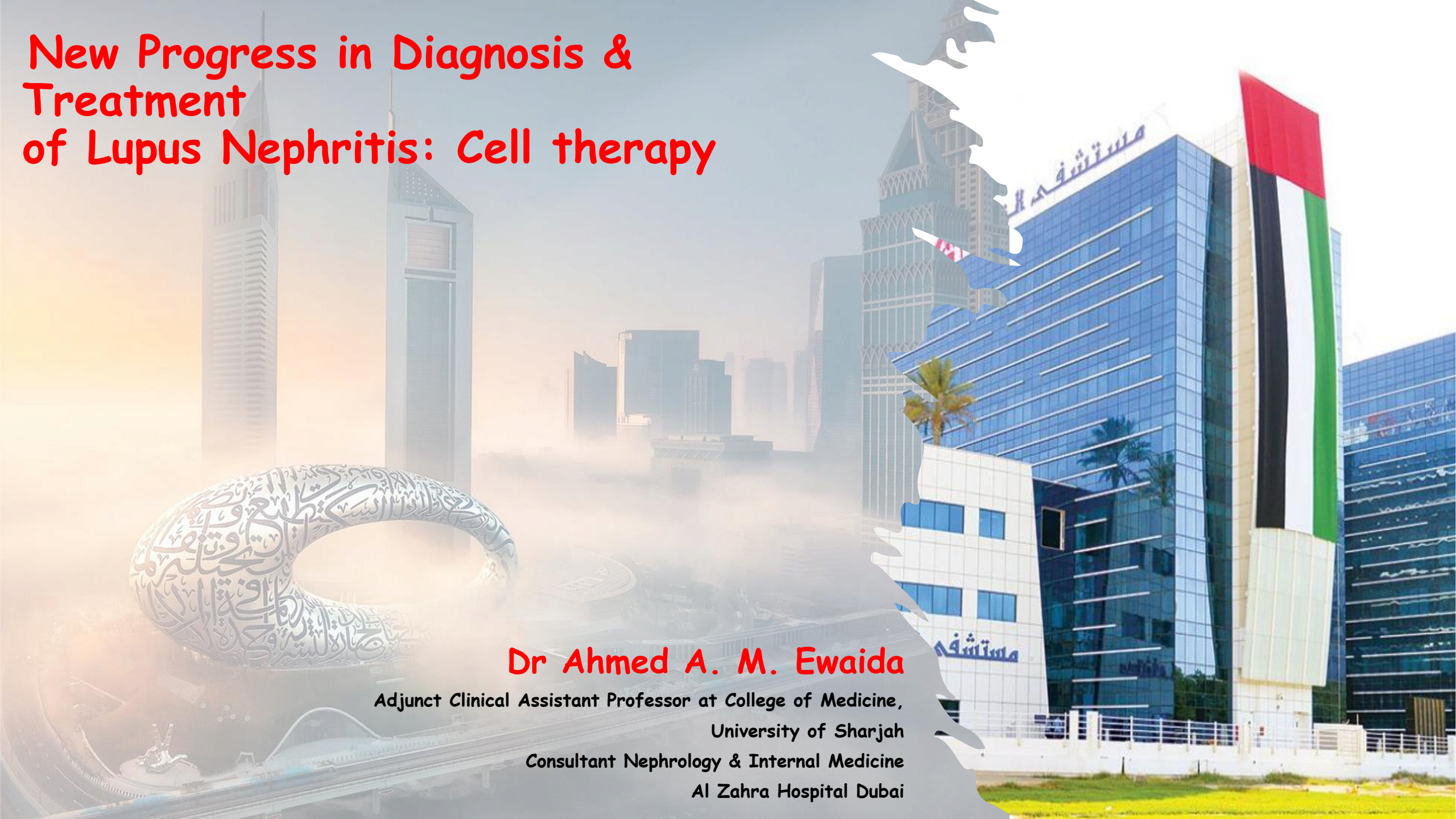
New Progress in Diagnosis & Treatment of Lupus Nephritis: Cell therapy



Dr Ahmed A. M. Ewaida

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Al Zahra Hospital Dubai

Epidimiology:

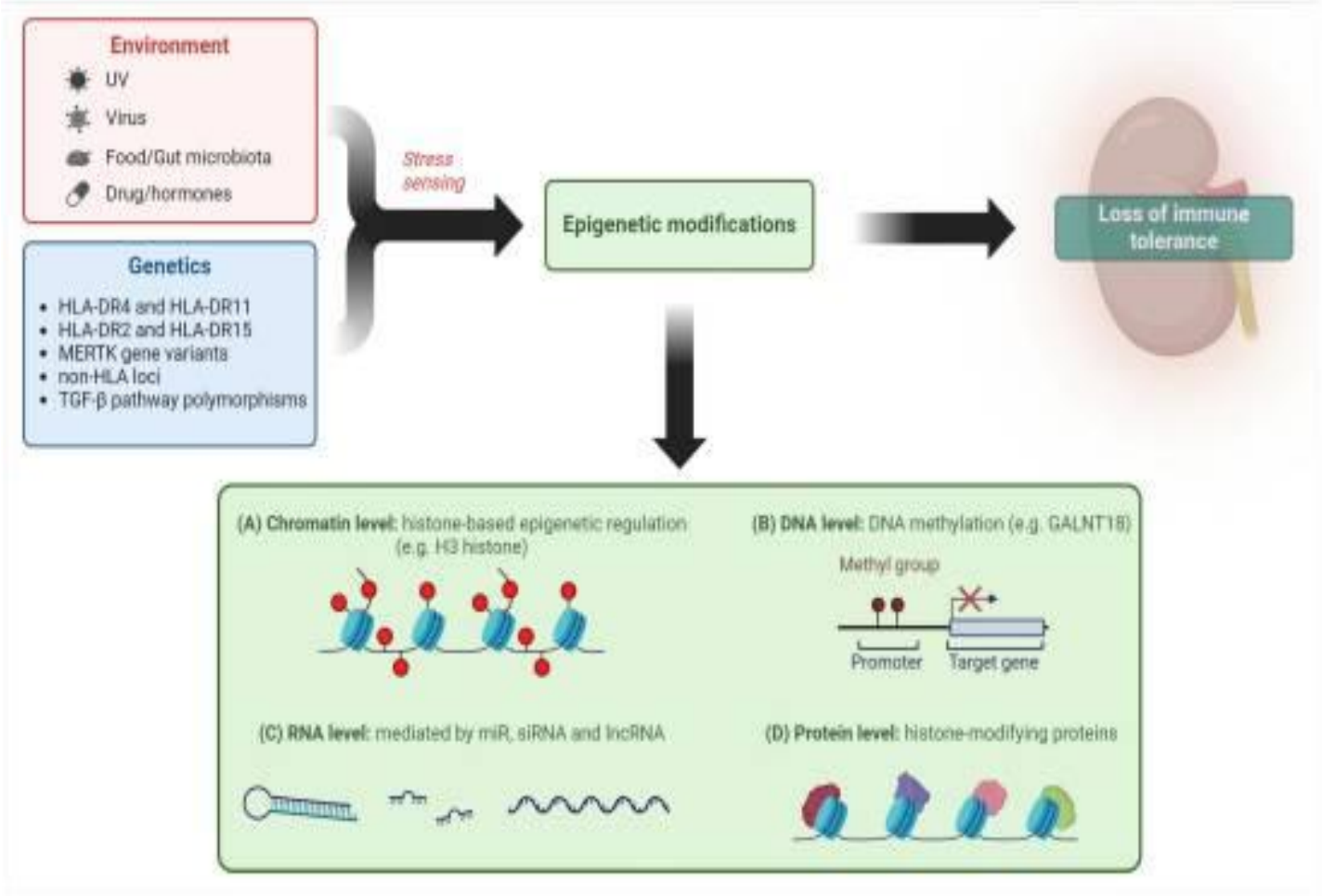
- **Higher Prevalence**: More common in Hispanic, African, and Asian individuals vs. Caucasians.
- **Prognosis:** 10–30% progress to ESRD within 10 years; outcomes remain unpredictable.
- **Ethnic Disparities:** Hispanic and African patients face higher disease activity, relapse rates, and faster CKD progression.
- **Risk Factor**: Poverty significantly increases LN progression risk across all ethnicities.

Annalisa Roveta et al, Int J Mol Sci. 2024 Aug 18;25(16)

Pathogenesis:

Complement Activation in Lupus Nephritis:

- **Circulating Complement Split Products:**
  - Elevated **C3dg, iC3b, C4d** linked to active SLE
  - Higher **C4d** levels in LN patients
- **Cell-Bound Complement Activation Product:**
  - **Erythrocyte-bound C4d** correlates better with disease activity than low plasma complement
  - **C4d in renal capillaries** predicts worse outcomes.

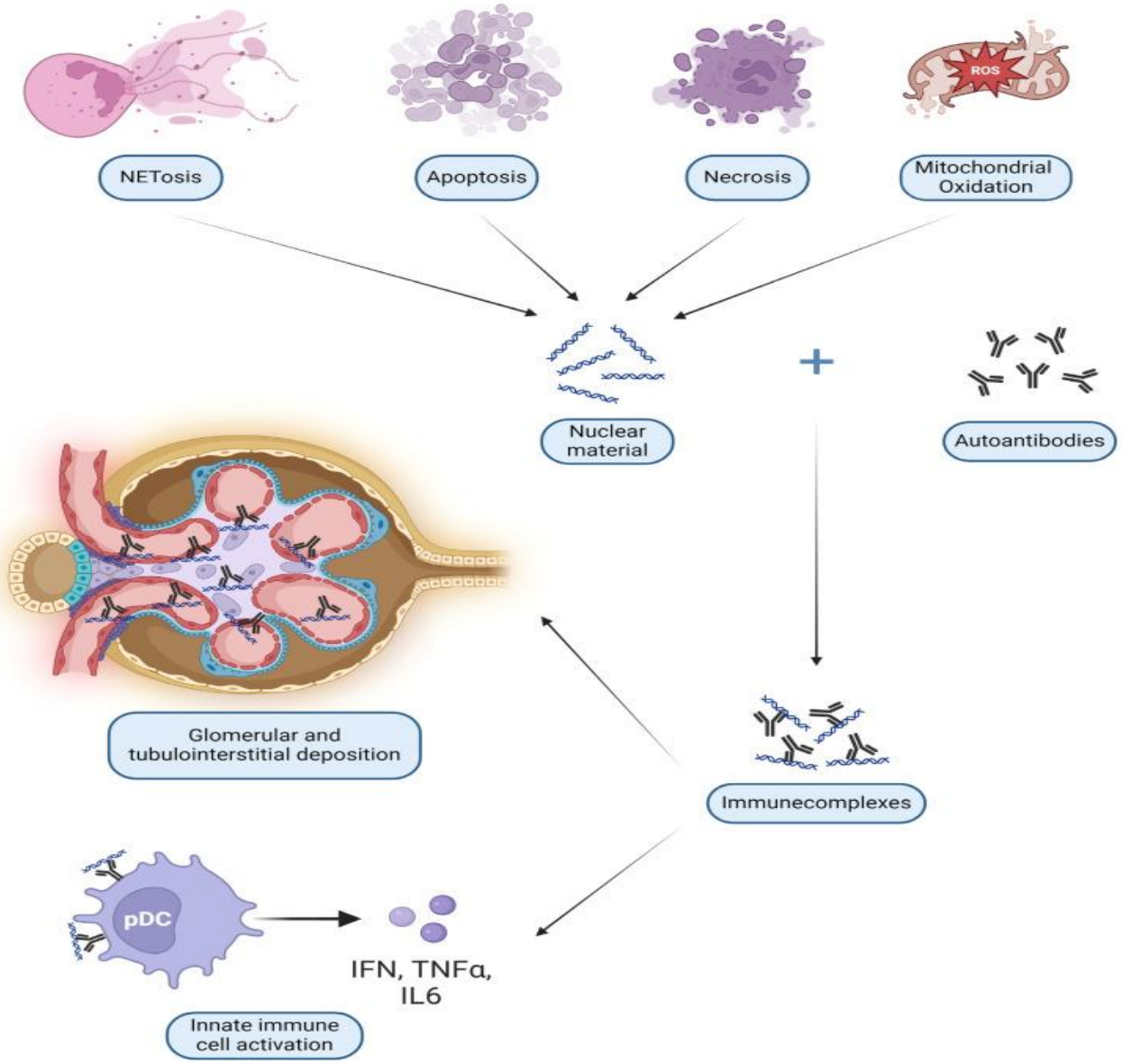


Annalisa Roveta et al, Int J Mol Sci. 2024 Aug 18;25(16)

Pathogenesis:

Autoantibodies in Lupus Nephritis:

- Weak link between **anti-dsDNA** and kidney disease.
- **Anti-ENO1** and **anti-H2 IgG2**:
  - Better markers for LN vs. non-renal SLE.
  - Levels decrease with immunosuppressive therapy.
- **Anti-SOD2**:
  - A "second wave" antibody.
  - May disrupt antioxidant defenses in late inflammation.



Annalisa Roveta et al, Int J Mol Sci. 2024 Aug 18;25(16)

Potential Biomarkers:

Biomarker	Biological Fluid	Associations
u-Gal-3BP	Urine	Histological disease activity
MCP-1	Urine	Clinical severity
TWEAK	Urine	Diagnosis
CAM	Urine	Clinical severity
miR146a miR135b	Urine	Histological disease activity; Response to therapy
UCD163	Urine	• Clinical severity • Histological activity • Differentiated active and inactive disease

Annalisa Roveta et al, Int J Mol Sci. 2024 Aug 18;25(16)

Treat to target – is uCD163 going to replace biopsies?

Objective

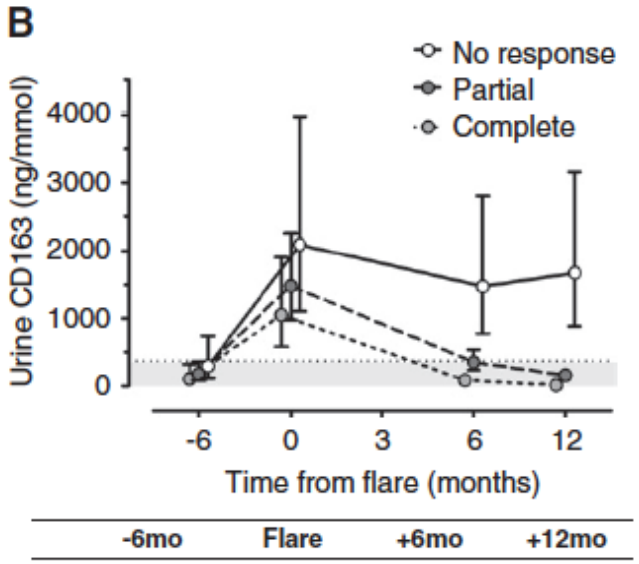
- To evaluate value of uCD163 for predicting flare and response in LN

Study design

- Test and validation cohorts
- Ohio n=129 and Mexico n=120 – diverse
- Cross sectional and longitudinal
- Clinical, histopathological, serological and urine correlations

Urinary CD163 associated with:

- Clinical severity
- Histological activity
- Differentiated active and inactive disease
- Modified by treatment



In responder's vs non responders

- declined faster than proteinuria /serology

uCD163 predictive of response both clinical and histological

- uCD163 <370ng/mmol at 6 months after treatment predicted CR at 12 months
- If still proteinuric at 6 months, uCD163 identified those who would go on to CR 6 months later
- Unlike proteinuria, uCD163 perfectly agreed with histological activity on repeat biopsy

Mejia-Vilet J et al JASN 2020 31;1335-47

Potential Biomarkers in serum

➢BAFF (B-cell activating factor):

- Supports autoreactive B cells; strongly linked to SLE pathogenesis.
- Correlates with disease activity and is overexpressed in class IV proliferative LN.
- Serum BAFF and IFN-I proposed as biomarkers for disease stratification (e.g., LN vs.blood/skin manifestations).

➢ APRIL (a proliferation-inducing ligand):

- Key in autoantibody production; associated with severe proliferative LN lesions.
- Predicts treatment outcomes:

- Low **BAFF** (<1.5 ng/mL) predicts response to IS therapy.
- High **APRIL** (>4 ng/mL) predicts treatment failure.

Annalisa Roveta et al, Int J Mol Sci. 2024 Aug 18;25(16)

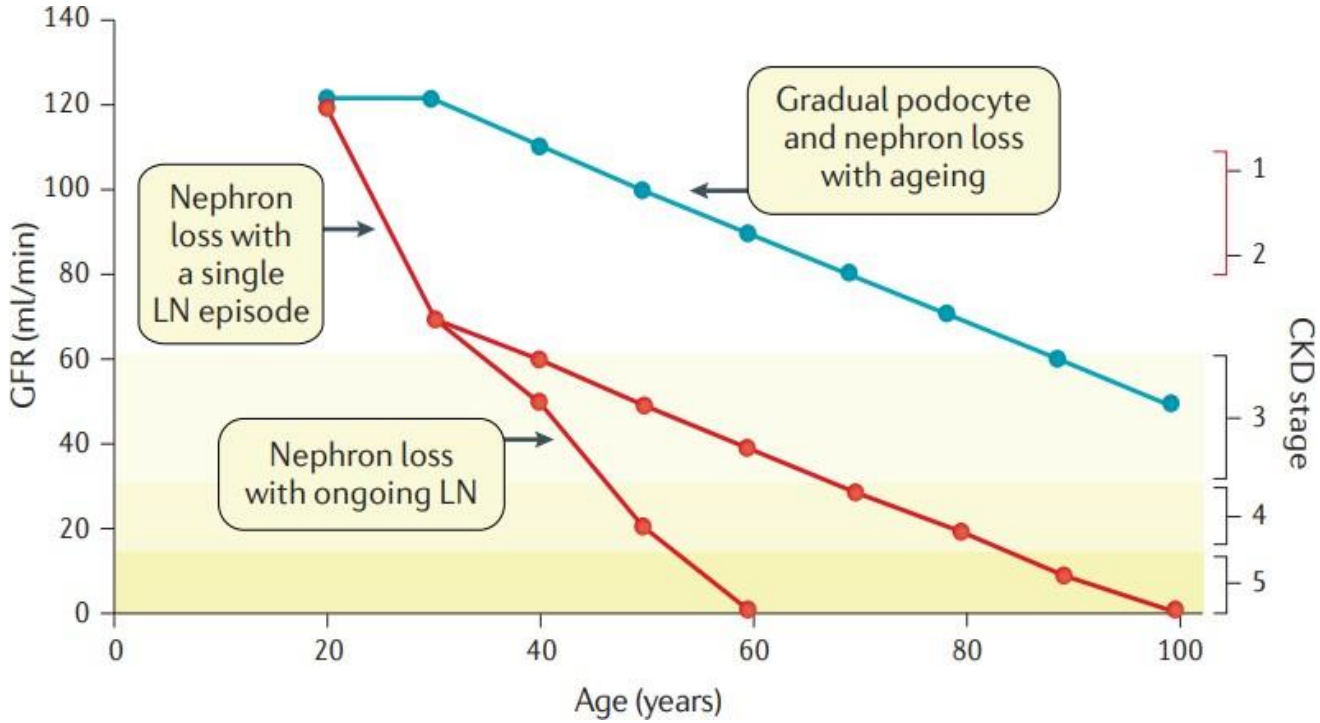
What matters to patients is the long term

- Preserve kidney function long term (treat promptly)
- Prevent kidney flares
- Prevent organ damage

- Reduce morbidity and mortality
- Prevent treatment related toxicity and damage
- Control comorbidities

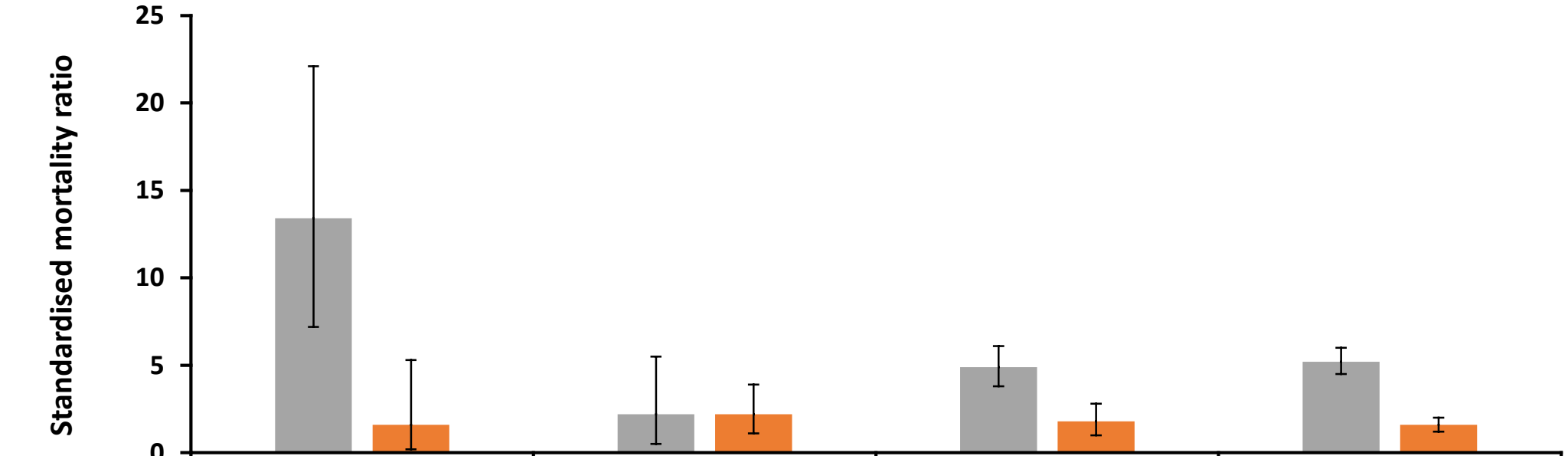
- Improve quality of life including preserving fertility

Risk of ESKD in LN patients over lifetime[1a]



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

Standardised mortality ratio for LN & non-LN in patients with SLE[1a]



	16–39 yo	40–59 yo	60–79 yo	≥80 yo
LN SMR	13.4	2.2	4.9	5.2
Non-LN SMR	1.6	2.2	1.8	1.6

Included all SLE patient's resident in Oslo Jan 1999 to Jan 2008; Median follow-up time: 14 (0-15) years

A prompt fall in proteinuria is associated with good long-term kidney outcome in LN[1]

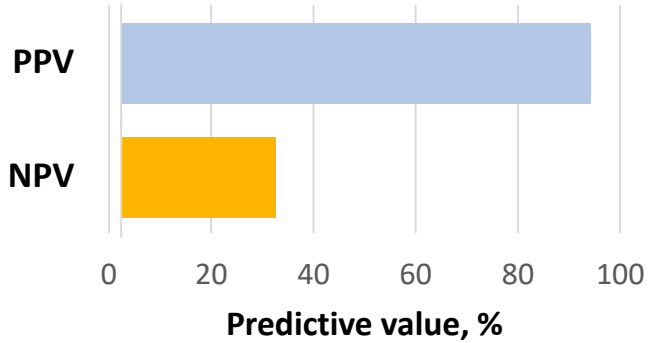
Clinical target

MAINTAIN nephritis trial[2] (N = 90)[a]

After 12 months of treatment, achievement of

proteinuria < 0.7 g/d

best predicted good long-term renal outcome[b]



94%

PPV (i.e. a positive outcome for 94% of those who **achieved the target**)

31%

NPV (i.e. a negative outcome for 31% of those who **did not achieve the target**)

Therefore, **69%** of patients not achieving the target will still have a good long-term kidney outcome

The challenge with this target:
How do we identify the one-third of patients who do not achieve this target and will suffer from long-term kidney impairment?

[a] Patients with long-term (at least 7 years) renal function data;
[b] Good long-term kidney outcome: serum creatinine value ≤ 1.0 mg/dL at 7 years.

1. Tamirou F and Houssiau F. J Clin Med 2021;10:670;
2. Tamirou F, et al. Lupus Sci Med 2015;12:2:e000123.

How to Improve the Prognosis of Lupus Nephritis?

❖ The adoption of a treat-to-target approach:

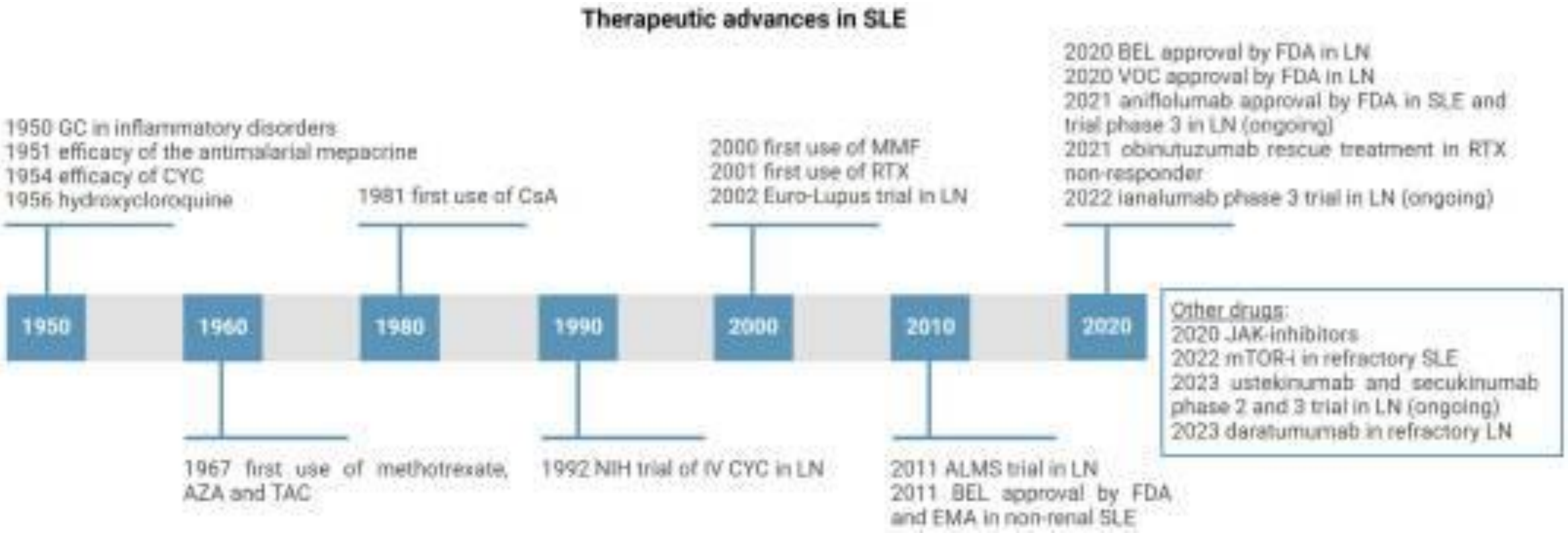
- clinical
- **pathological, or even immunological**

➢ repeated kidney biopsies performed after 12 months of IS treatment (as per protocol), might contribute to the identification of patients who require treatment intensification.

Tamirou F and Houssiau F. J Clin Med 2021;10:670

Immunosuppressive (IS) Therapies in LN

Annalisa Roveta et al, Int J Mol Sci. 2024 Aug 18;25(16)



Induction Therapy:

Meta-Analysis > Arthritis Rheumatol. 2024 Sep;76(9):1408-1418. doi: 10.1002/art.42920. Epub 2024 Jun 28.

Impact of Glucocorticoid Dose on Complete Response, Serious Infections, and Mortality During the Initial Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis of the Control Arms of Randomized Controlled Trials

Gabriel Figueroa-Parra [1], María C Cuéllar-Gutiérrez [2], Mariana González-Treviño [1], Alain Sanchez-Rodriguez [1], Jaime Flores-Gouyonnet [1], José A Meade-Aguilar [3], Larry J Prokop [1], M Hassan Murad [1], María Dall'Era [4], Brad H Rovin [5], Frédéric Houssiau [6], Farah Tamirou [6], Fernando C Fervenza [1], Cynthia S Crowson [1], Michael S Putman [7], Alí Duarte-García [1]

- **Meta-analysis of 50 RCTs**: GCs with MPA or CYC.

- **Conclusion:**

- Higher steroid doses improve renal outcomes
- Increased doses also raise risks of infections and mortality

Clin Rheumatol. 2024 Jan 10;43(3):985–992. doi:

Cumulative pulse methylprednisolone and its relation to disease activity, damage and mortality in systemic lupus erythematosus patients: A post hoc analysis of COMOSLE-EGYPT study

Nesreen Sobhy [1,✉], Yasser Ezzat [2], Sherif M Gamal [1], Shada A Ghoniem [1], Sarah S Nasr [3], Shaimaa Badran [1], Ahmed Soliman [4], Nermeen Ahmed Fouad [2]

Conclusion:

- Mortality risk rises with every gram of cumulative methylprednisolone.
- Doses >2.75–3.25 g linked to higher mortality.

Induction Therapy:

Medicine (Baltimore) 2020 Aug 14;99(33):e21121.

Mycophenolate mofetil in the treatment of Chinese patients with lupus nephritis - A PRISMA-compliant meta-analysis

Haitao Zhang [a,*], Minlin Zhou [a], Xiaoyan Han [b], Yang Yang [b], Xin Yu [b]

- **Meta-analysis (18 trials):**
  - **MMF** is more effective for induction than **CYC**
  - Fewer side effects: infections, amenorrhea, l leukopenia, and alopecia (Proliferative LN).

Meta-Analysis Lupus. 2022 Oct;31(12):1468-1476.

MULTITARGET THERAPY VERSUS MONOTHERAPY AS INDUCTION TREATMENT FOR LUPUS NEPHRITIS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

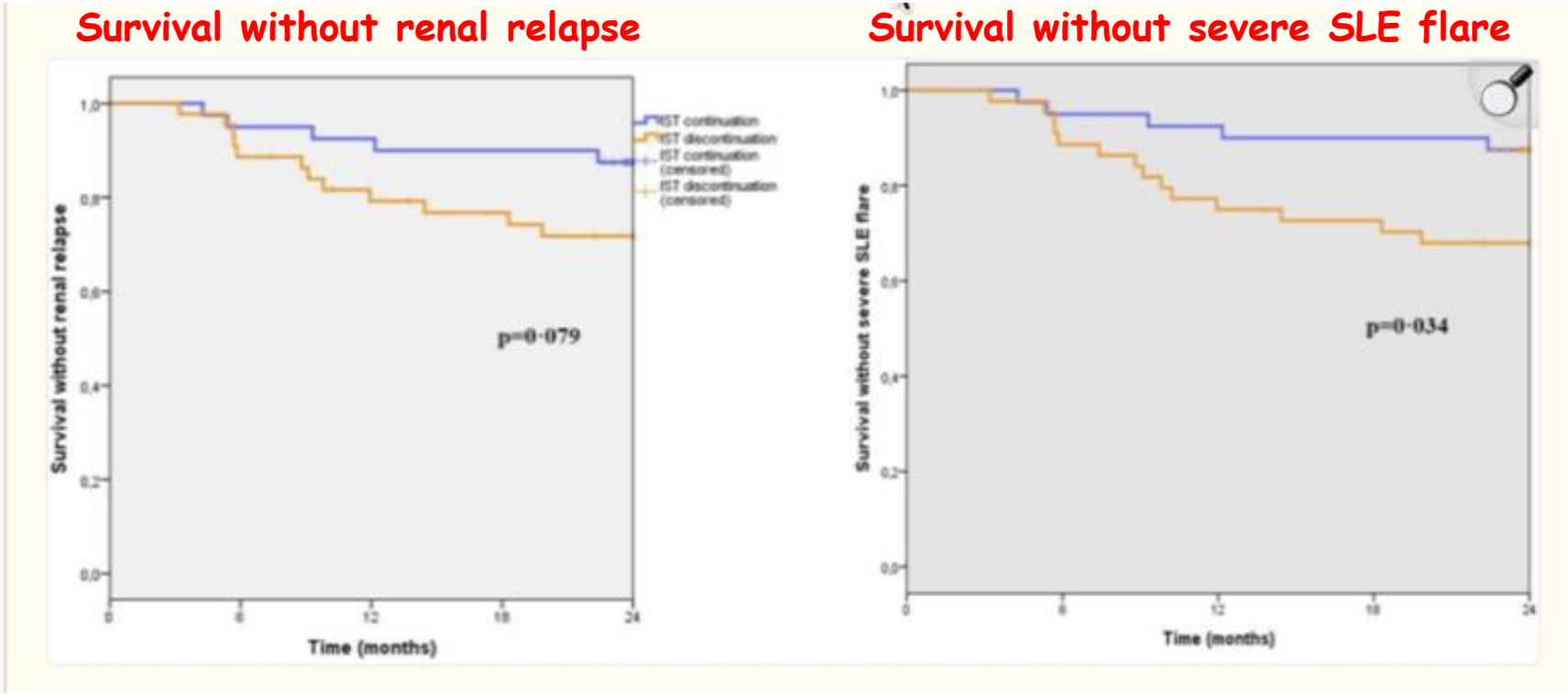
Young Ho Lee [1], Gwan Gyu Song [1]

- **Meta-analysis (6 RCTs, 1,437 patients)**
  - Multitarget therapy has higher complete remission rates than monotherapy (**OR: 2.155; p < 0.001**).

- **Subgroup Analysis:**
  - Higher remission rates with **TAC+MMF**, **VOC+MMF**, and **Belimumab+SOC** compared to monotherapy or SOC.

Maintenance Therapy:

Weaning of maintenance immunosuppressive therapy in lupus nephritis (WIN-Lupus): results of a multicentre randomised controlled trial



Conclusion: In this multicentre RCT, non-inferiority of IST discontinuation after 2–3 years was not demonstrated, although IST continuation was not significantly superior regarding LN relapse.

Figueroa-Parra G., et al Ann Rheum Dis, 2022 Jun 20;81(10):1420-1427

Maintenance Therapy:

Mycophenolate mofetil withdrawal in patients with systemic lupus erythematosus: a multicentre, open-label, randomised controlled trial

- **Disease Reactivation by Week 60:**
  - **Withdrawal Group**: 18% (9 of 51) had significant reactivation.
  - **Maintenance Group**: 10% (5 of 49) had significant reactivation.
  - **Risk Increase with Withdrawal**: 7% (upper limit: 15%).
- **Adverse Events:**
  - Similar in both groups (~90%).
- **Infections:**
  - Higher in the **Maintenance Group** (64%) vs. **Withdrawal Group** (46%).
- **Conclusion:**

- Stopping MMF in stable SLE patients slightly increases disease reactivation risk (7%) but reduces infections.
- Withdrawal is a reasonable option for stable patients.

Eliza F Chakravarty et al, Randomized Controlled Trial, Lancet Rheumatol, 2024 Mar;6(3):

How to Improve the Prognosis of Lupus Nephritis?

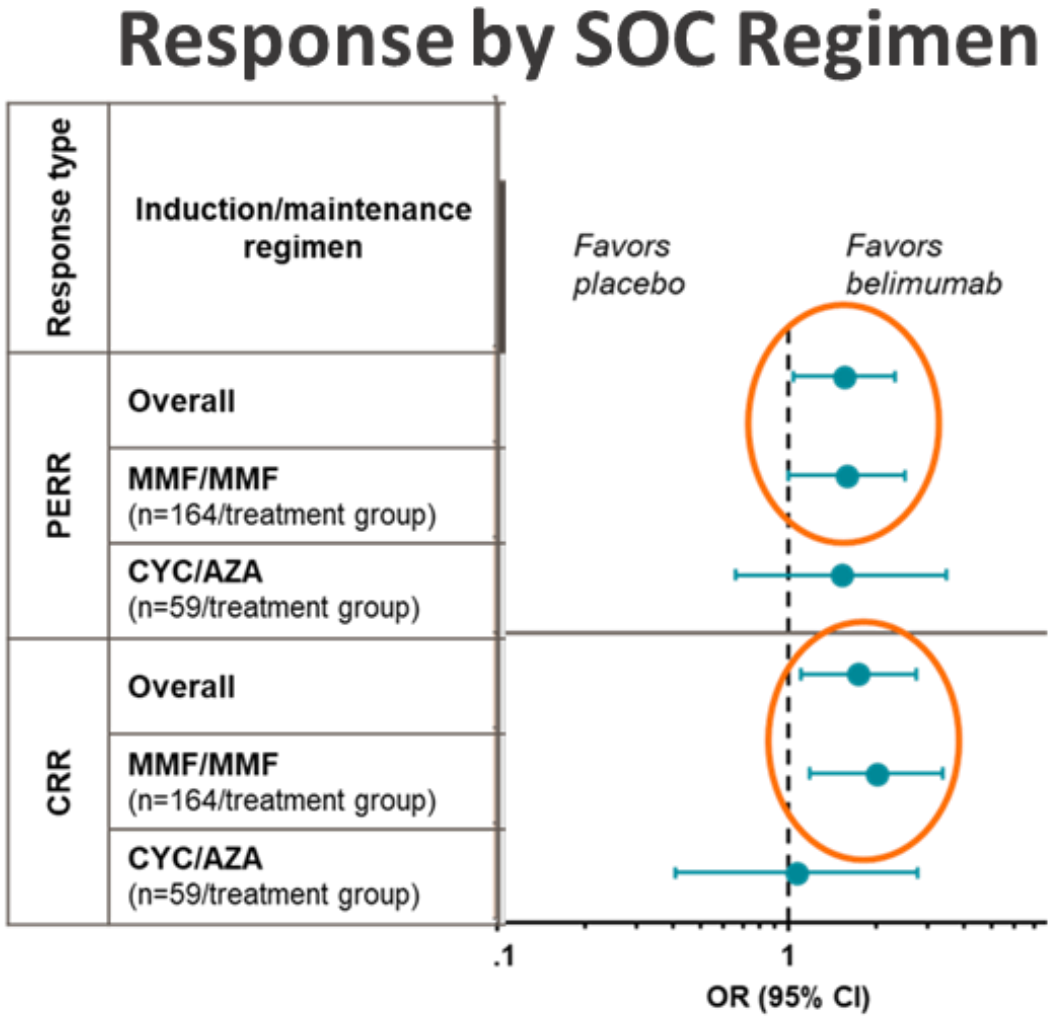
❖ By switching from sequential to combination therapy.

- Dec 2020 Belimumab for treatment of Lupus nephritis
- Jan 2021 Voclosporin for treatment of Lupus nephritis
- April 2021 Anifrolumab for treatment of moderate to severe Lupus

Tamirou F and Houssiau F. J Clin Med 2021;10:670

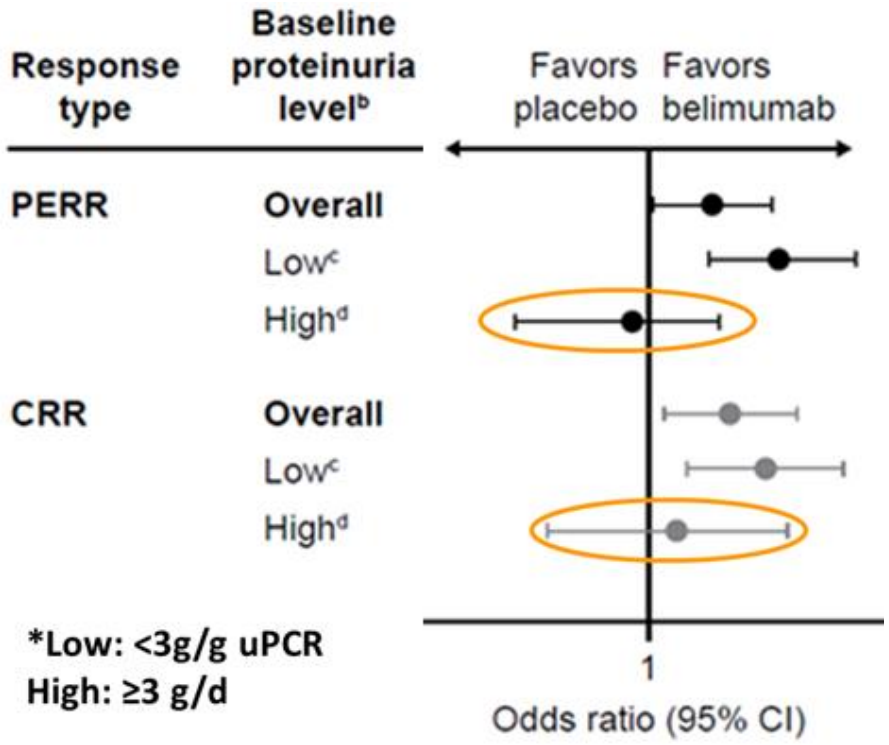
Study (Publication Year)	Drug	Main Results	Other Results and Comments
BLISS LN (2020)	BEL	43% vs. 32% in CRR trial vs. SOC ($p < 0.01$)	Reduced incidence of renal and extra-renal flares and of renal events or death. It can be used in renal failure and during pregnancy. Impaired response if proteinuria > 3 g/d. It can be associated with either CYC or MMF and GC (triple induction therapy).
BEAT LUPUS (2021)	RTX-BEL sequential therapy	Reduced incidence of post-RTX flares	BEL maintenance therapy after RTX may be necessary to prevent flares in SLE refractory to conventional therapy.
AURORA 1 (2021)	VOC	41% vs. 23% in CRR trial vs. SOC ($p < 0.01$)	Rapid decrease in proteinuria (50% in 1 month). Aggressive GC tapering (PDN 2.5 mg/d by 16 weeks) successful in 80% of patients. It can be associated with MMF and GC as triple induction therapy.
AURORA 2 (2022–2023)	VOC	Stable GRF and no evidence of chronic nephrotoxicity at renal biopsy after 3 years.	Less nephrotoxicity than CsA and TAC, but requires GFR > 45 mL/min.
TULIP-LN (2022) and extension (2023)	Anifrolumab	27.3% vs. 17.8% CRR in intensive-regimen Anifrolumab vs. placebo at 2 years.	Improvement of GRF numerically higher in both intensive and basic regimen of Anifrolumab. Higher incidence of Varicella Zoster.
NOBILITY (2022)	Obinutuzumab	Primary endpoint not met; however, 38% vs. 16% in CRR trial vs. SOC at 76 week ($p < 0.01$) with PDN <7.5 mg/d and improved renal responses through week 104.	Superior preservation of renal function and prevention of LN flares at post-hoc analysis.

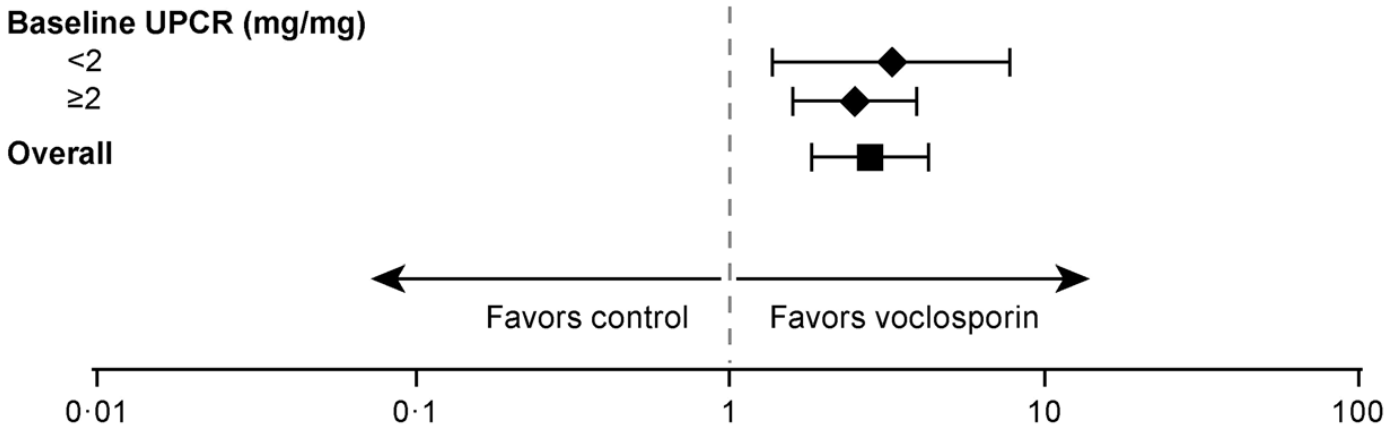
Subgroup analysis: Background therapy



Rovin et al, Kidney Int, 2022

Subgroup analysis: Baseline proteinuria



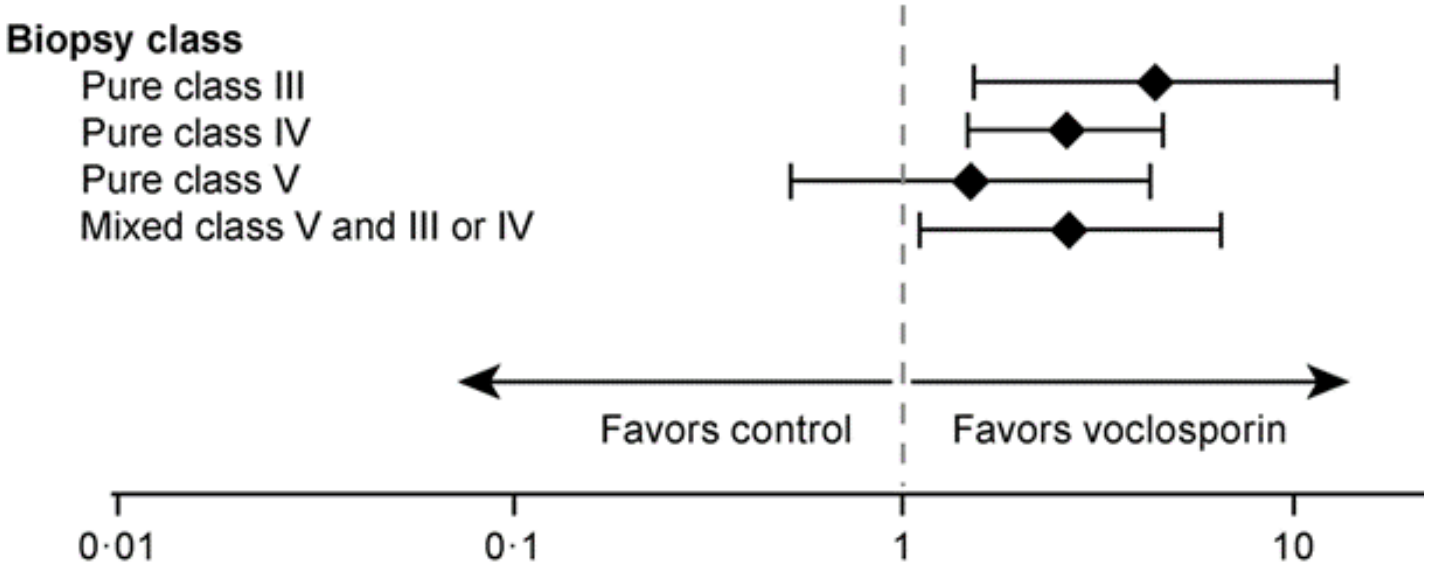


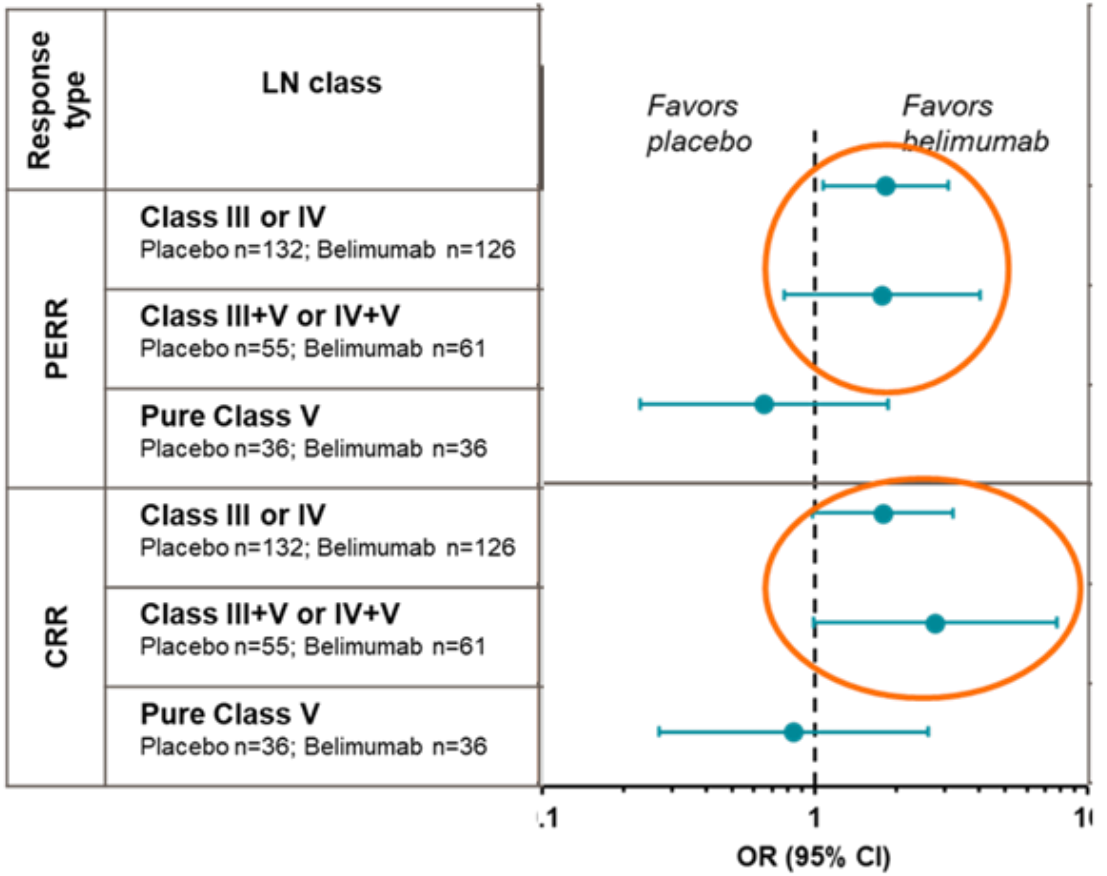
A post-hoc analysis was done with AURORA1 patients who had proliferative ± membranous LN and UPCR ≥3 g/d

Trial ARM	UPCR≥3 g/g (III, IV±V)		UPCR<3 g/g (III, IV±V)		UPCR<3 g/g (V)	
	% CRR	P	% CRR	P	% CRR	P
Voclo	34.2	0.001	46.6	0.13	63.1	0.05
Placebo	11.1		34.2		20	

Arriens et al, Arth Care Res, 2023; Rovin et al, Kidney Int, 2022; Menn-Josephy et al, CJASN, 2024

Subgroup analysis: LN class





Arriens et al, Arth Care Res, 2023; Rovin et al, Kidney Int, 2022

Longer-term data for voclosporin and belimumab

	Voclosporin n=116	Control n=100	OR (95% CI)	*P* value
	% (n/n)			
CRR				
Month 12	52.6 (61/116)	34.0 (34/100)	2.30 (1.30, 4.05)	0.004
Month 24	56.0 (65/116)	43.0 (43/100)	1.81 (1.04, 3.16)	0.035
Month 36	50.9 (59/116)	39.0 (39/100)	1.74 (1.00, 3.03)	0.051

Table 3. Primary efficacy renal response and complete renal response at open-label baseline and open-label week 28 (open-label modified intention-to-treat population, *N*=254)

	Placebo-to-Belimumab Intravenous 10 mg/kg, *N*=122		Belimumab-to-Belimumab Intravenous 10 mg/kg, *N*=132	
	Open-Label Baseline[a]	Open-Label Week 28	Open-Label Baseline[a]	Open-Label Week 28
Key secondary efficacy end points primary efficacy renal response and complete renal response using open-label phase criteria (observed cases)				
Primary efficacy renal response[b]				
N	122	118[c]	132	122[c]
Responders, n (%)	73 (60)[d]	79 (67)	93 (70)[d]	91 (75)
Complete renal response[b]				
N	122	118[c]	132	122[c]
Responders, n (%)	44 (36)[d]	57 (48)	63 (48)[d]	76 (62)

Saxena et al, Arth Rheum, 2023; Furie et al, CJASN, 2022

Safety data*

	Voclosporin (n=116)	Control (n=100)	Belimumab (n=132)	Control→Bel (n=123)
Adverse Event	92.3%	95%	70%	62%
Treatment-related AE	50%	31%	18%	20%
SAE	26.7%	28%	8%	4%
Treatment-related SAE	4.3%	4%	-	-
Infections	60.8%	72%	42%	49%

***Safety results are taken from the population exposed to voclosporin or placebo for 3 years and for the BLISS-LN cohort those completing the 6-month extension of the 2-year BLISS-LN study**

Saxena et al, Arth Rheum, 2023; Furie et al, CJASN, 2022

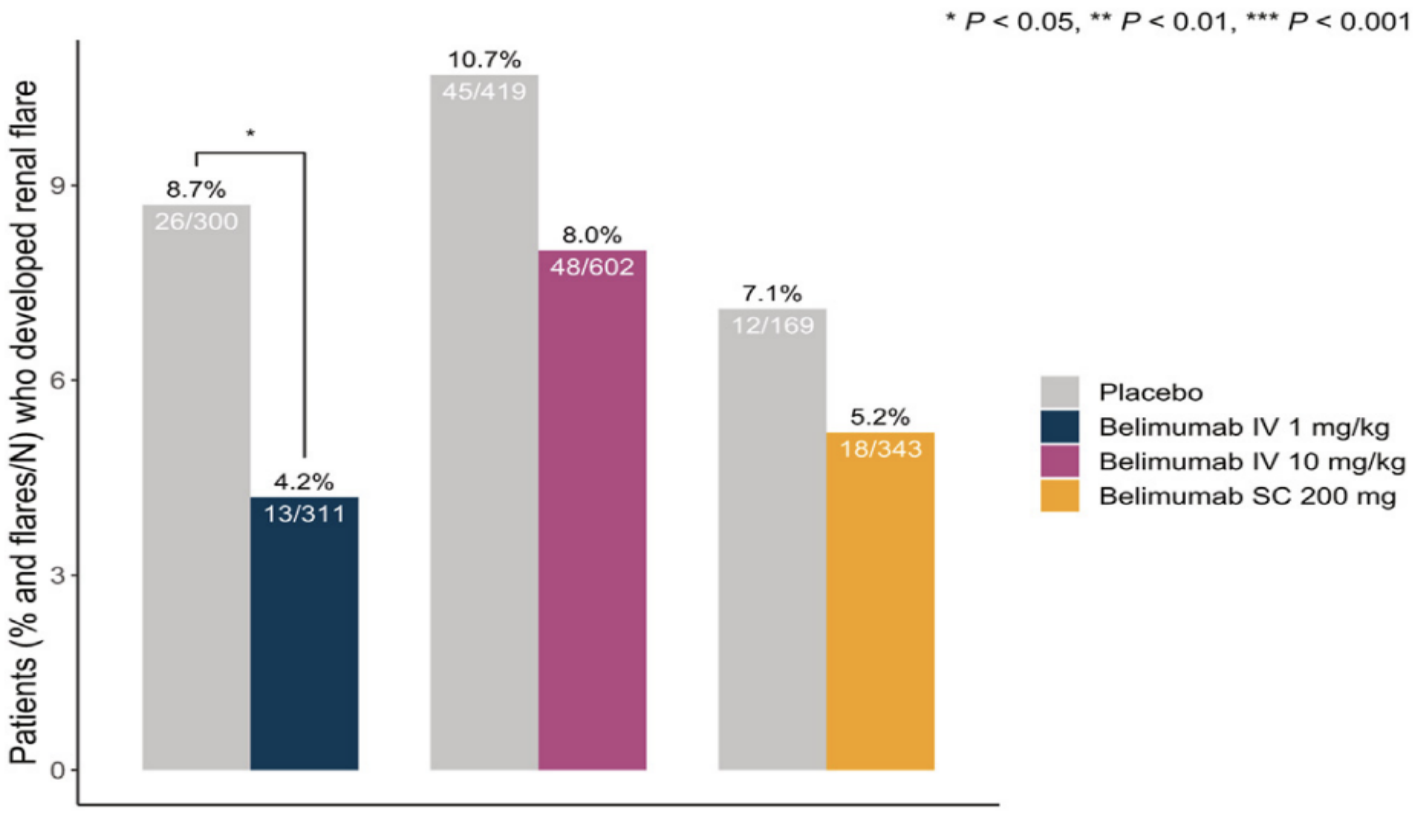
Is voclosporin nephrotoxic-repeat biopsy data

Variable	Control (n=10)		Voclosporin (n=16)	
	Baseline	≈18 Months	Baseline	≈18 Months
Activity Index	3 (3.3)	0.4 (1.0)	1.8 (3.0)	0.4 (1.0)
Chronicity Index	2.9 (2.3)	2.8 (2.7)	3.8 (3.5)	4.1 (3.3)
Global Glom Sclerosis	1.3 (1.0)	1.5 (1.0)	1.3 (1.4)	1.4 (1.2)
Fibrous Crescents	0.2 (0.4)	0.1 (0.3)	0.4 (0.6)	0.2 (0.4)
Tubular Atrophy	0.7 (0.7)	0.6 (1.0)	1.1 (1.1)	1.3 (1.2)
Interstitial Fibrosis	0.7 (0.7)	0.6 (1.0)	1.1 (1.1)	1.2 (1.2)
	Baseline	36 Months	Baseline	36 Months
uPCR	4.7 (2.6)	2.1 (4.6)	4.6 (2.5)	1 (1.4)
eGFR	83 (12)	86 (13)	80 (16)	83 (15)
CRR %	-	40	-	63
PRR %	-	70	-	81

Parikh et al., Am Soc Nephrol Annual Meeting, 2023

Effect of Belimumab on Preventing *de novo* Renal Lupus Flares

They evaluate the efficacy of belimumab in preventing *de novo* renal flares in nephritis-naïve patients with SLE, who are receiving add-on belimumab or placebo.

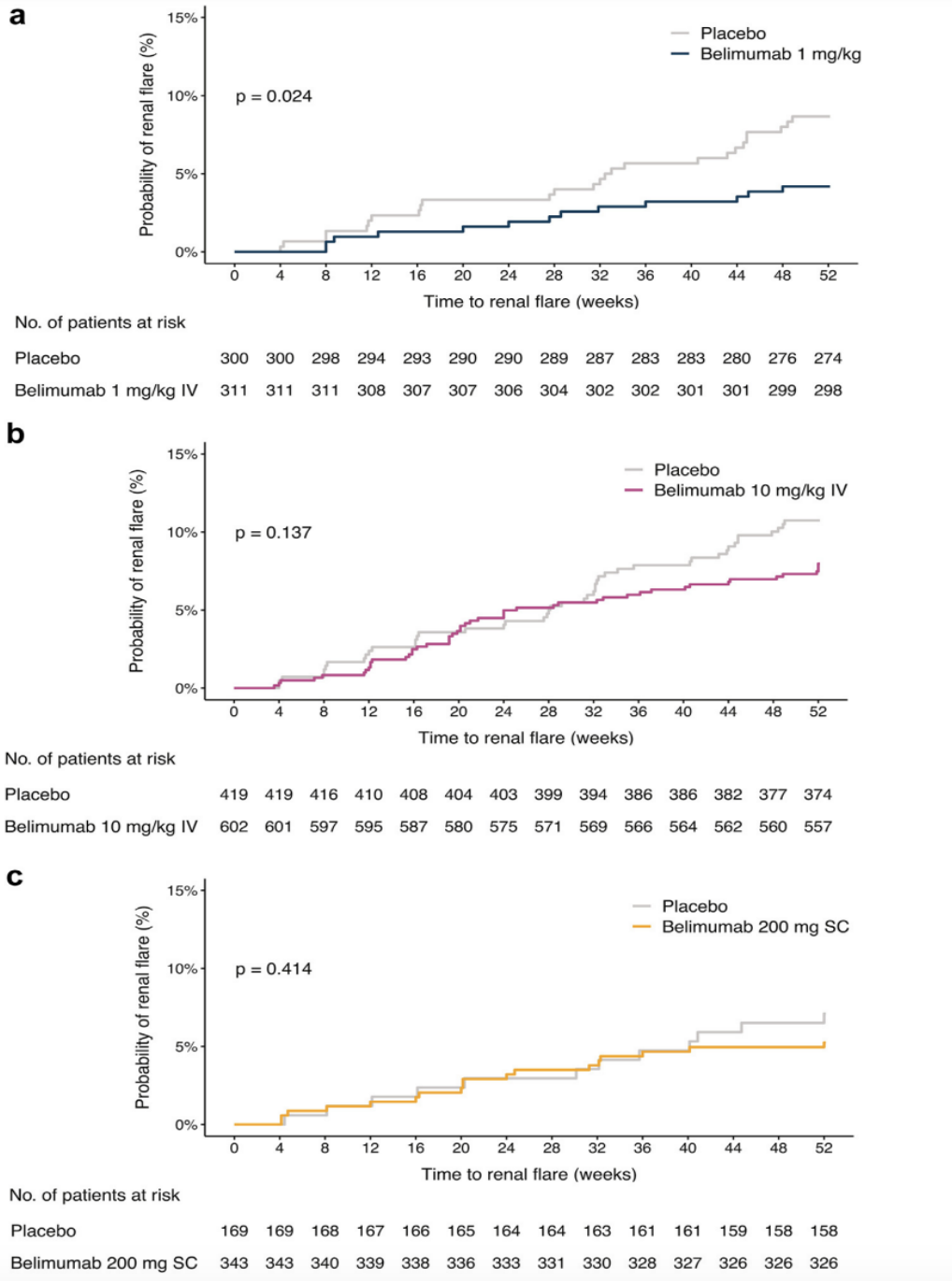


I Parodis et al.: Belimumab Effect on Preventing de novo Renal SLE; Kidney International Reports (2023) 8, 1822–1830

Effect of Belimumab on Preventing *de novo* Renal Lupus Flares

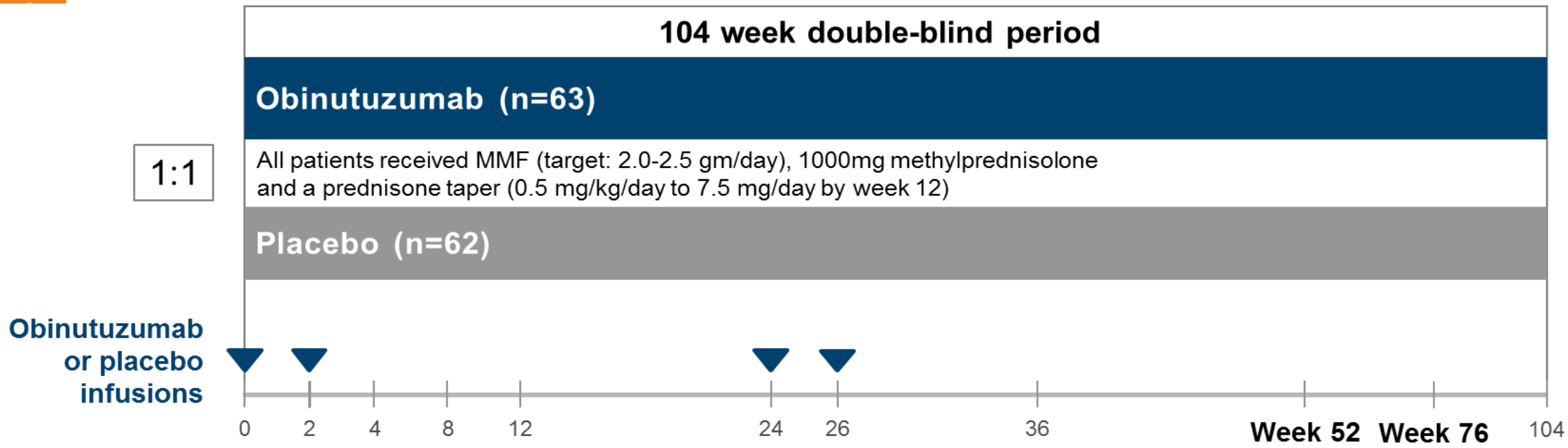
Conclusion:

- patients of Asian origin appeared more susceptible to new onset renal involvement.
- Add-on low-dose IV 1 mg/kg and SC 200 mg belimumab in addition to nonbiological ST appeared protective against renal flares in patients with SLE who have no prior history of nephritis,
- whereas addition of the approved IV dose (10 mg/kg) no clear protection



Parodis et al.: Belimumab Effect on Preventing de novo Renal SLE; Kidney International Reports (2023) 8, 1822–1830

The Nobility trial – phase II RCT Obinutuzumab added to SoC with MMF & Pred vs Soc; class III/IV ± V



Key inclusion criteria:
- ISN/RPS Class III or IV LN within six months, concomitant class V permitted
- UPCR ≥1 on 24-hour collection

Key exclusion criteria:
- Rapidly progressive glomerulonephritis
- eGFR <30 mL/min
- >50% of glomeruli with sclerosis

Primary endpoint:
- Complete renal response (CRR) at week 52

Key secondary endpoints:
- Overall renal response (CRR or PRR)
- Change in levels of dsDNA, C3, C4

Prespecified alpha level = 0.2

Furie RA, et al. Ann Rheum Dis 2022;81:100–107.

NOBILITY phase 2 study: Obinituzumab group had continued improvement vs placebo more than 18 months post last dose

- 102 patients (82%) completed 104 weeks of follow up.
- CRR (UPCR <0.5 + sCreat ≤ ULN lab + sCreat ≤115% patient's baseline ≠ <10RBC)

	Obinutuzumab	placebo	p value
Week 52	35%	23%	**0.115**
Week 76	40%	18%	**0.007**
Week 104	41%	23%	**0.026**

- Obinutuzumab patients: greater improvement in eGFR, UPCR, anti-dsDNA, C3 & C4, and fewer required initiation of a new rescue therapy through week 104.
- Durable response despite 92% having detectable B cells at week 104

SAEs	25%	30%	Phase 3 study ongoing
Serious infections	1%	8%	REGENCY fully recruited
Deaths	1	4	

Furie RA, et al. Ann Rheum Dis 2021

Sodium-Glucose Cotransporter-2 Inhibitors and Nephritis Among Patients With Systemic Lupus Erythematosus

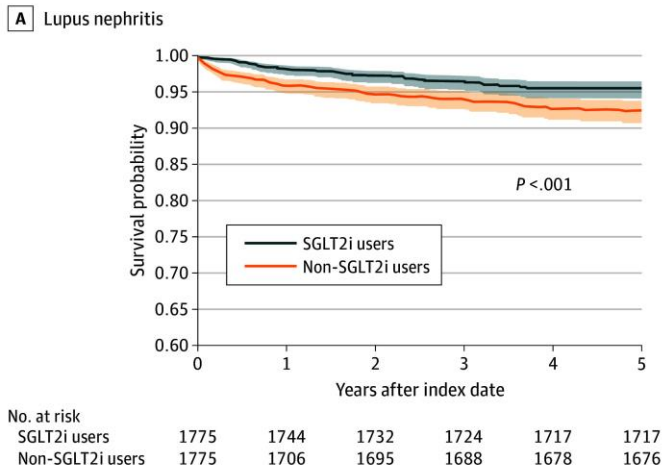
➢ **Study Highlights:**

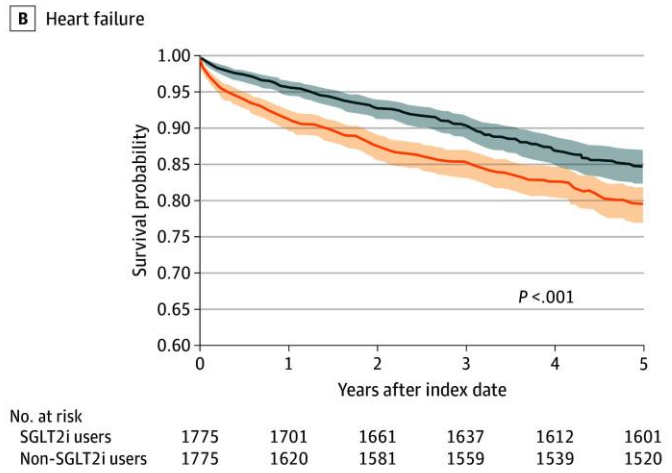
- Multicenter retrospective cohort study
- 1,775 matched pairs with SLE and DMt2
- Compared SGLT2i users vs. non-users

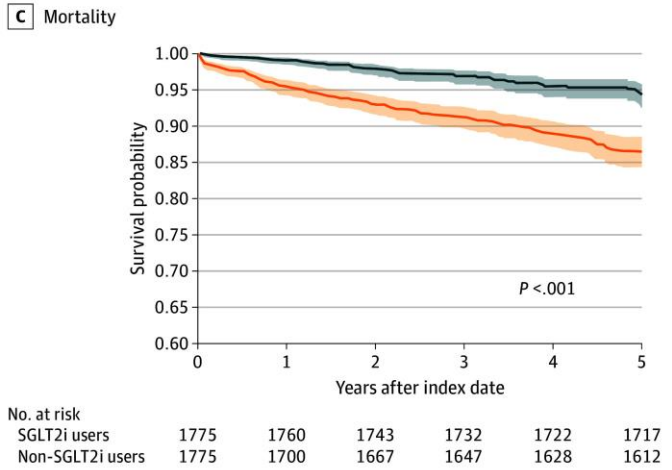
➢ **Conclusion:**

❑ **Significantly reduced risk of:**

- Lupus nephritis
- Dialysis and kidney transplant
- Heart failure
- All-cause mortality







Fu-Shun Yen et al, JAMA Netw Open, 2024 Jun 12;7(6):e2416578

CAR T in SLE

- These are the first 5 SLE patients treated with CAR T
- No real data on the kidney histology
- At least one patient did not have active LN (by proteinuria)
- These were by and large very young patients
- They were treated and did not respond to two SOC therapies but at least some did not get cyclophosphamide for LN and few received a really good B cell depleting agent

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics					
Age (years)	22	23	22	24	18
Sex (female/male)	F	M	F	F	F
Disease duration (years)	4	1	6	9	3
Disease activity SLEDAI-2K (score)	16	16	10	8	9
Laboratory values					
Baseline hemoglobin (g dl^{-1})	10.0	14.60	9.60	13.10	12.20
Baseline white blood cells (*N* μl^{-1})	8.69	5.36	5.85	3.88	7.25
Baseline lymphocytes (*N* μl^{-1})	0.7	1.2	1.4	1.4	1.4
Baseline platelets (*N* μl^{-1})	279	188	198	398	278
Baseline C3 (mg dl^{-1})	49	43	56	88	68
Baseline anti-dsDNA (U ml^{-1})	5,600	2,060	479	4	52
Baseline ANA (titer)	1:10,000	1:3,200	1:10,000	1:3,200	1:1,000
Proteinuria (mg per 24 h)	2,015	3,080	6,539	8,096	88
Other autoantibodies	NUC, Sm	NUC, Sm Ro60	NUC, PCNA	NUC, Sm, Ro60	NUC, Sm, Ku
Organ involvement					
Skin (presence/absence)	+	+	+	+	+
Kidney (presence/absence)	+ (stage III)	+ (stage III)	+ (stage IV)	+ (stage III/V)	+ (stage III/V)
Joints (presence/absence)	–	+	+	+	+
Lungs (presence/absence)	+	–	+	+/–	–
Heart (presence/absence)	+	–	–	+	–
Other (presence/absence)	HEM	–	SER	MYO	HEM
Treatments					
Glucocorticoid pulses (yes/no)	+	+	+	+	+
Hydroxychloroquine (yes/no)	+	+	+	+	+
MMF (yes/no)	+	+	+	+	+
Azathioprine (yes/no)	–	–	–	+	+
Cyclophosphamide (yes/no)	+	+	+	–	–
Rituximab (yes/no)	+	–	–	–	–
Belimumab (yes/no)	+	+	+	+	+
Other (yes/no)	TAC	–	–	MTX, LEF	–

Mackensen et al, Nat Med, 2022

CAR T therapy: 100% CRR in 3 months and no LN relapses over 2 years off immunosuppression!

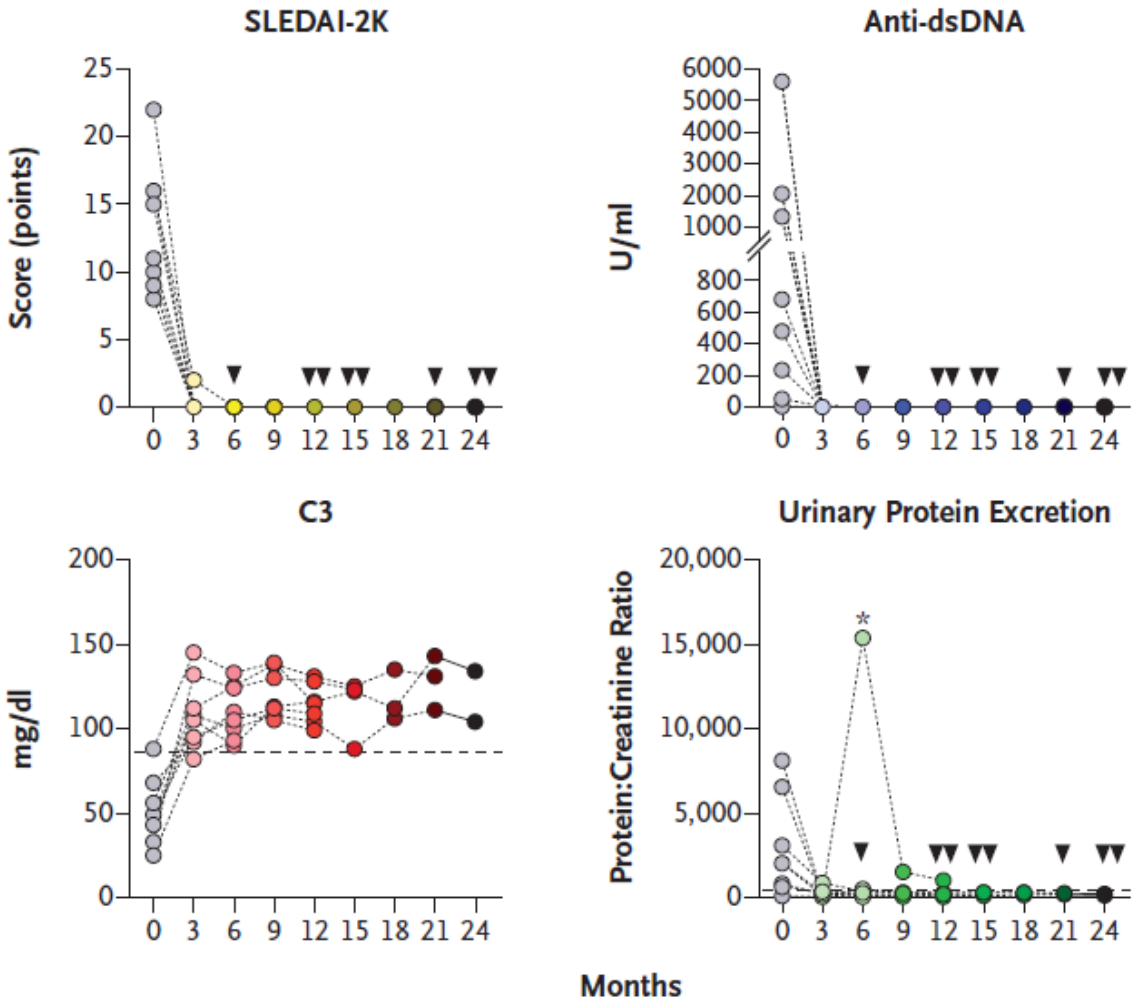


Table 2. Short-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE
CRS (grade)	0	1	1	1	0	1	0	1
ICANS (grade)	0	0	0	0	0	0	0	0
Bone marrow toxicity†	0	0	0	0	0	0	0	0
TOC treatment	0	0	0	+	0	+	0	+
GLC treatment	0	0	0	0	0	0	0	0
Low IgG	+	+	+	0	0	0	0	+‡
IgG substitution	0	+	0	0	0	0	0	+

- These 8 lupus patients are off all immunosuppressive agents and glucocorticoids
- Remission has been sustained up to 29 months

Mueller et al, NEJM, 2024

What are CAR T therapies doing that others are not?

- CAR T results in deep B cell depletion
- CAR T also takes out plasmablasts (can we combine anti-CD20 and anti-CD38?)
- CAR T gets into the kidney better and this is where LN therapies need to be (will obi address)
- CAR T "resets" the B cell population (how does reconstitution of the B cell compartment differ between anti-CD20 and CAR T therapies?)

Study (Publication Year)	Drug	Main Results	Other Results and Comments
BLISS LN (2020)	BEL	43% vs. 32% in CRR trial vs. SOC ($p < 0.01$)	Reduced incidence of renal and extra-renal flares and of renal events or death. It can be used in renal failure and during pregnancy. Impaired response if proteinuria > 3 g/d. It can be associated with either CYC or MMF and GC (triple induction therapy).
BEAT LUPUS (2021)	RTX-BEL sequential therapy	Reduced incidence of post-RTX flares	BEL maintenance therapy after RTX may be necessary to prevent flares in SLE refractory to conventional therapy.
AURORA 1 (2021)	VOC	41% vs. 23% in CRR trial vs. SOC ($p < 0.01$)	Rapid decrease in proteinuria (50% in 1 month). Aggressive GC tapering (PDN 2.5 mg/d by 16 weeks) successful in 80% of patients. It can be associated with MMF and GC as triple induction therapy.
AURORA 2 (2022–2023)	VOC	Stable GRF and no evidence of chronic nephrotoxicity at renal biopsy after 3 years.	Less nephrotoxicity than CsA and TAC, but requires GFR > 45 mL/min.
TULIP-LN (2022) and extension (2023)	Anifrolumab	27.3% vs. 17.8% CRR in intensive-regimen Anifrolumab vs. placebo at 2 years.	Improvement of GRF numerically higher in both intensive and basic regimen of Anifrolumab. Higher incidence of Varicella Zoster.
NOBILITY (2022)	Obinutuzumab	Primary endpoint not met; however, 38% vs. 16% in CRR trial vs. SOC at 76 week ($p < 0.01$) with PDN <7.5 mg/d and improved renal responses through week 104.	Superior preservation of renal function and prevention of LN flares at post-hoc analysis.

So how should we use these new agents?

- Start simple – standard of care and add on belimumab / CNI when improvement not optimal?
- Or should we go in big guns at the outset and then pull back? Sequential or early combinations?
  - Which preserves nephrons better?
  - But which has higher risk of adverse events?
- CNI for the more proteinuric
- Belimumab for the long term

10.2.3 Class III or Class IV lupus nephritis

10.2.3.1 Initial therapy of active Class III/IV lupus nephritis

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either one of the following:

i. mycophenolic acid analogues (MPAA) (1X); or

i. low-dose intravenous cyclophosphamide (1X); or

i. belimumab and either MPAA or low-dose intravenous cyclophosphamide (X); or

i. MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (for example estimated glomerular filtration rate [eGFR] ≤45 ml/min per 1.73 m2) (1X)

Practice Points

- A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement

- Intravenous cyclophosphamide should be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.

- An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure.

- Initial therapy with an immunosuppressive regimen that includes a CNI (voclosporin, tacrolimus, or cyclosporine) may be preferred in patients with relatively preserved kidney function and nephrotic-range proteinuria likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.

Practice Points

- A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be considered in patients with repeated renal flares or at high-risk for progression to kidney failure.

- Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs,

- Newer biologic and non-biologic therapies are under development and may offer future options for the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy.

10.2.3.2 Maintenance therapy for Class III and Class IV lupus nephritis

Recommendation 10.2.3.2.1: We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance (1B).

Practice Points

- The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be ≥36 months.

- Patients treated with triple immunosuppressive regimens that include belimumab or a CNI in addition to standard immunosuppressive therapy can continue with triple immunosuppressive regimen as maintenance therapy

- If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine or leflunomide can be considered.

Management of unsatisfactory response to treatment

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative first-line regimen when there is persistent disease activity
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

Non-immune-mediated injury in LN

BUT ALSO ADDRESS THIS!

Non-immunological drivers of CKD progression[2]

Hemodynamic and metabolic nephron overload

Cardio-Renoprotective drugs ***(CARPDs)***

Low birth weight, Obesity (steroids), diabetes, salty diet, High protein diet, pregnancy, other kidney injuries, HTN, drug toxicity (NSAIDs, PPI), aging, genetics (APOL1, …)

2 Luyckx VA, et al. Nat Rev Nephrol 2022;18:171–183.

So how do we really preserve renal function in LN?

Minimise SLE activity Prevent relapse	Attenuate progression of CKD/CVD		Infection control
ADHERENCE	**DMARDs** (Disease-modifying anti-rheumatic drugs)	**CARPDs** (Cardio-renoprotective drugs)	**STEROIDS** **VACCINATION**
Patient education Literature Special clinics/1 doctor Medication app BP protocol Prescription intervals Drug levels Shared decision taking	HCQ, CYC, CyA, leflunomide AZA, MMF/MPA TAC, Voclo, BEL, RTX/OBI, ANI?	ACEi, ARB SGLT2i, MRA? BMI, BP, diabetes smoking, salt intake	3x 250-500 mg IV Oral taper to 5 mg or < No oral steroids for flares. & Influenza, Corona, Varicella Pneumococci, etc.

Prof. Anders ERA-EDTA

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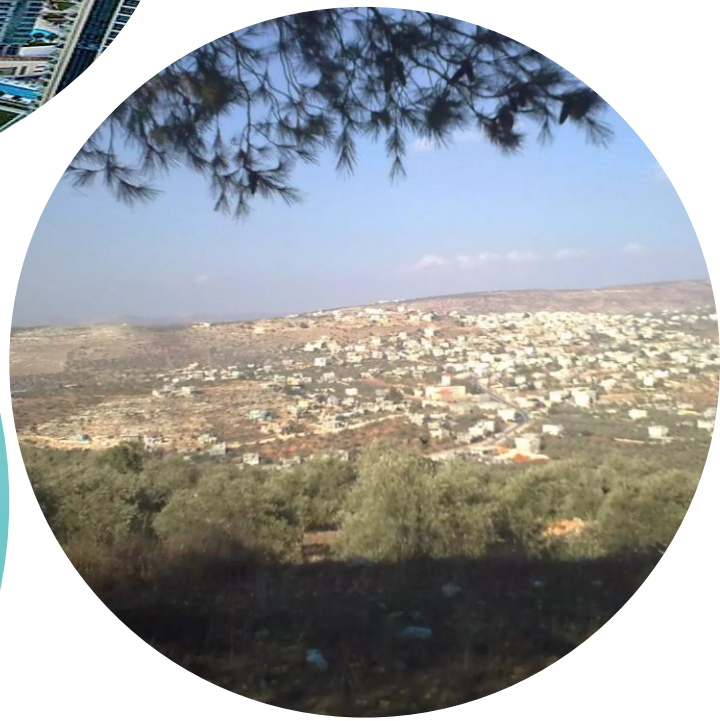


BLISS-LN met Primary and key secondary endpoints

Primary e/point: RR at Week 104

- eGFR ≥ 60 mL/min/1.73 m^2 or no more than 20% below pre-flare value, and
- Urine protein:creatinine ratio ≤ 0.7, and
- Not a treatment failure

Secondary e/p CRR Week 104

- eGFR ≥ 90 mL/min/1.73 m^2 or no more than 10% below pre-flare value, and
- Urine protein:creatinine ratio < 0.5, and
- Not a treatment failure[b]

Secondary e/p Time to renal-related event or death

1) ESKD, or
2) Doubling of serum creatinine, or
3) Renal worsening (increased proteinuria and/or impaired kidney function), or
4) Renal disease-related treatment failure[b]

Had to meet all three components of RR or CRR at 2 consecutive visits to be considered a responder

Patients on belimumab had:

55%

greater odds of achieving RR at **Week 104**

OR = 1.55 (95% CI: 1.04–2.32)
p = 0.0311

74%

greater odds of achieving CRR at week 104

OR=1.74 (95%CI:1.11-2.74)
p=0.02

49%

relative reduced risk of a renal-related event or death

HR = 0.51 (95% CI: 0.34–0.77)
***P* = 0.001**

Furie R, et al. N Engl J Med 2020

BLISS-LN trial POST HOC analysis

- Belimumab did not improve outcome when added to CyP/Aza or in those with pure class V

BUT:

Patients on belimumab:

- had significantly reduced the risk of a renal flare with both SoCs & across all classes of LN

55%

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

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

- were much less likely to have a 30% or 40% fall in eGFR – predictive of future ESKD

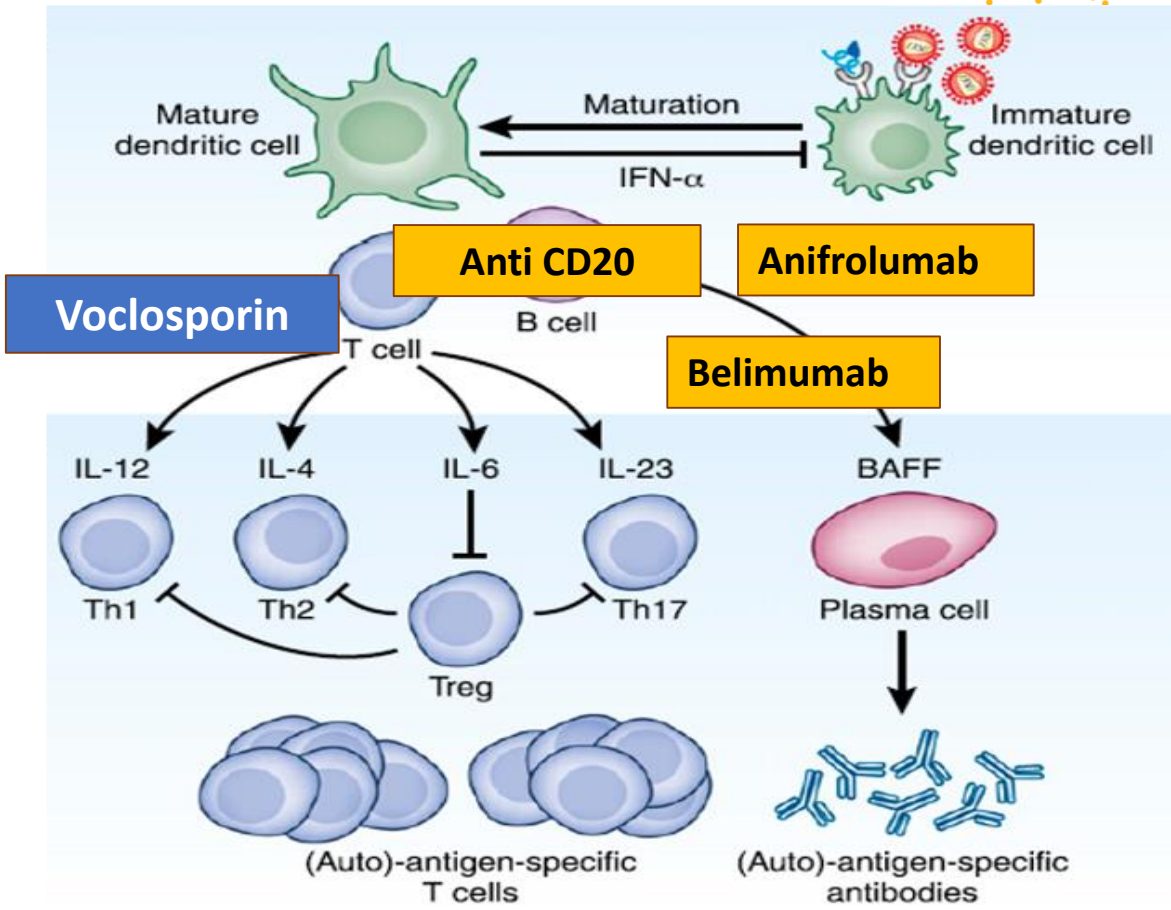
48% and 62%

risk reduction of experiencing a 30% and 40% decline in eGFR, respectively, vs patients who received SoC alone (*P* < 0.05)

Rovin BH, et al. Kidney Int. 2021.

Voclosporin – calcineurin inhibition

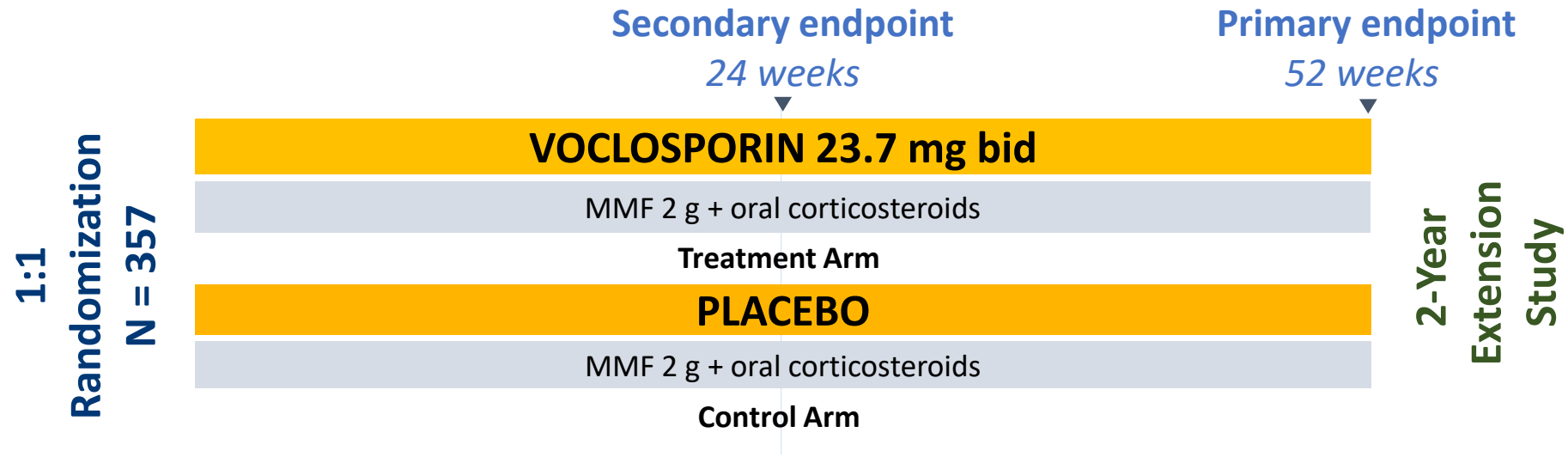
- Novel CNI, approved for LN
- Reduces T-cell activation
- Direct anti-proteinuric effect on podocytes within 2 weeks
- Biomarkers of SLE activity hardly affected, extrarenal SLE?
- SLE/LN flares?
- Now 3 years of data, no nephrotoxicity or metabolic AE[2]

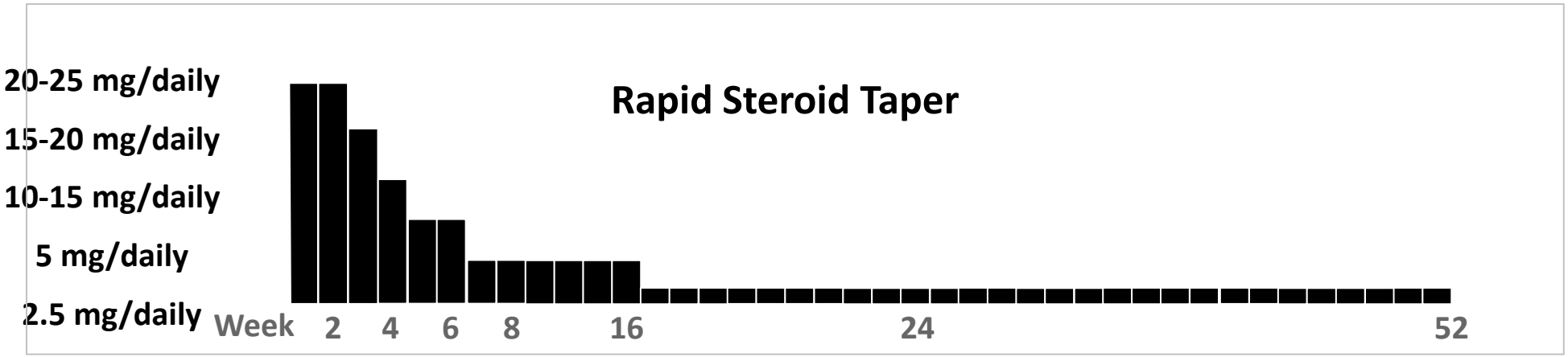


1. Rovin BH, et al. Lancet 2021;397:2070;
2. Saxena A, et al. ACR Convergence 2021;Abstract 1459;
3. Lech M and Anders HJ. JASN 2013;24:1357.

AURORA 1 Phase 3 Study Design

Primary endpoint: Renal Response at 52-Weeks

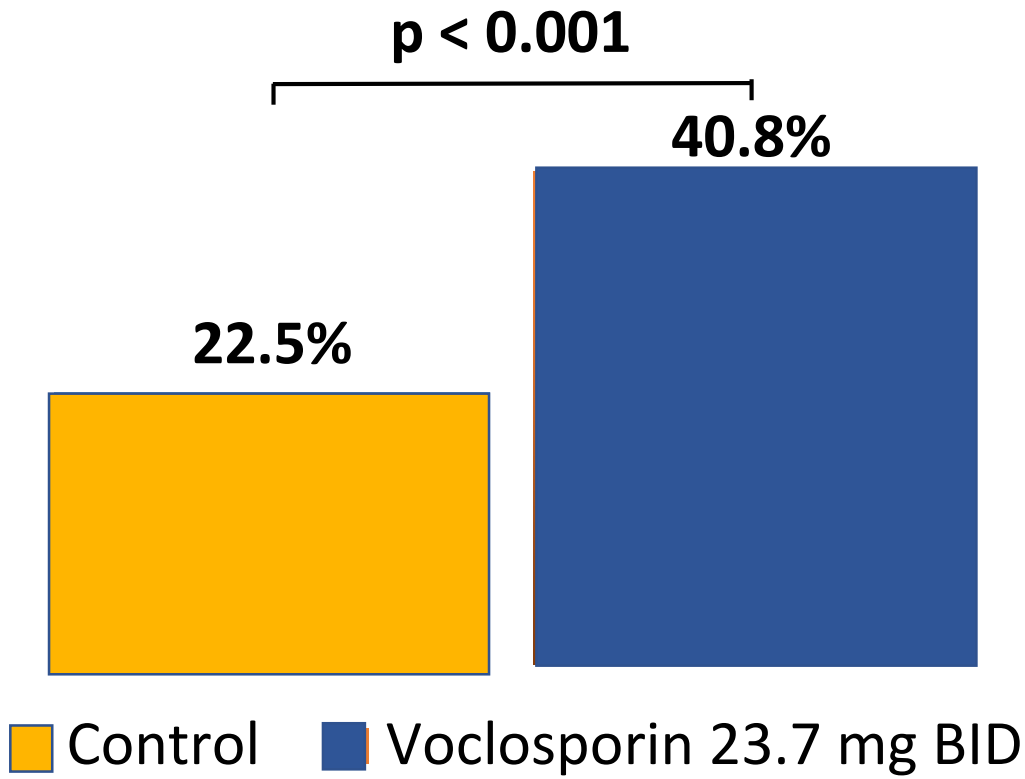




Rovin et al 2021 Lancet 397: 2070-80

AURORA - What was novel?

- Large study
- Stringent primary end point
- Radical steroid sparing
- Met primary endpoint and all secondary endpoints.
- No increase in adverse events
- BUT need repeat biopsies

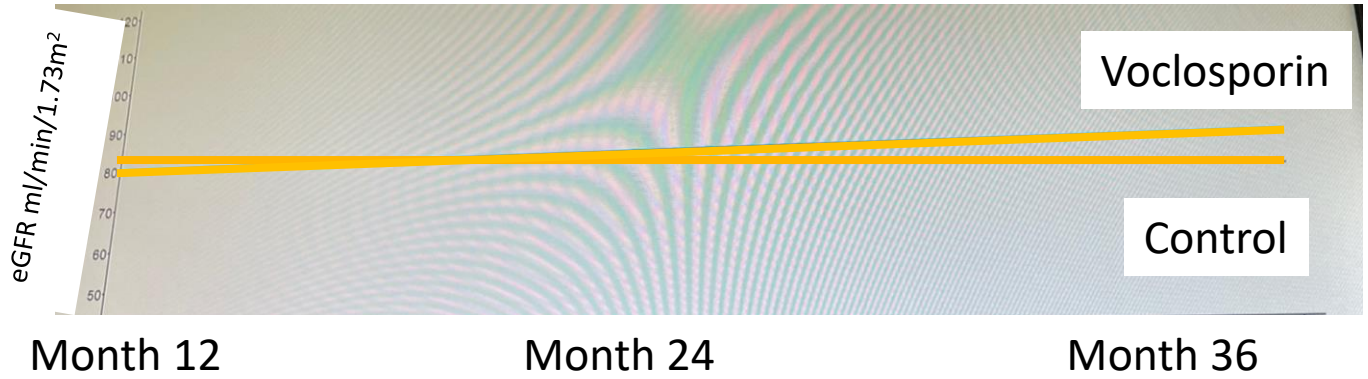


Rovin et al 2021 Lancet 397: 2070-80

Aurora 2 blinded extension study for further 24 months – primary e/p safety

Enrolled if had completed 12mths

Baseline uPCR (SD) at pre-treatment AURORA1 6.02 (2.29) mg/mg VCS arm & 6.08 (2.46) mg/mg control arm.



	SAEs	CRR	1yr	2yr	3yr	Flare rate	eGFR slope
Voclosporin							
N = 116	21.3%		**46.8%.**	**46.8%.**	**53.2%**	23.8%	-0.2ml
Control	27%		21.6%	35.1%.	35.1%	26%	-5.4ml
N= 100							
OR,			**4.41**	**3.08**	**2.92**		
95% CI			1.47, 13.26;	1.17, 8.1	1.07, 7.94		
P value			p=0.008	p=0.022.	p=0.036		

Teng O et al 59th ERA May 22

TH-PO486 Parikh S et al ASN Nov 22

FR-OR58 Menn-Josephy H et al ASN Nov 22