Welcome to

ERKNet Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

15/02/22

KDIGO Guideline on Immune Glomerulopathies II: Lupus/Vasculitis

Speaker: Dario Roccatello (Turin, Italy)

Moderator: Jack Wetzels (Nijmegen, Netherlands)

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The European
Rare Kidney Disease
Reference Network

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LUPUS NEPHRITIS

Approach to the diagnosis of kidney involvement in systemic lupus erythematosus (SLE)

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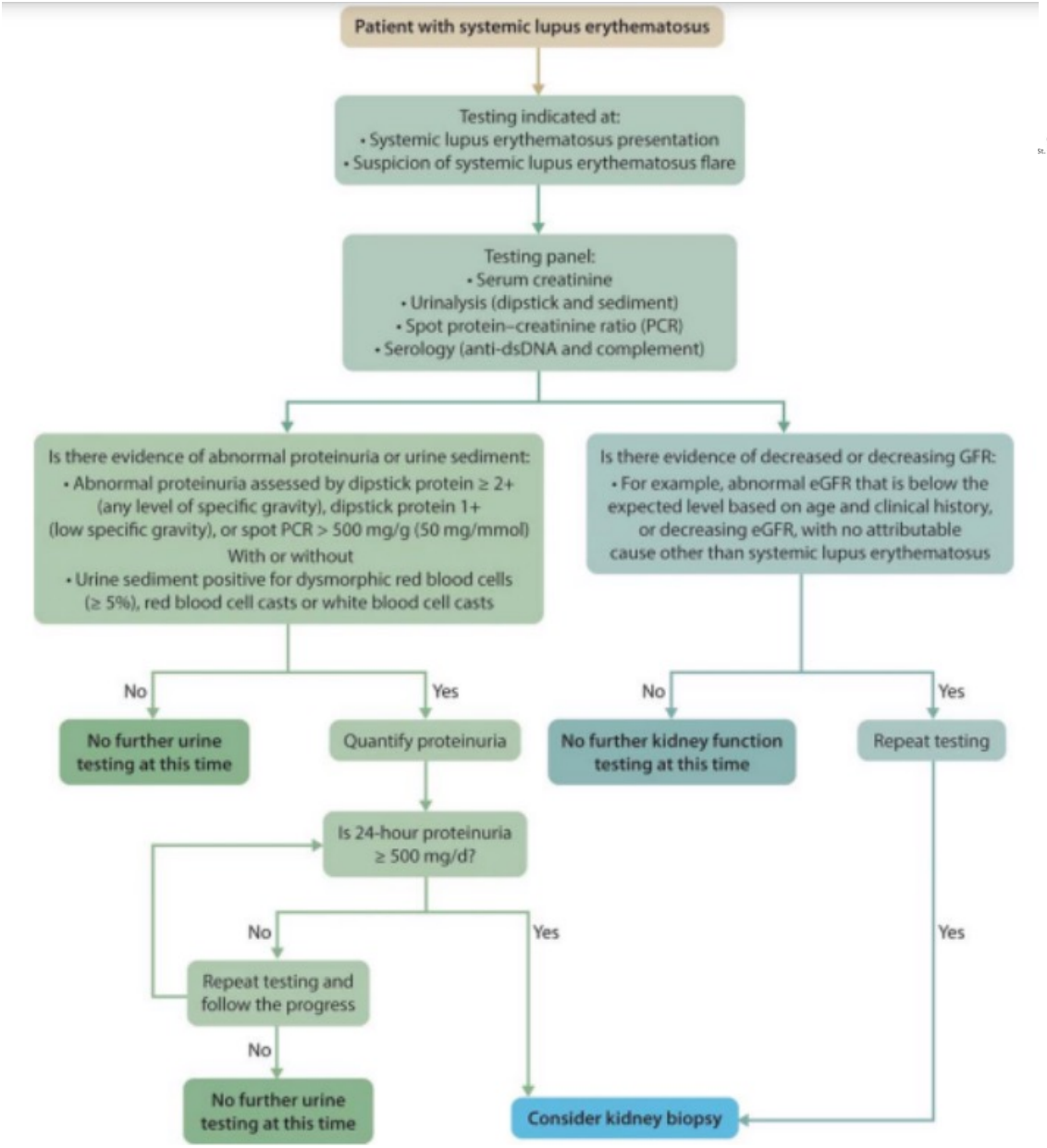

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Activity and chronicity items included in LN kidney biopsy report

Components of the activity index	Score	Calculating the activity score Extent of lesion	Points
• Endocapillary hypercellularity	0–3	Not present	0
• Neutrophils and/or karyorrhexis	0–3	Present in <25%	1
• Fibrinoid necrosis	(0–3) × 2	Present in 25%–50%	2
• Hyaline deposits (wire loop and/or hyaline thrombi)	0–3	Present in >50%	3
• Cellular/fibrocellular crescents	(0–3) × 2		
• Interstitial inflammation (interstitial leukocytes)	0–3		
	Total: 0–24		

Items included into the NIH chronicity score	Score	Calculating the chronicity score Extent of lesion	Points
• Total glomerulosclerosis (global + segmental)	0–3	Present in <10%	0
• Fibrous crescents	0–3	Present in 10%–25%	1
• Interstitial fibrosis	0–3	Present in 25%–50%	2
• Tubular atrophy	0–3	Present in >50%	3
	Total: 0–12		

Other histologic findings not included in the activity or chronicity score

- Foot process effacement (lupus podocytopathy)
- Collapsing lupus glomerulopathy
- Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis)

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Commonly used definitions of response to therapy in 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 • Stabilization or improvement in kidney function (±10%–15% of baseline) • 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 • Stabilization or improvement in kidney function (±10%–15% of baseline) • 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

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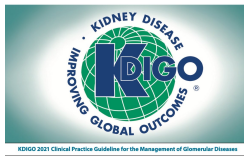

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General management of patients with lupus nephritis

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 contraindicated

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Question 1:

Do you consider Mycophenolate mofetil and Cyclophosphamide to be similarly effective?

- Yes

- No

Question 2:

Do you have any preference for Cyclophosphamide dosing regimens in induction phase?

- CYC (NIH scheme)
- CYC (Eurolupus)
- Oral CYC (1.5 mg/Kg/day for 2-6 months)

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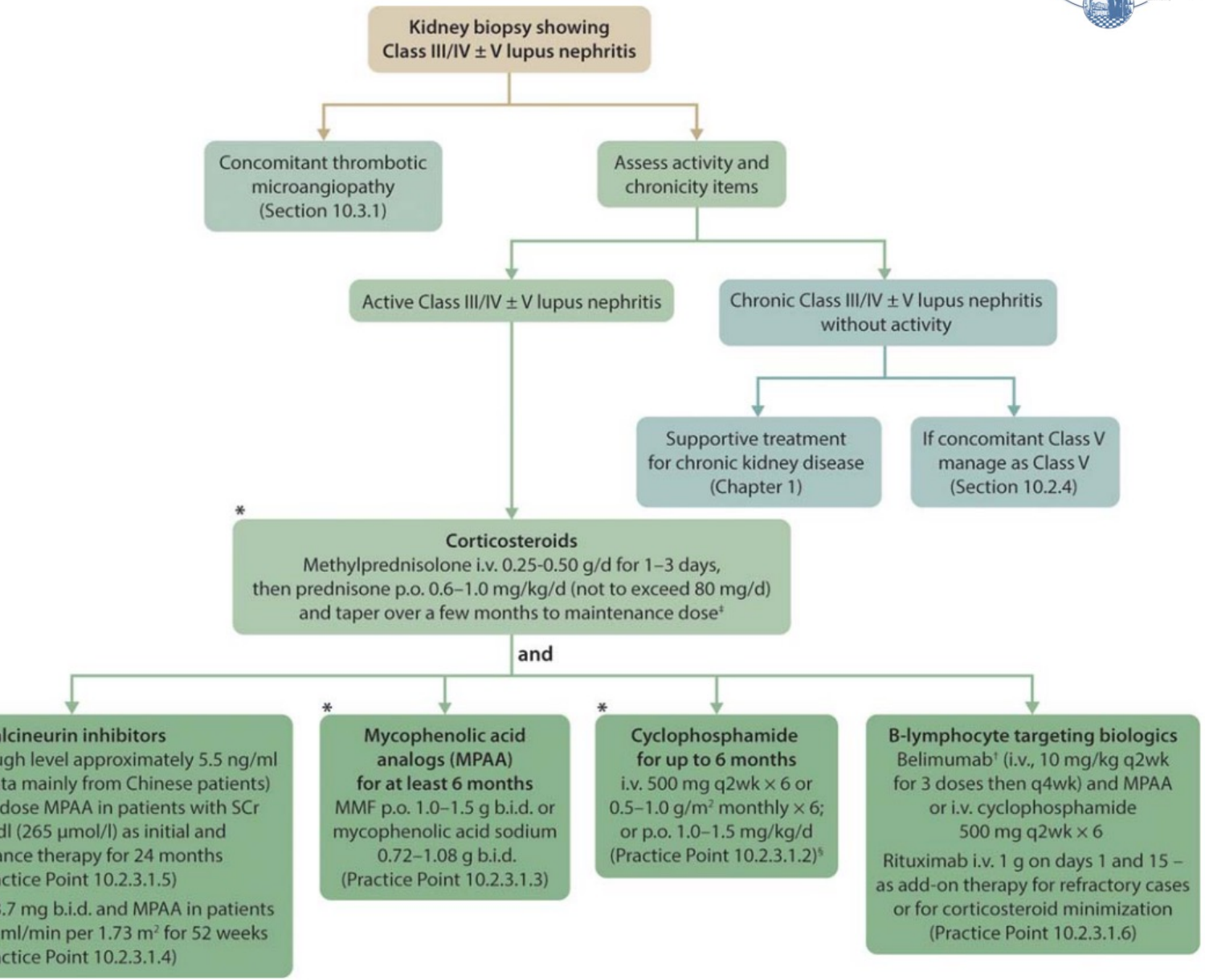
Cyclophosphamide dosing regimens, combined with glucocorticoids, in initial treatment for active Class III/IV LN

	Intravenous cyclophosphamide – modified (NIH regimen)	Intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of Afro/Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

Recommended approach for initial therapy of active Class III/IV LN



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

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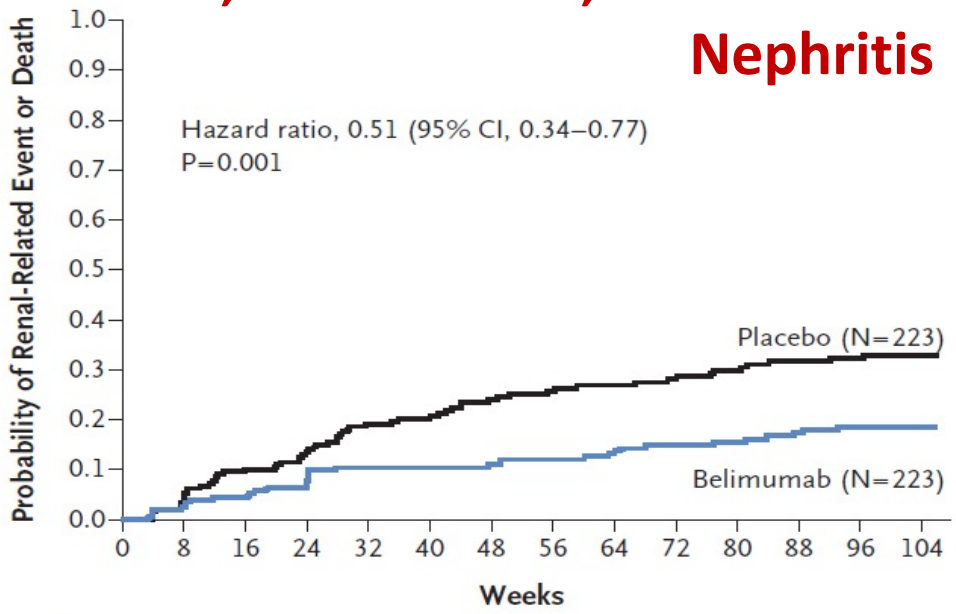

No. at Risk

Placebo	203	185	175	154	147	137	129	126	120	116	112	110	78
Belimumab	209	192	186	167	162	159	157	151	142	139	133	130	102

Time to a Renal-Related Event or Death in the Modified Intention To-Treat Population.

B

Event	Belimumab (N=223)	Placebo (N=223)
	no.	
Any event	35	63
Death from any cause	1	2
Progression to ESKD	0	1
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	17	39
Treatment failure related to kidney event	16	20

Furie et al, NEJM 2020

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Example of glucocorticoid regimens for LN

	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

Question 3:

What is your favorite maintenance regimen in SLE?

- Mycophenolate mofetil
- Cyclophosphamide
- Cyclosporine
- Prolonged glucocorticosteroid regimen

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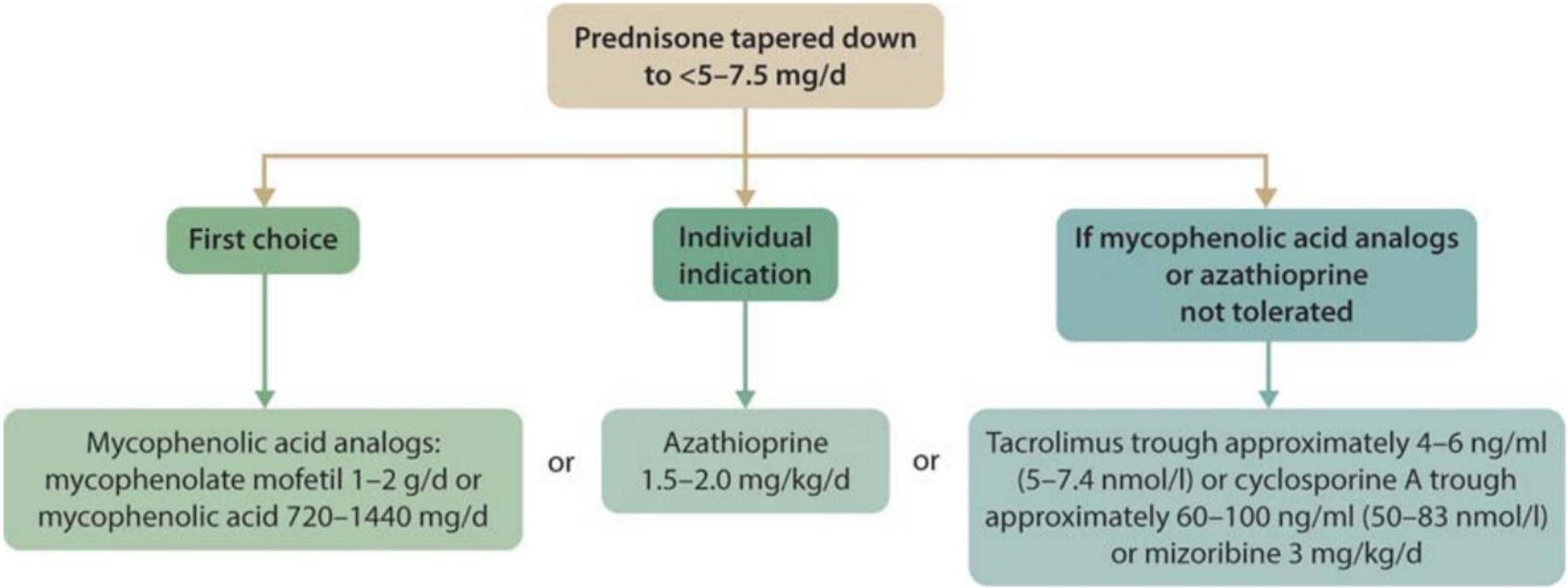
Maintenance therapy for Class III and Class IV LN



Maintenance immunosuppressive regimens in patients with LN

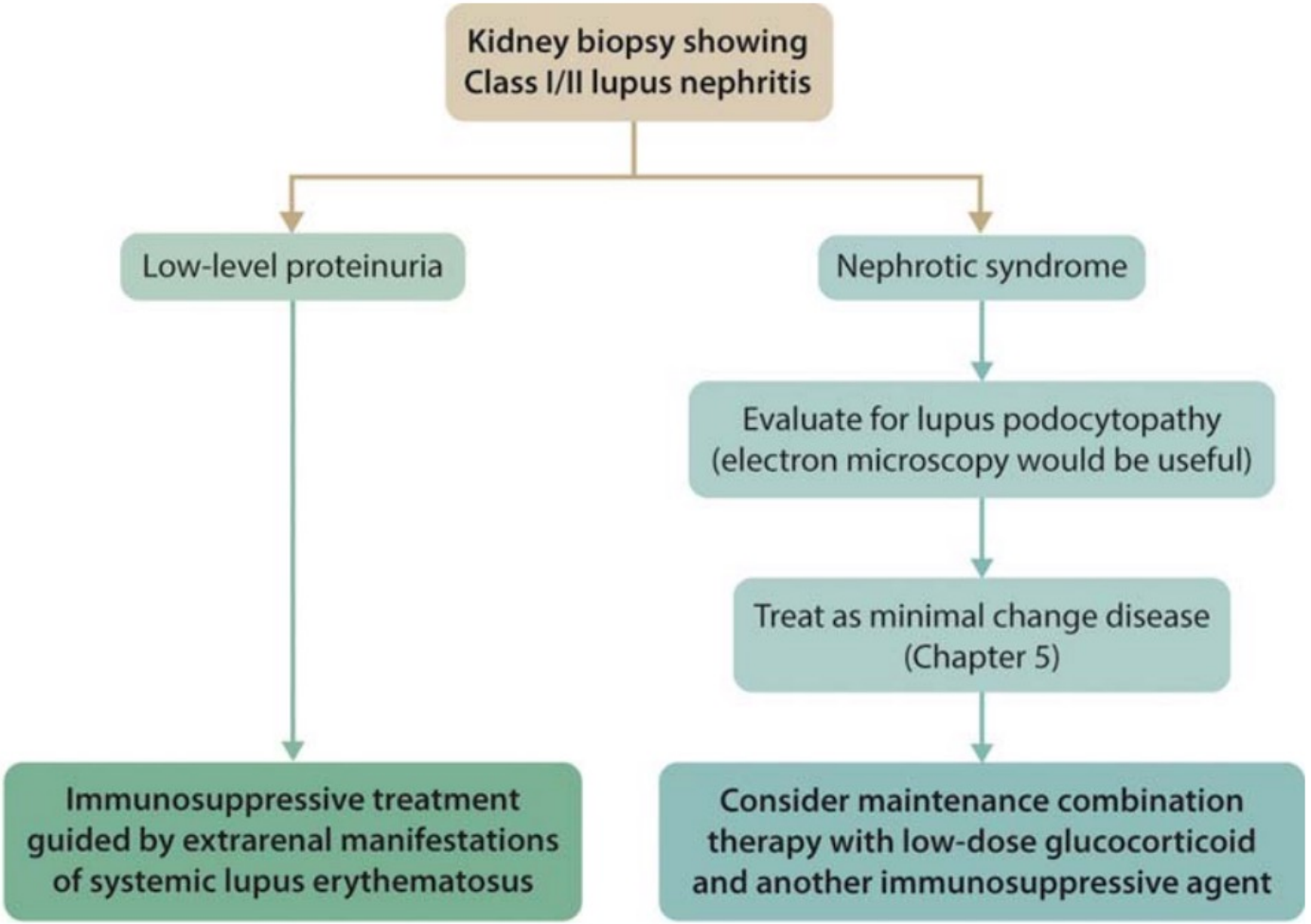
Maintenance immuno-suppressive regimens	Low-dose glucocorticoid AND				
	Mycophenolic acid analogs	AZA	CNI	Mizoribine	Mycophenolic acid analogs and CNI
Comments	Preferred treatment based on high-quality evidence Lower flare rate than alternative regimens such as AZA	Safe in pregnancy Low medication cost	Tacrolimus or cyclosporine Safe in pregnancy	Data mostly from Japanese patients	Data predominantly from Chinese and Japanese patients Long-term safety data of triple immunosuppression required

Question 4:

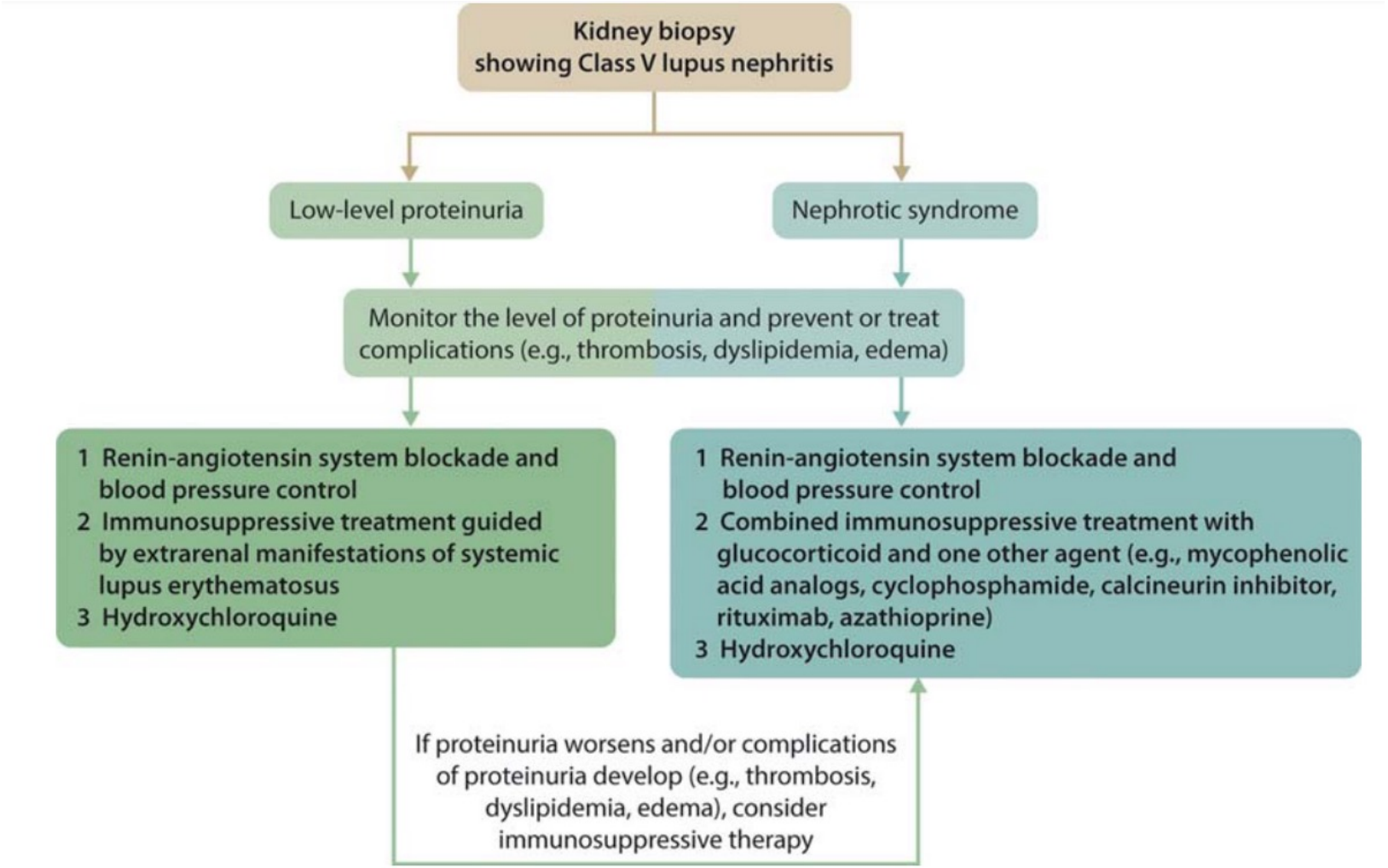
How long immunosoppressive maintenance therapy should be continued in SLE?

- ≥36 months
- Indefinitely
- Until kidney biopsy shows the absence of inflammation

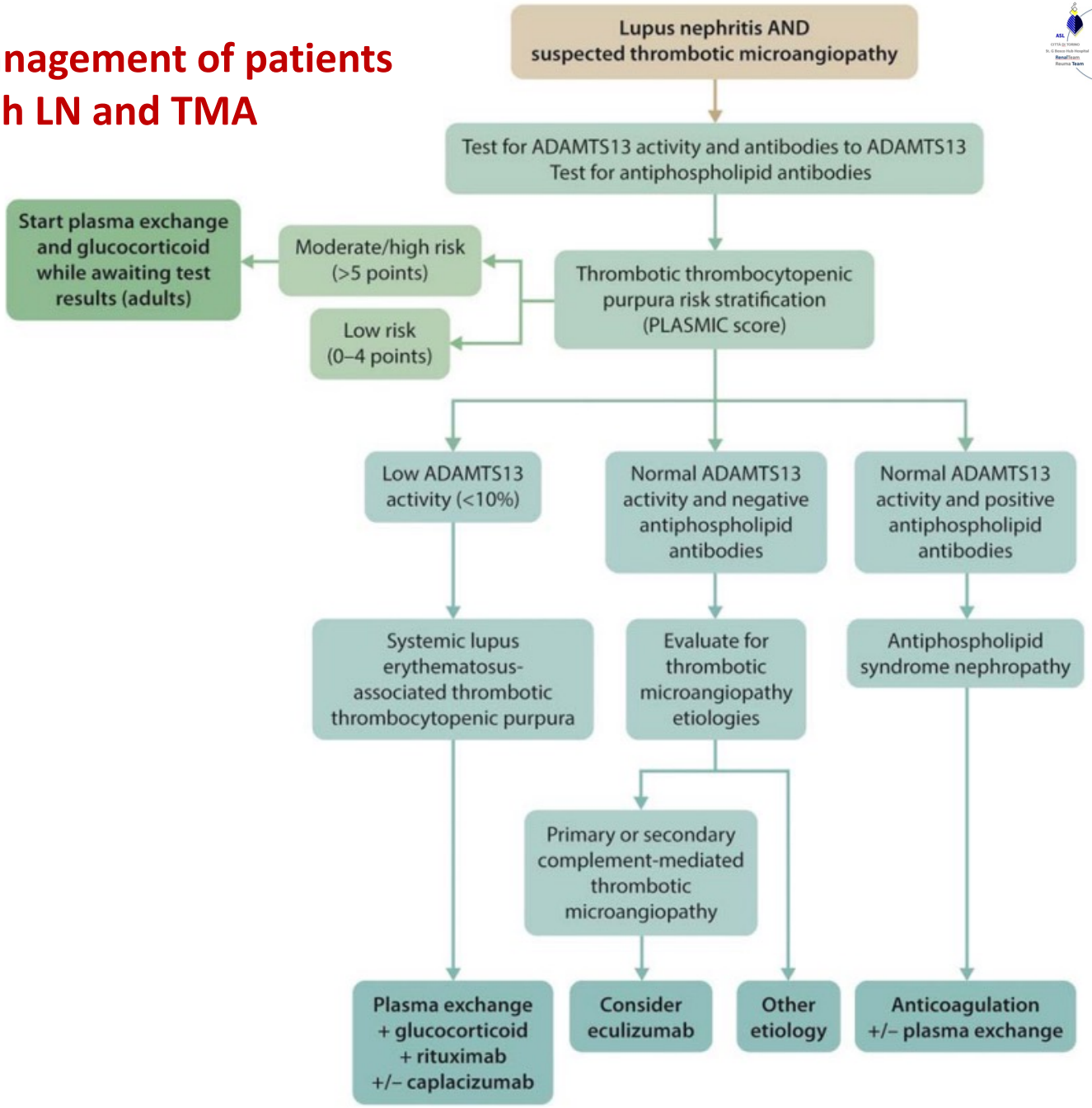
Immunosuppressive treatment for patients with Class I or Class II LN



Management of patients with pure Class V LN



Management of patients with LN and TMA



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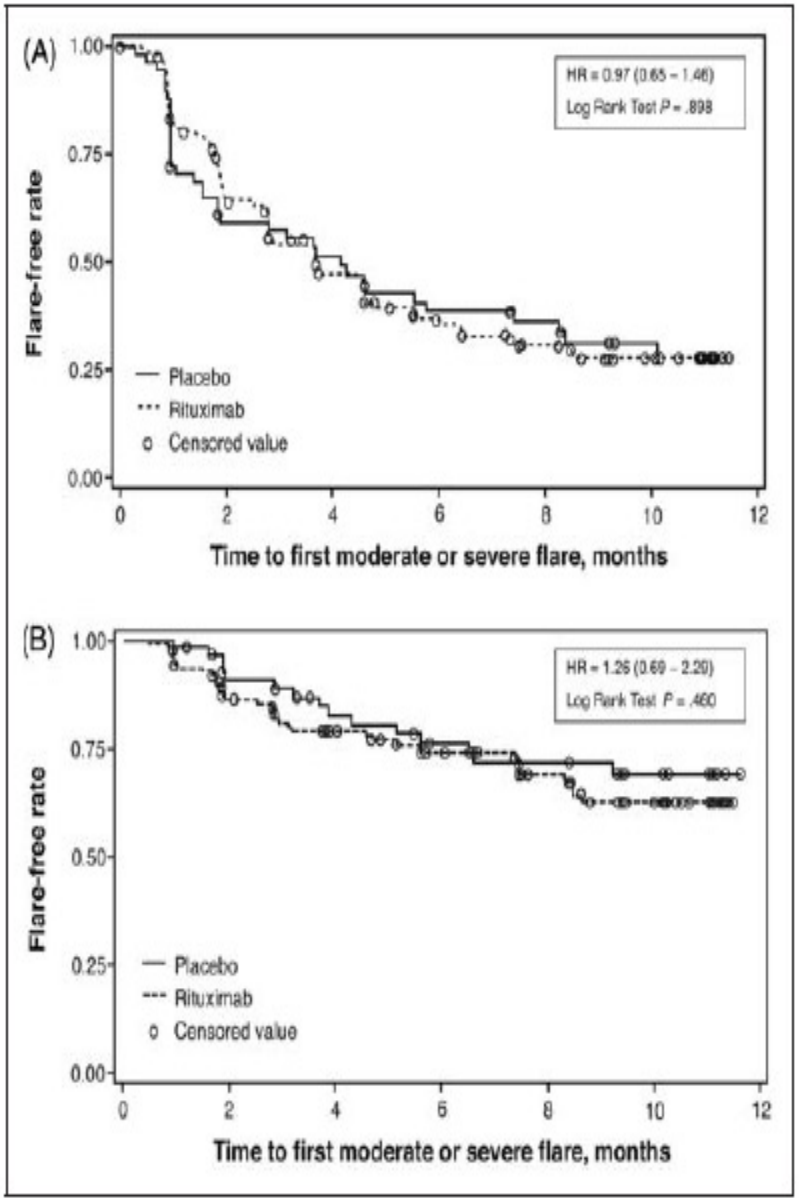
Management of patients who show unsatisfactory response to initial therapy for active LN

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 (mycophenolic acid analogs to cyclophosphamide-based regimen or vice versa)
5	Consider the following in patients refractory to first-line treatment regimens: • Combined mycophenolic acid analogs and calcineurin inhibitor therapy, or • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide



Background: numberless open trials mainly in refractory patients published in the last two decades showing CR+PR always ranged between 60 and 100 %

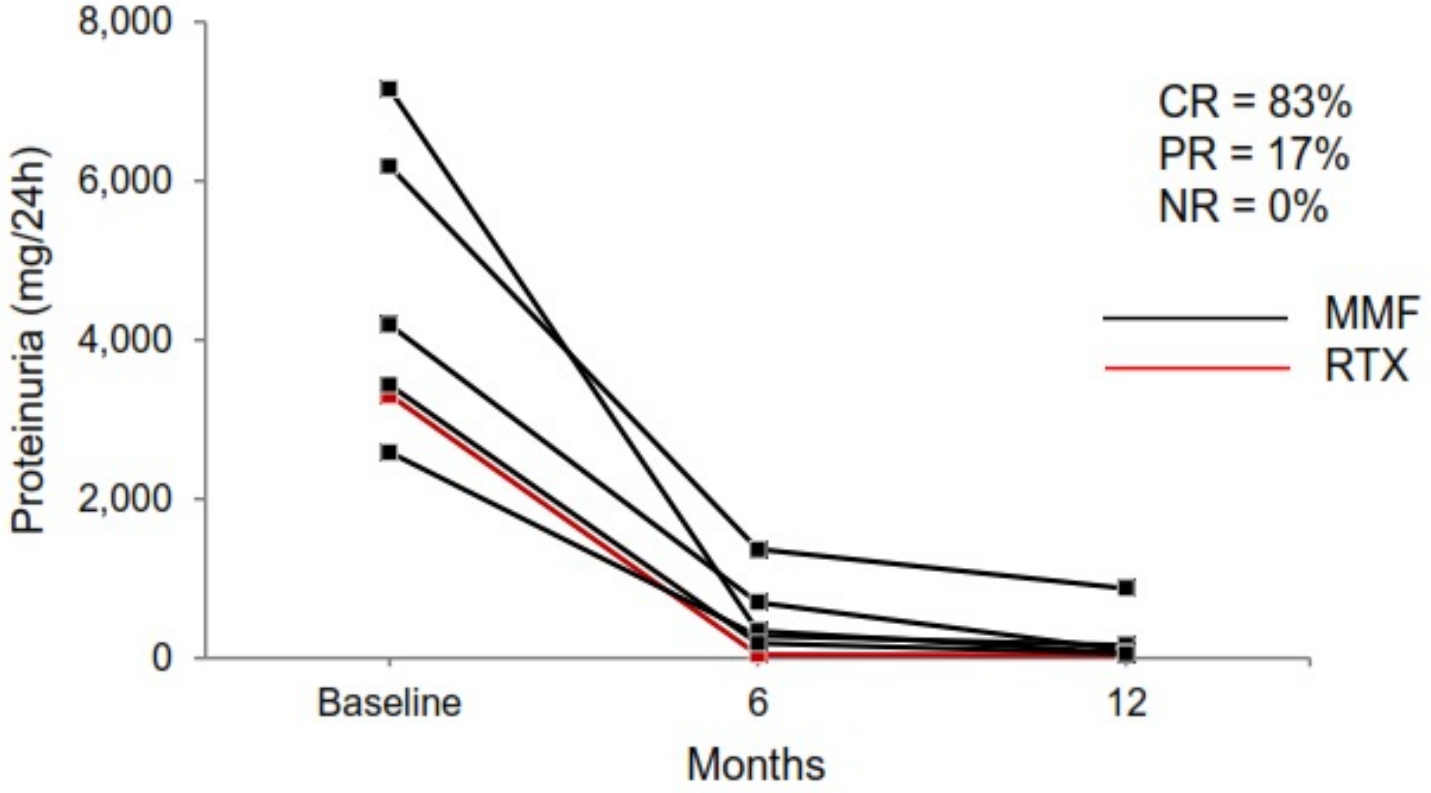
Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus

The Randomized, Double-Blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial

LUNAR trial

Randomixed double blind placebo-controlled trial of RTX for proliferative Lupus Nephritis

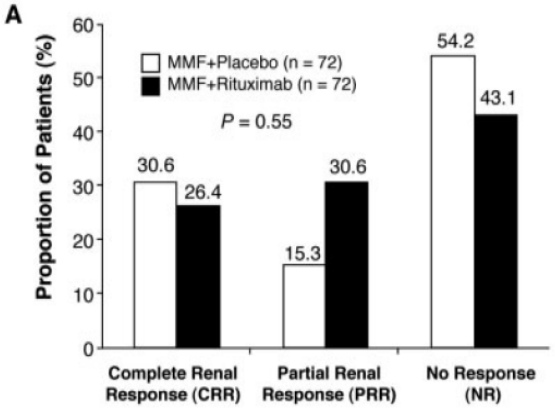
"Standard of care" therapy with MMF plus RTX or Placebo

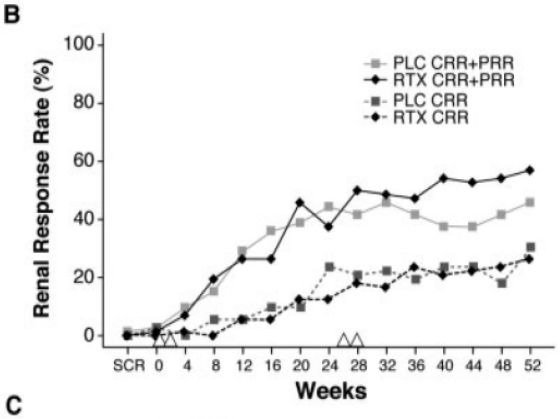


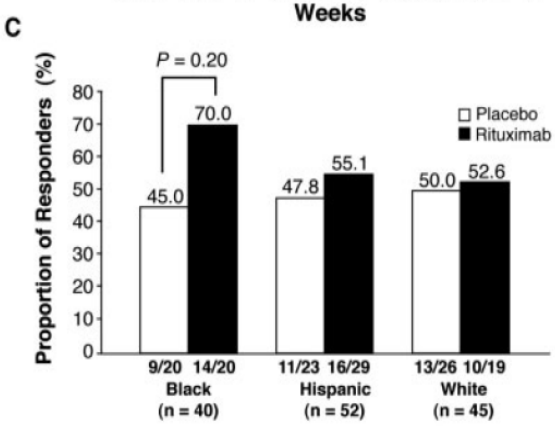
LUNAR Individual Site "X" Analysis = 6 patients

III = 1
IV-S (A/C) = 1
IV-S (A) = 1
IV-G (A) = 1
IV-S (A/C) + V = 2

Fervenza, personal communication







Efficacy end points

CR plus PR were 57 (RTX) vs 46%
Cyclo requirement at 52 weeks: 0 vs 9 pts
Overall trend: < proteinuria, > renal function

POINTS TO BE CONSIDERED

Backgroung therapy
# of centers involved
Selection of nonrefractory patients
Type of clinical outcome instruments
Relatively short follow-up (52 weeks vs 104 of Belimumab study)
Duration of B cell depletion
Extent of B cell depletion

Extent of Peripheral Blood B Cell Depletion after Rituximab needed to achieve Complete Response in LN

Table 1. Number of patients from the LUNAR trial treated with rituximab that achieved the three different definitions of B cell depletion at week 52 and 78 and maximum time to depletion in days

Definition of B Cell Depletion	Patients Who Achieved Depletion by Week 52, *n* (% of Total)	Patients Who Achieved Depletion by Week 78, *n* (% of Total)	Maximum Time to Achievement of Depletion in Days
CD19<20 cells/μl	68 (100)	68 (100)	86
CD19<5 cells/μl	68 (100)	68 (100)	182
CD19=0 cells/μl	53 (78)	53 (78)	365

LUNAR, the Lupus Nephritis Assessment with Rituximab study.

There was substantial **variability in peripheral blood B cell depletion** in patients with lupus nephritis treated with rituximab from Incomplete peripheral blood B cell depletion after rituximab in LN might correlate with **inability to reduce tubulointerstitial lymphoid aggregates** in the kidney, which together could be responsible for **inadequate response to treatment.**

Achievement of complete peripheral depletion (#0) as well as a duration of complete peripheral depletion (>71 days) were associated with complete response at week 78

Liliana Michelle Gomez Mendez et al. CJASN doi:10.2215/CJN.01070118

Obinotuzumab

type II MoAb anti-CD20

- ✓Does not elicitCD20 redistribution
- ✓Reduced CD20 internalization
- ✓Geater affinity for FcgammaRIII
- ✓Greater ADCC
- ✓More direct B-ceellkilling
- ✓Less reliance on CDCC

1 g or placebo on
day 1 and weeks 2, 24, 26.
Follow-up 104 weeks

Furie Ann Rheum Dis 2022

Table 1 Baseline characteristics and demographics

	Obinutuzumab (n=63)	Placebo (n=62)
Age—years	33.1±9.8	31.9±10.1
Female—no (%)	55 (87)	51 (82)
Region—no (%)		
Latin America and the Caribbean	38 (60)	47 (76)
Europe and Israel	18 (29)	7 (11)
USA	7 (11)	8 (13)
Hispanic or Latino ethnicity—no (%)	42 (67)	49 (79)
Race—no (%)		
White	28 (44)	26 (42)
American Indian or Alaska Native	11 (18)	17 (27)
Black or African American	6 (10)	5 (8)
Asian	3 (5)	2 (3)
Other or unknown	15 (24)	12 (20)
Prior history of lupus nephritis—no (%)	32 (51)	32 (52)
Class IV lupus nephritis—no (%)	40 (64)	35 (57)
Concomitant class V lupus nephritis—no (%)	20 (32)	17 (27)
Serum creatinine—mg/dL	0.87±0.34	0.80±0.33
eGFR—mL/min/1.73 m^2	102.0±30.6	102.1±32.9
UPCR—g/g	3.3±2.7	2.9±2.5
Anti-dsDNA Ab >30 IU/mL—no (%)	42 (67)	46 (74)
C3 <90 mg/dL—no (%)	43 (68)	37 (60)
C4 <16 mg/dL—no (%)	37 (59)	44 (71)

eGFR was calculated using the CKD-EPI creatinine equation.
Ab, antibody; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

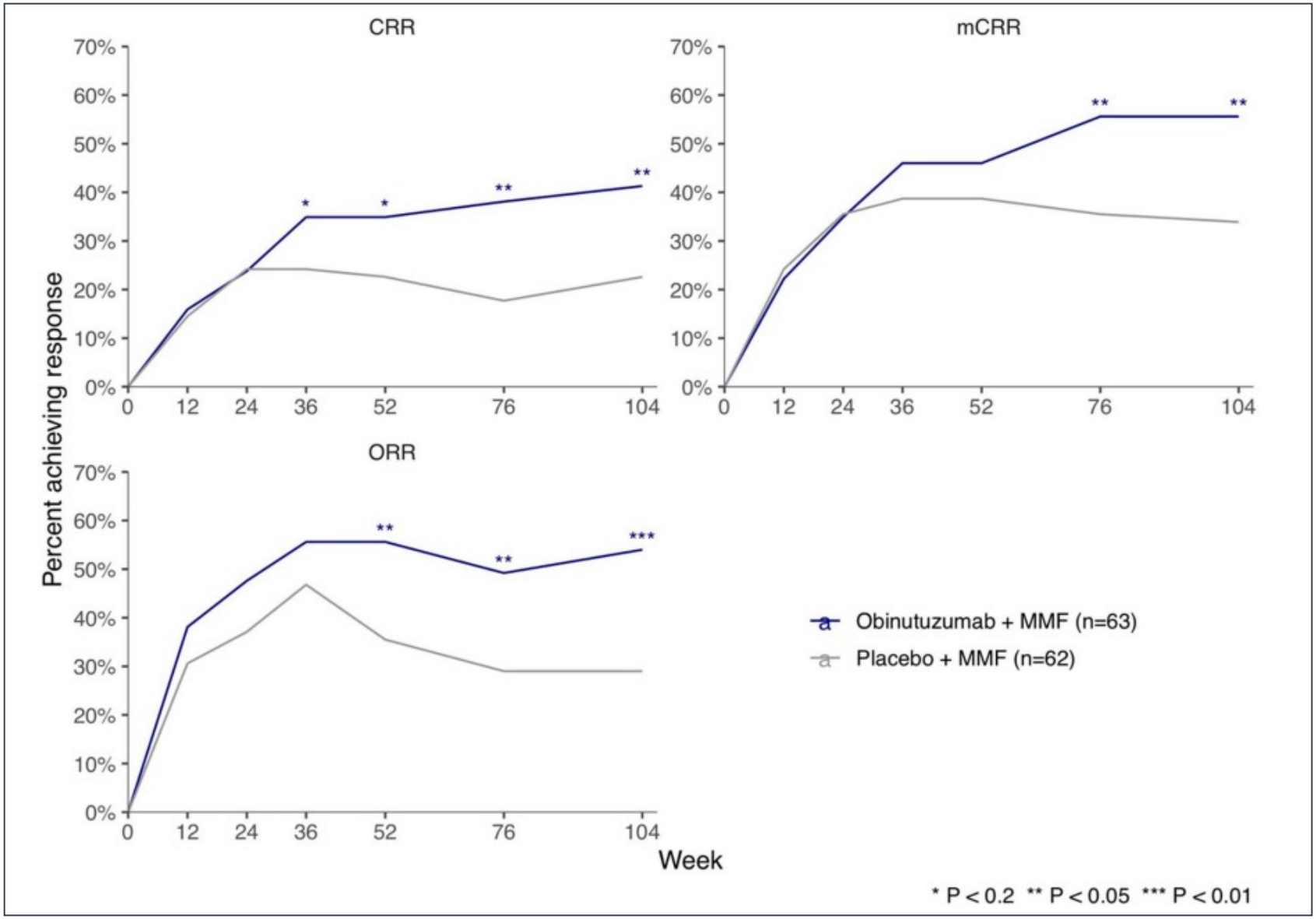
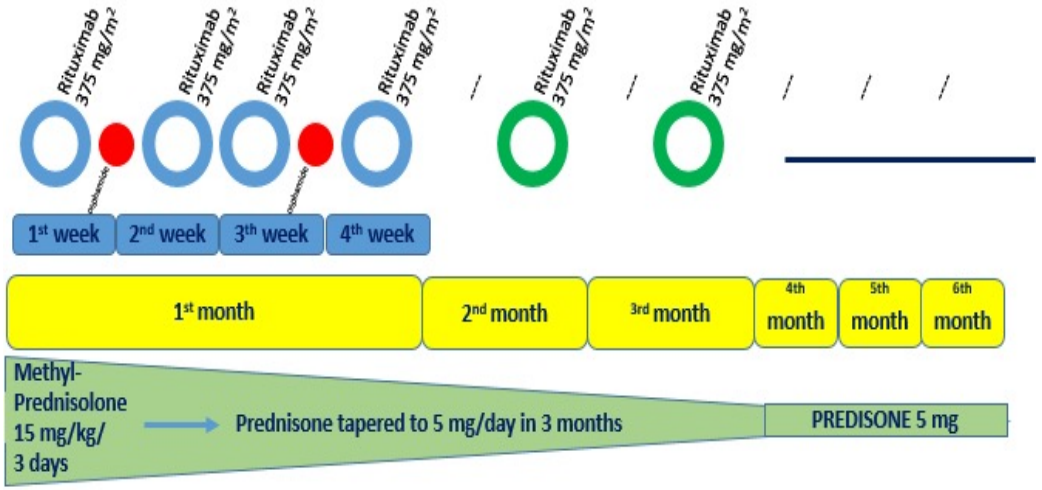
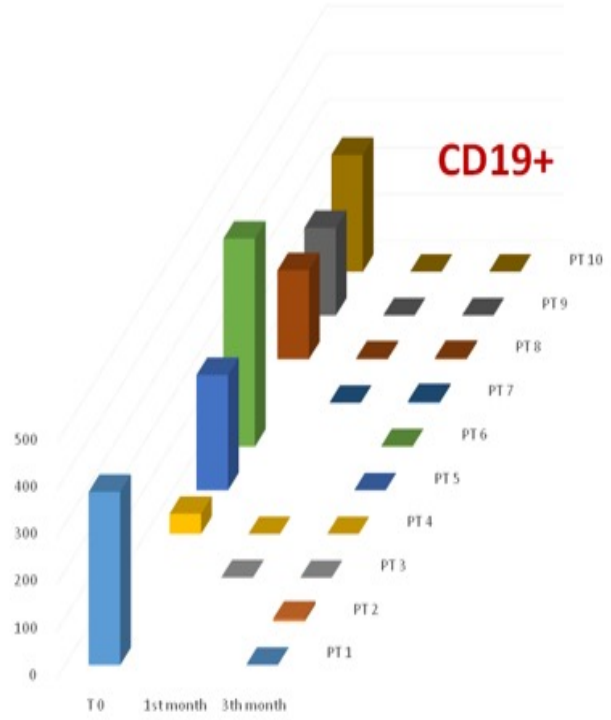


Figure 2 Renal responses over time. CRR, complete renal response; mCRR, modified CRR; MMF, mycophenolate mofetil; ORR, overall renal response.

Furie Ann Rheum Dis 2022

The intensified B cell depletion regimen achieves a complete disappearance of CD19 B cell from the circulation within 3 months





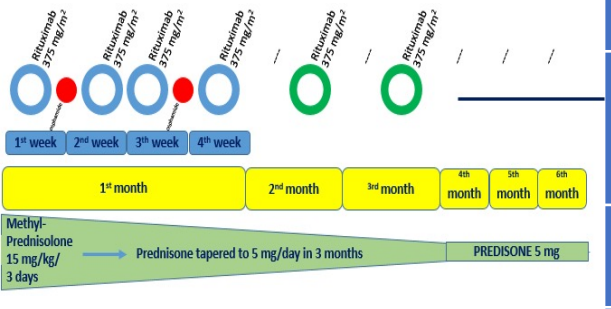
A 4-YEAR OBSERVATION ON LN PTS AFTER IBCD TREATM
WITHOUT
FURTHER MAINTENANCE IMMUNOSUPPRESSION

Roccatello Autoimmunity Reviews 2015

Baseline characteristics of patients

	IBCDT N=30	MMF n=20	CYC N=10	p=
Class IV* N. (%)	10 (33.3)	6 (30)	4 (40)	
Class III/V N. (%)	10 (33.3)	6 (30)	4 (40)	
Class V (N. %)	10 (33.3)	8 (40)	2 (20)	
sCr mg/dl, median (IQR)	0.91(0.6-1.5)	0.83 (0.6-1.4)	0.98 (0.6-1.7)	0.56
C3/C4 mg/dl, median (IQR)	61 (40-99)/13 (4-16)	59 (45-101)/12 (5-21)	62 (44-93)/11 (4-17)	0.63
Proteinuria g/24h, median (IQR)	5.0 (3.7-9.1)	4.6 (3.0-8.6)	5.2 (3.7-9.9)	0.45
Anti-DNA IU median (IQR)	176 (37-212)	145 (31-189)	181 (41-199)	0.39
Albuminemia g/dl, median (IQR)	3.0 (2.8-3.8)	2.89 (2.6-3.7)	3.0 (2.8-3.5)	0.57
Urinary red blood cells, median (IQR)	37 (10-100)	51 (5-100)	41 (5-100)	0.45
SLEDAI, median (IQR)	21.5 (14-25)	18 (14-24)	21 (16-25)	0.45
First-line treatment *(%)	15 (50)	10 (50)	5 (50)	1
New Flare** (%)	9 (30)	6 (30)	3 (30)	1
Refractory LN (%)	6 (20)	4 (20)	2 (20)	1

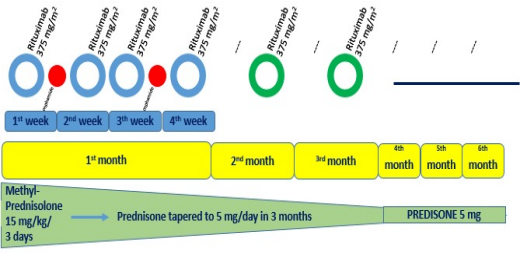
Roccatello
Kidney Int Reports, 2021



Intensified B Depletion Regimen with no Immunosuppressive Maintenance Therapy versus Standard Immunosuppressive Induction plus 3-year Maintenance Treatment in Lupus Nephritis patients

Clinical and serological profile *at 12 months*

Roccatello
Kidney Int Reports, 2021

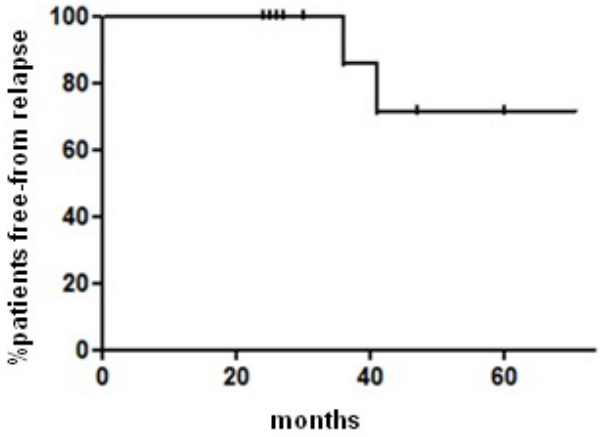


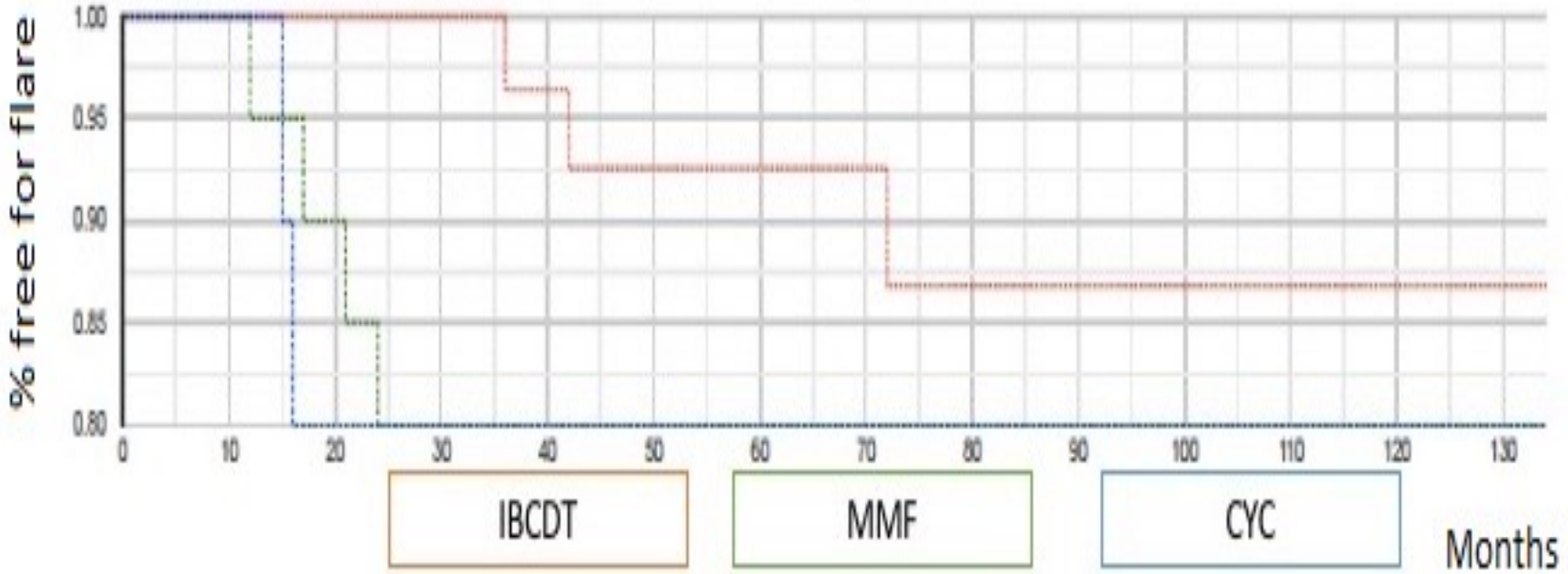
Intensified B Depletion Regimen with no Immunosuppressive Maintenance Therapy versus Standard Immunosuppressive Induction plus 3-year Maintenance Treatment in Lupus Nephritis patients

	IBCDT N=30	MMF n=20	CYC N=10	p=
sCr	0.89 (0.6-1.4)	0.85 (0.6-1.4)	0.97 (0.6-1.7)	0.68
ESR, median (IQR)	10.2 (7-27)	14(8-28)	21 (8-30)	0.71
Proteinuria g/24h, median (IQR)	0.46 (0.37-0.50)	0.71 (0.30-0.91)	0.51 (0.33-0.82)	0.78
C3/C4 mg/dl, median (IQR)	97 (79-120)/20 (11-37)	95 (81-120)/21 (13-40)	99 (80-120)/20 (10-40)	0.74
SLEDAI median, (range)	4 (1-5)	6 (2-8)	4 (2-8)	0.57
Complete Renal Response (N. %)	28 (93)	13 (65)	7 (70)	0.03
Partial Renal Response (N. %)	2 (7)	4 (20)	3 (30)	0.15
No Renal Response (N. %)	0 (0)	3 (15)	0 (0)	0.37
Any Renal Response (N. %)	30 (100)	17 (85)	10 (100)	0.32
Time to Complete Renal Response (median months IQR)	9 (6-11)	8 (6-11)	7(6-11)	0.87

Roccatello Kidney Int Reports, 202

Intensified B Depletion Regimen with <u>no</u> Immunosuppressive Maintenance Therapy versus Standard Immunosuppressive Induction plus 3-year Maintenance Treatment in Lupus Nephritis patients





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ANCA ASSOCIATED VASCULITIS

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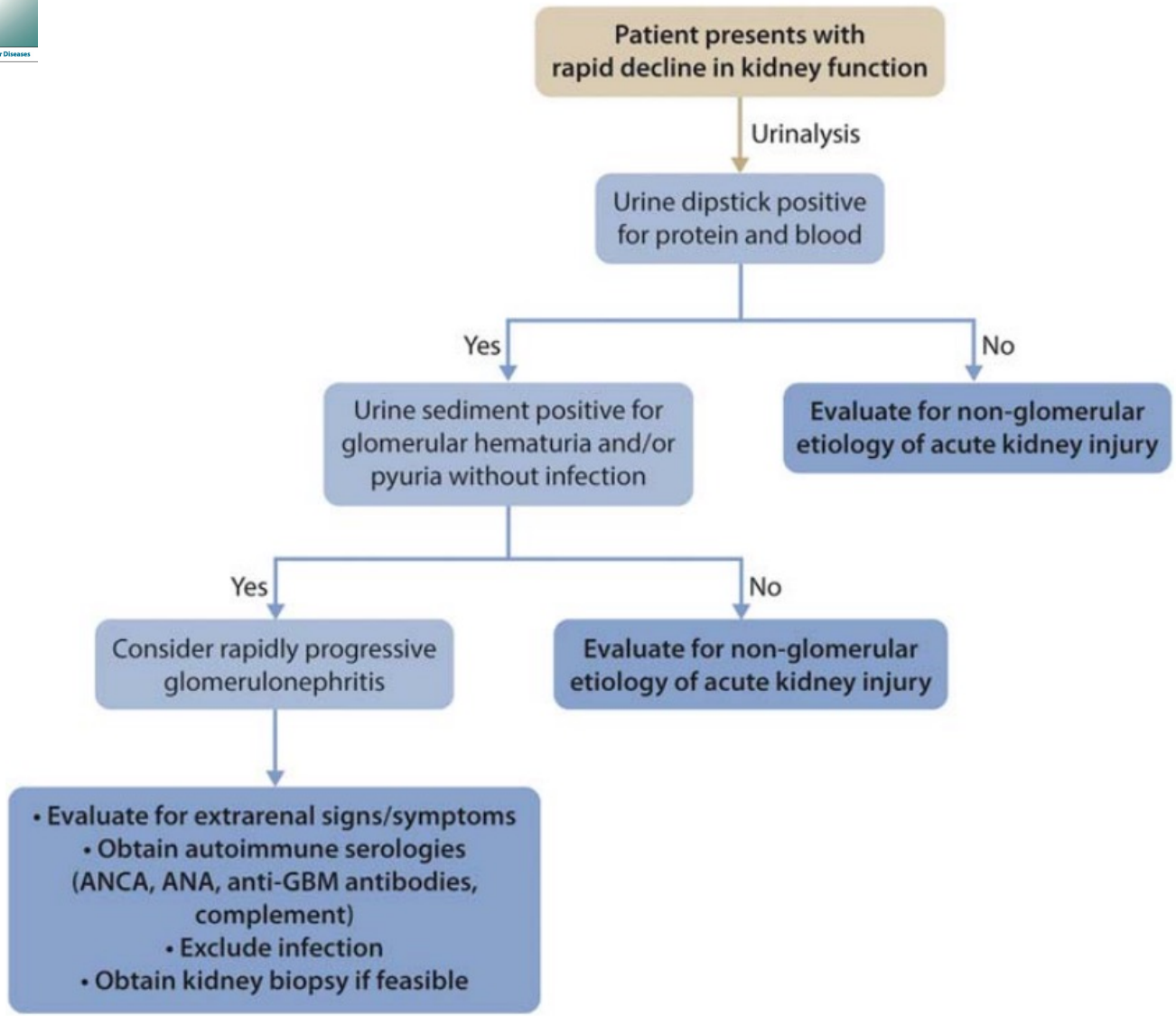
Diagnostic strategy in rapidly progressive glomerulonephritis



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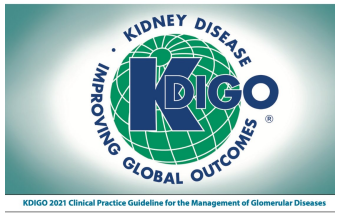

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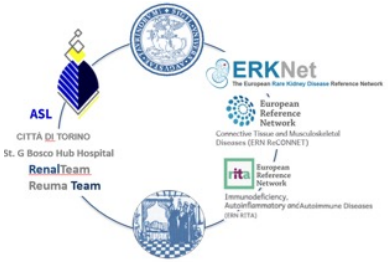
Frequency of organ involvement in AAV



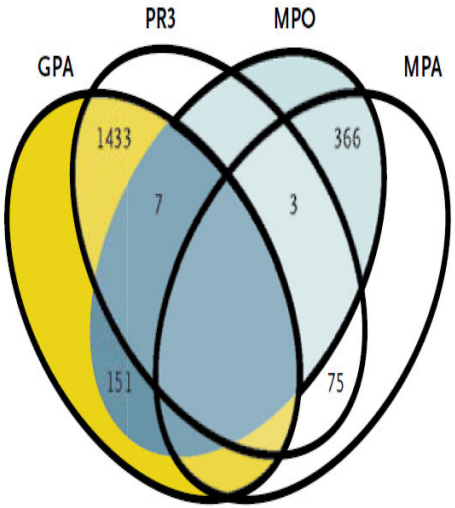
Organ system	Microscopic polyangiitis (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (eGPA) (%)
Cutaneous	40	40	60
Kidney	90	80	45
Pulmonary	50	90	70
Ear, nose, and throat	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

Question 5:

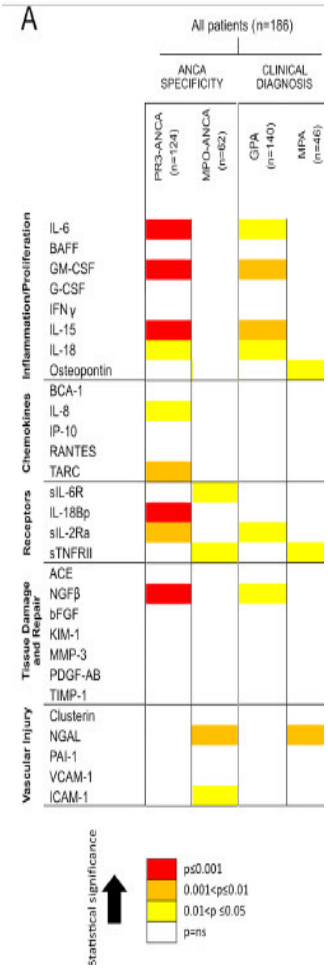
Do you consider MPO-AAV and PR3-AAV the same disease?

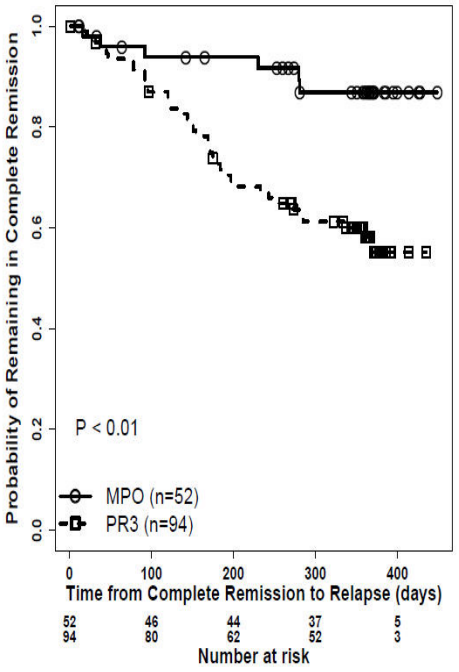
- Yes
- No

ANCA Type matters: PR3- *vs* MPO-ANCA



MHC ***HLA-DP*** ***HLA-DQ***
Non-MHC ***SERPINA1***
PRTN3

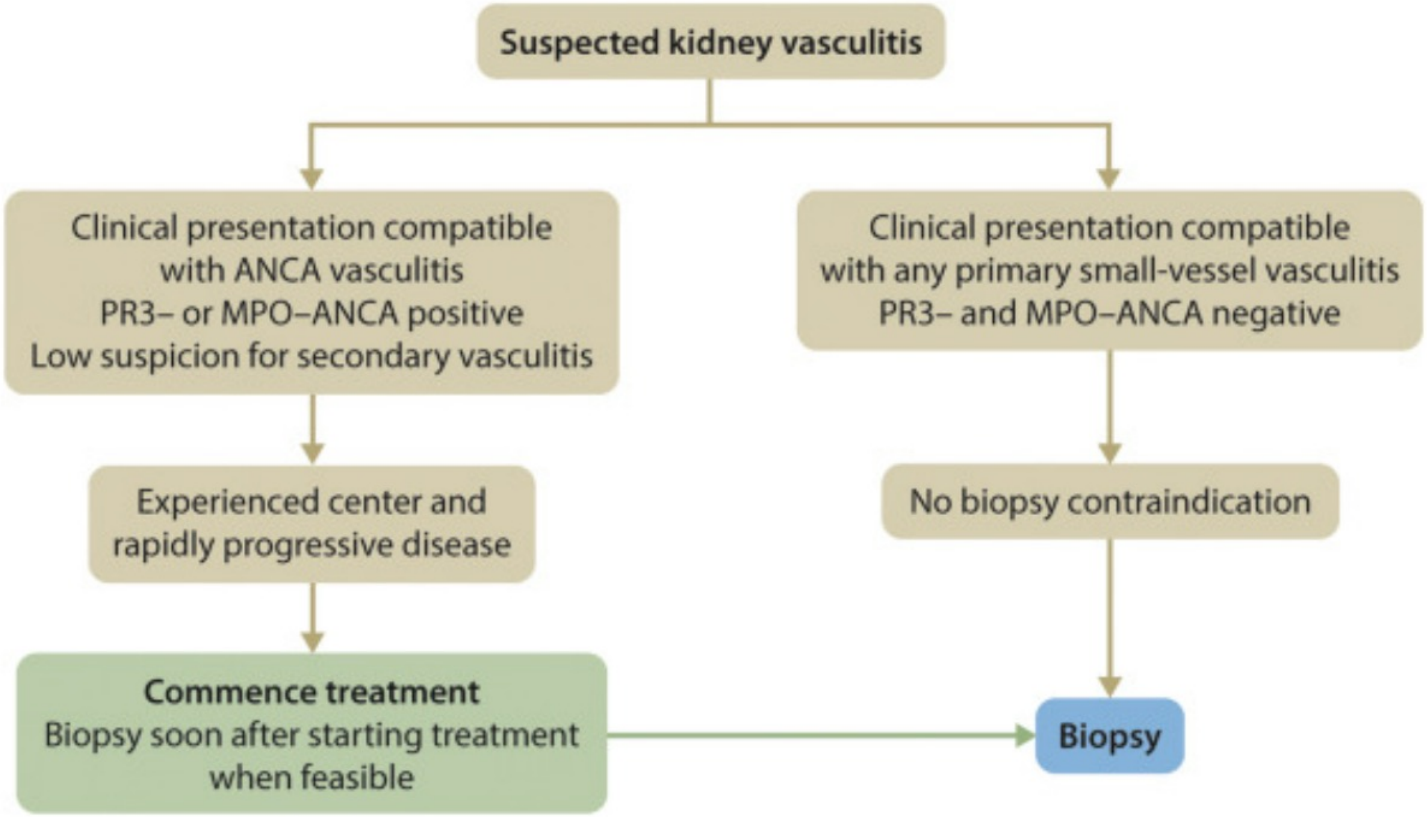




- **Epidemiology & Demographics**
- **Disease phenotype**
- **Relaping rate**

Lyons NEJM 2012 **Berti A&R 2017** **Specks NEJM 2013**

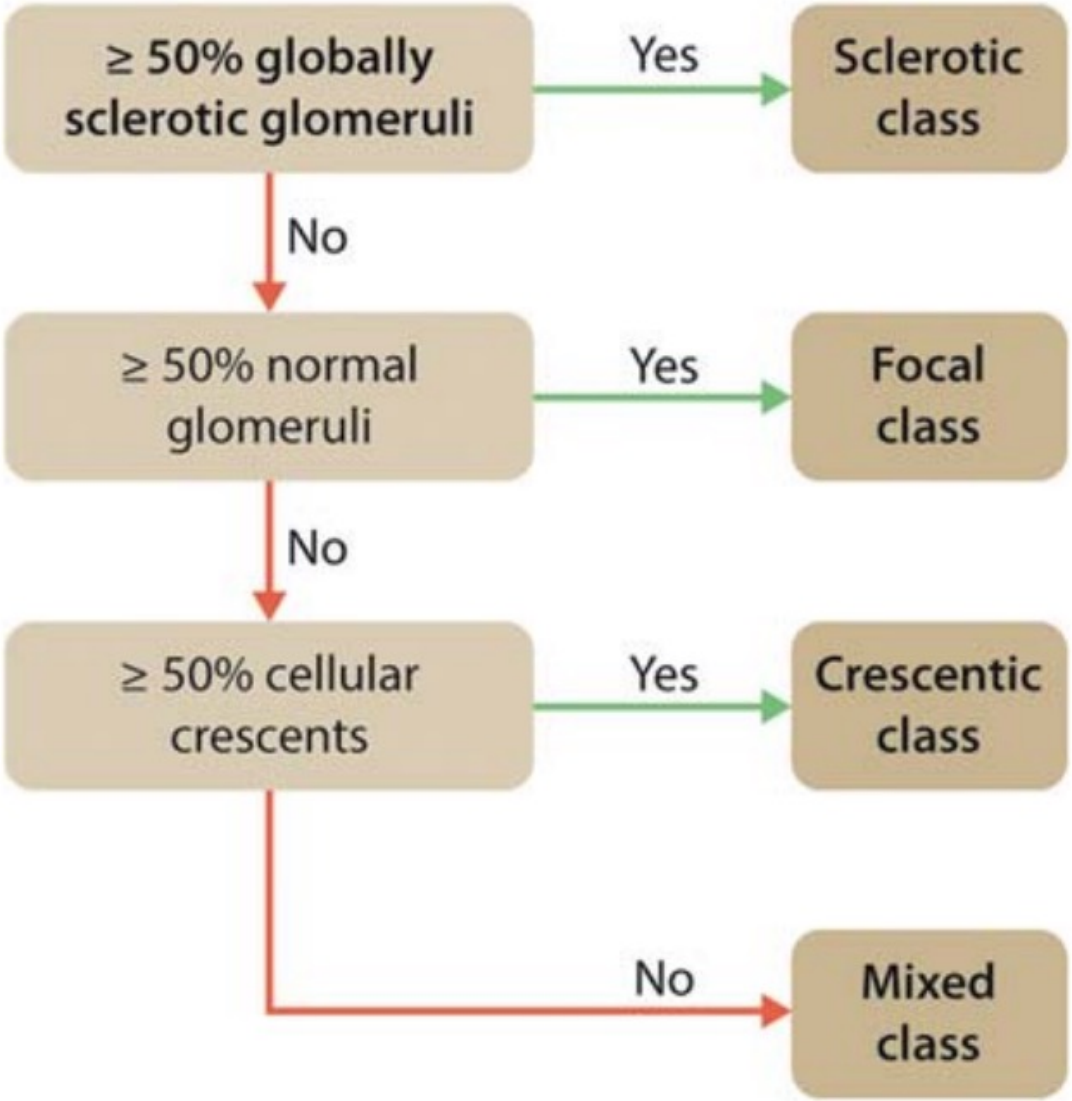
Biopsy strategy in suspected kidney vasculitis



SUPPLEMENT TO kidney INTERNATIONAL

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

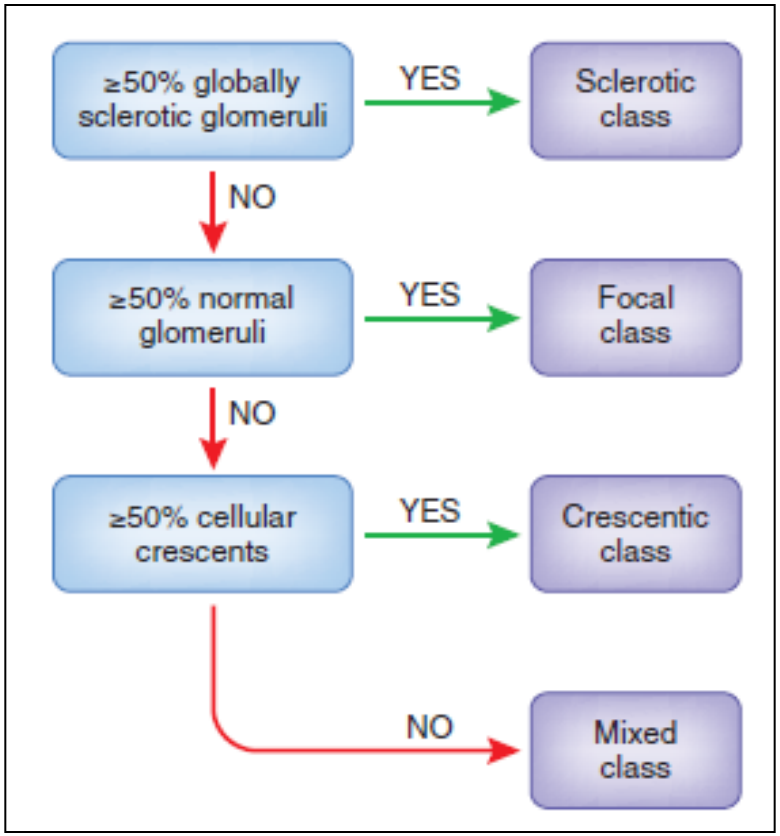
Histopathologic classification of ANCA-associated glomerulonephritis

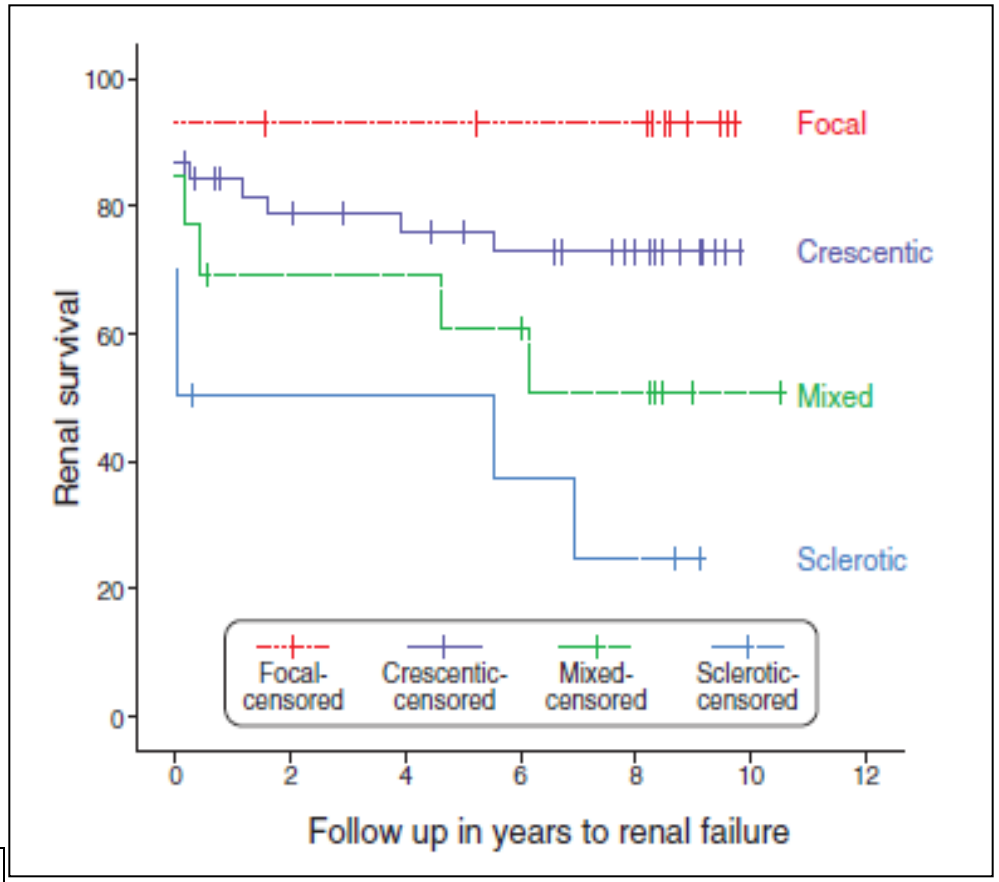


SPECIAL ARTICLE www.jasn.org

Histopathologic Classification of ANCA-Associated Glomerulonephritis

Annelies E. Berden,* Franco Ferrario,† E. Christiaan Hagen,‡ David R. Jayne,§ J. Charles Jennette,‖ Kensuke Joh,¶ Irmgard Neumann,** Laure-Hélène Noël,†† Charles D. Pusey,‡‡ Rüdiger Waldherr,§§ Jan A. Bruijn,* and Ingeborg M. Bajema*





Class	Inclusion criteria[a]
Focal	⩾50% Normal glomeruli
Crescentic	⩾50% Glomeruli with cellular crescents
Mixed	<50% Normal, <50% crescentic, <50% globally sclerotic glomeruli
Sclerotic	⩾50% Globally sclerotic glomeruli

Berden AE et al. J Am Soc Nephrol 2010;21(10):1628-1636

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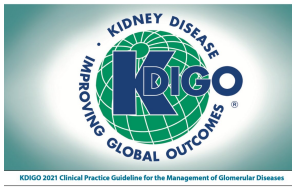

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Definition of disease activity, remission, relapse, and treatment-resistant disease in AAV

Disease activity of ANCA-associated vasculitis represents signs or symptoms attributable to active disease in any organ system

Remission is defined as the absence of manifestations of vasculitis and GN. For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease

Relapse is defined as the occurrence of increased disease activity after a period of partial or complete remission. A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided into major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse include diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis threatening vision

Treatment-resistant disease is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy

Question 6:

In induction phase do you have any preference for

- i.v. Cyclophosphamide
- oral Cyclophosphamide
- Rituximab

RITUXIMAB: REMISSION INDUCTION

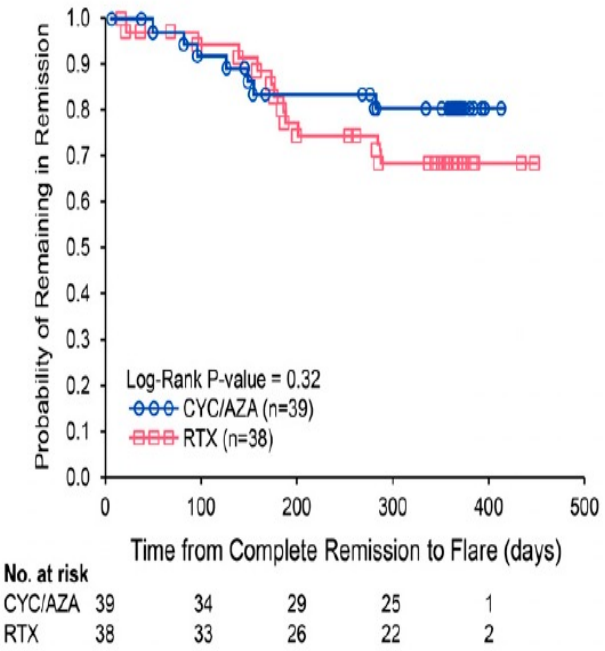
RTX is an effective alternative to CYC for the induction of remission in patients with AAV, including patients with renal involvement

RTX was more effective than CYC in patients with relapsing disease

RTX was superior to CYC for inducing remission in PR3-ANCA-positive patients

RAVE	197 pts with newly diagnosed AAV or with a relapse of AAV median age 53 yrs; GPA/MPA 76:24%; anti-PR3/anti-MPO 67:33; GFR 60 ml/min/1.73m^2 (in a subgroup of 52 pts with renal involvement) BVAS/WG at entry 8; VDI at entry 1 3 deaths during 6-month FU	RTX (375 mg/m2 per week for 4 weeks) vs. CPH (2 mg/kg/day) with CS tapered off	6 mo	Primary end point remission of disease without the use of CS at 6 mo	Primary endpoint reached in 64% in RTX vs. 53% in the control group, RTX more effective than CPH in relapsing pts (67% vs. 42% p=0.01), no difference between RTX and CPH in pts with major renal disease, or alveolar hemorrhage, no difference in AE rate	Stone, 2010 [33]

RTX vs CYC in ANCA-associated Renal Vasculitis (102/197 pts): *2-year results of the RAVE trial*



Stone JH et al, N Engl J Med. 2010; 363(3):221-32.

Name of the study	Study population	Treatment	FU	Primary outcome	Results	Reference
RITUXVAS	44 pts with newly diagnosed AAV and renal involvement; median age 68 yrs; GPA/MPA/RLV 22:16:6; cANCA/pANCA 25:19; GFR 18 ml/min/1.73m^2; BVAS at entry 19; 1-yr mortality 18%	Pts randomised in 3:1 ratio to RTX (375 mg/m2 per 4 weeks) + 2 iv CPH pulses + CS, or iv CPH pulses for 3 to 6 mo + CS followed by AZA	1 yr	Primary end points: sustained remission rates at 12 mo and SAE	Sustained remission in 76% of RTX and 82% of CPH group, SAE rate 42% pts in RTX and 36% of pts in CPH group, no difference in death rate, increase of GFR at 12 mo (19 ml/min vs. 15 ml/min	Jones, 2010 [32]

In patients with *GFR<20 ml/min*, a rituximab-based regimen (*RITUXVAS* trial) equals to the administration of standard corticosteroids with intravenous cyclophosphamide for 3 to 6 months followed by azathioprine

***At 24 months relapses* occurred in 21% of patients of the rituximab group and 18% of the controls**

Jones RB et al, N Engl J Med. 2010 ;363(3):211-20; Stone JH et al, N Engl J Med. 2010; 363(3):221-32.

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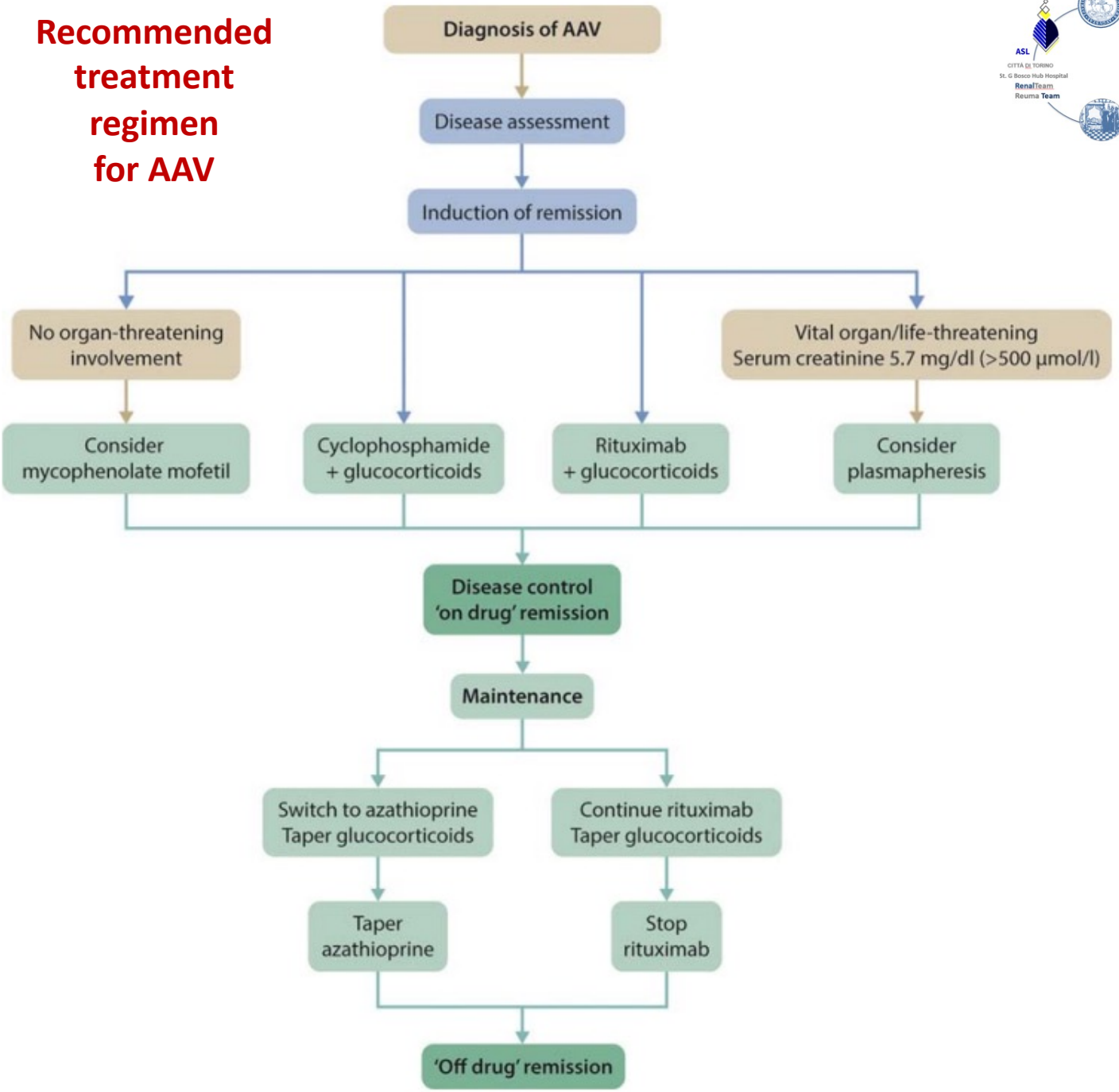
Recommended treatment regimen for AAV



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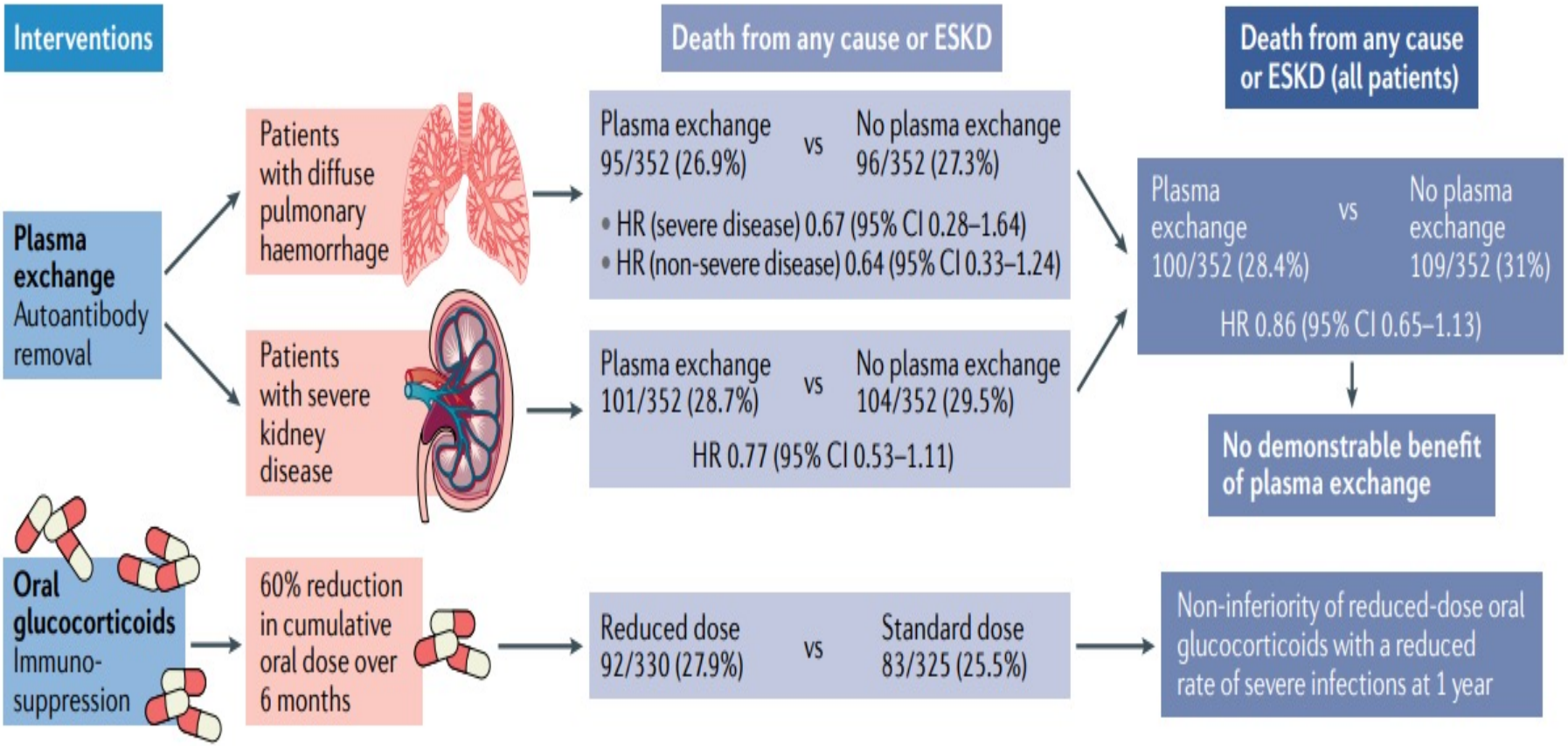
Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

Considerations for the route of administration of cyclophosphamide for AAV

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Key findings of PEXIVAS trial



Walsh, M. et al. N. Engl. J. Med. 382, 622–631 (2020)

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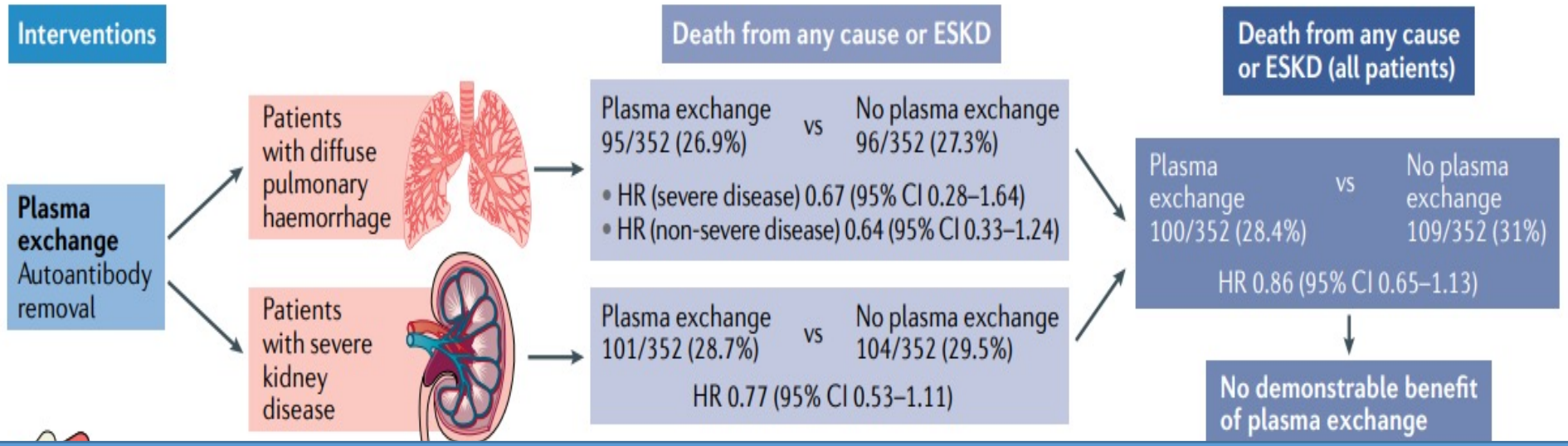
Prednisolone tapering regimen for AAV

Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<50 kg	50–75 kg	>75 kg
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	Investigators' local practice		

Walsh, M. et al. N. Engl. J. Med. 382, 622–631 (2020)



Use of PEX did not result in a lower incidence of ESKD or death

Results of **PEXIVAS trial** indicate that PEX **does not reduce the risk of ESKD** and **death** in AAV

However, this study included
- patients with **eGFR<50 ml/min** per 1.73 m^2 ,
- evidence of **pulmonary haemorrhage** only in one third of cases (and with <85% ox saturation only in 61 out of 191)
- **hemodialysis requirement** in one fifth.

Inclusion of substantial proportion of patients with mild disease might have obscured the detection of benefit for the most critical outcomes

Kidney biopsy was not required for entry *into the study so that the extent of chronicity of renal lesions could not be determined. Patients with advanced fibrosis from a long-term smouldering course would not be expected to improve with any treatment, including plasma exchange.*

The study also lacked of ***stratification*** *aimed at identifying the cases with extremely reduced renal function, which was the main indication to PEX*

Estimates in **subgroup analyses** showed a possible benefit of PEX in patients with severe hemorrhage

The **effect of RTX** had been **probably diminished** when combined with plasma exchange because the procedure was withheld for only 48 hours after the initial RTX dose. Due to RTX kinetics, this short interval causes a considerable removal of RTX by PEX

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Plasma exchange dosing and frequency for AAV

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

Factors that increase relapse risk for AAV

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

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Question 7:

What is your favorite maintenance regimen in AAV?

- Azatioprine
- Fixed Rituximab
- Rituximab on demand
- Mycophenolate mofetil

MAINTENANCE THERAPY

CYCAZAREM: substitution of CYC (3 mths) with AZA, similar outcome

WGENT: MTX has similar efficacy as AZA

IMPROVE: MMF inferior to AZA

MAINRITSAN: RTX 500 x 2, then 500 each 6 months for 3 times

AZA 2mg/kg/day for 12 months, 1.5 for 6, 1 for 4

RITAZAREM: RTX 1000 each 4 months for 5 times

AZA 2mg/kg/day for 24 months

MAINRITSAN 2: RTX 500 each 6 months

RTX 500 when CD19 repopulate or ANCA rise

MAINRITSAN 3: Extended fo-up with additional 18 months of RTX

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Considerations for using rituximab or azathioprine for AAV maintenance therapy

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Hepatitis B exposure (HBsAg positive) • Limited availability of rituximab

Question 8:

How long immunosoppressive maintenance therapy should be continued in AAV?

- 18 months
- 36 months
- 48 months
- Until kidney biopsy shows the absence of inflammation

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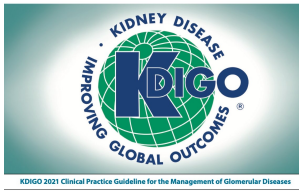


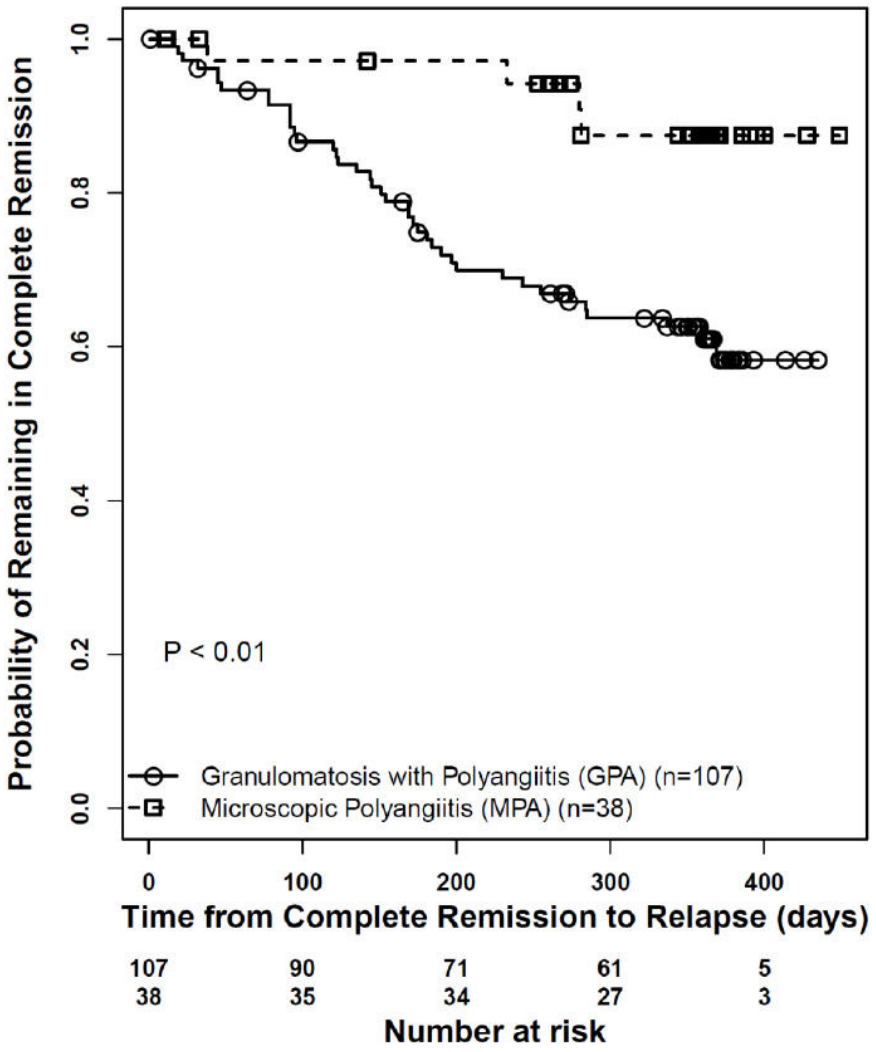
Immunosuppressive dosing and duration of AAV maintenance therapy

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yrs
	Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo	

Relapse Risk in Severe AAV

Long-term RAVE data by Diagnosis

MPA (N=48): 79% CR
GPA (N=148): 72% CR



Specks U et al. NEJM 2013; 369:417-27

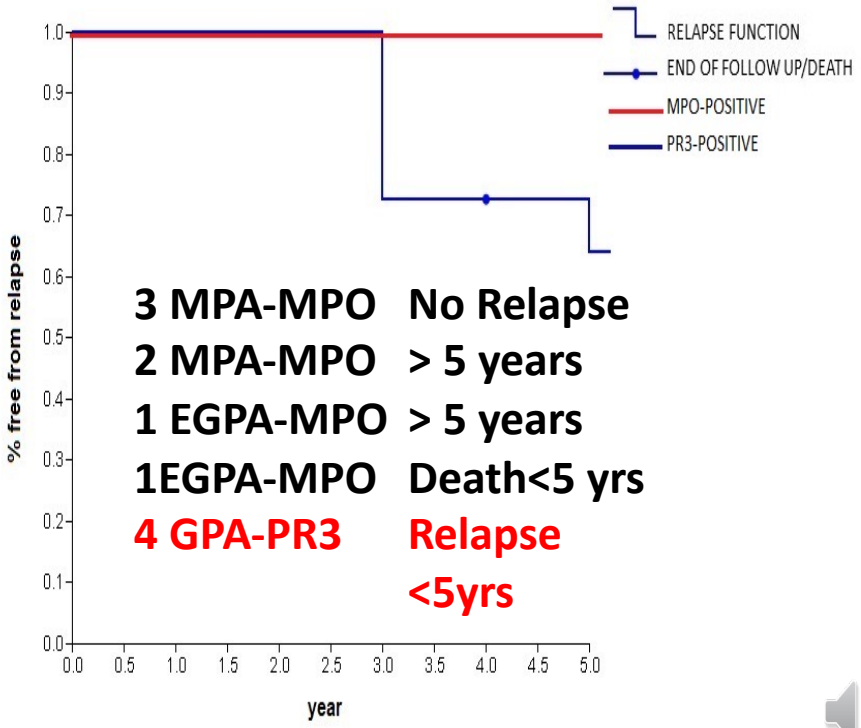
Prognosis based on ANCA specificity

Variable	Hazard ratio (95% CI)	p
ANCA at switching to maintenance therapy		
ANCA-positive	1	0.004
ANCA-negative	0.57 (0.38–0.84)	
ANCA at trial entry		
MPO-ANCA	1	0.002
PR3-ANCA	1.99 (1.30–3.04)	
Patient age (per decade)	0.79 (0.70–0.90)	<0.001
Serum creatinine at entry (per 50 μmol/L)	0.87 (0.80–0.95)	0.002
Clinical diagnosis		
GPA	1	0.002
MPA	0.72 (0.59–0.89)	
Initial induction treatment		
Daily oral cyclophosphamide	1	0.016
Pulsed cyclophosphamide	1.64 (1.10–2.45)	
Initial maintenance therapy		
AZA	1	<0.001
MMF	2.13 (1.42–3.19)	
Time to remission (per month)	1.07 (0.95–1.21)	0.279

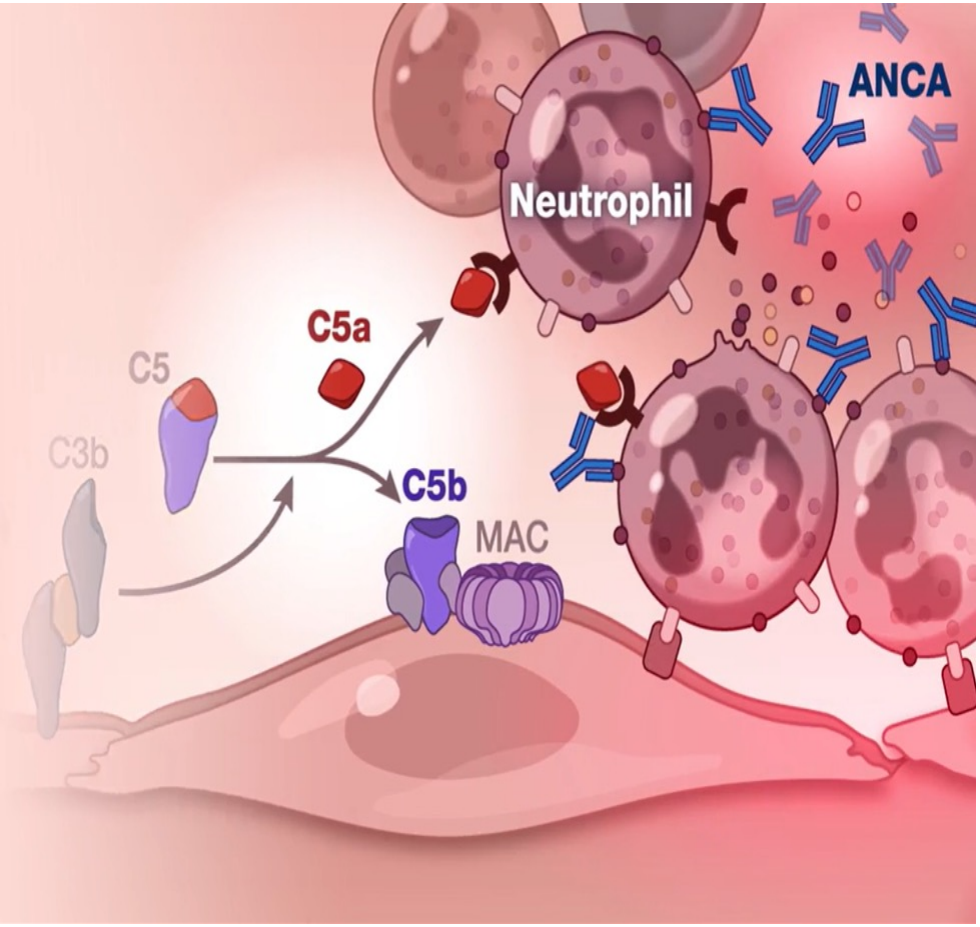
Univariate survival analysis of factors potentially associated with the risk of relapse during follow-up

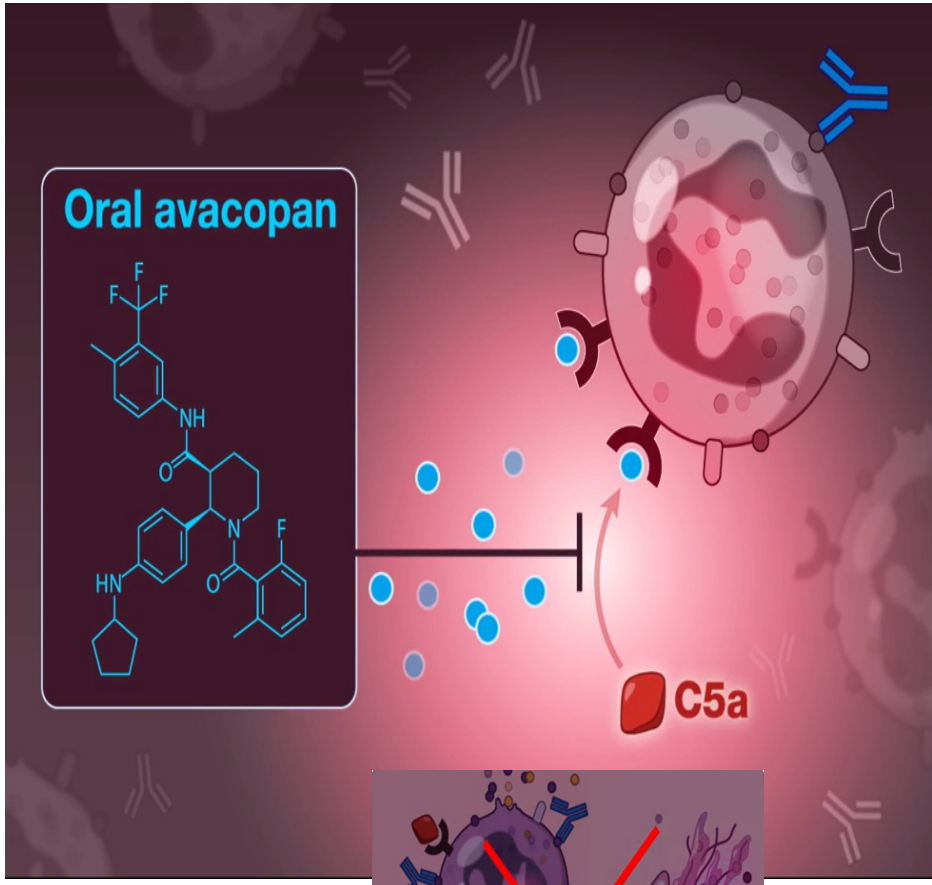
Becoming ANCA- before the switch to maintenance → reduced risk of relapse

Relapse more frequent in PR3- ANCA

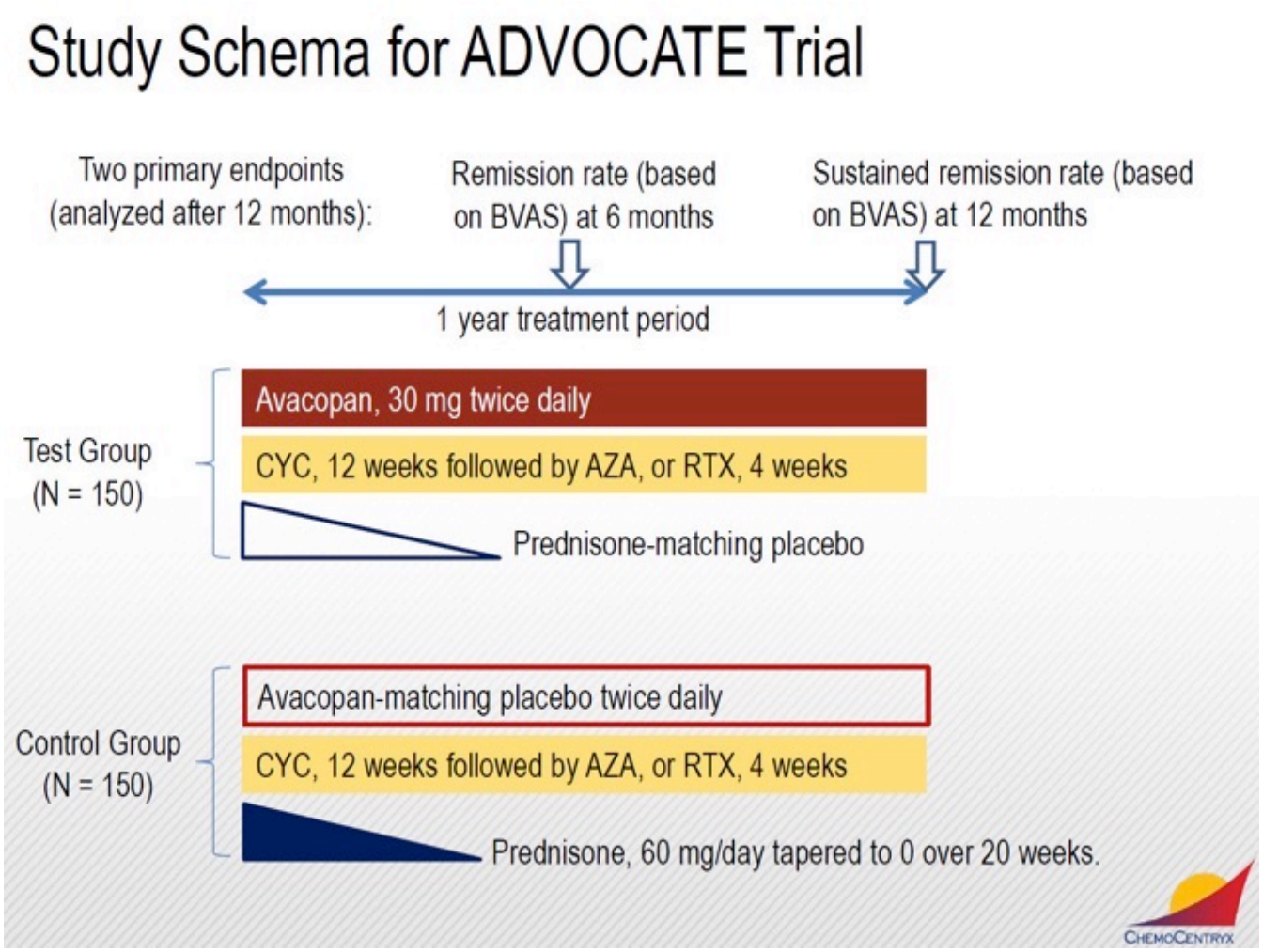


Roccatello et Al, Oncotarget 2017

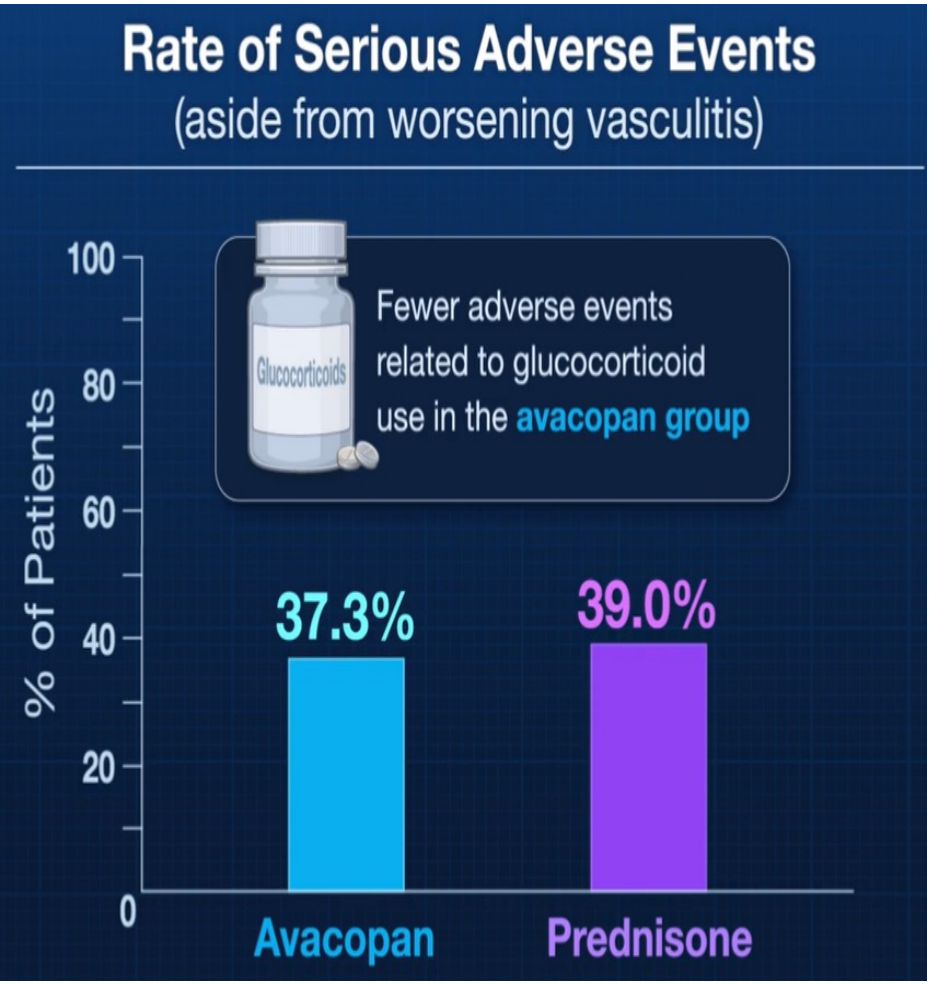

ANCA
Neutrophil
C5a
C5
C3b
C5b
MAC

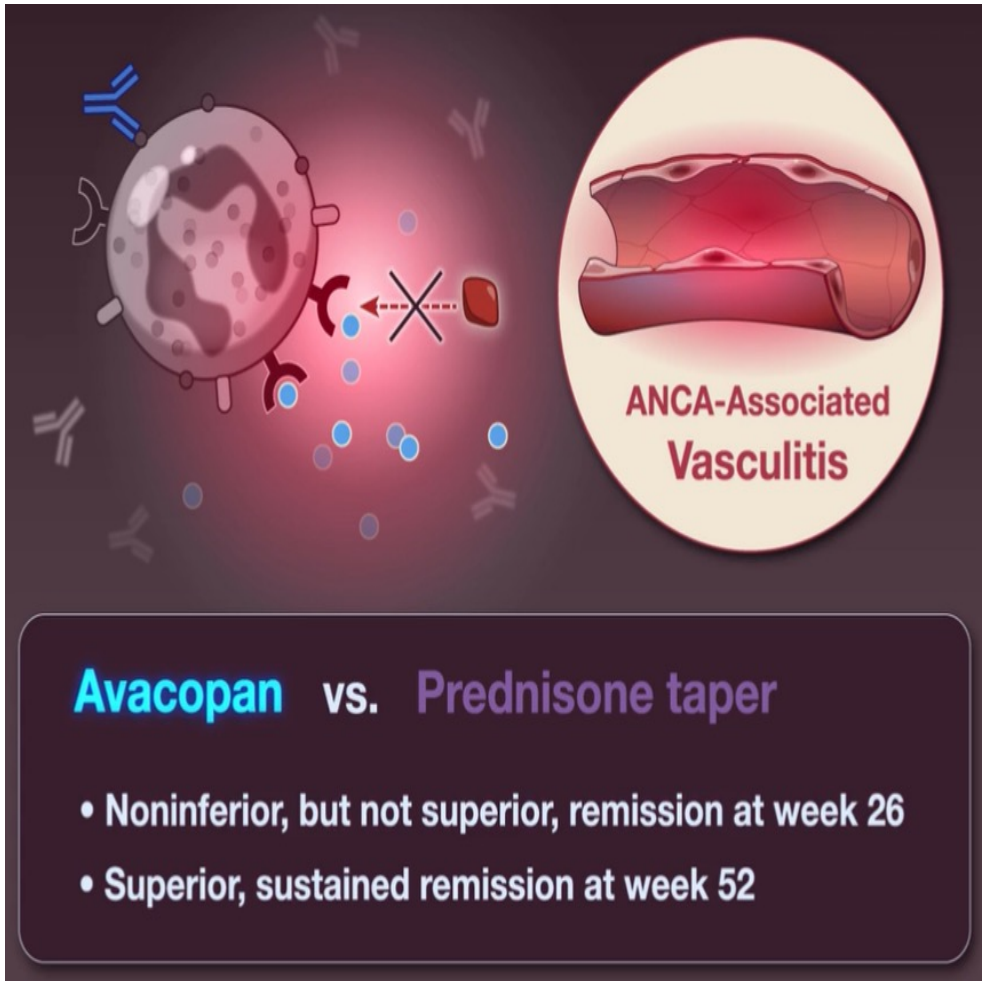

Oral avacopan
F
F
F
NH
O
N
F
HN
O
C5a

Management of ANCA-associated Vasculitis



Rate of Serious Adverse Events
(aside from worsening vasculitis)

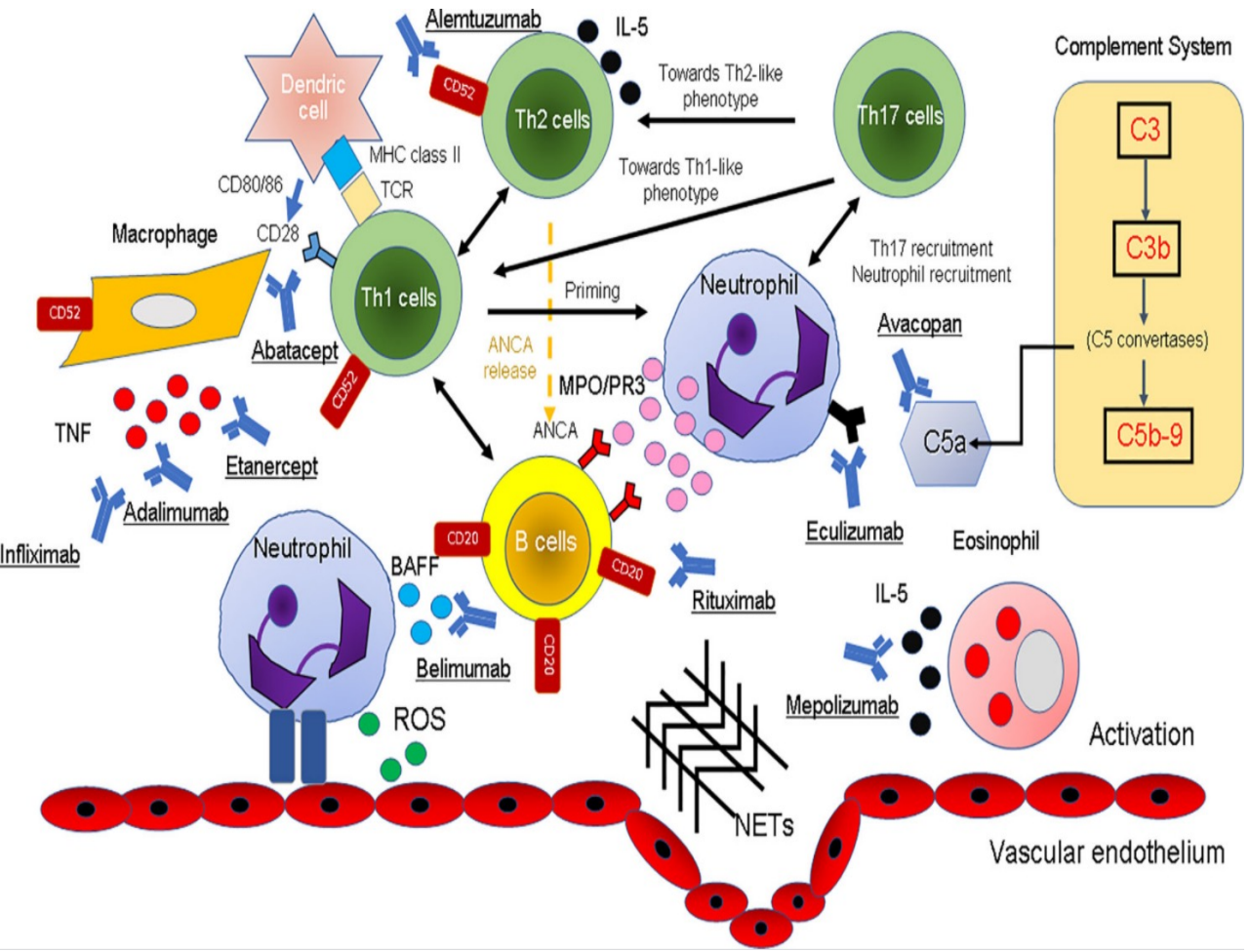




Putative indications

- Diabetes
- Risks of fractures
- Glaucoma
- ANCA negative patient
- Low basal level of complement (possibly associated to severe renal involvement and TMA in AAV)
- High risk of infection (?)

Next future



Frontiers Immunol. 2021

ALEVIATE: ***alemtuzumab in induction***
COMBIVAS: ***Belimumab + RTX/CS***
ENDURRANCE: ***RTX+CYC low-dose***
ABROGATE: ***ABA in maintenance***
INFLARX: ***anti-C5a MoAb (IFX-1) vs CS***

2° generation anti-CD20 drugs
Ofatumumab (cdct/adct/apoptosis)
Obinotuzumab (enhanced adct)
Octrelizumab

Bortezobib: ***as a CD20-ve target therapy***

Inhibition of peptidylarginine deiminase 4, ***which is essential for NET formation (extracellular meshes of chromatin and granular proteins induced by ANCA, that activates autoreactive B cells and complement and injuries endothelium)***

Anti-IL17 or IL23 MoAbs:
Seku /Usteki

NEXT WEBINARS

22/02/22

The genetics of human renal agenesis and renal dysplasia
Adrian Woolf (Manchester, UK)

22/03/22

Mendelian and non-mendelian inheritance
Kalman Tory (Budapest, Hungary)

05/04/22

Fabry disease
Olivier Lidove & Wladimir Mauhin (Paris, France)

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