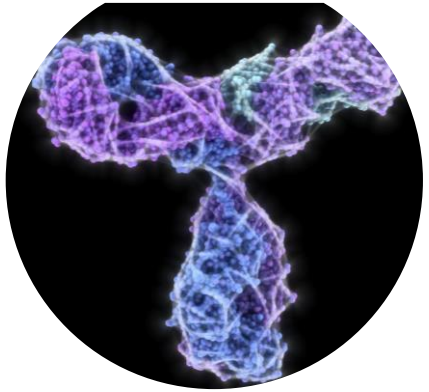
7º CONGRESO de la
**SOCIEDAD GALLEGA de NEFROLOGÍA**

**26 Y 27 DE NOVIEMBRE DE 2021**
SEDE: **AFUNDACIÓN** VIGO



# Actualización en el tratamiento de la Nefritis Lúpica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*Grupo Español de Enfermedades Glomerulares (GLOSEN) - RedInRen*
*Immunonephrology Working Group (IWG) - European Renal Association (ERA)*


Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud

SGAN sociedad gallega de nefrología

UAM Universidad Autónoma de Madrid

## Conflictos de Interés

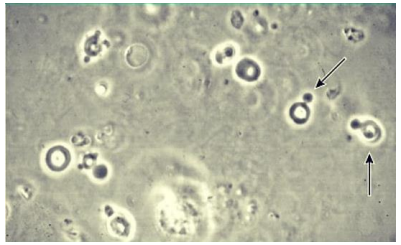
- GlaxoSmithKline España (GSK)
- Alexion Pharma Spain S.L.
- Otsuka Pharmaceutical S.A.

## Puntos a presentar y discutir

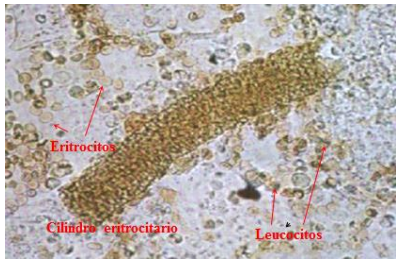
1. El paciente con LES en Nefrología: ¿Qué le interesa al nefrólogo?
2. Objetivos del tratamiento y necesidades no resueltas
3. ¿Cómo estamos tratando a los pacientes con Nefritis lúpica en 2021?
4. Nuevas evidencias y perspectivas en el tratamiento:
    - *Terapias combinadas (antiguos y nuevos fármacos)*
    - *Terapias biológicas dirigidas (inmunomodulación)*
5. Conclusiones

# ¿Qué le interesa al Nefrólogo en el LES?

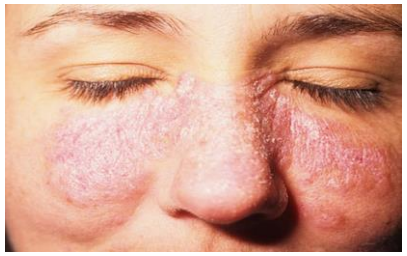
*Hasta 40%-60% de los pacientes con LES pueden desarrollar afectación renal a lo largo de su vida*

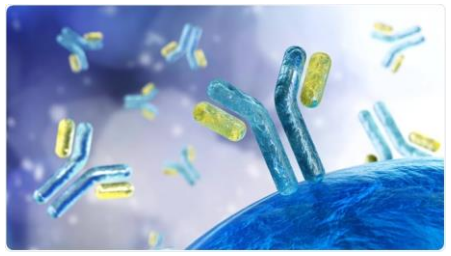


- La afectación renal y vascular:
  - Proteinuria (> 150 mg/24 h) ~ 100%.
  - Hematuria (> 3-5 hematíes/campo en orina) ~ 80%.
  - Deterioro de función renal (CrS/eGFR) ~ 40-80%.
  - Desarrollo de Hipertensión arterial ~ 15-50% (con o sin MAT).




- La actividad inmunológica y sistémica.





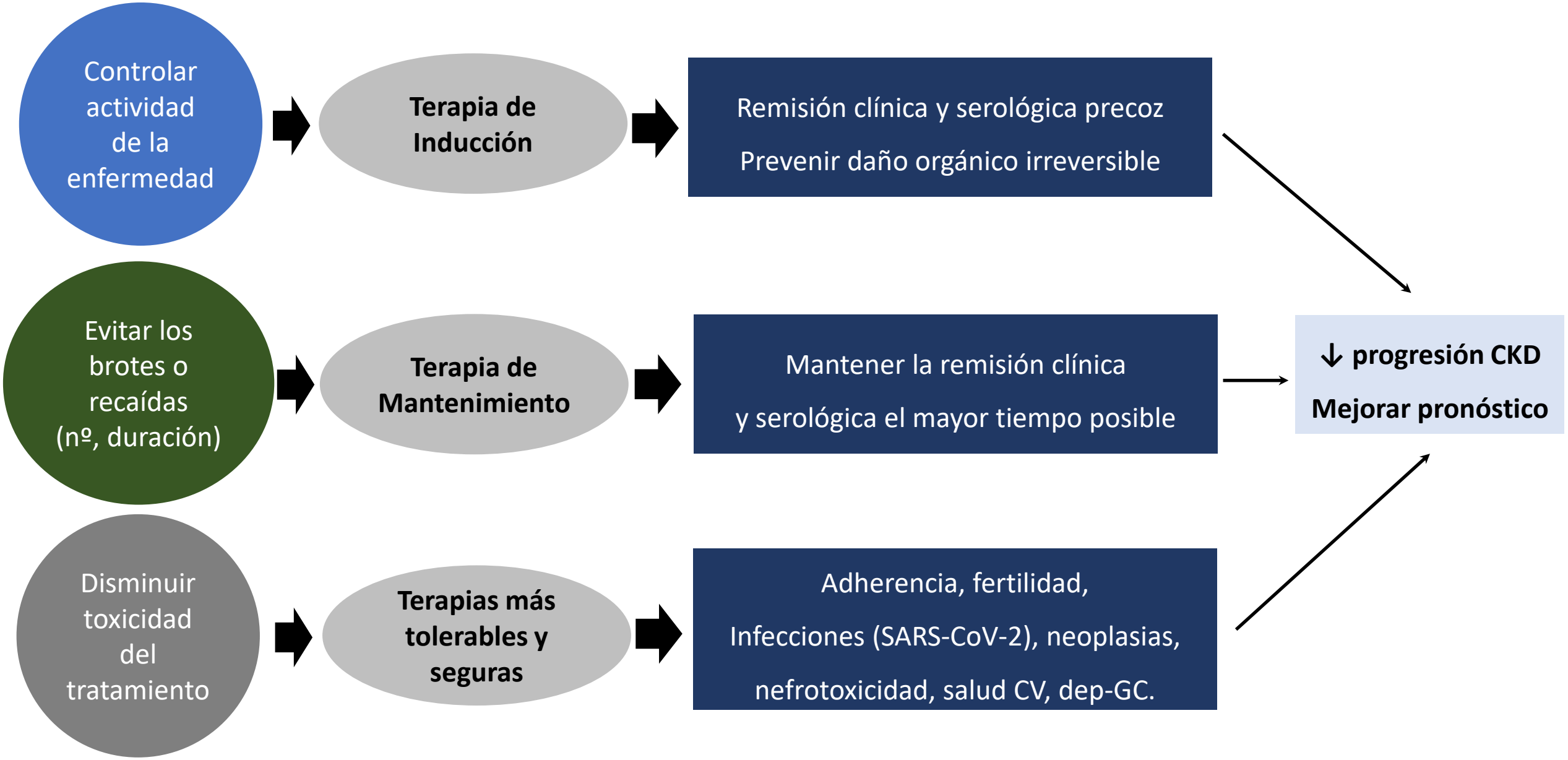
*Brad Rovin. Management of Lupus Nephritis. Early Program: UpDate in Glomerular Diseases.* ***ASN Kidney Week October 2020****.*

# ¿Qué le podemos ofrecer en el 2021 a nuestros pacientes?

- Mujer 33 años, caucásica, IMC 30, DM-2 (HbA1c 6%), DL y HTA controladas.
- Cuadro debut LES: renal, cutáneo/articular, inmunológico.
- Afectación renal:
  - *Edemas en tercio inferior de ambos MMII.*
  - *Proteinuria subnefrótica ( 3.2 g/24h), UACR 1.1 g/g.*
  - *Microhematuria (30 H/c), cilindros eritrocitarios, leucocitos.*
  - *FRA AKIN 1 (Cr 1.3, eGFR 60.6), 3 meses antes Cr 0.85, eGFR 96.7.*
- Actividad inmunológica: anti-DNAds ++, C3 y C4 bajos, anti-Sm +.
- Indicación de biopsia renal: valorar pronóstico y guiar tratamiento.

*Informe de la Biopsia renal: NL clase IV-V, IA 7/24, IC 1/12, IF: IgG 3+, IgA 2+, IgM 2+, C1q 3+, sin datos de nefropatía diabética ni de afectación vascular relevante*

# ¿Cuáles son los grandes objetivos de nuestra intervención?



# Necesidades no resueltas en el tratamiento de Nefritis Lúpica

**5-15%** → **Riesgo de muerte (26X)**

**20-30%** → **Riesgo de ESKD a 10-15 años** (~73% < 50a)

**15-40%** → **Remisión completa post-tratamiento**

**~35%** → **Recaídas o brotes post-remisión**

**10-25%** → **Enfermedad refractaria o resistente**

→ **¿Duración del tratamiento?**

**Costes (2006-2014)**
**43000-107000 USD/año**

*Tektonidou MG, et al.* ***Arthritis Rheum 2016****, Moroni G, et al.* ***Ann Rheum Dis 2018****, Jorge A, et al.* ***Arthritis Rheum 2019****, Lateef A, Petri M.* ***Arthritis Res Ther 2012****.*

# Cambios en el enfoque terapéutico de la NL en los último 30 años

**Esquema NIH**
MP IV/PO
+
CYC IV mensual y luego trimestral por 2 años

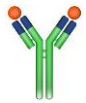
**Eurolupus (ELNT)**
CYC 0.5 g/2 sem x 6 luego AZA PO
**AMLS (ASPREVA)**
GC + MMF PO
**MAINTAIN**
MMF vs AZA PO

**Terapia "Multitarget"**
GC+MMF+TAC
**Terapias anti-B cells**
Rituximab
Belimumab (SLE)

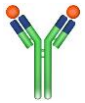
**Terapias Biológicas**
- Targeting B/T cells
- Co-signaling/stimulation
- CAR-T therapy
- Complement inhibitors
- Targeting IFN signaling

**1990s** → **2000-2010** → **2010-2015** → **2019-2021**

**Rituximab**
(LUNAR, rescate)



**Belimumab**
(BLISS 52 y 76)



**Belimumab**
(BLISS-LN, 2020)

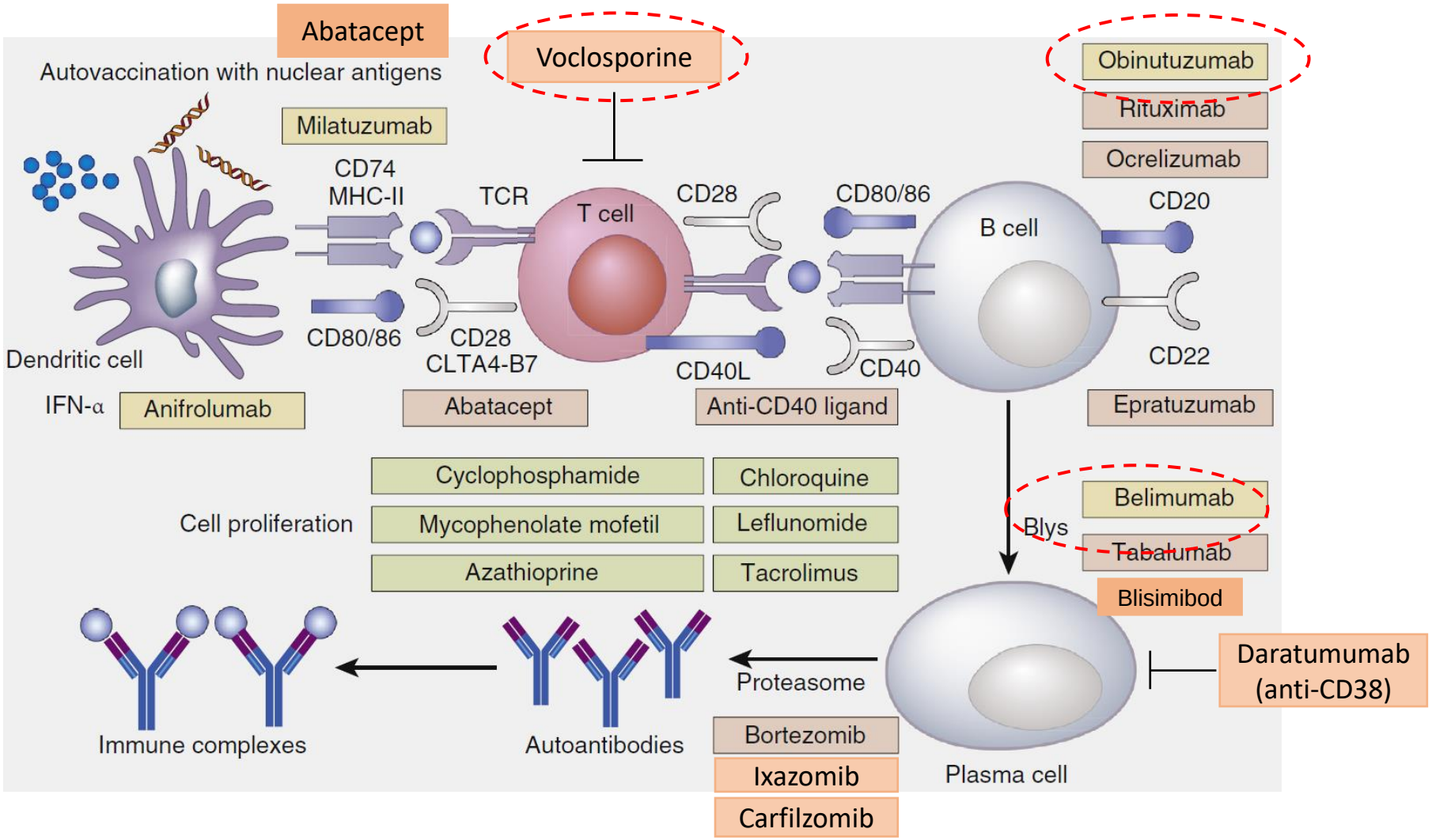
**Voclosporina**
AURA-LN (2019)
AURORA 1 (2021)
AURORA 2 (2022)

↑ Toxicidad

↑ Especificidad, > seguridad

Inmunosupresión inespecífica → Inmunomodulación selectiva

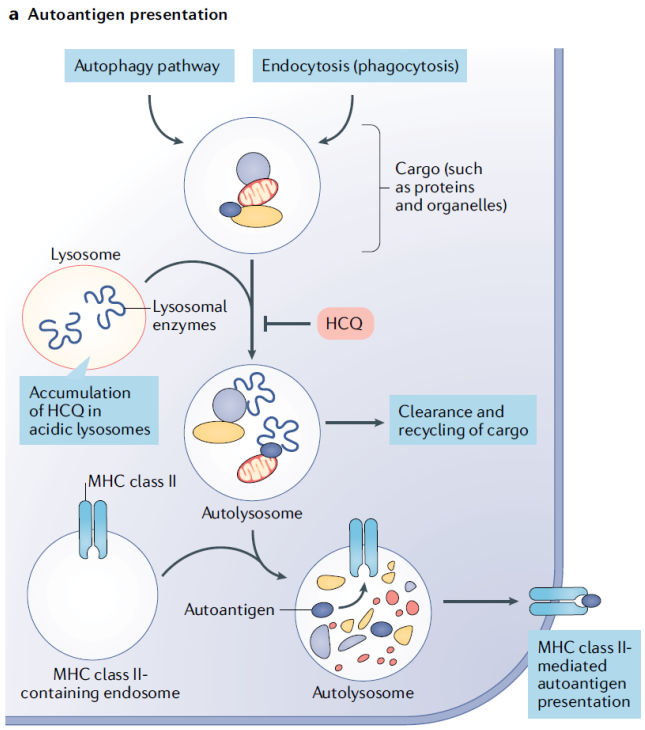
# Terapia dirigida a la patogénesis en Nefritis Lúpica (“targeted therapy”)

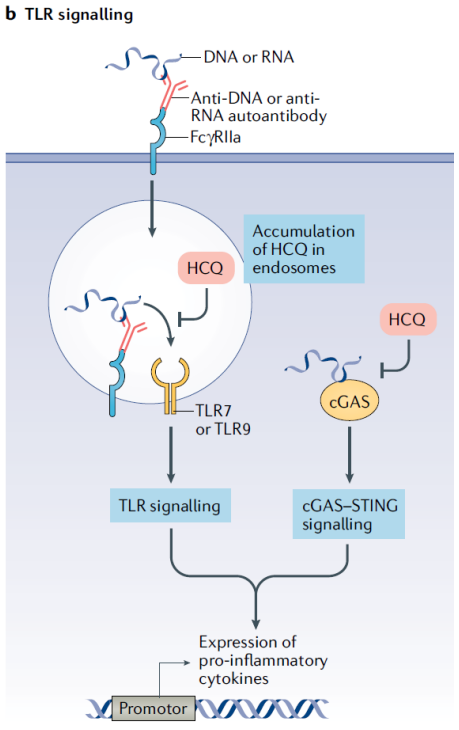



*Anders HM, Rovin B. A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis.* ***Kidney Int 2016****.*

# KDIGO 2021 GCP for the Management of Glomerular Diseases

**Recommendation 10.2.1.1: We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contra-indicated *(1C)*.**



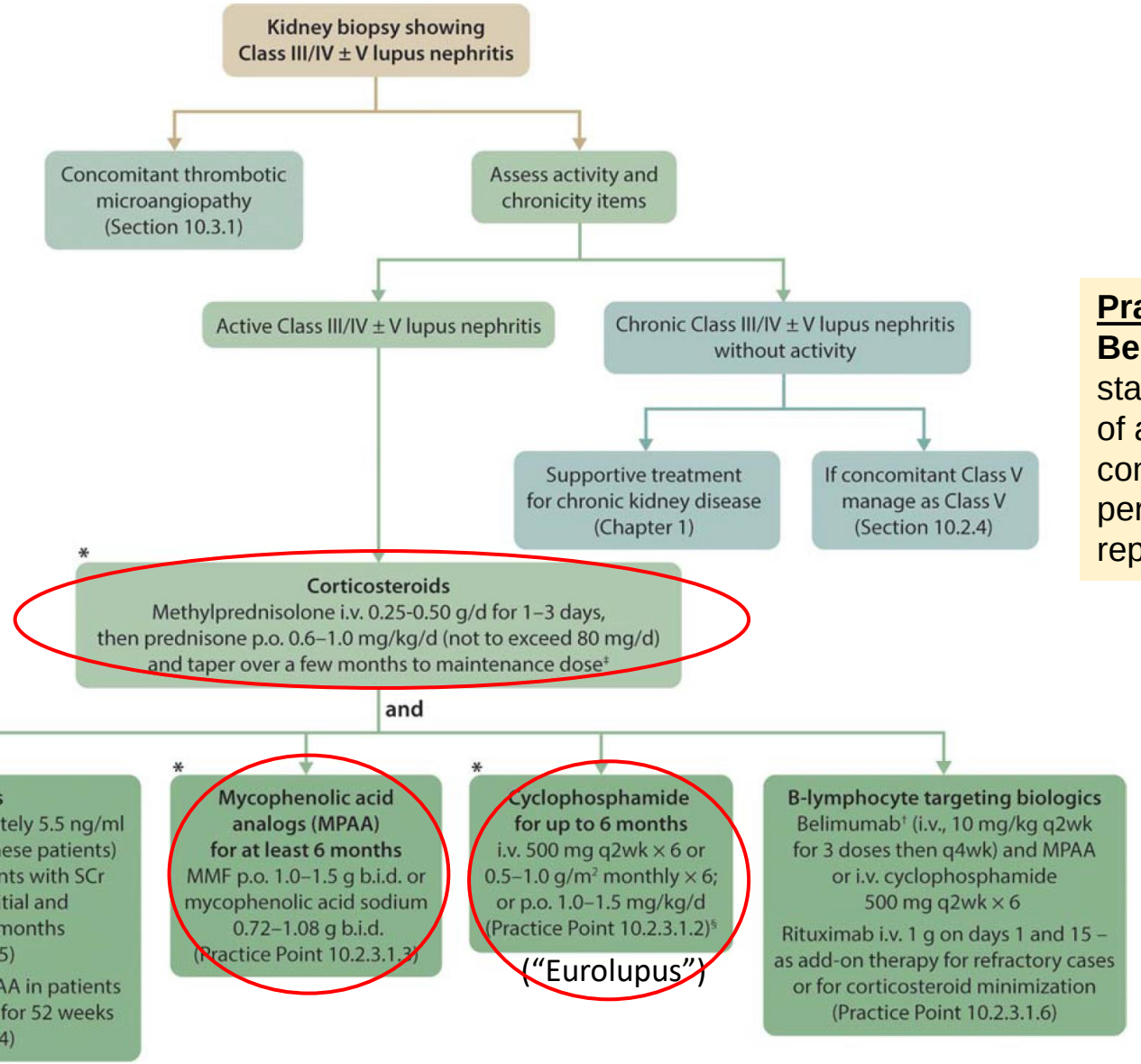




- Acumulación en liso/autofagosomas y cambio pH local.
- Inhibe expression de MHC class II.
- Inhibe presentación de Antígenos.
- Inhibe actividad inmune (↓ CD154 LT).
- Inhibe citocinas inflamatorias (IL-1, IFNα, TNF).
- Interfiere la señalización TLR7/TLR9.
- Evidencia clínica y epidemiológica de disminuir riesgo de brote renal y de progression de ERC.

*Alarcon GS, et al.* ***Ann Rheum Dis 2007****, Pons-Estel GJ, Alarcon GS, et al.* ***Arthr Rheum 2009****, Schrezenmeier E, Dorner T.* ***Nat Rev Rheum 2020****, Lee S-J, et al.* ***Nat Rev Nephrol 2011****, KDIGO Guidelines for Glomerular diseases,* ***Kidney Int 2021****.*

# KDIGO 2021 GCP for the Management of Glomerular Diseases

## Induction Therapy for Active LN



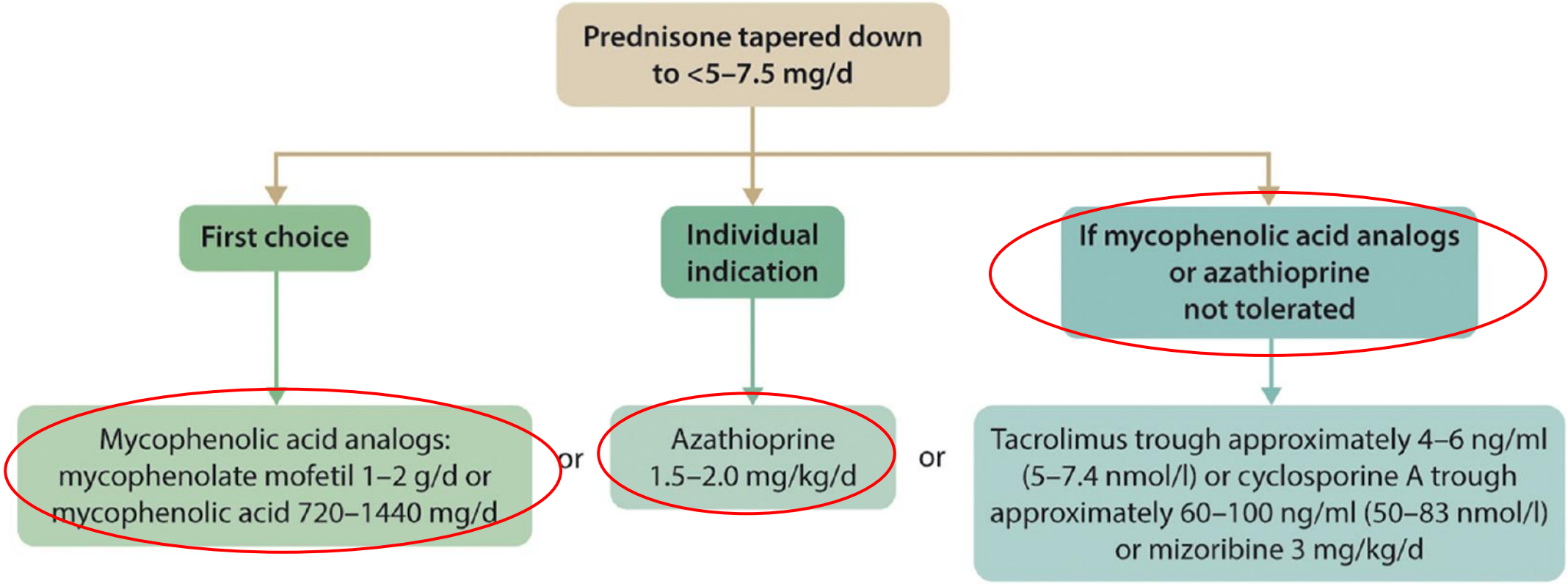

**Practice Point 10.2.3.1.5:**
In patients with baseline eGFR ≥ 45 mL/min/1.73 m², **Voclosporin** can be added to MPAA and GC as initial therapy for 1-y.

**Practice Point 10.2.3.1.6:**
**Belimumab** can be added to standard therapy in the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or repeated flares.

# KDIGO 2021 GCP for the Management of Glomerular Diseases

## Maintenance Therapy for Class III, IV LN

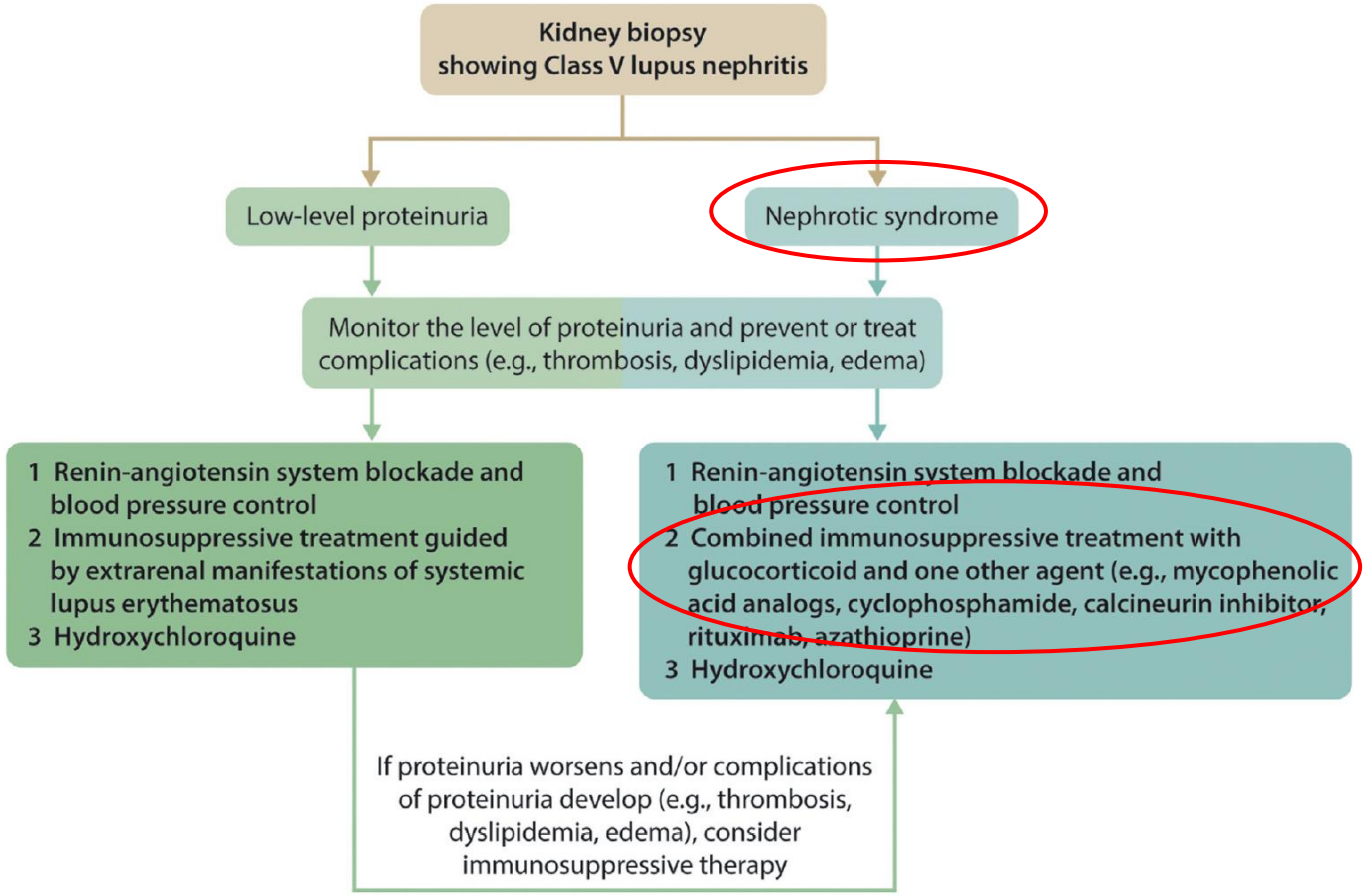
**Recommendation 10.2.3.2.1: We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance *(1B)*.**




*KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases* ***Kidney Int, Oct 2021***.

# KDIGO 2021 GCP for the Management of Glomerular Diseases

## Management of patients with pure Class V LN




*KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases* ***Kidney Int, Oct 2021***.

# Quick tapering of corticoids dose

| | Standard-dose scheme | Moderate-dose scheme | Reduced-dose scheme |
|---|---|---|---|
| **Methylprednisolone intravenous pulses** | Nil or 0.25–0.5 g/day up to 3 days as initial treatment | 0.25–0.5 g/day up to 3 days often included as initial treatment | 0.25–0.5 g/day up to 3 days usually included as initial treatment |
| **Oral prednisone equivalent (/day)** | | | |
| Week 0–2 | 0.8–1.0 mg/kg (max 80 mg) | 0.6–0.7 mg/kg (max 50 mg) | 0.5–0.6 mg/kg (max 40 mg) |
| Week 3–4 | 0.6–0.7 mg/kg | 0.5–0.6 mg/kg | 0.3–0.4 mg/kg |
| Week 5–6 | 30 mg | 20 mg | 15 mg |
| Week 7–8 | 25 mg | 15 mg | 10 mg |
| Week 9–10 | 20 mg | 12.5 mg | 7.5 mg |
| Week 11–12 | 15 mg | 10 mg | 5 mg |
| Week 13–14 | 12.5 mg | 7.5 mg | 2.5 mg |
| Week 15–16 | 10 mg | 7.5 mg | 2.5 mg |
| Week 17–18 | 7.5 mg | 5 mg | 2.5 mg |
| Week 19–20 | 7.5 mg | 5 mg | 2.5 mg |
| Week 21–24 | 5 mg | <5 mg | 2.5 mg |
| Week >25 | <5 mg | <5 mg | <2.5 mg |

*KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases* ***Kidney Int, Oct 2021***.

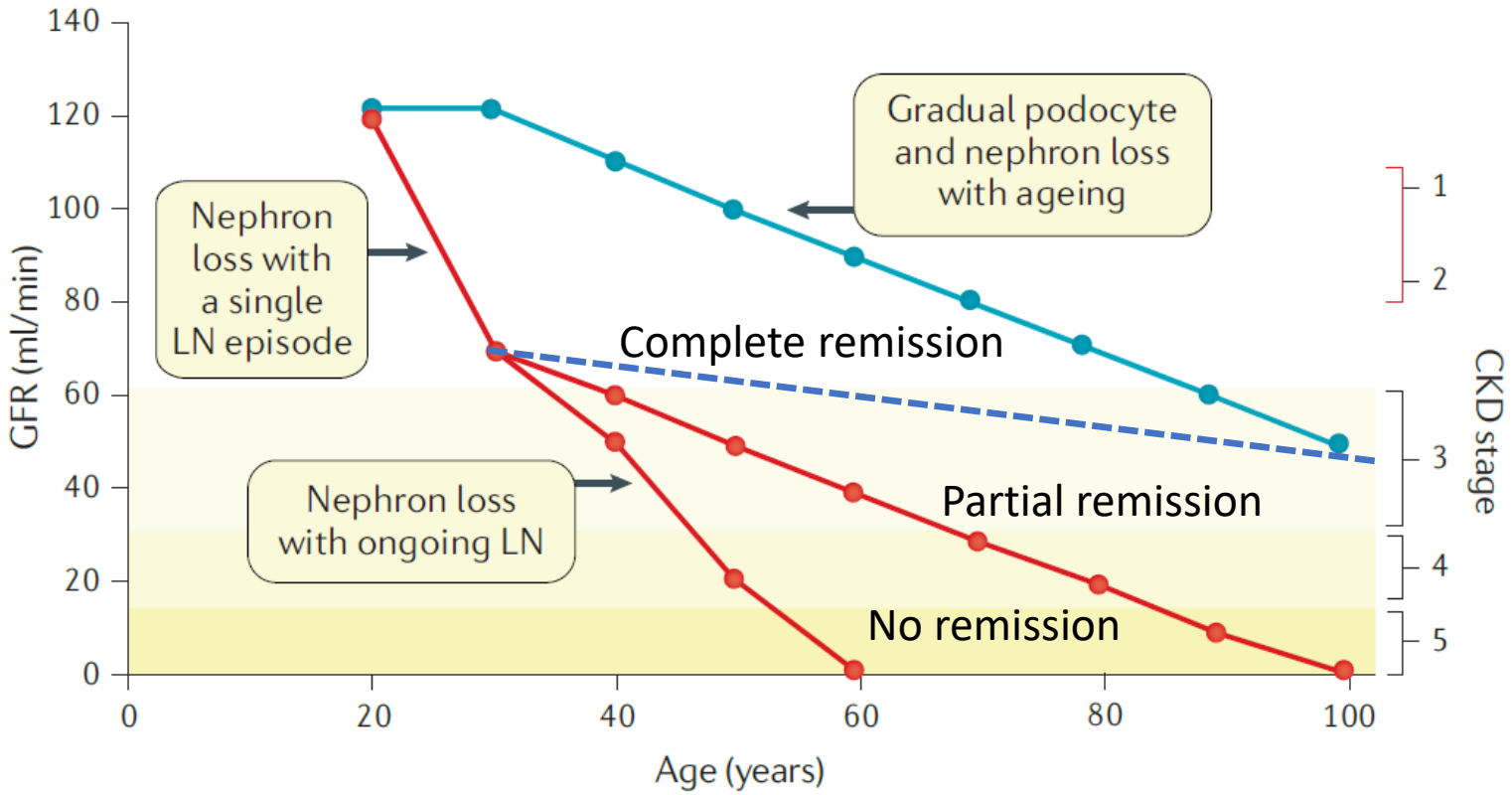
# KDIGO 2021 GCP for the Management of Glomerular Diseases

## Definitions of clinical responses used in the treatment of LN

| Criteria | Definition |
|---|---|
| Complete response* | • Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection<br>• Stabilization or improvement in kidney function (±10%–15% of baseline)<br>• Within 6–12 mo of starting therapy, but could take more than 12 mo |
| Partial response | • Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection<br>• Stabilization or improvement in kidney function (±10%–15% of baseline)<br>• Within 6–12 mo of starting therapy |
| No kidney response | • Failure to achieve a partial or complete response within 6–12 mo of starting therapy |

*KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases* ***Kidney Int, Oct 2021***.

# Risk of ESKD in patientes with Lupus Nephritis throughout life




**2019 EULAR/ERA-EDTA**

**Goals of treatment**

- At 3-mo: ↓ ≥ 25% proteinuria
- At 6-mo: ↓ ≥ 50% proteinuria
- At 12-mo: <0.5-0.7 g/24h

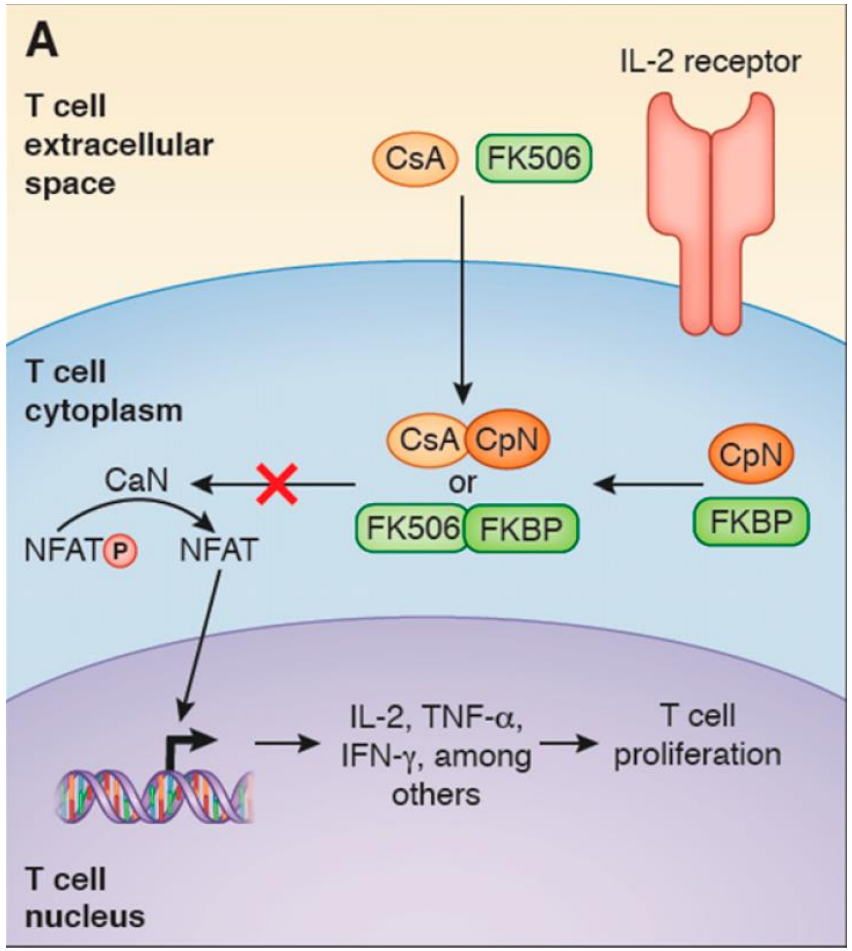
  (Complete clinical remission)
- In Nephrotic pts: 18-24-mo

*Anders HJ, Rovin B.* ***Kidney Int 2016****, Anders HJ, Jayne DJ, Rovin BH.* ***Nat Rev Nephrol 2016****, Anders HJ, et al. Lupus Nephritis.* ***Nat Rev Dis Primers 2020****, Fanouriakis et al.* ***Ann Rheum Dis 2020****.*

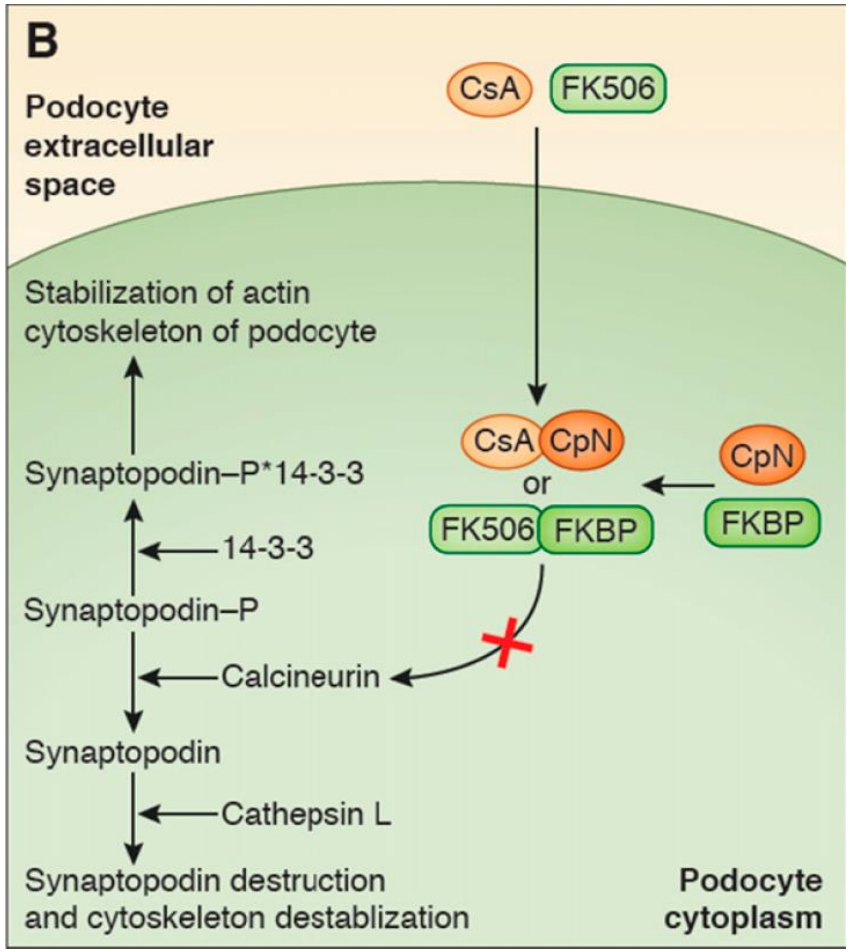
# The Evolving Role of Calcineurin Inhibitors in Treating Lupus Nephritis

*Yonatan Peleg, Andrew S. Bomback, and Jai Radhakrishnan*

**Immunosuppressive effect**




**Effect on podocyte cytoarchitecture**



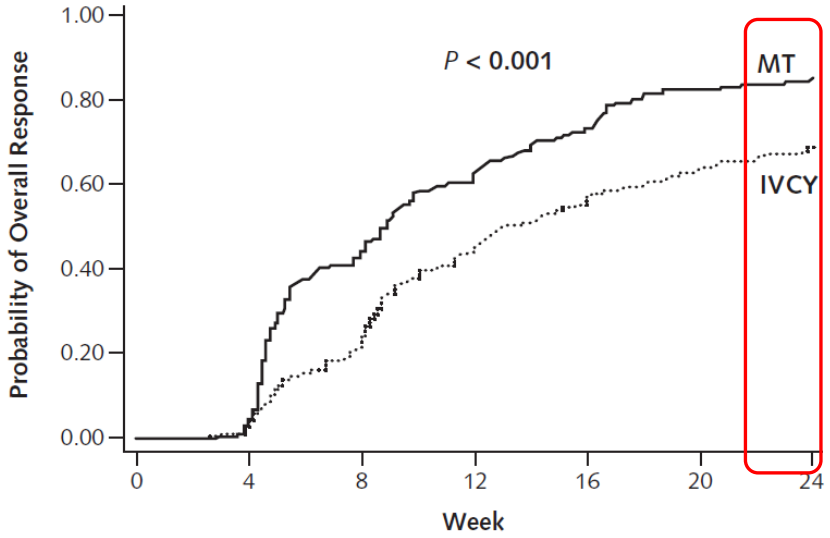
ORIGINAL RESEARCH

Annals of Internal Medicine

# Multitarget Therapy for Induction Treatment of Lupus Nephritis

## A Randomized Trial

Zhihong Liu, MD; Haitao Zhang, MD; Zhangsuo Liu, MD; Changying Xing, PhD; Ping Fu, MD; Zhaohui Ni, MD; Jianghua Chen, MD; Hongli Lin, MD; Fuyou Liu, MD; Yongcheng He, MD; Yani He, MD; Lining Miao, MD; Nan Chen, MD; Ying Li, MD; Yong Gu, MD; Wei Shi, MD; Weixin Hu, MD; Zhengzhao Liu, MD; Hao Bao, MD; Caihong Zeng, PhD; and Minlin Zhou, MD




Patients at risk, *n*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MT | 181 | 175 | 98 | 67 | 45 | 29 | 20 |
| IVCY | 181 | 176 | 132 | 91 | 71 | 58 | 45 |

MT = multitarget; IVCY = intravenous cyclophosphamide.

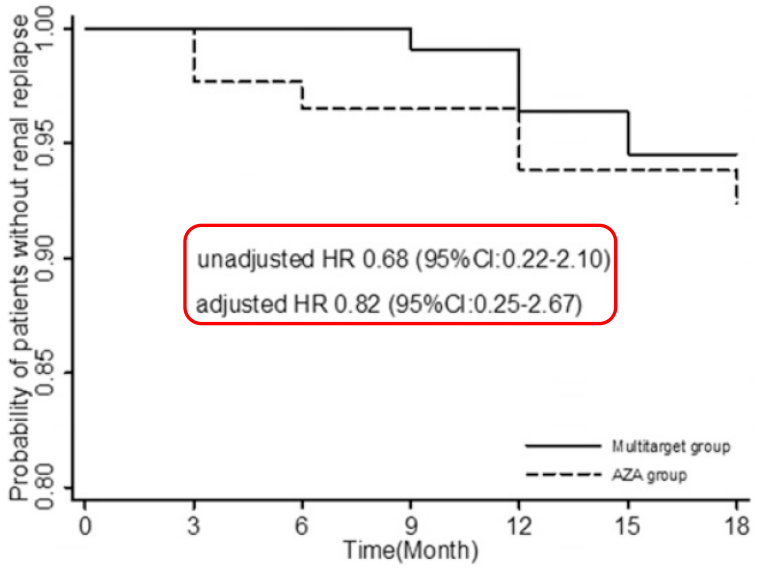
Annals of Internal Medicine • Vol. 162 No. 1 • 6 January 2015

**MT vs. CYC**

***CRR:*** *45.9% vs. 25.6%*

***SAEs:*** *50% vs. 52%*

# Multitarget Therapy for Maintenance Treatment of Lupus Nephritis




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Multitarget group | 116 | 116 | 113 | 112 | 109 | 104 | 101 |
| AZA group | 90 | 87 | 83 | 76 | 72 | 66 | 64 |
| **No.of relapse** | | | | | | | |
| Multitarget group | 0 | 0 | 0 | 1 | 3 | 2 | 0 |
| AZA group | 0 | 2 | 1 | 0 | 2 | 0 | 1 |

*J Am Soc Nephrol* 28: ●●●–●●●, 2017. doi: https://doi.org/10.1681/ASN.2017030263

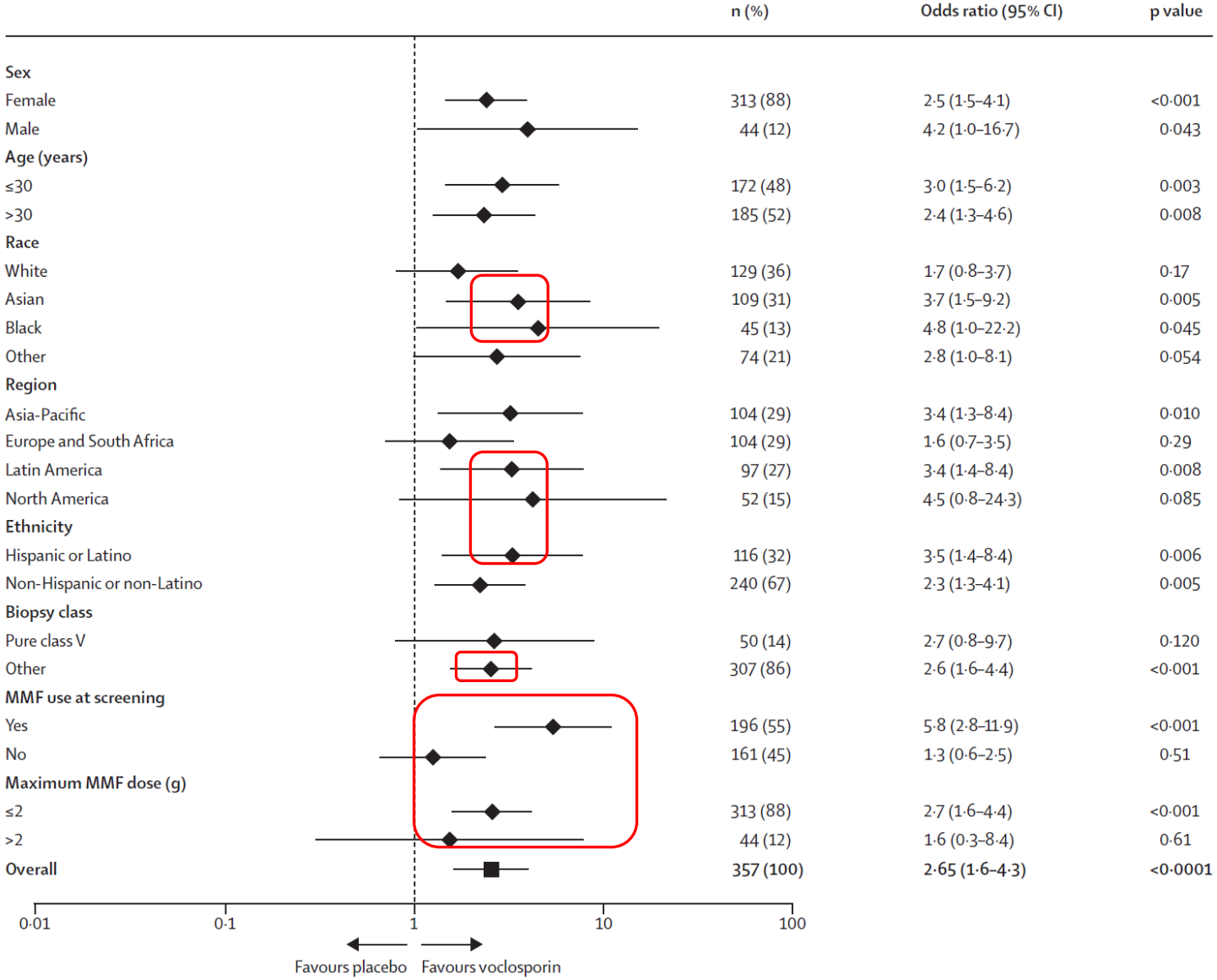
**Practice Point 10.2.3.1.4:** *Initial therapy with a triple immunosuppressive regimen that includes a CNI (tacrolimus or cyclosporine) with reduced-dose MPAA and glucocorticoids is reserved for patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.*

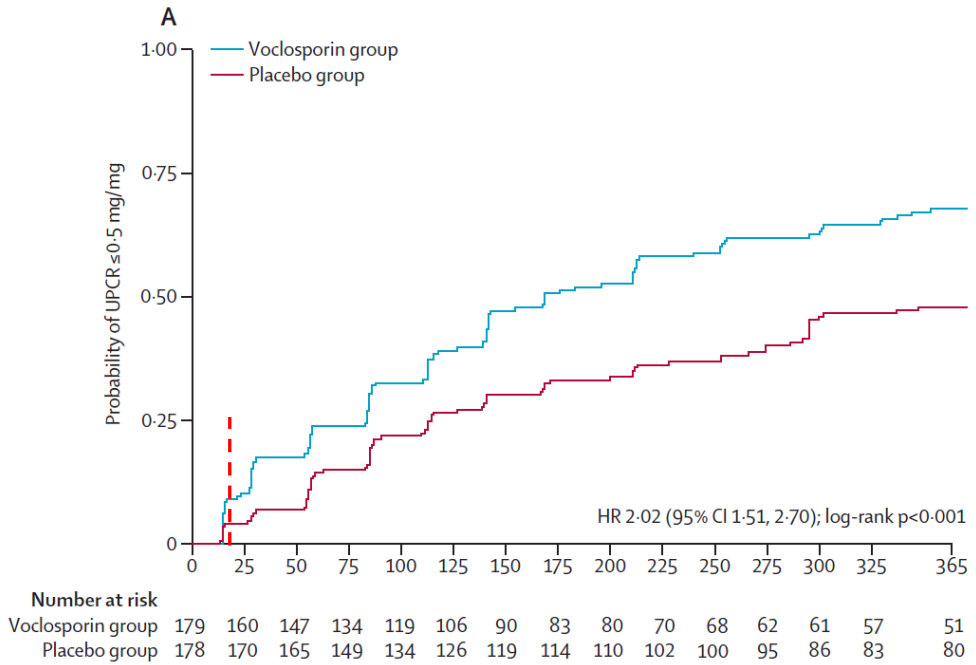
# Studies with Voclosporin added on SoC in Lupus Nephritis: What is the Evidence?

| Characteristic | AURA-LN (2019) | | | AURORA 1 (2021) | | |
|---|---|---|---|---|---|---|
| Design | Phase 2 | | | Phase 3 | | |
| N | 265 (88 vs. 88 vs. 88) | | | 367 (179 vs. 178) | | |
| Sex, female | 76 (85.4%) vs. 81 (92%) vs. 73 (83%) | | | 161 (90%) vs. 152 (85%) | | |
| Age (SD or IQR) | 33.1 (10) vs. 31.4 (11.8) vs. 30.6 (9.6) | | | 31 (18-62) vs. 32 (18-72) | | |
| Patients with LN | Class III, IV ± V on SoC (GC + MMF), | | | Class III, IV ±V on SOC (GC + MMF) | | |
| Comparisons | **VCS (23.7 mg b.i.d.)** | **Placebo** | | **VCS (23.7 mg b.i.d.)** | **Placebo** | |
| UPCR (SD) (mg/mg) | 5.16 (4.2) | 4.43 (3.6) | | 4.14 (2.71) | 3.87 (2.36) | |
| GFR (mL/min/1.73m$^2$) | 95.3 (28.4) | 100.2 (27.1) | | 92.1 (30.6) | 90.4 (29) | |
| SLEDAI (SD) | | | | 13.2 (6.5) | 11.8 (6.1) | |
| **Efficacy** | **Response** | **P-value** | **OR (95%CI)** | **Response** | **P-value** | **OR (95%CI)** |
| **Primary endpoint** | **CRR at 24-w 32.6% vs. 19.3 %** | **0.046** | **2.0 (1.0-4.1)** | **CRR at 52-w 73 (41%) vs. 40 (23%)** | **< 0.0001** | **2.7 (1.6-4.3)** |
| **Secondary endpoint** | **CRR at 48-w 49.4% vs. 23.9%** | **< 0.001** | **3.2 (1.7-6.1)** | **CRR at 24-w 58 (32%) vs. 35 (20%)** | **0.002** | **2.2 (1.3-3.7)** |
| **Any AE with death** | **10 (11.2%)** | **1 (1.1%)** | | **1 (<1%)** | **5 (3%)** | |

*Rovin BH, Solomons N, Perdergraft IIIWF, et al.* ***Kidney Int 2019****, Rovin BH, Onno Teng YK, Ginzler EM, et al.* ***Lancet 2021****.*

## Subgroup analysis of primary outcome of complete renal response at week 52 (intention-to-treat population)




| | Voclosporin group (n=178) | Placebo group (n=178) |
|---|---|---|
| **Adverse event summary** | | |
| Adverse event | 162 (91%) | 158 (89%) |
| Serious adverse event | 37 (21%) | 38 (21%) |
| Serious adverse event of infections and infestations | 18 (10%) | 20 (11%) |
| Treatment-related serious adverse event | 8 (4%) | 8 (4%) |
| Adverse event leading to study drug discontinuation | 20 (11%) | 26 (15%) |
| Death* | 1 (<1%) | 5 (3%) |
| Treatment-related adverse event leading to death | 0 | 0 |

*Rovin BH, Onno Teng YK, Ginzler EM, et al.* ***Lancet 2021****.*

# Mensajes claves del estudio AURORA 1 en pacientes con NL

1. El 2º ensayo más grande en NL con seguimiento y adherencia adecuadas.
2. Representación geográfica y étnica mejor balanceada que el BLISS-LN.
3. El endpoint primario fue más exigente: CR (UPCR ≤ 0.5 mg/mg).
4. RC al año 41% (mejor que 30% del BLISS-LN) y caída más precoz de UPCR.
5. Permitió un esquema con dosis bajas de GCs (2.5 mg: 16s ~ 82%, 52s ~ 75%)
6. Mayor efecto en formas proliferativas (III, IV) vs. Membranosa (clase V).
7. Las biopsias con > 6 meses pre-screenning posible pronóstico diferente.
8. Más RC con uso reciente de MMF y dosis ≤2 g/d → ¿casos menos graves?.
9. Perfil de seguridad y cardio-metabólico aceptable, no evidencia de nefrotoxicidad.
10. El paso siguiente: seguimiento a largo plazo (AURORA 2) y análisis C-E y C-U.

POS0681

# VOCLOSPORIN FOR LUPUS NEPHRITIS: INTERIM ANALYSIS OF THE AURORA 2 EXTENSION STUDY


A. Saxena[1], P. Mina-Osorio[2], C. Mela[3], V. Berardi[2]. [1]*NYU Langone Health, Rheumatology, New York, United States of America*; [2]*Aurinia Pharmaceuticals, Inc., Medical Affairs, Victoria, Canada*; [3]*Aurinia Pharmaceuticals, Inc., Clinical Science, Victoria, Canada*

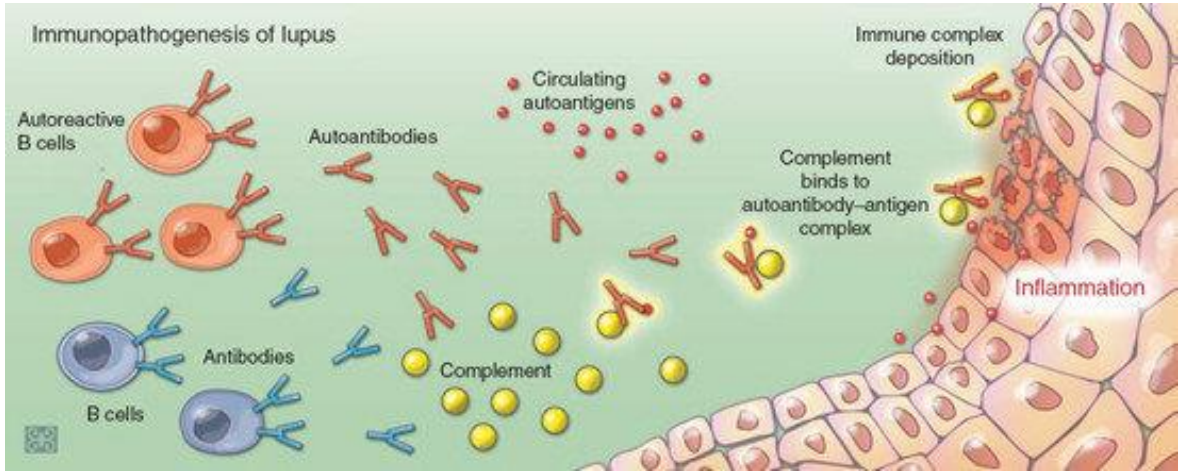
**Table 1. UPCR**

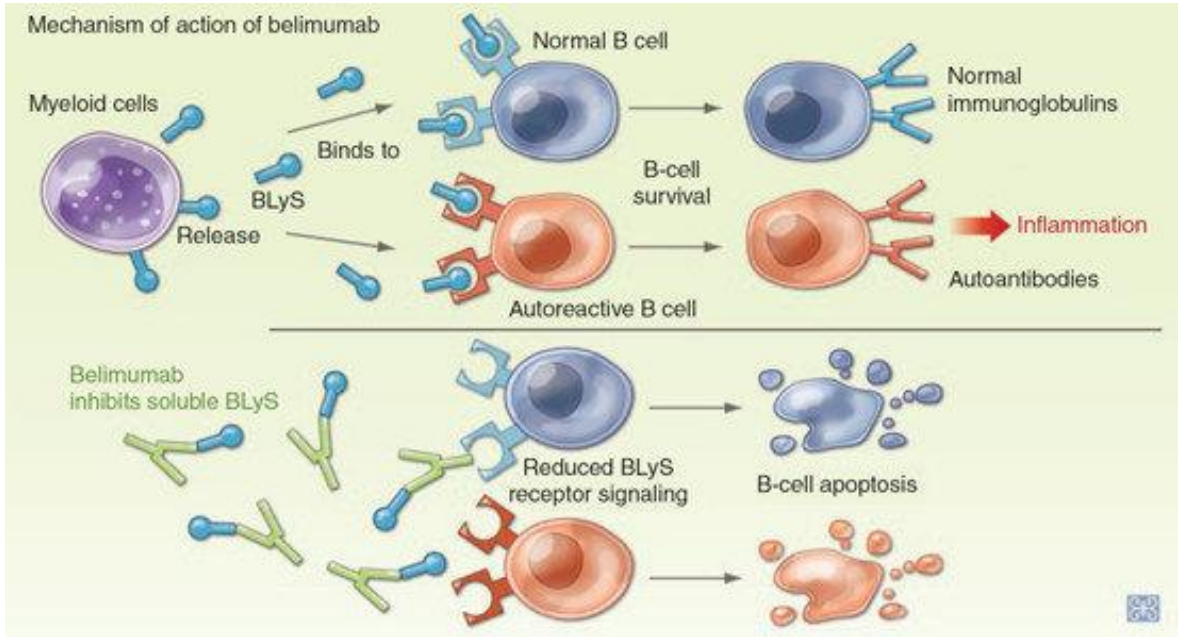
| | Control (n=100) | | Voclosporin (n=116) | | Treatment Comparison of Voclosporin to Control | |
|---|---|---|---|---|---|---|
| | n | UPCR (mg/mg) | n | UPCR (mg/mg) | UPCR (mg/mg) | p-value |
| Pre-treatment baseline, mean | 100 | 3.87 | 116 | 3.94 | NC | NC |
| Change from pre-treatment baseline, LS mean | | | | | | |
| Year 1 | 100 | -2.4 | 116 | -3.0 | -0.6 | 0.0080 |
| Year 2 | 51 | -2.1 | 73 | -3.1 | -1.0 | 0.0004 |

**Conclusion:** Patients in the voclosporin treatment arm maintained meaningful reductions in proteinuria with no change in mean eGFR at two years of treatment. Additional AURORA 2 efficacy and safety data will be provided at the conclusion of the study.

# Terapia mejorada anti-células B: Belimumab

- mAb humano de IgG1λ.
- Belimumab se une a sBLyS (BAAF).
- Inhibe las señales que produce BLyS en sus receptores de B-cells.
- ↓ supervivencia cél B (autorreactivas).
- ↓ diferenciación cél B → plasmocitos.
- Evidencia previa: BLISS-52 y BLISS-76.




*Dennis GJ. Belimumab: a BlyS specific inhibitor for the treatment of systemic lupus erythematosus.* ***Clin Pharmacol Ther 2012***.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

N ENGL J MED 383;12 NEJM.ORG SEPTEMBER 17, 2020

**PERR**

- eGFR ≥ 60 mL/min/1.73m$^2$ o no ↓pre-brote >20%
- uPCR ≤ 0.7 g/g
- No tratamiento de rescate

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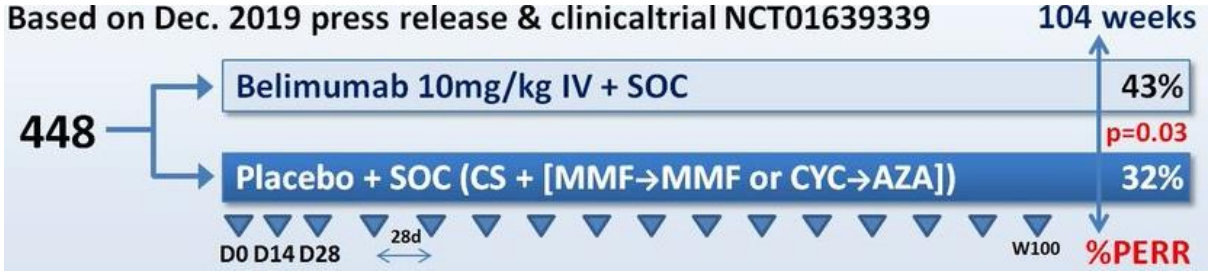
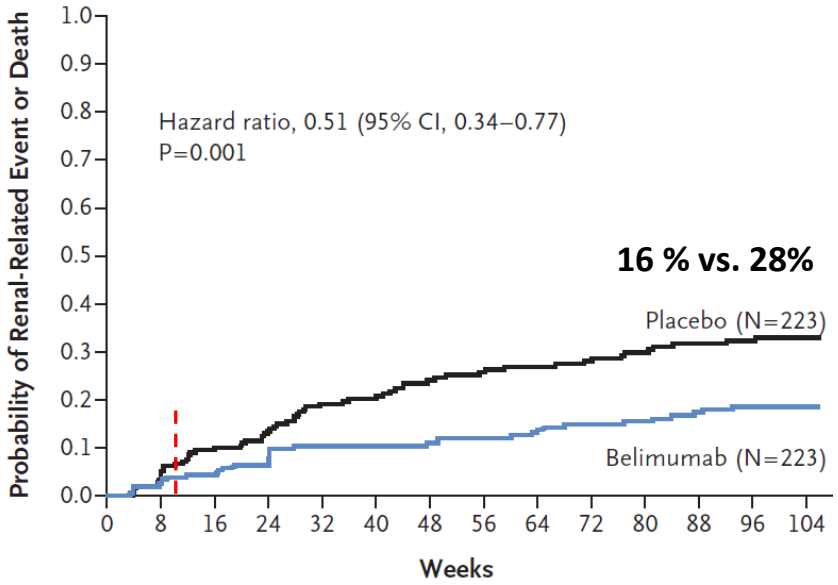
*Nephrologist*
*Ohio, US*




At 24-w
GC 10≤ mg/d

**Table 2. Primary and Major Secondary Efficacy End Points in the Modified Intention-to-Treat Population.**

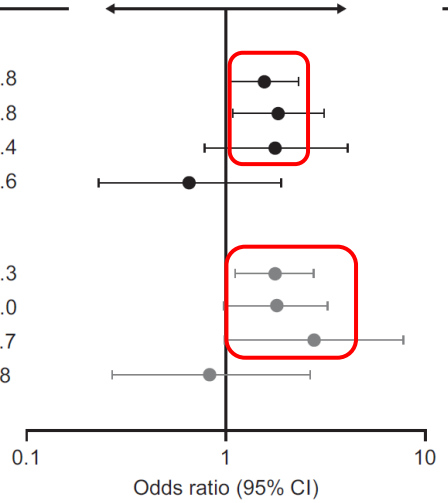
| End Point | Belimumab (N=223) | Placebo (N=223) | Difference | Odds Ratio or Hazard Ratio (95% CI)* | P Value |
|---|---|---|---|---|---|
| | *number (percent)* | | *percentage points* | | |
| Primary end point: primary efficacy renal response at wk 104† | 96 (43) | 72 (32) | 11 | 1.6 (1.0 to 2.3) | 0.03 |
| Major secondary end points | | | | | |
| Complete renal response at wk 104‡ | 67 (30) | 44 (20) | 10 | 1.7 (1.1 to 2.7) | 0.02 |
| Primary efficacy renal response at wk 52§ | 104 (47) | 79 (35) | 11 | 1.6 (1.1 to 2.4) | 0.02 |
| Time to renal-related event or death¶ | NA | NA | NA | 0.5 (0.3 to 0.8) | 0.001 |
| Ordinal renal response without urinary sediment at wk 104‖ | | | | | |
| Complete renal response | 67 (30) | 44 (20) | 10 | NA | 0.01 |
| Partial renal response** | 39 (18) | 38 (17) | <1 | NA | |
| No response | 117 (52) | 141 (63) | −11 | NA | |



# BLISS-LN: Secondary analysis on kidney outcomes

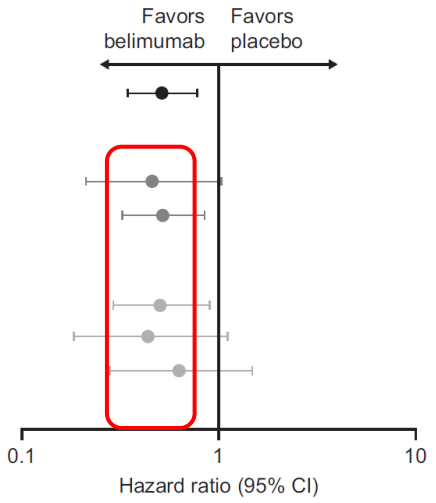
## PEER and CCR at 104 weeks (mITT análisis)

| LN class | Responders, *n* (%) Placebo (*n* = 223) | Belimumab 10 mg/kg i.v. (*n* = 223) | Treatment difference (%) | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| **PERR** | | | | | |
| Any class | 72 (32.3) | 96 (43.0) | 10.8 | 1.55 (1.04, 2.32) | 0.0311 |
| Class III or IV[a] | 42 (31.8) | 60 (47.6) | 15.8 | 1.82 (1.08, 3.08) | |
| Class III + V or IV + V[b] | 15 (27.3) | 23 (37.7) | 10.4 | 1.76 (0.77, 4.05) | |
| Class V[c] | 15 (41.7) | 13 (36.1) | –5.6 | 0.65 (0.23, 1.86) | |
| **CRR** | | | | | |
| Any class | 44 (19.7) | 67 (30.0) | 10.3 | 1.74 (1.11, 2.74) | 0.0167 |
| Class III or IV[a] | 25 (18.9) | 39 (31.0) | 12.0 | 1.78 (0.98, 3.21) | |
| Class III + V or IV + V[b] | 8 (14.5) | 16 (26.2) | 11.7 | 2.76 (0.99, 7.72) | |
| Class V[c] | 11 (30.6) | 12 (33.3) | 2.8 | 0.83 (0.27, 2.62) | |



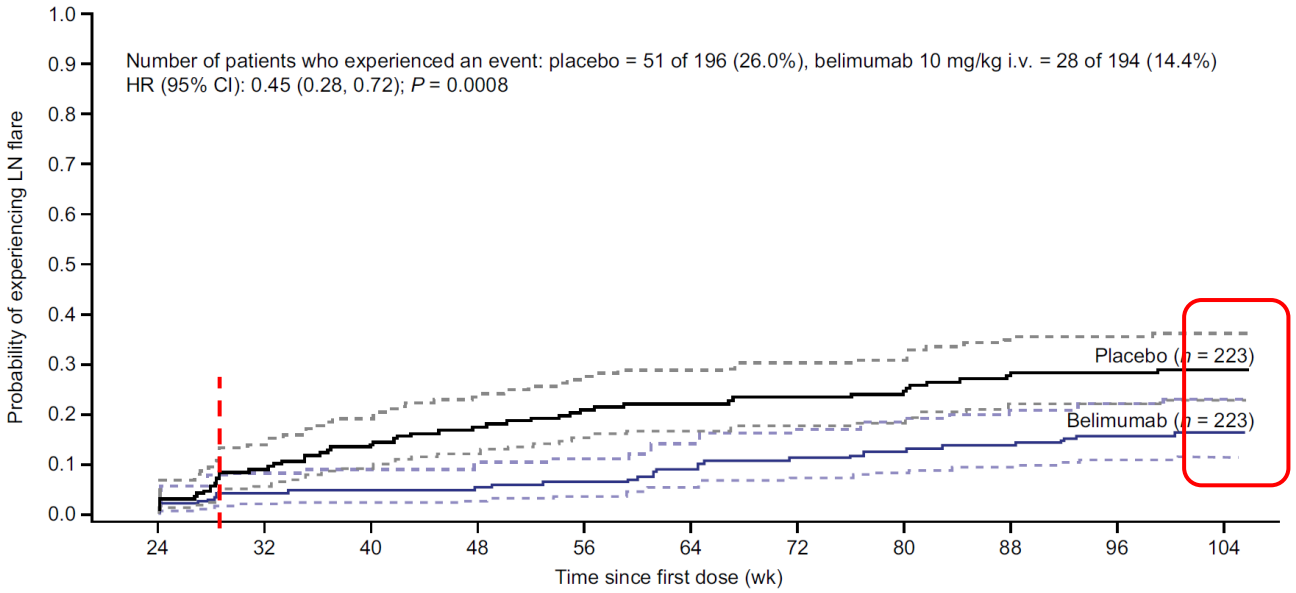

## Time to kidney-related event or death (mITT analysis)

| | Patients with an event,[b] *n* (%) Placebo (*n* = 223) | Belimumab 10 mg/kg i.v. (*n* = 223) | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|
| **Overall** | 63 (28.3) | 35 (15.7) | 0.51 (0.34, 0.77) | 0.0014 |
| **Treatment regimen[c]** | | | | |
| CYC/AZA | 19 (32.2) | 9 (15.3) | 0.46 (0.21, 1.02) | |
| MMF | 44 (26.8) | 26 (15.9) | 0.52 (0.32, 0.84) | |
| **LN class[d]** | | | | |
| Class III or IV | 34 (25.8) | 19 (15.1) | 0.51 (0.29, 0.89) | |
| Class III + V or IV + V | 14 (25.5) | 7 (11.5) | 0.44 (0.18, 1.10) | |
| Class V | 15 (41.7) | 9 (25.0) | 0.64 (0.28, 1.48) | |




*Rovin BH, Furie R, Onno Teng YK, et al.* ***Kidney Int 2021****.*

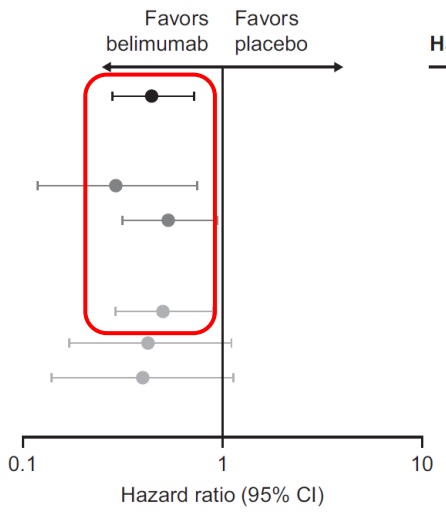
# Lupus Nephritis flares with Belimumab




Number of patients at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 196 | 167 | 154 | 142 | 133 | 131 | 127 | 124 | 117 | 115 | 68 |
| Belimumab | 194 | 175 | 167 | 164 | 161 | 153 | 144 | 139 | 134 | 130 | 93 |

| | Patients with an LN flare,[b] *n* (%) | | | |
|---|---|---|---|---|
| | Placebo (*n* = 223) | Belimumab 10 mg/kg i.v. (*n* = 223) | Hazard ratio (95% CI) | *P* value |
| **Overall**[c] | 51 (26.0) | 28 (14.4) | 0.45 (0.28, 0.72) | 0.0008 |
| **Treatment regimen**[d] | | | | |
| CYC/AZA | 18 (35.3) | 7 (14.3) | 0.30 (0.12, 0.75) | |
| MMF | 33 (22.8) | 21 (14.5) | 0.55 (0.32, 0.96) | |
| **LN class**[e] | | | | |
| Class III or IV | 27 (23.3) | 16 (14.3) | 0.51 (0.27, 0.95) | |
| Class III + V or IV + V | 13 (27.1) | 7 (13.5) | 0.43 (0.17, 1.13) | |
| Class V | 11 (34.4) | 5 (16.7) | 0.40 (0.14, 1.15) | |




*Rovin BH, Furie R, Onno Teng YK, et al.* ***Kidney Int 2021****.*

# Preservation of kidney function with Belimumab

## eGFR slope from week 24 to week 104 (modified ITT analysis)

| Variable | On treatment[b] | | On study[c] | |
|---|---|---|---|---|
| | Placebo ($n$ = 223) | Belimumab 10 mg/kg i.v. ($n$ = 223) | Placebo ($n$ = 223) | Belimumab 10 mg/kg i.v. ($n$ = 223) |
| Patients with ≥1 eGFR value from week 24, *n* | 198 | 196 | 198 | 196 |
| Patients with eGFR value at week 104, *n* | 128 | 140 | 163 | 173 |
| eGFR (SE) at week 24[d] | 106.6 (2.49) | 109.4 (2.36) | 106.8 (2.55) | 109.5 (2.39) |
| eGFR slope (SE), ml/min per 1.73 $m^2$ per yr[d] | −3.18 (1.10) | −0.99 (0.77) | −5.72 (1.46) | −2.12 (0.97) |
| eGFR slope difference vs. placebo (SE)[d] | | 2.19 (1.34) | | 3.61 (1.76) |
| 95% CI[d] | | −0.45 to 4.84 | | 0.15 to 7.06 |
| *P* value[d] | | 0.1041 | | 0.0407 |

| Variable | Placebo ($n$ = 223) | Belimumab 10 mg/kg i.v. ($n$ = 223) |
|---|---|---|
| Sustained 30% decrease in eGFR | | |
| *n* (%) | 25 (11.2) | 8 (3.6) |
| Observed difference vs. placebo (%) | −7.62 | |
| OR (95% CI) | 0.29 (0.13–0.68) | |
| *P* value | 0.0042 | |
| Sustained 40% decrease in eGFR | | |
| *n* (%) | 15 (6.7) | 4 (1.8) |
| Observed difference vs. placebo (%) | −4.93 | |
| Odds ratio (95% CI) | 0.25 (0.08–0.78) | |
| *P* value | 0.0166 | |

*Rovin BH, Furie R, Onno Teng YK, et al.* ***Kidney Int 2021***.

# Comentarios “PRO” a los estudios con Belimumab en pacientes con NL

1. El estudio sobre NL con la N más grande y un seguimiento adecuado.
2. Belimumab como terapia añadida al SoC alcanzó los objetivos primarios (PERR) y secundarios (CR, PR) de mejor respuesta.
3. Este beneficio fue consistente en las clases histológicas III y IV y en los pacientes que recibieron MMF como terapia de inducción.
4. Redujo el riesgo de brote renal, especialmente en las clases III y IV (post-hoc).
5. Preservó mejor la función renal a los 2 años de seguimiento (post-hoc).
6. Permitió reducir precozmente dosis de esteroides.
7. Menos eventos renales negativos vs. placebo y relativamente seguro.

# Comentarios “CON” a los estudios con Belimumab en pacientes con NL

1. Mayoría asiáticos, poca representación Lat-Am/negra (LES/NL más grave).
2. Sólo dos de cada 3 pacientes estaban con RASi.
3. Definición del “endpoint” primario diferente a los habituales (PERR).
4. PERR sólo fue 11% mejor que grupo control (43% vs. 32%).
5. Remisión completa 30% (10% mejor que control) y los no respondedores > 50%.
6. La respuesta parece ser menor si la terapia de inducción es con CYC.
7. La respuesta no fue clara en la clase V (n pequeña).
8. Pendiente análisis costo-efectividad.

# ¿Y qué nos dice la vida real?: el estudio BeRLiSS-LN (cohorte Italiana)

Achievement of complete renal response and primary efficacy renal response: N (%).

| | 6 months | 12 months | 24 months |
|---|---|---|---|
| | N = 91 | N = 81 | N = 59 |
| **Primary Efficacy Renal Response** | **44 (48.4)** | **50 (61.7)** | **39 (66.1)** |
| **Complete Renal Response** | **22 (24.2)** | **28 (34.5)** | **22 (37.3)** |
| Proteinuria <0.5 g/24 h | 43 (47.2) | 46 (56.7) | 28 (47.4) |
| Proteinuria <0.7 g/24 h | 493 (53.8) | 51 (62.9) | 31 (52.4) |
| Inactive sediment | 57 (62.6) | 49 (60.5) | 51 (86.4) |
| eGFR ≥90 ml/min/1.73m2 | 44 (48.4) | 45 (55.6) | 32 (54.2) |
| eGFR ≥60 ml/min/1.73m2 | 74 (81.3) | 73 (90.1) | 55 (93.2) |

Baseline predictors of PERR at different timepoints.

| | 6 months | 12 months | 24 months |
|---|---|---|---|
| | N = 91 | N = 81 | N = 59 |
| **Proteinuria levels at baseline** | **OR 0.21 CI95% 0.09–0.53 *p* = *0.001*** | **OR 0.19 CI95% 0.069–0.57 *p* = *0.003*** | *OR 0.89 CI95% 0.44-1.8* p = 0.77 |
| **Baseline creatinine** | **OR 0.97 CI95% 0.94–0.99 *p* = *0.008*** | OR 0.99 CI95% 0.99–1.01 p = 0.46 | OR 0.98 CI95% 0.95–1.02 p = 0.19 |
| **Hypertension** | **OR 0.26 CI95% 0.076–0.81 *p* = *0.021*** | OR 0.27 CI95% 0.06–1.18 p = 0.08 | OR 0.57 CI95% 0.09–3.39 p = 0.54 |
| **Smoke** | OR 0.25 CI95% 0.06–1.7 p = 0.19 | – | – |
| **PERR at 6 months** | – | **OR 14.4 CI95% 3.28–63.6 *p* = *0.001*** | **OR 11.7 CI95% 2.7–48.7 *p* = *0.001*** |
| **Anti-Sm positivity** | – | **OR 5.52** CI95%0.98–30.9 *p = 0.05* | **OR 19.8 CI95% 2.01–186.7 *p* = *0.009*** |

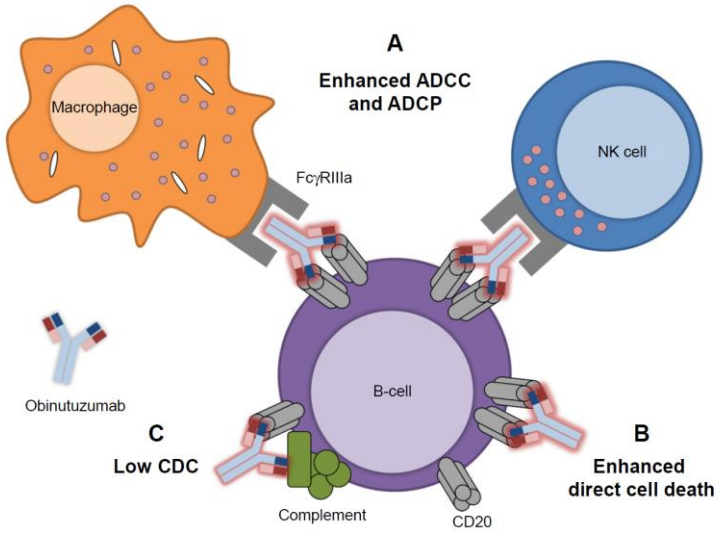
*Gatto M, et al.* ***J Autoimmunity 2021.***

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals
MEETING ABSTRACTS



ABSTRACT NUMBER: 0988

# Two-Year Results from a Randomized, Controlled Study of Obinutuzumab for Proliferative Lupus Nephritis




Phase 2 study, OBI vs. PBP + SoC (MMF + PRD)

126 pts with classs III and IV active LN.

OBI: 0, 2, 4, 24 and 26-w, CRR at 52 and 104-w

| Week 104 endpoint | OBI (n=63) | PBO (n=62) | Difference (80% CI) | *P* value |
|---|---|---|---|---|
| CRR | 41% | 23% | 19% (8, 29) | 0.026 |
| ORR | 54% | 29% | 25% (14, 36) | 0.005 |
| mCRR | 56% | 33% | 22% (11, 33) | 0.015 |
| C3 >90 mg/dL | 76% | 47% | 29% (19, 40) | 0.008 |
| C4 >10 mg/dL | 95% | 74% | 21% (13, 29) | 0.001 |
| Mean change in eGFR from baseline (mL/min/1.73 $m^2$) | +6.5 | -3.2 | 9.7 (1.7, 18) | 0.018 |
| Mean change in UPCR from baseline | -2.3 | -1.4 | -0.96 (-1.4, -0.57) | 0.002 |

CRR=UPCR <0.5, serum creatinine (SCr) ≤upper limit of normal (ULN) and ≤115% of baseline, <10 red blood cells per high power field (RBCs/HPF), and no RBC casts.
ORR = CRR or partial renal response=UPCR <1 (<3 if baseline UPCR ≥3) and ≤50% of baseline, SCr ≤115% of baseline, and ≤50% increase in urinary RBCs (or <10 RBCs/HPF).
mCRR = UPCR <0.5, SCr ≤ ULN.

# ¿Por qué sería interesante añadir Belimumab o Voclosporina en este paciente?

*33 años, obesidad, DM2, DL, HTA, NL IV-V*

**Tratamiento general**

1. Actividad física y estilos de vida
2. Nefrocardioprotección: RASi, SGLT2i, HbA1c, DL, PA
3. Uso de antimaláricos

**Objetivo de la IS**

1. Remisión precoz (clínica y serológica)
2. Usar baja dosis de GC (es diabética)
3. Mejorar tolerancia
4. Evitar riesgo de infecciones y toxicidad
5. Mantener bajo riesgo CV ( FRCV)
6. Preservar fertilidad

Bx renal

*¿Enfoque tradicional?*

**Inducción** (↑↑ GC + MMF o CYC) → **Mantenimiento** (GC + MMF o AZA) → **Stop IS?**

*¿Cambio de paradigma en el abordaje de la NL?*

**Una sola fase: terapia combinada continuada**

(↓GC+MMF+Beli o VCS → ↓MMF+Beli o VCS)

**Necesidades no resueltas**

*RC, ↓precoz UPCR, sin brotes, ↓toxicidad (GC)*

**Mejorar pronóstico**

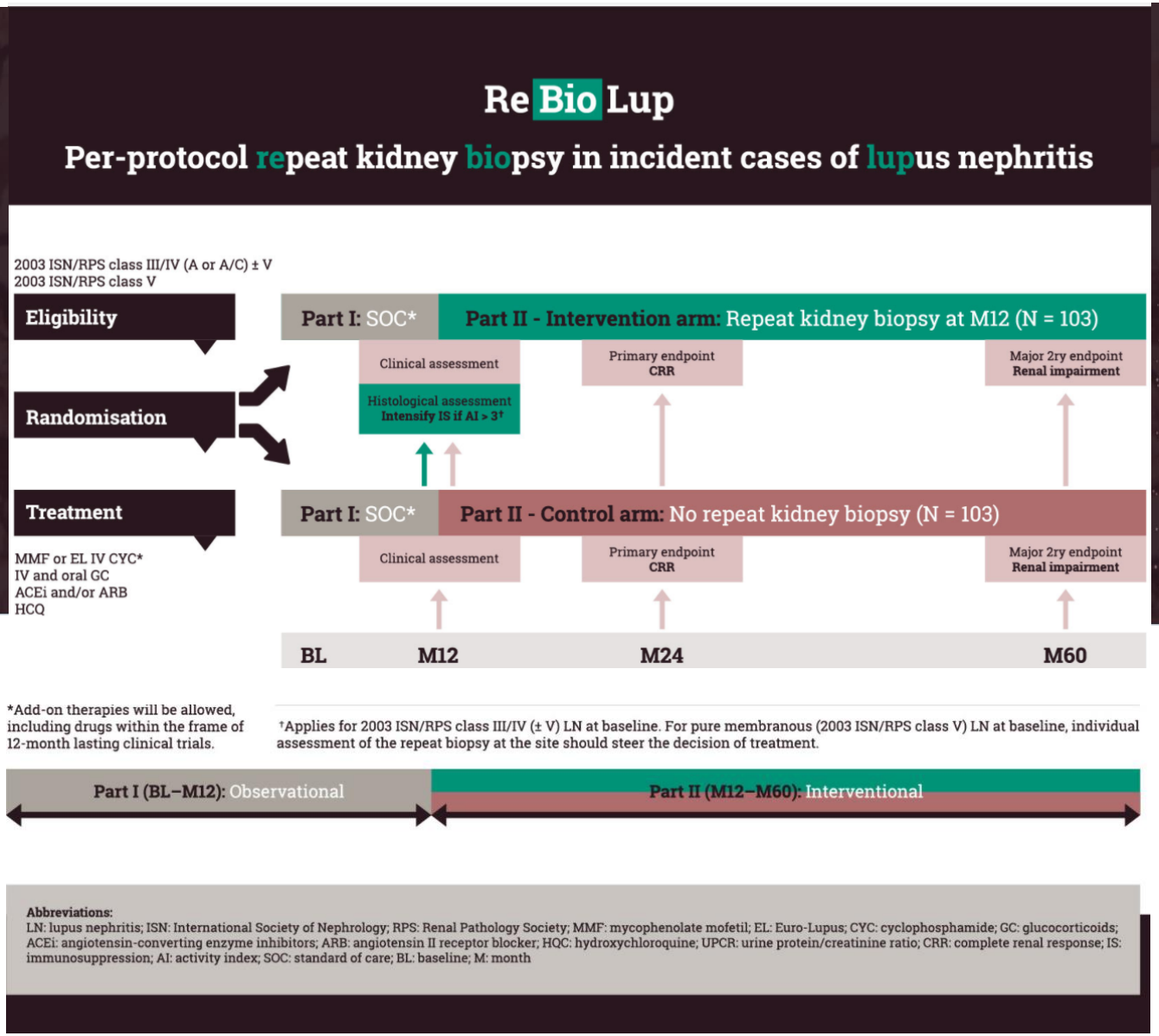
- Preservar eGFR
- ↑ calidad de vida

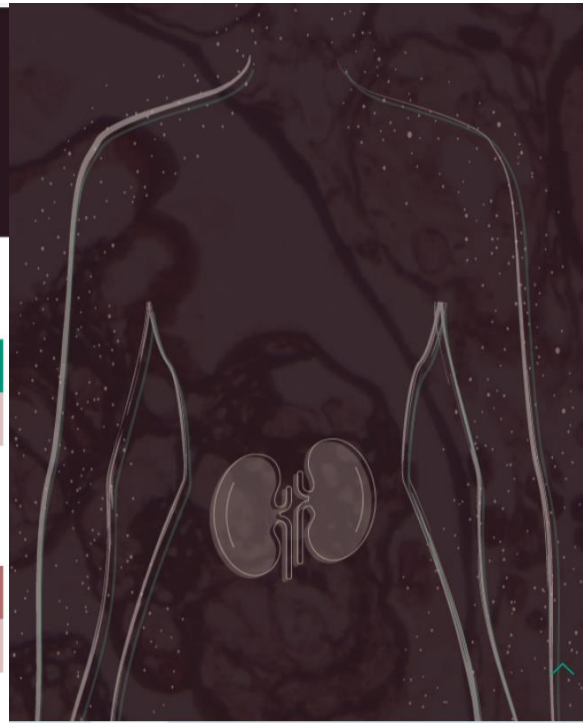
*Anders H, Lei Y, Rovin B. Induction and maintenance therapy of Lupus Nephritis: an obituary.* ***Kidney Int 2021****.*

ReBioLup

# Per-protocol repeat kidney biopsy in incident cases of lupus nephritis

NCT04449991



**Lupus Nephritis Trials Network (LNTN)**
www.lupusnephritis.org

**http://www.rebiolup.com/**

# Conclusiones (Take-home messages)

1. **Nuestros objetivos de tratamiento en NL clases III, IV ± V:**
   - ❖ *Corto plazo: abortar la inflamación aguda precozmente con baja toxicidad.*
   - ❖ *Largo plazo: mantener remisión clínica/serológica, ↓ brote y toxicidad (GCs).*
2. **EULAR-ERA 2019 y KDIGO 2021:**
   - ❖ *Recomiendan dosis más bajas de GCs en inducción y mantenimiento → stop.*
   - ❖ *MMF+GC y CYC-IV+GC (Eurolupus) continúan siendo el tto de elección para la NL proliferativa.*
3. La terapia **"multitarget"** (GC+MMF+CNIs) es una opción eficaz y segura (ya no sólo en Asiáticos).
4. **Belimumab y Voclosporina: ¿nueva terapia "multitarget" continuada?**
   - ❖ *Han demostrado buena tolerancia, eficacia y seguridad como terapia añadida al SoC.*
   - ❖ *Permiten ↓ precoz de GCs, ↓ riesgo de brotes y preserva mejor eGFR (belimumab).*
5. **Nuevos biológicos:** B-cells (OBN), plasma cells (anti-CD38), IFN-sig, con resultados alentadores.
6. **Pendiente:** ensayos pragmáticos, ↑ tasas de RC, monoterapia vs. retiro de IS, evaluación económica.

# ¡MUCHAS GRACIAS POR LA ATENCIÓN PRESTADA!

*Comentarios, preguntas o réplicas: jerori2003@yahoo.com / JERojas@fjd.es*