Στοχεύοντας το βελτιωμένο έλεγχο στις ANCA αγγειίτιδες:

Η σημασία της αναστολής του συμπληρώματος με avacopan

Σ. Λιονάκη

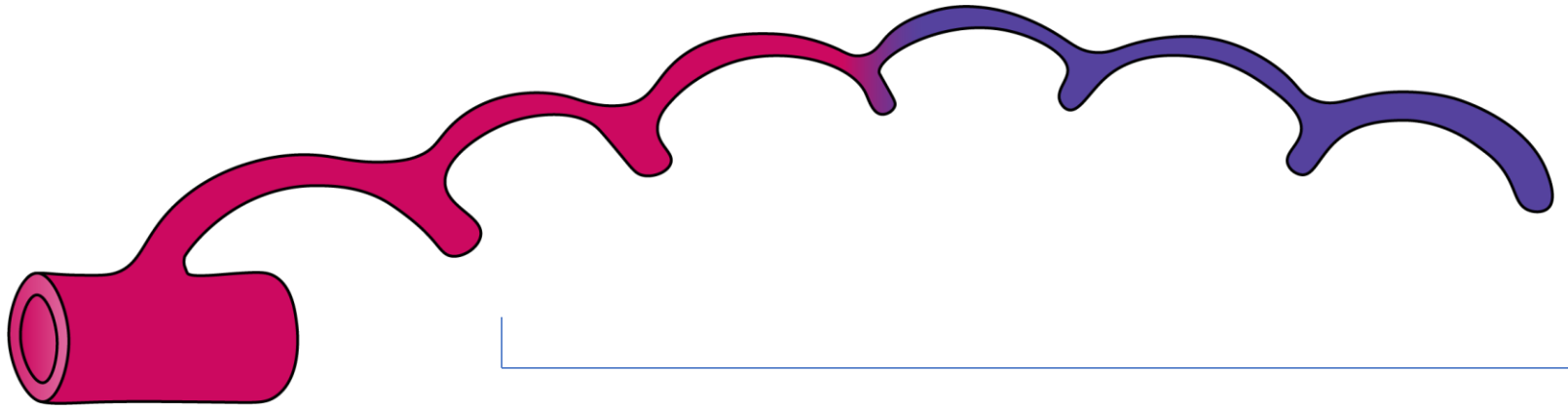
Επ. Καθηγήτρια Νεφρολογίας, ΕΚΠΑ

Π.Γ.Ν ΑΤΤΙΚΟΝ

Σύγκρουση συμφερόντων

- Τιμητική αμοιβή από την Γένεσις Φάρμα ΑΕ

Kidney involvement in ANCA-vasculitis: 77-85% within 2 yrs of dx

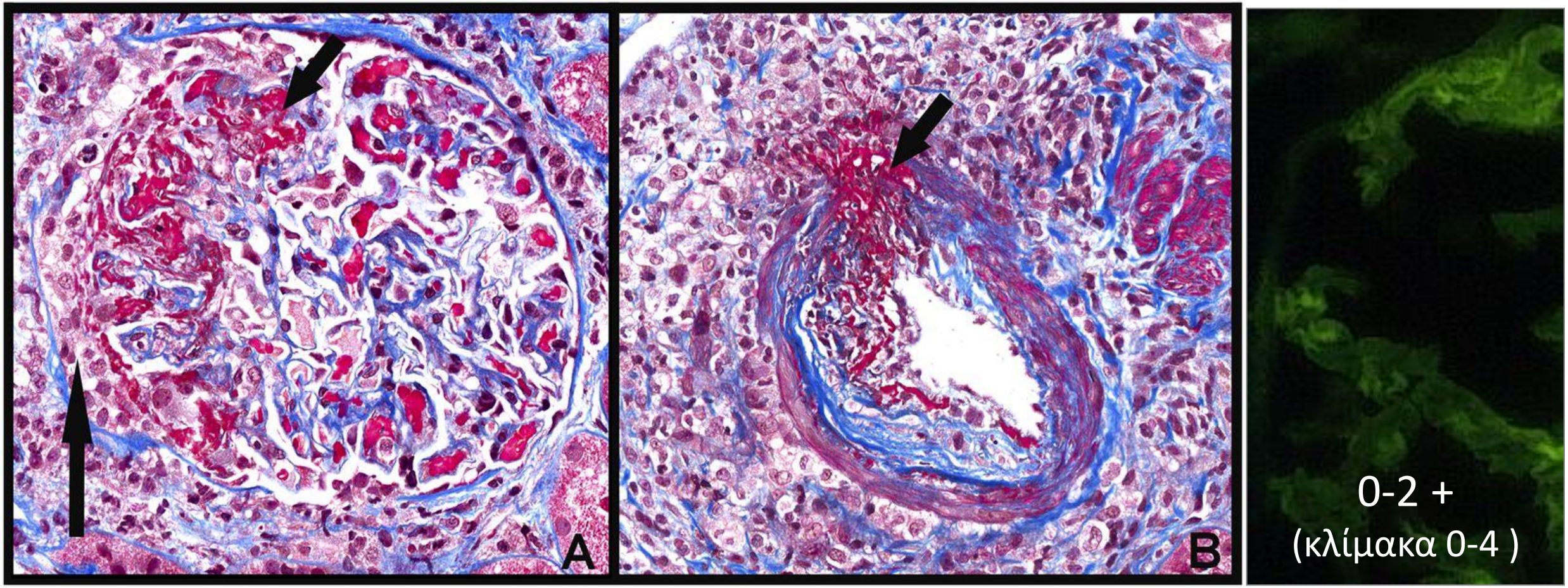


ANCA-associated small vessel vasculitis

- Microscopic polyangiitis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

Kitching A, et al. Nat Rev Dis Primers. 2020;27;6(1):71.

Ανοσοπενική Σπειραματονεφρίτιδα (ΣΝ)



>85% των ασθενών είναι ANCA (+)

J. Charles Jennette, UNC Kidney Center

Στόχοι θεραπείας

Επίτευξη ύφεσης

- Σταθεροποίηση ή/και βελτίωση της νεφρικής λειτουργίας.
- Εξαφάνιση της σπειραματικής αιματουρίας (<5 RBCs/hpf).
- Εξαφάνιση εξωνεφρικών αγγειϊτιδικών εκδηλώσεων.

Αποφυγή υποτροπής

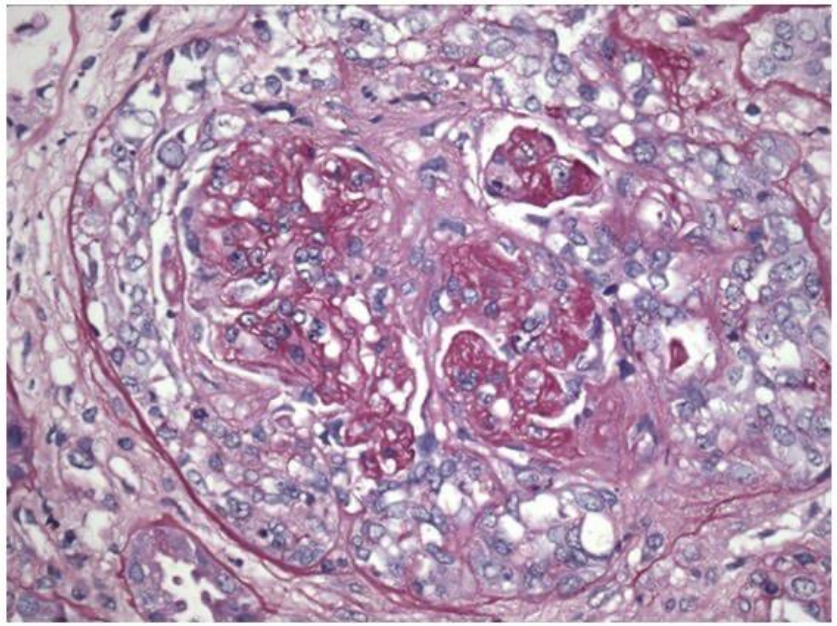
- Νέα αγγειϊτιδικά συμπτώματα /σημεία σε οποιοδήποτε όργανο/σύστημα σε ασθενή στον οποίο είχε επιτευχθεί ύφεση.
- Σπειραματική αιματουρία ± ↑ κρεατινίνης ορού.

Rate and time to remission

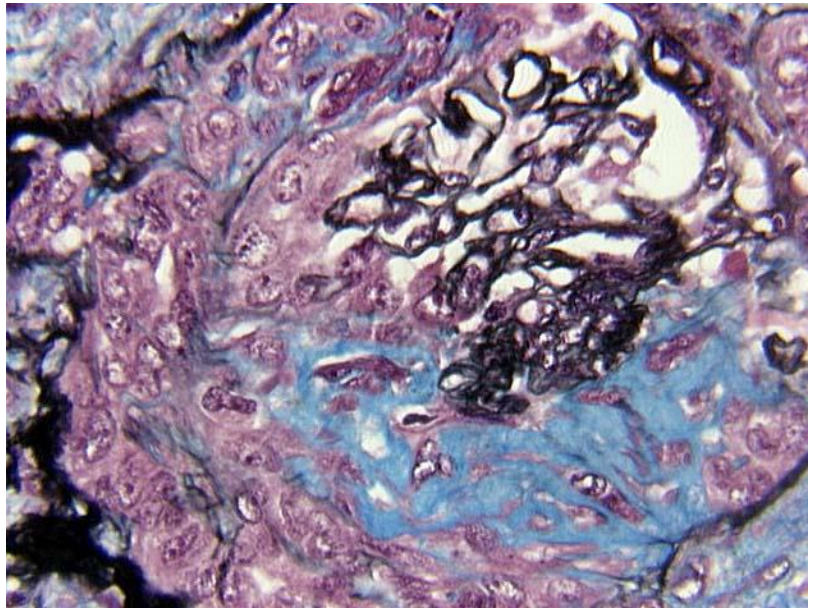
	Protocol	Response rate	**Time to remission**
Cycazarem	Cyclophosphamide p.o + GC	93%	3-6 months
CYCLOPS	Cyclophosphamide IV + GC	88%	2-6 months
WGET	Etarnecept	91%	3-6 months
RITUXVAS	Rituximab + CYC iv + GC	76%	6-12 months
RAVE	Rituximab + GC	64%	6 months
Combined therapy	Rituximab + low dose Cyclophosphamide + GC	94%	1.5 months

Aging crescent

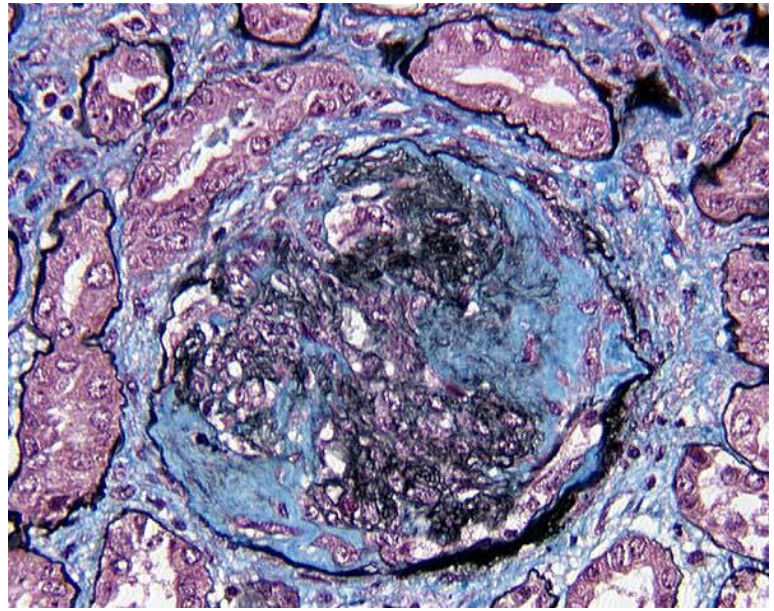
Cellular



Fibro-cellular

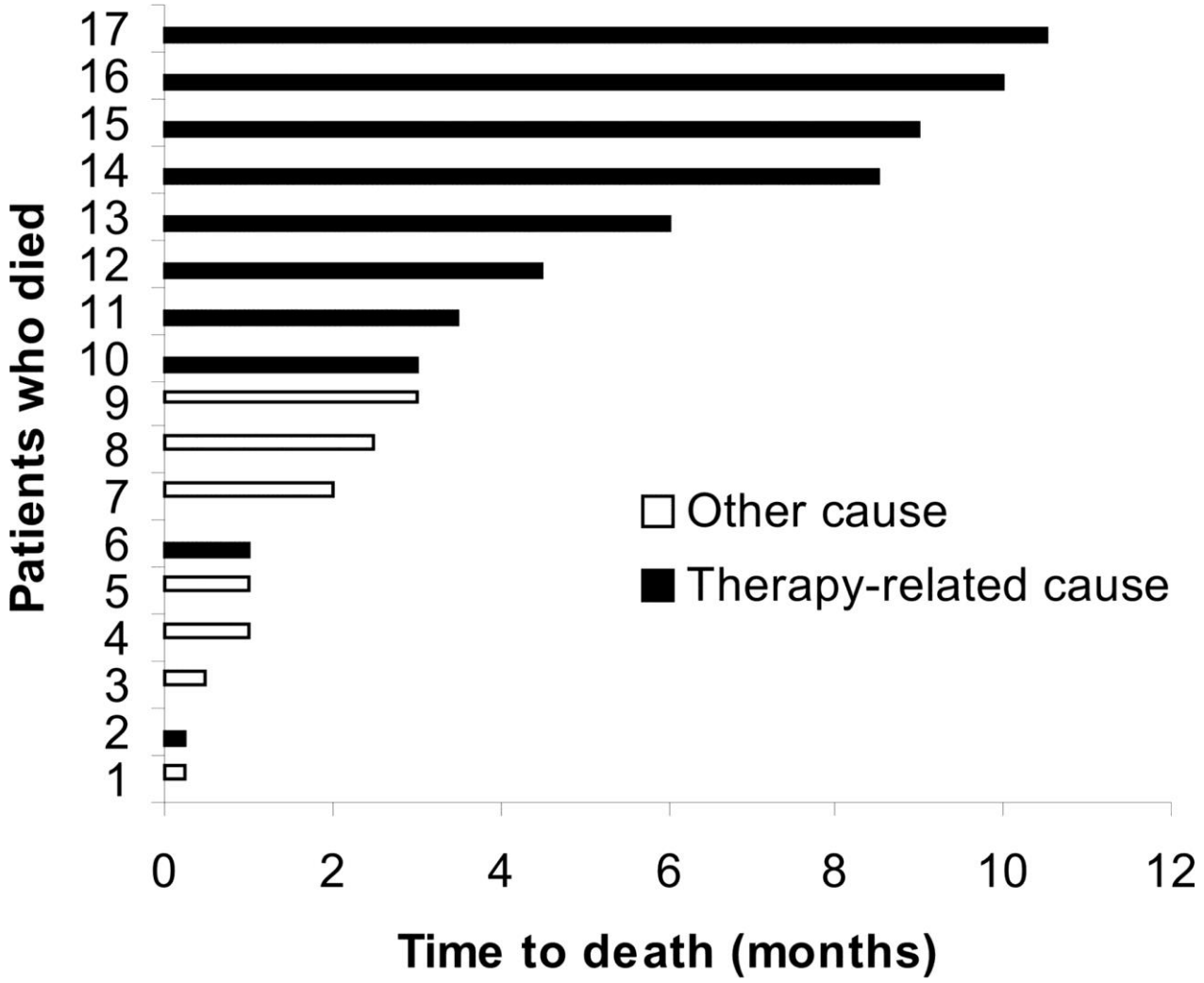


Fibrous



Time

Causes of death 1 year: Therapy related



de Lind van Wijngaarden, R. A.F. et al. J Am Soc Nephrol 2007;18:2189-2197

JASN

RAVE: Rituximab instead of Cyclophosphamide

- **No difference in adverse events!**
- Total GS exposure: Major role in mediating adverse events.

Glucocorticoids duration and infection

Events (per patient year)	0 prednisone at 6th month N=69	Prednisone >6th month N=78	p value
Incidence of infection months 0-6	0.39	0.64	<0.0001
Incidence of infection 6th month-end	0.23	0.42	<0.0001

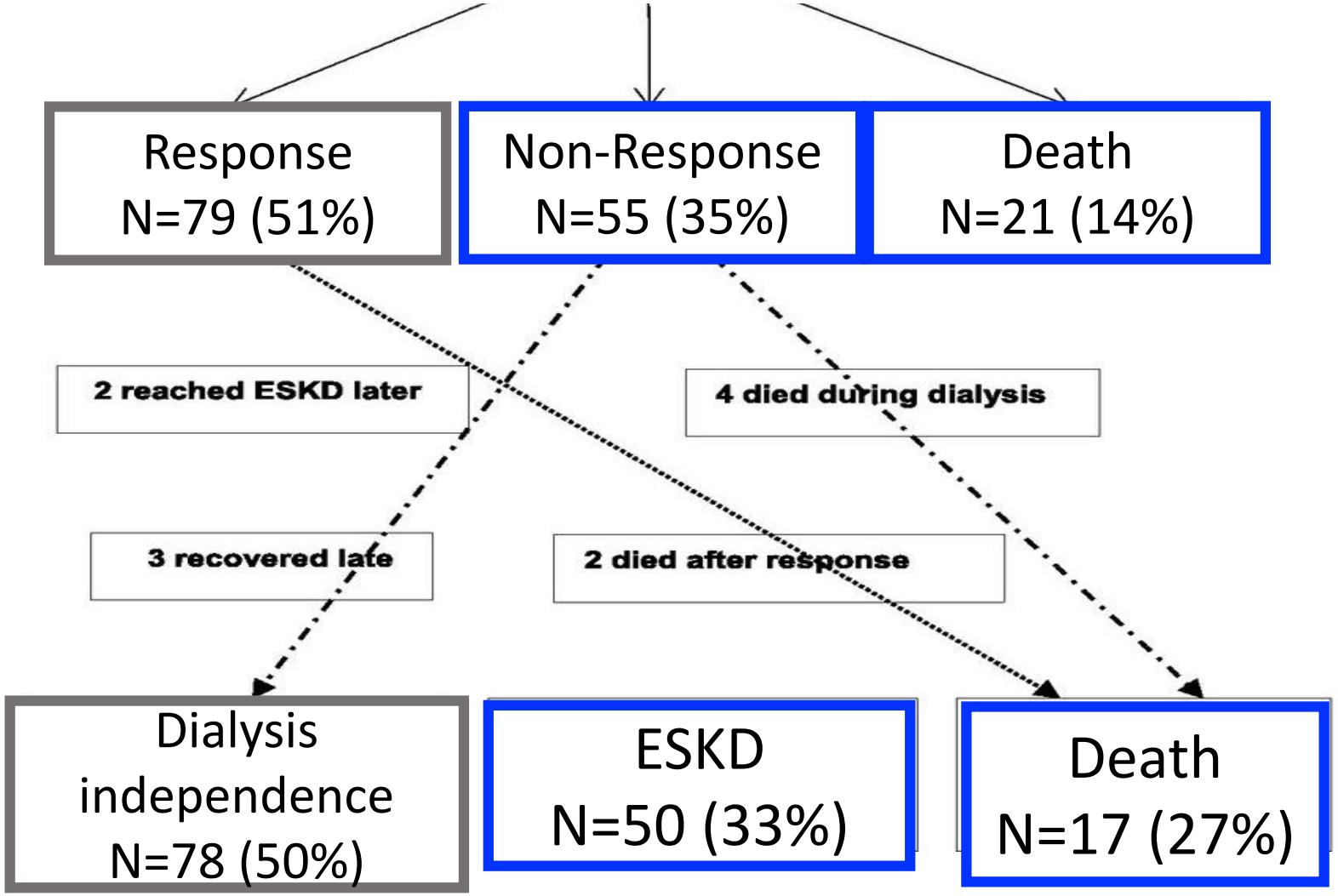
McGregor JG et al. Clin J Am Soc Nephrol. 2012

Glucocorticoids duration:
Meta-analysis of 13 studies (n=983)

Glucocorticoid duration	Number of studies	Relapses (%)	p value
Early withdrawal	8	48	<0.001
Late withdrawal	3	29	0.13
No withdrawal	3	14	Reference

Arthritis Care & Research, Volume: 62, Issue: 8

Predictors of treatment outcome in ANCA vasculitis with severe kidney failure at diagnosis



Lee T. et al Clin J Am Soc Nephrol 2014

ANCA-glomerulonephritis ending in ESKD

N=523 patients

Median follow up time=3.3 years

26% (136) developed ESKD:

New onset of vasculitis	51%
Progressive chronic kidney disease without active vasculitis	43%
Relapsing vasculitis	6%

Lionaki S et al. Kidney Int. 2009;76(6):644.

ANCA-GN in chronic dialysis

Characteristic	**pre-ESKD**	**ESKD**	p value
Relapse rate (episodes/patient-year)	0.2	0.08	p<0.0001
Mortality rate (deaths/person-year)	0.07 (0.05–0.08)	0.31 (0.26–0.36)	p<0.0001

Lionaki S et al. Kidney Int 2009 Sep;76(6):644-51.

Βελτίωση της θεραπείας των ANCA-αγγειιτίδων

- **Ταχύτερη ανταπόκριση**

(↓ μη αναστρέψιμων βλαβών)

- **Αύξηση του % ασθενών που ανταποκρίνονται**

(↓ αντίστασης στη θεραπεία)

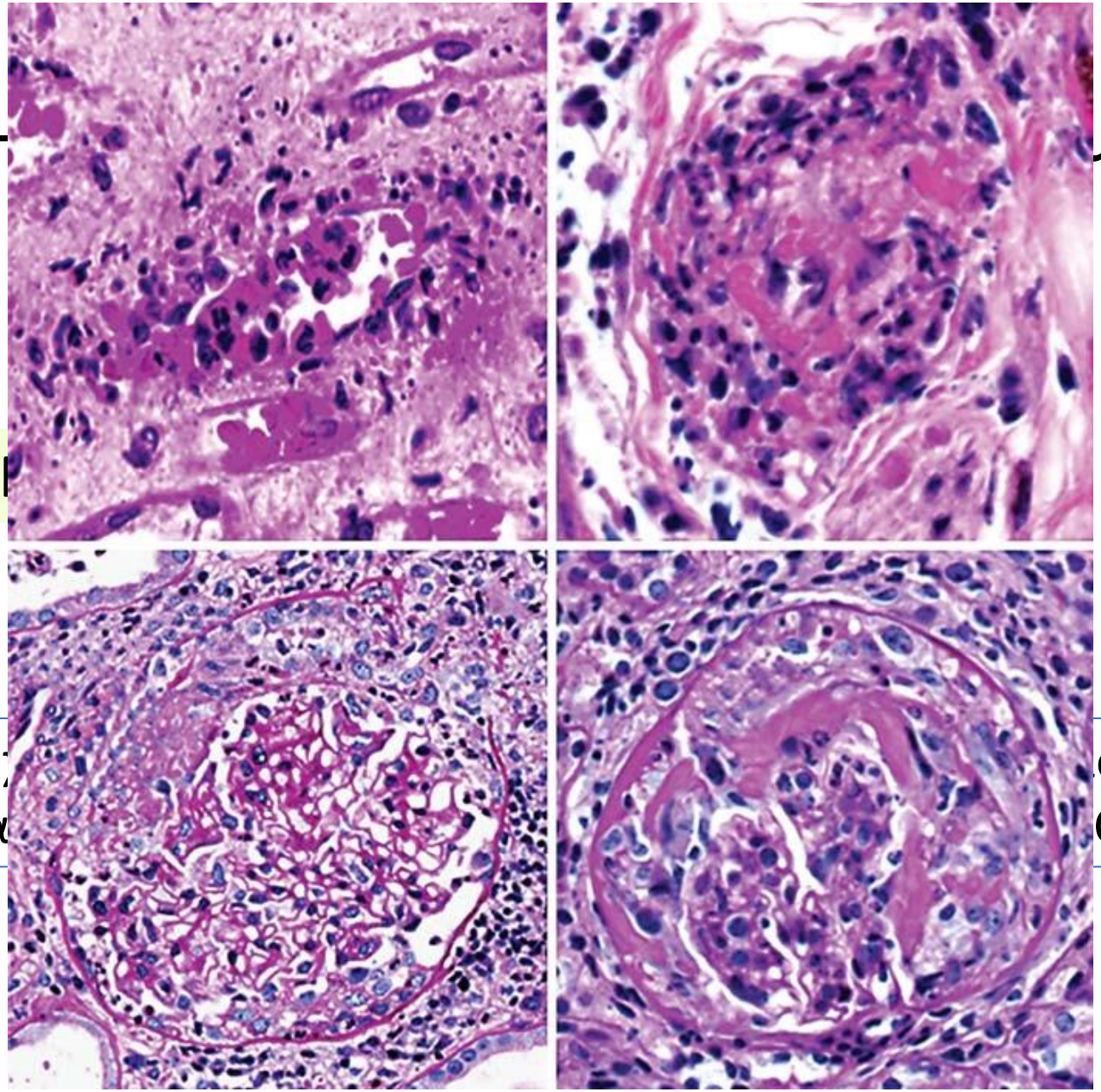
- **Πολύ επιθετική νόσος**

(Πιο αποτελεσματικές θεραπείες)

- **Μείωση τοξικότητας**

(↓ ανεπιθύμητων ενεργειών- ↓ γλυκοκορτικοειδών)

ANCA-



use model

Injection anti-MI

ANCA-GN

Ενδοφλέβια

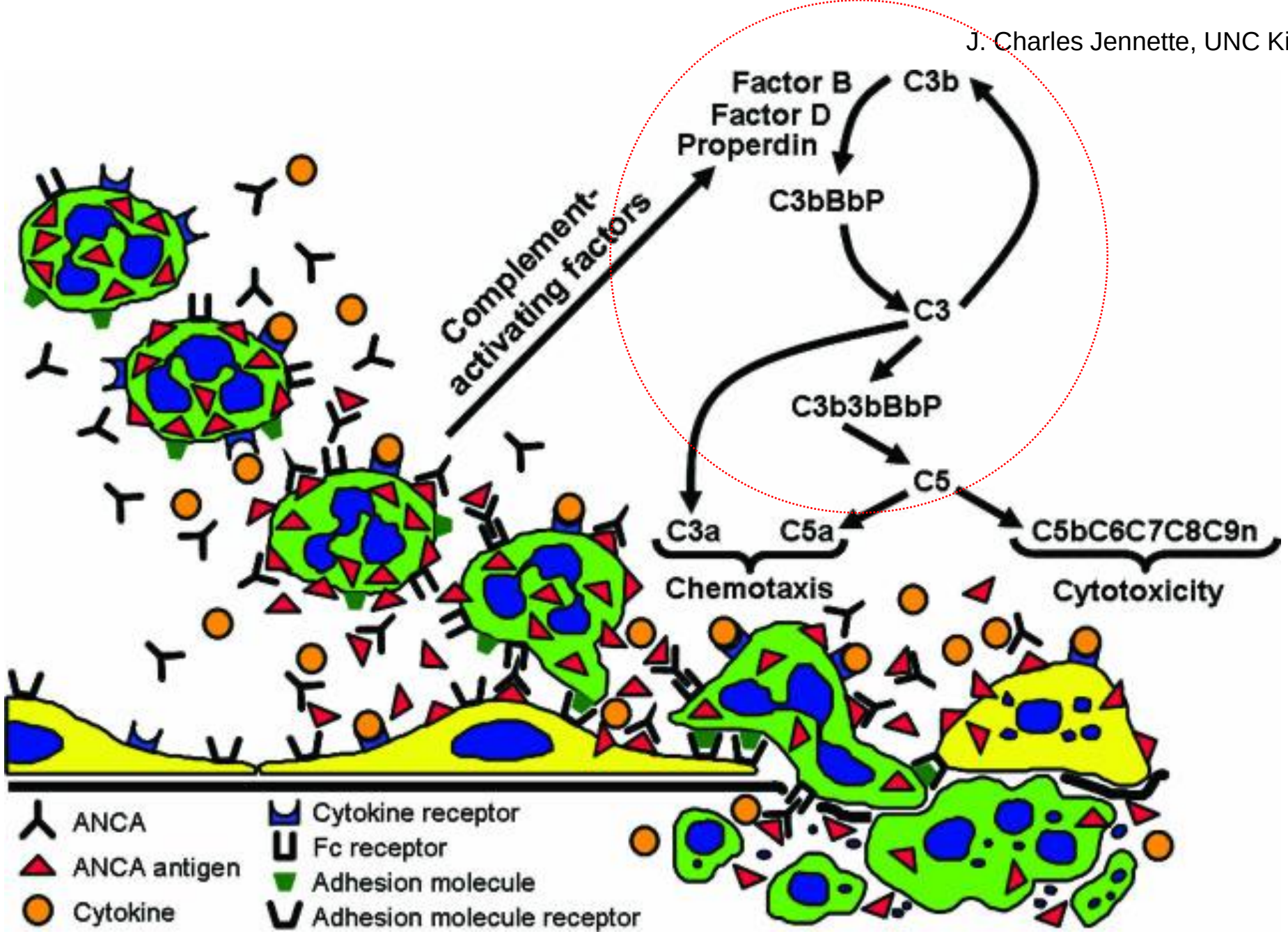
οντικού προκαλεί

α

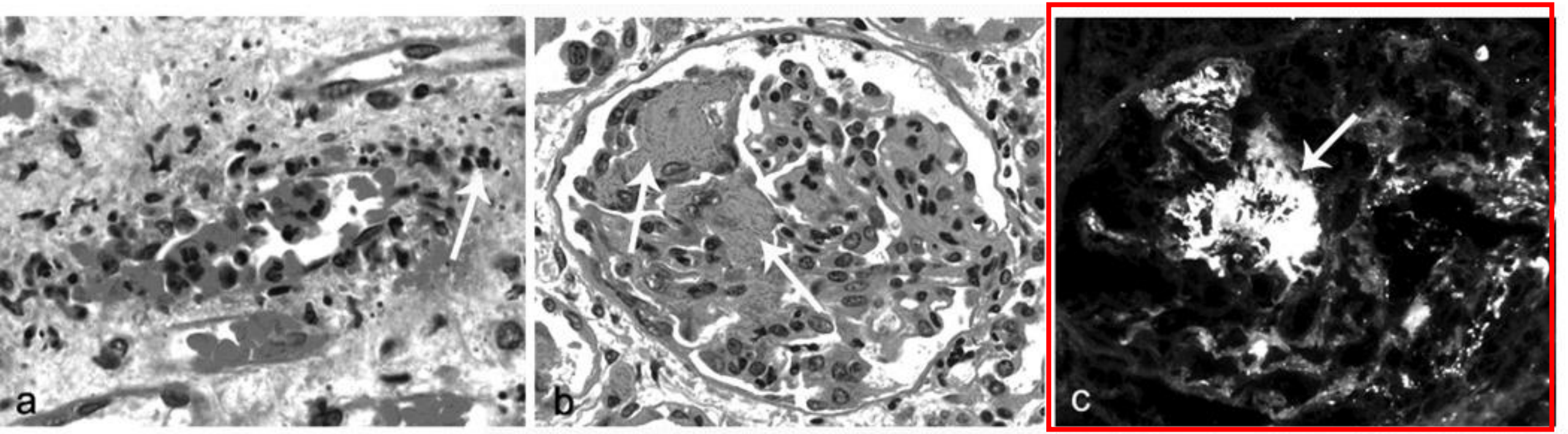
CA ΣΝ

Xiao H et al. J Clin Invest 2002

J. Charles Jennette, UNC Kidney Center



Οξεία νεκρωτική ANCA ΣΝ: Εστιακή χρώση για το C3 (IFF) σε περιοχές ινιδοειδούς νέκρωσης

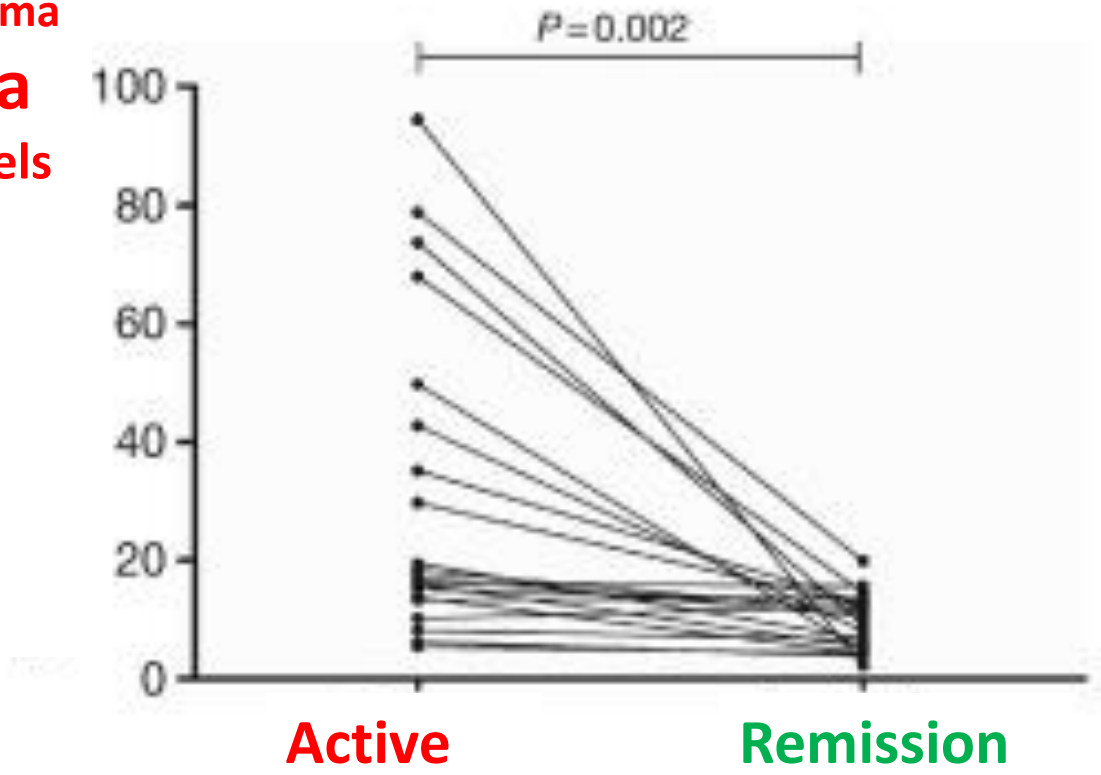


Jennette JC. et al. Sem Nephr. 2013. Nov.

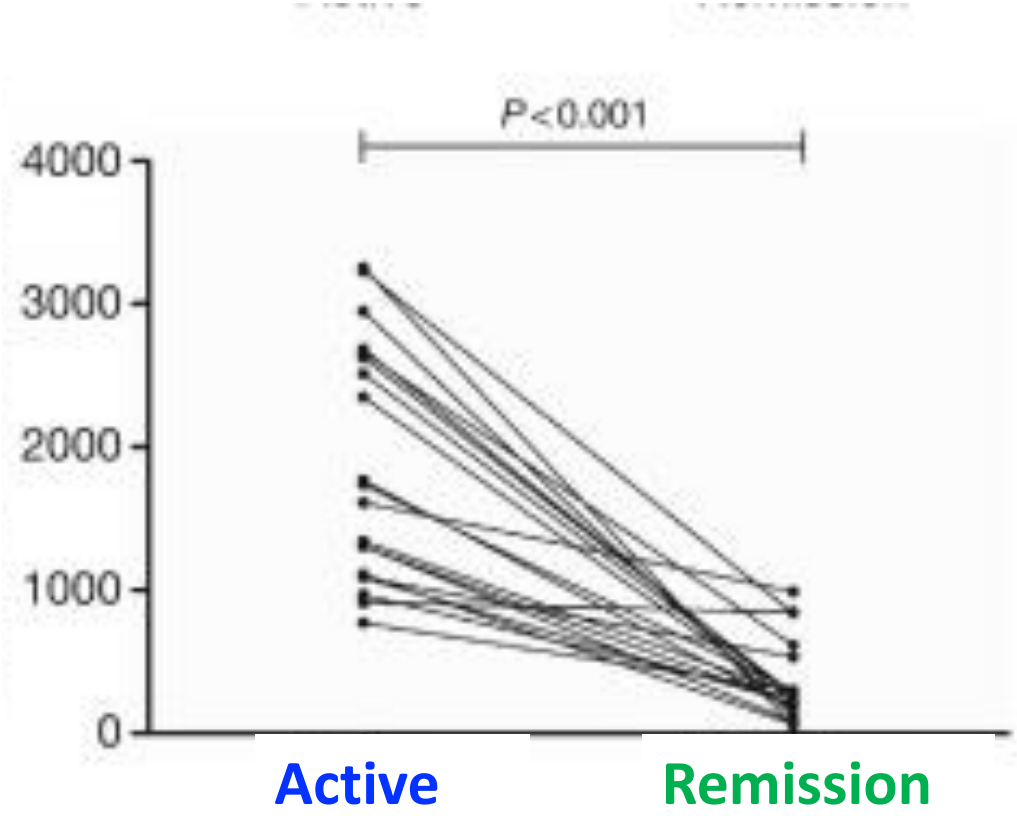
Complement levels in ANCA vasculitis: Active disease versus remission

Complement activation occurs in both MPO- & PR3-ANCA vasculitis

Plasma
C3a
Levels



Plasma
C5a
Levels

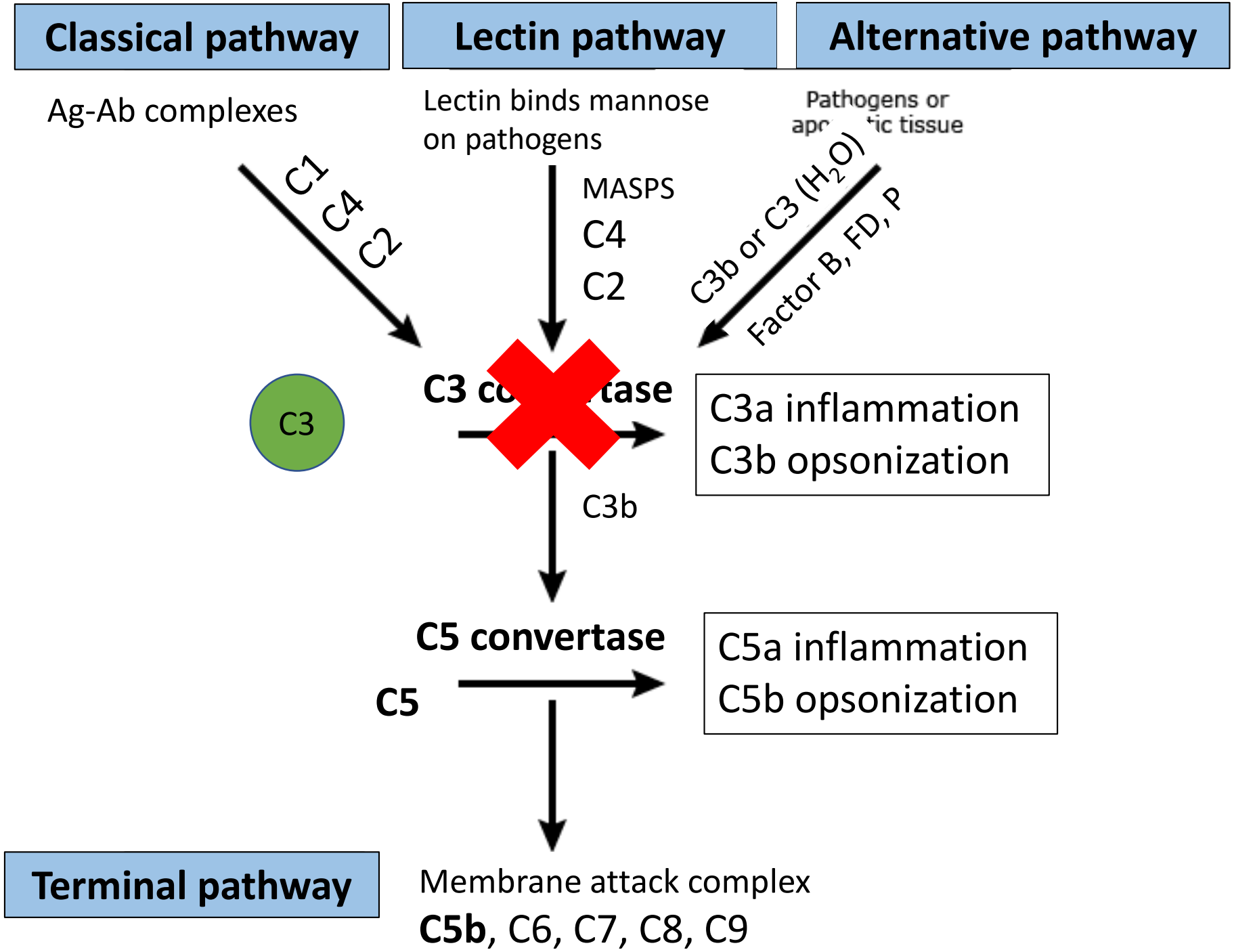


Gou et al Kidney International 2013 83129-137

Low C3 at diagnosis: 6.5 times ESKD or vasculitis-related death 1 year after ANCA-GN diagnosis

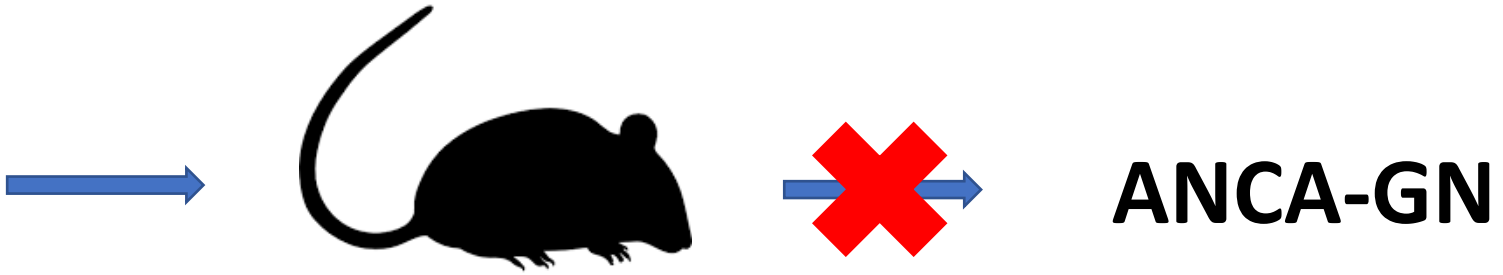
Parameter	Hazard ratio (95% CI)	p value
Low serum C3, mg/dl	**6.47 (1.47–28.35)**	**0.013**
Oliguria, present versus absent	29.57 (4.74–184)	<0.0001
Chronicity score	1.77 (1.23–2.54)	0.002
Serum creatinine, mg/dl	0.82 (0.57–1.19)	0.3
Estimated GFR >30 ml/min per 1.73 m^2	0.08 (0.0001–52.1)	0.44
Normal glomeruli >10%	1.22 (0.13–3.13)	0.59
Activity score	1.37 (0.85–2.24)	0.19
Acute dialysis requirement	0.85 (0.12–5.81)	0.87

Lionaki, S et al. Kidney international reports vol. 6,9 2425-2435.


Classical pathway
Lectin pathway
Alternative pathway
Ag-Ab complexes
Lectin binds mannose on pathogens
Pathogens or
ic tissue
C1
C4
C2
MASPS
C4
C2
C3b or C3 (H_2O)
Factor B, FD, P
C3
C3a inflammation
C3b opsonization
C3b
C5 convertase
C5
C5a inflammation
C5b opsonization
Terminal pathway
Membrane attack complex
C5b, C6, C7, C8, C9

Complement deficient mice

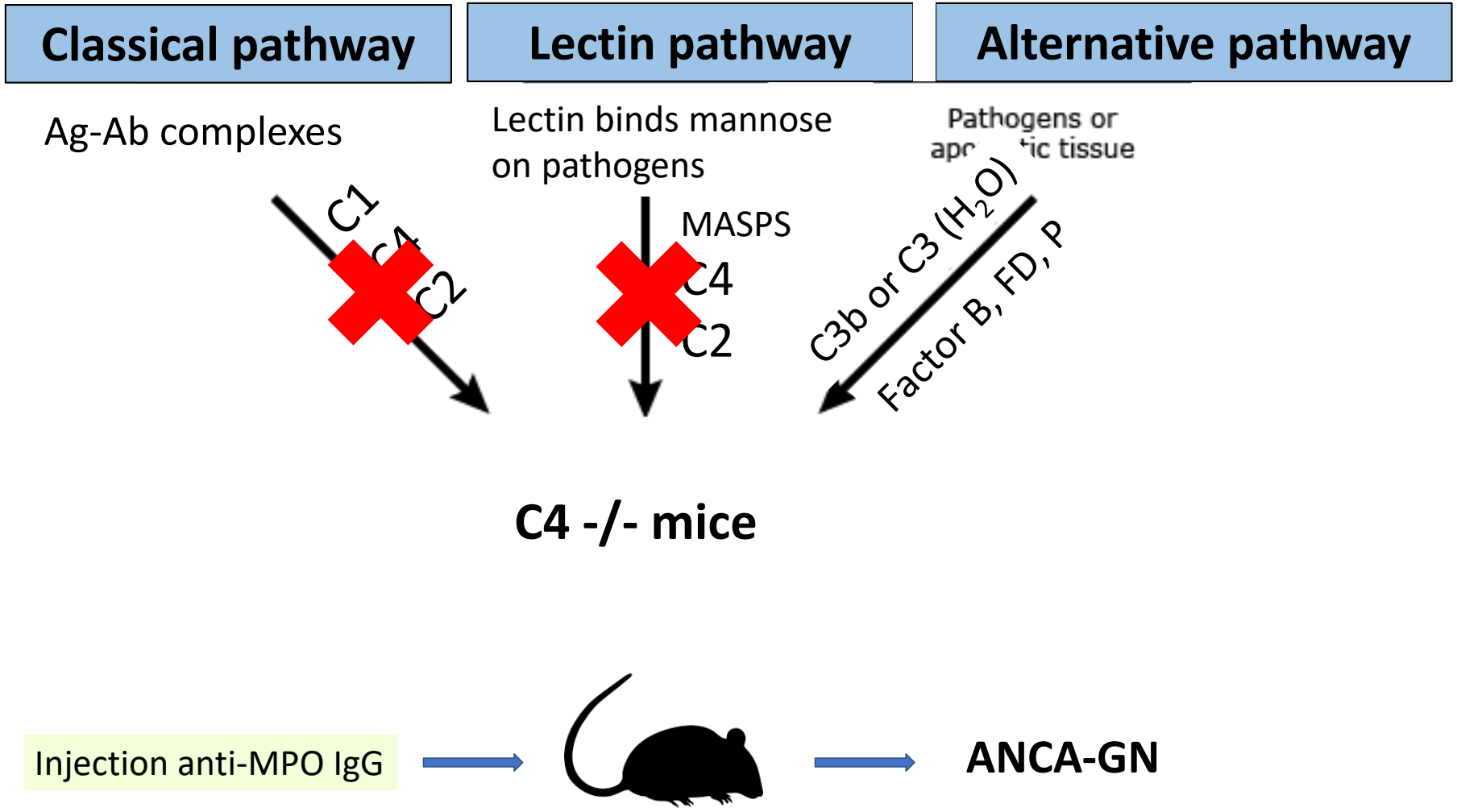
Injection anti-MPO IgG



ANCA-GN

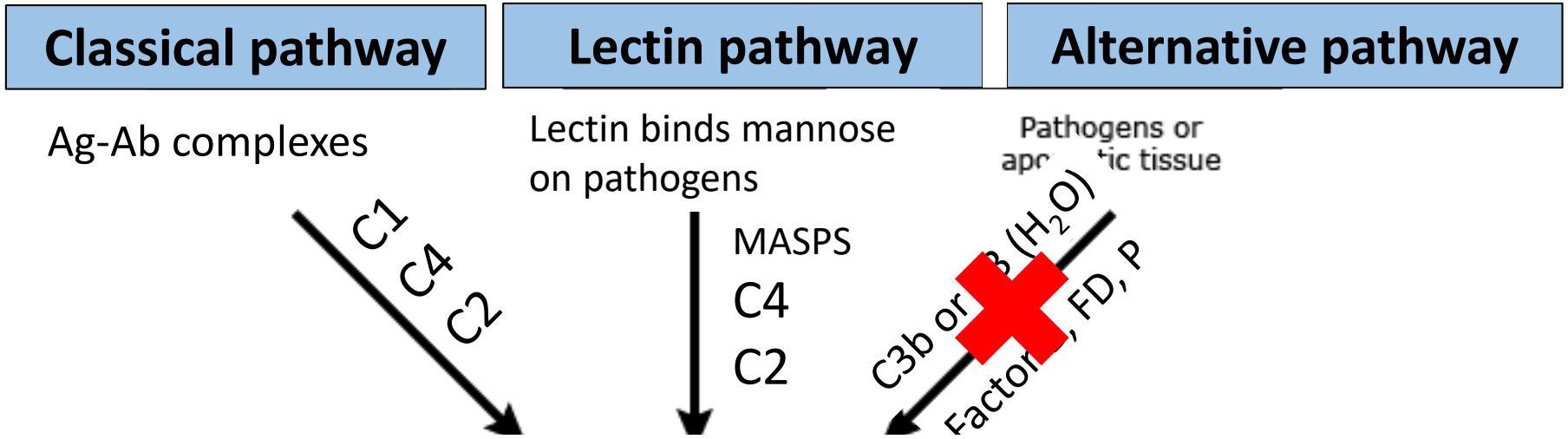
- Η εξάλειψη του συμπληρώματος προστατεύει από την εκδήλωση ANCA-ΣΝ που οφείλεται στη χορήγηση anti-MPO IgG στα ζωικά μοντελα.
- **Το συμπλήρωμα είναι σημαντικός διαμεσολαβητής στην ANCA αγγειίτιδα.**

Xiao et al. AJP January 2007, Vol. 170.



Η κλασική και η οδός της λεκτίνης δεν είναι απαραίτητες για την επαγωγή της ανοσοπενικής ΣΝ.

Xiao et al. AJP January 2007, Vol. 170.

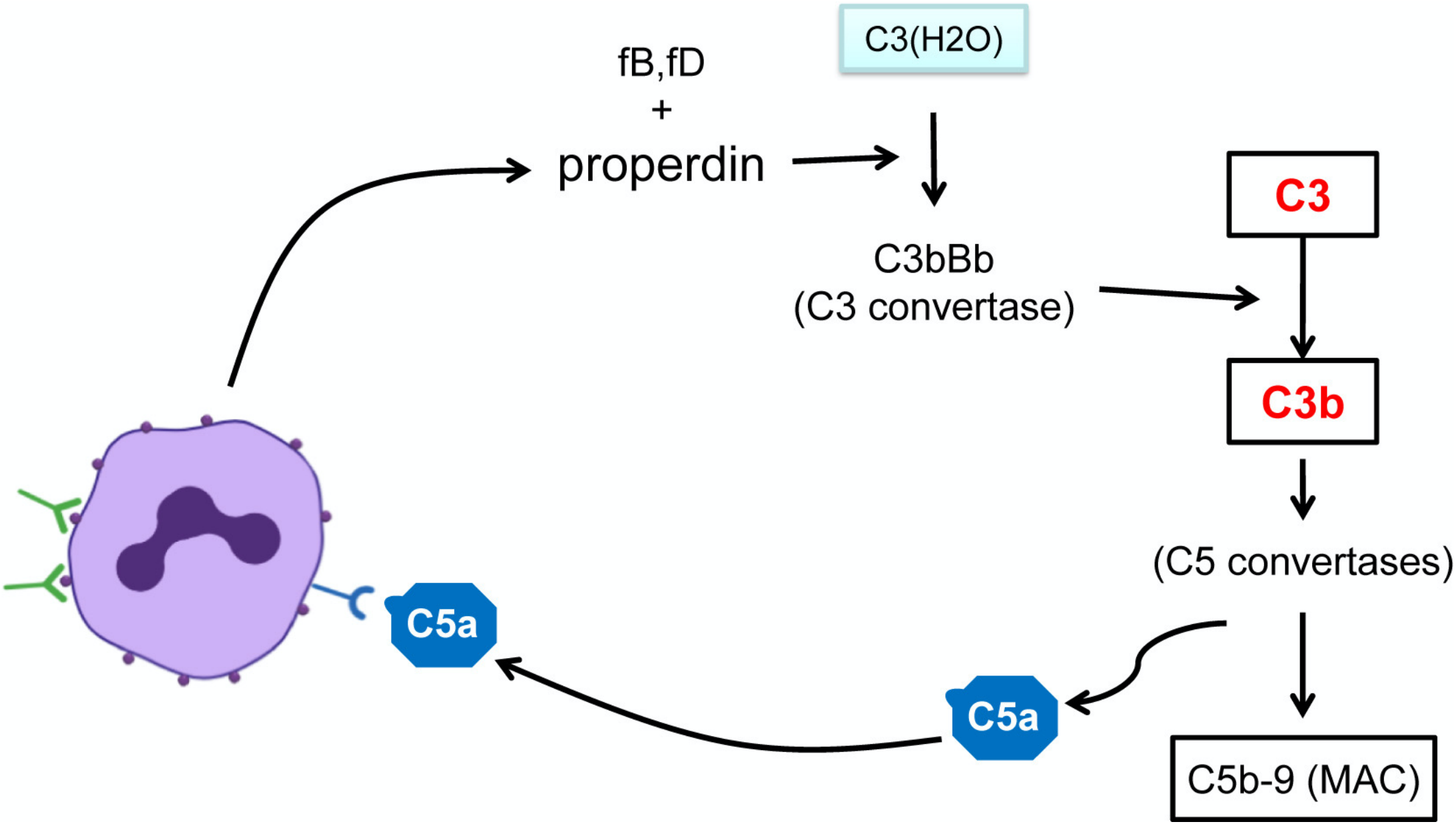


Factor B -/- mice

Η εναλλακτική οδός του συμπληρώματος είναι απαραίτητη για την επαγωγή της ανοσοπενικής ΣΝ μετά τη χορήγηση anti-MPO IgG.

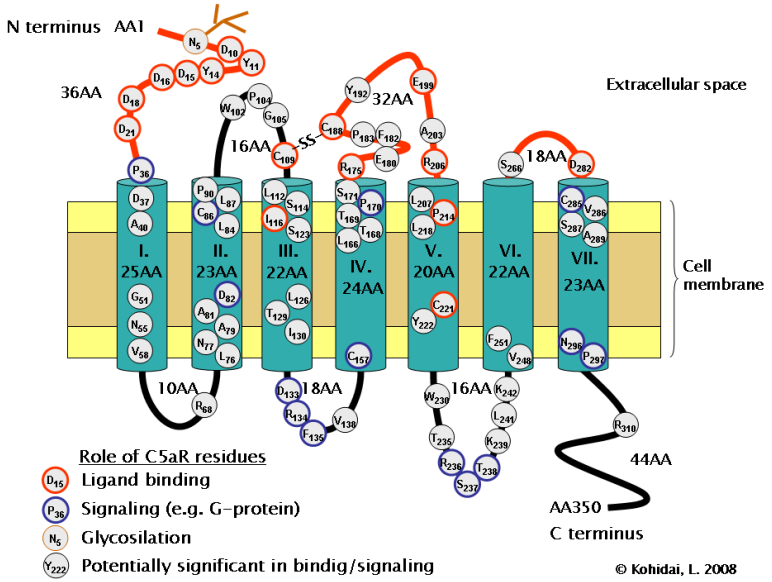
Xiao et al. AJP January 2007, Vol. 170.

- Μήπως δε χρειάζεται πλήρης αποκλεισμός του συμπληρώματος αλλα μια πιο εκλεκτικη παρέμβαση?

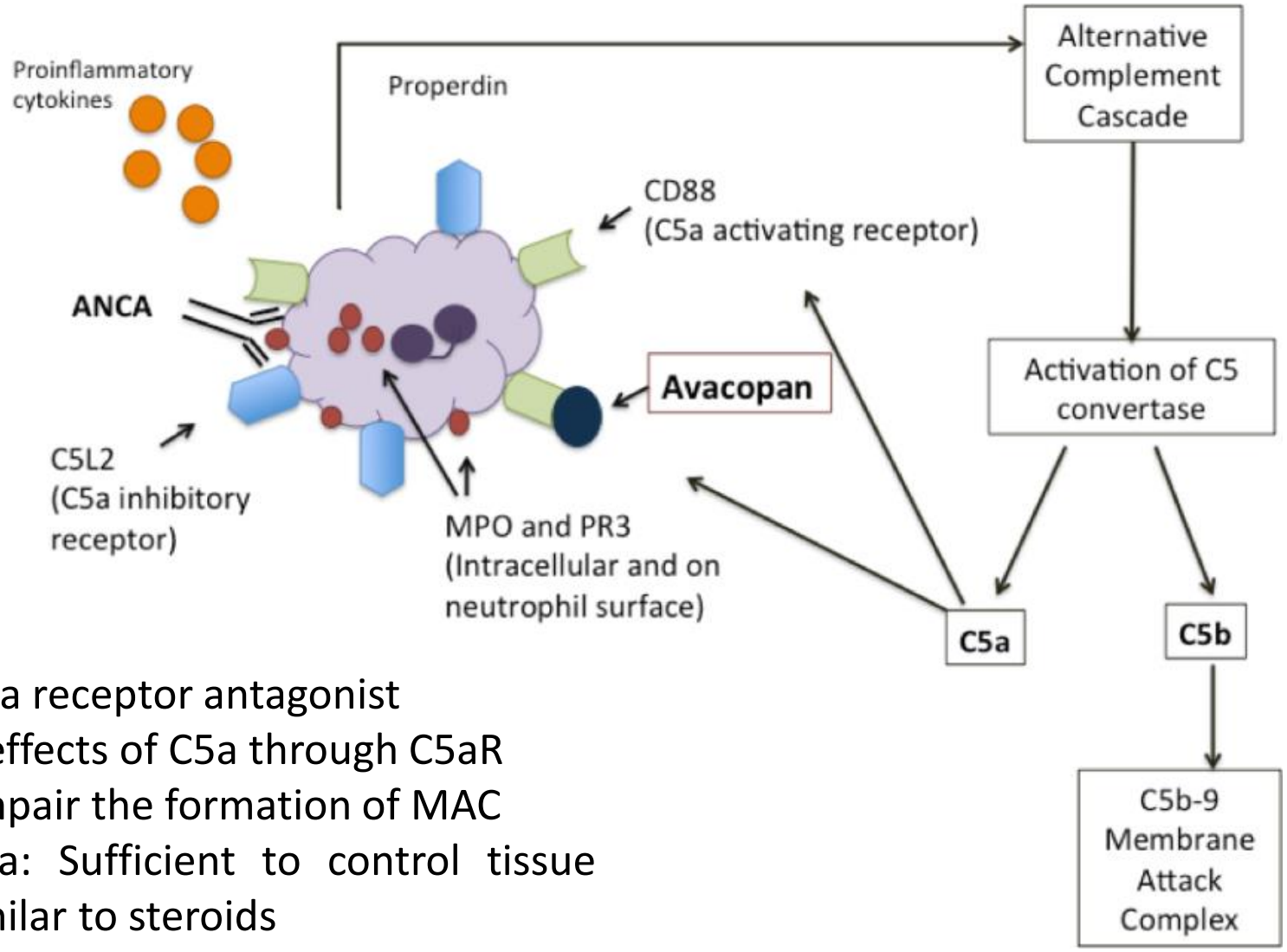

C3(H2O)
fB,fD
+
properdin
C3bBb
(C3 convertase)
C3
C3b
(C5 convertases)
C5a
C5a
C5b-9 (MAC)

C5a αναφυλατοξίνη

- Ισχυρότατος διαμεσολαβητής φλεγμονής
- Χημειοελκυστικός παράγοντας για τα ουδετερόφιλα
- Η σύνδεση του στον υποδοχέα C5aR ενεργοποιεί τα ουδετερόφιλα
- Προάγει την αποκοκκίωση των μαστοκυττάρων



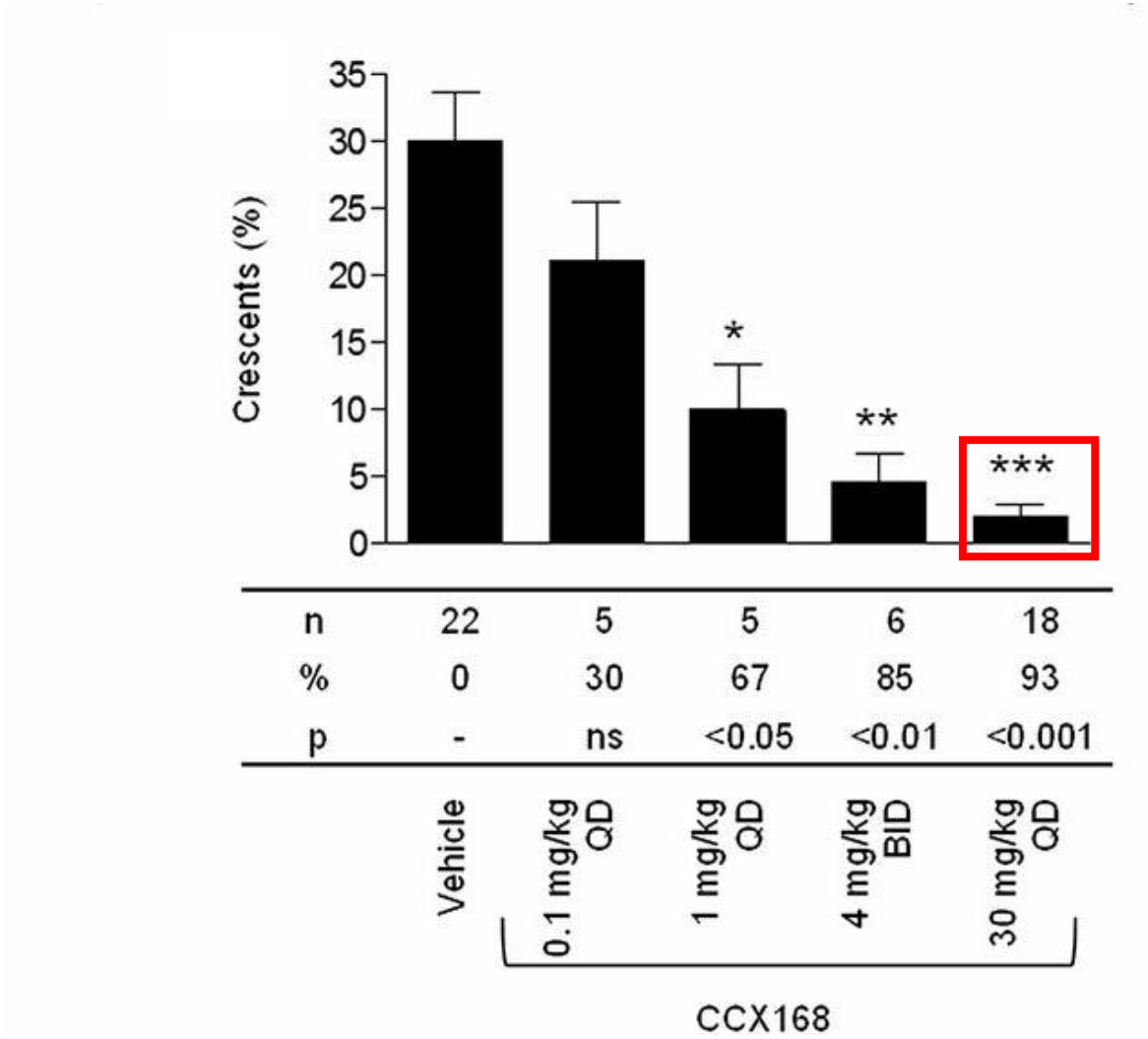
CCX168 (Avacopan): Μικρό μόριο που δρα ως ανταγωνιστής του ανθρώπινου C5aR



- Orally administered C5a receptor antagonist
- Selectively blocks the effects of C5a through C5aR
- Avacopan does **NOT** impair the formation of MAC
- Selective blocking C5a: Sufficient to control tissue necroinflammation similar to steroids
- FDA approved 2021

CCX168 (Avacopan): Μικρό μόριο που δρα ως ανταγωνιστής του ανθρώπινου C5aR

Glomerular crescent, necrosis formation: Reduced in animals receiving CCX168

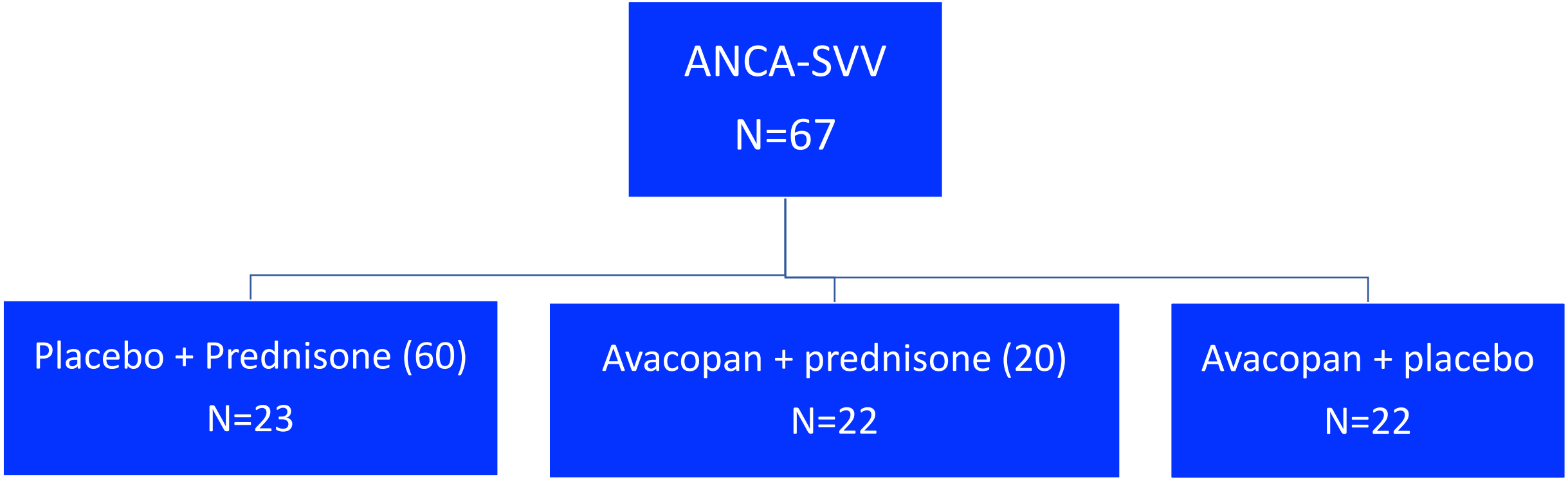


Η χορήγηση σε πειραματικό μοντέλο ποντικού, που εκφράζει τον υποδοχέα C5aR/CD88 είχε ως αποτέλεσμα τη σημαντική βελτίωση της ΣΝ που προκλήθηκε μετά τη χορήγηση anti-MPO-ANCA ορού.

Hong Xiao et al. JASN 2014;25:225-231

CLEAR STUDY: placebo-controlled Trial

Can Avacopan replace oral glucocorticoids without compromising efficacy?



All in combination with CYC followed by AZA or RTX

Primary efficacy measure: Proportion of patients achieving a ≥50% reduction in BVAS by week 12

David R.W. Jayne et al. JASN 2017;28:2756-2767

Clear study - Clinical responses

- 70% of the standard treatment group
- **86% of the avacopan with low-dose prednisone group**

(*p*= 0.002 for noninferiority vs standard care)

- 81% of the avacopan without prednisone group
  (*p* = .01 for noninferiority vs standard of care).
- Avacopan:
  - Rapid improvement in proteinuria
  - **Fewer GC-associated adverse effects**

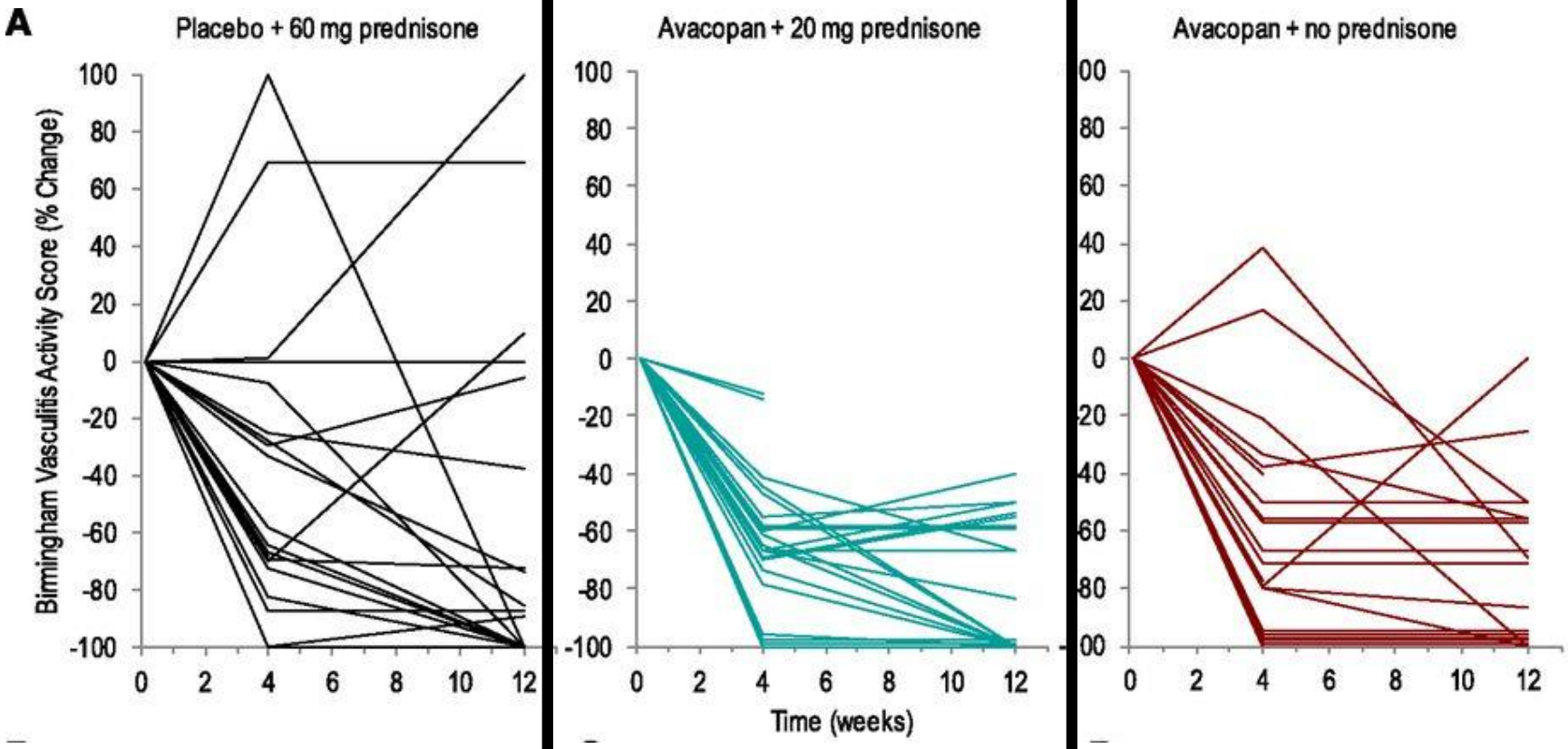
David R.W. Jayne et al. JASN 2017;28:2756-2767

Changes in disease activity, in the 3 treatment groups during the study

Placebo + 60 mg prednisone

Avacopan + 20 mg prednisone

Avacopan + no prednisone



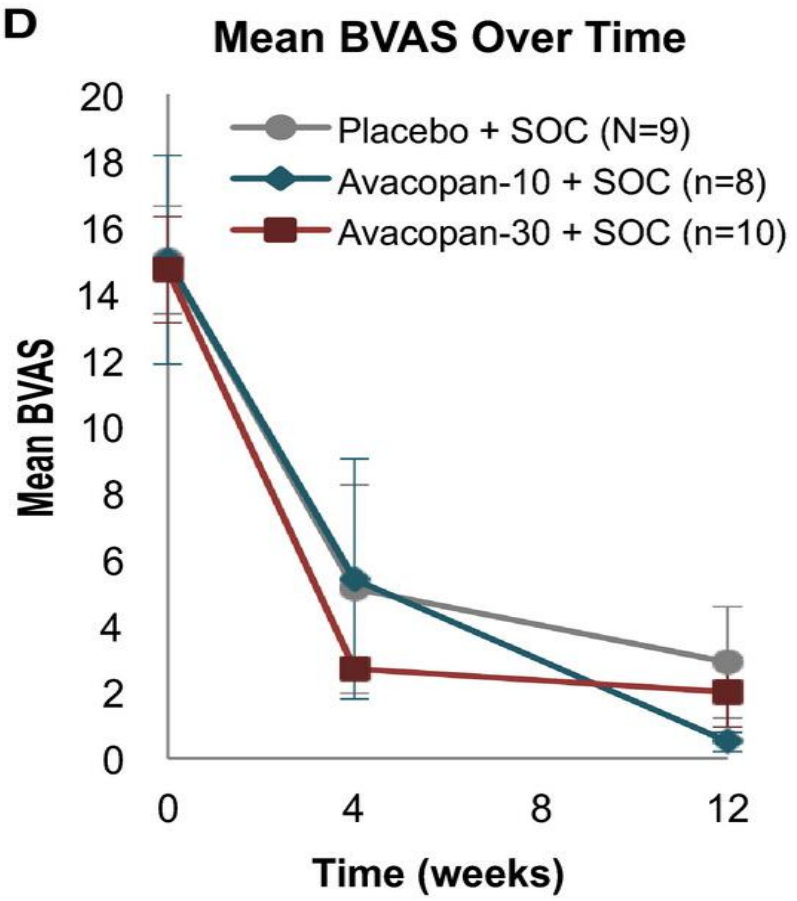
David R.W. Jayne et al. JASN 2017;28:2756-2767

Safety results with Avacopan

	Placebo + prednisone 60 mg	Avacopan + prednisone 20 mg	Avacopan, no prednisone
Any adverse event	2 (9%)	2 (9%)	2 (9%)
Any grade 3 or greater adverse event	2(8%)	2(9%)	1(5%)
Any serious adverse event	4(17%)	3(14%)	8(36%)
Any adverse event potentially related to glucocorticoids	15(65%)	4(18%)	11(50%)
Safety laboratory abnormalities	2(8%)	4(20%)	8(38%)

David R.W. Jayne et al. JASN 2017;28:2756-2767

CLASSIC STUDY: Evaluated 2 doses of avacopan + standard of care (SOC) vs. SOC in ANCA-vasculitis



The **30-mg twice daily dose** appeared to improve:

- Clinical activity
- eGFR- Renal response
- Quality of life

Merkel P et al. ACR , Volume: 2, Issue: 11, Pages: 662-671, October 2020

ADVOCATE trial: Avacopan vs. high-dose GCs in ANCA-vasculitis

Σκοπός

- Η σύγκριση της αποτελεσματικότητας ενός θεραπευτικού σχήματος με βάση **το Avacopan** στην επαγωγή και διατήρηση της ύφεσης σε ασθενείς με ANCA-αγγείτιδα (GPA/MPA) έναντι ενός σχήματος με βάση τα GCs

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE trial: Avacopan vs. high-dose GCs in ANCA-vasculitis

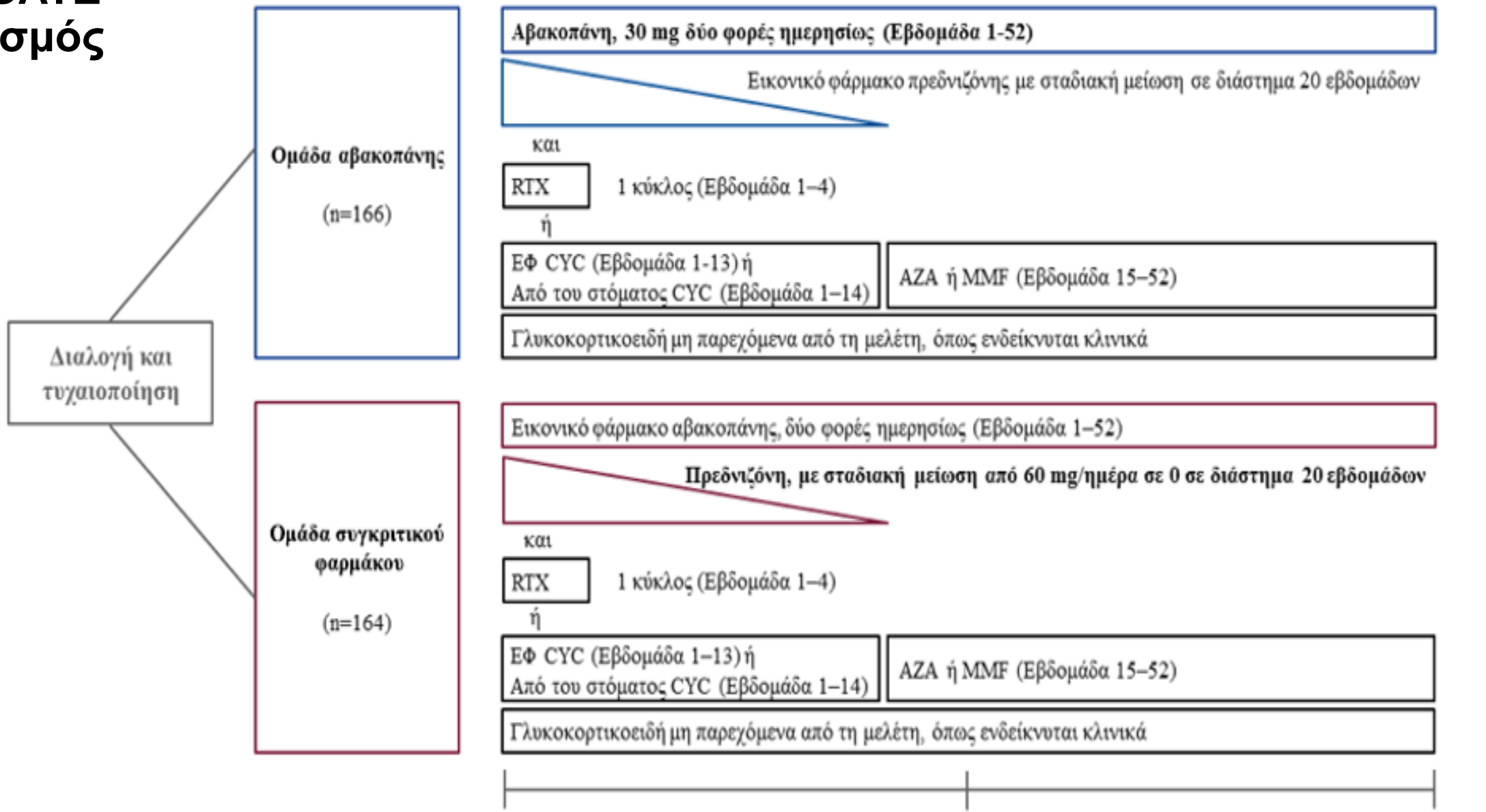
- Double-blind, parallel-arm, active-comparator randomized trial comparing
- N=331, newly diagnosed or relapsing GPA/MPA
- eGFR>15 mL/min/1.73 m^2 , mean BVAS 16
- Oral avacopan, 30 mg, q 12h or oral prednisone taper
- Co-administered with RTX or CYC , followed by AZA or MMF, for up to 1 year
- **Primary trial endpoints**:

➢% Remission at week 26 (BVAS=0), not taking GCs

➢ % Sustained remission (week 26-week 52)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE
Σχεδιασμός



Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE study: Results

Remission at week 26:

- 72.3% avacopan group
- 70.1% prednisone group

(p<0.001 for noninferiority; p= 0.24 for superiority)

Sustained remission at week 52:

- 65.7% avacopan group
- 54.9% prednisone group

(p<0.001 for noninferiority; p= 0.007 for superiority)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

Avacopan: Beneficial effect in renal function relative to GCs

eGFR change from baseline (all patients)

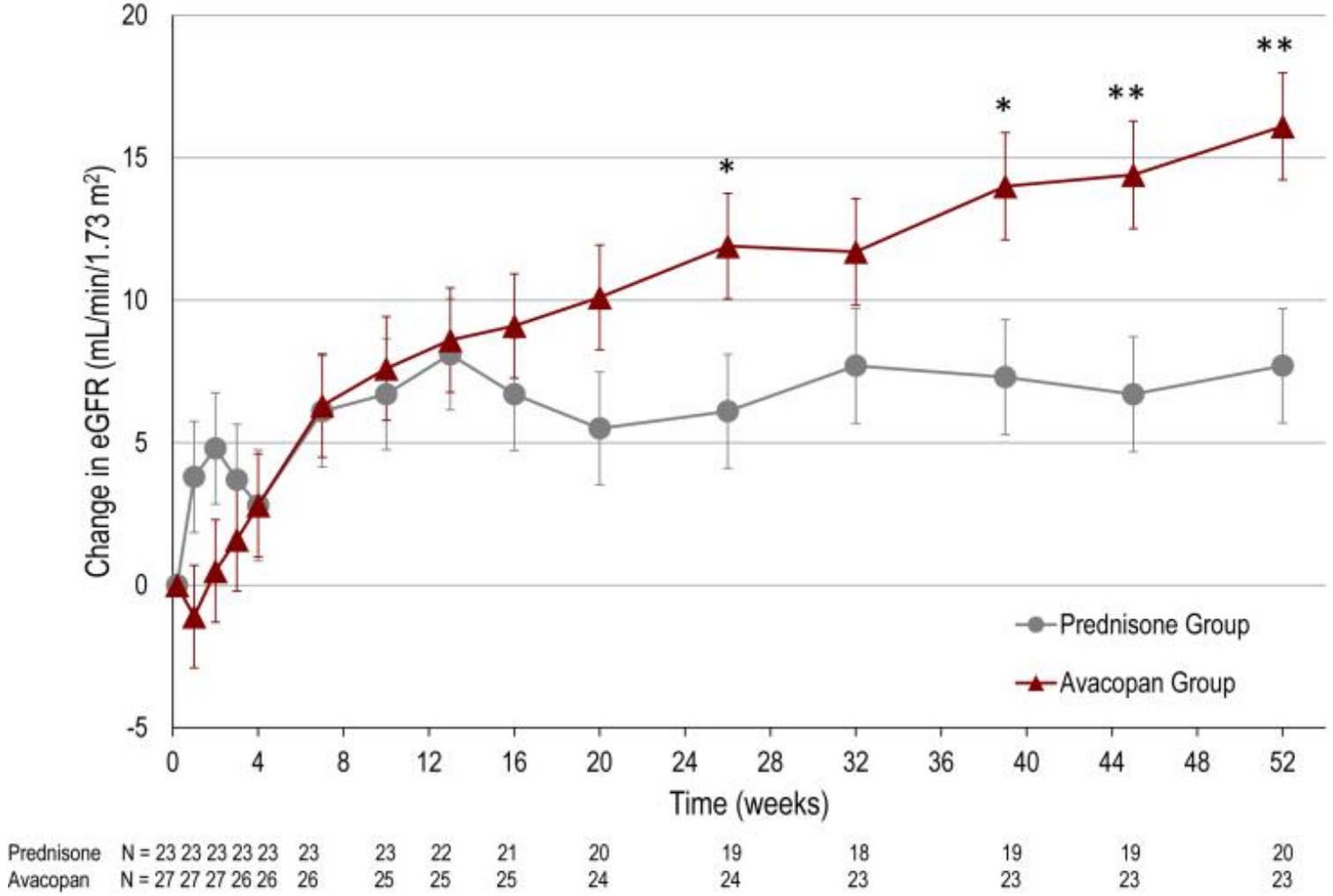
- **Avacopan group**: 7.3 mL/min/1.73 m^2
- **Prednisone group**: 4.1 mL/min/1.73 m^2
  (difference: 3.2 mL/min/1.73 m^2; 95% CI, 0.3-6.1)

Among patients with stage 4 CKD

- **Avacopan group**: 13.7 mL/min/1.73 m^2
- **Prednisone group**: 8.2 mL/min/1.73 m^2
  (difference: 5.6 mL/min/1.73 m^2; 95% CI, 1.7-9.5)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE trial: Change in kidney function in patients with baseline eGFR ≤20 ml/min/1.73 m²

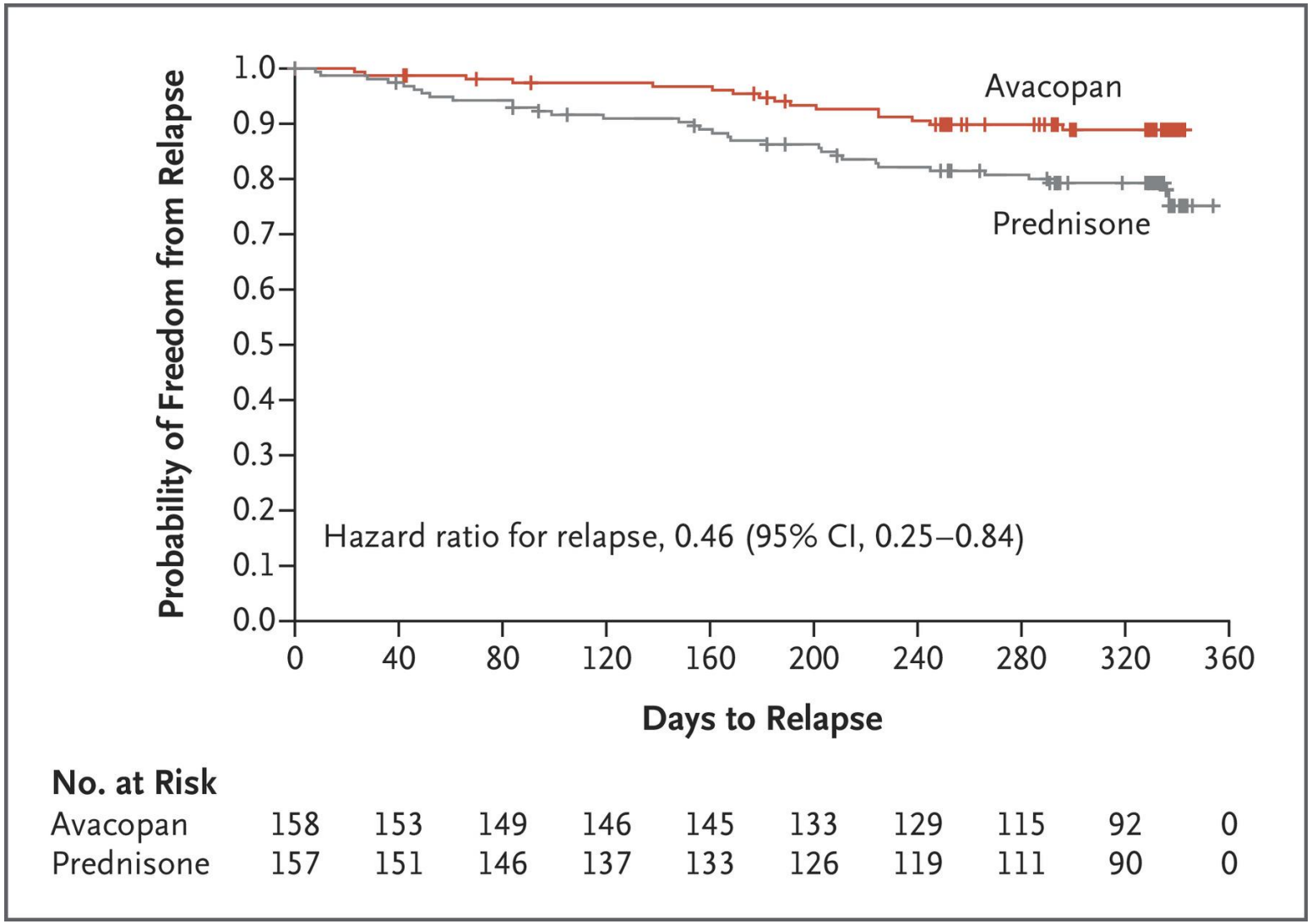


Avacopan

Prednisone

Kidney Int Rep. 2023 Apr; 8(4): 860–870.

ADVOCATE study: Probability of disease relapse

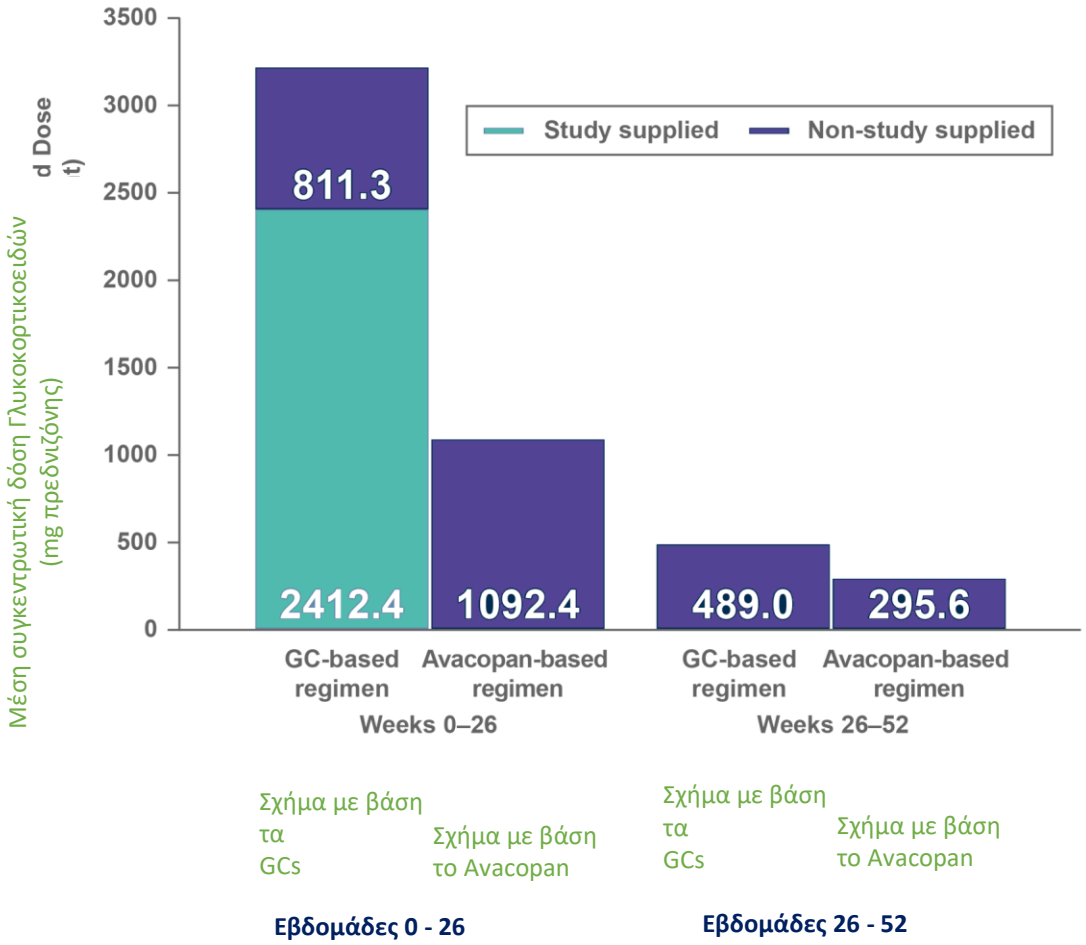


Relapses

- 10.1%, avacopan group
- 21.0%, prednisone group
- HR for relapse after remission (avacopan vs prednisone): 0.46 (95% CI, 0.25-0.84)

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

ADVOCATE: Θεραπευτικό σχήμα με Avacopan ↓ συνολικής δόσης των GCs



65%

Χαμηλότερη συνολική δόση GCs με το Avacopan

- Αθροιστική δόση GCs: **1.349 mg έναντι 3.655 mg**

40%

Χαμηλότερη δόση GCs με το Avacopan στο διάστημα 26–52 εβδομαδες

- Μέση συνολική δόση GC: **295,6 mg έναντι 489,0 mg**

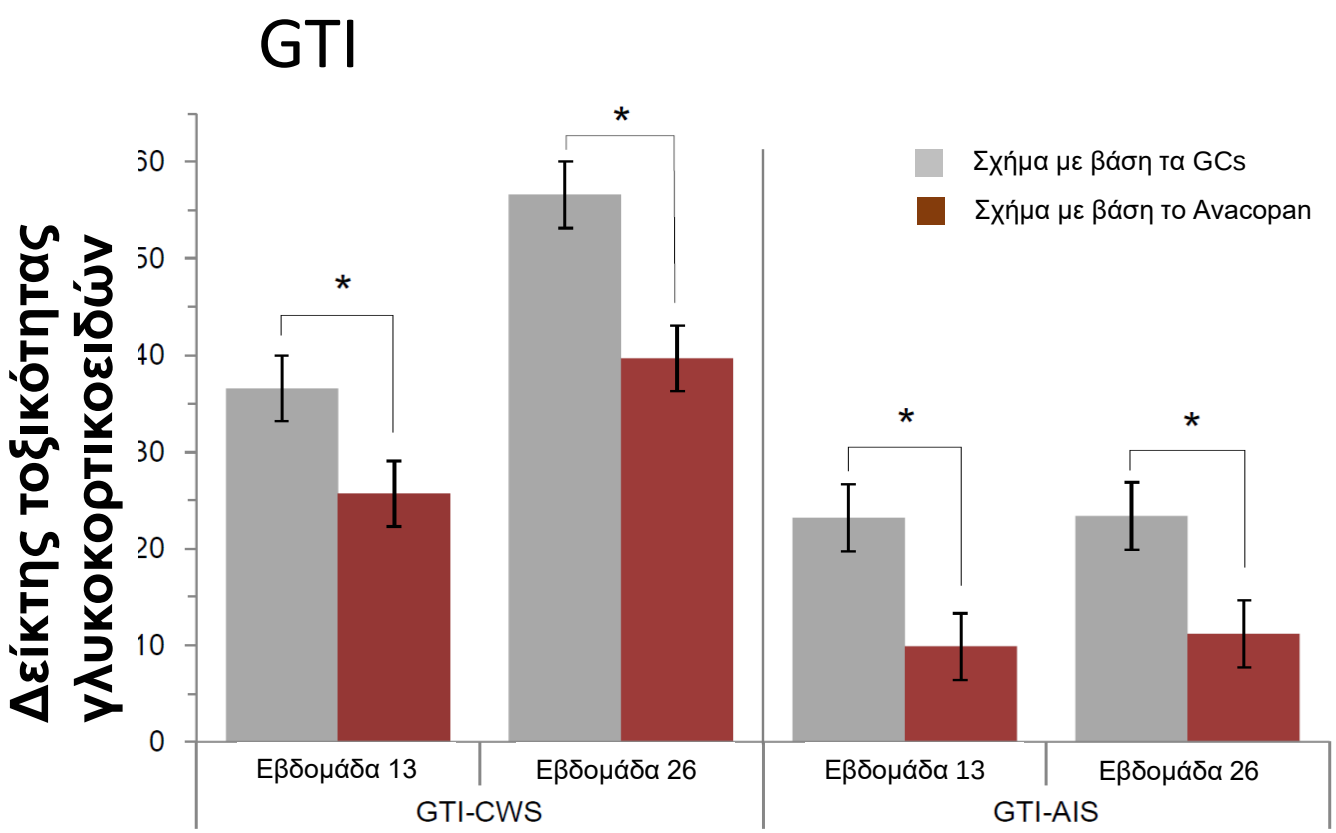
2/3

Ασθενών που έλαβαν θεραπεία με το Avacopan δεν έλαβαν GCs στο διάστημα 26–52

1. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609.
2. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609 [Suppl Appendix].

ADVOCATE

Σχήμα με Avacopan: ↓ Δείκτη τοξικότητας γλυκοκορτικοειδών (GTI)



- **↓ 16,9 μονάδες του GTI CWS** στο σχήμα με το Avacopan έναντι του σχήματος με τα GCs (week 26) (95% CI, -25,6 έως -8,0).
- **↓12,1 μονάδες του GTI AIS** στο σχήμα με το Avacopan έναντι του σχήματος με τα GCs (week 26) (95% CI, –21,1 έως –3,2)

Jayne D, et al. N Engl J Med 2021;384(7):599–609.

ADVOCATE trial
Avacopan in ANCA-vasculitis

- In addition to standard of care: **Well tolerated**
- Avacopan (30 mg q 12h): **Improved time to remission**

Kidney Int Rep. 2023 Apr; 8(4): 860–870.

Jayne DRW et al. ADVOCATE Study Group. N Engl J Med. 2021 Feb 18;384(7):599-609

Real-World data With Avacopan in ANCA-Vasculitis

- Multicenter retrospective analysis, N=92 patients
- Newly diagnosed or relapsing ANCA-vasculitis
- All received therapy with avacopan
- Outcome measures: clinical remission at 26 and 52 weeks

Zonozi R, et al. Kidney International Reports (2024)

Induction regimen	
Combination therapy (RTX + low-dose CYC)[a]	43 (47%)
RTX	44 (48%)
CYC (standard dosing)	2 (2%)
Other	2 (2%)
Plasma exchange	13 (14%)
Methylprednisolone	
Received i.v. pulse	59 (64%)
Cumulative dose, mg	1340 (1319)
Prednisone, mg	
Dose at wk26	1.8 (3.7)
Dose at wk52	0.6 (2.5)
Cumulative dose at wk 12	1797 (1104)
Cumulative dose at wk 52	2212 (1550)
Off prednisone (as of last follow-up)	64 (72%)
Time to start avacopan (from start of induction), wk	3.6 (2.1–7.7)
Time to stop prednisone (from start of avacopan), wk	5.6 (3.3–9.5)

Μετά την επαγωγή της ύφεσης
65 ασθενείς (71%) ξεκίνησαν θεραπεία συντήρησης με:

- Rituximab (n = 64) ή
- AZA (n = 3)

Zonozi R, et al. Real-world Experience with Avacopan in ANCA Vasculitis: A Multi-center Retrospective Cohort Analysis, Kidney International Reports (2024)

Real-World data With Avacopan in ANCA-Vasculitis

- 23% (n = 21) baseline eGFR< 15 ml/min/1.73 m^2
- 10% (n=9) on kidney replacement therapy
- Enrollment eGFR was 33 (27) ml/min/1.73 m^2
- Time to start avacopan was 3.6 (2.1–7.7) weeks
- Time to discontinue prednisone after starting avacopan 5.6 (3.3–9.5) weeks
- **Clinical remission:**
- **90% of patients at week 26**
- **84% of patients at week 52**

Zonozi R, et al, Kidney International Reports (2024)

Αποτελέσματα

Αύξηση του eGFR

- 12,2 ml/min/1,73 m^2 στους 6,5 μήνες
- 19,8 ml/min/1,73 m^2 στους 12 μήνες

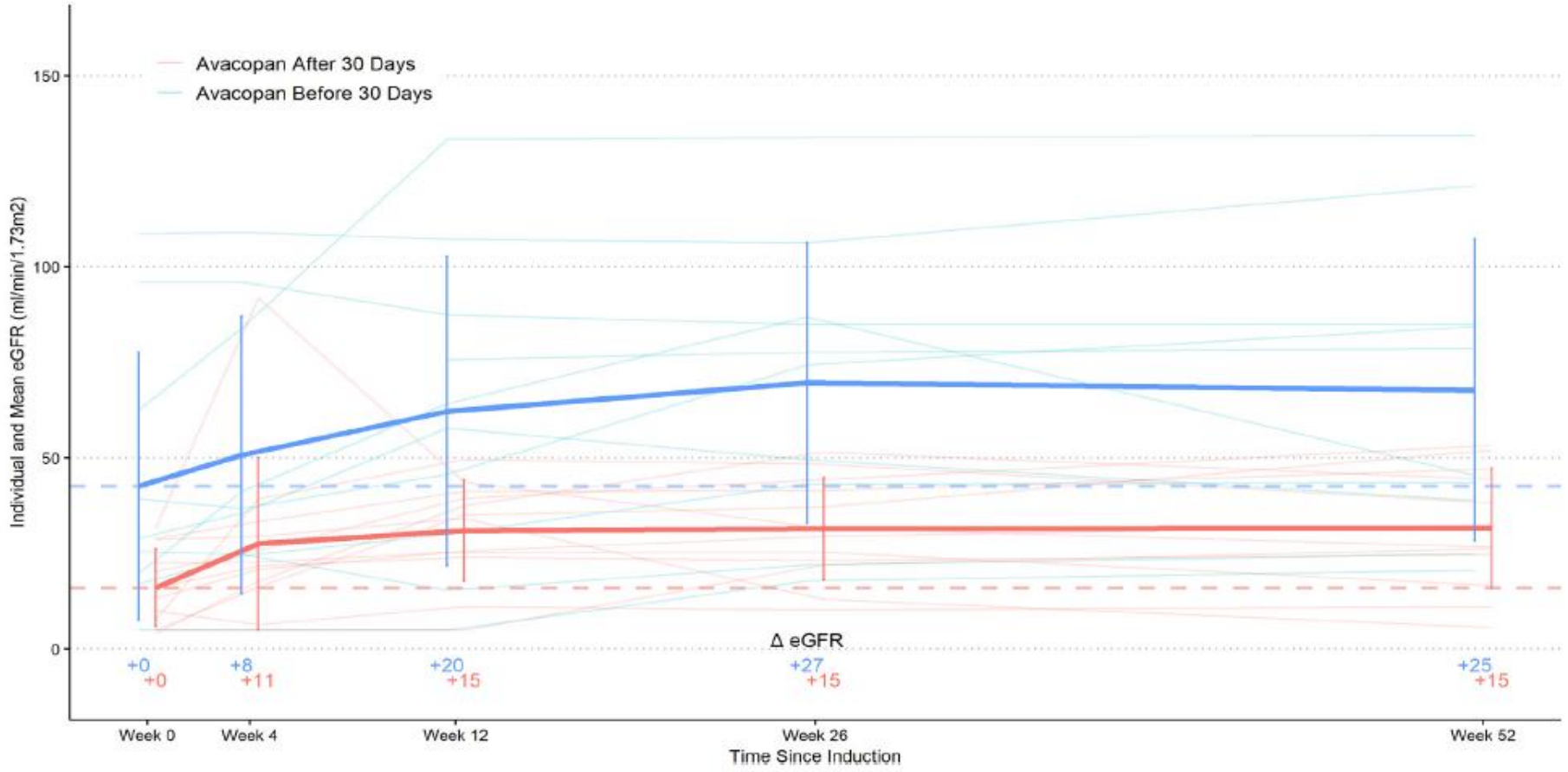
Αθροιστική δόση πρεδνιζόνης p.o

- 1,8 g (1,1) στις 12 εβδομάδες
- 2,2g (1,6) στις 52 εβδομάδες

Zonozi R, et al., Kidney International Reports (2024)

Does delayed initiation of avacopan affect response?

Avacopan After 30 Days vs. Avacopan Before 30 Days of induction therapy



+25

mL /min/ 1.73m²

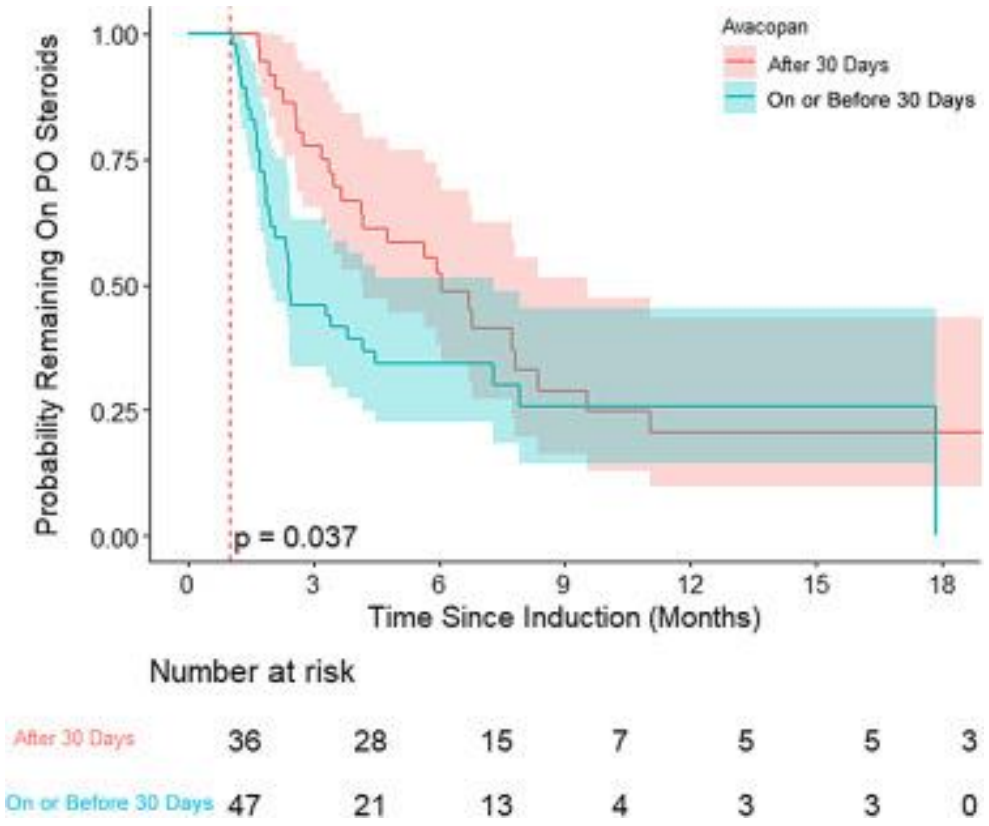
+15

mL /min/ 1.73m²

Zonozi R, et al. Kidney International Reports (2024)

Real-World Experience With Avacopan in ANCA-Vasculitis

Probability on remaining in GCs per os



Οι ασθενείς που ξεκίνησαν το avacopan μετά από 30 ημέρες από την έναρξη της θεραπείας επαγωγής της ύφεσης έλαβαν **μεγαλύτερες αθροιστικές δόσεις κορτιζόνης** την εβδομάδα 12 (αθροιστική δόση: 2.1 g VS 1.6 g, P=0.03), και την εβδομάδα 52 (αθροιστική δόση: 2.6 g vs. 1.9 g, p=0.03)

Διακοπή θεραπείας για άλλο λόγο

- ↑ Τρανσαμινασών (n = 4)
- Γαστρεντερικές διαταραχές (n=3)

Zonozi R, et al. Real-world Experience with Avacopan in ANCA Vasculitis: A Multi-center Retrospective Cohort Analysis, Kidney International Reports (2024)

Real-World Experience With Avacopan in ANCA-Vasculitis
Advanced kidney disease

- 9 patients dialysis-dependent at diagnosis
- 5/9 (56%) off dialysis

Patients with eGFR<15 ml/min vs. patients with GFR>15 ml/min

- More frequent PLEX use (43%)
- Delayed avacopan initiation [median 47(21-58) days vs. 21(14-49)]
- Higher risk for ESKD (30% vs. 0)
- Week 26: ↑ eGFR from baseline, 19.4 (22.7) vs 5 (25) ml/min
- Week 52: ↑ eGFR from baseline, 25.1 (15.6) vs 9.4 (25.6) ml/min

Zonozi R, et al. Real-world Experience with Avacopan in ANCA Vasculitis: A Multi-center Retrospective Cohort Analysis, Kidney International Reports (2024)

Avacopan use in special populations

Advanced kidney disease (eGFR<15ml/min/1.73m^2)

- Avacopan & M1 metabolite: Hepatically metabolized by CYP3A4
- Route of elimination is primarily fecal
- Oral administration ▶ 77% in feces and 10% in urine
- ▶ **Depressed kidney function cannot significantly alter pharmacodynamics or pharmacokinetics of avacopan**

National Center for Biotechnology Information. PubChem compound summary for CID 49841217, avacopan. https://pubchem.ncbi.nlm.nih.gov/compou nd/Avacopan

Avacopan use in special populations
Dialysis dependent patients at diagnosis

- Avacopan MW= 581.6 g/mol
- Uncharged
- Poorly water soluble (lipophilic)
- 99.9% protein-bound
- ▶ Dialysis is not expected to alter plasma concentrations significantly
- ▶ No need for dose adjustment

National Center for Biotechnology Information. PubChem compound summary for CID 49841217, avacopan. https://pubchem.ncbi.nlm.nih.gov/compou nd/Avacopan

Avacopan in difficult to treat ANCA vasculitis

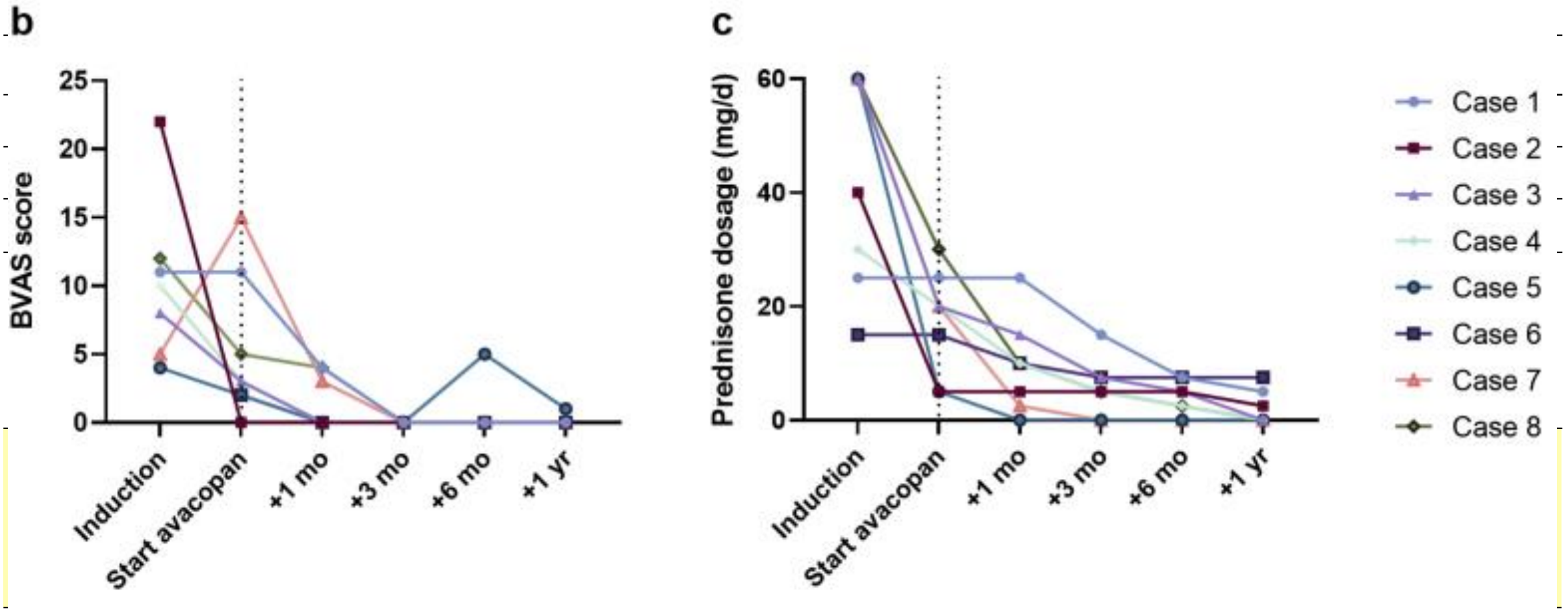
- Treatment resistance (steroid resistance)
- Steroid dependence (relapsing or grumbling when prednisone <15 mg/day)
- Necessity to avoid steroid-related toxicity (obesity, diabetes, severe steroid-related toxicity, psychosis)

van Leeuwen et al. Kidney Int Rep. 2021 Dec 8;7(3):624-628

Avoid avacopan

1. Active, untreated, and/or uncontrolled chronic liver disease
2. Taking moderate to strong CYP3A4 inducers
3. Probably reduced dose in patients on strong CYP3A4 enzyme inhibitors

Difficult-to-Treat ANCA Vasculitis: 8 adult patients with GPA and MPA



van Leeuwen et al. Kidney Int Rep. 2021 Dec 8;7(3):624-628

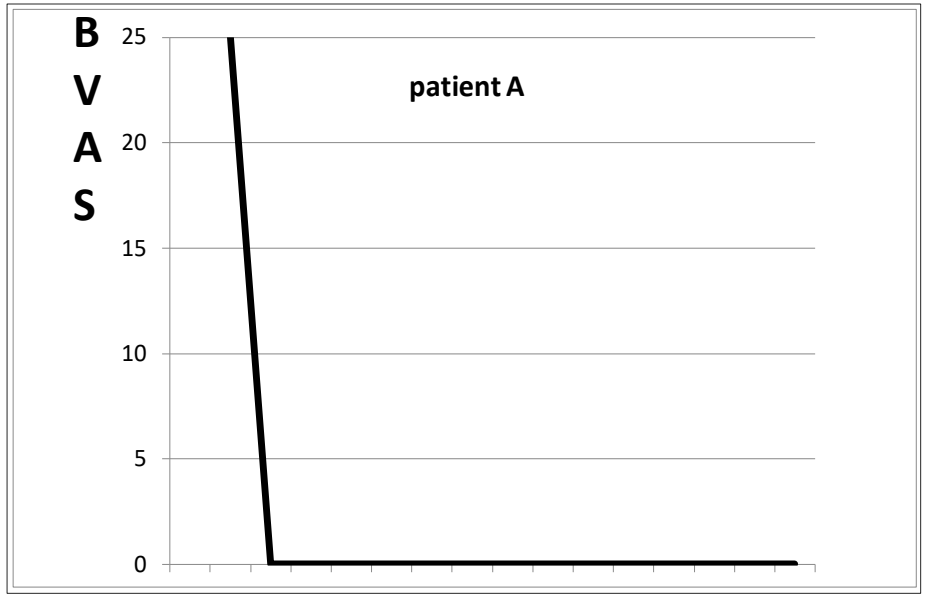
Avacopan in ANCA-SVV:

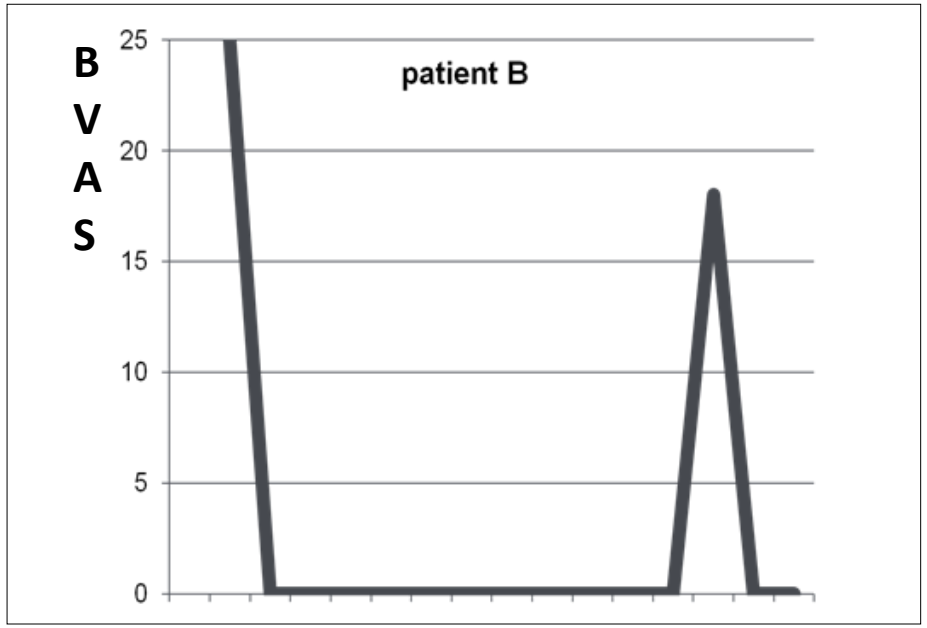
Patients with:

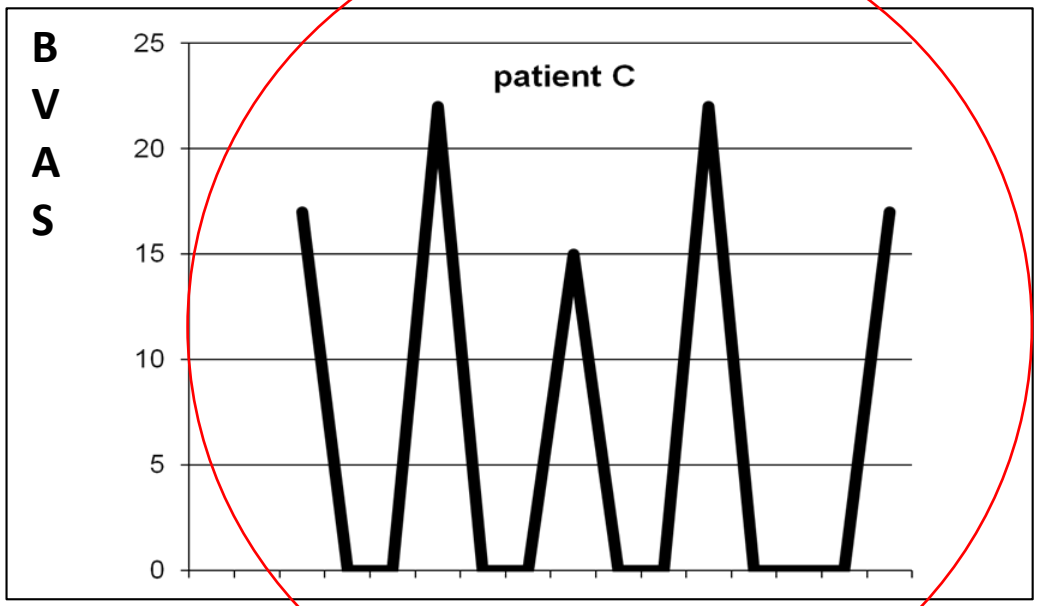
- Contraindications for high dose steroids
- Severe kidney disease
- C3 level lower than normal at onset
- Treatment resistance
- Steroid dependence
- Multiple relapsing course

- Age
- Diabetes
- Obesity
- Osteoporosis
- Pcychosis
- Myopathy

COURSE OF THE DISEASE

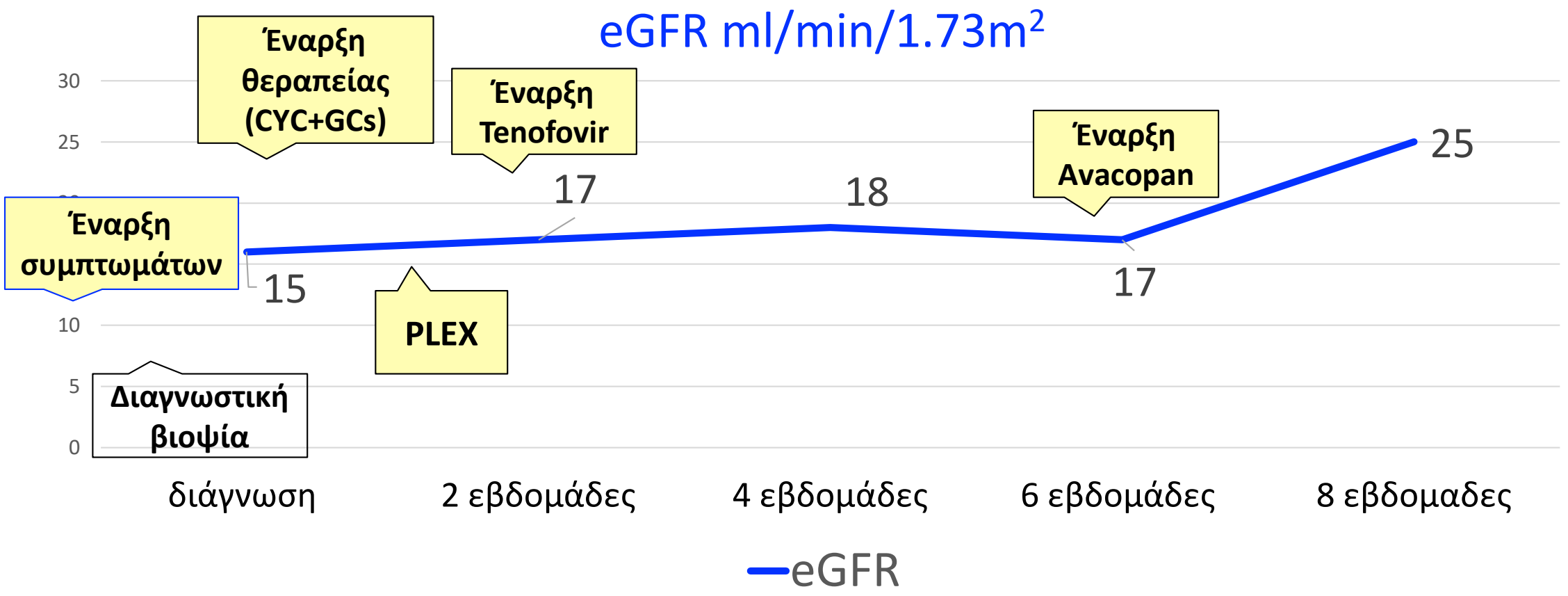




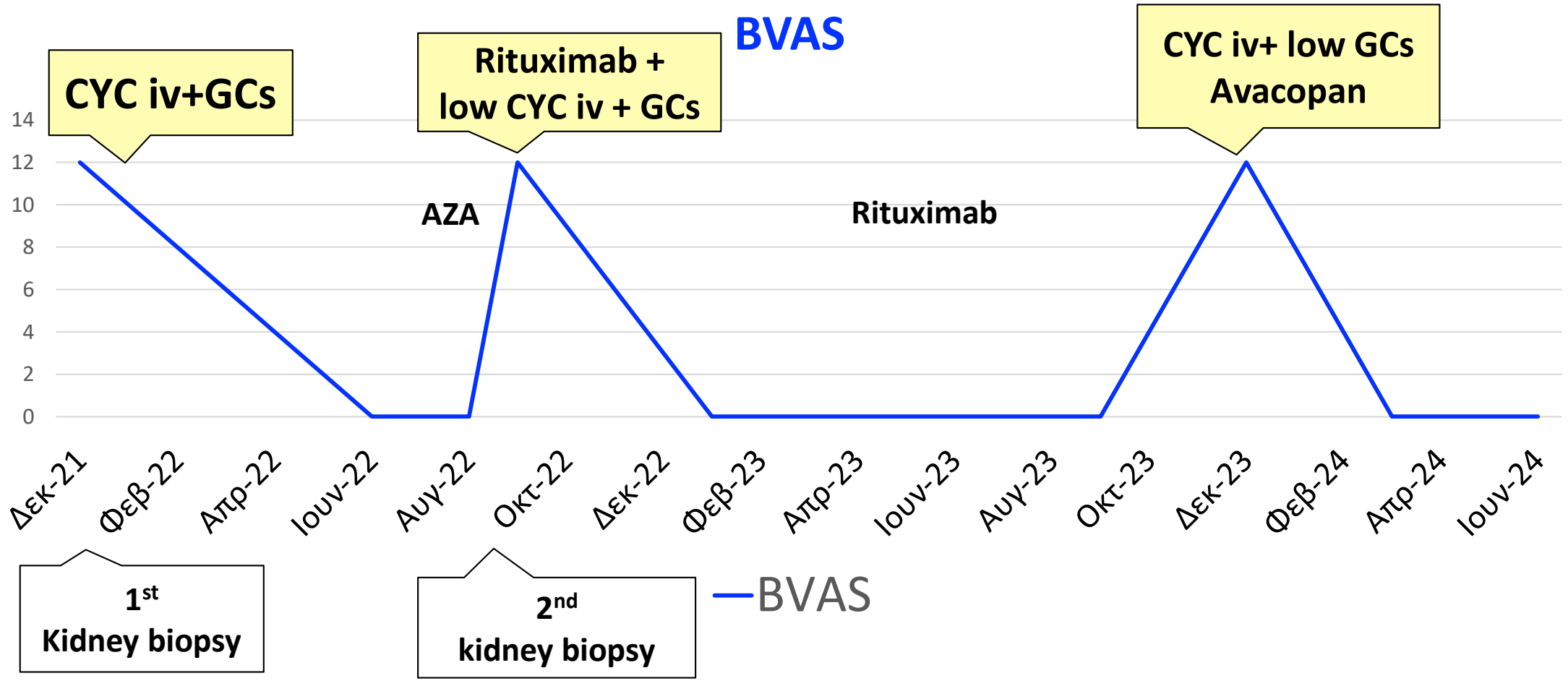


1. GCs cumulative dose
2. Pathogenetic effect

♂62 ετών, ΑΥ, BMI=38.6, PR3-ANCA αγγειίτιδα, ΤΕΣΝ, πνευμονική και ΩΡΛ συμμετοχή, BVAS=21



♀ 43 ετών, ONB, MPO-ANCA αγγειίτιδα, νόσος περιορισμένη στο νεφρό, BVAS=12



Συμπεράσματα

Θεραπευτικό σχήμα με το Avacopan έναντι αυτού με τα GCs

- Μη-κατώτερη κλινική ύφεση την εβδομάδα 26 και ανώτερη και παρατεταμένη κλινική ύφεση την εβδομάδα 52
- Μεγαλύτερη βελτίωση της νεφρικής λειτουργίας
- Μείωση της χρήσης των GCs και της σχετιζόμενης τοξικότητας
- Ευνοϊκό προφίλ ασφάλειας
- Η 1^{η} στοχευμένη θεραπεία για την ANCA-αγγειίτιδα

Ευχαριστώ!