Athens Greece 2022

SUGGESTED TREATMENT ALGORITHM FOR LUPUS NEPHRITIS
in addition to Hydroxychloroquine



ΕΚΠΑΙΔΕΥΤΙΚΟΙ ΣΤΟΧΟΙ

- Περίπτωση
- Στόχοι θεραπείας και χρονικός ορίζοντας επίτευξης
- Εξειδίκευση αναλογα με τον ιστολογικό τύπο και τη βαρύτητα
- Γενικός αλγόριθμος θεραπειας
- Περιπτωσεις ασθενών
- Σημαντικες λεπτομερεις και πιθανές αστοχίες
- Κυρια σημεία
- Ερωτησεις πολλαπλης επιλογής