LUGO

Salón de Actos H.U. Lucus Augusti

X CONGRESO de la
SOCIEDAD GALLEGA DE NEFROLOGÍA

Nuevas inmunosupresiones en enfermedades glomerulares

Xoana Barros Freiría
Servicio Nefrología
Fundació Puigvert
Barcelona

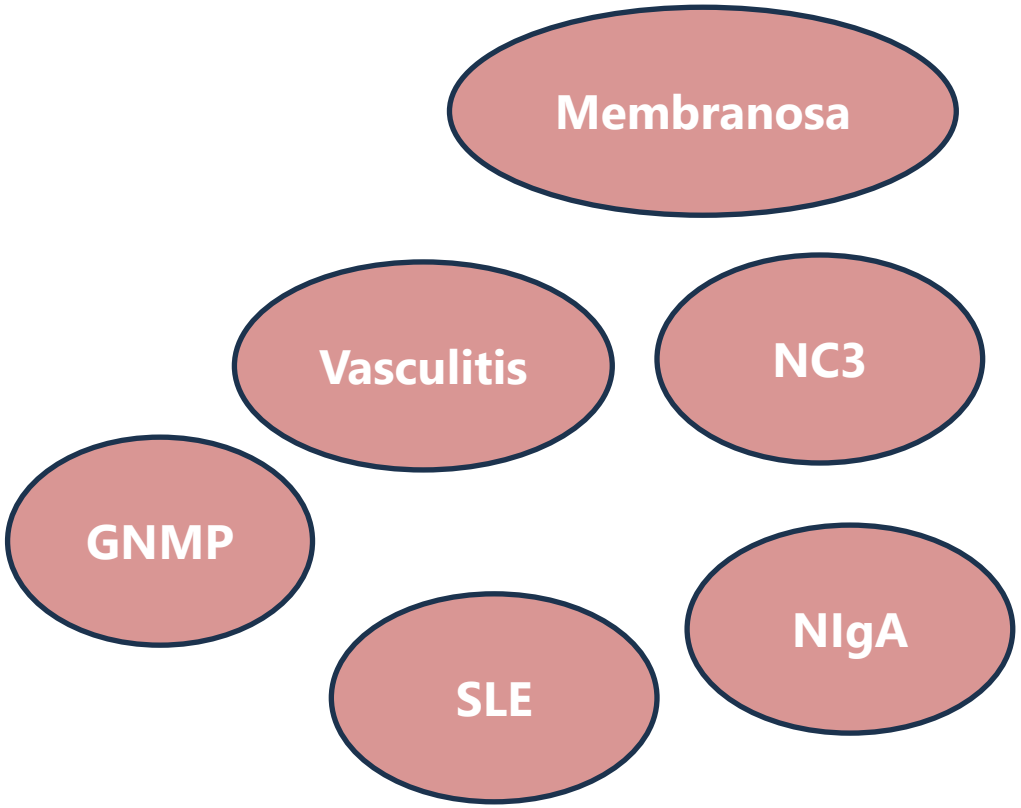
Lugo, 25 Outubro 2024

Conflicto de intereses

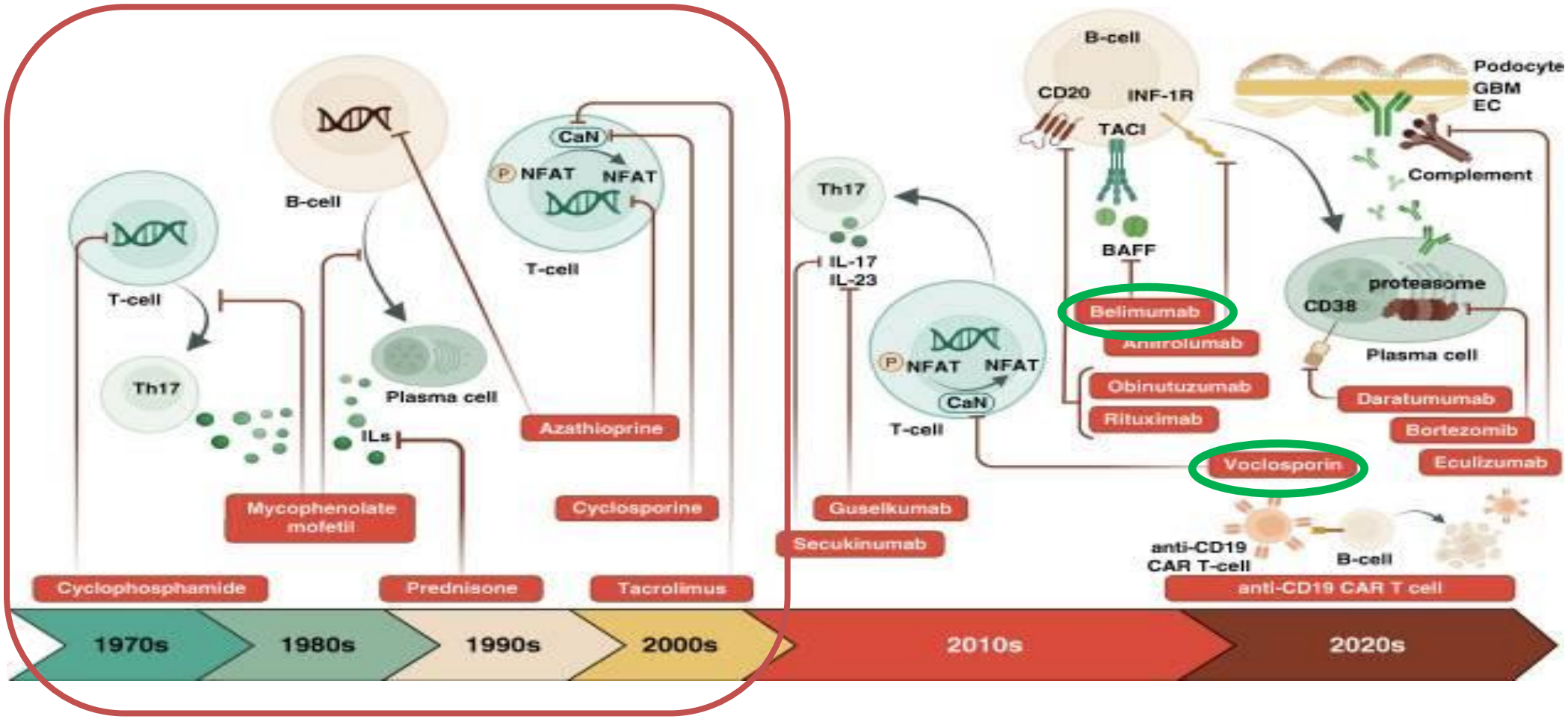
- Advisory Board and Fees: Samsung Bioepis

Nuevas inmunosupresiones en enfermedades glomerulares

- Iptacopan
- Ofatumumab
- Daratumumab
- Avacopan
- Obinituzumab
- Voclosporina
- Belimumab
- Mepolizumab
- Pegcetacoplan



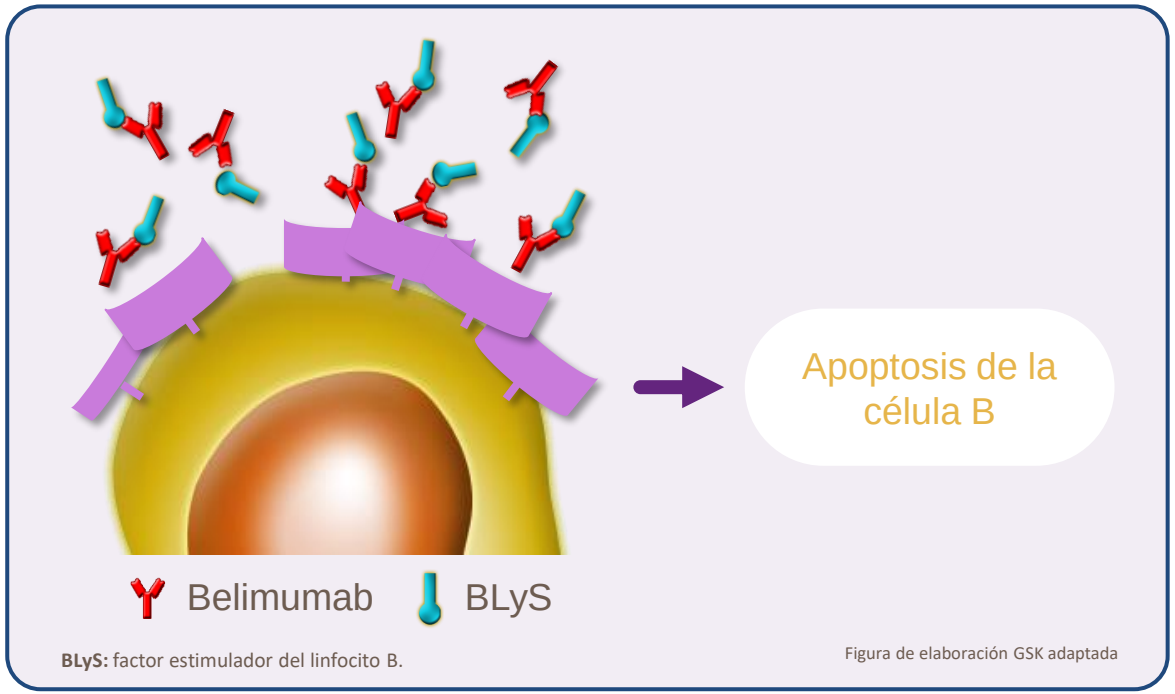
Lupus Nephritis: What do we have for treatment now?



KIDNEY360 4: 1503–1511, October, 2023

Belimumab

Belimumab no se une a las células B directamente, se une a BLyS soluble, inhibiendo las señales que produce BLyS en sus receptores de las células B



BLyS: factor estimulador del linfocito B.

Figura de elaboración GSK adaptada

La inhibición de la actividad de BLyS **favorece la apoptosis** de **las células B**, produciendo:

- Inhibición de la supervivencia de las células B, incluyendo células B autorreactivas.
- Reducción de la diferenciación de células B a células plasmáticas productoras de inmunoglobulinas.

Diapositiva de elaboración GSK adaptada

Ficha Técnica Benlysta IV GSK.
Baker KP, Edwards B, Main SH, *et al.* Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. Arthritis Rheum 2003; 48(11):3253–65.
Dennis GJ. Benlysta: A BLyS-Specific inhibitor for the Treatment of Systemic Lupus Erythematosus. Clin Pharmacol Ther. 2012; 91(1): 143-9.

Belimumab

ADMINISTRACIÓN INTRAVENOSA

- En pacientes con **LES o nefritis lúpica activa,** la dosis recomendada de Benlysta IV es **10 mg/kg** los Días 0, 14 y 28, y posteriormente en intervalos de 4 semanas.

- Puede administrarse premedicación incluyendo un **antihistamínico,** acompañado o no de un **antipirético.**

- **No se requiere ajustar dosis** en pacientes con:

  EDAD AVANZADA (>65AÑOS)

  INSUFICIENCIA RENAL

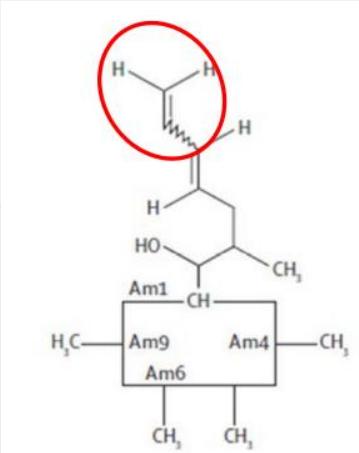
  INSUFICIENCIA HEPÁTICA

ADMINISTRACIÓN SUBCUTÁNEA

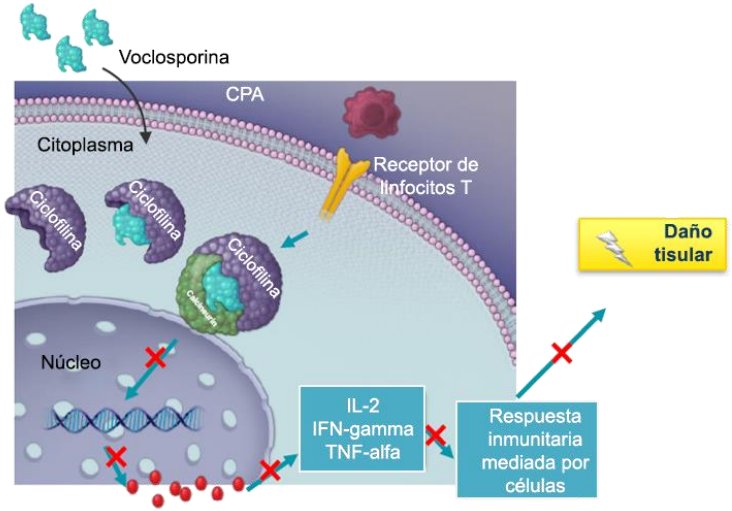
- **Nefropatía lúpica,** la pauta posológica recomendada es una dosis de 400 mg (dos inyecciones de 200 mg) una vez a la semana durante 4 semanas, y 200 mg una vez por semana a partir de entonces. En pacientes que continúan el tratamiento con Benlysta para la nefritis lúpica activa, se recomienda mantener la dosis de 200 mg una vez a la semana.

Diapositiva adaptada de GSK

Voclosporina



Mediante la inhibición de la calcineurina, bloquea la expresión de IL-2, reduciendo así las respuestas inmunitarias mediadas por los linfocitos T



Potencial estabilización de los podocitos en el riñón, lo que confiere protección frente a la apoptosis de los podocitos y la proteinuria

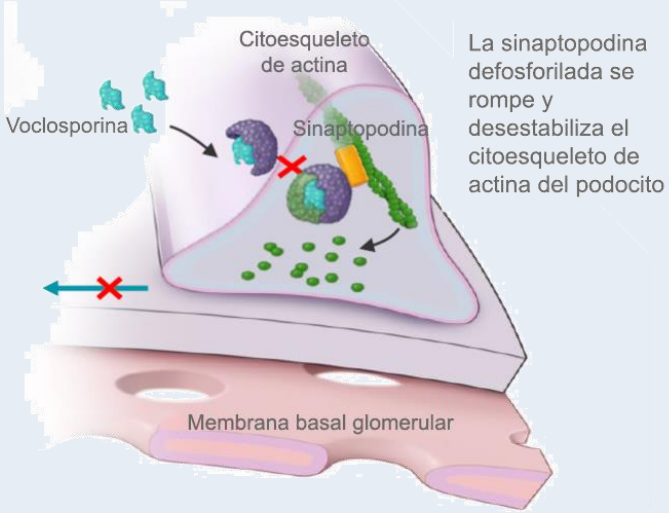
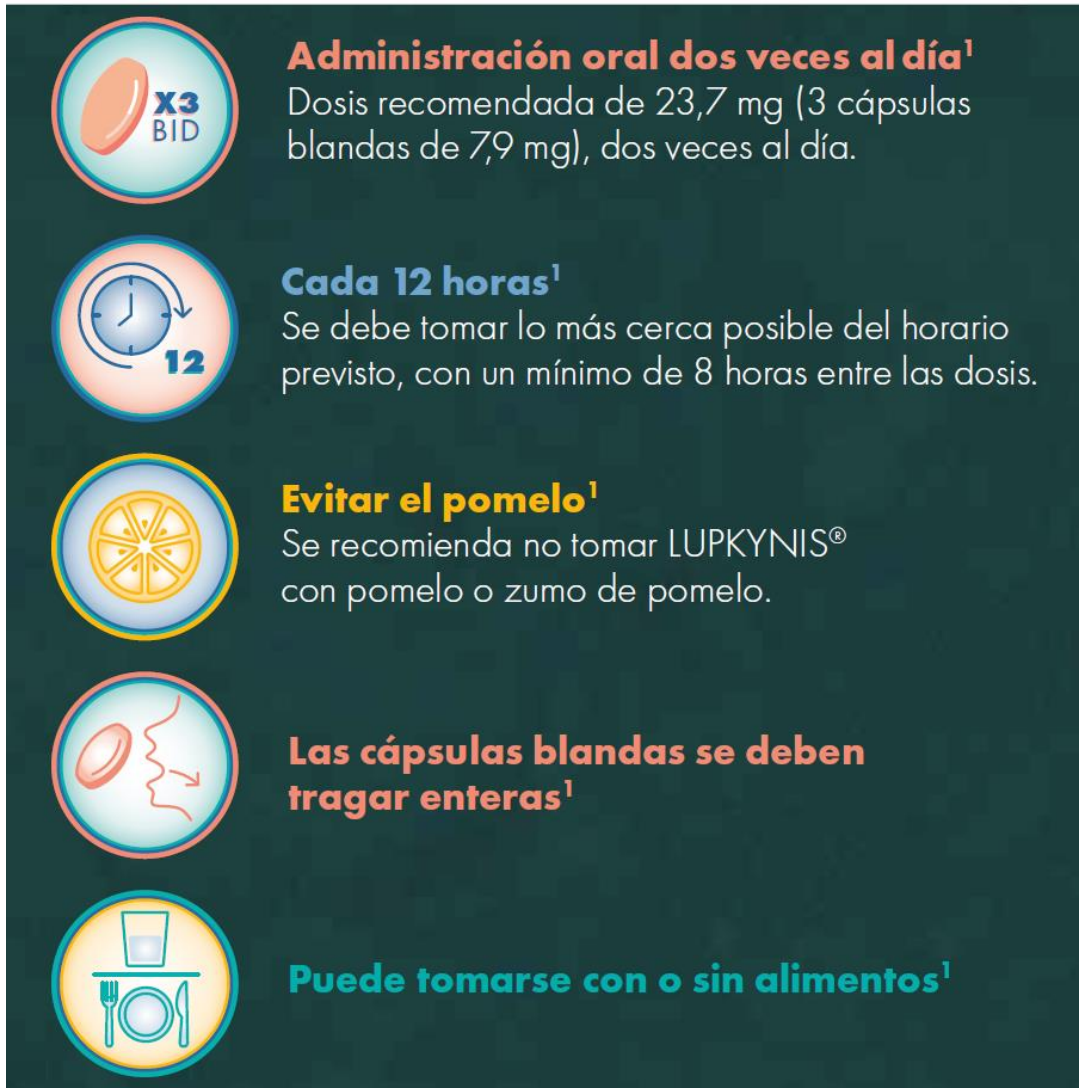


Imagen extraída de Huizinga RB *et al. The 12th International Congress on Systemic Lupus Erythematosus (LUPUS 2017) & the 7th Asian Congress on Autoimmunity (ACA 2017)*. Disponible en: https://pdfs.semanticscholar.org/525a/1896761de736000254216495375 4e62133bd.pdf (consultado en febrero 2022).
Tsuda K *et al. PLoS ONE*. 2012;7:e31465; Katsuyama T *et al. Front Immunol.* 2018;9:1088; Faul C *et al. Nature Med* 2008;14:931–8; Wakamatsu A *t al. Physiol Rep* 2016;4:e12679; Liao R *et al. PLoS One* 2015;10:e0132724

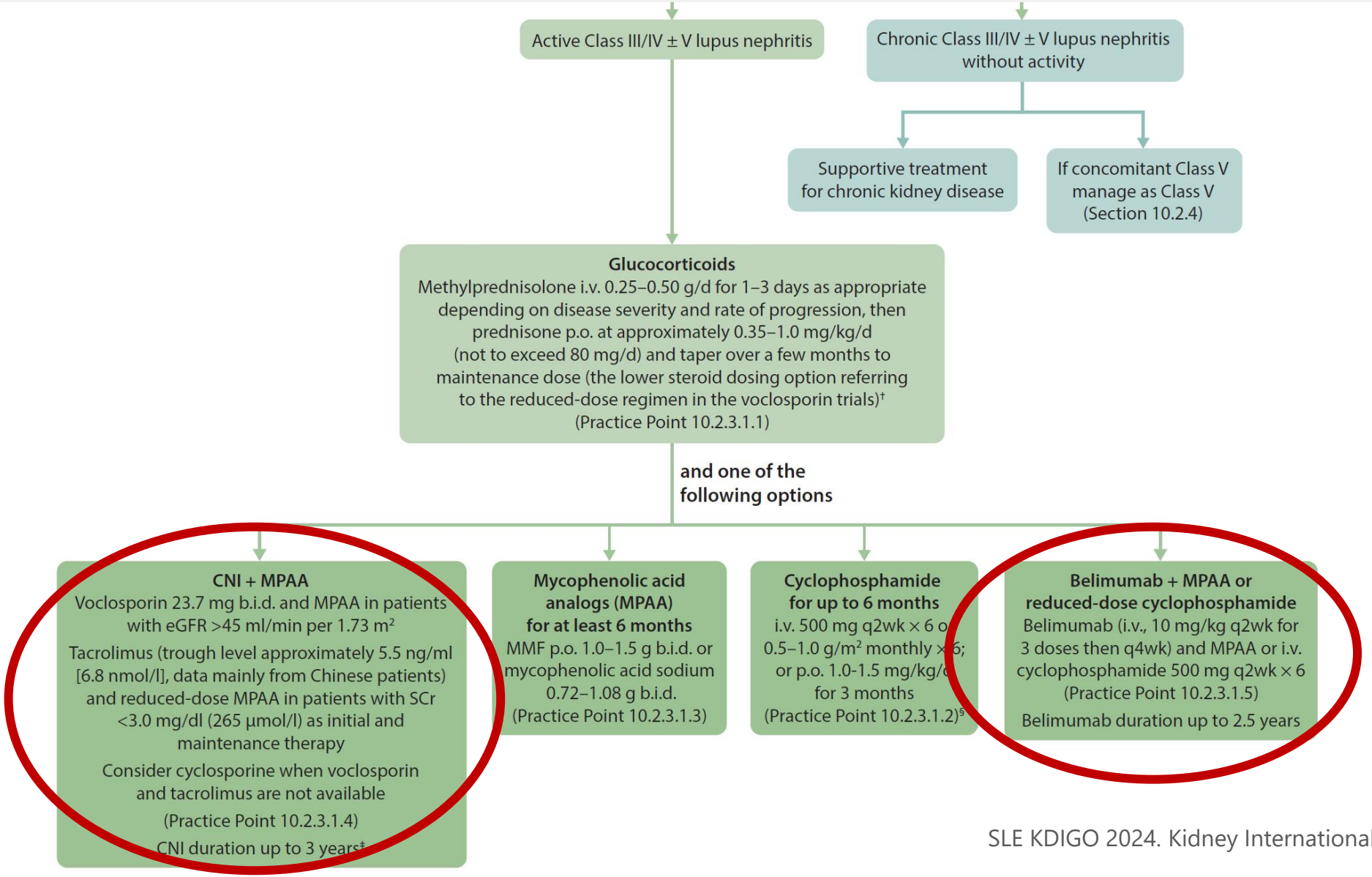
Diapositiva adaptada de Otsuka

Voclosporina



adaptado Otsuka

KDIGO SLE 2024



SLE KDIGO 2024. Kidney International (2024) 105 (Suppl 1S), S1–S69

Ensayos Fase 3 en Nefritis lúpica

Trial	BLISS-LN [2]	AURORA 1 [3]
Phase	3	3
Number of patients	448	357
Immunosuppression (background, induction)	- Euro-Lupus CYC (6 infusions CYC a fortnight apart) *or* MMF (target dose 3 g/day) - High-dose GCs (i.v. MP at investigator's discretion), followed by oral prednisone (0.5–1.0 mg/kg/day, max. 60 mg/day), 25 mg/day at Week 7 and 10 mg/day at Week 12	- MMF at a dose of 2 g/day (doses of up to 3 g/day were permitted with monitor approval) - MP 0.5 g/day or 0.25 g/day based on body weight (Day 1 and 2), 20–25 mg/day GC on Day 3, decreasing to 2.5 mg/day at Week 16
Immunosuppression (background, maintenance)	- AZA (2 mg/kg body weight/day, max. 200 mg/day a day) or MMF (1–3 g/day) - GCs: max. 10 mg/day by Week 24	- MMF - GCs: 2.5 mg/day (further reduction at investigator's discretion)
Active treatment arm	Belimumab (10 mg/kg body weight) on Days 1, 15, 29, and then every 28 days to Week 100)	Voclosporin 23.7 mg twice daily (6 tablets in total) for 52 weeks
Comparator (placebo) arm	Placebo	Placebo
LN class	III or IV: 56% vs 59% V: 16% vs 16% Mixed: 27% vs 25%	III or IV: 62% vs 59% V: 14% vs 14% Mixed: 24% vs 26%
Primary endpoint	96 (43%) vs 72 (32%)[a]	73 (41%) vs 40 (23%)[c]
Complete renal response	67 (30%) vs 44 (20%)	(See above, primary endpoint)
Proteinuria at baseline (UPCR)	3.2 ± 2.7 vs 3.5 ± 3.6	4.1 ± 2.7) vs 3.9 ± 2.4)
GFR at baseline (mL/min/1.73 m^2)	100.0 ± 37.7 vs 101.0 ± 42.7	92.1 ± 30.6) vs 90.4 ± 29.0)
Δ GFR change (mL/min/1.73 m^2) from baseline	Δ (approximately[b]) +10 vs +/– 0 (at Week 104)	Δ +1.0 vs 1.1 (at Week 52)
Follow-up time (weeks)	104	52
Serious adverse events	58 (26%) vs 67 (30%)	37 (21%) vs 38 (21%)
Serious infections/infestations	15 (7%) vs 18 (8%)	18 (10%) vs 20 (11%)

EULAR 2023 synopsis; Nephrol Dial Transplant, 2024, Vol. 39, No. 5

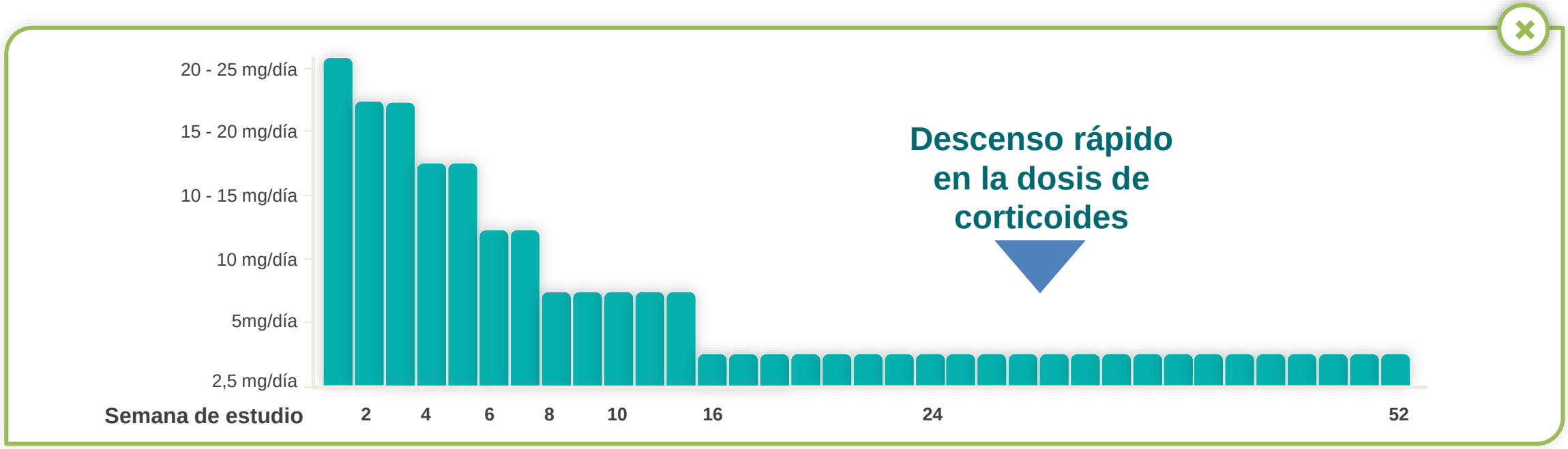
Corticoides en KDIGO SLE 2024

	High-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			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

SLE KDIGO 2024. Kidney International (2024) 105 (Suppl 1S), S1–S69

Esquema reducción de corticoides del Aurora

Día 1	Día 2	Día 3 a día 6	Semana 2 a semana 3	Semana 4 a semana 5	Semana 6 a semana 7	Semana 8 a semana 15	Semana 16 a final
0,5 g/día metilprednisolona **IV**	**0,5 g/día** metilprednisolona **IV**	**25 mg/día** prednisona **ORAL**	**20 mg/día** prednisona **ORAL**	**15 mg/día** prednisona **ORAL**	**10 mg/día** prednisona **ORAL**	**5 mg/día** prednisona **ORAL**	**2,5 mg/día** prednisona **ORAL**



Rovin BH, et al. Lancet 2021;397:2070-80 (adaptado Otsuka)

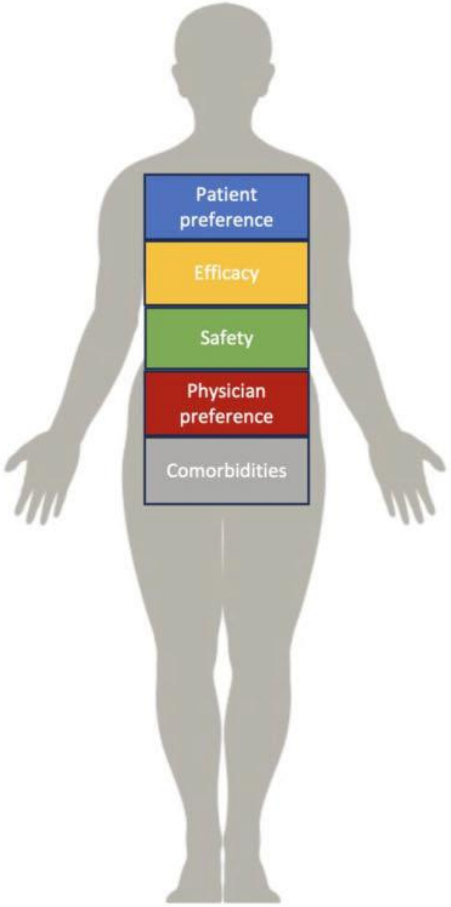
EULAR 2023

eGFR < 45 ml/min/1.73 m²
Belimumab (limited experience)

Proteinuria < 3 g/d
Belimumab or Voclosporin

Adherence
Belimumab (preferred option)

Background therapy
Use of cyclophosphamide (only tested with belimumab)



eGFR ≥ 45 ml/min/1.73 m²
Belimumab or Voclosporin

Proteinuria ≥ 3 g/d
Voclosporin (preferred option)

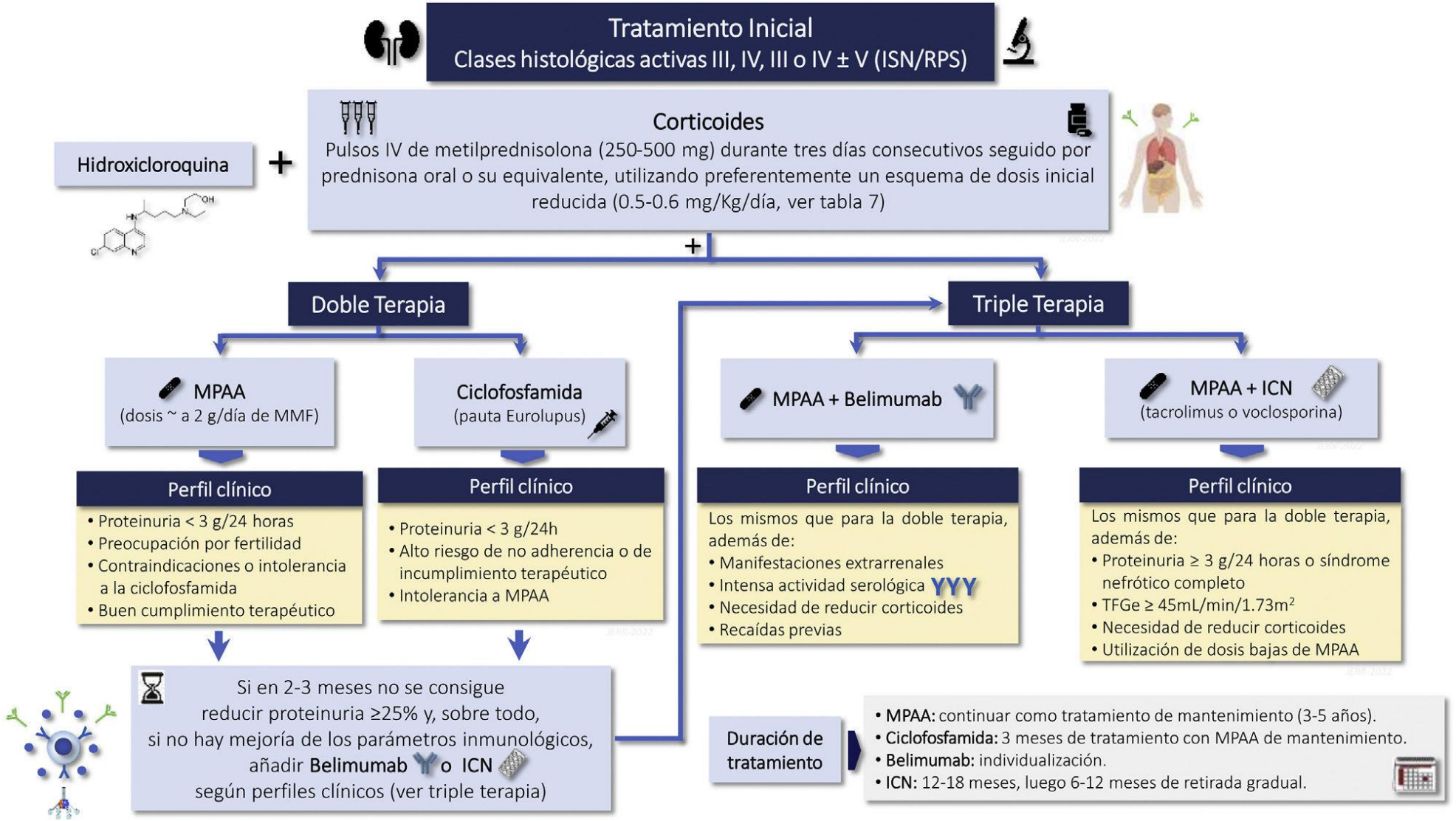
Patient preference
Oral medication (VCS; pill burden) versus i.v./s.c. administration (BEL)

Rigorous glucocorticoid tapering
Voclosporin (preferred option)

Extra-renal disease activity
Belimumab (preferred option)

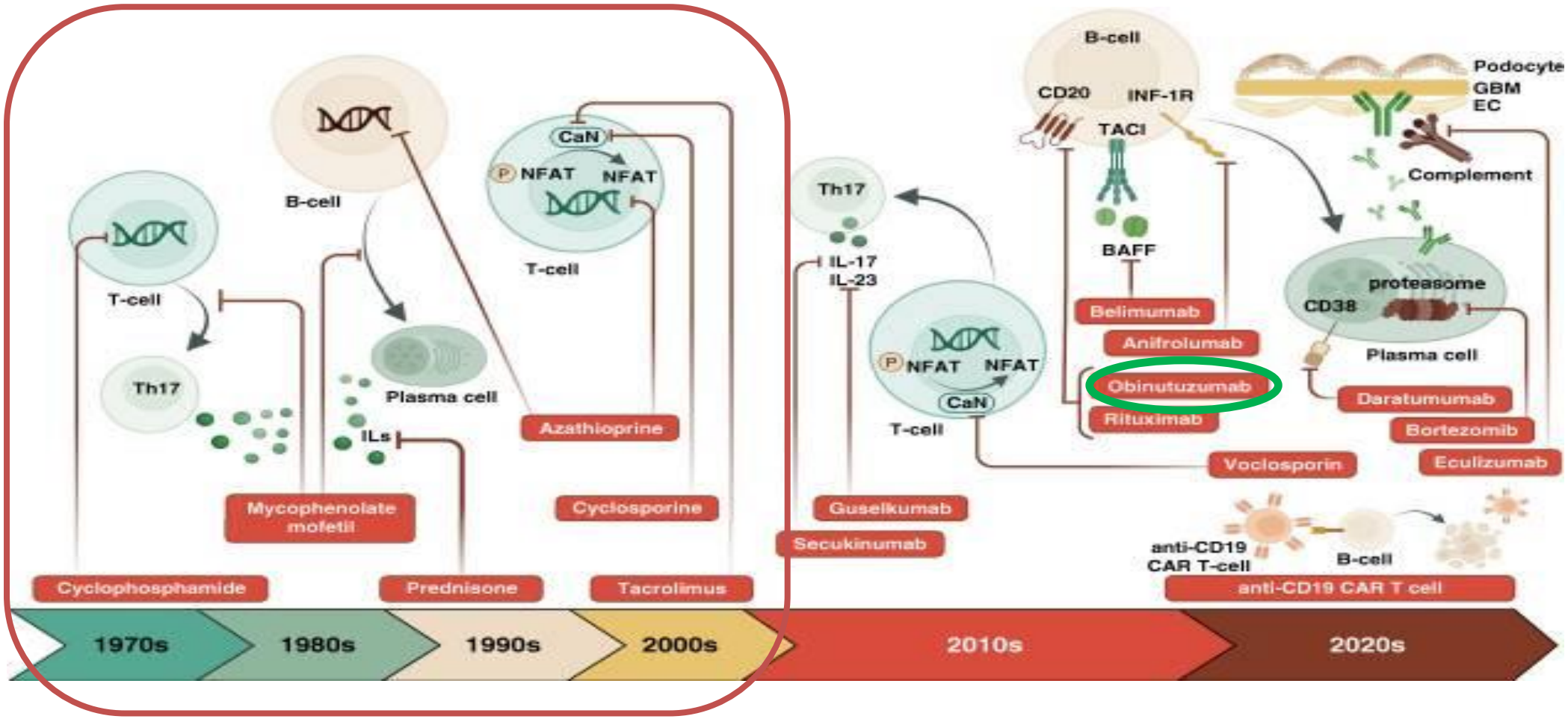
ERC-IWG perspective EULAR 2023; Nephrol Dial Transplant, 2024, Vol. 39, No. 5

Documento consenso GLOSEN nefritis lúpica



Nefrologia 2023;43(1):6–47

Lupus Nephritis: What do we have for treatment now?



KIDNEY360 4: 1503–1511, October, 2023

Obinituzumab

	Rituximab	Obinutuzumab
Antibody Type	Type I	**Type II**
Antibody Engineering[1]	Chimeric mAb (IgG_1)	Humanized mAB (IgG_1) **Glycoengineered Fc region**
FcγRIIIa binding Affinity[2,3]	+	+++
ADCC[2,3]	+	+++
CD20 Binding [4,5]	CD20 dimer can bind two different Fab arms	CD20 dimer can bind one Fab arm
CDC[2,3] (relative to RTX)	1 x	<0.01 x
B-cell depletion: mechanism of action	• CDC and ADCC[2] • Caspase-dependent DCD[6]	• **Greater B-cell depletion than type I antibodies and deeper B-cell depletion,** including organs such as spleen and lymph nodes[3] • Enhanced ADCC relative to RTX and OCR, and caspase-independent DCD[3] • Less CDC[3]

ADA, anti-drug antibodies; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; DCD, direct cell death; IRR, infusion-related reaction; OCR, ocrelizumab; RTX, rituximab.

1. Klein C et al. *mAbs*. 2013;5:22-33. 2. Morschhauser F et al. *Annals Oncol*. 2010;21:1870-1876. 3. Mossner E et al. *Blood*. 2010;115:4393-4402. 4. Beers SA et al. *Semin Hematol*. 2010. 47:107-114.5. Niederfellner G et al. *Blood*.2011;118:358-387. 6.Al-Zoobi L, et al. *Int Immunol*. 2014;26:451-465.

Obinituzumab en nefritis lúpica

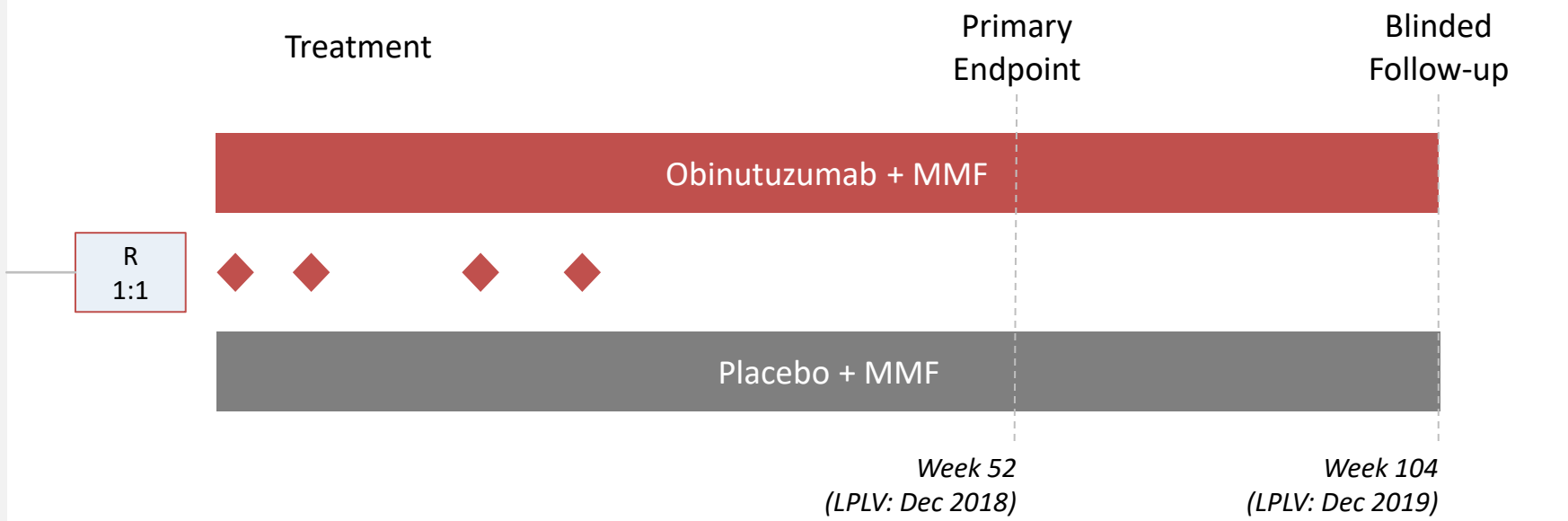
Phase 2 study (NOBILITY)

Screening

- Patients with class III/IV (+/-V) LN
- Hematuria
- Proteinuria
- Age 18-75 years

N = 127

◆ = IV infusions



- Primary endpoint: % of patients achieving CRR (Week 52)
- Additional key endpoints: Achievement of modified CRR definitions; improvement in C3 and anti-dsDNA antibody levels; improvement in UPCR; improvement in eGFR; exploratory analyses at Weeks 76 and 104

- Obinutuzumab 1000 mg IV/placebo: Days 1, 15, 168 (w24) and 182 (w26)
- MMF (or MPA): target dose 2.0-2.5 g/day (or equivalent)
- Corticosteroids: 1-3 infusions of 1000 mg IV methylprednisolone prior to randomization and oral prednisone 0.5 mg/kg tapered over 12 weeks

Furie R, et al. *Ann Rheum Dis* 2022; 81:100-107.
Oral presentation at ACR Virtual Meeting. November 5-9, 2020.

Obinituzumab en nefritis lúpica

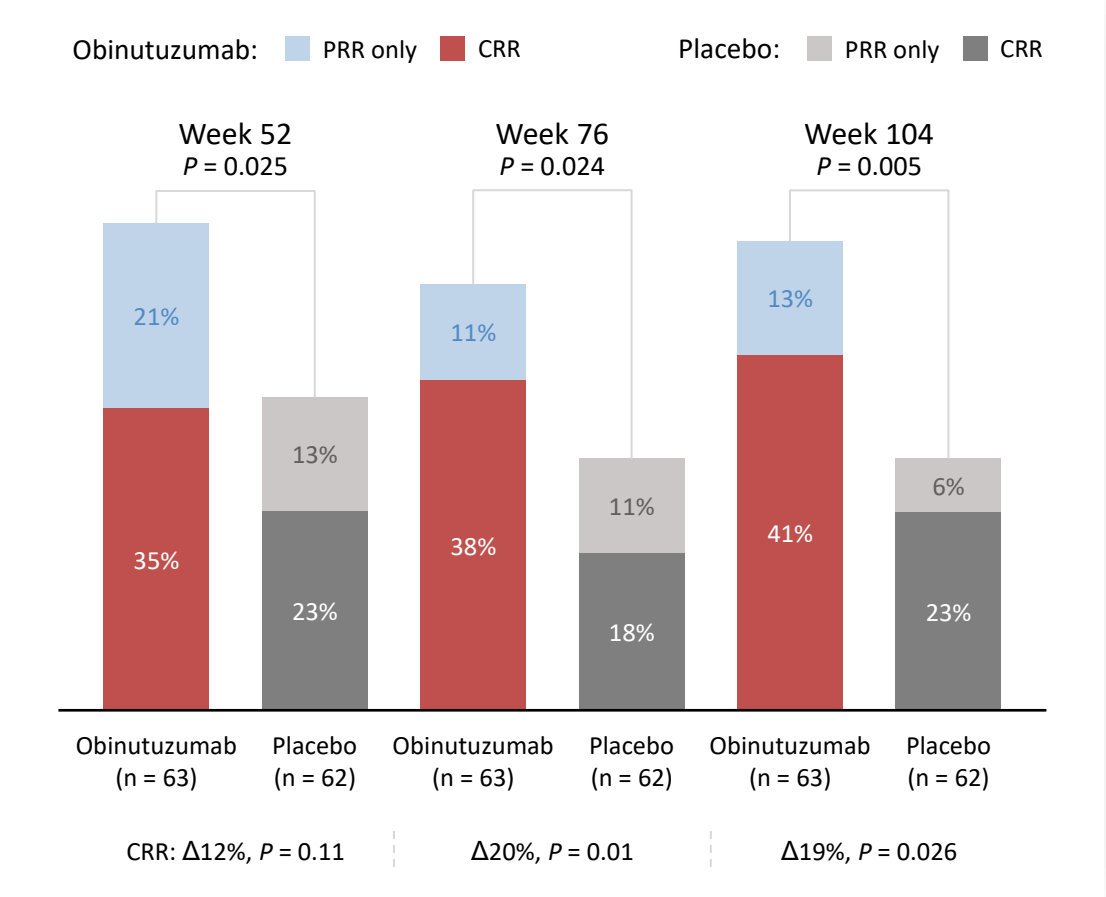
Phase 2 study (NOBILITY)

Key results

- Primary and secondary endpoints were met at Week 52
- Increased complete renal responses through Week 104
- Rapid and potent depletion of peripheral CD 19+ B cells without an increase in the incidence of serious adverse events, serious infections or death compared with placebo

Conclusion

- Obinutuzumab was superior to placebo in achieving renal response and improving serologies in patients with proliferative LN. The benefit of obinutuzumab was sustained through 104 weeks, 18 months after the last obinutuzumab treatment



Furie R, et al. *Ann Rheum Dis* 2022; 81:100-107.
Oral presentation at ACR Virtual Meeting. November 5-9, 2020.

Obinituzumab en nefritis lúpica

Phase 2 study (NOBILITY)

Obinutuzumab was **superior to placebo for the achievement of CRR and ORR** in patients with proliferative LN when added to mycophenolate and corticosteroids

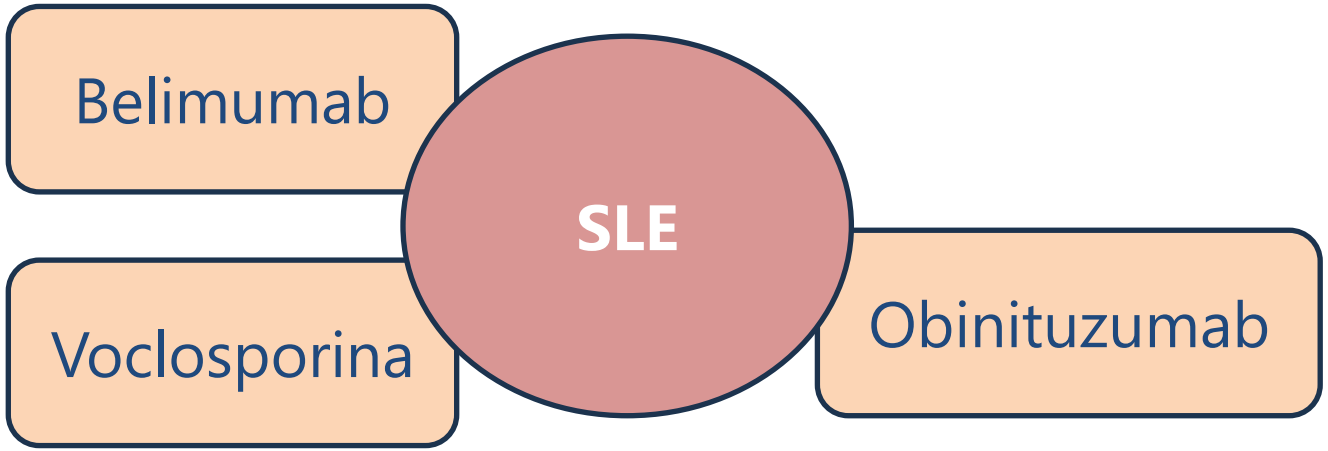
Obinutuzumab resulted in **rapid and deep depletion** of peripheral CD19+ B cells without an increase in the incidence of serious adverse events, serious infections or death compared with placebo

Results from this study indicate that **B cells play a key role in LN** pathogenesis

The use of obinutuzumab in proliferative LN is being further evaluated in a **global phase 3 study REGENCY** NCT04221477)

Furie R, et al. *Ann Rheum Dis* 2022; 81:100-107.
Oral presentation at ACR Virtual Meeting. November 5-9, 2020.

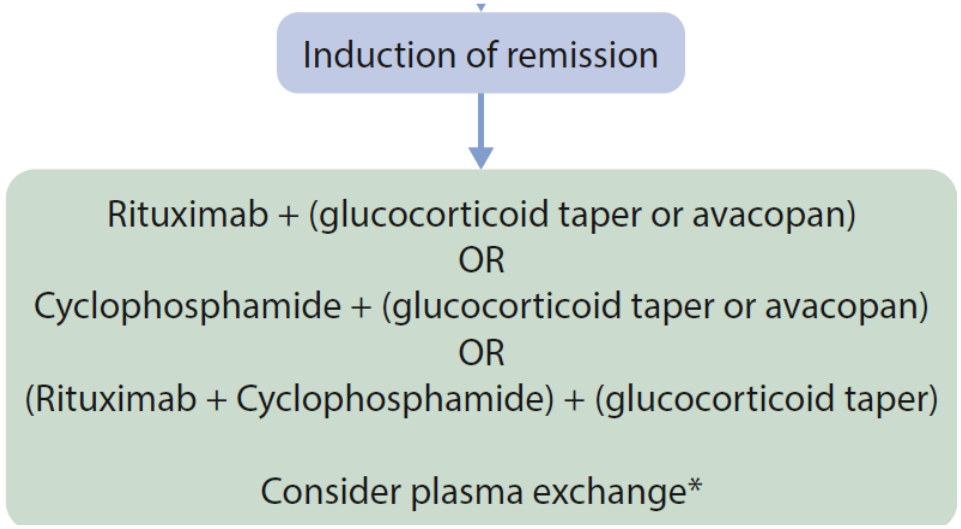
Nefritis lúpica



KDIGO Vasculitis 2024

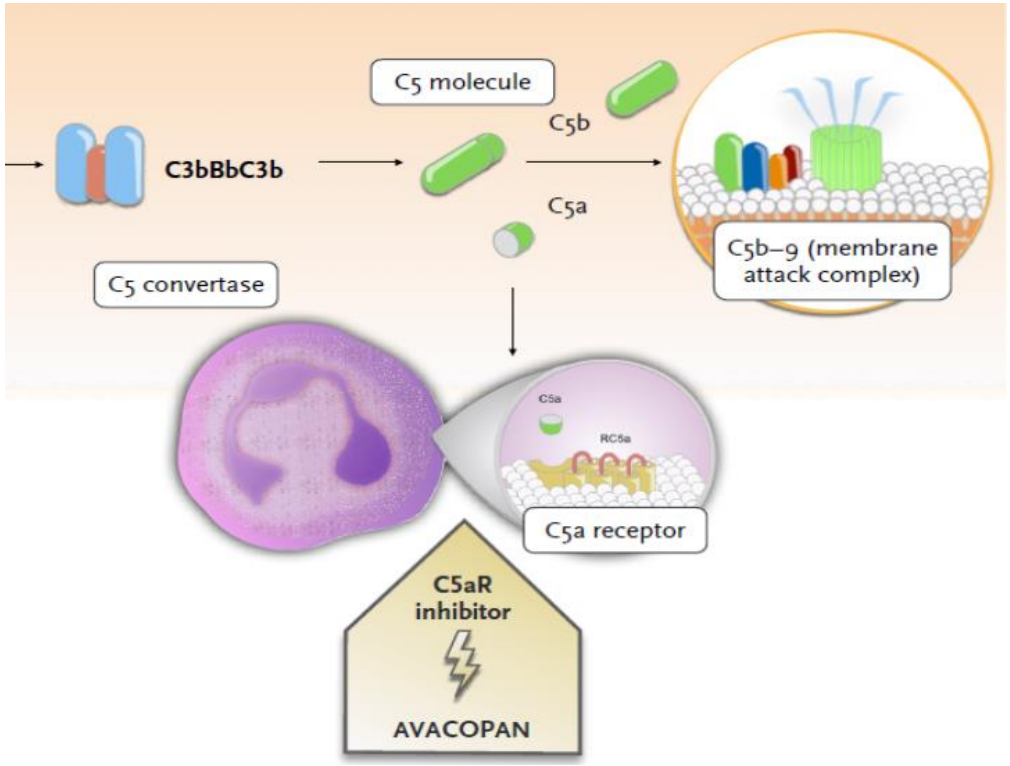
Avacopan

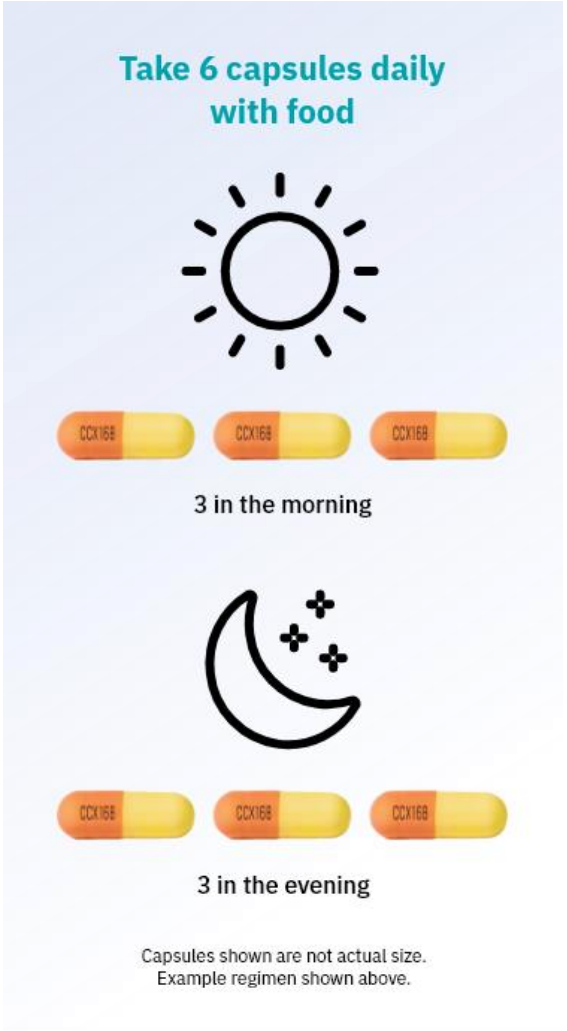
Practice Point 9.3.1.7: Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.



Kidney International (2024) 105 (Suppl 3S), S71–S116

Avacopan





Avacopan es aprobado para tratamiento de vasculitis en 2021

EULAR 2023: Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA as part of a strategy to substantially reduce glucocorticoid exposure. 1b B

30mg/12h

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

Table 2. Primary and Key Secondary End Points.*

End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (−6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖
Secondary end points			
GTI-CWS**			
Wk 13			
Patients evaluated	160	161	
Least-squares mean	25.7±3.4	36.6±3.4	−11.0 (−19.7 to −2.2)
Wk 26			
Patients evaluated	154	153	
Least-squares mean	39.7±3.4	56.6±3.4	−16.8 (−25.6 to −8.0)
Urinary albumin:creatinine ratio‖‖			
Baseline			
Patients evaluated	125	128	
Geometric mean (range)	433 (20–6461)	312 (11–5367)	
Percent change from baseline to wk 4			
Patients evaluated	121	124	
Least-squares mean ±SE	−40±10	0±9	−40 (−53 to −22)

Renal Recovery for Patients With ANCA-Associated Vasculitis and Low eGFR in the ADVOCATE Trial of Avacopan

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

ADVOCATE trial

Post hoc analysis

Patients with ANCA - associated vasculitis

eGFR ≤20mL/min/1.73m²
N = 50

Intervention

Prednisone group

n = 23

52 weeks follow-up

Avacopan group

n = 27

Results

	Baseline eGFR mL/min/1.73m²	Change in eGFR mL/min/1.73m²	Increase in eGFR of ≥2-fold (%)
Prednisone group	17.5	7.7	13.0
Avacopan group	17.6	16.1	40.7
P value	P = 0.846	P = 0.003	P = 0.030

ANCA, antineutrophil cytoplasmic antibody

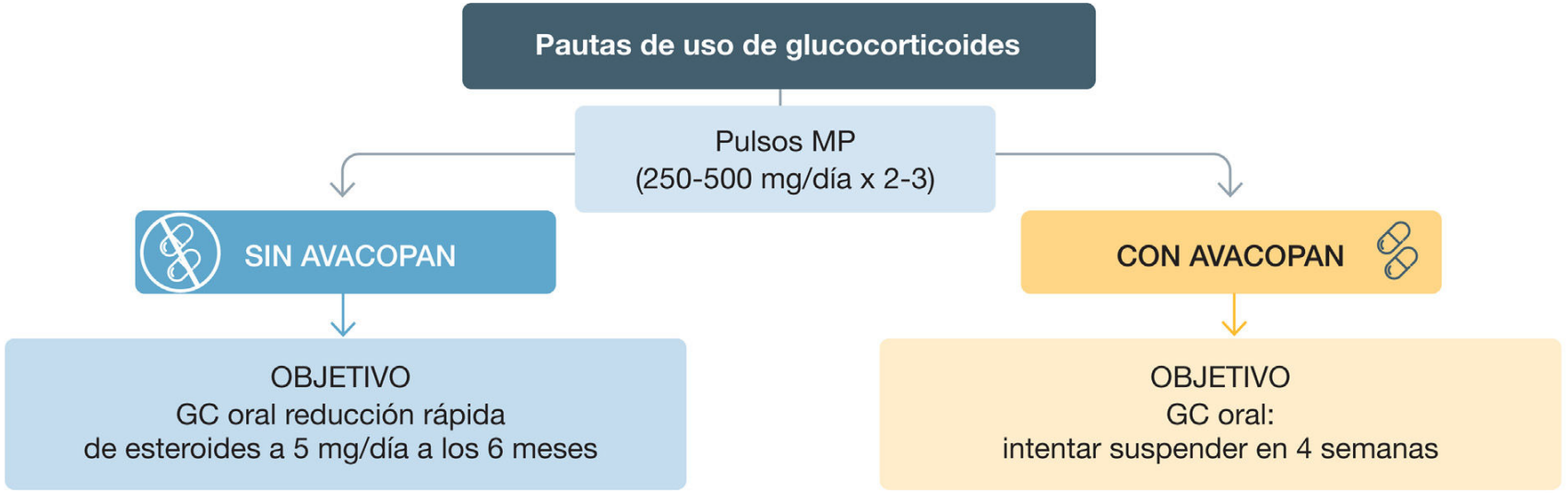
KI REPORTS
Kidney International Reports

Cortazar F et al, 2023

Visual abstract by:
Denisse Arellano, MD
@deniise_am

Conclusion Among patients with baseline eGFR ≤20 mL/min/1.73m² in the ADVOCATE trial, eGFR improved more in the avacopan group vs. the prednisone group.

Recomendaciones españolas Vasculitis



Semana	Pauta de reducción		
	<50 kg	50-75 kg	>75 kg
	Pulso	Pulso	Pulso
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12,5	15	20
9-10	10	12,5	15
11-12	7,5	10	12,5
13-14	6	7,5	10
15-16	5	5	7,5
17-18	5	5	7,5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5
>52	Práctica clínica local		

Semana	Pauta de reducción		
	<50 kg	50-75 kg	>75 kg
	Pulso	Pulso	Pulso
1	25	30	40
2	15	20	30
3	10	10	20
4	5	5	10
5	Stop	Stop	5
6			Stop

Recomendaciones para el dx y tto de las vasculitis asociadas a anticuerpos anticitoplasma de neutrófilo
Nefrología doi.org/10.1016/j.nefro.2024.07.004

Avacopan

› Rheumatology (Oxford). 2024 Oct 1:keae534. doi: 10.1093/rheumatology/keae534. Online ahead of print.

The real-world use and effectiveness of avacopan in routine practice for the treatment of ANCA vasculitis. First experiences in Spain

Juliana Draibe [1], Georgina Espigol-Frigolé [2], Maria Cinta Cid [3], M C Prados [4], E Guillén [5], J Villacorta [6], C Vega [7], J Martins [8], I daSilva [9], Ma Adoración Martin-Gomez [10], A Huerta [11], L Martinez-Valenzuela [1], Enrique Morales [12]

Case Reports › Cureus. 2024 Jun 20;16(6):e62759. doi: 10.7759/cureus.62759. eCollection 2024 Jun.

Limited Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Presenting With Diffuse Alveolar Hemorrhage: A Case Report and Literature Review

Hema Kondakindi [1], Joud Enabi [1], Kejal Shah [1], Duy Chung [2 3 4], Luan Ngo [5], Srikanth Mukkera [6]

› Rheumatology (Oxford). 2024 Jul 13:keae359. doi: 10.1093/rheumatology/keae359. Online ahead of print.

Avacopan for anti-neutrophil cytoplasm antibodies-associated vasculitis: a multicenter real-world study

Charlotte Gabilan [1], Julie Belliere [1 2 3], Olivier Moranne [4], Pierre Pfirmann [5], Maxime Samson [6], Vincent Delattre [7], Benjamin Thoreau [8], Victor Gueutin [9], Annabel Boyer [9], Amélie Leurs [10], Quentin Astouati [11], Charles Ronsin [12], Thomas Quemeneur [13], David Ribes [1], Alexandre Karras [14], Stanislas Faguer [1 2 3]

› ACR Open Rheumatol. 2024 Oct;6(10):707-716. doi: 10.1002/acr2.11726. Epub 2024 Jul 30.

Treatment of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis With Diffuse Alveolar Hemorrhage With Avacopan

Sam D Falde [1], Amos Lal [1], Rodrigo Cartin-Ceba [2], Lester E Mertz [2], Fernando C Fervenza [1], Ladan Zand [1], Matthew J Koster [1], Kenneth J Warrington [1], Augustine S Lee [3], Nabeel Aslam [3], Andy Abril [3], Ulrich Specks [1]

Nuevos Anti-CD20 en Vasculitis

RHEUMATOLOGY

Rheumatology 2022;61:3814–3817
https://doi.org/10.1093/rheumatology/keab916
Advance Access publication 27 December 2021

Concise report

Obinutuzumab as treatment for ANCA-associated vasculitis

Naomi A. Amudala [1,*], Sara Boukhlal [2,*], Brittany Sheridan[3], Carol A. Langford[4], Abdallah Geara[3], Peter A. Merkel[5] and Divi Cornec[2]

3 pacientes obinituzumab resistente a otros tratamientos y que habian presentado reaccion hipersensibilidad a Rituximab

Open access Protocol

BMJ Open

Study protocol for a randomised, phase II, double-blind, experimental medicine study of obinutuzumab versus rituximab in ANCA-associated vasculitis: ObiVas

Dominic Paul McGovern [1,2] Mark E McClure,[1,2] Matthew Coates,[1,2] Simon Bond [3] Marcos Martinez Del Pero,[2] Kim Mynard,[4] Jacinta Lee,[1] Rona M Smith [1,2] David R Jayne [1,2] Menna Ruth Clatworthy [1,5] Rachel B Jones,[1,2] on behalf of the ObiVas Investigators

RHEUMATOLOGY

Rheumatology 2016;55:1437–1442
doi:10.1093/rheumatology/kew199
Advance Access publication 19 April 2016

Concise report

Ofatumumab for B cell depletion therapy in ANCA-associated vasculitis: a single-centre case series

Stephen P. McAdoo[1,2], Rachna Bedi[1], Ruth Tarzi[2], Megan Griffith[1,2], Charles D. Pusey[1,2,*] and Thomas D. Cairns[1,*]

8 pacientes ofatunumab + low-dose CYC y Gcs vo

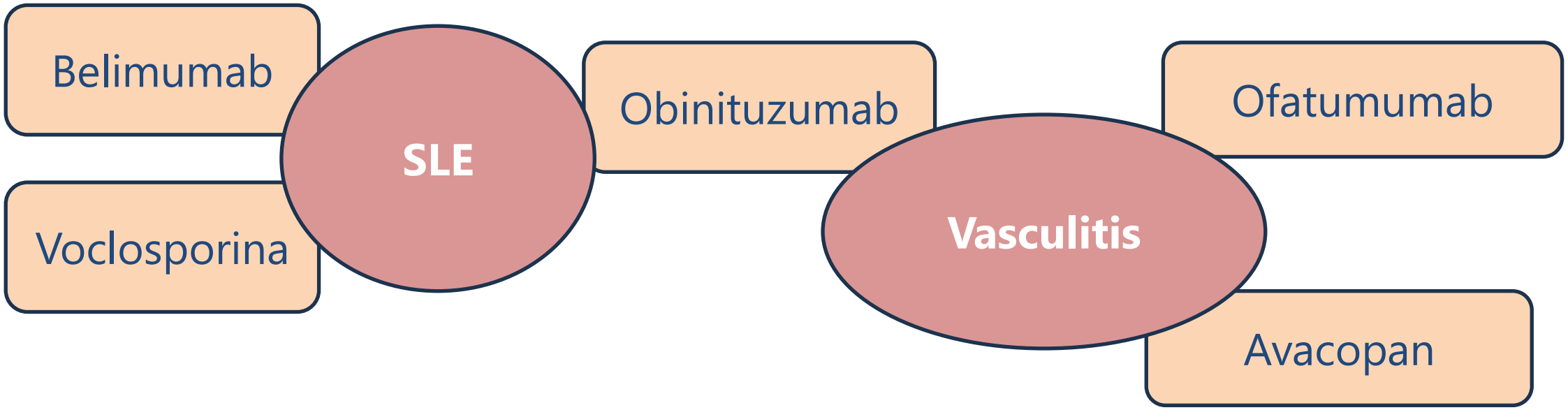
Deplecion linfos B en 1 mes y mantenida 6 m

BVAs 0 en 3 meses

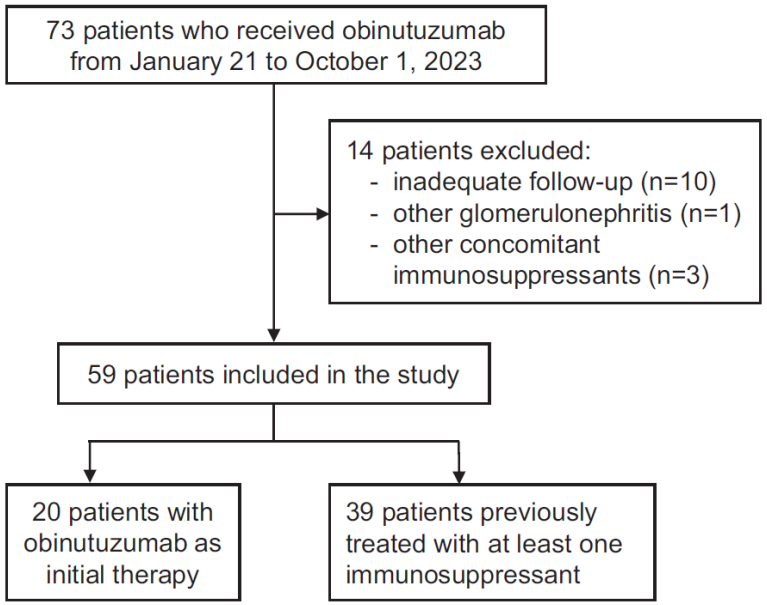
No recaídas en 24 meses

McGovern DP, et al. BMJ Open 2024;14:e083277. doi:10.1136/bmjopen-2023-083277

Añadimos...


Belimumab
Voclosporina
SLE
Obinituzumab
Vasculitis
Ofatumumab
Avacopan

Nuevos Anti-CD20 en N Membranosa



KI REPORTS
KIReports.org
CLINICAL RESEARCH

Obinutuzumab as Initial or Second-Line Therapy in Patients With Primary Membranous Nephropathy

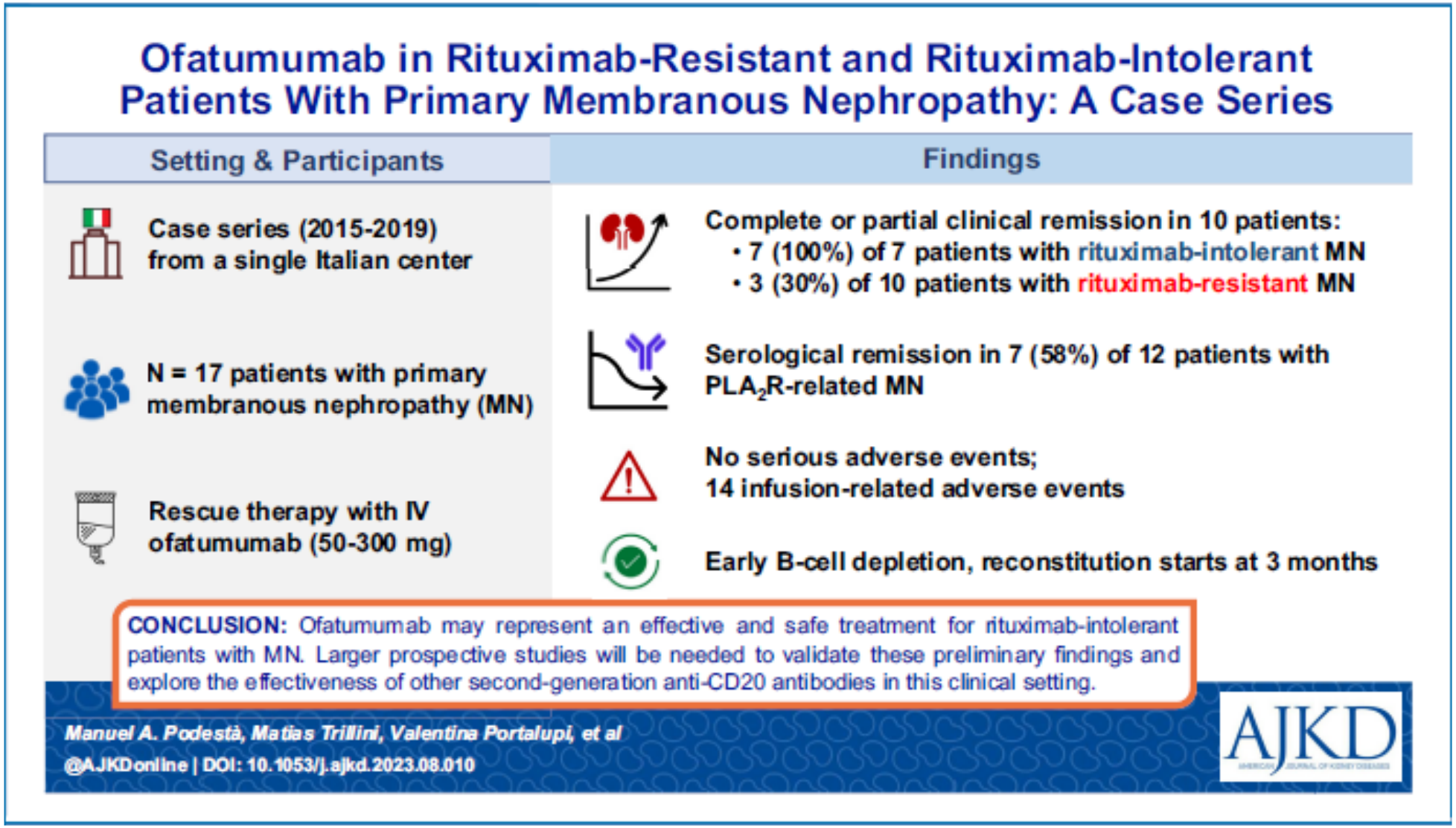
Xiaole Su[1,2,3,4], Binxin Wu[1,2,3,4], Xuan Tie[1,2,3], Xiaojiao Guo[1,2,3], Rongrong Feng[1,2,3], Xi Qiao[1,2,3] and Lihua Wang[1,2,3]

Outcomes	Overall	Grouped 1		Grouped 2	
		Initial therapy	Second-line therapy	RTX-resistant	RTX-naive
Clinical outcomes					
Number of patients	59	20	39	14	45
CR + PR	50 (84.7%)	18 (90.0%)	32 (82.1%)	9 (64.3%)	41 (91.1%)
CR	20 (33.9%)	7 (35.0%)	13 (33.3%)	3 (21.4%)	17 (37.8%)
PR	30 (50.8%)	11 (55.0%)	19 (48.7%)	6 (42.9%)	24 (53.3%)
Nonresponse	9 (15.3%)	2 (10.0%)	7 (17.9%)	5 (35.7%)	4 (8.9%)
Immunologic outcomes[a]					
Number of patients with detectable anti-PLA_2R	48[b]	17	31[b]	10	38[b]
Immunologic remission	43 (89.6%)	16 (94.1%)	27 (87.1%)	7 (70.0%)	36 (94.7%)
Immunologic nonresponse	5 (10.4%)	1 (5.9%)	4 (12.9%)	3 (30.0%)	2 (5.3%)

Ongoing prospective trial : Chinese Clinical Trial Registry (https://www.chictr.org.cn, ChiCTR2400082133)

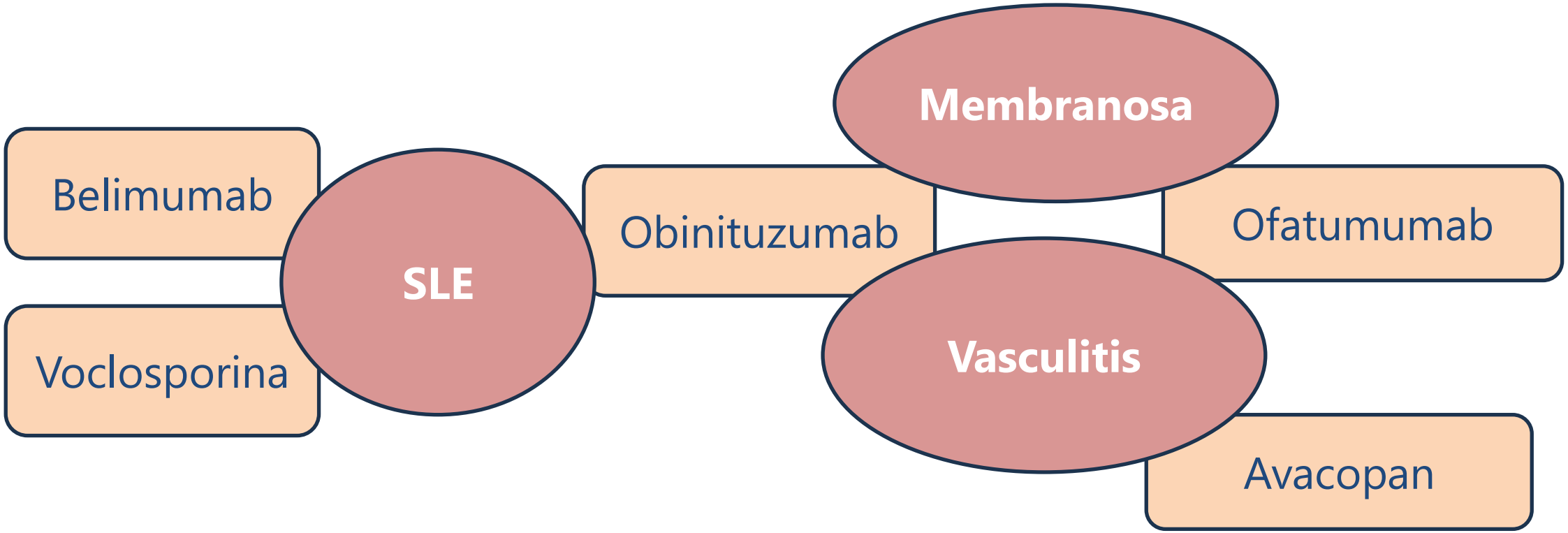
Xiaole Su et al, Kidney International Reports (2024) 9, 2386–2398

Nuevos Anti-CD20 en N Membranosa

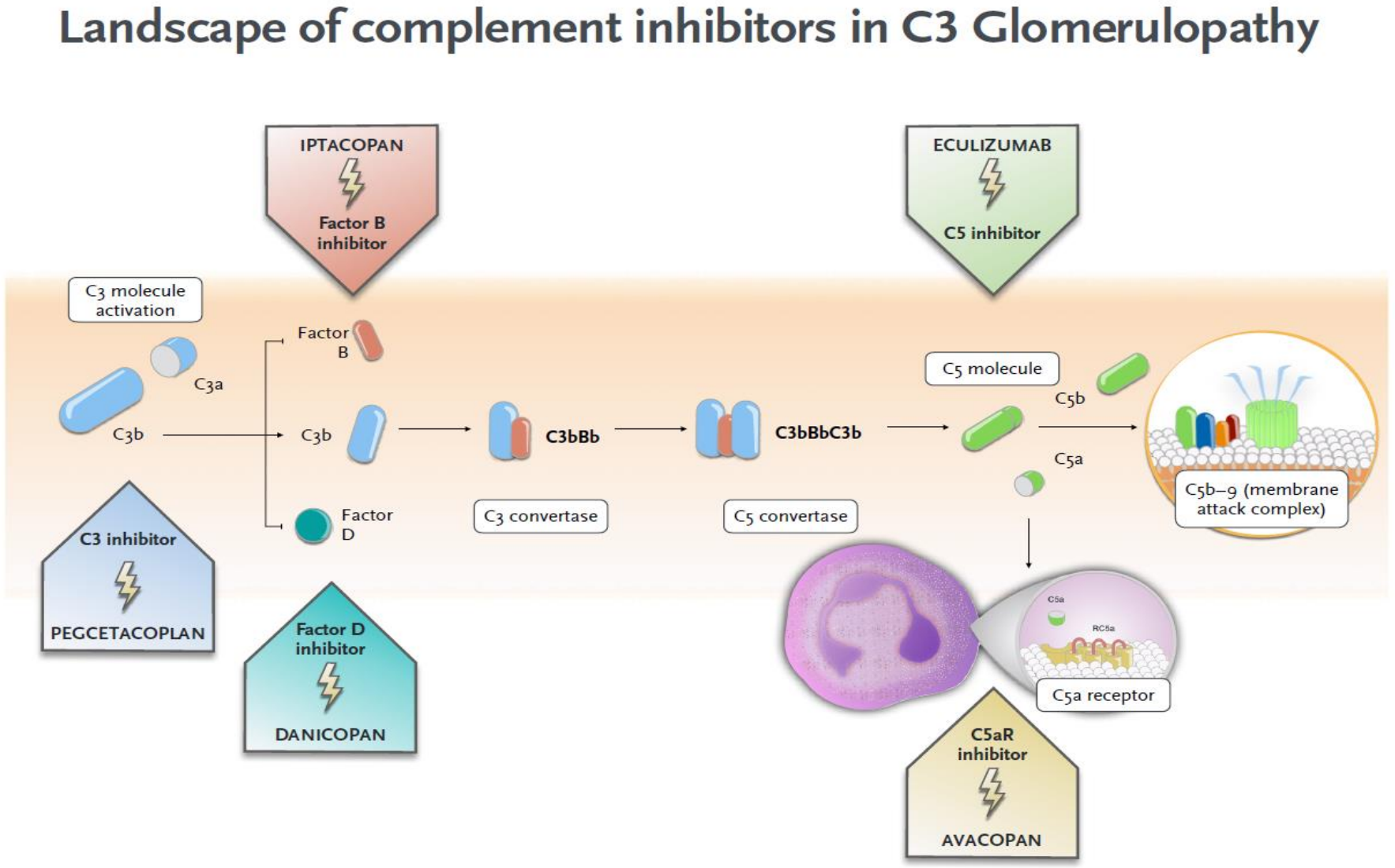


Am J Kidney Dis 83 (3): 340-349

Añadimos…


Membranosa
Belimumab
SLE
Obinituzumab
Ofatumumab
Voclosporina
Vasculitis
Avacopan

Targeting complement in C3 Glomerulopathy



Caravaca-Fontán et al. ERA NephManual Memmbranoproliferative GN and Complement-mediated Kidney Diseases

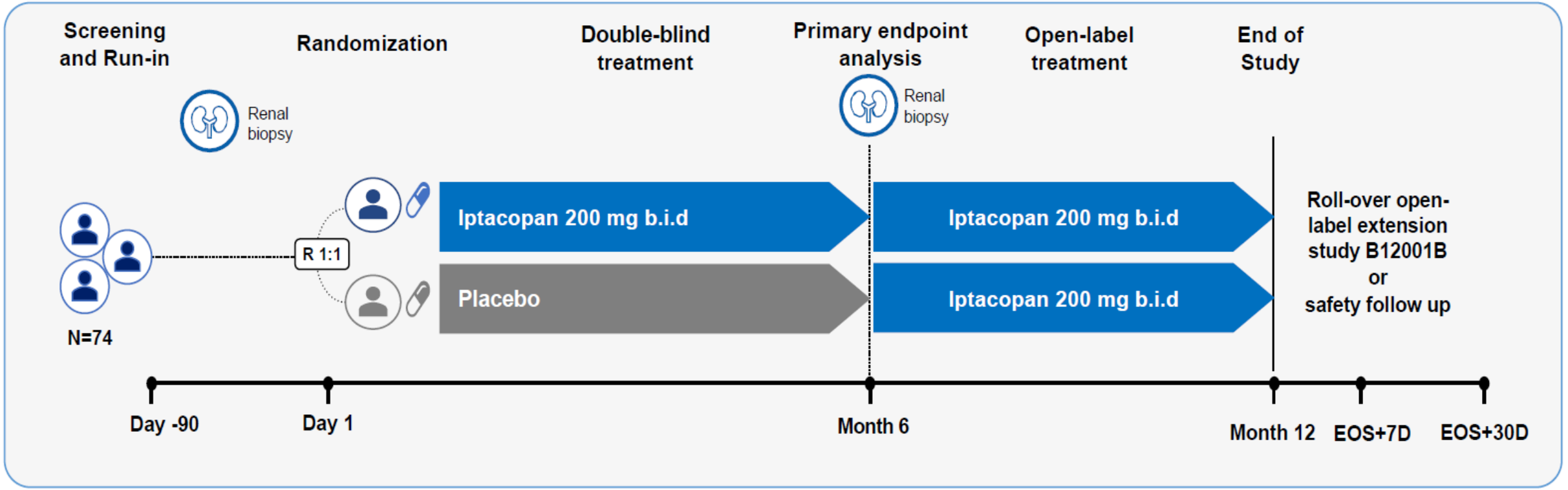
Targeting complement in C3 Glomerulopathy

Table S1: Clinical trials investigating the use of new complement inhibitors in C3 Glomerulopathy

Clinical trial	Drug	Target	Results	Transplant population
NCT03301467 (phase 2)	Avacopan	C5a receptor	Improvement in: - eGFR - Proteinuria - Histological chronicity index	Yes (2 patients)
NCT0383211 (phase 2)	Iptacopan	Factor B	1) Native kidneys: - Drop 45% proteinuria. - eGFR stabilization 2) Allograft: reduction of C3 deposition (even disappearance)	Yes (11 patients)
NCT04817618 (phase 3)			NA	Non-included
NCT04572854 (phase 2)	Pegcetacoplan	C3	NA	Yes (ongoing)
NCT03124368 (phase 2)	Danicopan	Factor D	NA	Non-included
NCT02682407 (phase 2)	Narsoplimab	MASP-2	NA	Non-included

Escudero-Saiz et al. Kidney Med. 6(6):100823

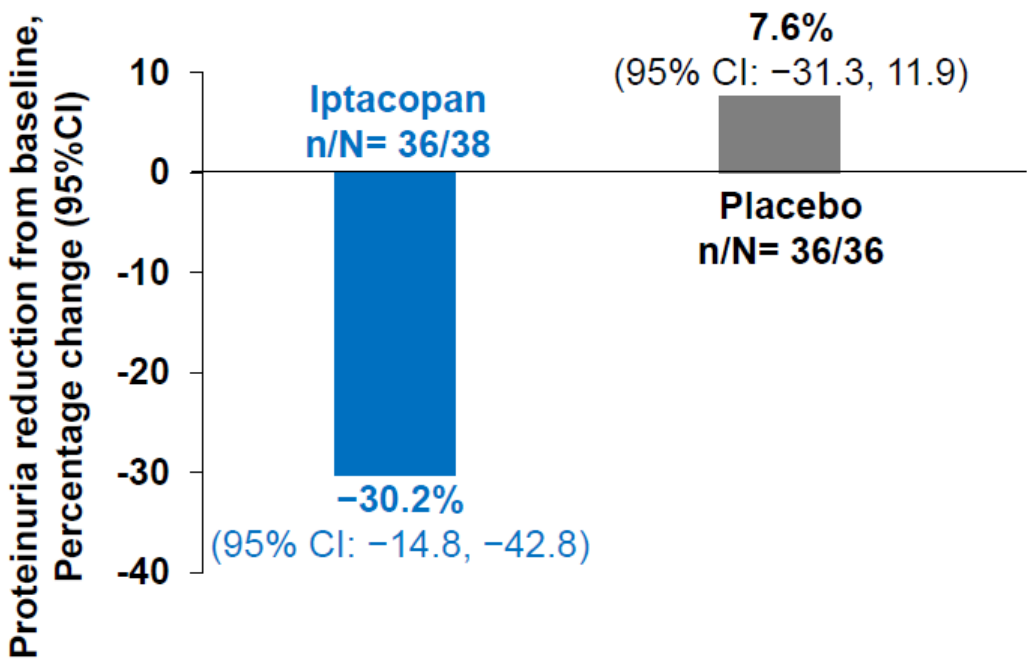
APPEAR-C3G: Study design



- APPEAR-C3G is a randomized, double-blind, parallel-group, multicenter, placebo-controlled Phase 3 study to evaluate the efficacy and safety of iptacopan 200 mg b.i.d vs placebo, on top of supportive care, in adult patients with C3G
- Results from 6-month double-blind treatment period are presented

PRIMARY ENDPOINT

Iptacopan achieved a statistically significant and clinically meaningful reduction in 24h-UPCR at Month 6



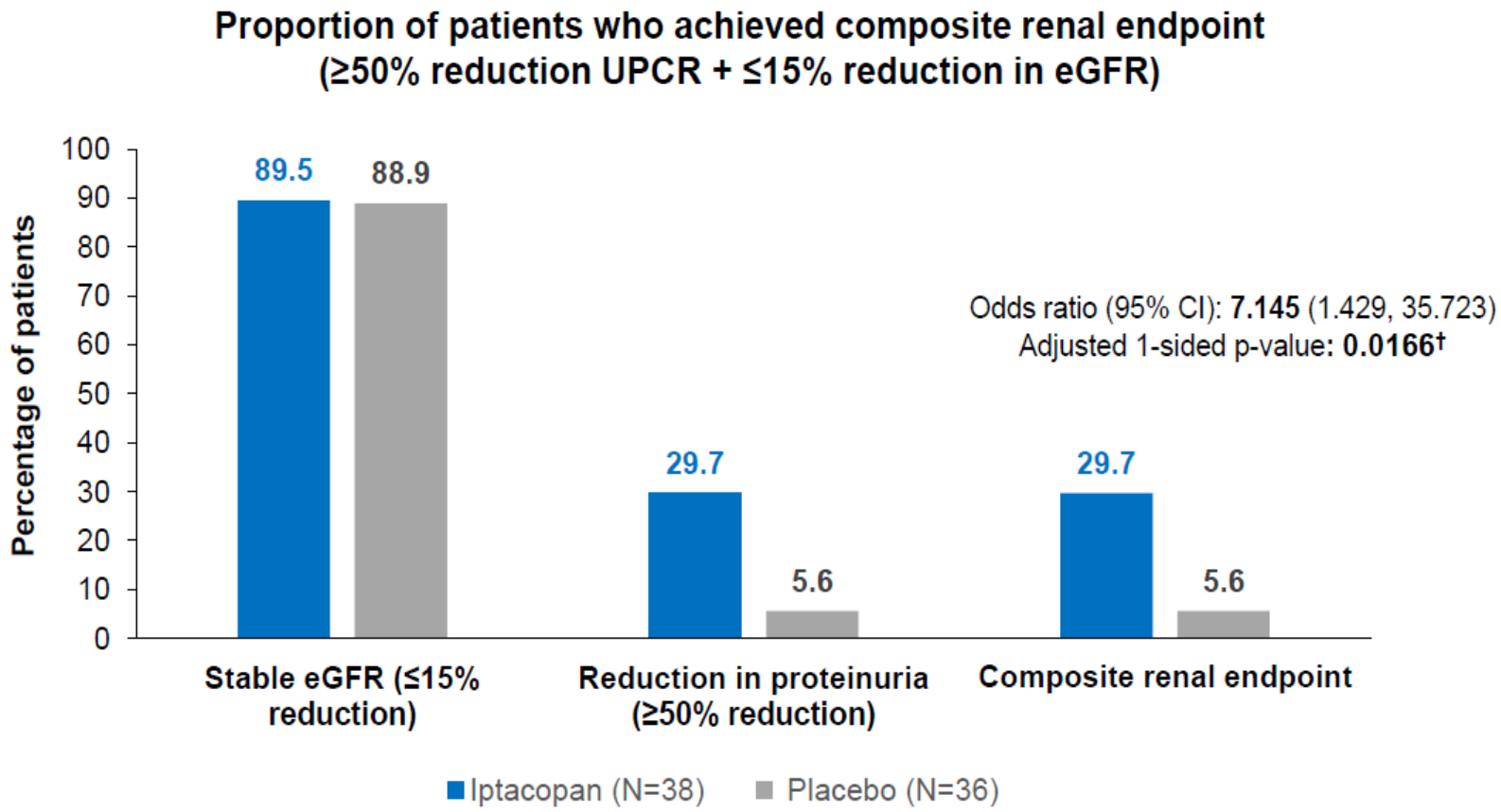
Relative percent reduction between iptacopan and placebo at Month 6 (95% CI):
35.1%; 1-sided p-value: **0.0014**

David Kavanagh et al , Late breaking clinical trials 61th ERA Congress

SECONDARY ENDPOINT

Iptacopan treatment resulted in significantly more patients meeting the composite renal endpoint at 6 months

Results driven by the proteinuria reduction component



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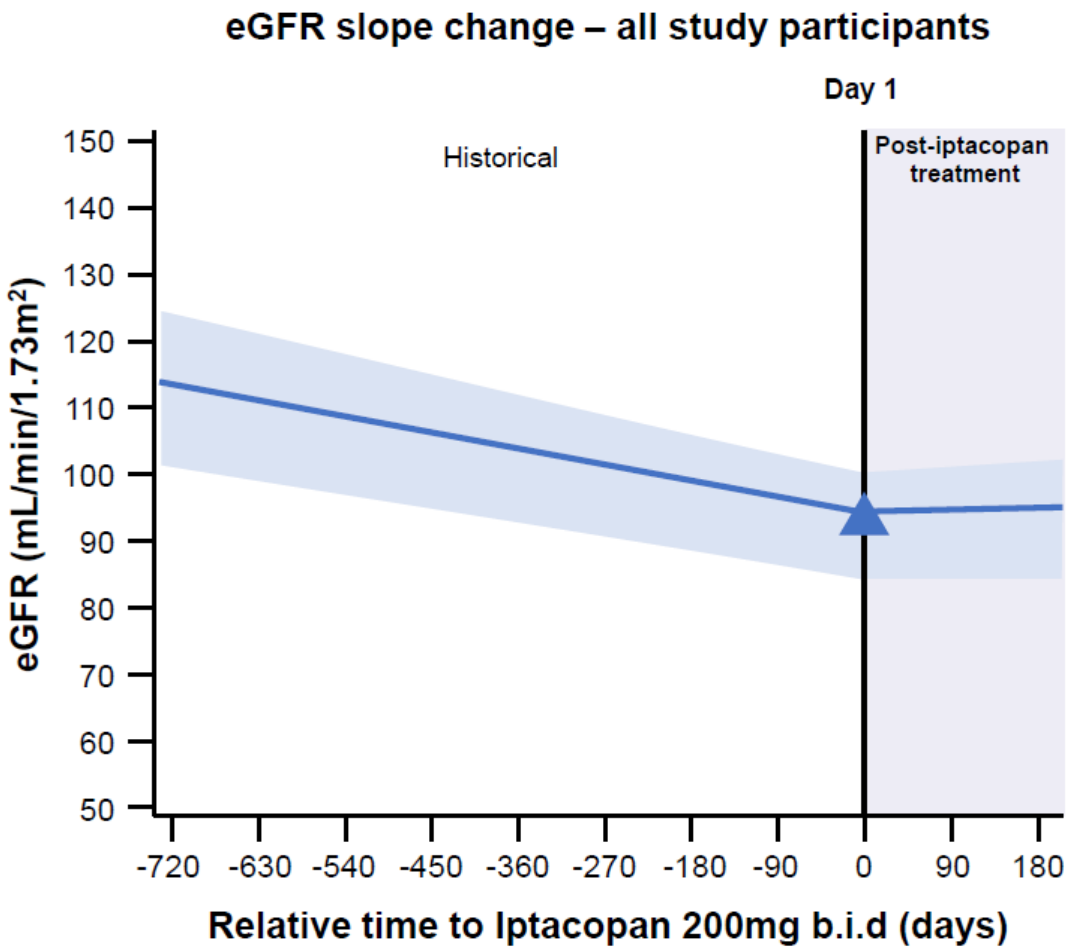
PRE-SPECIFIED EXPLORATORY ENDPOINT

Iptacopan treatment led to improvements in trajectory of renal function decline compared to historical patients' trend

61ST ERA CONGRESS STOCKHOLM & VIRTUAL MAY 23-26, 2024

	eGFR slope (mL/min/1.73m²/year)		
	Pre-treatment slope	**Post-treatment slope**	**Change in slope**
Estimate (95% CI)	**-7.35** (-10.39, -4.32)	**0.90** (-2.87, 4.66)	**8.25** (4.49, 12.01)
P-value			<0.0001



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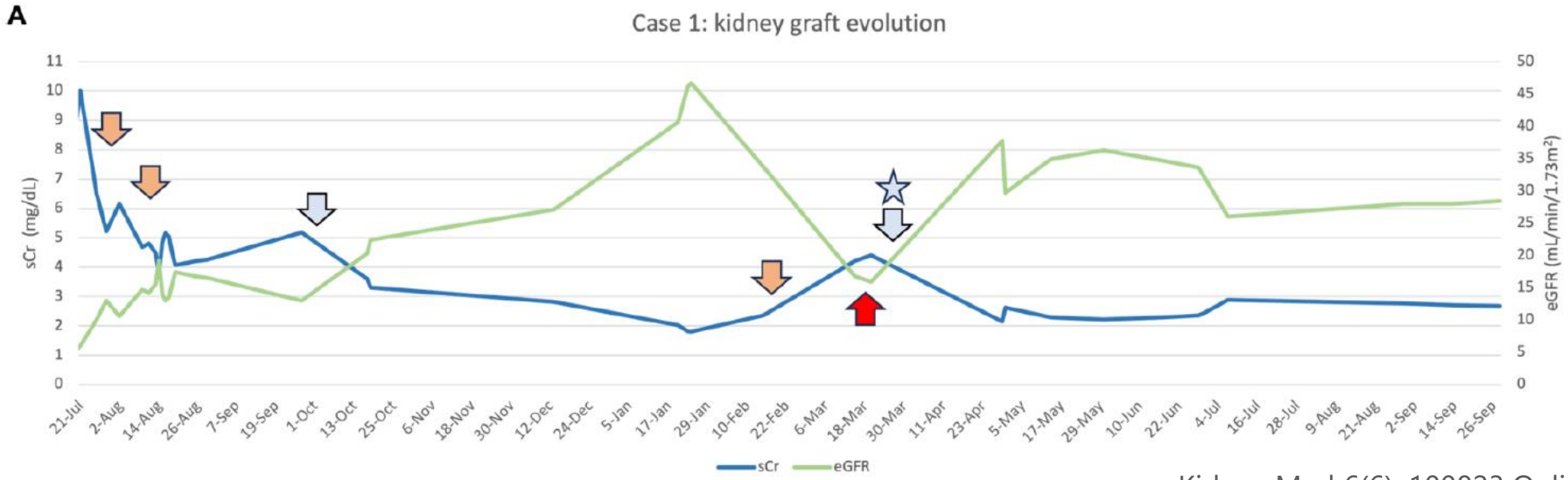
Caso clínico

Case Report

Kidney Medicine

Factor B Inhibition with Iptacopan in Recurrent C3 Glomerulopathy Following Kidney Transplant: A Report of Two Cases

Víctor J. Escudero-Saiz, Ángela Gonzalez, Adriana García-Herrera, Ana B. Larque, Andrew S. Bomback, Laura Morantes, Marta Martínez-Chillarón, Júlia Ollé, Elena Guillén, Marc Xipell, Alicia Molina-Andújar, Diana Rodríguez, Elena Cuadrado, Judit Cacho, Carolt Arana, Núria Esforzado, Carla Bastida, Esteban Poch, Fritz Diekman, David Cucchiari, Luis F. Quintana, and Miquel Blasco



Kidney Med 6(6): 100823 Online April 2024

Caso clínico

IgA con proliferación extracapilar

Tto con CFM + Rituximab + corticoides

Evolución a ERC terminal

Trasplante renal de donante vivo

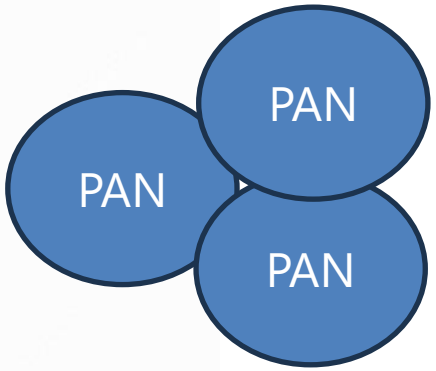
IgA con proliferación extracapilar

Tto con CFM + Rituximab + corticoides

Proteinuria > 1g/g

Leve descenso de FG: nueva Bx renal

Extensa proliferación extracapilar



Targeting complement in IgAN

Table 2: Summary of clinical trials with complement inhibitors in IgAN.

Agent	Target/mechanism of action	Compound/route	Company	Trial registration no./trial name	Phase	Design	Primary outcome	Results/status
Narsoplimab (OMS721)	MASP-2/LP inhibition	Monoclonal antibody against MASP-2/intravenous injection	Omeros	NCT02682407	2	Substudy 1: single-arm open-label study	Safety and tolerability	- Safe and well tolerated
						Substudy 2: RCT followed by open-label		- Proteinuria reduction with preserved eGFR
				NCT03608033/ ARTEMIS-IGAN	3	Randomized, double-blind, placebo-controlled	Change of proteinuria from baseline at 36 weeks	Ongoing
Iptacopan (LNP023)	Factor B/AP inhibition	Small molecule/orally administered	Novartis	NCT03373461	2	Randomized, double-blind, dose-ranging, parallel-group adaptive design	Safety and tolerability	- Well tolerated - Reduction in proteinuria - Strong inhibition of alternative pathway
				NCT04578834/ APPLAUSE-IgAN	3	Multi-center, randomized, double-blind, placebo-controlled	Ratio to baseline in UPCR (9 months) and annualized total eGFR slope (24 months)	Ongoing
IONIS-FB-L_{RX} (RG6299)	Factor B/antisense inhibitor of complement factor B	Oligonucleotide/ subcutaneous injection	Ionis	NCT04014335	2	Single-arm, open-label study	Change of proteinuria from baseline at 29 weeks	Ongoing

Caravaca-Fontán F et al, Targeting complement in IgA nephropathy CKJ 2023, vol 16, Suppl 2

Targeting complement in IgAN

Table 2: (Continued)

Agent	Target/mechanism of action	Compound/route	Company	Trial registration no./trial name	Phase	Design	Primary outcome	Results/status
Pegectacoplan (APL-2)	C3/AP inhibition	Pegylated peptide/subcutaneous injection	Apellis	NCT03453619	2	Single-arm, open-label study	Safety and efficacy in reduction of proteinuria at Week 48	Ongoing
Pelecopan (BCX9930)	Factor D/AP inhibition	Small molecule/orally administered	BioCryst Pharmaceuticals	NCT05162066	2	Open-label, proof-of-concept study	Safety and tolerability Percent change from baseline in UPCR	Terminated, no results available
Vemircopan (ALXN2050)	Factor D/AP inhibition	Small molecule/orally administered	Alexion	NCT05097989	2	Randomized, double-blind, placebo-controlled study	Percentage proteinuria change at Week 26	Ongoing
Ravulizumab (ALXN1210)	C5/TP inhibition	Monoclonal antibody/intravenous injection	Alexion/AstraZeneca	NCT04564339	2	Randomized, double-blind, placebo-controlled study	Percentage proteinuria change at Week 26	Ongoing
Cemdisiran (ALN-CC5)	C5/TP inhibition	Small interfering RNA/subcutaneous injection	Alnylam	NCT03841448	2	Randomized, double-blind, placebo-controlled study	Percentage proteinuria change at Week 32	Ongoing
Avacopan (CCX168)	C5aR1/inhibition of anaphylatoxin	Small molecule/orally administered	Chemocentryx	NCT02384317	2	Single-arm open-label study	Change in slope of the UPCR from the 8-week run-in period through the 12 weeks	Improvement in UPCR slope, with ~50% improvement in 3/7 patients

eGFR: estimated glomerular filtration rate; MASP-2: Mannan-associated lectin-binding serine protease-2; RCT: randomized controlled trial; UPCR: urinary protein-to-creatinine ratio.

Caravaca-Fontán F et al, Targeting complement in IgA nephropathy CKJ 2023, vol 16, Suppl 2

Targeting complement in IgAN

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IONIS-FB-L_{RX} (RG6299)	Factor B/antisense inhibitor of complement factor B	Oligonucleotide/ subcutaneous injection	Ionis	NCT04014335	2	Single-arm, open-label study	Change of proteinuria from baseline at 29 weeks	Ongoing

Caravaca-Fontán F et al, Targeting complement in IgA nephropathy CKJ 2023, vol 16, Suppl 2

APPLAUSE-IgAN: Phase 3, multicenter, randomized, double-blind, placebo-controlled study (NCT04578834)

Eligibility criteria

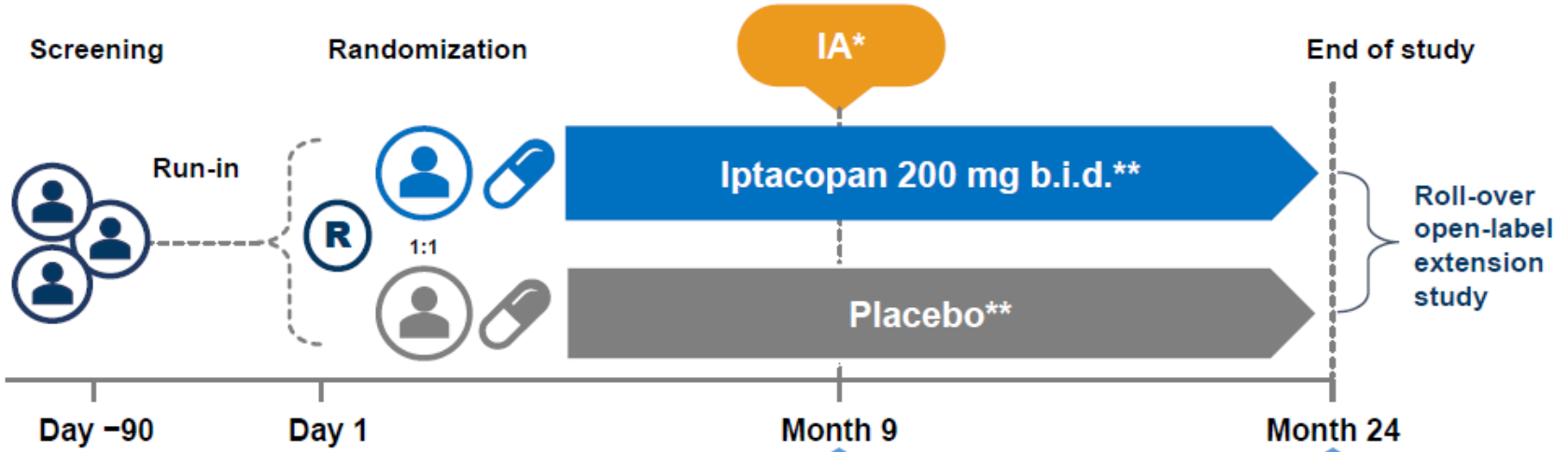
- Adults
- Biopsy-confirmed IgAN
- Proteinuria ≥1 g/g based on 24h-UPCR despite maximally tolerated RASi for ≥3 months, with or without SGLT2i

Main study population

eGFR ≥30 mL/min/1.73 m²

SRI population

eGFR 20–<30 mL/min/1.73 m²



*Pre-specified. **On top of optimal supportive care per KDIGO guidelines (maximally-tolerated stable [3 months] dose of RASi therapy) with or without other background therapy such as SGLT2i. Patients continued their supportive care treatment throughout the study.

IA primary endpoint

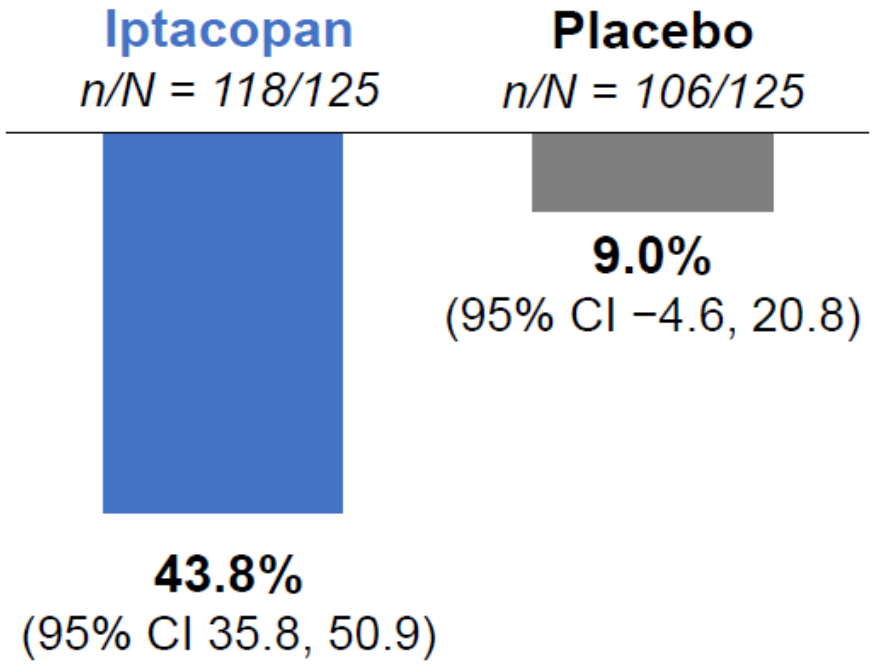
- Based on the first 250 patients of the main study population who reached Month 9 or discontinued the study
- Performed using an MMRM including all 24h-UPCR values collected from baseline up to and including the Month 9 visit or up to initiation of rescue/alternative medication or KRT†

IA additional analyses presented here

- Subgroup analyses of IA primary endpoint using the same approach as the IA primary analysis
- Safety endpoints were summarized descriptively for all patients in main study population who were randomized and received treatment at the IA data cut-off; (n=443)

Iptacopan achieved a statistically significant and clinically meaningful reduction in 24h-UPCR at Month 9

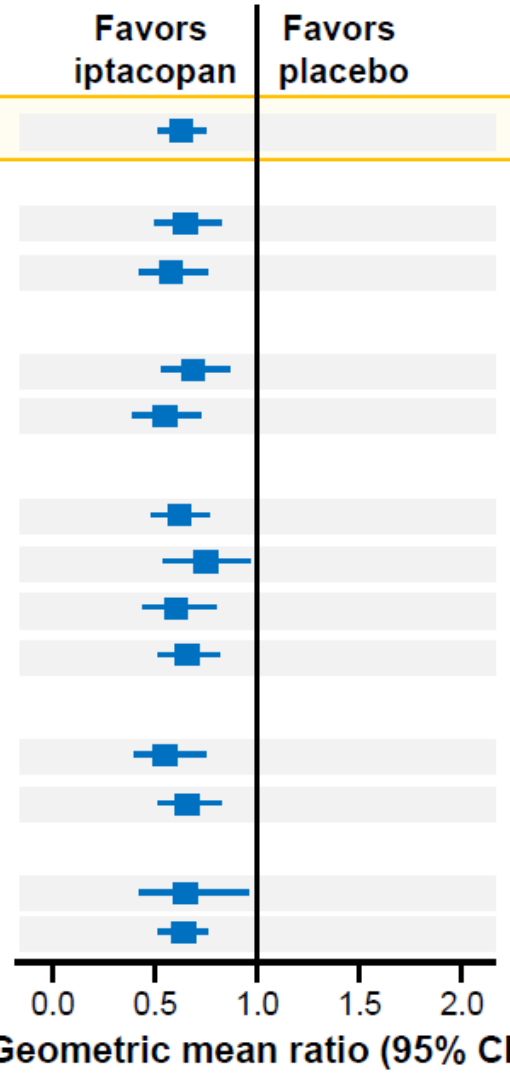
IA primary endpoint: Reduction in 24h-UPCR from baseline at Month 9



Relative percent reduction between iptacopan and placebo at Month 9:
38.3% (95% CI 26.0, 48.6); *P*<0.0001*

Proteinuria (24h-UPCR) reduction at Month 9 is consistent across prespecified subgroups

Group	Iptacopan n/N	Placebo n/N	Iptacopan vs placebo % reduction (95% CI)	
Overall	118/125	106/125	**38.3 (26.0, 48.6)**	*P*<0.0001*
Sex				
Male	68/71	49/60	35.5 (17.4, 49.7)	
Female	50/54	57/65	42.6 (24.5, 56.4)	
Geographic region†				
Asia	63/64	55/64	31.6 (13.4, 46.0)	
Non-Asia	55/61	51/61	45.5 (28.3, 58.5)	
Baseline 24h-UPCR category				
≥1.5 g/g	73/80	76/91	41.2 (26.0, 53.2)	
<1.5 g/g	45/45	30/34	27.3 (2.4, 45.9)	
≥2 g/g†	47/54	47/58	41.2 (20.9, 56.4)	
<2 g/g†	71/71	59/67	35.0 (18.8, 48.0)	
Baseline eGFR category†				
30–<45 mL/min/1.73m^2	32/36	27/34	45.4 (25.3, 60.1)	
≥45 mL/min/1.73m^2	86/89	79/91	35.1 (19.0, 48.0)	
SGLT2i use at baseline				
Yes	16/18	12/14	36.7 (4.4, 58.1)	
No	102/107	94/111	38.1 (24.4, 49.2)	



N, number of all patients included in the analysis (with non-missing baseline and covariates); n, number of patients with values non-missing/not imputed. *One-sided. †Stratification criteria at randomization.
CI, confidence interval; eGFR, estimated glomerular filtration rate; h, hour; SGLT2i, sodium-glucose transport protein 2 inhibitor; UPCR, urine–protein creatinine ratio.

Caso clínico

IgA con proliferación extracapilar

Tto con CFM + Rituximab + corticoides

Proteinuria > 1g/g

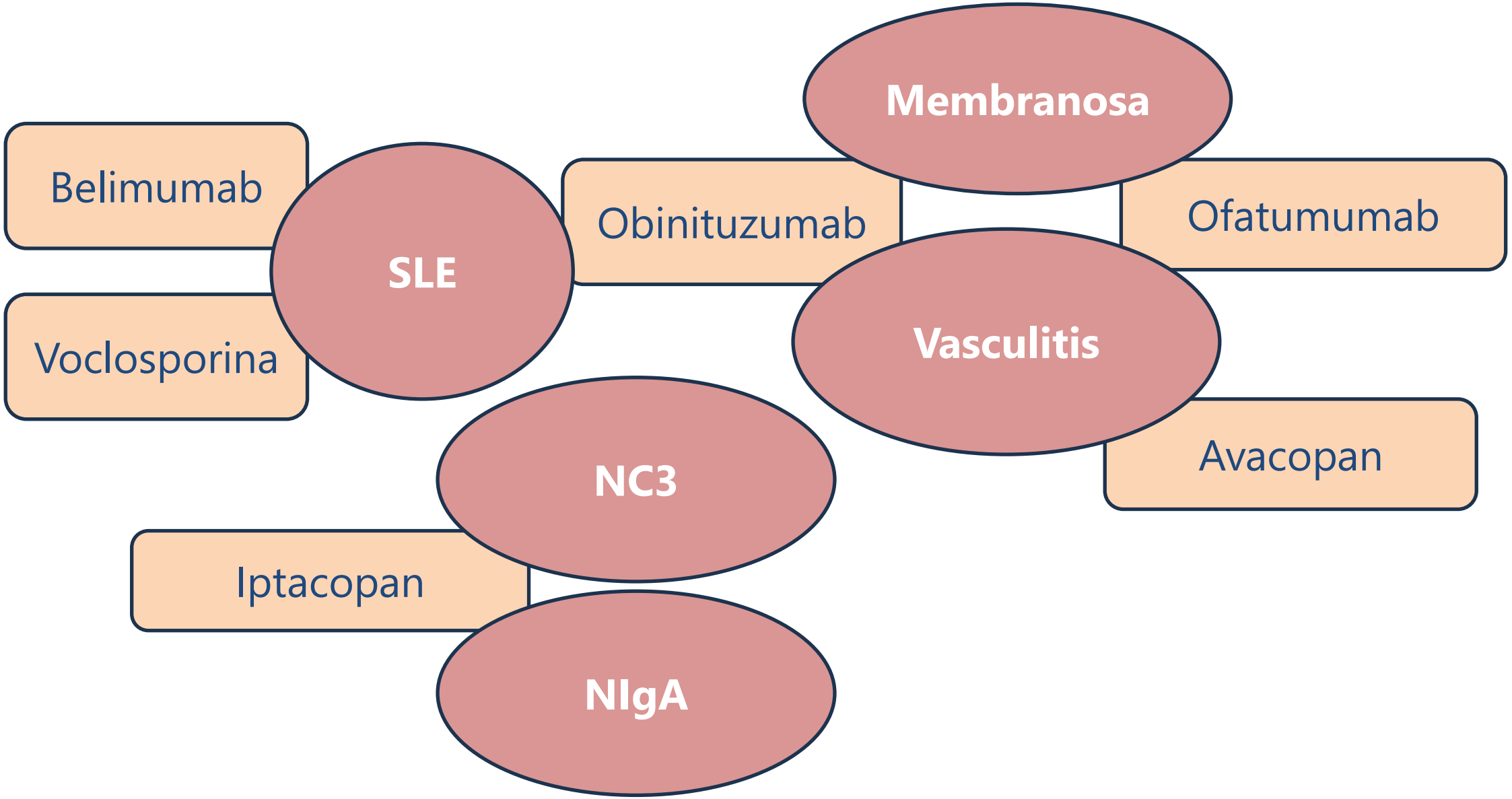
Leve descenso de FG: nueva Bx renal

Extensa proliferación extracapilar

IPTACOPAN

Mejoría de la proteïnúria por debajo 200mg/g

Para concluir



Mensajes para llevar a casa

- En **nefritis lúpica**: plantear triple terapia con belimumab o voclosporina sobre todo en pacientes con necesidad de reducción de corticoides.
- En **vasculitis**, plantear terapia con avacopan en pacientes con necesidad de reducción rápida de corticoides y en pacientes con FG más bajos y proteinuria.
- En **NIgA** y **NC3** tener en cuenta posibilidad de contar con bloqueadores del complemento.
- **Nuevos AntiCD20** como alternativa en pacientes resistentes a Rituximab o que han presentado reacción a Rituximab

SGAN
sociedad gallega de nefrología

Graciñas

Gracias

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08025, Barcelona
Barcelona, España

Contacto

xbarros@fundacio-puigvert.es

934169739 busca 4659

Móvil 629258514