Brainstorming Session 2

"Αντιμετώπιση Αγγειίτιδας στο εξωτερικό ιατρείο"

Χρήστος Κουτσιανάς MD, PhD

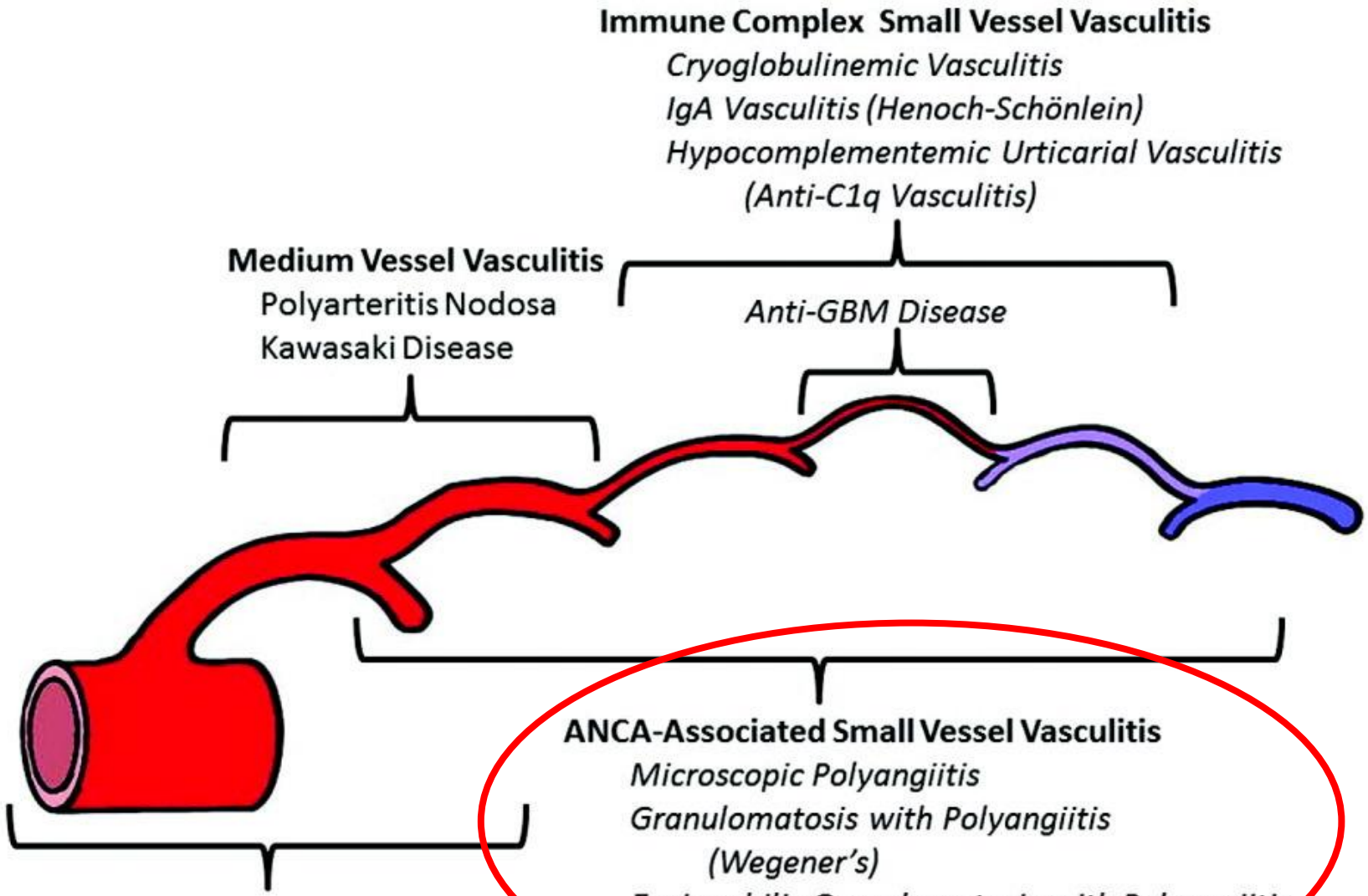
Επίκουρος καθηγητής Παθολογίας – Ρευματολογίας ΕΚΠΑ
Μονάδα Κλινικής Ανοσολογίας - Ρευματολογίας
Β' Πανεπιστημιακή Παθολογική Κλινική και Ομώνυμο Εργαστήριο, ΓΝΑ «Ιπποκράτειο»
Honorary Consultant, R&D, The Dudley Group NHS Foundation Trust

Σύγκρουση συμφερόντων

Καμία σχετική με αυτή την παρουσίαση

- Honoraria for lectures & advisory boards: Genesis Pharma, Abbvie, Novartis, Eli-Lilly, Pfizer, Aenorasis, UCB, GSK, Boehringer, Sobi, J & J, Vianex
- Hospitality: Eli-Lilly, Novartis, Viatris, UCB, Genesis Pharma, Abbvie, Faran, Sobi, J & J, Vianex
- Research:
  Sub-investigator: Roche, UCB, Eli-Lilly, Novartis, BMS, Pfizer, Genesis Pharma, AMGEN, Merck, Abbvie, Aenorasis, J & J, GSK

ANCA σχετιζόμενες αγγειίτιδες: αγγειίτιδες μικρών αγγείων



Jenette et al *Arthritis Rheum 2013*

Περίπτωση ασθενούς #1

Περίπτωση ασθενούς #1

Γυναίκα 30 ετών

- Παντρεμένη με ένα παιδί
- Ιστορικό μίας αποβολής στο α τρίμηνο
- Κάπνισμα (+) ~ 5 pack.years
- Κοινωνική λήψη αλκοόλ

MHx:

- Αλλεργική ρινίτιδα
- Βαρηκοΐα ΔΕ ωτός – χολοστεάτωμα εξαίρεση 2016

Rx

- Bilastin 10mgOD

<u>Αιτία προσέλευσης</u>

Μείωση ακουστικής οξύτητας και στο AP ους (2019)

Μαστοειδίτιδα (υποτροπιάζουσα)

Συχνές λοιμώξεις κατώτερου αναπνευστικού

ANCA (+)

Περίπτωση ασθενούς #1

Μείωση ακουστικής οξύτητας στο ΑΡ ους

- ✓ Trial Methylpred
- ✓ Αρχική βελτίωση

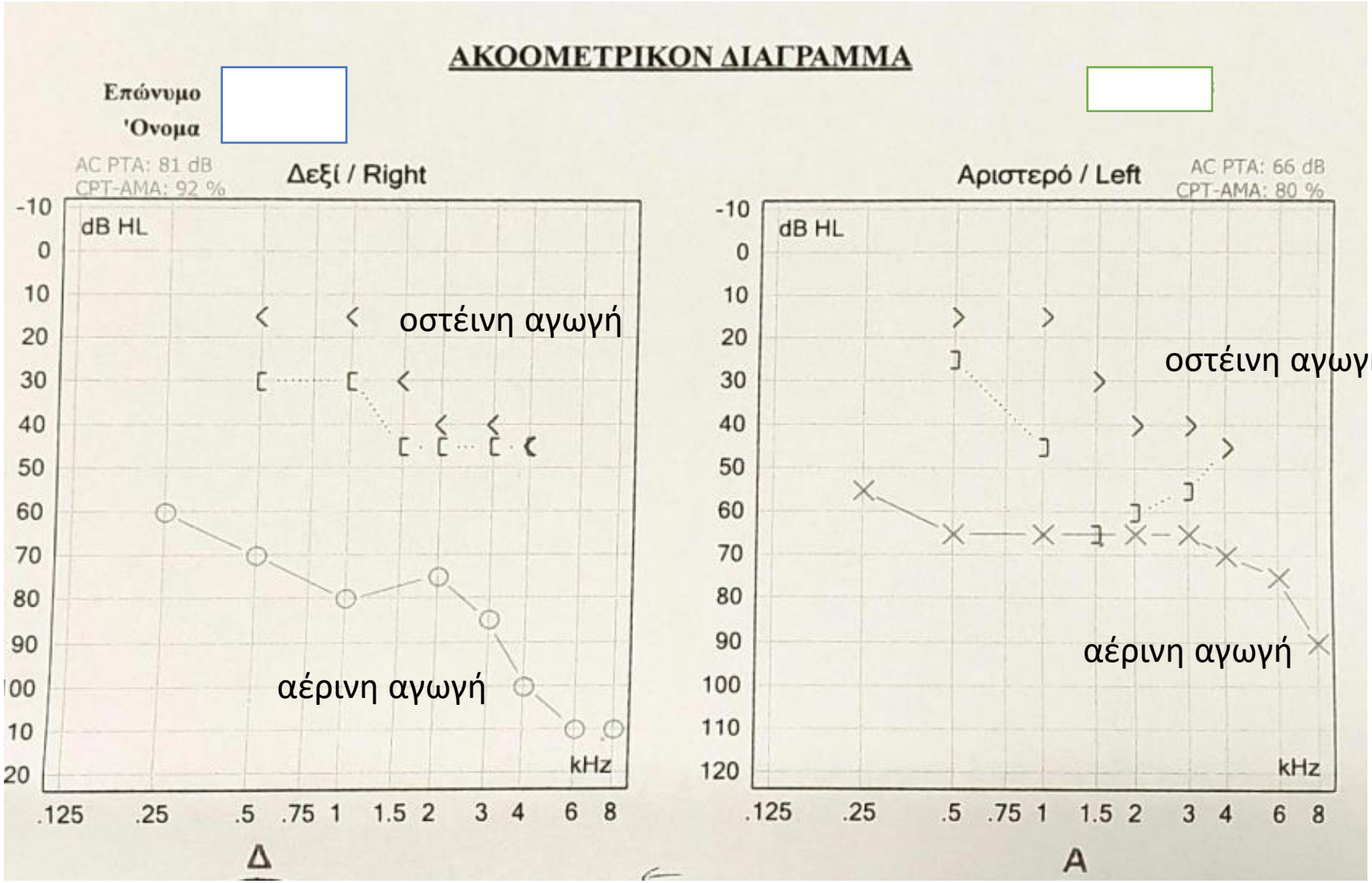
2019

2020

Εμμένοντα συμπτώματα με βαρηκοΐα άμφω

- ✓ CT λιθοειδών: κατάληψη του ΔΕ τυμπάνου και της ΑΡ κατώτερης τυμπανικής κοιλότητας από φλεγμονώδες υλικό

Περίπτωση ασθενούς #1



Σοβαρή βαρηκοΐα αγωγιμότητας άμφω

Περίπτωση ασθενούς #1

Μείωση ακουστικής οξύτητας στο ΑΡ ους

- ✓ Trial Methylpred
  - ✓ βελτίωση

Θεραπευτικές δοκιμές

Πολλαπλά αντιβιοτικά σχήματα και κορτικοειδή

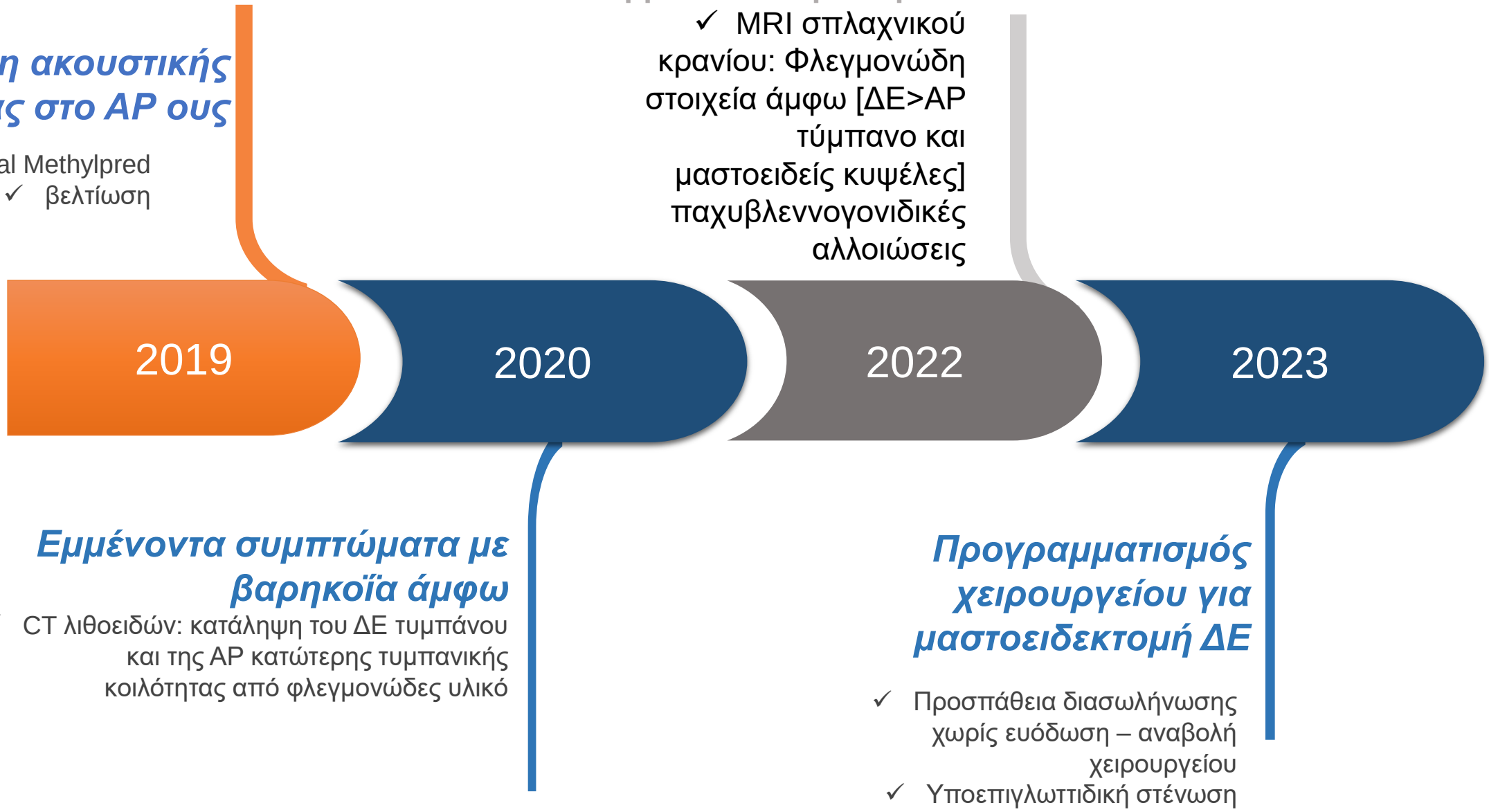
2019

2020

Εμμένοντα συμπτώματα με βαρηκοΐα άμφω

- ✓ CT λιθοειδών: κατάληψη του ΔΕ τυμπάνου και της ΑΡ κατώτερης τυμπανικής κοιλότητας από φλεγμονώδες υλικό

Περίπτωση ασθενούς #1



Περίπτωση ασθενούς #1: σύνοψη

Γυναίκα 30 ετών

Βαρηκοΐα άμφω

Προσβολή παραρρινίων κόλπων / μαστοειδίτιδα

Θετικά MPO αντισώματα

Διάγνωση?

Ερώτηση: σοβαρή νόσος ή όχι?

Table 2 Examples of organ/life-threatening and not organ/life-threatening manifestations in patients with AAV

Examples of potentially organ/life-threatening manifestations*	Examples of manifestations that are not ultimately organ/life-threatening*
Glomerulonephritis	Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
Pulmonary haemorrhage	Skin involvement without ulceration
Meningeal involvement	Myositis (skeletal muscle only)
Central nervous system involvement	Non-cavitating pulmonary nodules
Retro-orbital disease	Episcleritis
Cardiac involvement	
Mesenteric involvement	
Mononeuritis multiplex	

*These are just examples of typical disease manifestations ar exist. Assessment of severity in the individual patient may differ (eg, scleritis can become organ threatening under certain circumstances).
AAV, antineutrophil cytoplasmic antibody-associated vasculiti

Hellmich B, *et al*. *Ann Rheum Dis* 2023;**0**:1–18. doi:10.1136/ard-2022-223764

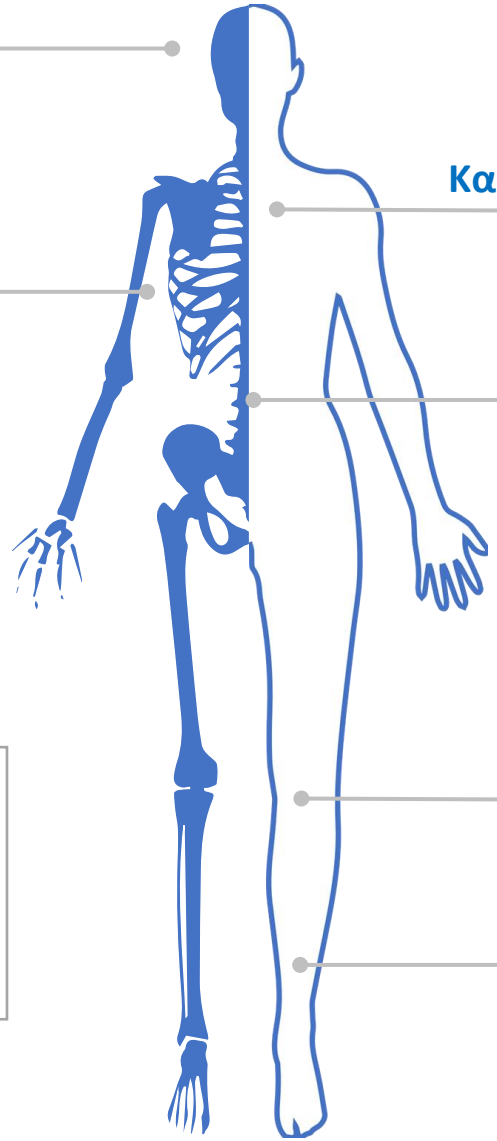
Έχει σημασία?

Περίπτωση ασθενούς #1

Κεφαλή: Ευαισθησία στην περιοχή των μαστοειδών αποφύσεων

Πνεύμονες : ΑΨ ομότιμο στα πνευμονικά πεδία, αλλά παρουσία εισπνευστικού συριγμού

ΜΣΚ : χωρίς εικόνα αρθρίτιδας



Καρδιά : S1,S2, ρυθμικοί, χωρίς φυσήματα

Κοιλιά : ΜΕΑ, Ήπαρ – Σπλην (-)

Δέρμα : χωρίς εξανθήματα

ΠΝΣ : χωρίς παθολογικά ευρήματα

ΑΠ=120/70mmHg, Σφύξεις=80/min,

Θ=36.2 ^{o}C, Αναπνοές=15/min

$SatO_2$=98%

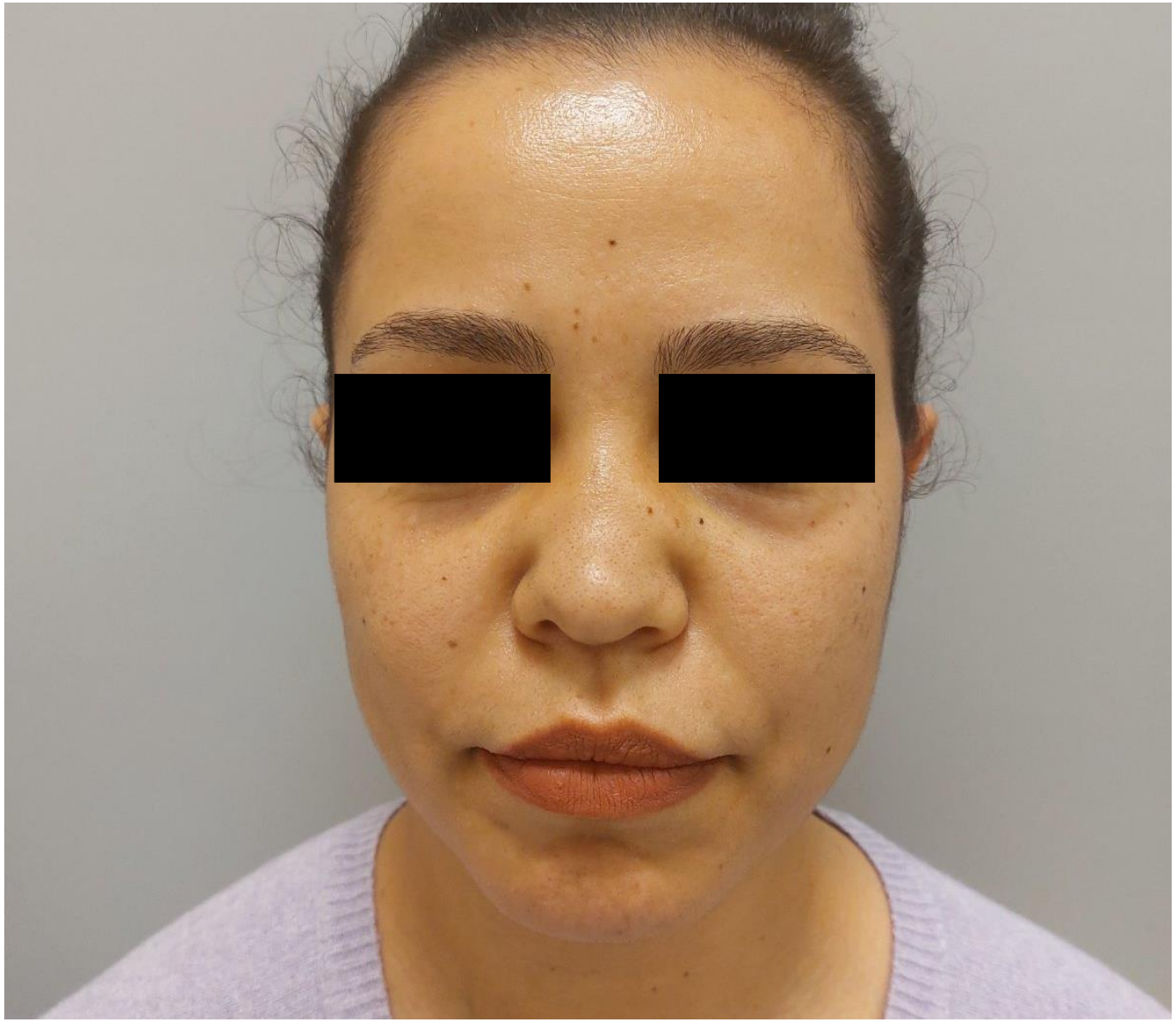
Περίπτωση ασθενούς #1

Γενική Αίματος	
WBC (Neut / Lymph / Eos)	7920 (65/24/1)
Hb / Hct	13 / 40.7
MCV	81.2
PLT	384.000
Βιοχημικές Εξετάσεις	
Ουρία/ Κρεατινίνη	22 / 0.6
SGOT / SGPT	17 / 11
LDH	210
PT / INR / APTT	11.5 /1.0 / 28.3
Ολικά Λευκώματα / Αλβουμίνη	5.9 / 3.4

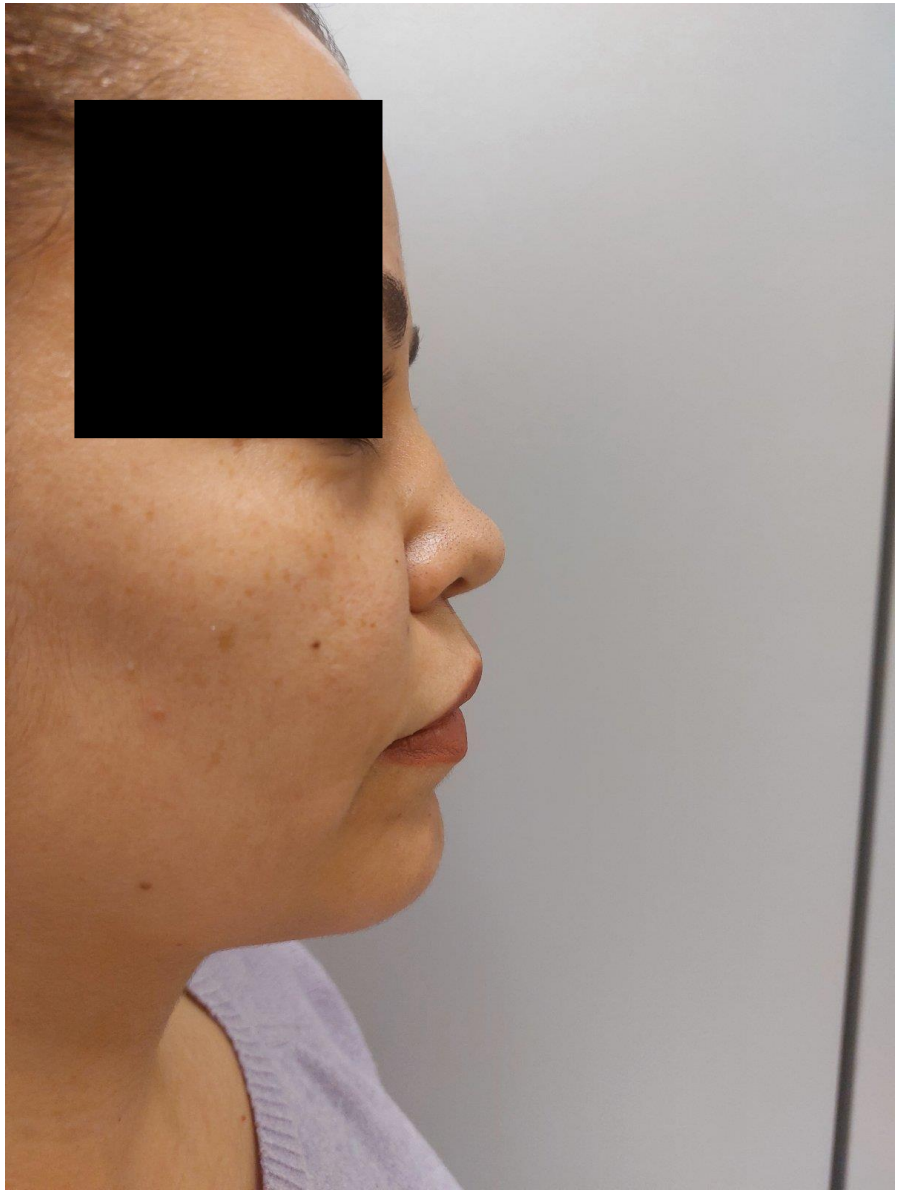
Βιοχημικές-Ανοσολογικές Εξετάσεις	
CRP / ESR	6.2 / 22
C3/C4	109/19
RF	(-)
ANA / ENA	(-)
IgG / IgM / IgA	1680/209/249
SPEP / IF	(-)
Cryos	(-)

Γενική ούρων	
Wbc : 0-1	
RBC : 0-1	Λεύκωμα (-)

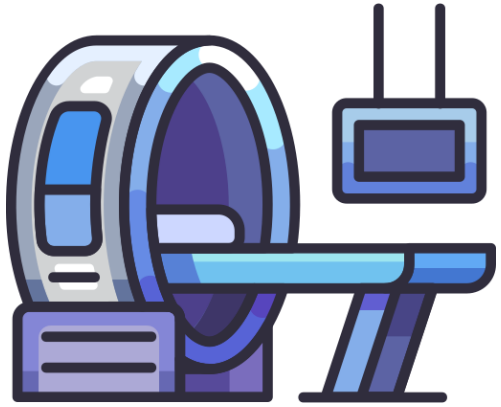
Περίπτωση ασθενούς #1



Περίπτωση ασθενούς #1

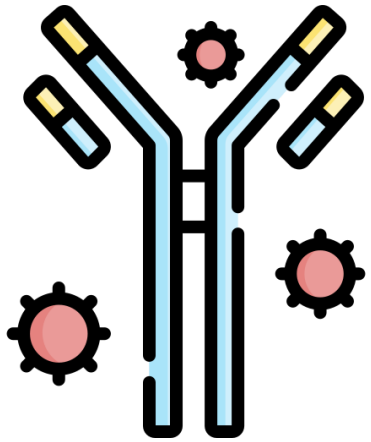


Περίπτωση ασθενούς #1



<u>CT thorax</u>:
Υπεζωκοτική ή περικαρδιακή συλλογή (-)
Οστικός έλεγχος κφ.
Χωρίς LN διογκώσεις

Στην έσω παρυφή του AP κάτω λοβού ομαλών ορίων όζος με υπόπυκνη απεικόνιση περιφερικά και υπέρπυκνα στοιχεία στο εσωτερικό του 9.6x10.5mm (αμάρτωμα?)



<u>ANCA αντισώματα</u>

c-ANCA (-) / PR3 negative
p-ANCA (+) / MPO (+) 52 (<20)

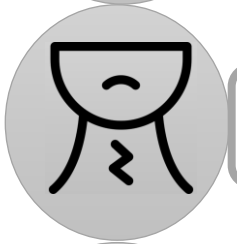
Περίπτωση ασθενούς #1: σύνοψη

Γυναίκα 30 ετών

Βαρηκοΐα άμφω

Προσβολή παραρρινίων κόλπων / μαστοειδίτιδα

Θετικά MPO αντισώματα



Υποεπιγλωττιδική στένωση

Saddle-nose deformity

ANCA αγγειίτιδες: κριτήρια κατάταξης

Arthritis & Rheumatism

Official Journal of the American College of Rheumatology

THE AMERICAN COLLEGE OF RHEUMATOLOGY
1990 CRITERIA FOR THE CLASSIFICATION
OF VASCULITIS

THE AMERICAN COLLEGE OF RHEUMATOLOGY
1990 CRITERIA FOR THE CLASSIFICATION OF
WEGENER'S GRANULOMATOSIS

RANDI Y. LEAVITT, ANTHONY S. FAUCI, DANIEL A. BLOCH, BEAT A. MICHEL, GENE G. HUNDER, WILLIAM P. AREND, LEONARD H. CALABRESE, JAMES F. FRIES, J. T. LIE, ROBERT W. LIGHTFOOT, JR., ALFONSE T. MASI, DENNIS J. McSHANE, JOHN A. MILLS, MARY BETTY STEVENS, STANLEY L. WALLACE, and NATHAN J. ZVAIFLER

Table 3. 1990 criteria for the classification of Wegener's granulomatosis (traditional format)*

Criterion	Definition
1. Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiograph	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities
3. Urinary sediment	Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
4. Granulomatous inflammation on biopsy	Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

* For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least 2 of these 4 criteria are present. The presence of any 2 or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%.

Leavitt et al, Arthritis Rheum . 1990 Aug;33(8):1101-

ANCA αγγειίτιδες: κριτήρια κατάταξης 2022 ACR/EULAR

Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 393–399
DOI 10.1002/art.41986

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Granulomatosis With Polyangiitis

Joanna C. Robson,[1] Peter C. Grayson,[2] Cristina Ponte,[3] Ravi Suppiah,[4] Anthea Craven,[5] Andrew Judge,[6] Sara Khalid,[5] Andrew Hutchings,[7] Richard A. Watts,[8] Peter A. Merkel,[9] and Raashid A. Luqmani[5]

Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 400–406
DOI 10.1002/art.41983

2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Microscopic Polyangiitis

Ravi Suppiah,[1] Joanna C. Robson,[2] Peter C. Grayson,[3] Cristina Ponte,[4] Anthea Craven,[5] Sara Khalid,[5] Andrew Judge,[6] Andrew Hutchings,[7] Peter A. Merkel,[8] Raashid A. Luqmani,[5] and Richard A. Watts[9]

GPA: κριτήρια κατάταξης 2022 ACR/EULAR

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **GRANULOMATOSIS WITH POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Sum the scores for 10 items, if present. A score of ≥ 5 is needed for classification of GRANULOMATOSIS WITH POLYANGIITIS.

Cut-off of 5

Ευαισθησία 92.5% [86.9-96.2%]
Ειδικότητα 93.8% [88.9–97.0%]
Area under the curve (AUC) 0.98

MPA: κριτήρια κατάταξης 2022 ACR/EULAR

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **MICROSCOPIC POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having microscopic polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect / perforation	-3

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
Fibrosis or interstitial lung disease on chest imaging	+3
Pauci-immune glomerulonephritis on biopsy	+3
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Sum the scores for 6 items, if present. A score of ≥ 5 is needed for classification of MICROSCOPIC POLYANGIITIS.

Cut-off of 5

Ευαισθησία 90.8% [84.9-95.0%]
Ειδικότητα 94.2% [91.5–96.3%]
Area under the curve (AUC) 0.98

Περίπτωση ασθενούς #1

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or st… bronchial involvement, or sa… deformity)	+2
C… ural hearin…	+1

LABORA…

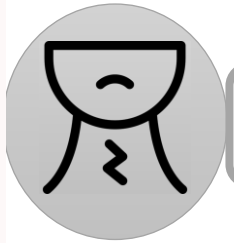
	+5
	+2
…psy	+2
	+1
Pauci-immune glo… biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Total score 4
Not fulfilling definition for GPA!!!

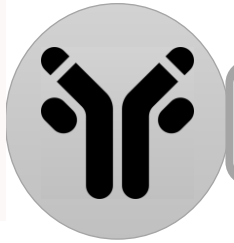
Βαρηκοΐα άμφω

Saddle-nose deformity

Προσβολή παραρρινίων κόλπων / μαστοειδίτιδα



Υποεπιγλωττιδική στένωση



Θετικά MPO αντισώματα

AAV: κριτήρια κατάταξης 2022 ACR/EULAR

- ✓ **Κριτήρια κατάταξης!!!**
- ✓ **Σκοπός τους είναι η διαφοροποίηση της διάγνωσης σε ασθενείς με αγγειίτιδα ώστε να μπορέσουν να τυχαιοποιηθούν σε μελέτες σε setting έρευνας**
- ✓ **Πρέπει λοιπόν να εφαρμόζονται μόνο όταν**
  - **η διάγνωση της αγγειίτιδας έχει τεθεί**
  - **οι πιθανοί μιμητές αγγειίτιδας έχουν αποκλεισθεί**
- ✓ **Δεν πρέπει να χρησιμοποιούνται για τη διάγνωση των AAV**

Περίπτωση ασθενούς #2

Περίπτωση ασθενούς #2

Άνδρας 67 ετών

- Παντρεμένος, συνταξιούχος τραπεζικός
- Κάπνισμα: πρώην ~ 25 pack.years
- Κοινωνική λήψη αλκοόλ

MHx:

- Στεφανιαία νόσος
- ΤΒ παχυπλευρίτιδα (πλήρης αγωγή)

Rx

- Amlodipine 10mgOD
- ASA 100mg OD
- Metoprolol 50mg BD
- Rosuvastatin 10mg OD

<u>Αιτία προσέλευσης</u>

Πυρετός

Επιδείνωση νεφρικής λειτουργίας

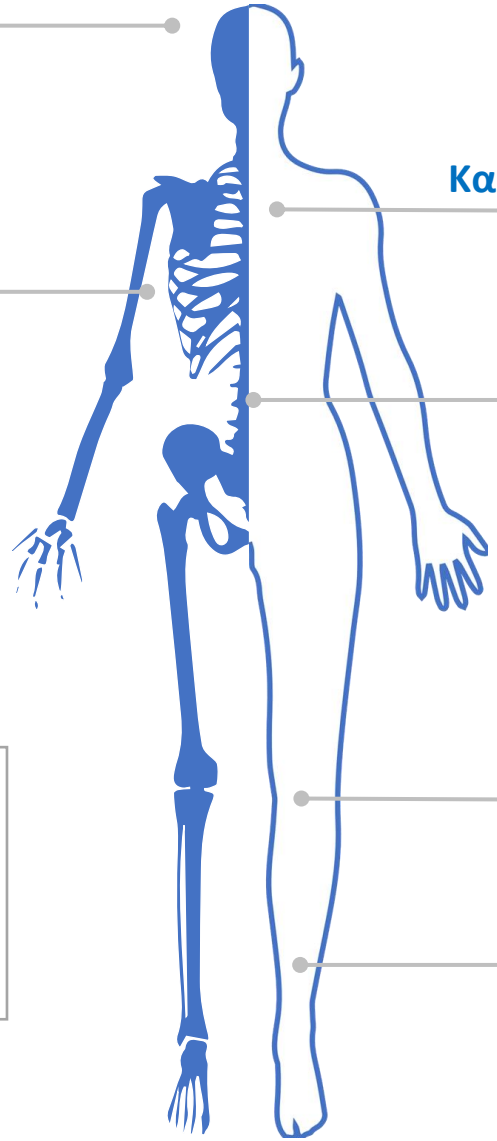
Δύσπνοια - υποξυγοναιμία

Περίπτωση ασθενούς #2

Κεφαλή: χωρίς παθολογικά ευρήματα

Πνεύμονες : ΑΨ ομότιμο, μη μουσικοί ρόγχοι στα κάτω πνευμονικά πεδία

ΜΣΚ : ευαισθησία στην ψηλάφηση των μετακαρποφαλαγγικών άμφω



Καρδιά : S1,S2, ρυθμικοί, χωρίς φυσήματα

Κοιλιά : ΜΕΑ, Ήπαρ – Σπλην (-)

Δέρμα : χωρίς εξανθήματα

ΠΝΣ : χωρίς παθολογικά ευρήματα

ΑΠ=**150/85mmHg**, Σφύξεις=**101**/min,

Θ=**37.4** ^{o}C, Αναπνοές=**16**/min

$SatO_2$=95%

Περίπτωση ασθενούς #2

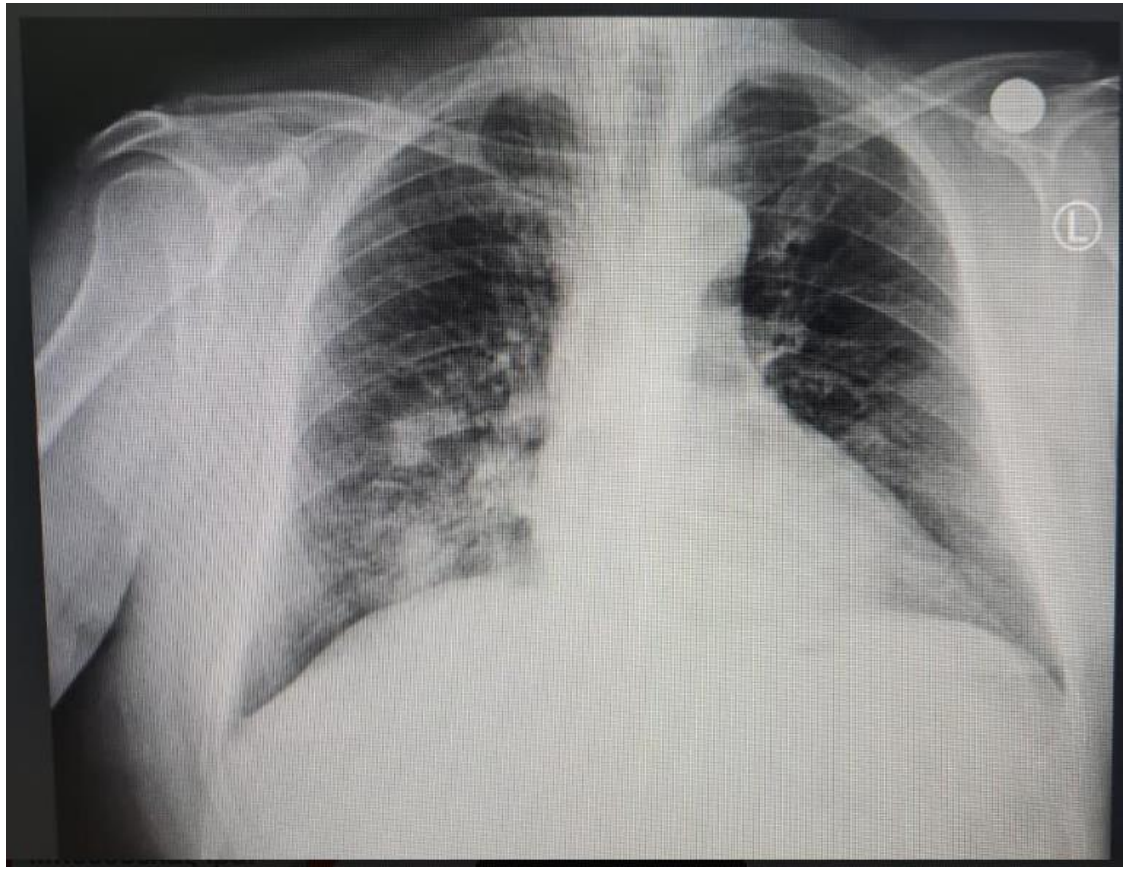
Γενική Αίματος	
WBC (Neut / Lymph / Eos)	9450 (75/18/1)
Hb / Hct	10.1 / 30.7
MCV	84
PLT	414.000

Βιοχημικές Εξετάσεις	
Ουρία/ Κρεατινίνη	44 / 1.2 (eGFR: 61ml/min)
SGOT / SGPT	15 / 18
LDH	210
PT / INR / APTT	13.8 /1.05 / 34.1
Ολικά Λευκώματα / Αλβουμίνη	7.4 / 4.1

Βιοχημικές-Ανοσολογικές Εξετάσεις	
CRP / ESR	98 / 120
C3/C4	118/25
RF	(+) 44.2
ANA / ENA	(-)
IgG / IgM / IgA	1680/209/249
SPEP / IF	(-)
Cryos	(-)

Γενική ούρων	
Wbc : 4-5	
RBC : 15-20	Λεύκωμα (++)

Περίπτωση ασθενούς #2



Βρογχοσκόπηση:
Αναμνηστικό:
Χημειο-ακτινοθεραπεία-ανοσοκαταστολή:
Καπνιστής: ΝΑΙ ☐ ΟΧΙ ☑

Ποσότης υγρού (ml) εισάγεται : #
εξάγεται : #

Αριθμός κυττάρων/ml: **21.5** $x10^4$ ml
Φυσιολογικές τιμές <13 $x10^4$ ml

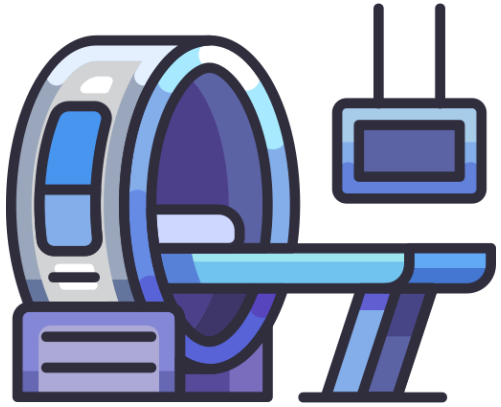
Υπότυποι λεμφοκυττάρων(επί % λεμφοκ.)

	Ευρημ.	Φυσ. Τιμ.		Ευρ.	Φυσ. Τιμ.
Αναλογία κυττάρων :			Β - Ολικά:		(0-12)
Μακροφάγα:	**75.7%**	> 83%	Τ - Ολικά:		(63-88)
Λεμφοκύτταρα :	**3%**	10%-15%	Τ - Helper:		(36-70)
Ηωσινόφιλα:	**3%**	< 1%	Τ - Suppresor:		(20-40)
Λοιπά πολυμορφοπύρηνα:	**18.1%**	< 3%	Τ – Helper / Τ - Suppresor:		(0,9-2,5)
Πλασματοκύτταρα :		0%	Natural Killer :		(2-14)
Μαστοκύτταρα :		< 0,5%	CD1a (% όλων των κυττάρων)		<5
			Σωμάτια αμιάντου :		

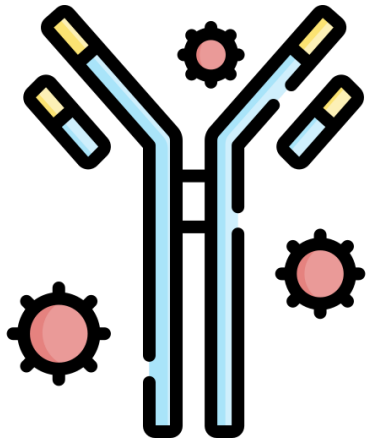
Αρνητικό: για κακοήθεια.
Ύποπτο:
Θετικό:

Παρατηρήσεις: Χρώση αιμοσιδηρίνης (+). Σιδηροφάγα 90% των μακροφάγων.

Περίπτωση ασθενούς #2



<u>CT thorax</u>:
εκτεταμένα πνευμονικά διηθήματα άμφω κάτω λοβών, μεσότητας και άνω λοβού δεξιά



<u>ANCA αντισώματα</u>

c-ANCA (+) / PR3 (+) 63.2 (<20)
p-ANCA (-) / MPO negative

Περίπτωση ασθενούς #2: σύνοψη

Άνδρας 67 ετών

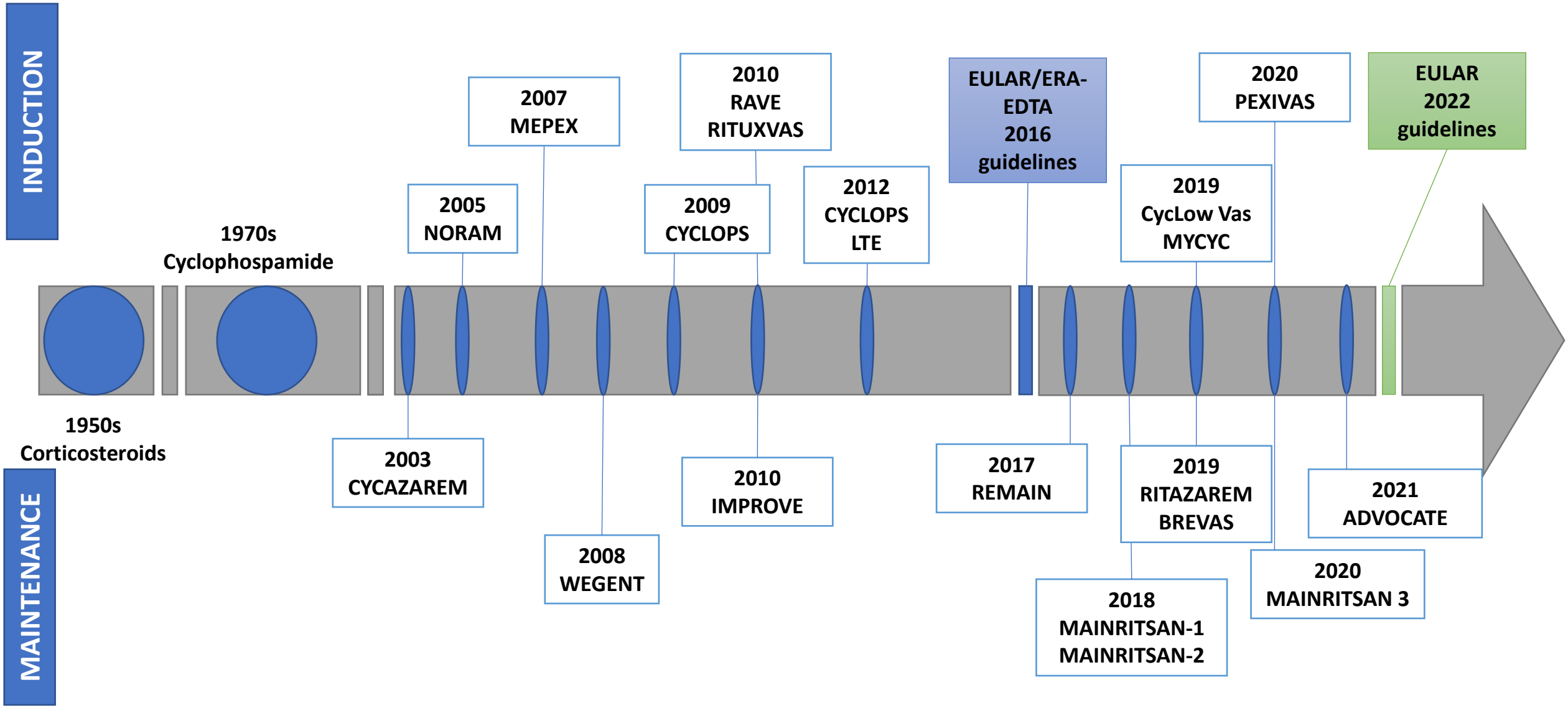
- Πνευμονικά διηθήματα / κυψελιδική αιμορραγία
- Προσβολή νεφρού (ενεργό ίζημα, επιδείνωση νεφρικής λειτουργίας)
- Αρθρίτιδα
- Συστηματικά συμπτώματα
- Θετικά PR3 αντισώματα

GPA

ACR/EULAR 2022 criteria score 7

Ερώτηση: τι θεραπεία induction θα δώσετε?

ANCA αγγειίτιδες: θεραπευτική



GPA/MPA κατευθυντήριες οδηγίες

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2021, pp 1–18
DOI 10.1002/art.41773

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the … Antineutrophil Cytoplasmic A…

Sharon A. Chung,[1] Carol A. Langford,[2] Mehrdad Maz,[3] A…
Doyt L. Conn,[8] Kathy A. Full,[9] Peter C. Grayson,[10] Maria…
Rennie L. Rhee,[12] Philip Seo,[13] John H. Stone,[14] Sa…
Ann Warner,[18] Kevin Byram,[19] Anisha B. Dua,[7] Nedaa H…
Yih Chang Lin,[23] Jason M. Springer,[3] Marat Turgunba…
Reem A. Mustafa[25]

Recommend…

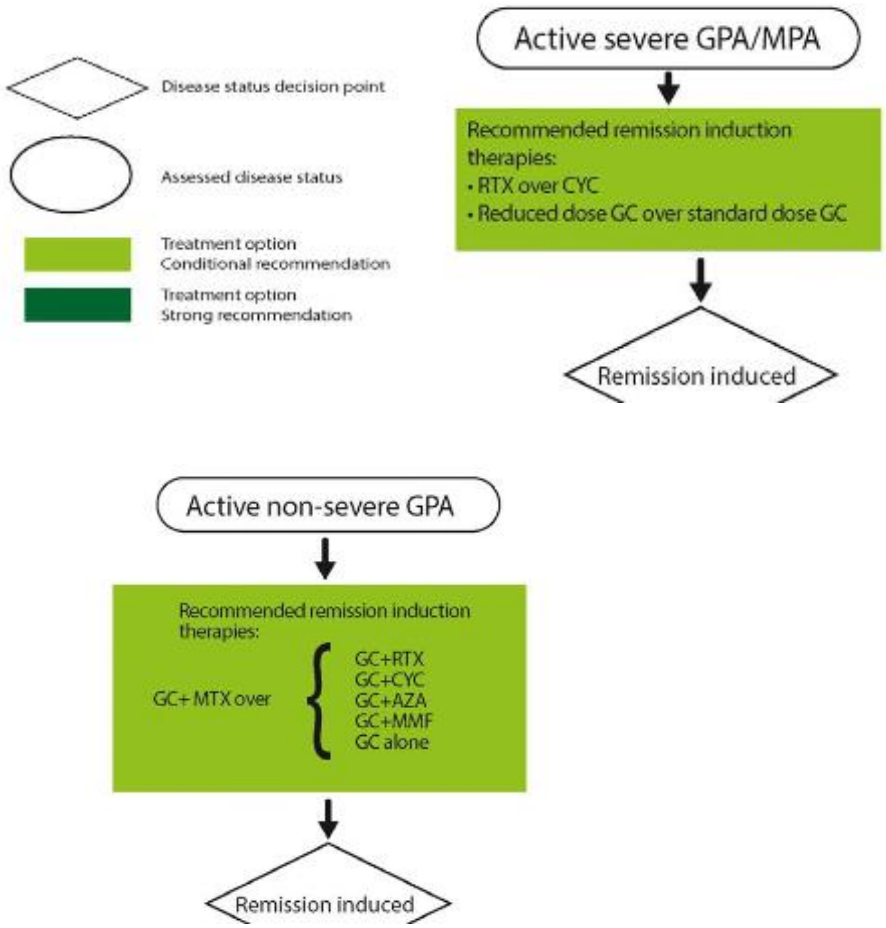
EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

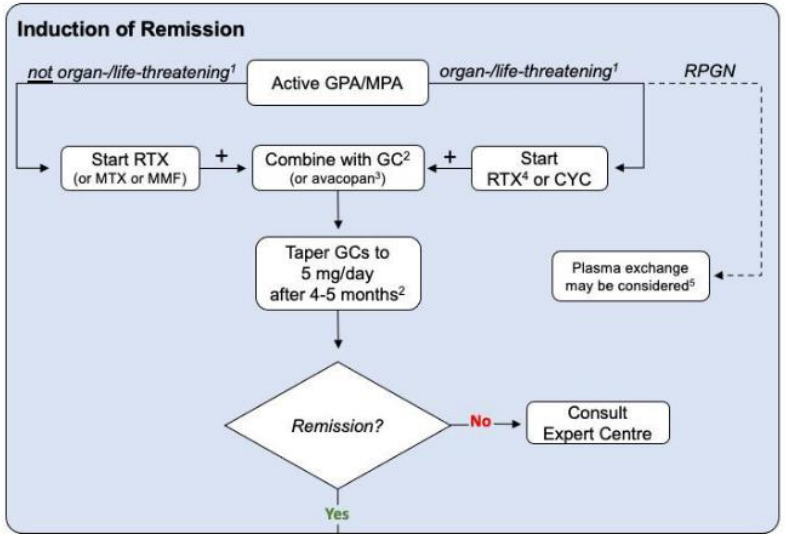
Bernhard Hellmich ,[1] Beatriz Sanchez-Alamo,[2] Jan H Schirmer,[3] Alvise Berti ,[4,5]
Daniel Blockmans,[6] Maria C Cid ,[7] Julia U Holle,[8] Nicole Hollinger,[1] Omer Karadag,[9]
Andreas Kronbichler,[10,11] Mark A Little,[12] Raashid A Luqmani,[13] Alfred Mahr,[14]
Peter A Merkel ,[15] Aladdin J Mohammad ,[11,16] Sara… [17,18]
Chetan B Mukhtyar ,[19] Jacek Musial,[20] Fiona Price-Ku…
Y K Onno Teng ,[22] Benjamin Terrier ,[23] Gunnar Tom…
Augusto Vaglio ,[26] Dimitrios Vassilopoulos ,[27] Pete…
David Jayne [11]

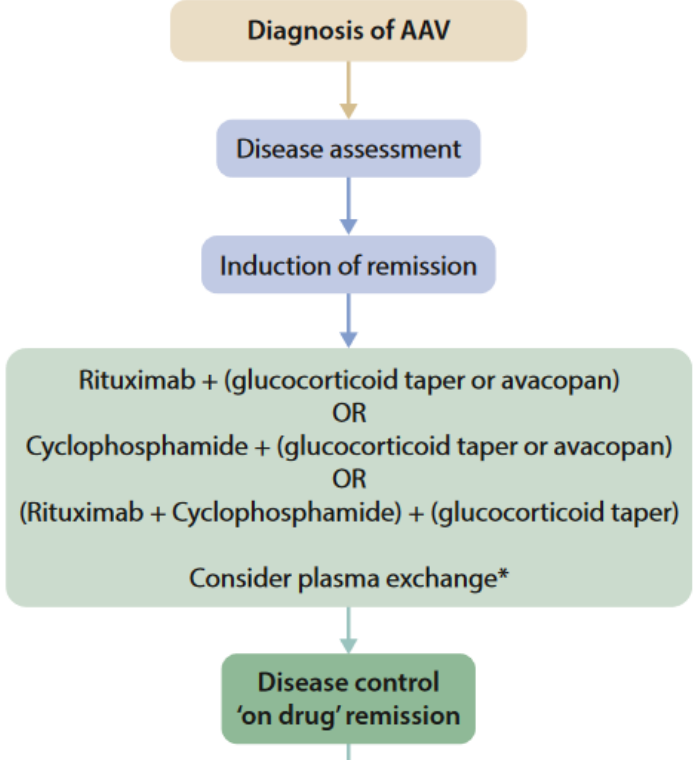
contents
www.kidney-international.org
VOL 105 | ISSUE 3S | MARCH 2024
kidney INTERNATIONAL

KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

GPA/MPA guidelines: remission induction



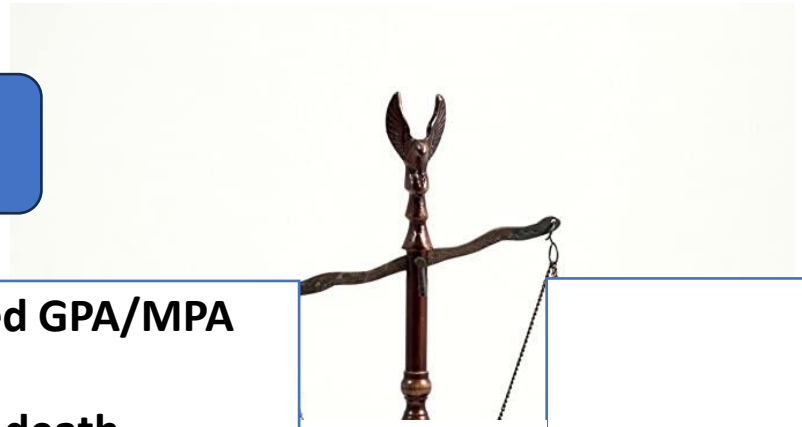




RTX vs CYC in induction remission (one better than the other?)

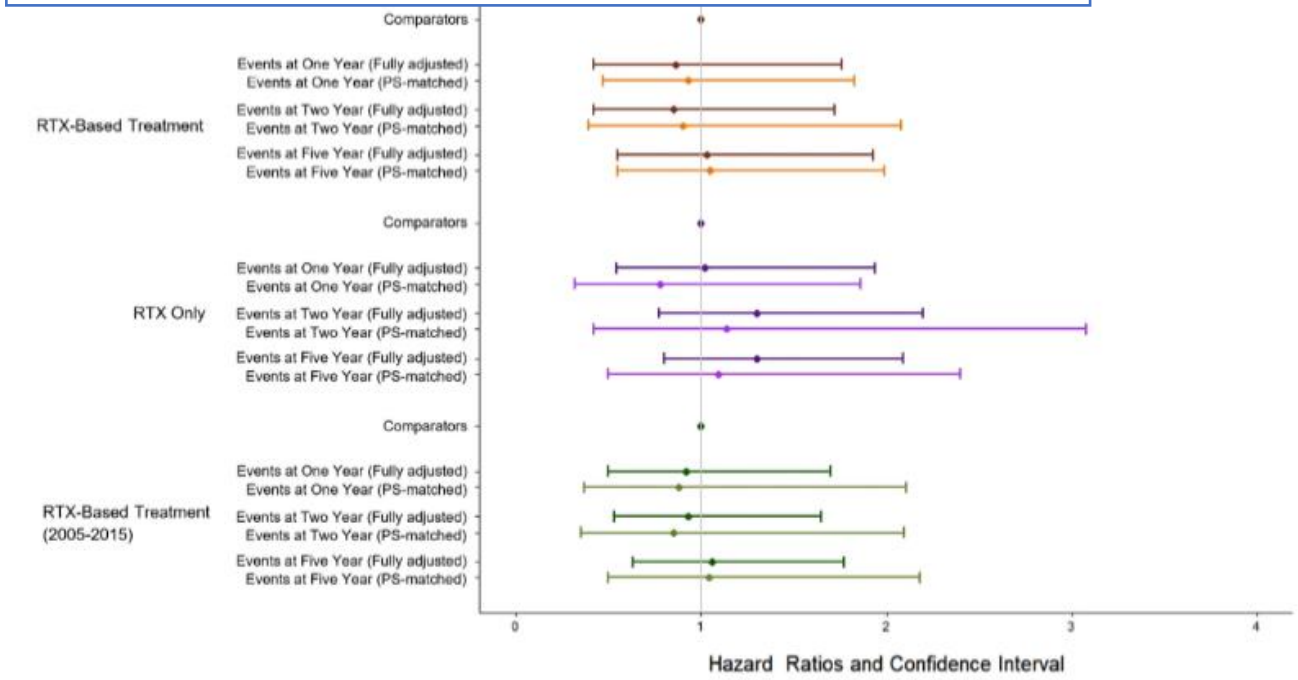
Rituximab

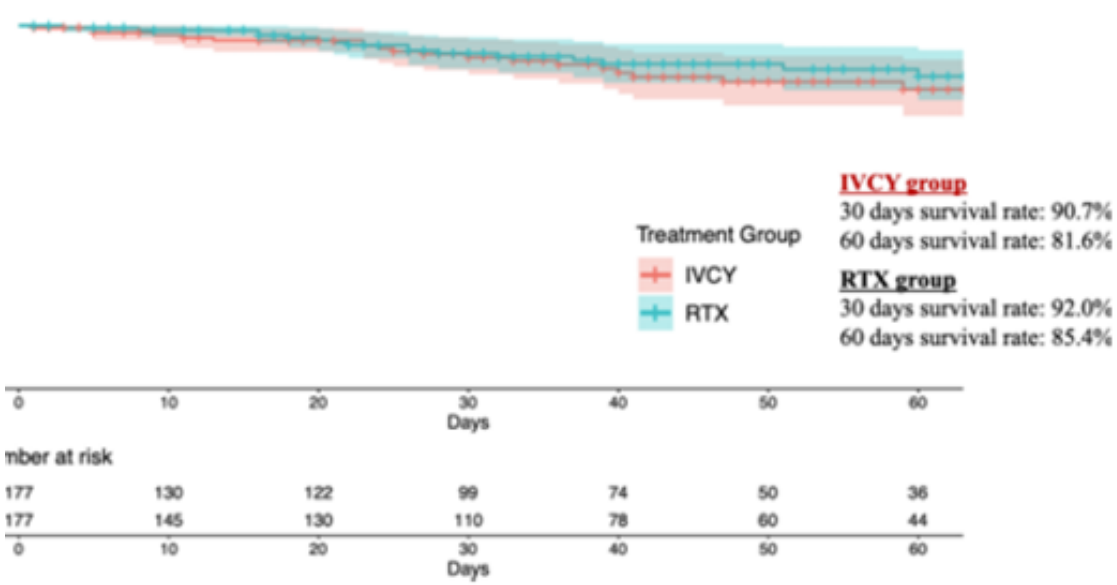
Cyclophosphamide



N=595 patients with newly diagnosed GPA/MPA
~70% MPO+
Composite of kidney failure or death

N=177 vs 177 in each group
65% MPA, 80% RPGN



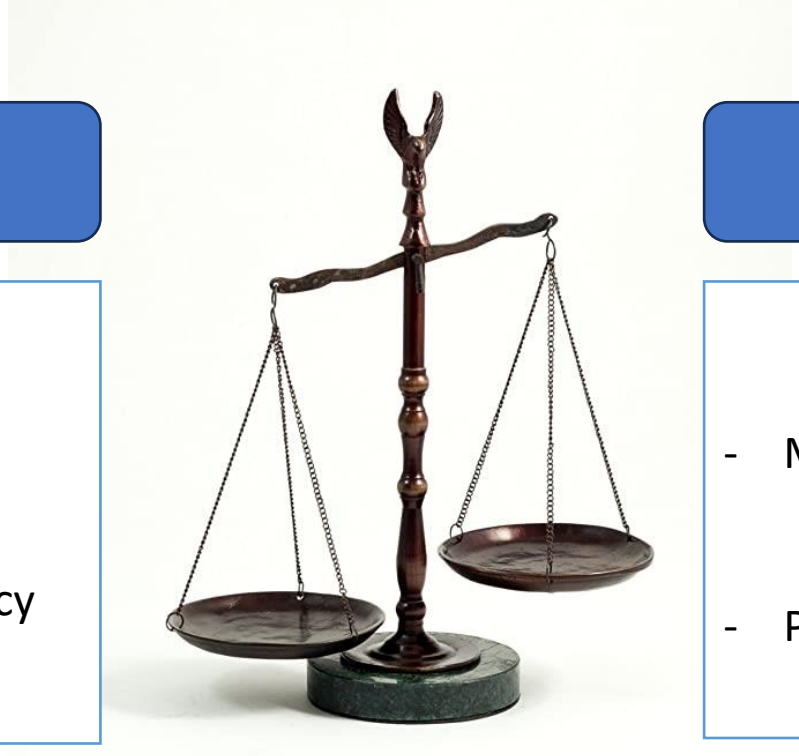


Wallace ZS, et al . Arthritis Rheumatol. 2023 Sep;75(9):1599-1607Ishikawa Y et al *Annals of the Rheumatic Diseases* 2024;**83:**103-

RTX vs CYC in induction remission

Rituximab

- Favorable side effect profile
  - Neutropenia
  - Fertility
  - Alopecia
  - Concern for malignancy
- Previously treated with CYC
- Relapsing disease



Cyclophosphamide

- More severe disease:
  - Pulmonary haemorhage
  - Severe kidney disease
- Previously treated with RTX

Combination?

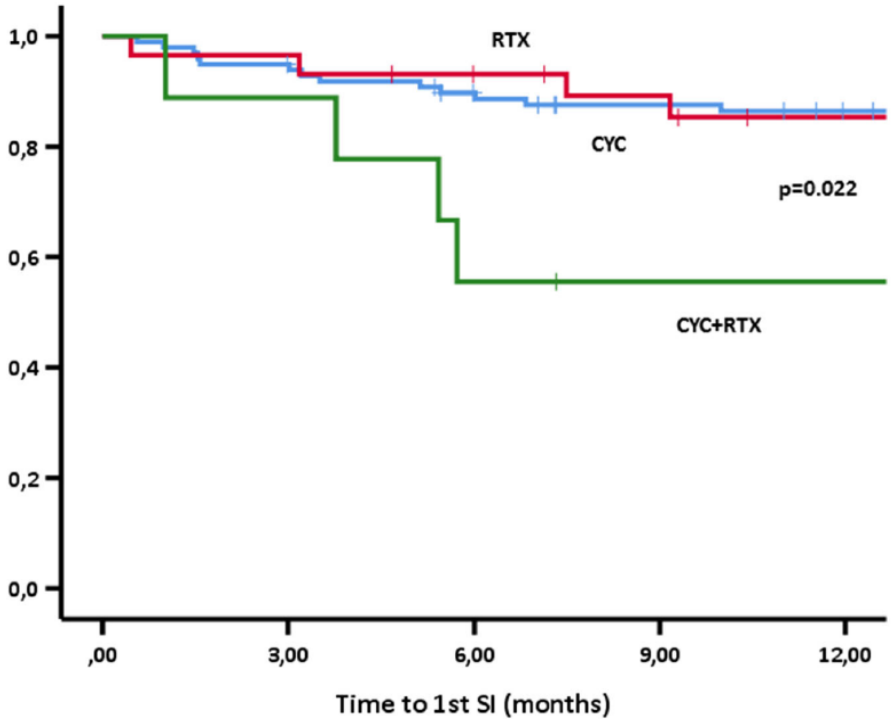
RITUXVAS
CycLowVas

Higher infection risk with CYC+RTX?

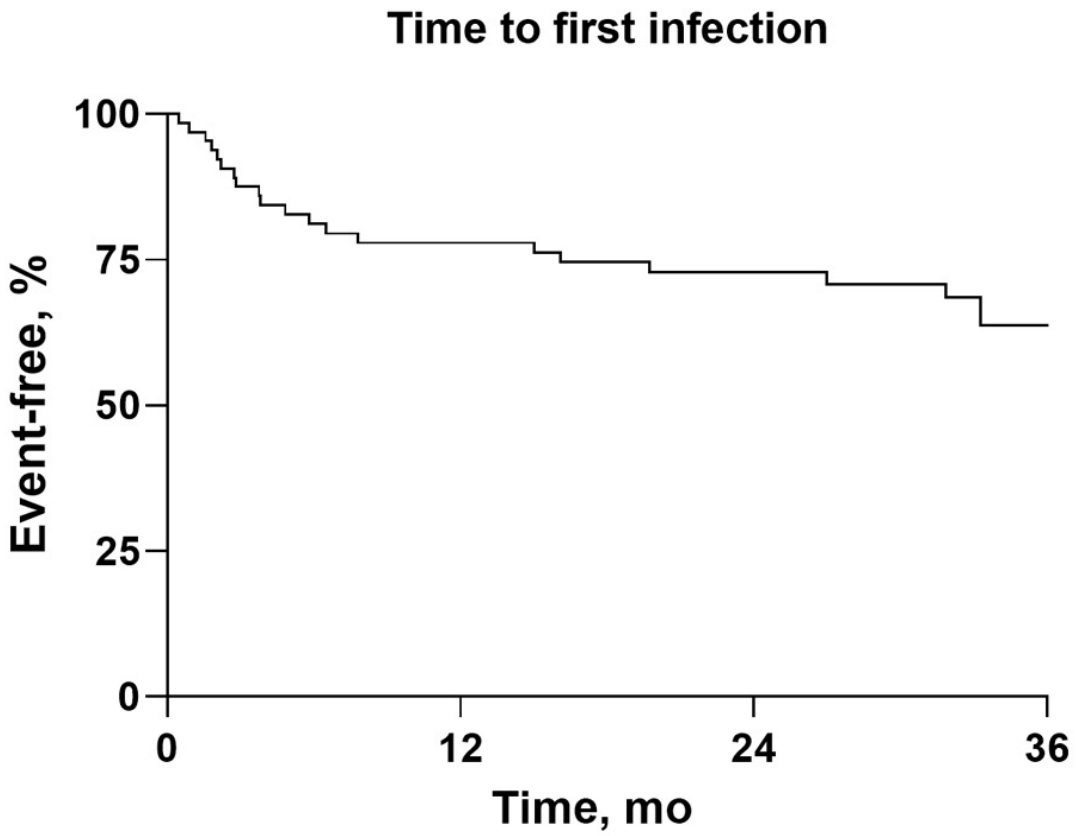
RESEARCH ARTICLE Open Access

Serious infections in ANCA-associated vasculitides in the biologic era: real-life data from a multicenter cohort of 162 patients

Konstantinos Thomas[1], Evangelia Argyriou[2†], Noemin Kapsala[3†], Alexandros Panagiotopoulos[1], Aglaia Chalkia[4], Emilia Hadziyannis[1], Kyriaki Boki[2], Pelagia Katsimbri[3], Dimitrios T. Boumpas[3], Panagiota Giannou[4], Dimitrios Petras[4] and Dimitrios Vassilopoulos[1*]



Free of infection survival (%)

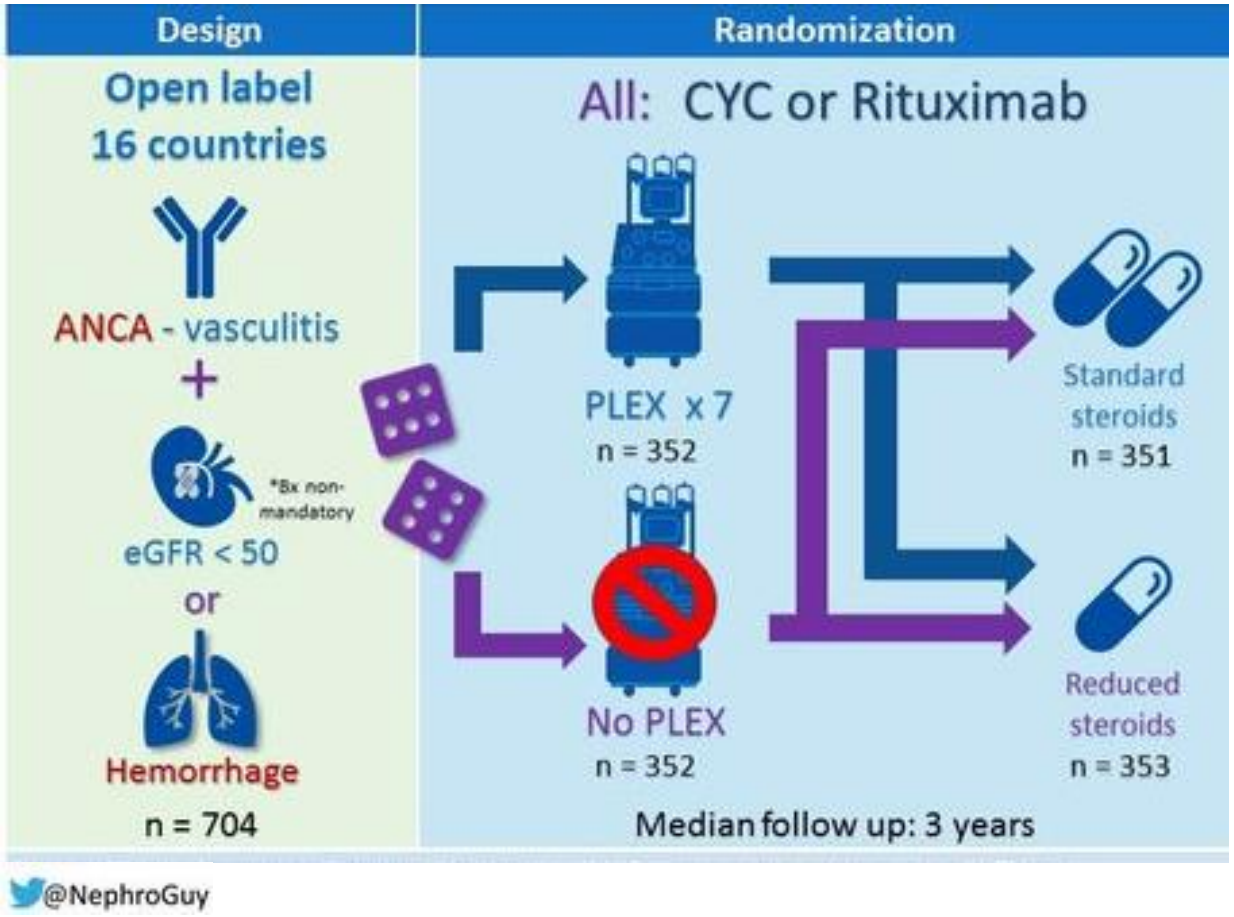


Gulati K, et al. Kidney International 2021

Ερώτηση: ο ασθενής έχει κυψελιδική αιμορραγία. Θα χρειαστεί πλασμαφαίρεση?

PEXIVAS

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis



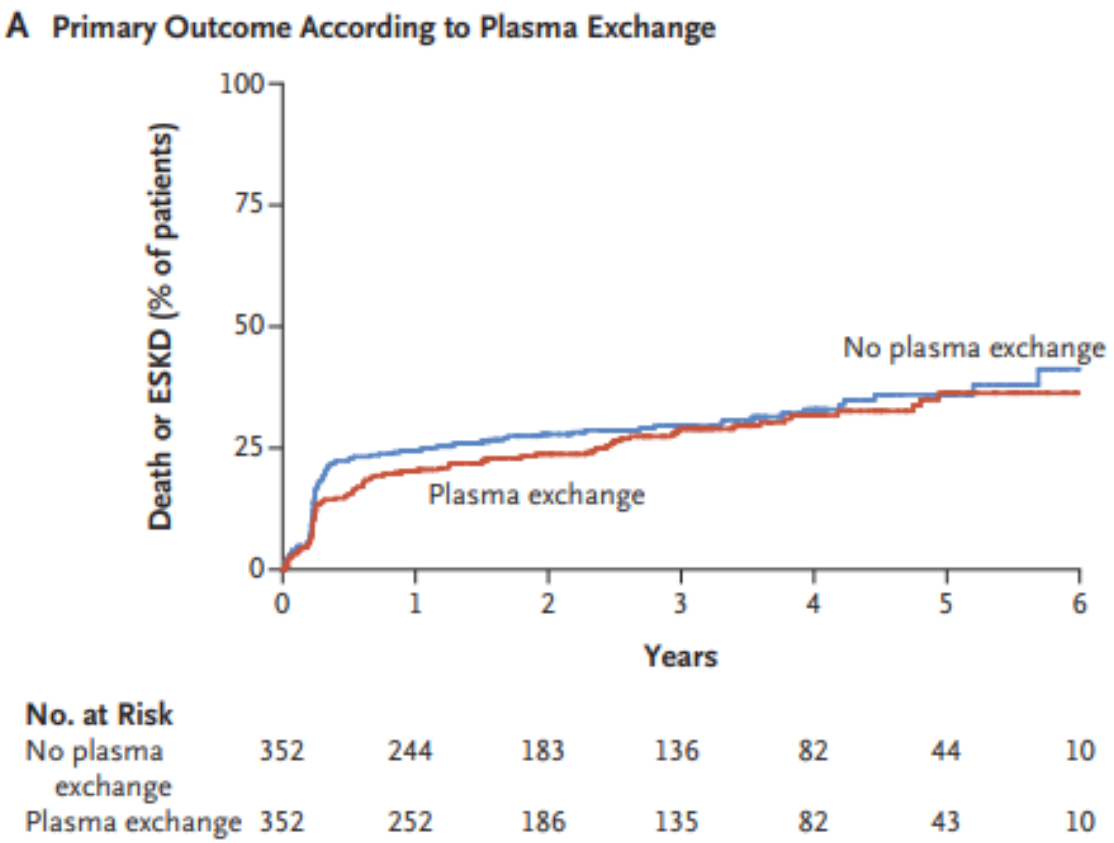
- ✓ Σχεδιασμός 2-by-2
  προσπάθεια απάντηση σε δύο κλινικά ερωτήματα:
  - PLEX
  - Steroid regimen

- ✓ **N=704 ασθενείς**
  ~29% creat > 500μmol/L or dialysis
  ~27% DAH (σοβαρή DAH <10%)

- ✓ Πρωτογενές καταληκτικό σημείο: Composite of death or ESRD

Walsh et al NEJM 2020

To PLEX or not to PLEX: that is the question…

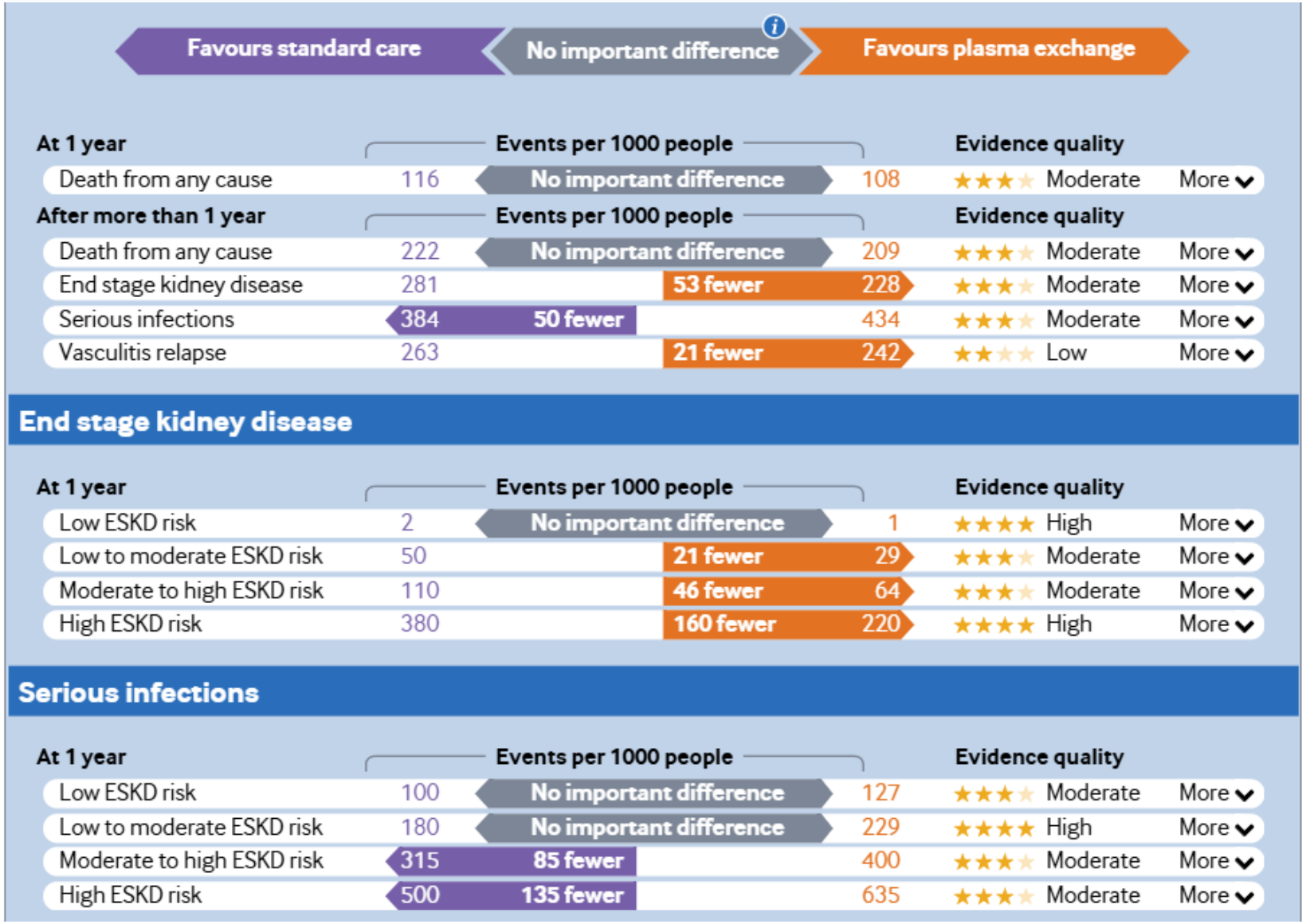


PLEX	No PLEX	HR (95%CI)
28.4%	**31.0%**	0.86 (0.65-1.13)

PLEX did not result in a lower incidence of death or ESKD than no PLEX

Walsh et al NEJM 2020

Does PLEX still have indications in AAV?



Consider PLEX

1. **at high risk for kidney failure** (large chance of benefit)
2. **At low risk for infections** (low risk of harm)

Young patient with high creatinine at baseline and need for dialysis

Walsh et al BMJ 2022;376:e064604
Walsh M 21st International Vasculitis Meeting Barcelona 2024

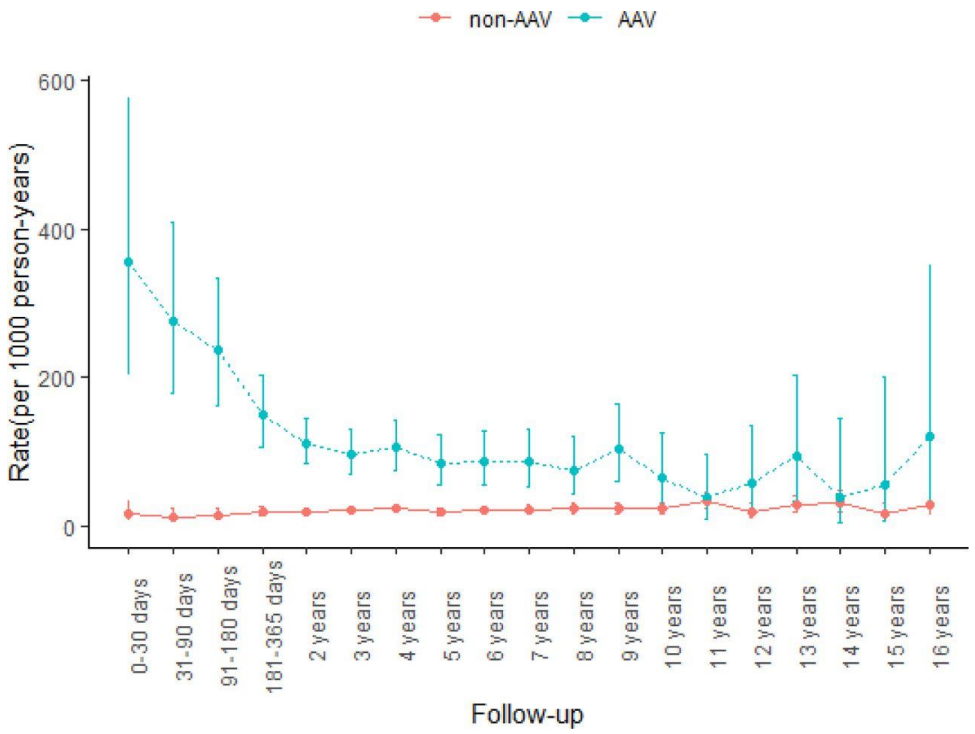
Ερώτηση: what about steroids?

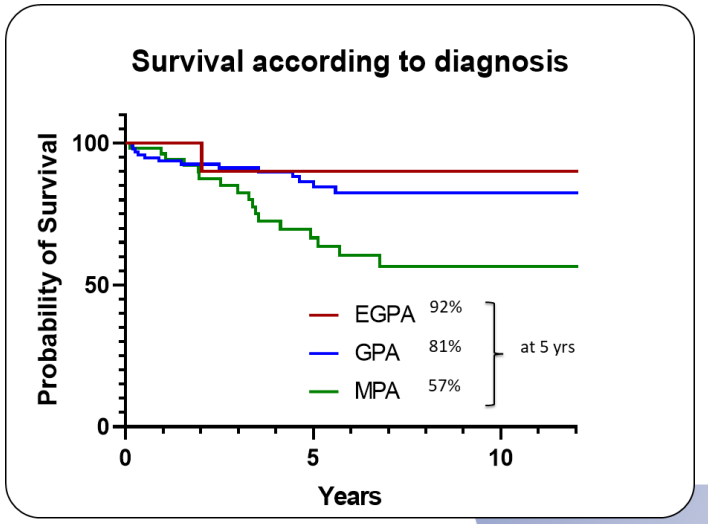
Increased risk for severe infections (SI)

Patients with AAV have increased infection risk during the induction period

n=549 pts, **one in three** developed SI
3.8 x infection risk vs matched controls

at time of diagnosis OR=77.02 for SI



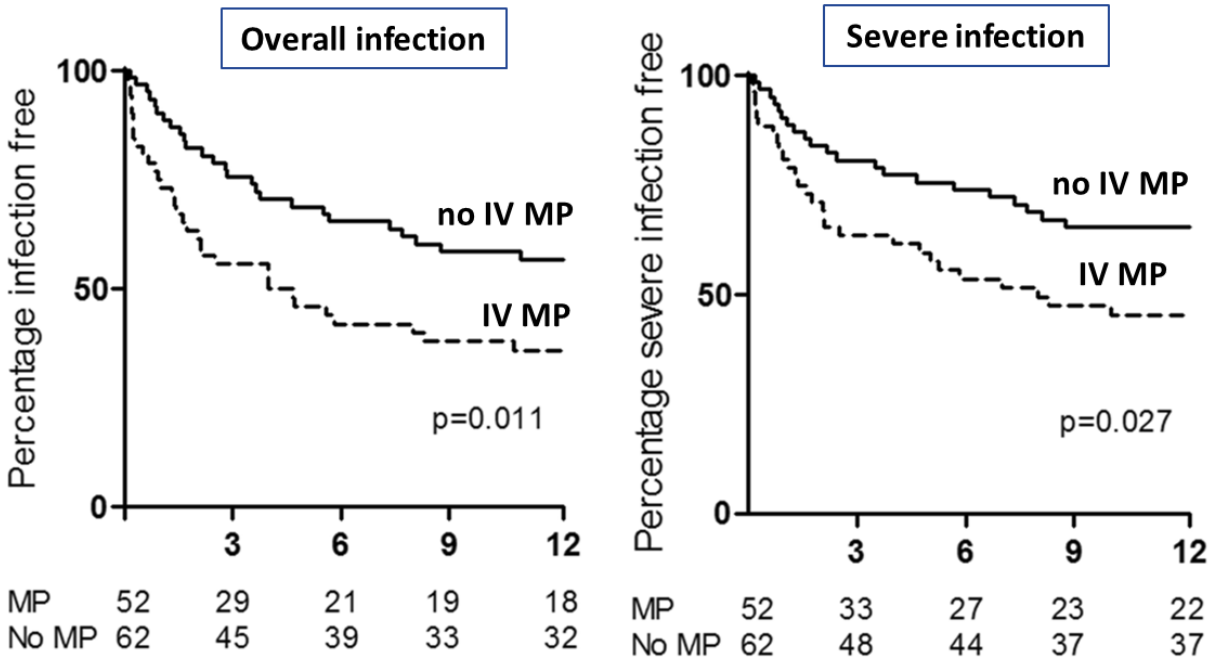


- **Infections (52%)**
- **Cardiovascular events (24%)**
- **Disease Flares (14%)**
- **Malignancies (10%)**

Zhao et al EULAR 2024 OP0142; Koutsianas et al EULAR 2022 POS0832

Increased risk for severe infections (SI)

High dose glucocorticoids associated with high risk for infections



Odds ratios (95 % CI) for the risk of severe infection (N = 98).

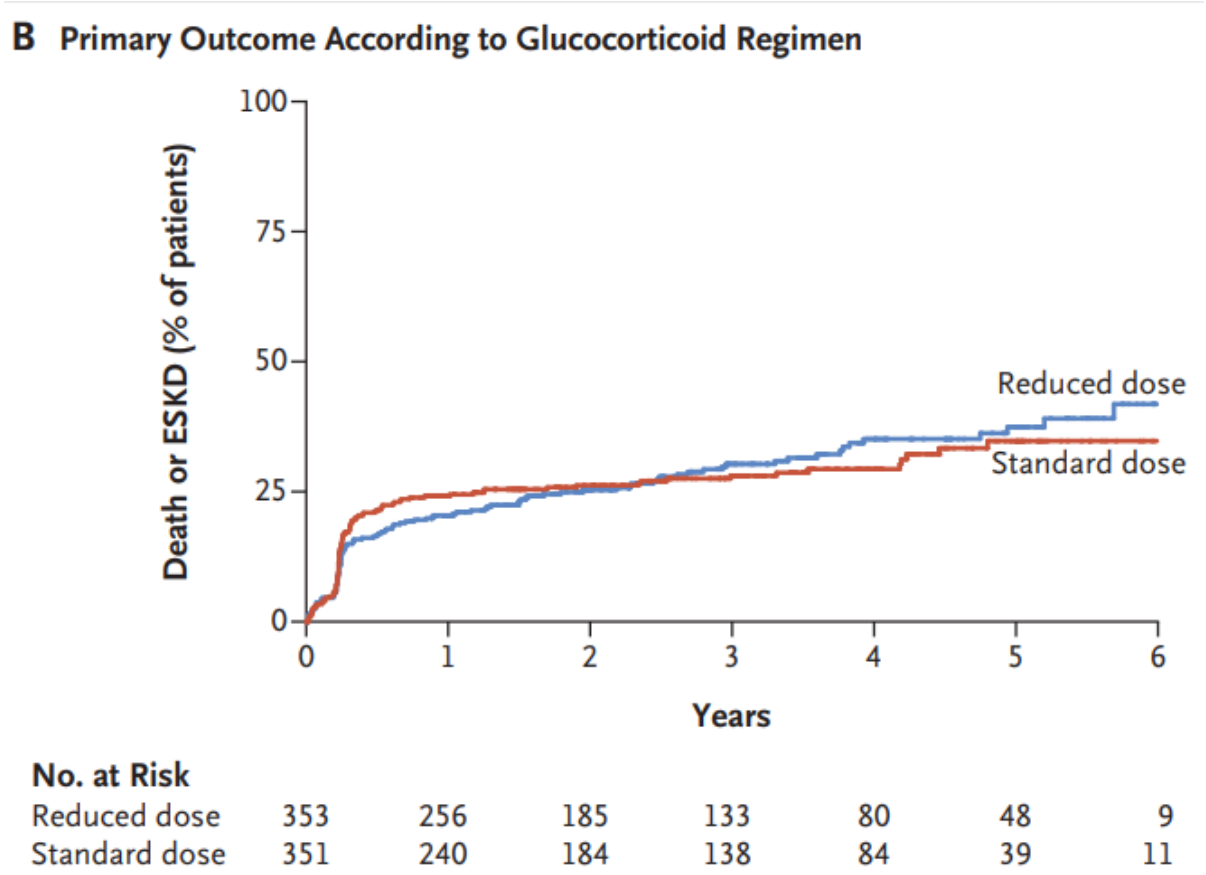
	Overall (N = 98)	N events (%)	*Risk of severe infection*	
			Univariate OR (95%CI)	Multivariate OR (95%CI)
Gammaglobulin <6 g/L at month 0	26 (26.5)	4 (15.4)	2.6 (1.2–5.6)	
Gammaglobulin decline >25 % between induction and month 0	49 (50)	6 (12.2)	4.4 (1.8–10.9)	
Gammaglobulin <6 g/L AND decline >25 %	19 (19.4)	4 (21.1)	3.2 (1.5–7.0)	2.3 (1.0–5.1)
Pulses of methylprednisolone at induction	31 (31.6)	31 (31.6)	6.8 (2.9–15.9)	5.6 (2.3–13.4)

HR=Hazard ratios; 95 % CI = 95 % confidence interval.

Chanouzas D et al BMC Nephrol 2019 Feb 18;20(1):58; Liberatore et al Journal of Autoimmunity 142 (2024) 103130

Use less steroids: there is no question!

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis



	Standard dose	Reduced dose	
Primary outcome	**25.5%**	**27.9%**	ARD=2.3% (-4.5 - 9.1 CI)
Serious infections	**33.0%**	**27.2%**	IRR=0.69 (0.52-0.93 CI)

Το σχήμα με τη μειωμένη δόση GCs δεν ήταν κατώτερο της συνήθους δόσης και συσχετίστηκε με λιγότερες λοιμώξεις

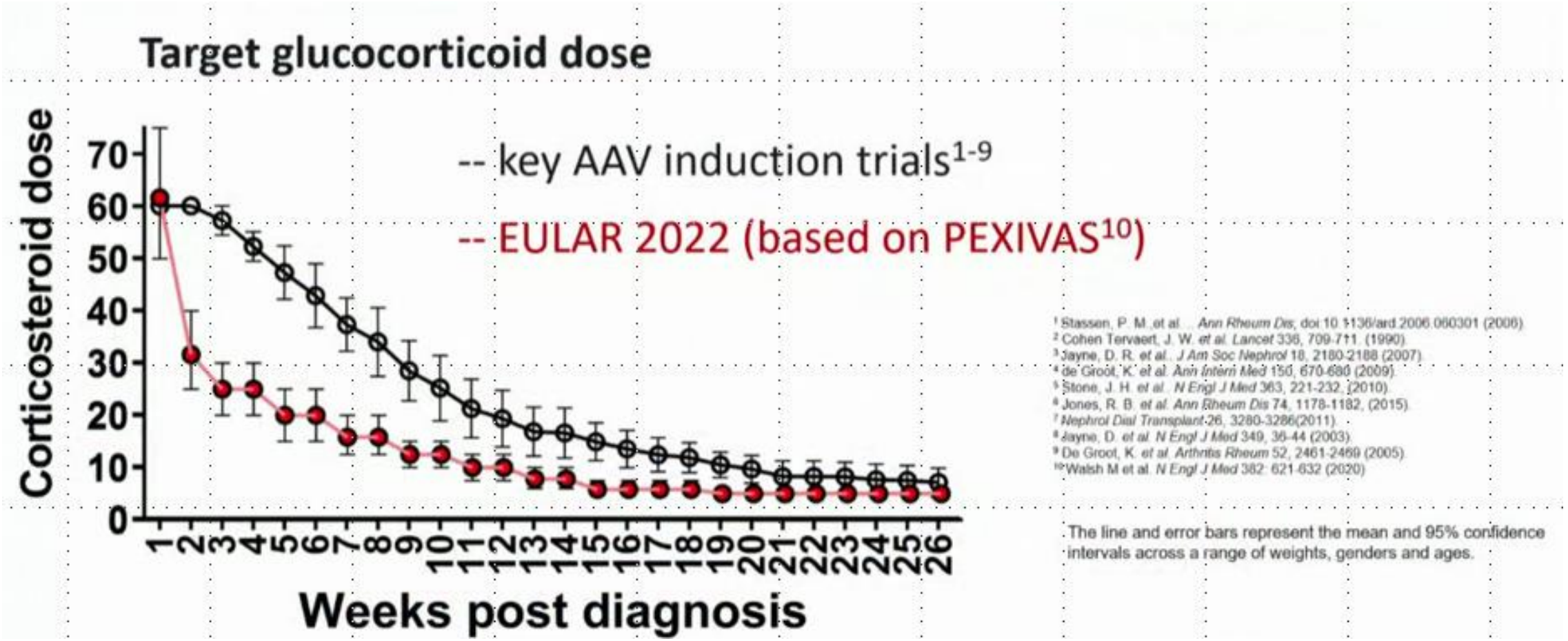
Walsh et al NEJM 2020

Use less steroids: there is no question!

Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	pulse	pulse	pulse	pulse	pulse	pulse
1	50	60		50	60	75
2	50	60		25	30	40
3-4	40	50	60	20	25	30
5-6	30		50	15	20	25
7-8	25		40	12.5	15	20
9-10	20		30	10	12.5	15
11-12	15		25	7.5	10	12.5
13-14	12.5		20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10		5	5	7.5
19-20		7.5		5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

Walsh et al NEJM 2020

Reduced steroid regimen should be standard of care



….or not?

Vasculitis

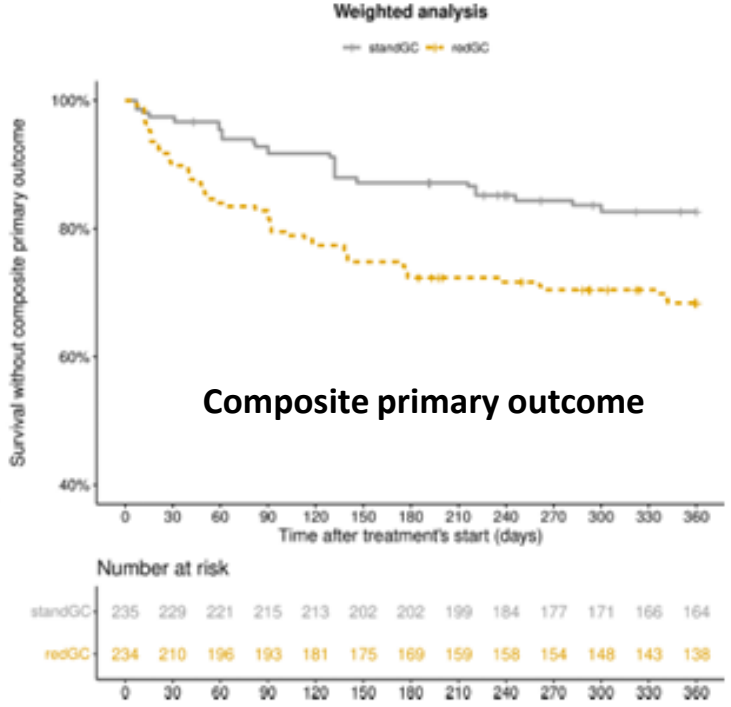
CLINICAL SCIENCE

Real-life use of the PEXIVAS reduced-dose glucocorticoid regimen in granulomatosis with polyangiitis and microscopic polyangiitis

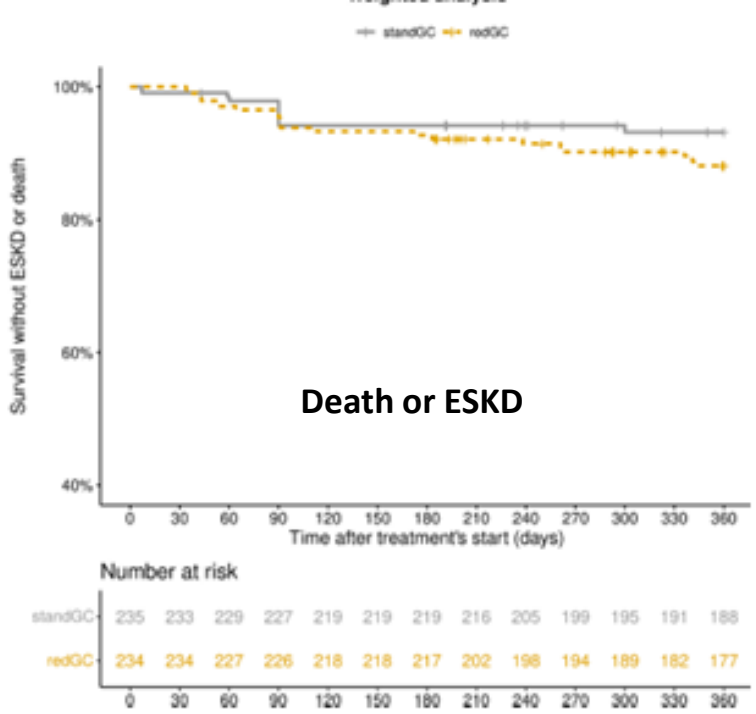
Sophie Nagle ,[1,2] Yann Nguyen ,[3,4] Mary-Jane Guerry,[5] Thomas Quemeneur,[5] Dimitri Titeca-Beauport,[6] Thomas Crépin,[7] Rafik Mesbah,[8] Idris Boudhabhay,[9] Grégory Pugnet,[10,11] Céline Lebas,[12] Antoine Néel,[13] Alexandre Karras,[14,15] Eric Hachulla,[16] Juliette Woessner,[17] Vincent Pestre,[17] Raphaël Porie ,[18]

- **Retrospective study (2018-22)**
- **New (75%)/relapsing (25%)**
- **Cr (median) 1.52 mg/dL**
  Cr > 3.4 mg/dL 25%
- **Induction**
  - **RTX 74%**
  - **CYC 30%**
  - **PLEX 17%**

Composite primary outcome
- *Outcome contributing to the primary outcome*
- *Progression before achieving remission*
- *Minor relapse*
- *Major relapse*
- *ESKD*
- *Death*



Composite primary outcome



Death or ESKD

	Standard dose GC	Reduced dosed GC	HR, p
Composite primary outcome	19.9	31.1	**2.03 (1.08-3.83) p=0.028**
Death or ESKD	7.8	11.4	1.73 (0.70-4.24) p=0.2
Remission	96.8	114	1.01 (0.75-1.37) P>0.9
Minor or Major relapse	9.8	9.3	1.17 (0.39-3.46) P=0.8

Nagle S, et al. Ann Rheum Dis 2024; doi:10.1136/ard-2024-226339

Ερώτηση: μπορώ να διακόψω τα κορτικοειδή στο maintenance?

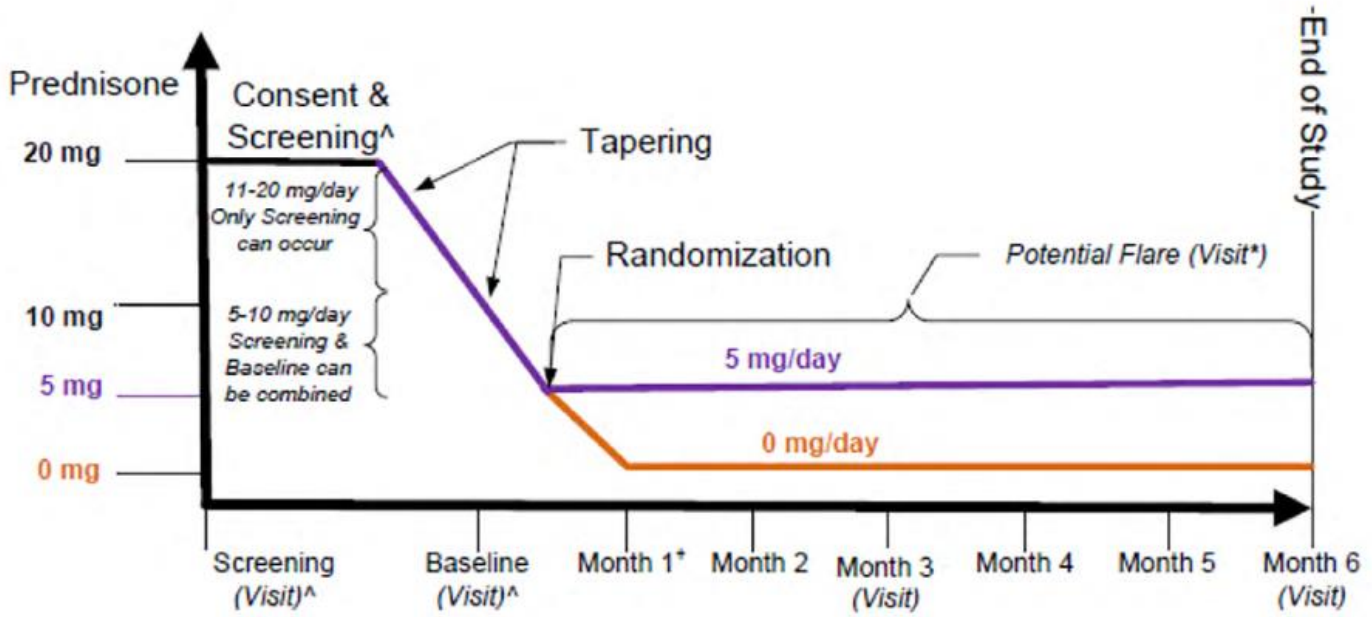
Maintenance of remission in GPA/MPA

Are GCs needed to maintain remission?

The Assessment of Prednisone In Remission Trial (TAPIR)

TAPIR

Peter Merkel, Christian Pagnoux, Nader Khalidi, Ulrich Specks, Curry Koening, Carol Langford, Larry Moreland, Paul Monach, Jason Springer, Shubhasree Banerjee, Simon Carette, Rennie Rhee, Medha Soowamber, Kenneth Warrington, Renée Borchin, Cristina Burroughs, Carol McAlear, David Cuthbertson, Jeffrey Krischer, for the Vasculitis Clinical Research Consortium



^Prednisone dose between 11 mg and 20 mg/day: subjects can be screened & enrolled
Prednisone dose between 6 mg and 10 mg/day: subjects can be screened, enrolled, and have a baseline visit
Prednisone dose of 5 mg/day: subjects can be screened, enrolled, have baseline visit and be randomized
*Flare visit is the early termination visit
+At month 1, Coordinator will call subject to confirm prednisone dose

n= 159 GPA pts eligible for TAPIR if they were

i) within one year of receiving treatment to induce remission;

ii) in remission (BVAS/WG=0); and

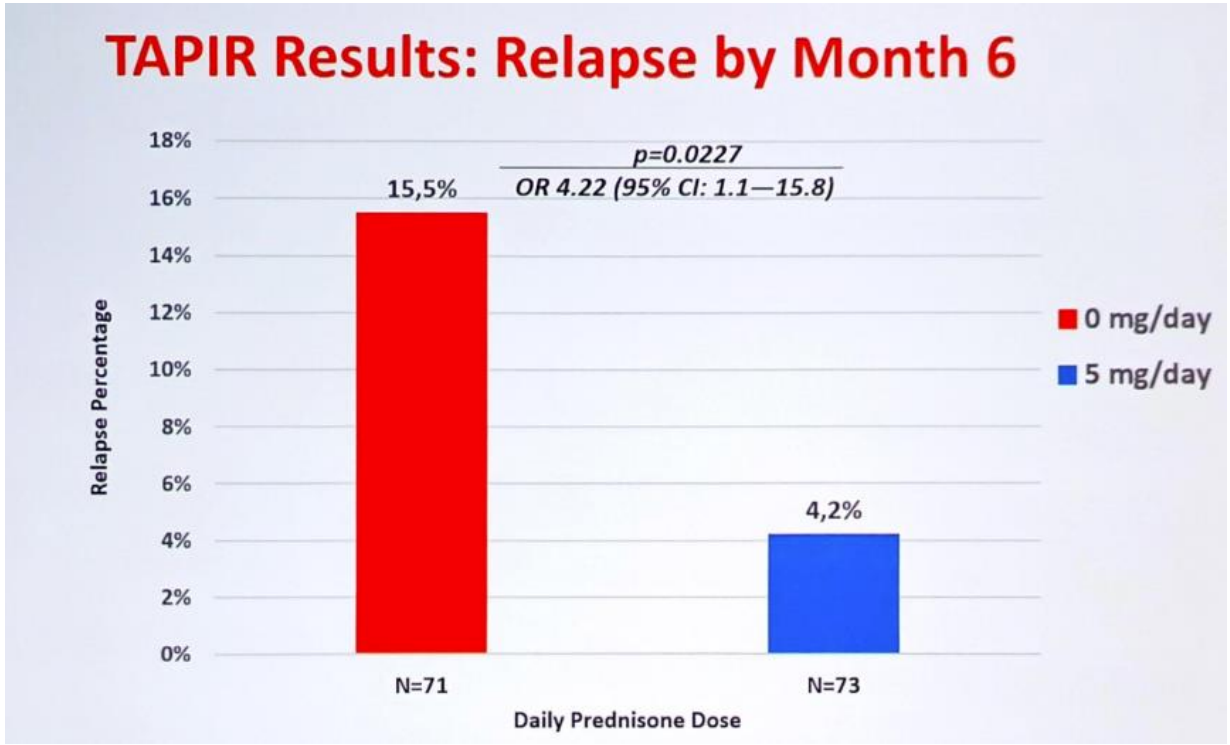
iii) receiving treatment with prednisone at a daily dose of 5-20 mg

Merkel et al 21st Internation Vasculitis Workshop 2024 O-009

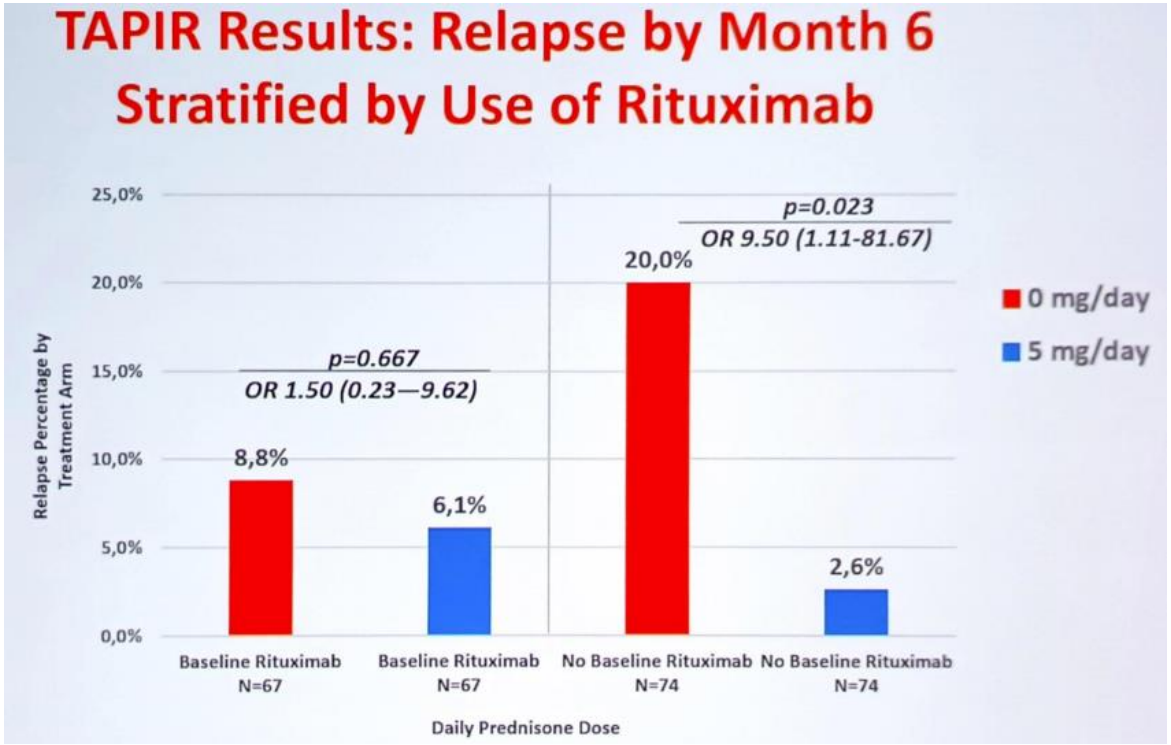
Maintenance of remission in GPA/MPA

Are GCs needed to maintain remission?

Primary outcome



Stratification by RTX



Merkel et al 21st Internation Vasculitis Workshop 2024 O-009

Maintenance of remission in GPA/MPA

Are GCs needed to maintain remission?

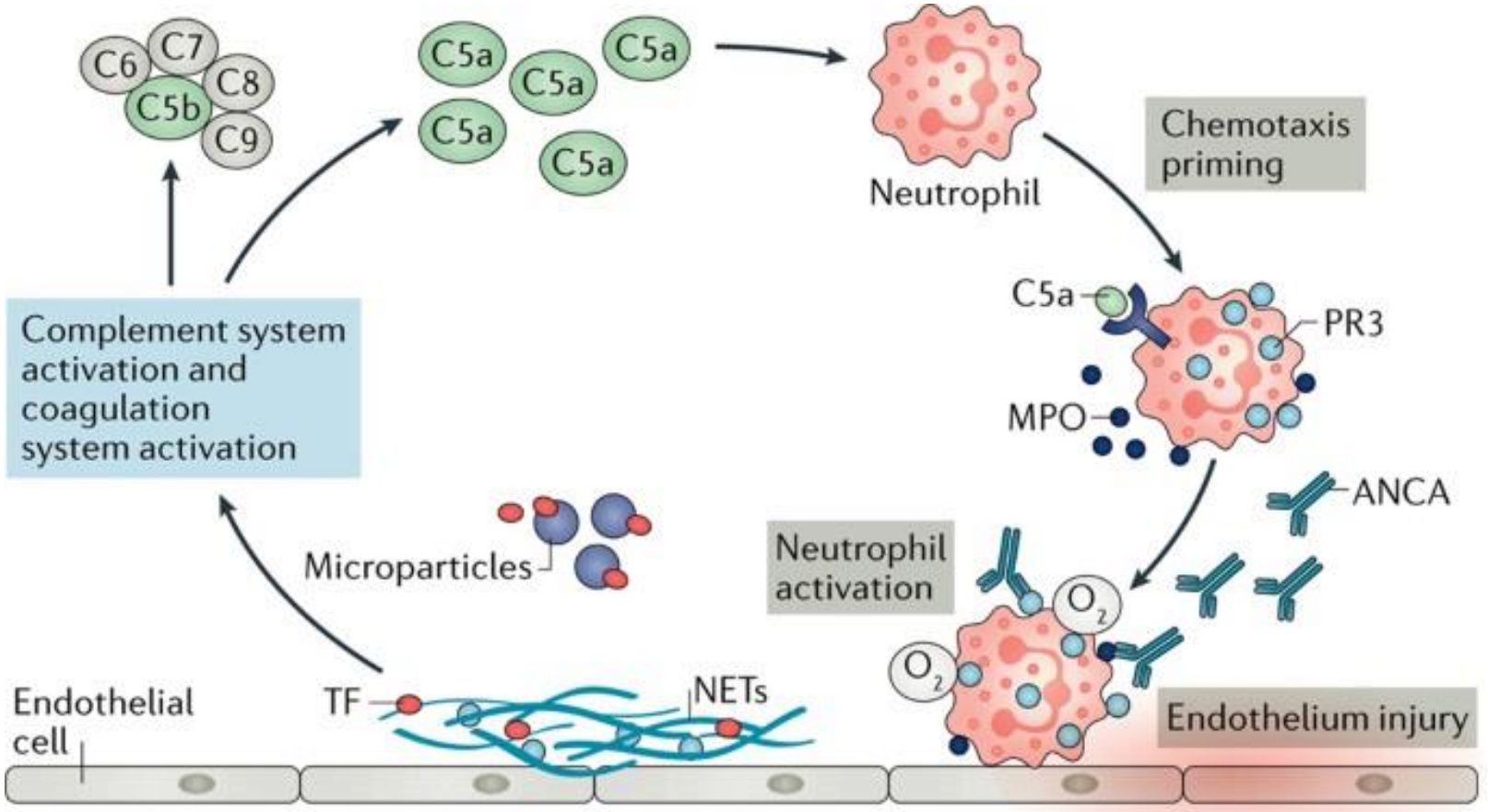
Takeaway key points

For GPA pts, after remission induction:

- ✓ Use of **low dose PRE prevents more disease relapses** over 6mo VS no PRE
- ✓ The relapses were mostly minor
- ✓ The benefit of PRE is seen **only on patients having received a non-RTX-based regimen**
- ✓ The rate of minor relapses among RTX treated pts is the same whether on low dose PRE or not

Ερώτηση: τι άλλο μπορώ να κάνω για να μειώσω περαιτέρω τα κορτικοστεροειδή?

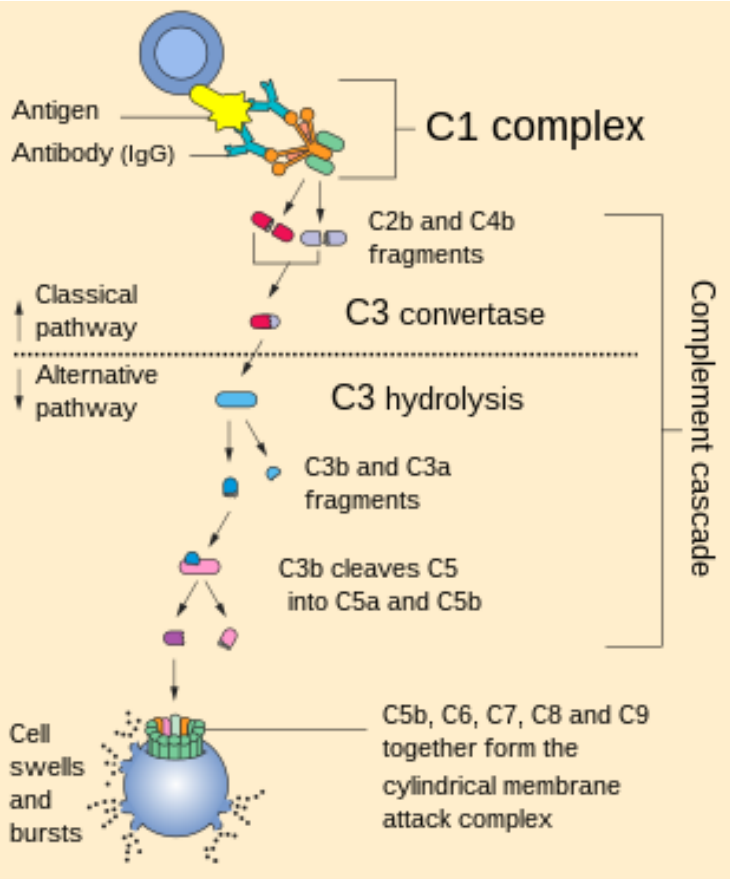
Inflammation in AAV: the role of complement

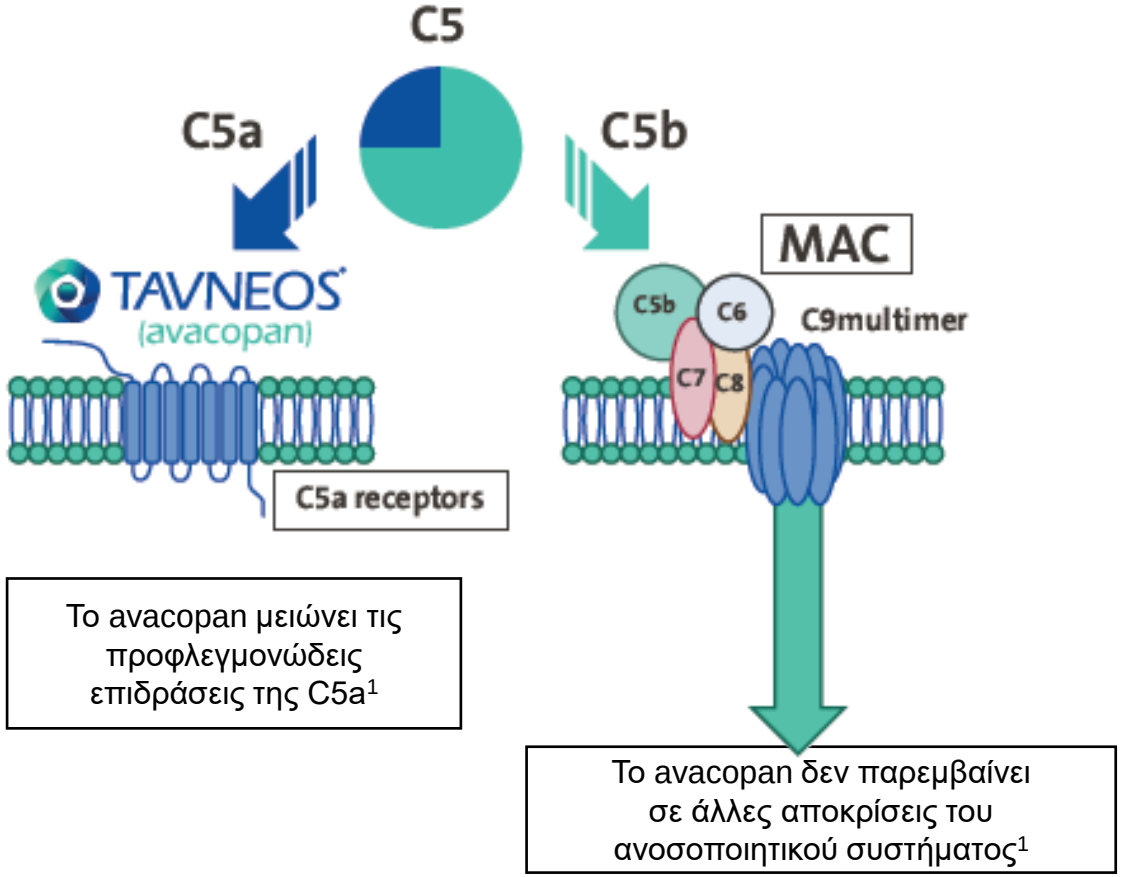


Chen et al Nat Rev Nephrol 2017;13:359

Avacopan: C5aR inhibitor

Το avacopan στοχεύει εκλεκτικά τον C5aR – δεν επηρεάζει το σχηματισμό του MAC[1,2]





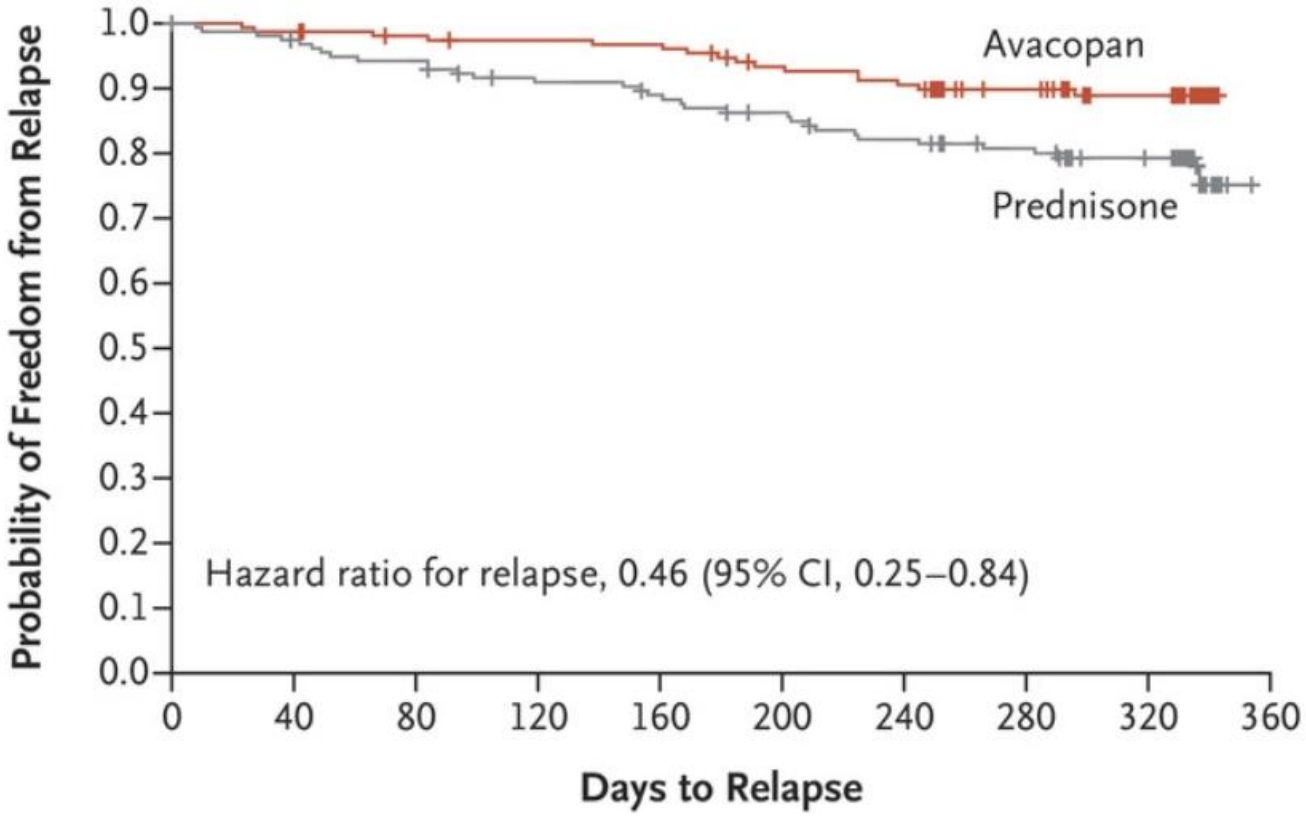
Το avacopan μειώνει τις προφλεγμονώδεις επιδράσεις της C5a[1]

Το avacopan δεν παρεμβαίνει σε άλλες αποκρίσεις του ανοσοποιητικού συστήματος[1]

- AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasm antibodies; C, complement protein; MAC, membrane attack complex; MoA, mechanism of action.

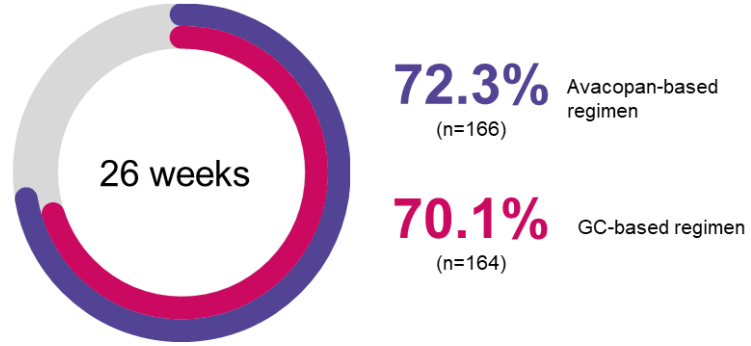
1. Bekker P, et al. *PLoS One* 2016;11(10):e0164646.
2. Thurman JM, Holers VM. *J Immunol* 2006;176(3):1305–10.

ADVOCATE trial: efficacy



Equivalent disease remission (week 26)

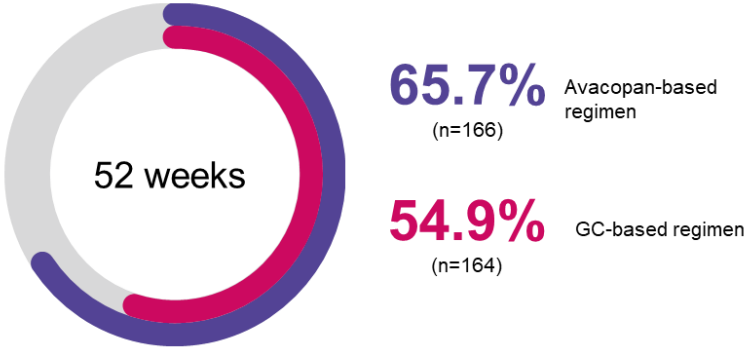
Avacopan-based regimen demonstrated equivalent remission at 26 weeks vs GC-based regimen



P<0.0001 for non-inferiority

Superior sustained remission (week 52)

Avacopan-based regimen demonstrated superior sustained remission at 52 weeks vs GC-based regimen

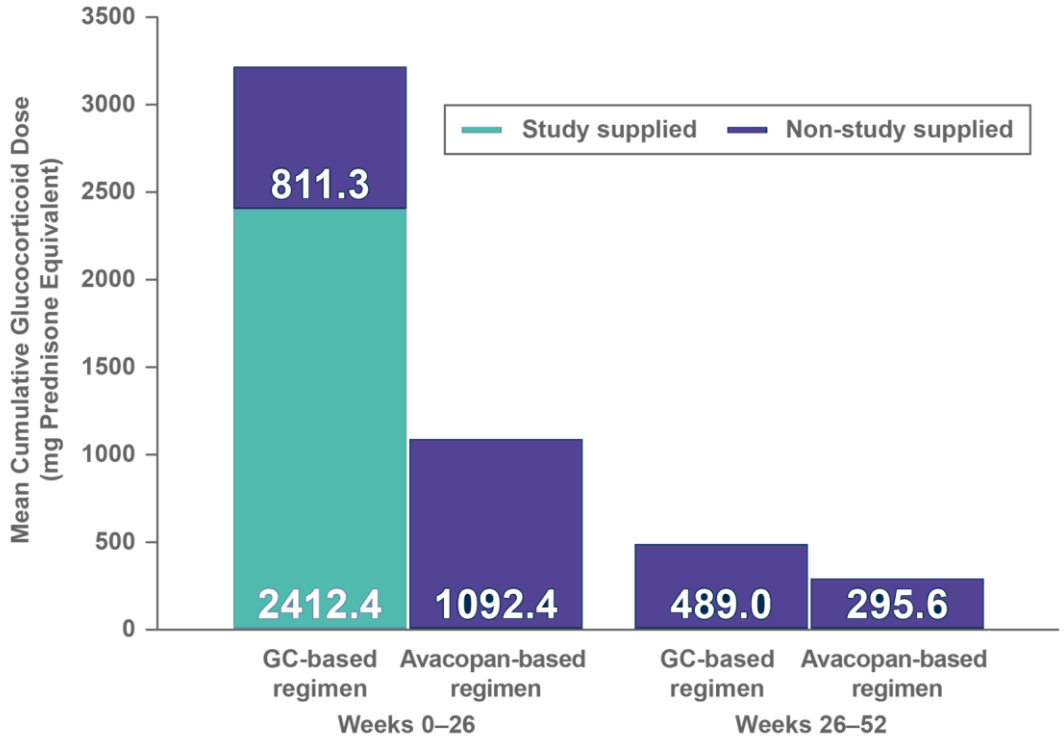


P=0.007 for superiority

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

Avacopan: important role in reduced GC dose

Lower GC dosing with Avacopan-based regimen, including weeks 26-52



- GC, glucocorticoid.

Approximately

65%

lower overall GC dose with Avacopan-based regimen[1,2]

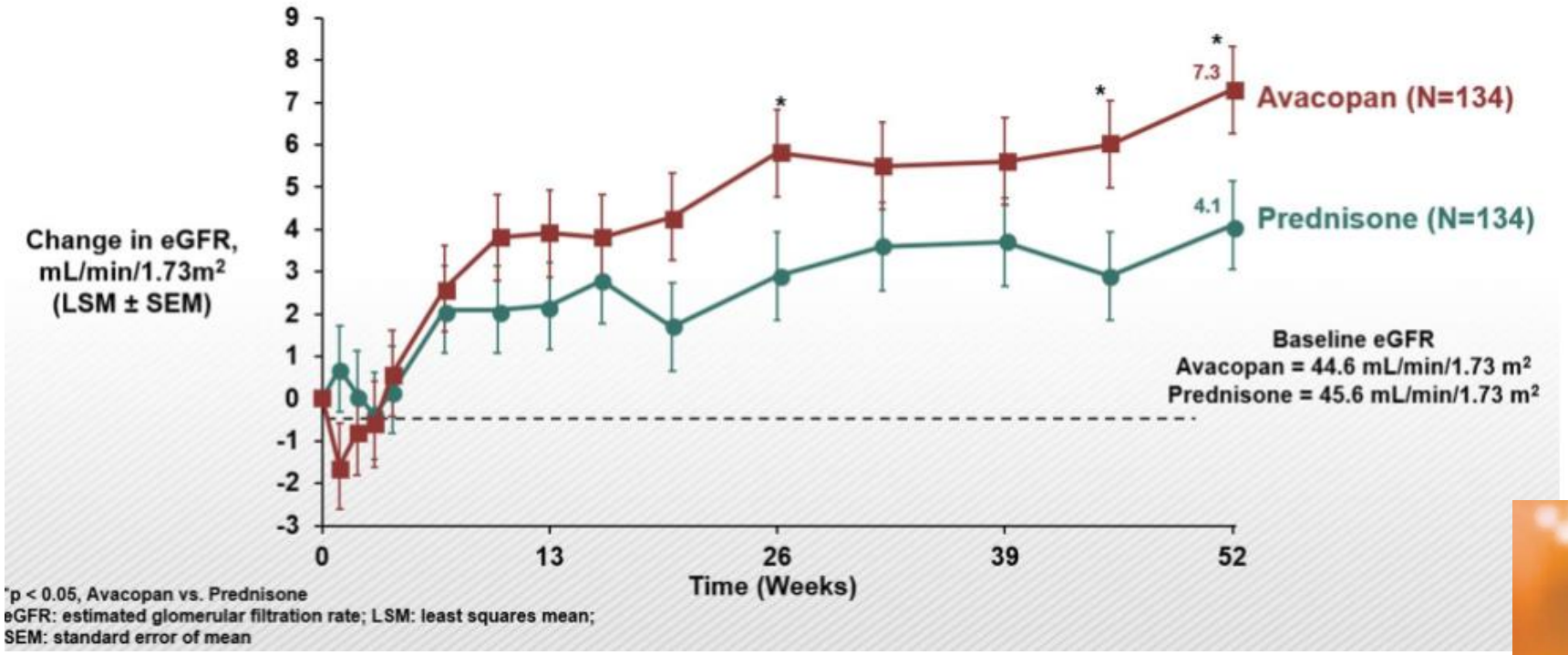
- Mean total GC dose: **1,349 mg vs 3,655 mg**

2/3

patients treated with the Avacopan-based regimen were GC-free during Weeks 26–52[3]

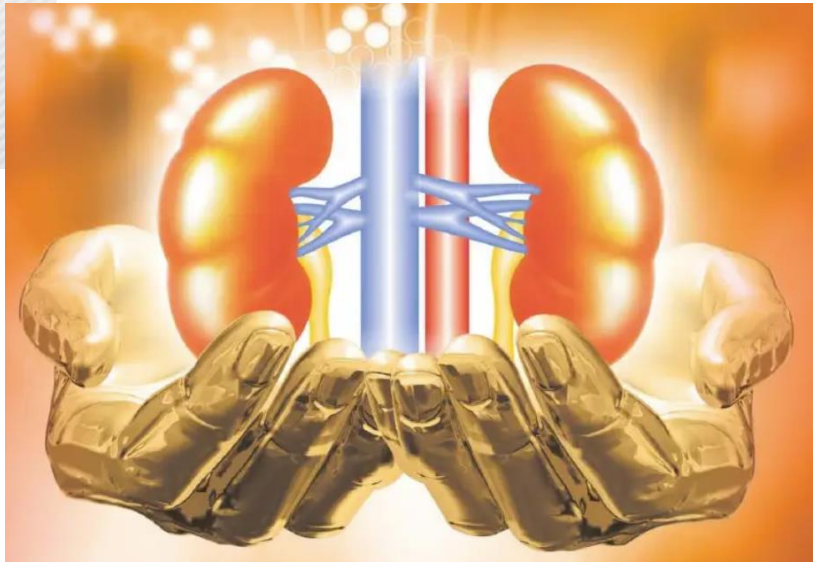
1. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609.
2. Jayne D, et al. *N Engl J Med* 2021;384(7):599–609 [Suppl Appendix].
3. Vifor Pharma. Clinical Study Report: CL010_168. Data on file.

Avacopan: early eGFR response



*p < 0.05, Avacopan vs. Prednisone
eGFR: estimated glomerular filtration rate; LSM: least squares mean; SEM: standard error of mean

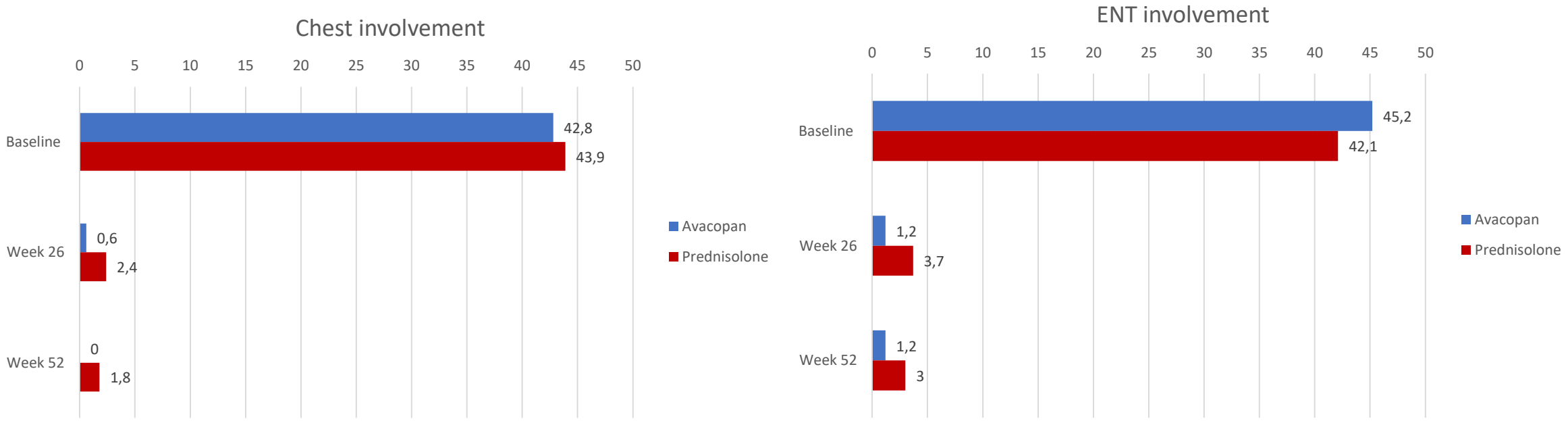
Save the nephrons



Geetha et al Ann Rheum Dis 2023;0:1–10

Avacopan in non-renal manifestations

Insights from ADVOCATE: post-hoc, subanalysis



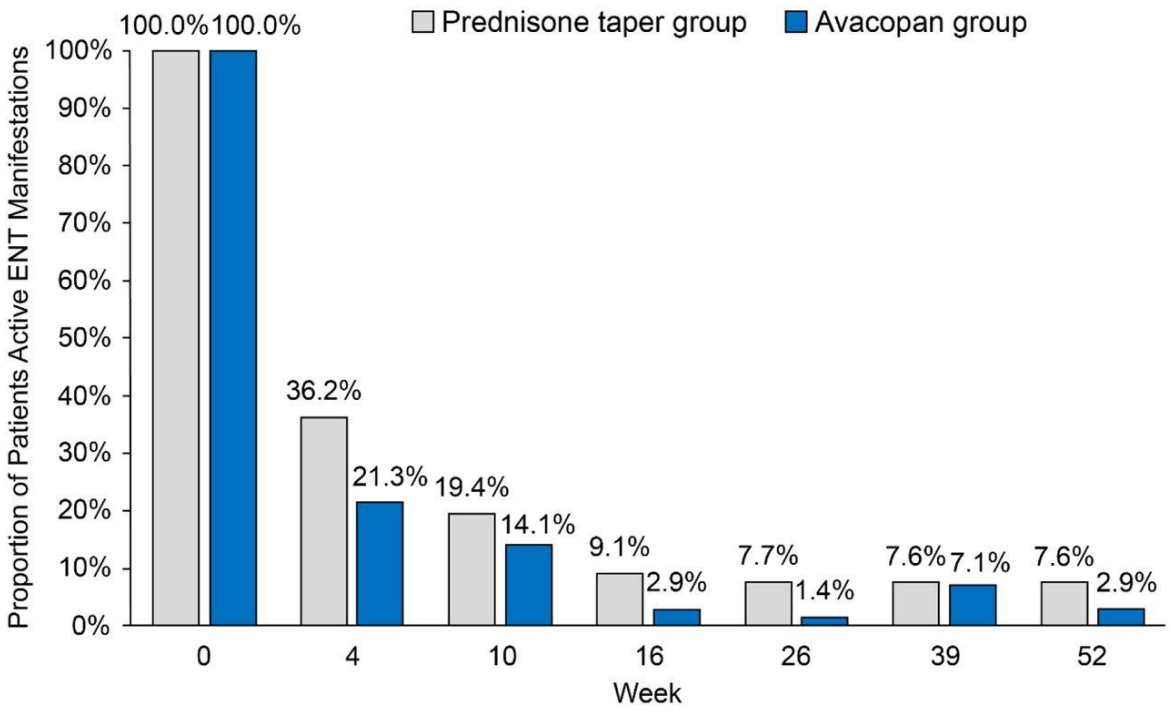
the avacopan group achieved numerically lower (but not statistically significant) rates in both lung and ENT involvement at Weeks 26 and 52 compared to the prednisone group.

Specks U et al Am J Respir Crit Care Med 2022;205:A4780

Avacopan in non-renal manifestations

Results from ADVOCATE: Faster resolution of ENT manifestations

Figure: The proportion of patients with any active ear, nose, or throat manifestations, based on Birmingham Vasculitis Activity Score, at different timepoints during the ADVOCATE trial in the two treatment groups: avacopan (N=75) or a prednisone taper (N=69).

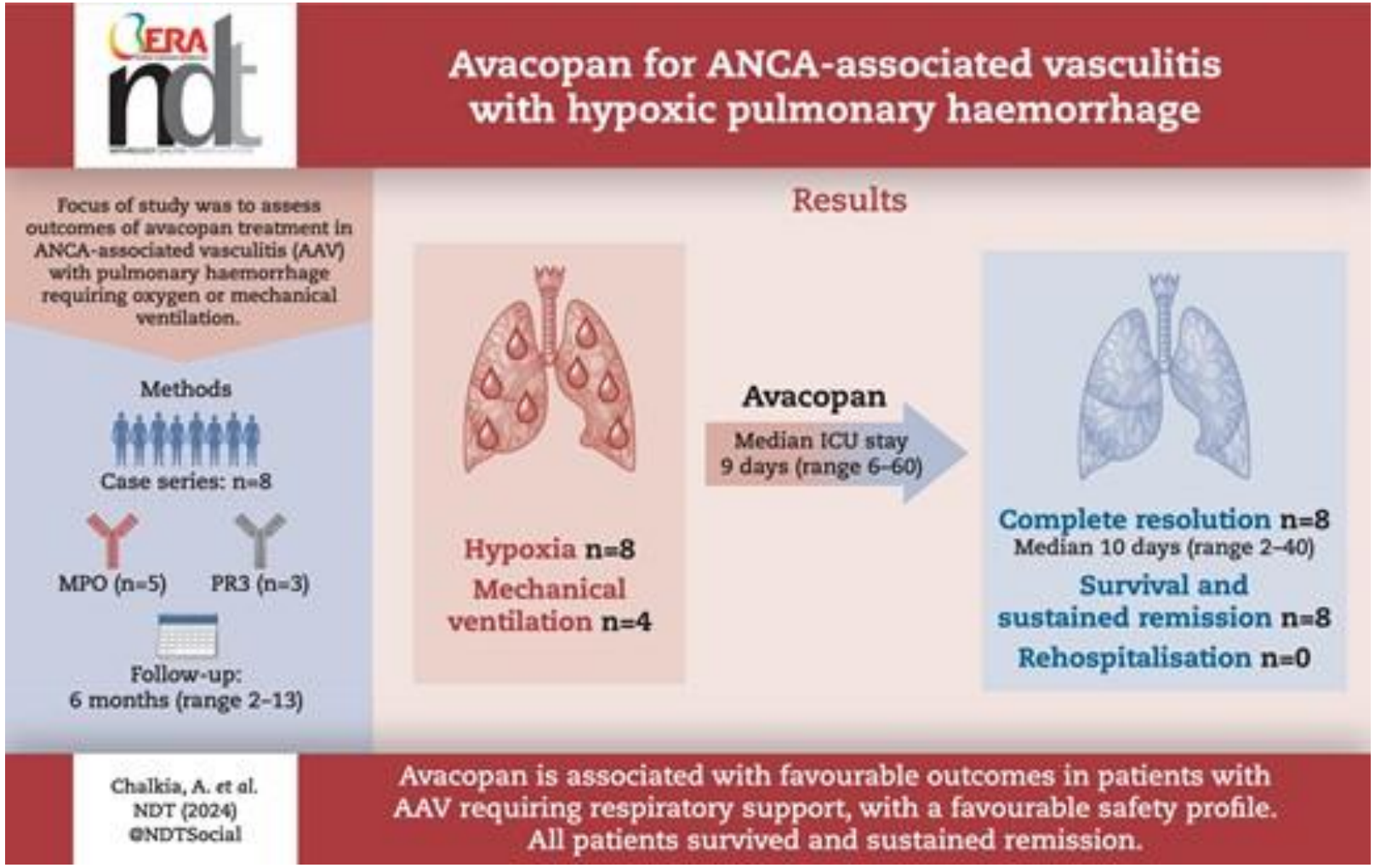


	Prednisone taper group (N=69)	Avacopan group (N=75)	Difference in percentage points or LSM difference ± SEM (95% CI)
Baseline characteristics (data are mean ± standard deviation [SD] or n [%])			
Male / female	34 (49.3) / 35 (50.7)	39 (52.0) / 36 (48.0)	
Newly diagnosed / relapsed	40 (58.0) / 29 (42.0)	48 (64.0) / 27 (36.0)	
PR3-ANCA / MPO-ANCA	46 (66.7) / 23 (33.3)	45 (60.0) / 30 (40.0)	
GPA / MPA	56 (81.2) / 13 (18.8)	58 (77.3) / 17 (22.7)	
Rituximab / cyclophosphamide	49 (71.0) / 20 (29.0)	54 (72.0) / 21 (28.0)	
Efficacy outcomes (data are n (%), n/N' (%), or LSM ± SEM)			
Remission[a] at week 26	49 (71.0)	54 (72.0)	1.0 (-13.8, 15.7)
Sustained remission[b] at week 52	37 (53.6)	47 (62.7)	9.0 (-7.0, 25.1)
Overall relapse[c] rate after BVAS of 0 was achieved at any time	14/66 (21.2)	10/72 (13.9)	
ENT relapse[c] rate after ENT BVAS of 0 was achieved at any time	13/66 (19.7)	11/74 (14.9)	
GTI-CWS/GTI-AIS[d] at week 26	52.3 ± 5.0/ 19.5 ± 5.5	45.9 ± 5.0/ 18.4 ± 5.4	-6.4 ± 6.4 (-19.0, 6.2)/ -1.1 ± 6.9 (-14.8, 12.6)
SF-36 PCS/MCS score,[e] change from baseline to week 52	2.0 ± 1.2/ 5.5 ± 1.3	4.8 ± 1.1/ 6.5 ± 1.3	2.8 ± 1.5 (-0.2, 5.8)/ 1.0 ± 1.7 (-2.4, 4.3)
EQ-5D-5L Index/EQ-5D-5L VAS,[f] change from baseline to week 52	-0.026 ± 0.024/ 7.7 ± 2.3	0.043 ± 0.024/ 13.8 ± 2.2	0.07 ± 0.03 (0.00, 0.13)/ 6.2 ± 2.9 (0.4, 11.9)
Safety outcomes (data are n patients [%]; n events)			
Any adverse events	67 (97.1); 1006	74 (98.7); 822	
Any infection	49 (71.0); 124	55 (73.3); 109	
Any serious adverse event	24 (34.8); 57	29 (38.7); 48	
Any serious infection	4 (5.8); 5	8 (10.7); 10	

Spiera et al EULAR 2024 OP0174

Avacopan in non-renal manifestations

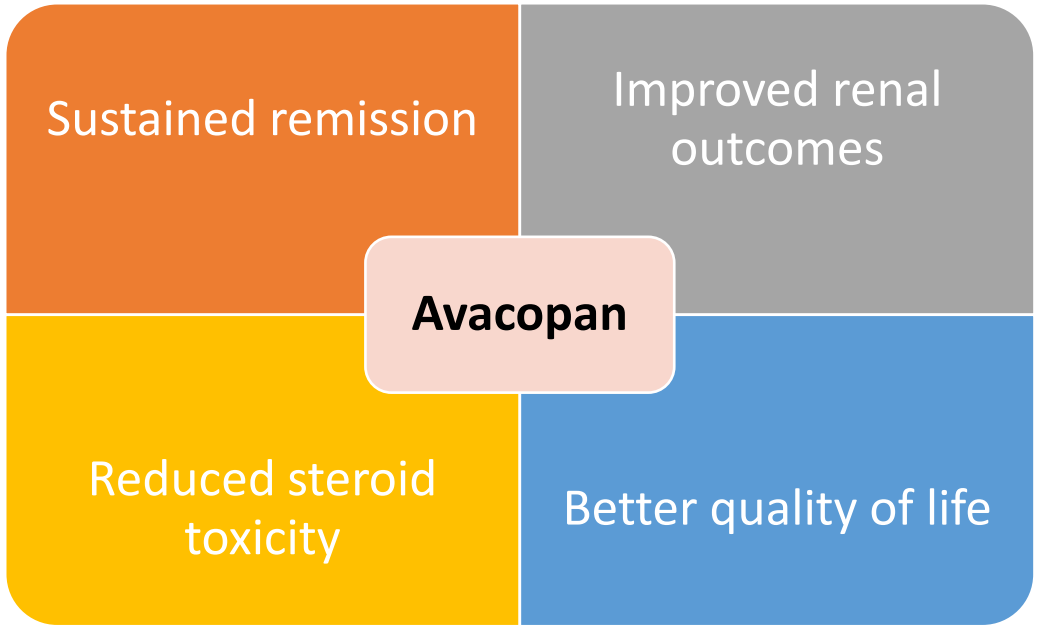
Efficacy in pulmonary haemorrhage



Chalkia et al Nephrol Dial Transplant 2024 Aug 30;39(9):1473-1482

Avacopan in daily clinical practice

When to use?



- Patients where GCs are contraindicated or there is a high risk for GC-related toxicity (e.g. older age, DM, osteoporosis)
- Patients presenting with low eGFR and at risk for RPGN
- Patients with refractory/relapsing disease

Personal opinion

Our experience with Avacopan

Rheumatology and Renal Vasculitis Clinic

Νεφρολογικό Τμήμα
Κέντρο Εμπειρογνωμοσύνης για Σπάνιες Σπειραματοπάθειες

Μονάδα Κλινικής Ανοσολογίας-Ρευματολογίας
Β' Παθολογική Κλινική

	N=8
Clinical characteristics	
• New disease/ relapse	7/1
• Age, years, median (IQR)	61 (60-78)
• MPO/PR3/negative	5/2/negative
Organ involvement	
• Kidney	8
eGFR<15ml/min/1.73m^2	5
• Lung	5
• Skin	1
• ENT	1
Induction treatment	
• RTX	6
• RTX+CYC	2
Avacopan Indication	
• Steroid sparring	5
• Severe kidney disease	6

- The median (IQR) time to start avacopan was **14.5 (5–75) days** after start of induction of remission therapy.
- At time of avacopan initiation the median (IQR) dose of MP was **32 (0-60) mg.**
- The median (IQR) time to terminally taper MP after starting avacopan was **4 (4–6) weeks.**

OUTCOMES - SAFETY

- 3 serious infections (COVID-19, UTI infection)
- 4 temporal discontinuation
  - 1 hepatotoxicity
  - 4 neutropenia (↓ dosage 20mg x2 in one patient)
- 1 permanent discontinuation (7th month) due ESKD
- All survived
- All remission

Unpublished data

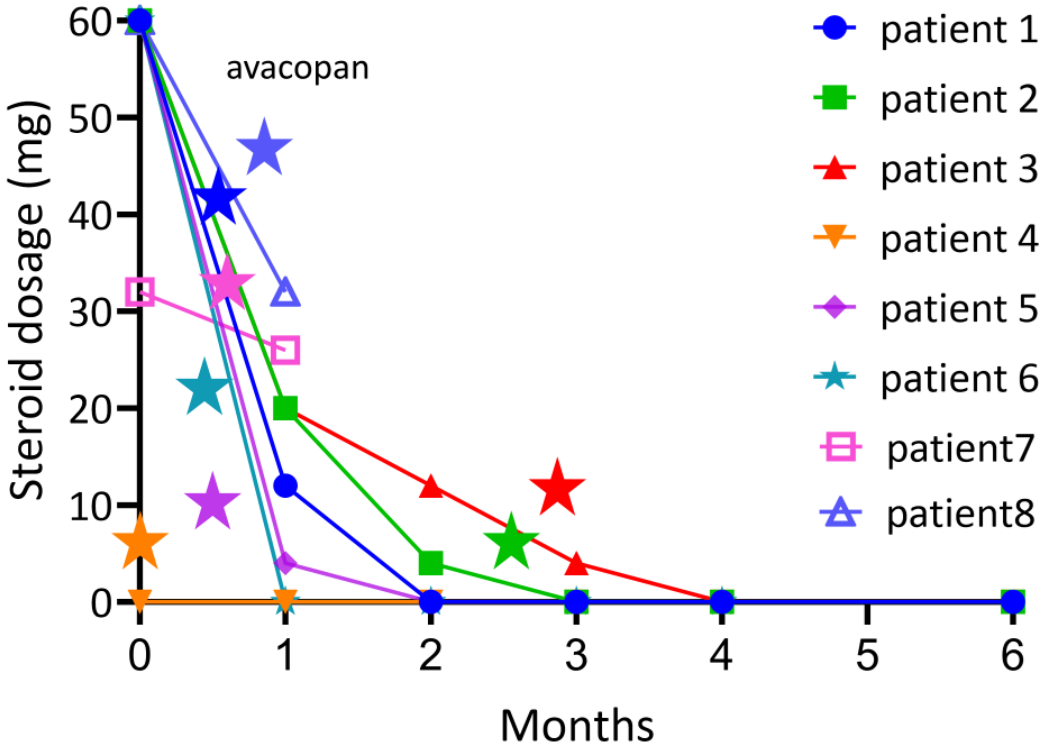
Our experience with Avacopan

Rheumatology and Renal Vasculitis Clinic

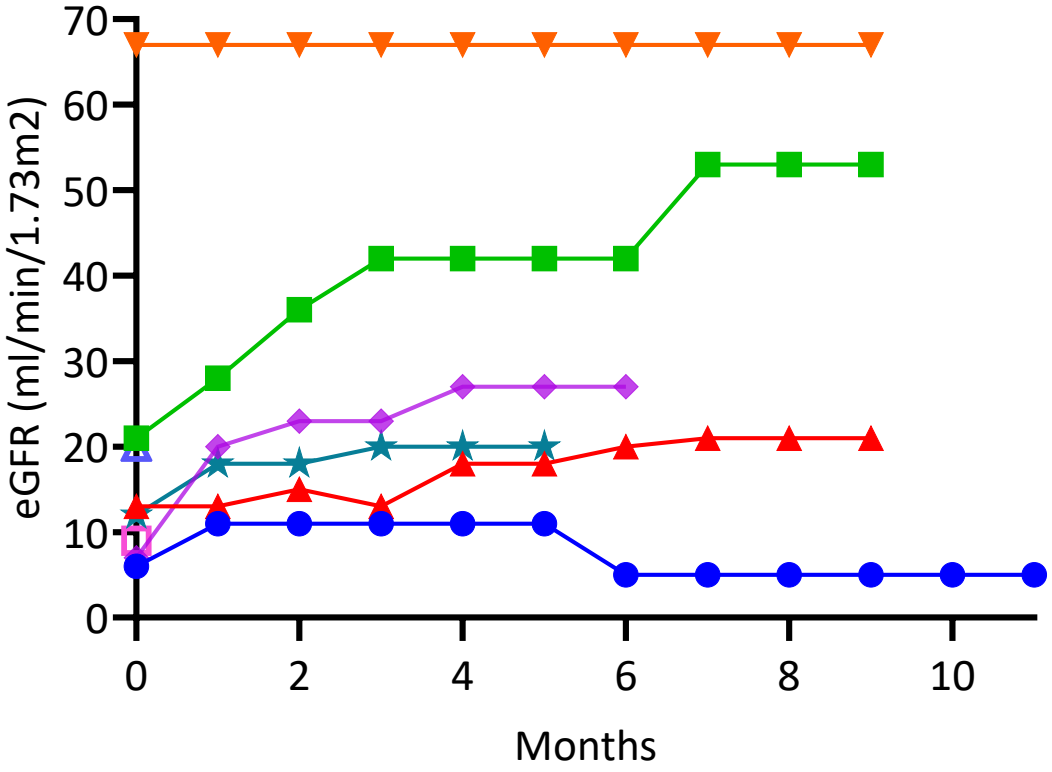
Νεφρολογικό Τμήμα
Κέντρο Εμπειρογνωμοσύνης για
Σπάνιες Σπειραματοπάθειες

Μονάδα Κλινικής Ανοσολογίας-Ρευματολογίας
Β' Παθολογική Κλινική

Steroid tapering



eGFR recovery

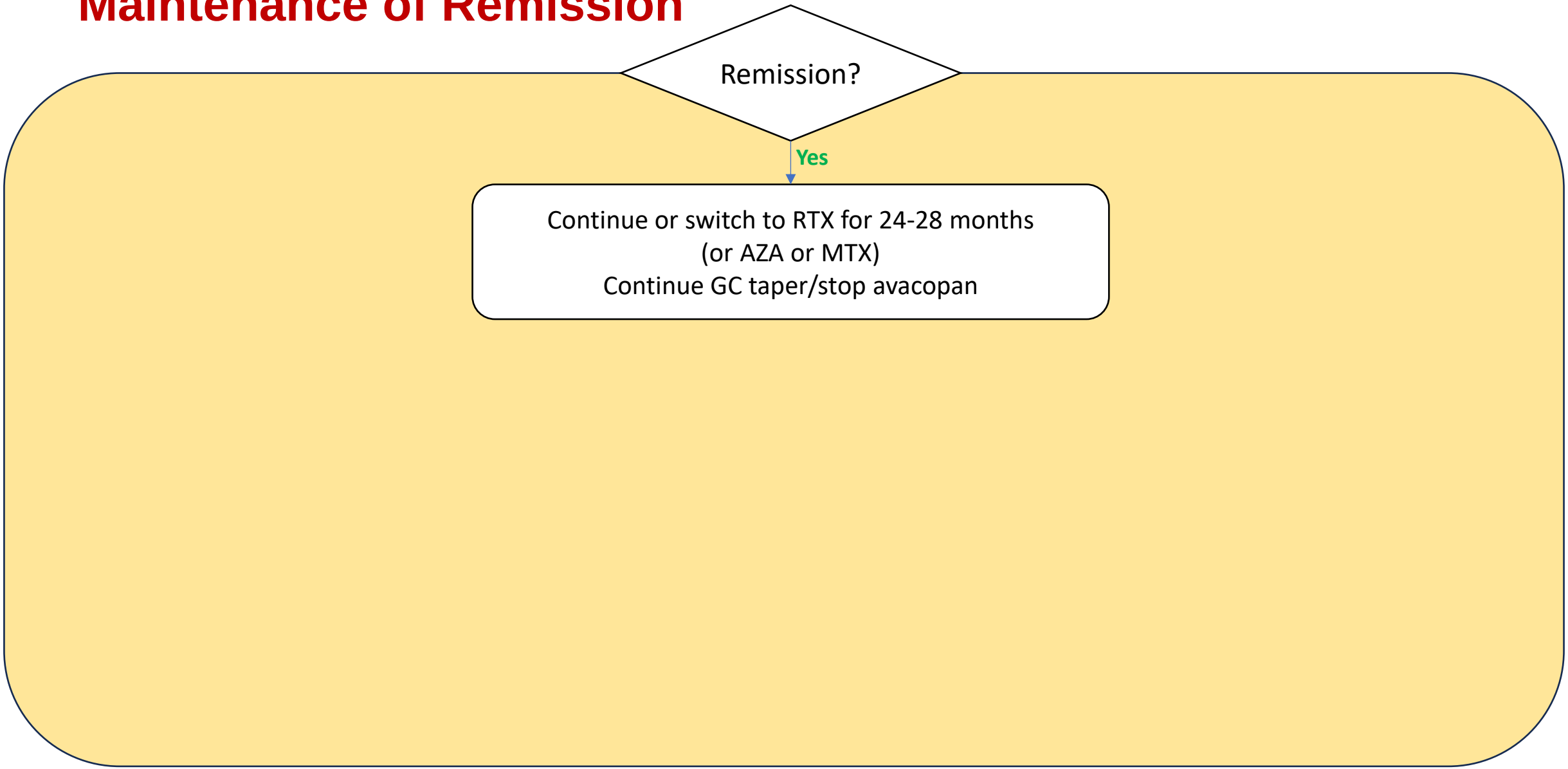


Unpublished data

Ερώτηση: ποια είναι η καλύτερη θεραπεία διατήρησης της ύφεσης και για πόσο?

GPA/MPA treatment in 2025

Maintenance of Remission

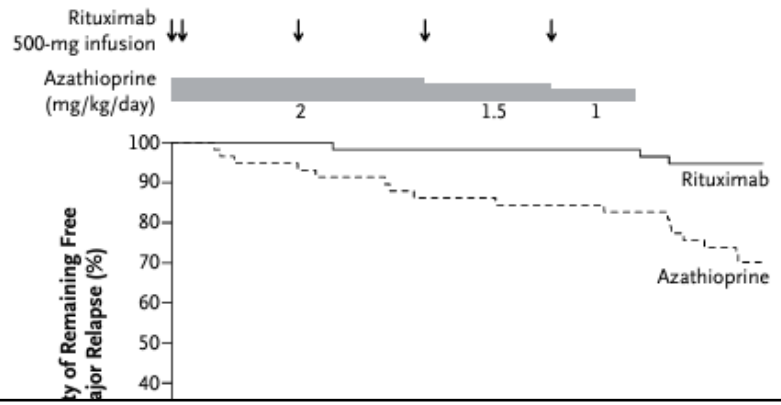


Maintenance of remission in GPA/MPA

Rituximab is the new standard: it is more effective vs AZA

MAINRITSAN

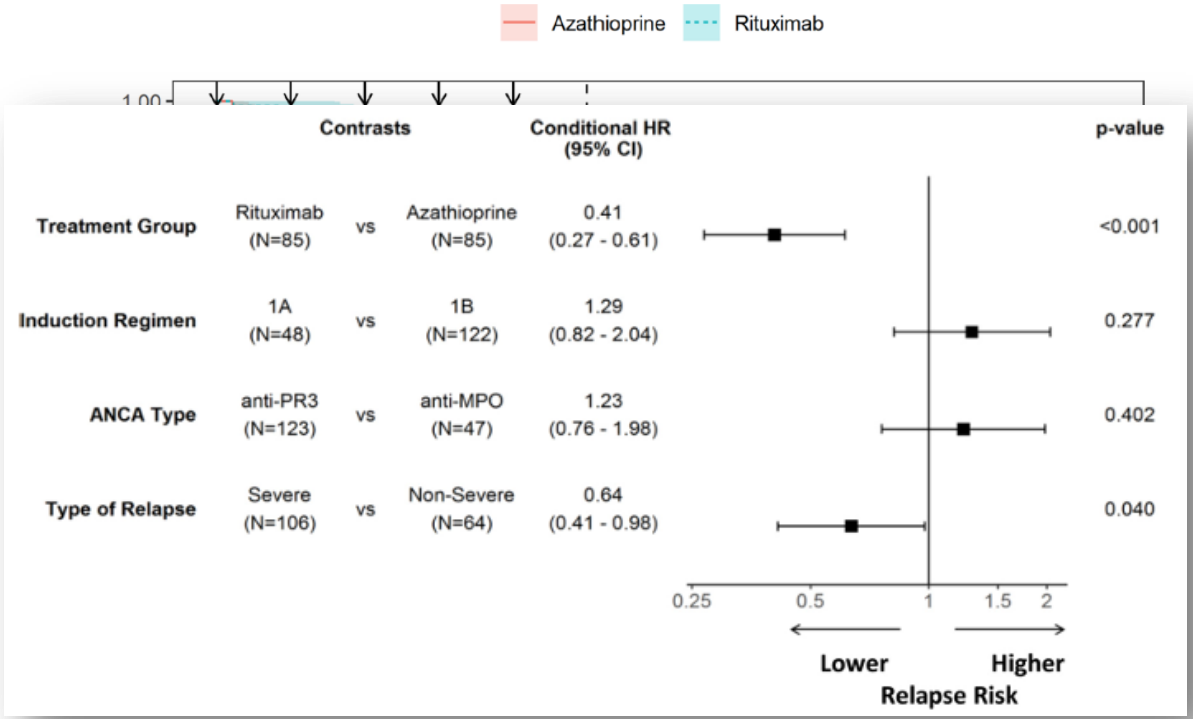
RTX 500mg q6mo



The hazard ratio for major relapse for patients in the azathioprine group, as compared with rituximab recipients, was **6.61** (95% CI, 1.56 to 27.96; P = 0.002)

RITAZAREM

RTX 1g q4mo



Guillevin L et al, N Engl J Med 2014 Nov 6;371(19):1771-80; Smith RM, et al. Ann Rheum Dis 2023;82:937–944

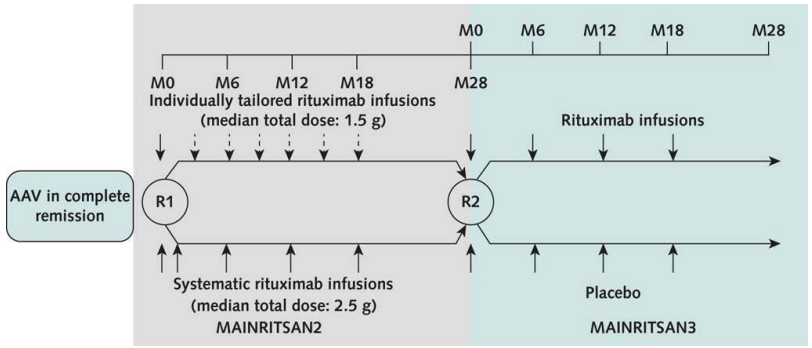
Maintenance of remission in GPA/MPA

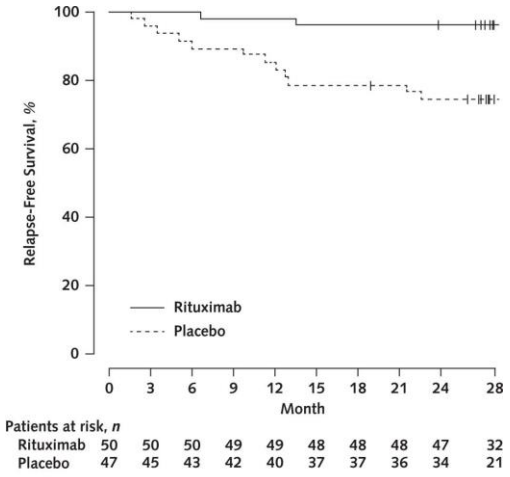
Prolonged RTX treatment is associated with less re

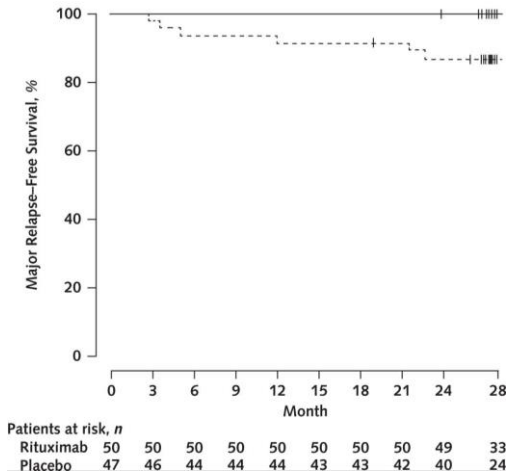
CLINICAL SCIENCE

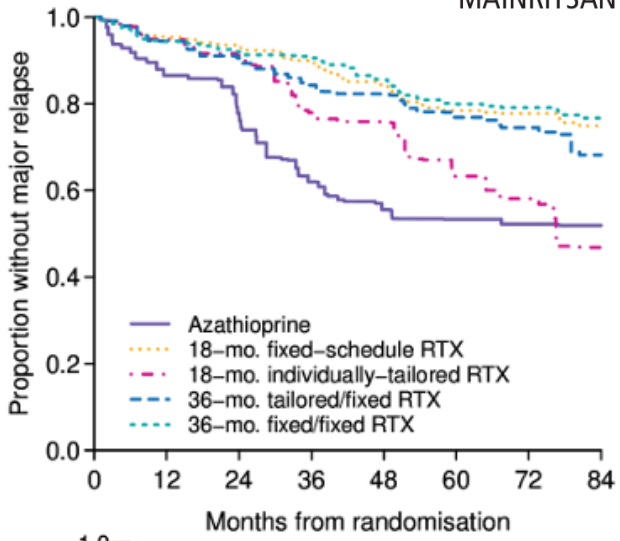
Rituximab as maintenance therapy for ANCA-associated vasculitides: pooled analysis and long-term outcome of 277 patients included in the MAINRITSAN trials

MAINRITSAN 3

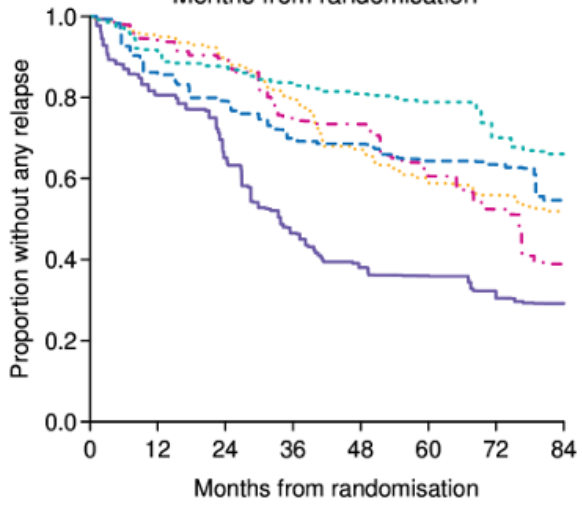








31% reduction in relapse risk in 36mo vs 18mo

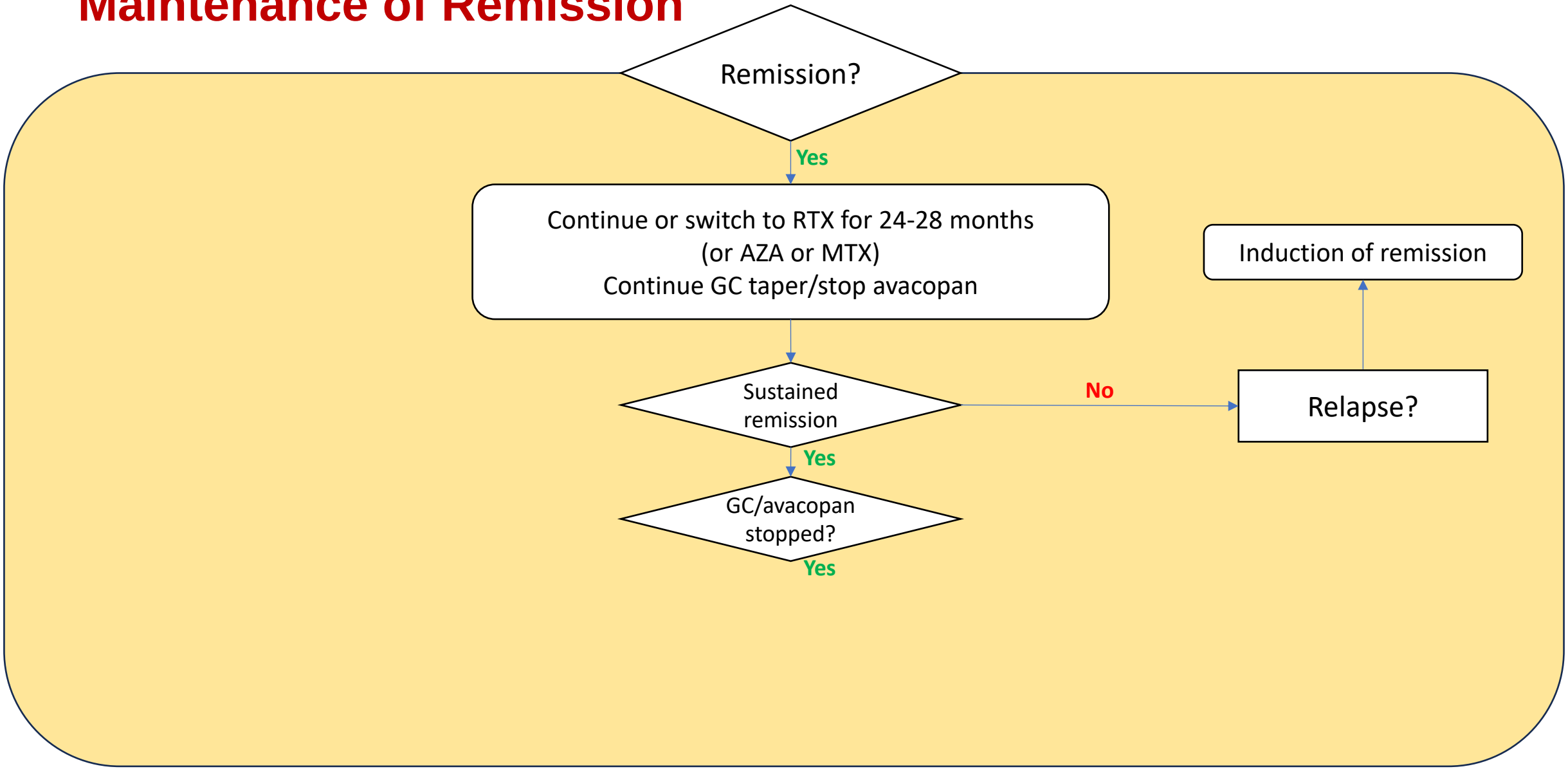


Reduced risk of major relapses

Charles P et al, Ann Intern Med 2020 Aug 4;173(3):179-187Delestre F, et al. Ann Rheum Dis 2024;83:233–241

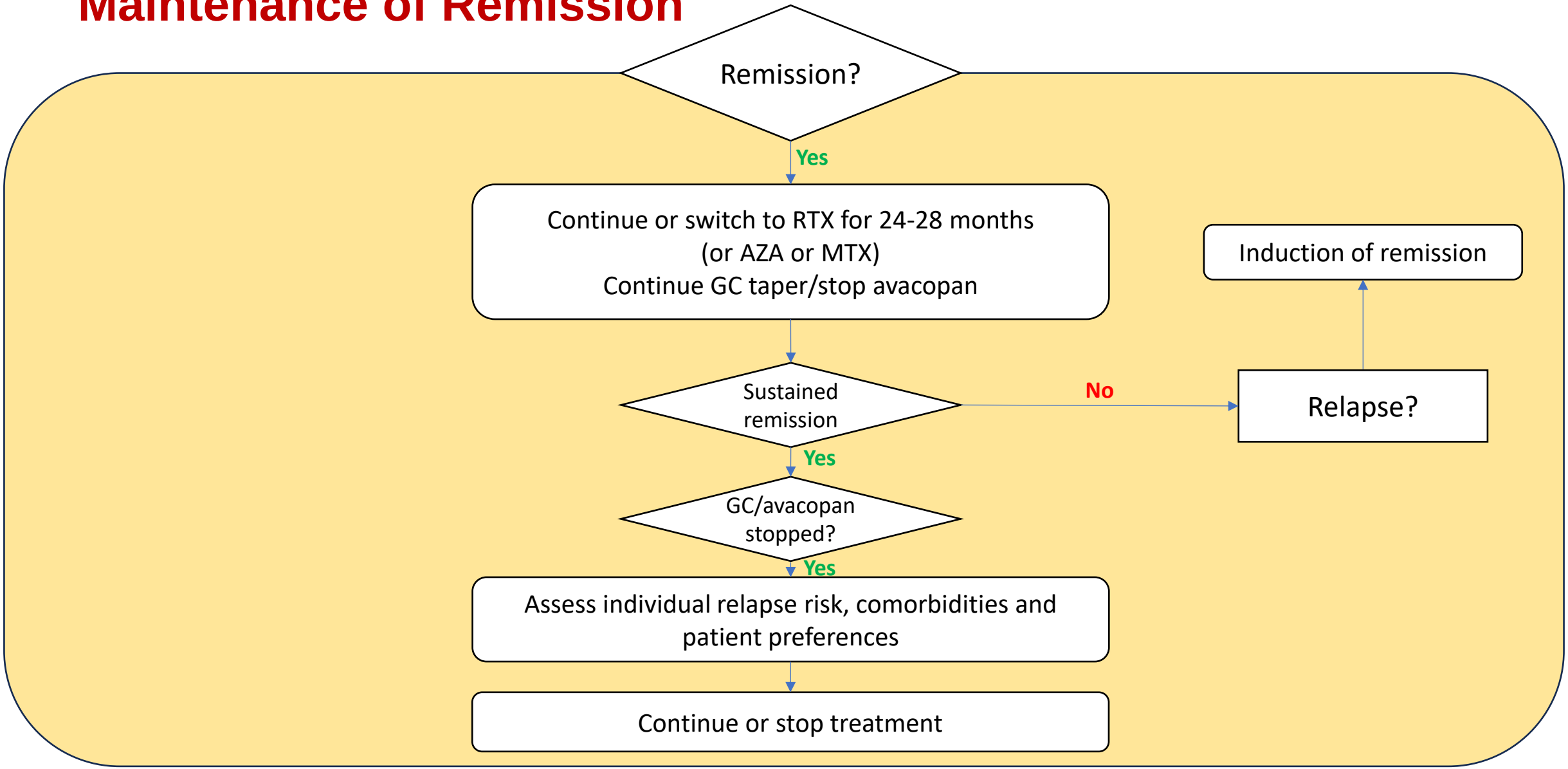
GPA/MPA treatment in 2025

Maintenance of Remission



GPA/MPA treatment in 2025

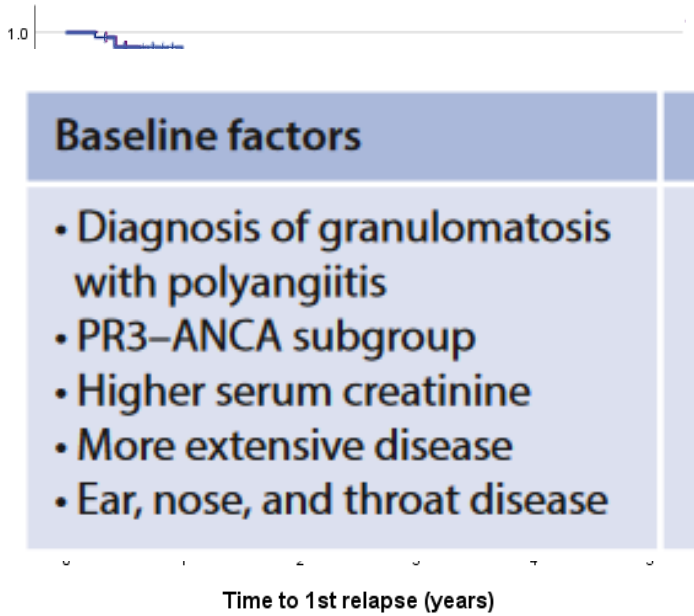
Maintenance of Remission



Maintenance of remission in GPA/MPA

Relapse risk should individualise the decision about stopping Rx

N=101	
GPA 69% MPA 31%	PR3 52% MPO 41%



According to renal involvement

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher 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

2000mg: 20%, variable: 19%

30 relapses, in 24 patients:

- 17 major and 13 minor
- IR 10.2/100 PY
- most occurred the first 2 years

Relapse free survival rate at year-2

- 0.80 (95% CI 0.69 to 0.88)

Gialouri et al 21st International Vasculitis Meeting Barcelona 2024

Περίπτωση ασθενούς #3

Περίπτωση ασθενούς

Γυναίκα 25 ετών
Ιούλιος 2021

- Πυρετός
- Οξείας έναρξης διάχυτο κοιλιακό άλγος
- Διάρροιες με ζωηρό ερυθρό αίμα

Ατομικό αναμνηστικό

- Ιστορικό **αλλεργικής ρινίτιδας** από **<u>παιδική ηλικία</u>**

Ατομικό αναμνηστικό

- Ιστορικό **αλλεργικής ρινίτιδας** από παιδική ηλικία

- **<u>Νοέμβριος 2020</u>**: βήχας με απόχρεμψη, δύσπνοια, συριγμός

Διάγνωση **αλλεργικού βρογχικού άσθματος**

Έναρξη αγωγής με:

- x formoterol + beclomethasone, tiotropium
- x montelukast

Ατομικό αναμνηστικό

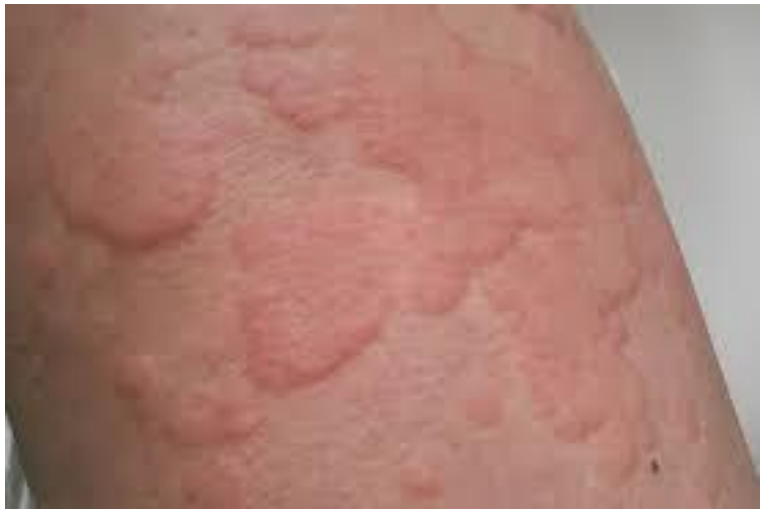
- **<u>Ιούνιος 2021</u>**:

  - εύκολη κόπωση / αδυναμία

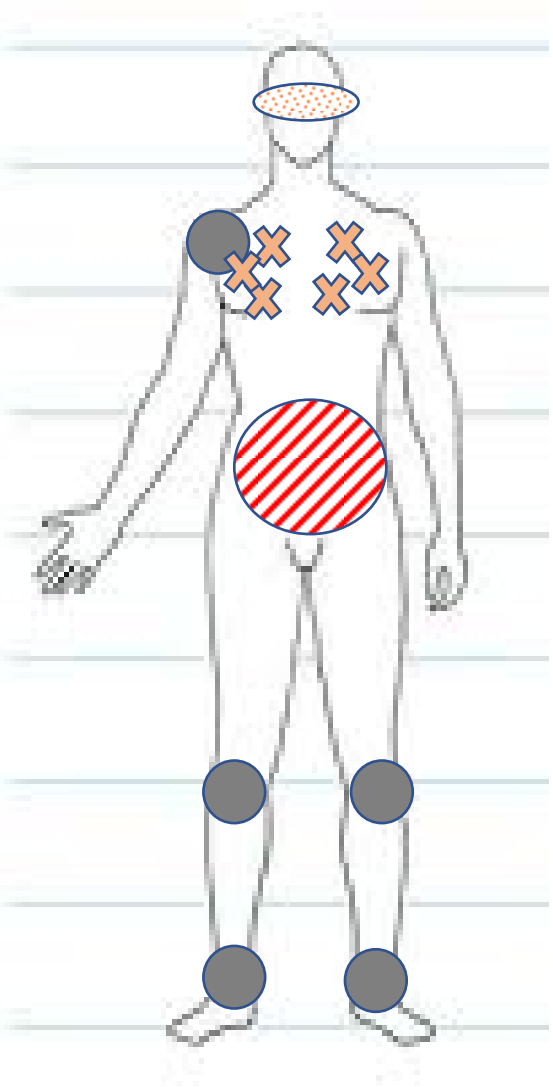
  - αρθραλγίες ώμων, γονάτων και ΠΔΚ

  - εξάνθημα άνω και κάτω άκρων (πομφοί?)

  x σημαντική ανταπόκριση σε μεθυλπρεδνιζολόνη



Κλινική εξέταση



ΑΠ= **90/60mmHg**, Σφύξεις=90/min,
Θ=**37.9 ^{o}C**, Αναπνοές=**18/min**, $SatO_2$=96% (FiO2: 0.21)

Όψη: **πάσχουσα** - θρέψη καλή

Κεφαλή: **ευαισθησία στην ψηλάφηση των παραρρινίων περιοχών άμφω**

Αναπνευστικό: **διάχυτοι μουσικοί ρόγχοι άμφω**

Καρδιαγγειακό: S1,S2 ρυθμικοί, ευκρινείς, χωρίς φυσήματα,

Κοιλία: μαλακή, ευπίεστη,
διάχυτη ευαισθησία, μειωμένοι εντερικοί ήχοι – DRE (+) για αίμα

MSK: **ευαισθησία στην ψηλάφηση του ΔΕ ώμου, των κατά γόνυ και ποδοκνημικών αρθρώσεων άμφω**

Αγγεία: χωρίς φυσήματα

Νευρικό: χωρίς παθολογικά ευρήματα

Παρακλινικός έλεγχος

Hb: 14.6 g/dl Ht: 44.5%, MCV/MCH: 86/24

WBC: 25,300 (N 40%, L 14%)

Eos: 10,370 (41%)

PLTs: 311,000

CRP: 17 (<5 mg/dl), ΤΚΕ 18 mm/h

BUN: 9 mg/dL, Cr:0.6 mg/dl

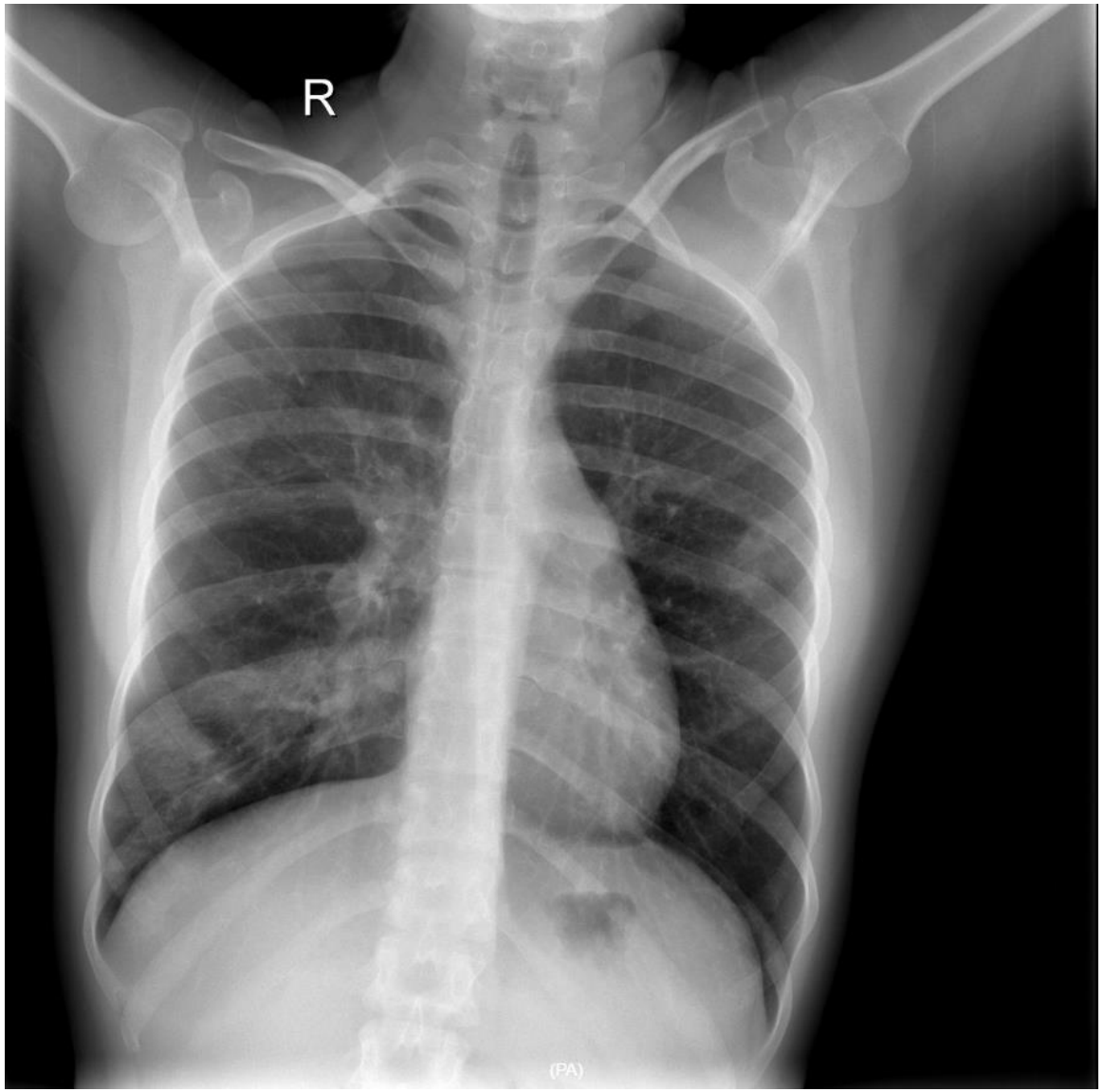
Glu: 74 mg/dl

AST/ALT: 39/20 U/L (<34/<55)

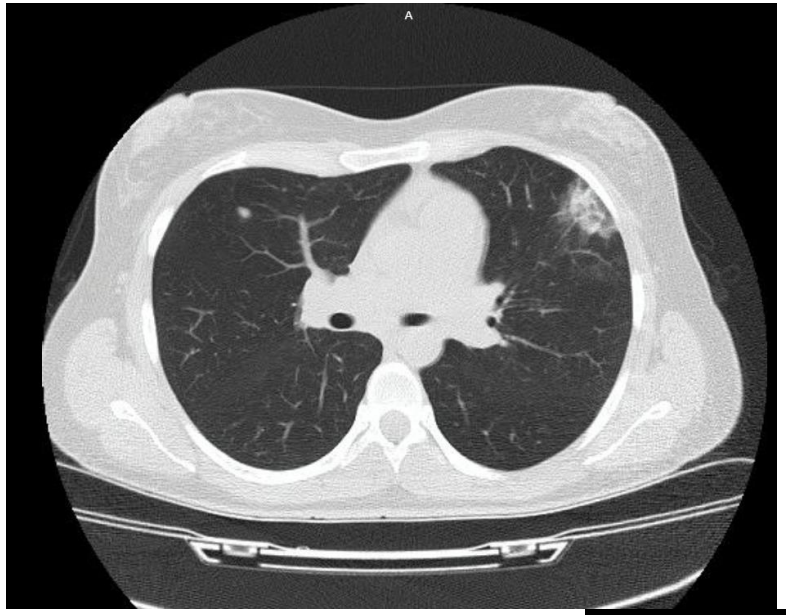
LDH 424 IU/I CPK 64 IU/I

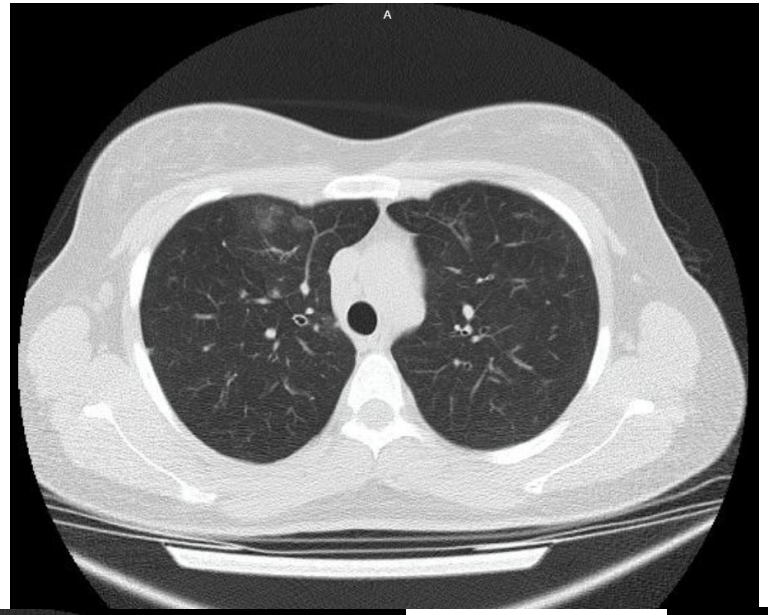
Γενική ούρων: WBC 0-1, RBC: 0-1

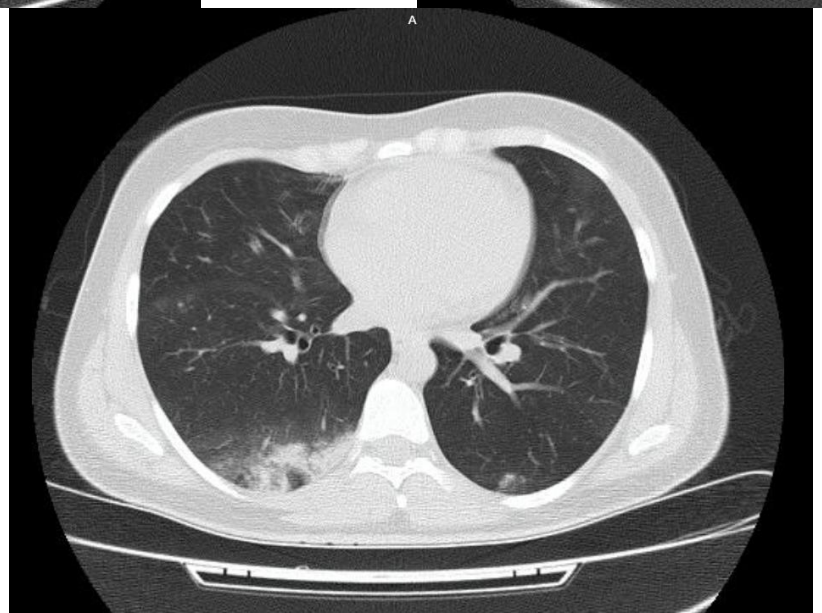
Hb (-) Pro: (-)

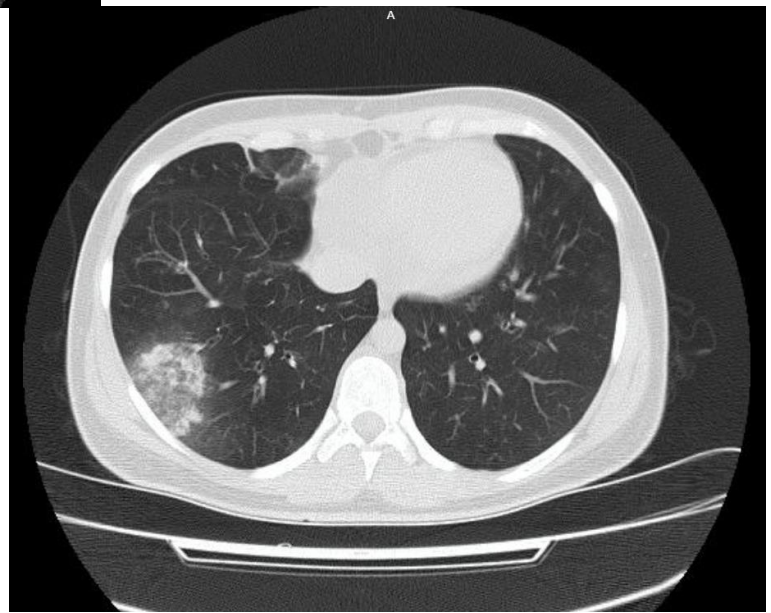


Περαιτέρω απεικονιστικός έλεγχος









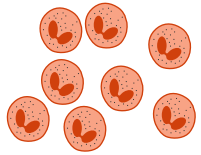
Σύνοψη περίπτωσης

Πυρετός – φλεγμονώδες σύνδρομο

Προσβολή εντέρου (κολίτιδα)

Άσθμα – διηθήματα πνεύμονα

Ευαισθησία παραρρινίων



Εκσεσημασμένη περιφερική ηωσινοφιλία

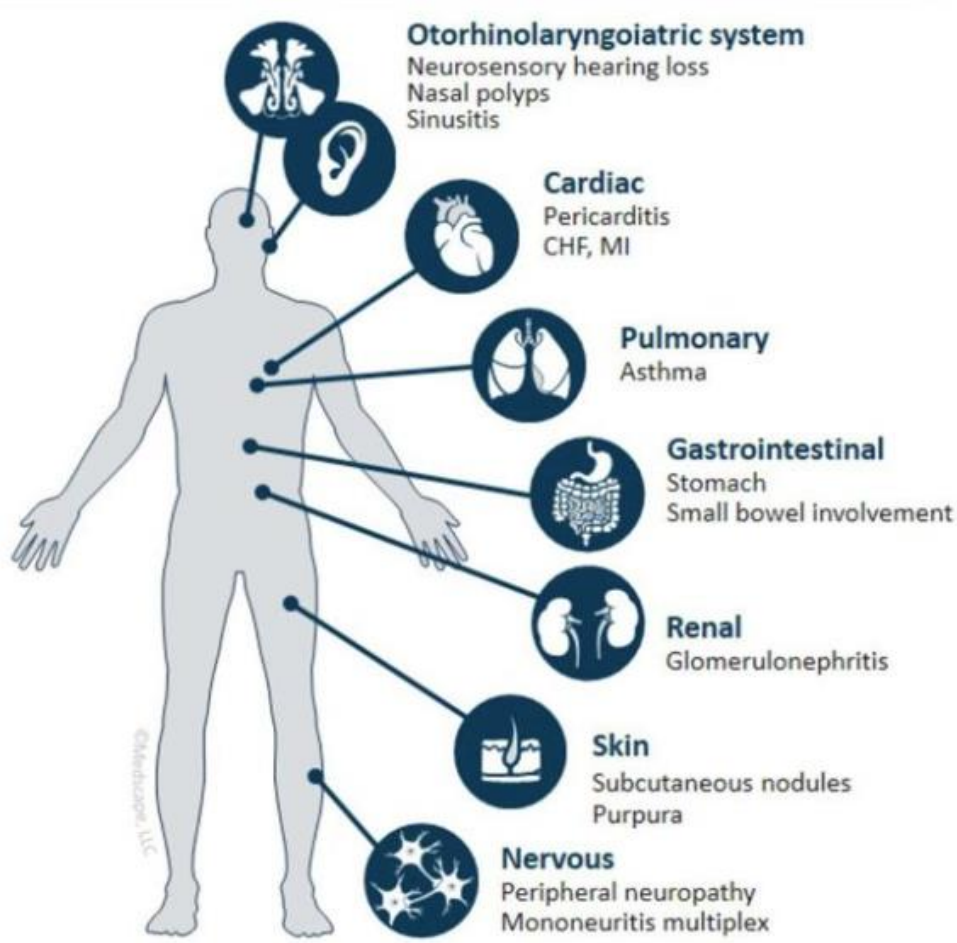
Αρθραλγίες

Κνιδωτικό εξάνθημα

Ηωσινοφιλική κοκκιωμάτωση με πολυαγγειίτιδα (σύνδρομο Churg Strauss)

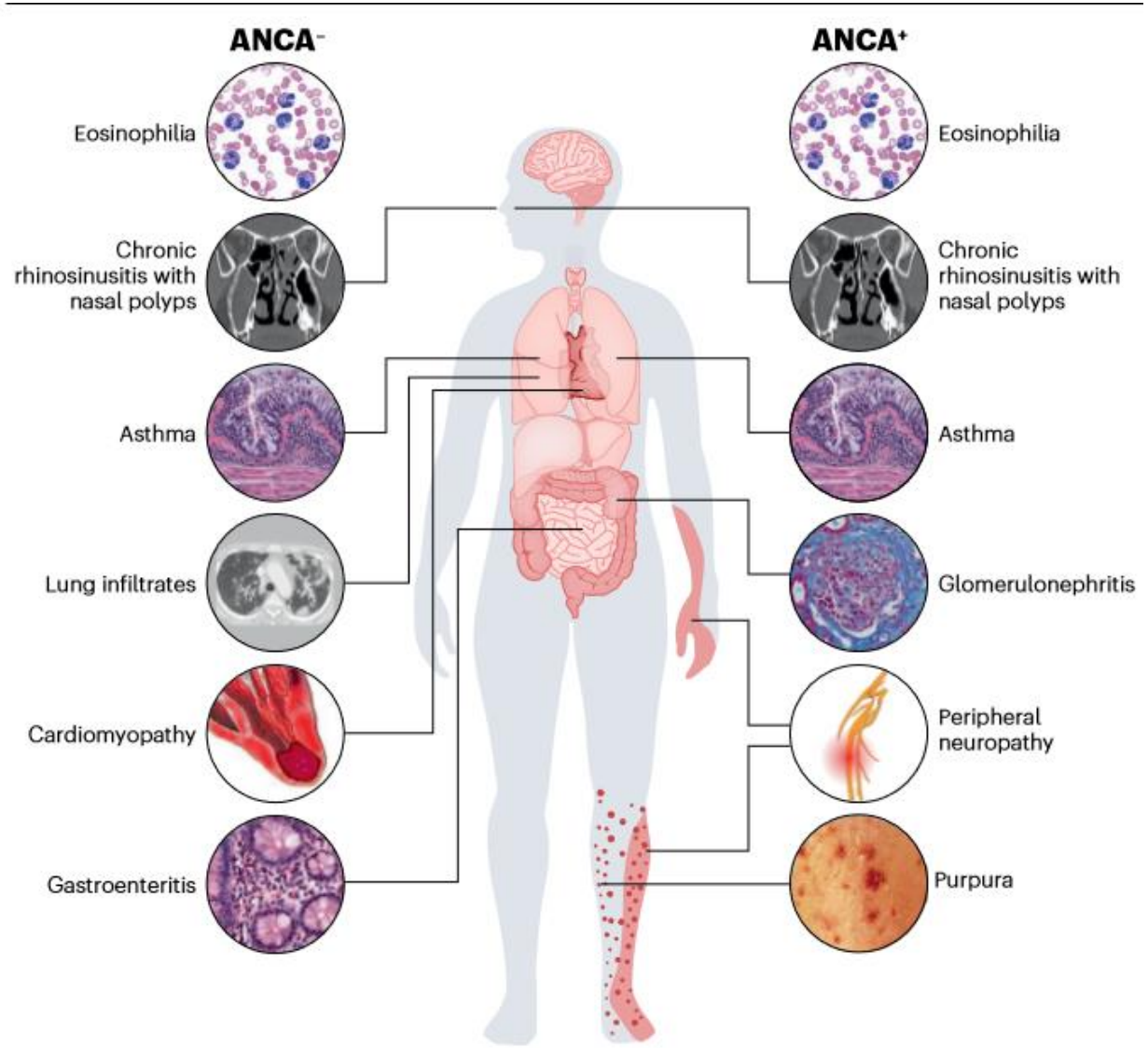
Eosinophilic granulomatosis with polyangiitis

- Incidence 0.6 – 3.4 cases / million[1]
- Males : Females equally affected[2]
- Median age at onset 49-59 years old[2]
- Often delay in diagnosis for several years[1]



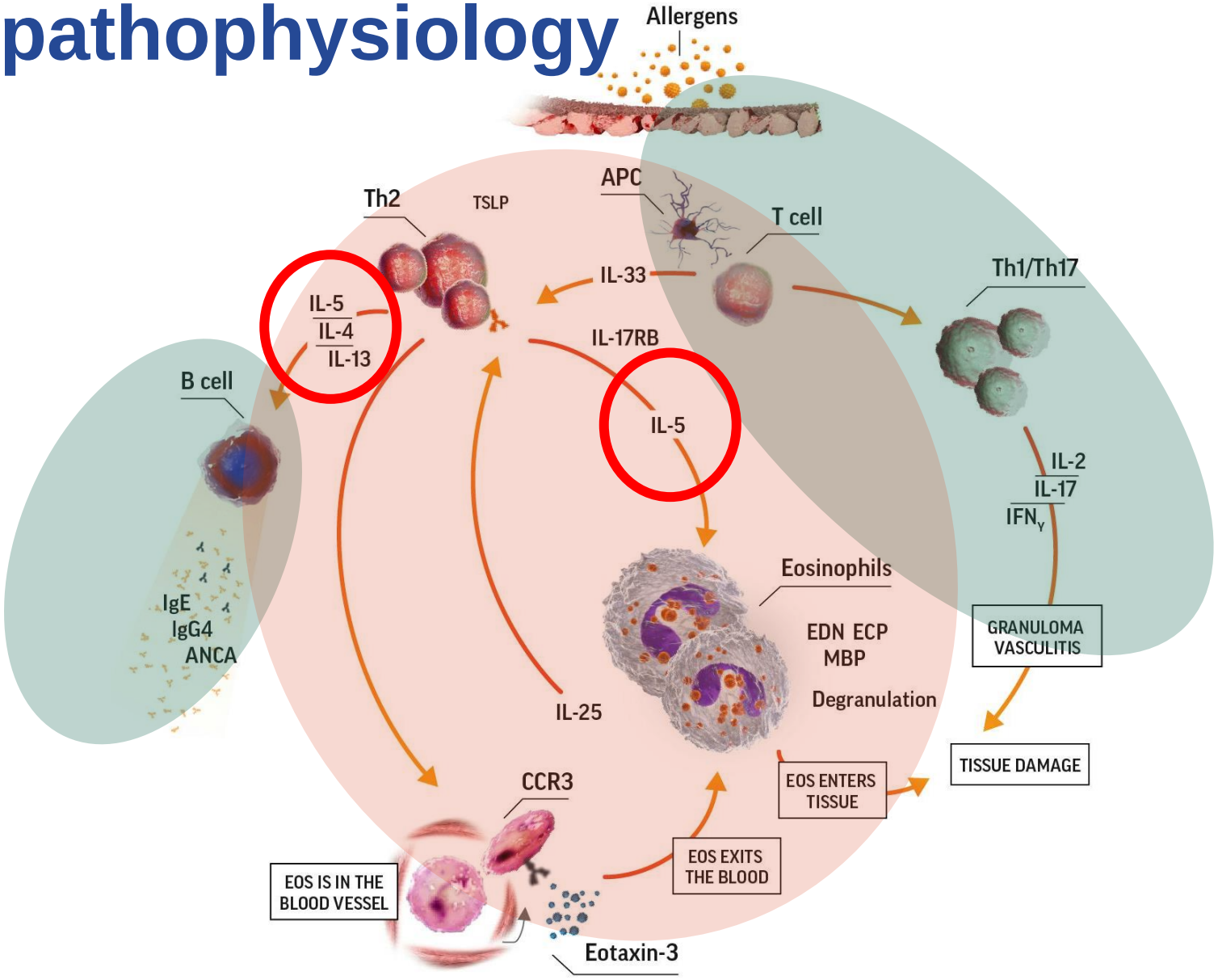
1. Gokhale M et al. J Clin Rheumatol. 2021; 27(3):107-113. 2. Furuta S et al. Allergol Int. 2019;68(4):430-436

Eosinophilic granulomatosis with polyangiitis



Uzzo et al Front Med 2021;8:754434; Emmi et al Nat Rev Rheumatol 2023;19:378-93

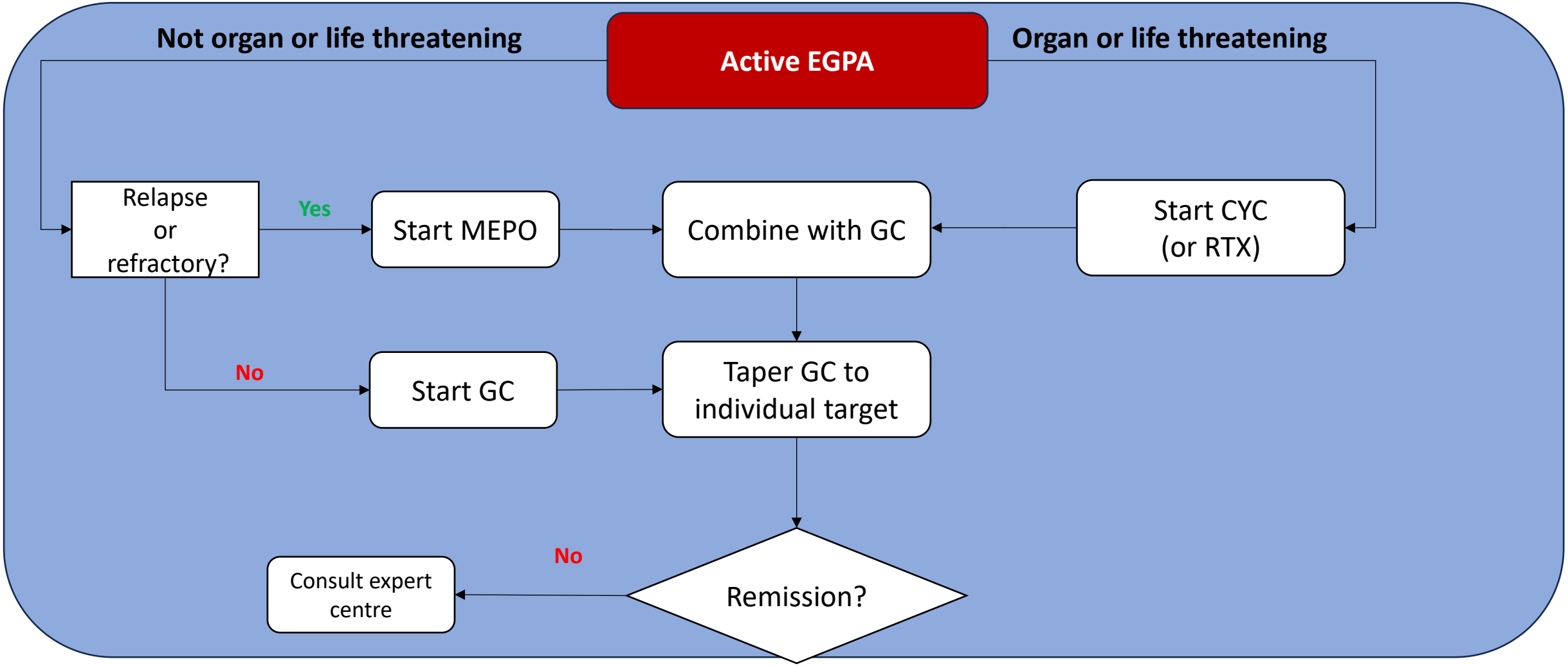
EGPA: pathophysiology



https://eosinophilosophy.com/disease-state/egpa/

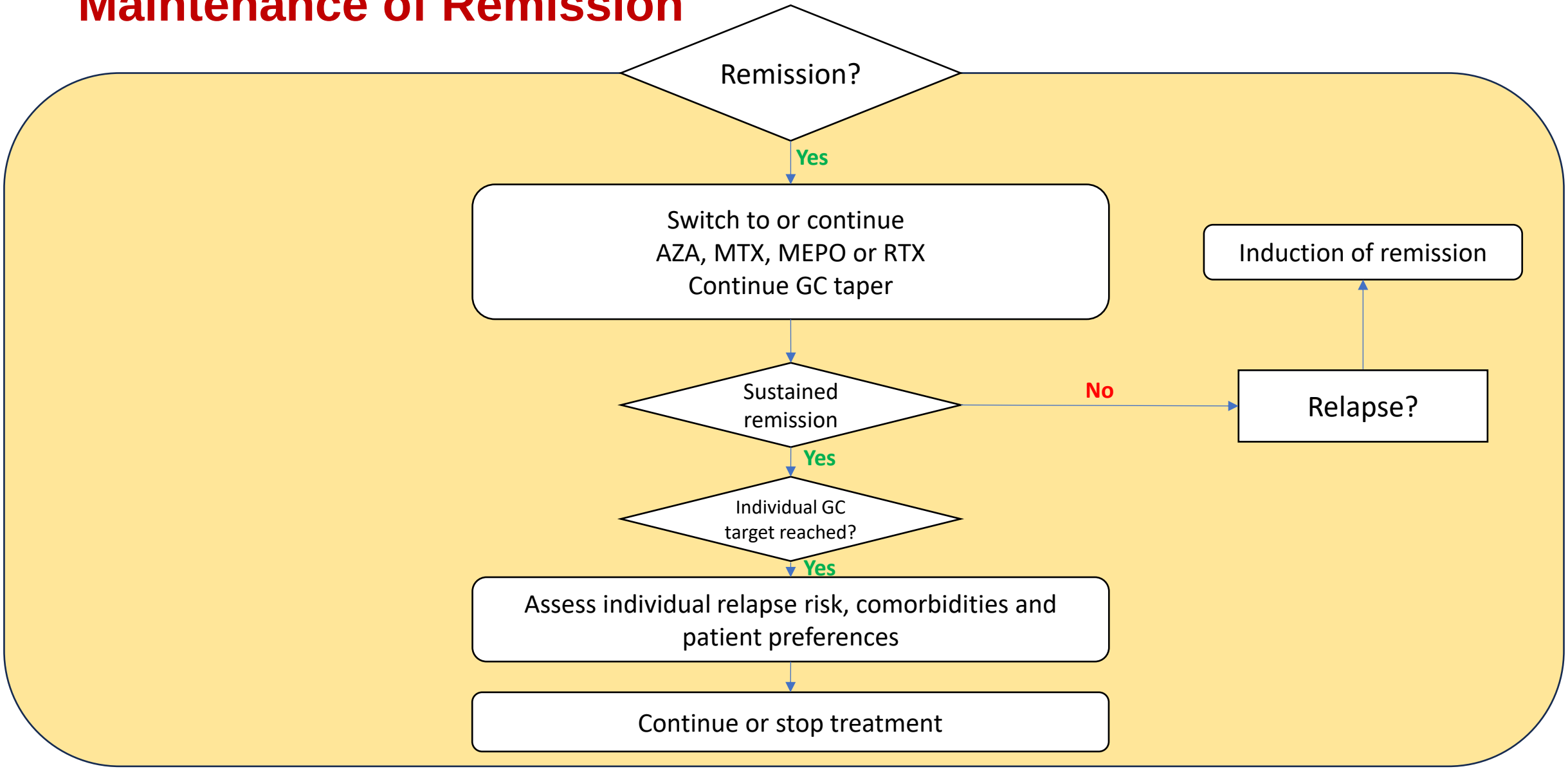
EGPA treatment in 2024

Induction of Remission



EGPA treatment in 2024

Maintenance of Remission



Mepolizumab: MIRRA trial

REMISSION:
BVAS=0 AND PRED ≤ 4mg OD

ORIGINAL ARTICLE

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

M.E. Wechsler, P. Akuthota, D. Jayne, P. Khoury, A. Klion, C.A. Langford, P.A. Merkel, F. Moosig, U. Specks, M.C. Cid, R. Luqmani, J. Brown, S. Mallett, R. Philipson, S.W. Yancey, J. Steinfeld, P.F. Weller, and G.J. Gleich, for the EGPA Mepolizumab Study Team*

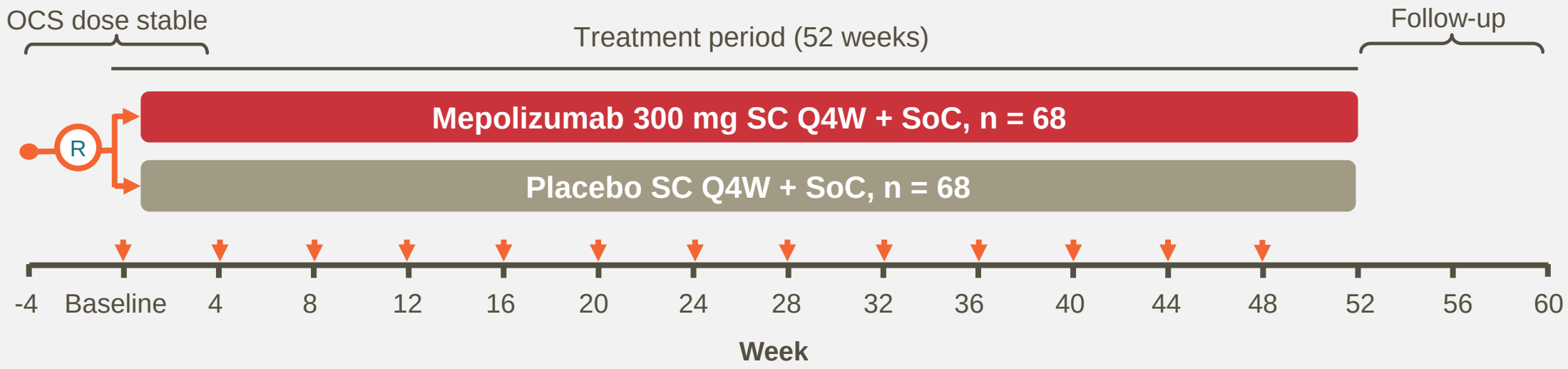
Refractory / relapsing EGPA (>6mo), majority 90% ANCA (-)

- Stable GC and IS
- No organ or life-threatening disease

Endpoints:

- accrued total weeks in remission
- proportion of participants in remission at both week 36 and 48

n=136

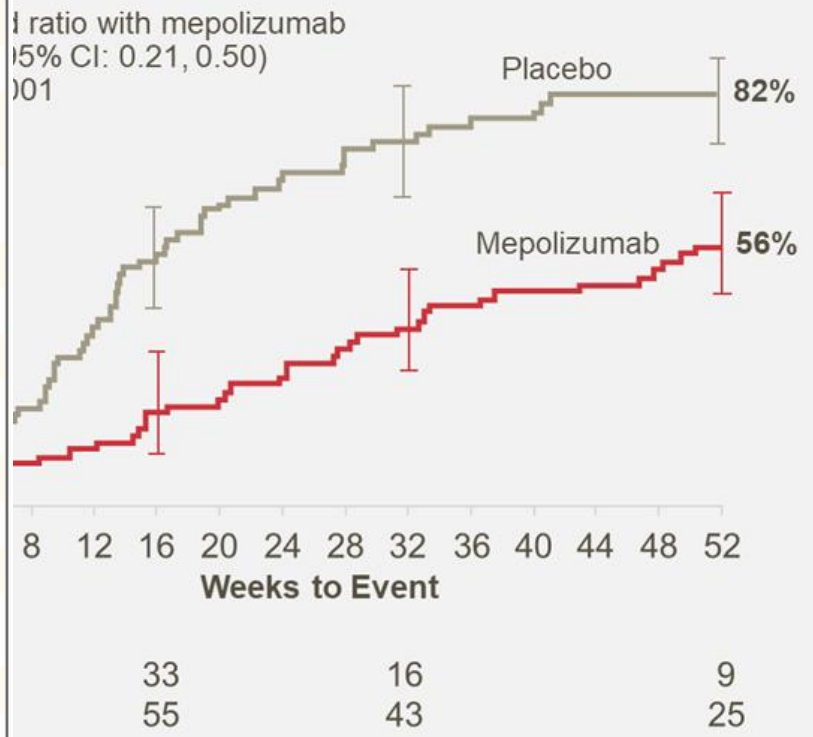


Wechsler ME, et al. N Engl J Med. 2017;376:1921-1932

MIRRA trial: patients on mepolizumab had higher proportion of accrued remission and less risk for relapses

Table 3. Adverse Events and Serious Adverse Events.*

Event	Mepolizumab (N=68)	Placebo (N=68)
	no. of participants (%)	
Adverse event		
Any event	66 (97)	64 (94)
Event considered by the investigator to be related to the trial agent	35 (51)	24 (35)
Event leading to trial-agent discontinuation or trial withdrawal	2 (3)	1 (1)
Death	1 (1)†	0
Serious adverse event‡		
Any event	12 (18)	18 (26)
Event considered by the investigator to be related to the trial agent	3 (4)	3 (4)
Systemic or local-site reaction§		
Systemic reaction	4 (6)	1 (1)
Local-site reaction	10 (15)	9 (13)
Anaphylaxis considered by the investigator to be related to the trial agent	0	0
Cardiovascular adverse event¶		
Arrhythmia	2 (3)	3 (4)
Stroke or TIA	1 (1)	0
Congestive heart failure	0	1 (1)
Myocardial infarction or unstable angina	1 (1)	1 (1)



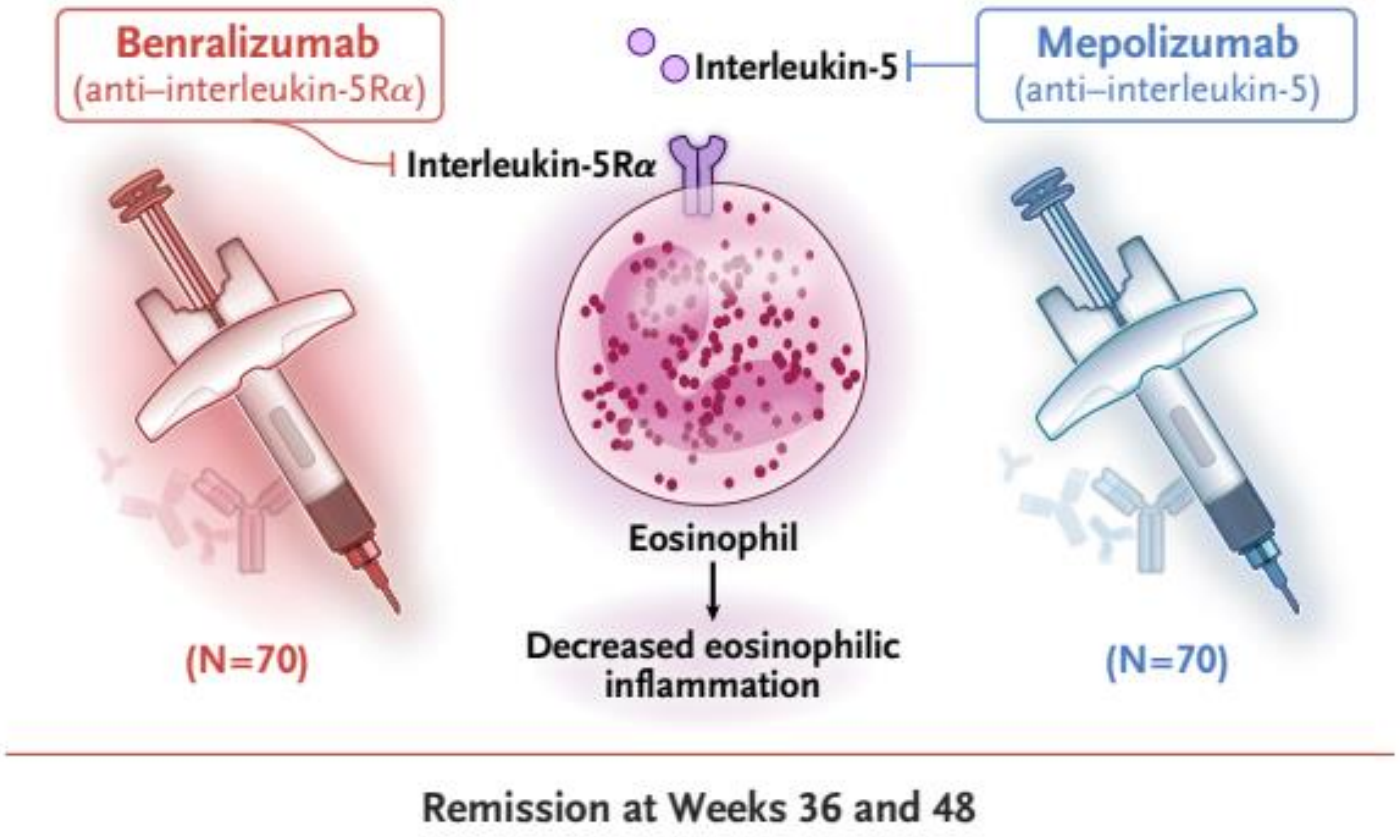
Wechsler ME, et al. N Engl J Med. 2017;376:1921-1932

MANDARA trial: BENRA vs MEPO in EGPA

ORIGINAL ARTICLE

Benralizumab versus Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis

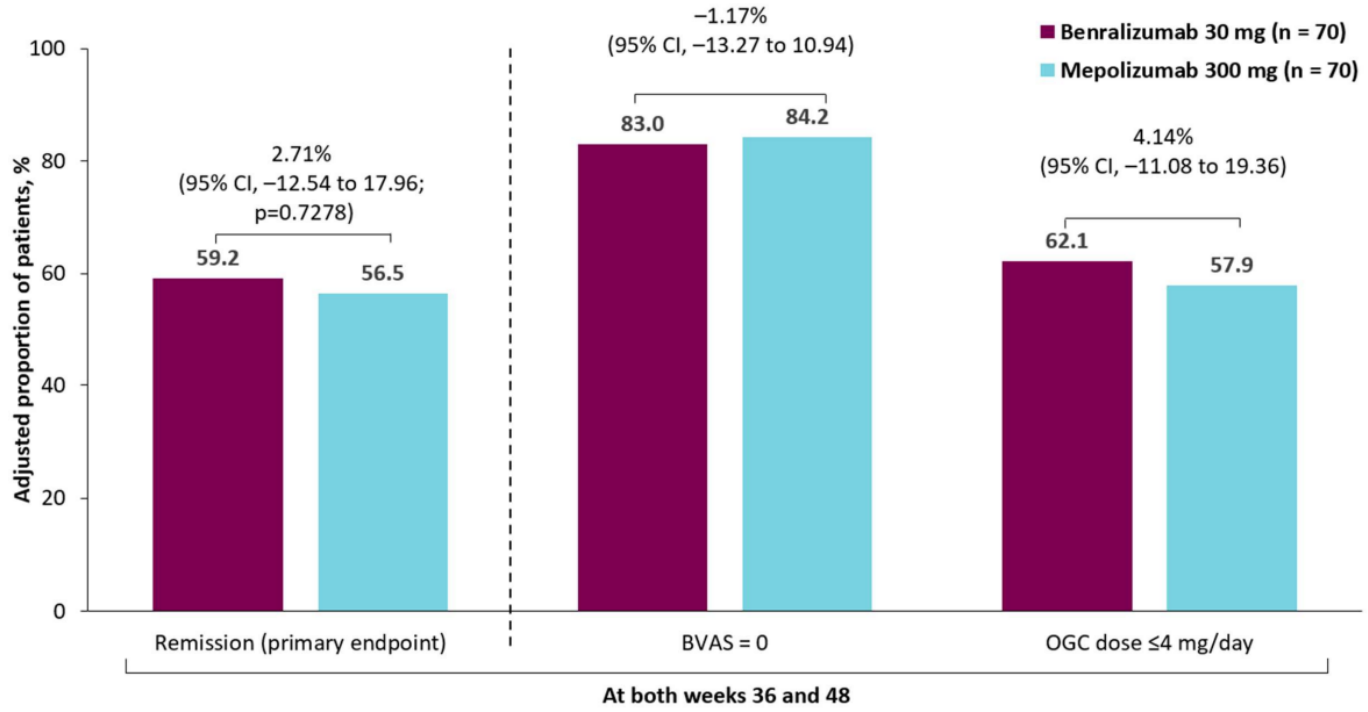
Michael E. Wechsler, M.D., M.M.Sc., Parameswaran Nair, M.D., Ph.D., Benjamin Terrier, M.D., Ph.D., Bastian Walz, M.D., Arnaud Bourdin, M.D., Ph.D., David R.W. Jayne, M.D., David J. Jackson, F.R.C.P., Ph.D., Florence Roufosse, M.D., Ph.D., Lena Börjesson Sjö, Ph.D., Ying Fan, Ph.D., Maria Jison, M.D., Christopher McCrae, Ph.D., Sofia Necander, M.D., Anat Shavit, D.V.M., Claire Walton, M.Sc., and Peter A. Merkel, M.D., M.P.H., for the MANDARA Study Group*



Wechsler M et al NEJM 2024;390:911-21

MANDARA trial – primary endpo

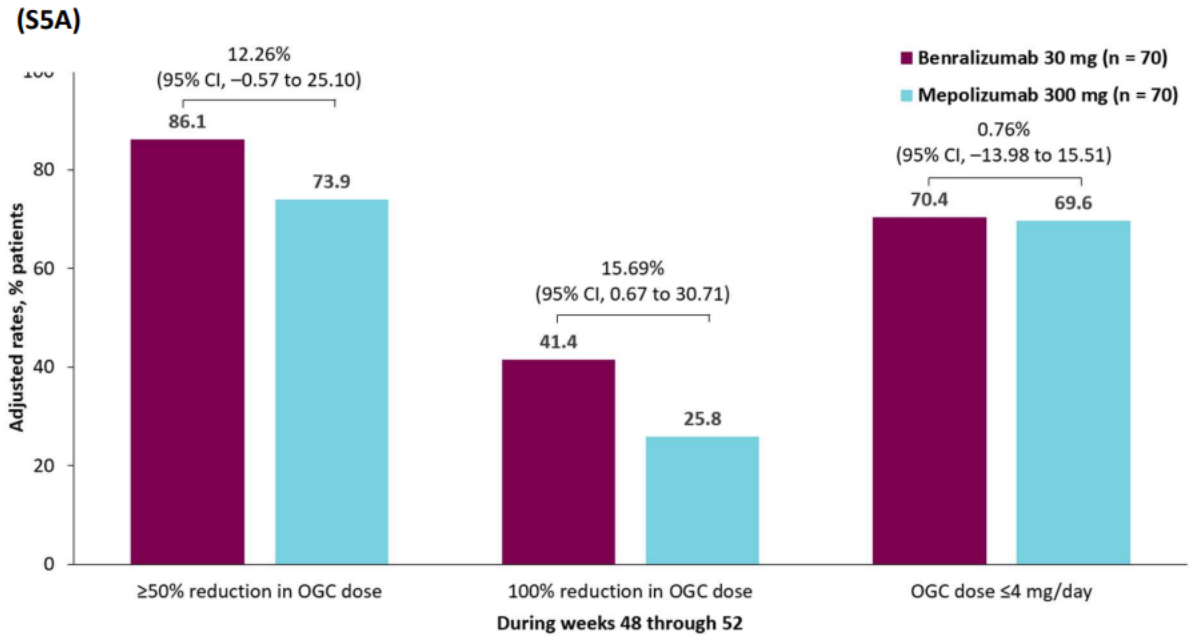
REMISSION:
BVAS=0 AND PRED ≤ 4mg OD

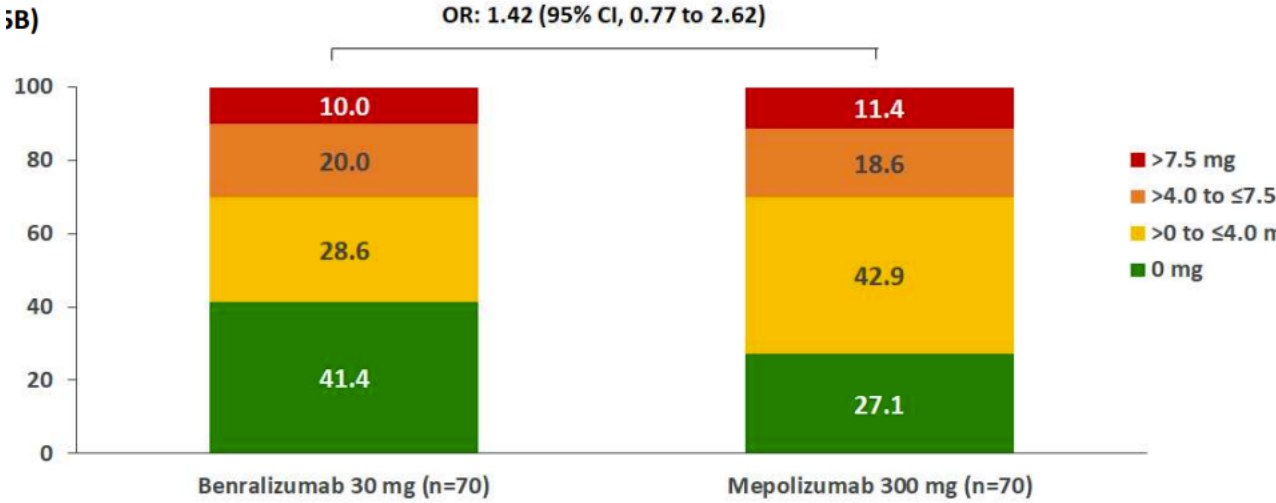


Benralizumab is non-inferior (but not superior) to Mepolizumab in patients with refractory/relapsing EGPA

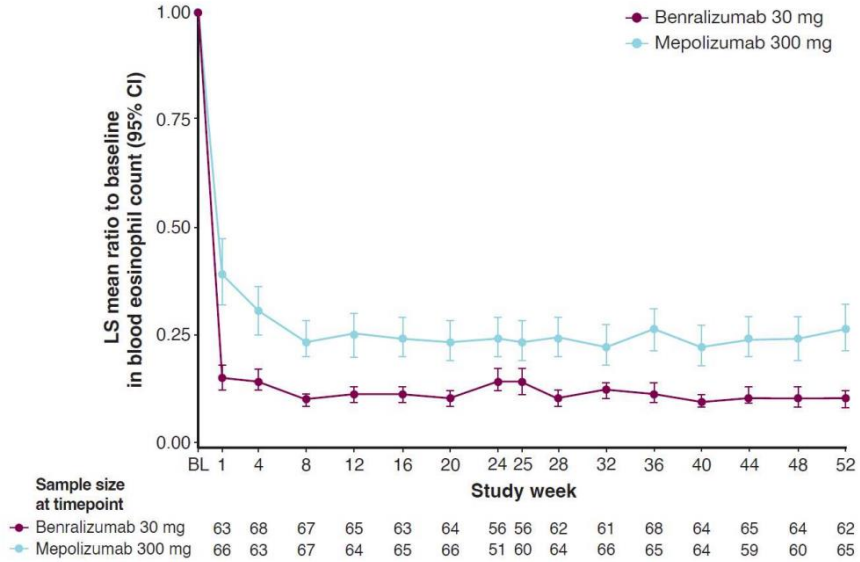
Wechsler M et al NEJM 2024;390:911-21

MANDARA trial: GC dose reduction



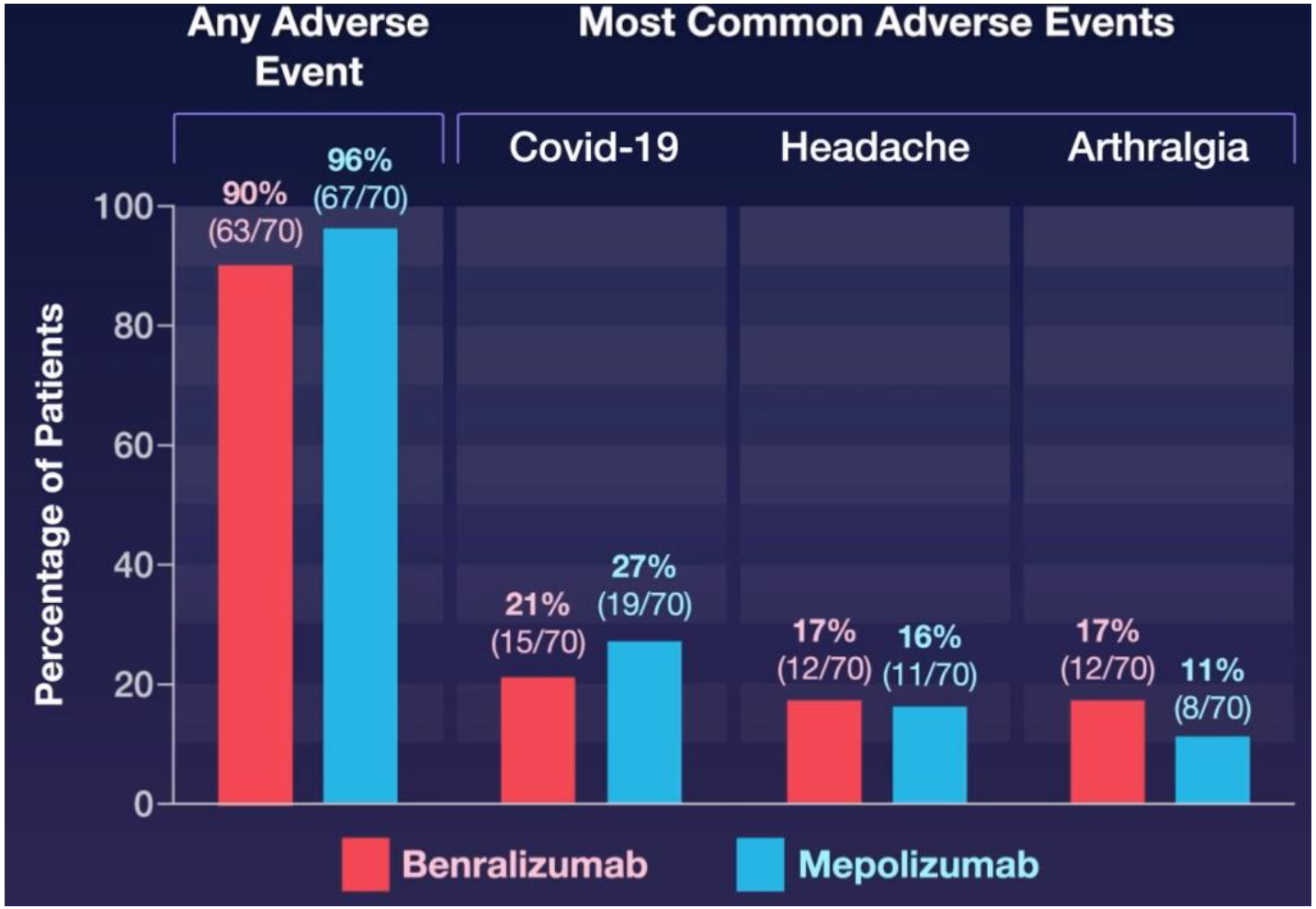


Greater proportion of patients with BENRA reached GC dose of 0mg compared with MEPO



Wechsler M et al NEJM 2024;390:911-21

Comparable safety between IL-5 inhibitors



MedDRA-preferred term, n (%)	Benralizumab 30 mg (N = 70)	Mepolizumab 300 mg (N = 70)
Any adverse event	51 (72.9)	61 (87.1)
COVID-19	15 (21.4)	19 (27.1)
Headache	12 (17.1)	11 (15.7)
Arthralgia	12 (17.1)	8 (11.4)
Nasopharyngitis	6 (8.6)	10 (14.3)
Sinusitis	5 (7.1)	8 (11.4)
Fatigue	5 (7.1)	6 (8.6)
Bronchitis	5 (7.1)	5 (7.1)
Sinusitis bacterial	5 (7.1)	3 (4.3)
Upper respiratory tract infection	4 (5.7)	4 (5.7)
Influenza-like illness	4 (5.7)	3 (4.3)
Nausea	1 (1.4)	6 (8.6)
Viral upper respiratory tract infection	1 (1.4)	6 (8.6)
Asthenia	6 (8.6)	0 (0.0)
Hypertension	1 (1.4)	5 (7.1)
Injection site bruising	2 (2.9)	4 (5.7)
Injection site pain	3 (4.3)	3 (4.3)
Oral candidiasis	2 (2.9)	4 (5.7)
Rash	4 (5.7)	2 (2.9)
Urinary tract infection	5 (7.1)	1 (1.4)
Back pain	2 (2.9)	3 (4.3)
Diarrhea	2 (2.9)	3 (4.3)
Myalgia	4 (5.7)	1 (1.4)
Skin laceration	1 (1.4)	4 (5.7)
Tooth infection	3 (4.3)	2 (2.9)
Abdominal pain	0 (0.0)	4 (5.7)
Adrenal insufficiency	1 (1.4)	3 (4.3)
Asthma	1 (1.4)	3 (4.3)
Contusion	1 (1.4)	3 (4.3)
Muscle spasms	3 (4.3)	1 (1.4)
Pain in extremity	0 (0.0)	4 (5.7)
Rhinitis	1 (1.4)	3 (4.3)
Vomiting	1 (1.4)	3 (4.3)
Constipation	3 (4.3)	0 (0.0)
Herpes zoster	0 (0.0)	3 (4.3)
Osteopenia	0 (0.0)	3 (4.3)

Wechsler M et al NEJM 2024;390:911-21

Benralizumab: FDA approved for EGPA

Fasenra approved in the US for eosinophilic granulomatosis with polyangiitis

PUBLISHED
18 September 2024

Take home messages

Take-home messages

GPA/MPA

Rituximab: invaluable for induction in both non-severe and severe disease
"standard of care" for maintenance of remission
Use for at least 24-48 months – individualise discontinuation according to relapse risk

PLEX: consider in severe pulmonary haemorrhage and RPGN
more benefit in pts with high risk for ESRD and low risk for infections

Glucocorticoids: taper as rapidly as possible to reduce side effects and infections
may not be needed in RTX-based regimens

Avacopan: significant aid in reducing GC exposure
likely benefit in preserving kidney function early in disease
promising role in non-kidney involvement

EGPA

IL-5 inhibitors: helpful in reducing GC exposure, esp in eosinophilic manifestations
safe medications – likely will be used earlier in the disease in the future