university of groningen

Nieuwe Behandelingen in Vasculitis

Systeemziekten Symposium 3 Februari 2023

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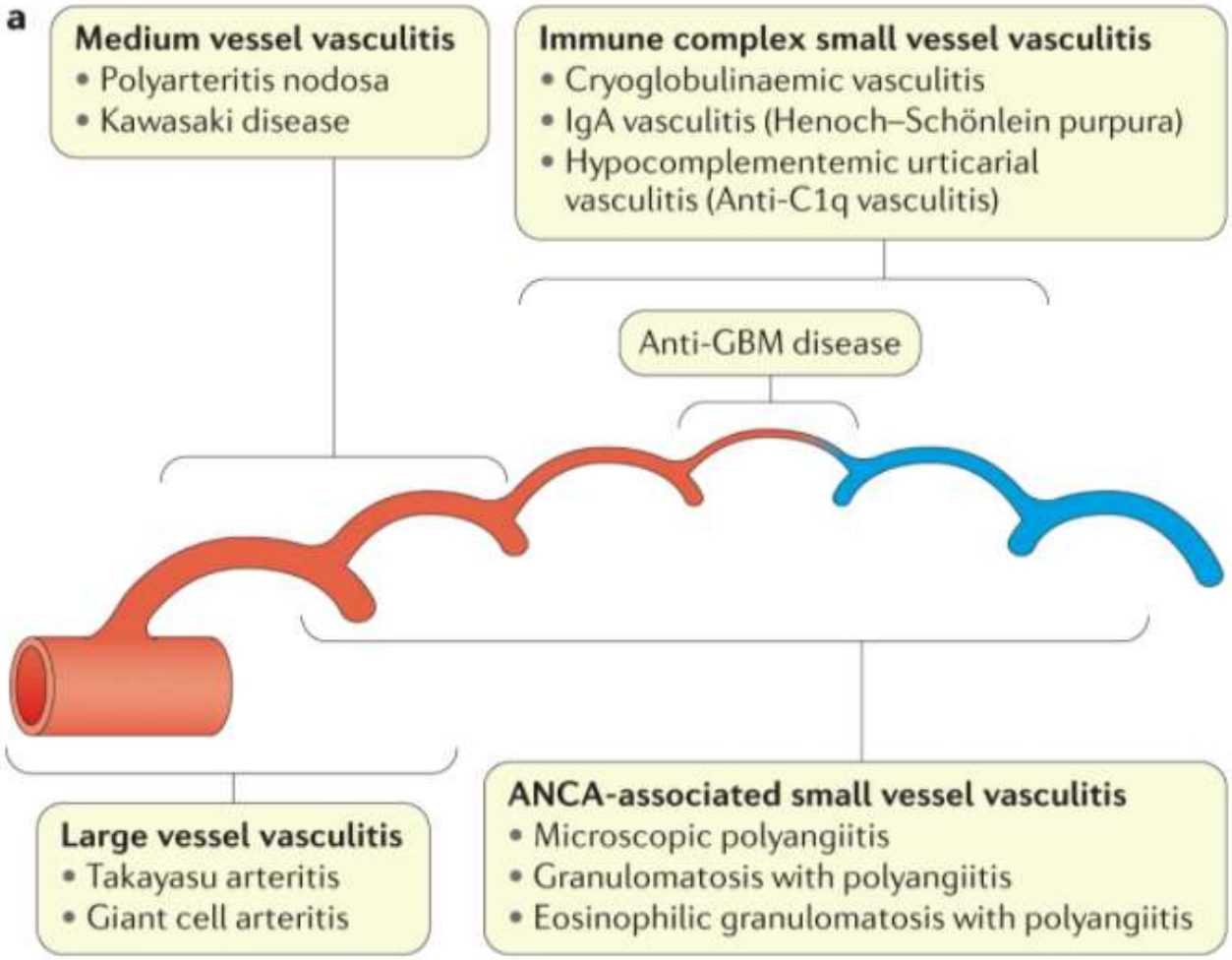
Rheumatology and Clinical Immunology

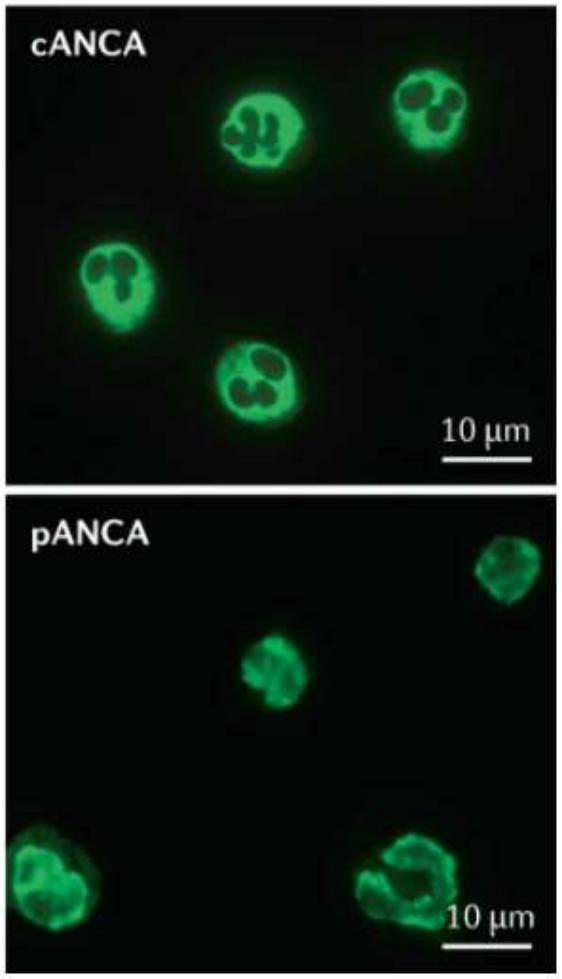
VASCULITIS EXPERTISE CENTER GRONINGEN

Disclosure slide

(potentiële) belangenverstrengeling	Geen of zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijven: geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• Onderzoeksgeld Reuma Nederland en EU Immune Image • Geen • Nvt • Bestuurslid ARCH Autoimmune Research Collaboration Hub

2012 Chapel Hill Consensus criteria

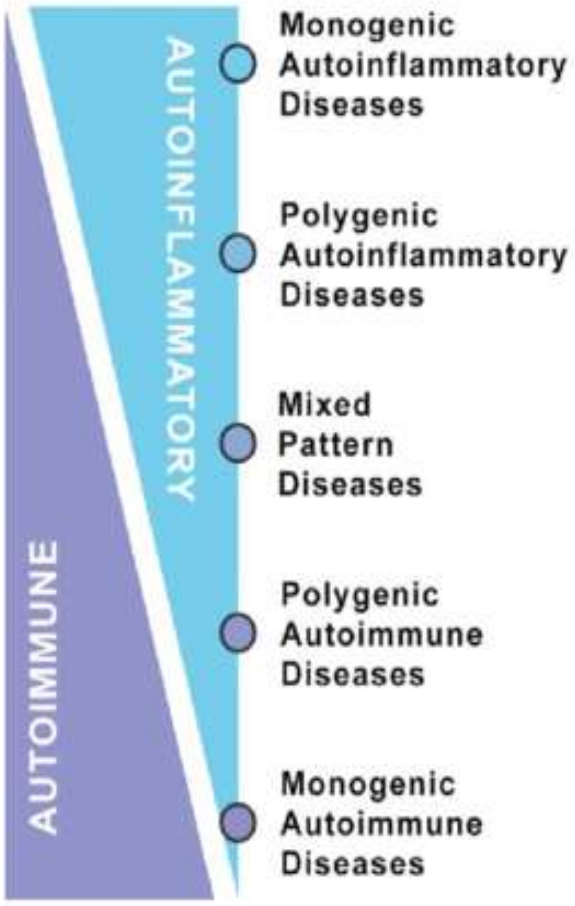




Data from Jennette, J. C. et al. 2012 Revised International Chapel Hill consensus Conference Nomenclature of Vasculitides. Arthritis Rheumatol. 65, 1–11 (2013).

Kitching, A.R., Anders, H., Basu, N. et al. ANCA-associated vasculitis. Nat Rev Dis Primers 6, 71 (2020). https://doi.org/10.1038/s41572-020-0204-y

Het vasculitis spectrum



- ADA-2 deficiëntie
- VEXAS
- Ziekte van Behcet's
- RCA en PMR
- AAV
- CTLA4 and IFN pathies

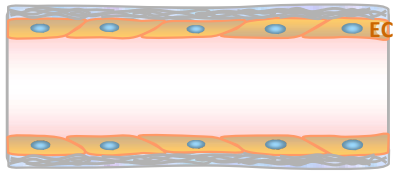
Adapted McGonagle PlosMed 2006

Indeling

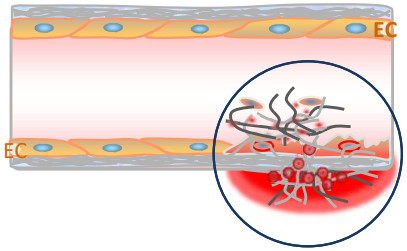
- **Kleine vaten vasculitis**
- Middelgrote vaten vasculitis
- Grote vaten vasculitis

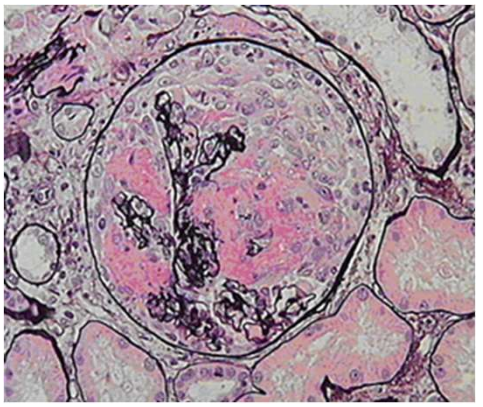
Pathogenese kleine vaten vasculitis

Normaal klein bloedvat



Ontstoken klein bloedvat



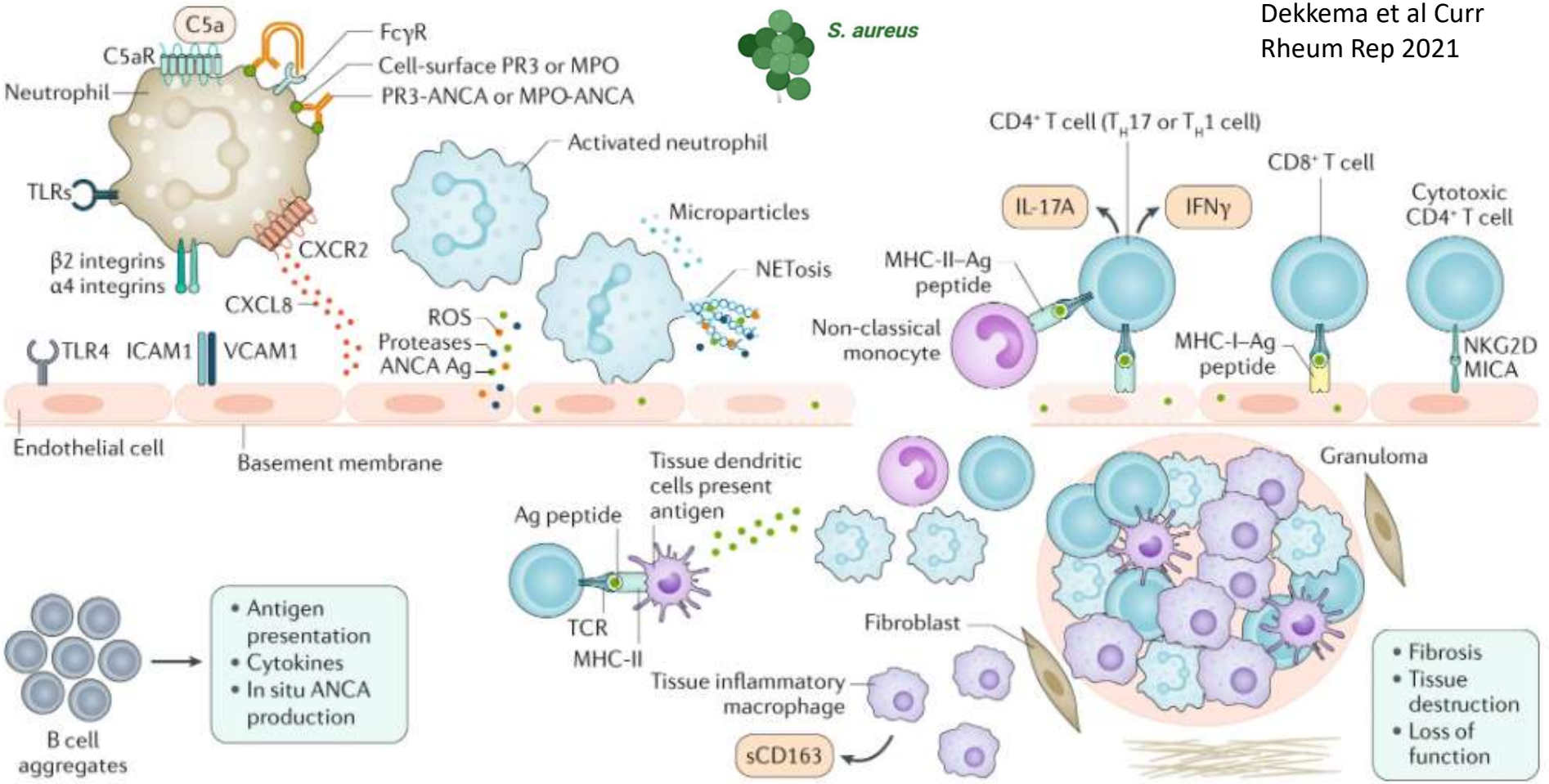


Ontsteking

- Kan in principe optreden in elk bloedvat in het lichaam.
- Kan tot gevolg hebben dat organen niet meer goed werken.

Pathogenese AAV

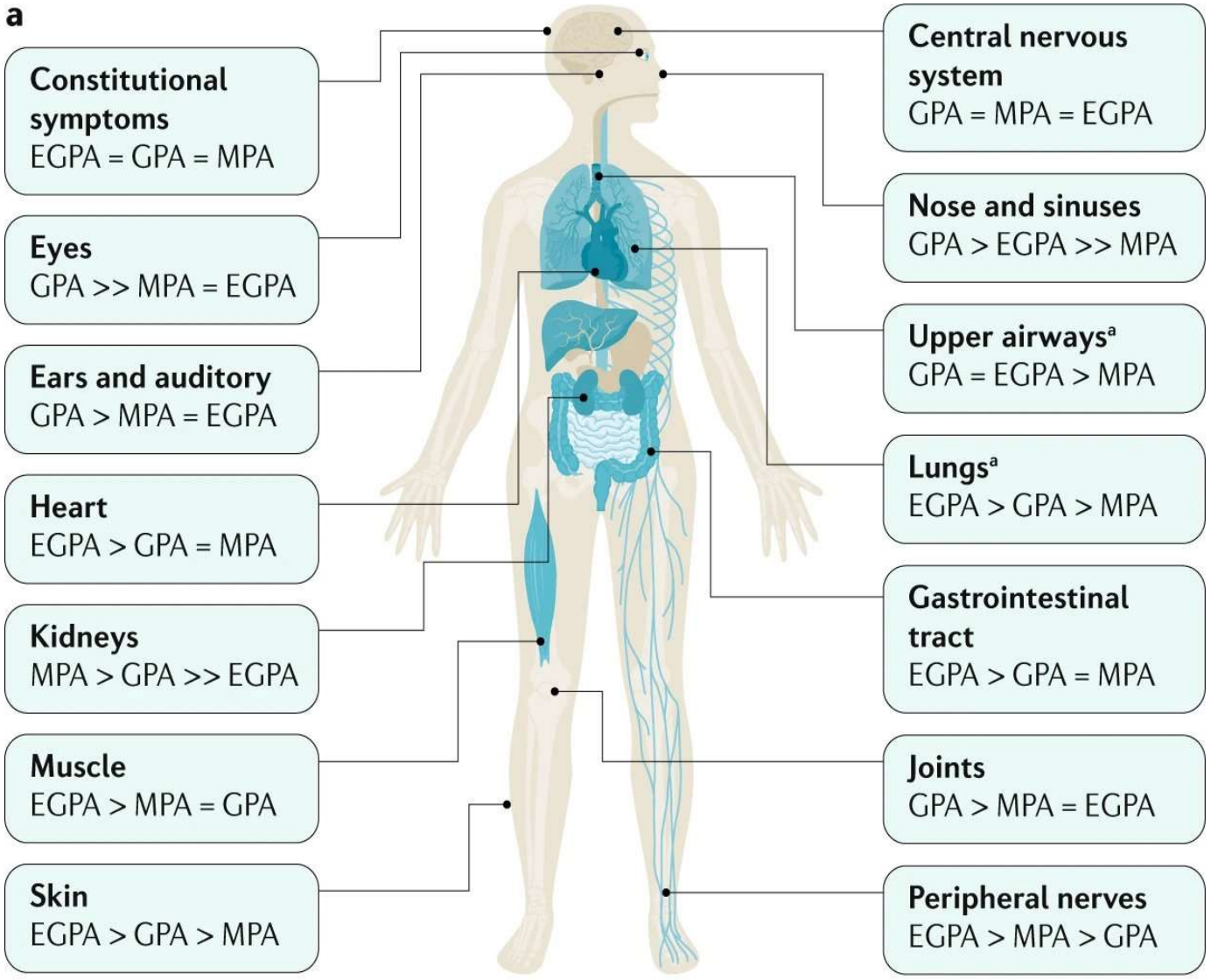
Dekkema et al Curr Rheum Rep 2021



Kitching, A.R., Anders, H., Basu, N. et al. ANCA-associated vasculitis. Nat Rev Dis Primers 6, 71 (2020). https://doi.org/10.1038/s41572-020-0204-y

Kleine vaten vasculitis

RICHTLIJN DIAGNOSTIEK KLEINE VATEN VASCULITIS CBO 2010



Kitching, A.R., Anders, HJ., Basu, N. *et al.* ANCA-associated vasculitis. *Nat Rev Dis Primers 2020*

2022 ACR / EULAR classificatie GPA

kleine of middelgrote vaten vasculitis is vastgesteld

Klinische criteria	
Neusbetrokkenheid: Bloed bij het snuiten, korsten ulcera, verstopping, defect dan wel perforatie septum	+ 3
Kraakbeen schade (zadel-) neus of oor, hese stem, kraakbeen luchtwegen	+ 2
Gehoorsverlies door defecte geleiding dan wel innervatie	+ 1
Lab imaging en biopsie criteria	
Positive cANCA test of anti-PR3 antistoffen	+ 5
Nodulaire, massa of caverneuze afwijkingen longen	+ 2
Granulomatouze ontsteking en/ of reuscellen	+ 2
Sinusitis of Mastoiditis	+ 1
Pauci-immuun glomerulonefritis	+ 1
Positive pANCA test of anti-MPO antistoffen	- 1
Eosinofiele granulocyten ≥ 1*109/Liter	- 4

Score ≥ 5 Classificatie GPA

Robson JC, Grayson PC, Ponte C, et al. Ann Rheum Dis doi:10.1136 2022

Ernst AAV

- I. Limited (inclusief loco-regionaal; veelal KNO en eventueel longnoduli)
- II. Early systemic (kreatinine <150, non major organs)
- III. Systemic
- IV. Severe/refractory

Severe: kreatinine >500, of snelle progressieve achteruitgang nierfunctie, ernstige longbloedingen, ernstige mononeuritis multiplex, CZS betrokkenheid, gangreen, tractus.digestivus bloedingen, etc; Refractory: geen verbetering cq progressie na 2-3 weken therapie [de Joode 2014]

Behandeling AAV UMCG Richtlijn

I. Limited

A. Lokalisatie KNO met weinig systemische klachten en laag CRP. Behandeling met hoog gedoseerde cotrimoxazol kan worden geprobeerd. Succeskans groter bij laag aanvangs CRP

B. Lokalisatie anders dan KNO en of systemische klachten en/of hoog CRP (bijvoorbeeld >12): behandelen als II

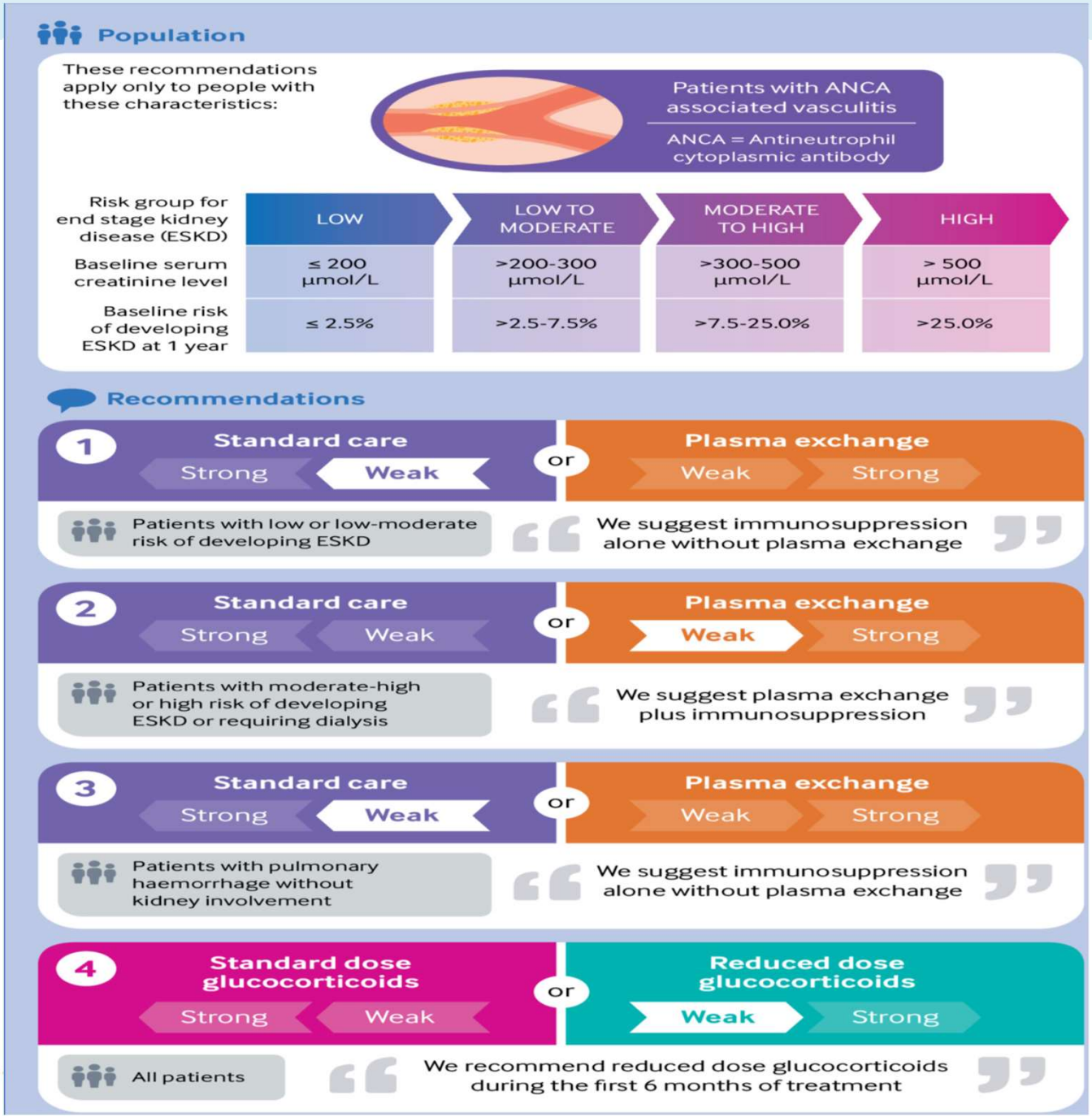
II. Early systemic Cyclofosfamide of rituximab (RTX), als alternatief methotrexaat (MTX) of Mycofenolaat mofetil (MMF) in alle gevallen mét prednisolon)

III. Systemic Cyclofosfamide, of rituximab in beide gevallen mét prednisolon

IV. Severe/ Refractory Cyclofosfamide, of bij (relatieve) contra-indicaties rituximab gecombineerd met methylprednisolon en/of plasmaferese* met prednisolon

* Belangrijke meta-analyse over de rol van plasmaferese bij ernstig AAV laat zien dat er ruimte is voor toepassen van plasmaferese bij een kreatinine >300 umol/l, zeker bij aanwijzingen voor snelle progressie. Dit gaat wel gepaard met een verhoogd infectie risico (http://dx.doi.org/10.1136/bmj-2021-064597)

Plasmaferese en GC behandeling



Zeng Walsh BMJ 2022;376:e064597

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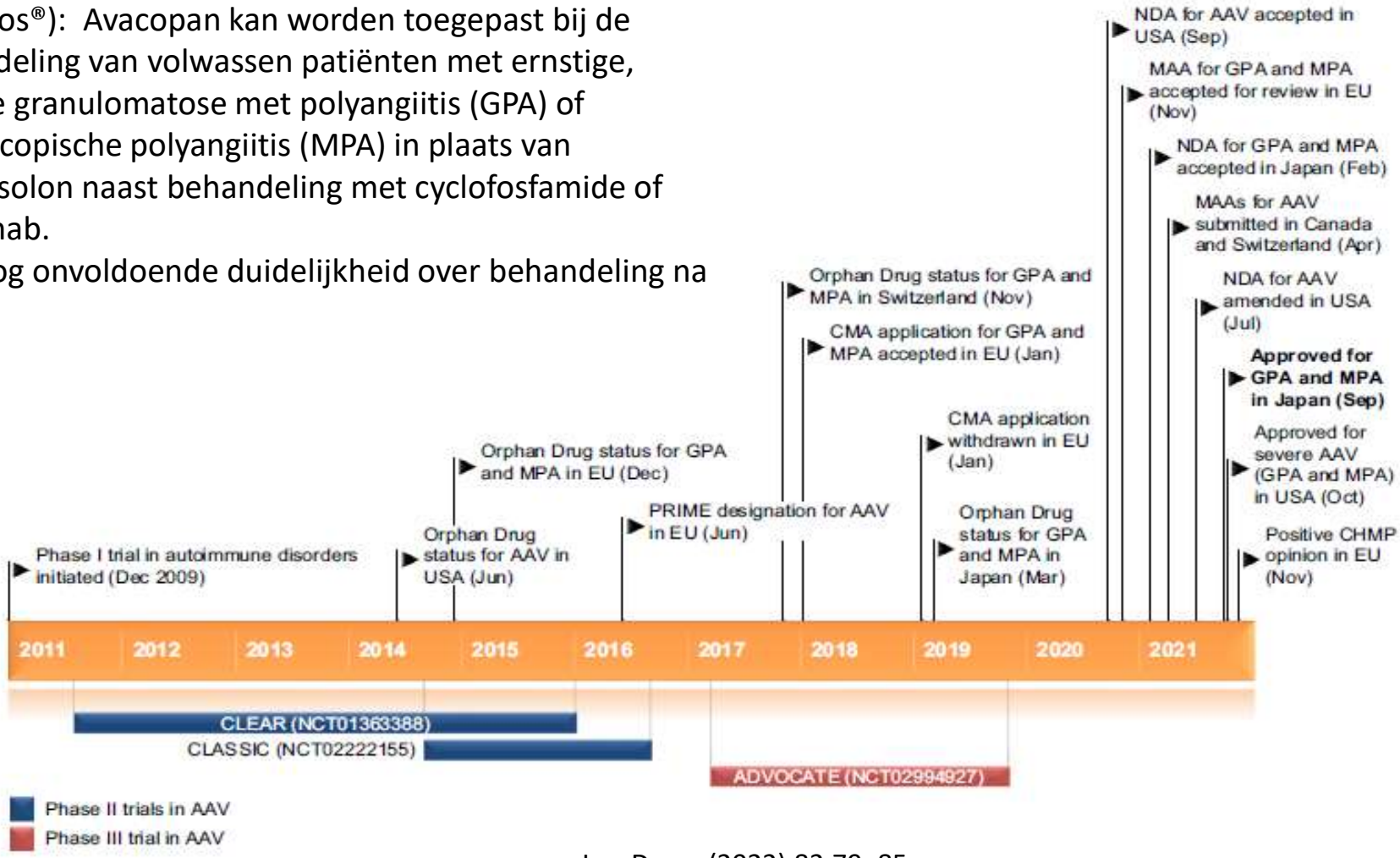
Snelle prednisolon taper

Dag	methylprednisolon IV	rituximab IV	cyclofosfamide IV	prednisolon oraal
1	250mg	1000mg*	500mg	
2-7				1 dd 60mg
8-14				1 dd 45mg
15	250mg	1000mg*	500mg	
16-21				1 dd 30mg
22-28				1 dd 15mg
29			500mg	
43			500mg	
57			500mg	
71			500mg	

McAdoo SP, Medjeral-Thomas N, Gopaluni S, et al. Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. Nephrol Dial Transplant 2019;34:63-7

Avacopan for AAV

Wetenschappelijke Adviesraad (WAR) over avacopan (Tavneos®): Avacopan kan worden toegepast bij de behandeling van volwassen patiënten met ernstige, actieve granulomatose met polyangiitis (GPA) of microscopische polyangiitis (MPA) in plaats van prednisolon naast behandeling met cyclofosfamide of rituximab.
Er is nog onvoldoende duidelijkheid over behandeling na 1 jaar



Lee Drugs (2022) 82:79–85

2022 ACR / EULAR classificatie EGPA

kleine of middelgrote vaten vasculitis is vastgesteld

klinische criteria	
Obstructie klachten luchtwegen	+ 3
Neuspoliepen	+ 3
Mononeuritis multiplex	+ 1
Lab en biopsie criteria	
Eosinofiele granulocyten ≥ 1*109/Liter	+ 5
Aanwezigheid van een meerderheid van eosinofiele granulocyten in het biopt	+ 2
C-ANCA of anti-PR3 antistoffen	- 3
Hematurie	- 1

Score ≥ 6 Classificatie EGPA
Sensitiviteit 87% en specificiteit 95%
Grayson PC, Ponte C, Suppiah R, et al.
Ann Rheum Dis 2022;81:309–314

IL-5 blockade in EGPA

Table 1 Characteristics of anti-IL-5 agents for EGPA

	Mepolizumab	Reslizumab	Benralizumab
Trade name	Nucala	Cinqair	Fasenra
Specifics	Humanized IgG1 kappa mAb	Humanized IgG4 kappa mAb	Humanized IgG1 kappa mAb
Target	IL-5	IL-5	IL-5 receptor alpha
Root of administration	Subcutaneous	Intravenous	Subcutaneous
Dosage	300 mg every 4 weeks (100 mg every 4 weeks under evaluation)	3 mg/kg every 4 weeks	30 mg every 4 weeks for the first three doses, and then 30 mg every 8 weeks
Evidence in EGPA	RCT involving 136 patients	Pilot studies	Open-label pilot study
	An open-label extension study to evaluate long-term efficacy is ongoing (NCT03298061)		Case reports
			A phase 3 trial comparing benralizumab to mepolizumab is ongoing (NCT04157348)

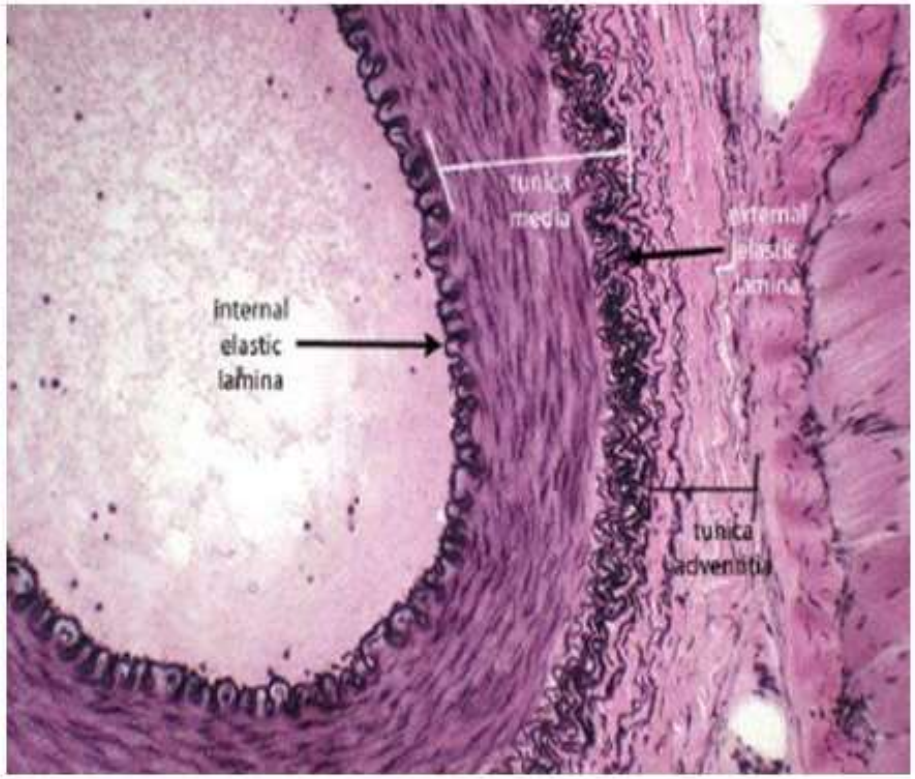
EGPA eosinophilic granulomatosis with polyangiitis, *IL-5* interleukin-5, *mAb* monoclonal antibody, *RCT* randomized controlled trial

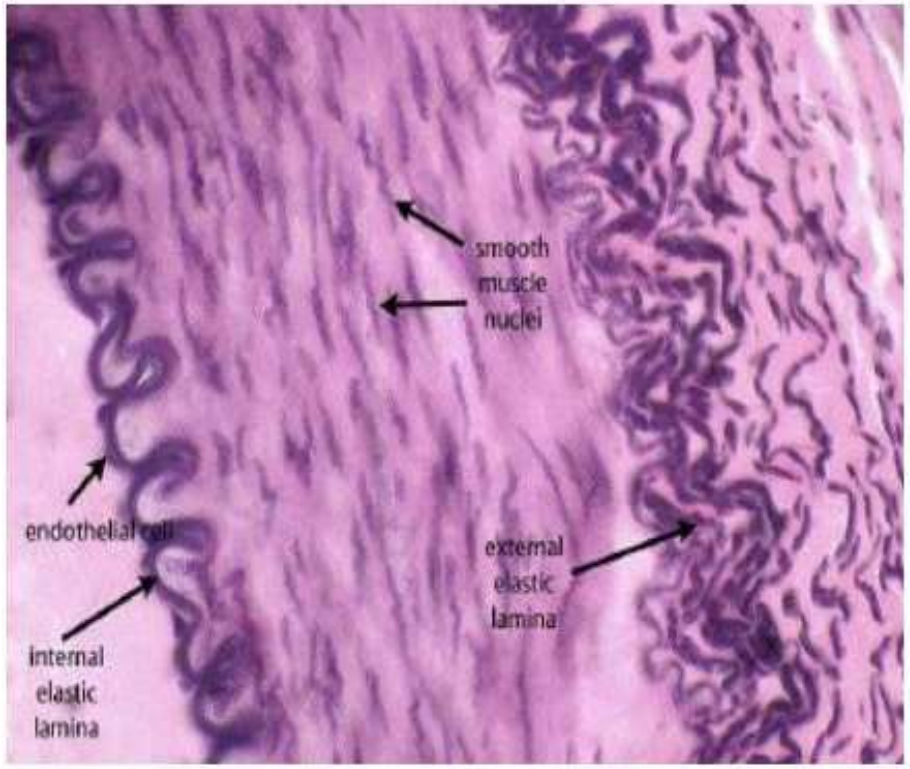
Koike (2023) 40:25–40 Adv Ther

Indeling

- Kleine vaten vasculitis
- **Middelgrote vaten vasculitis**
- Grote vaten vasculitis

Middelgrote vaten < 0,5 mm

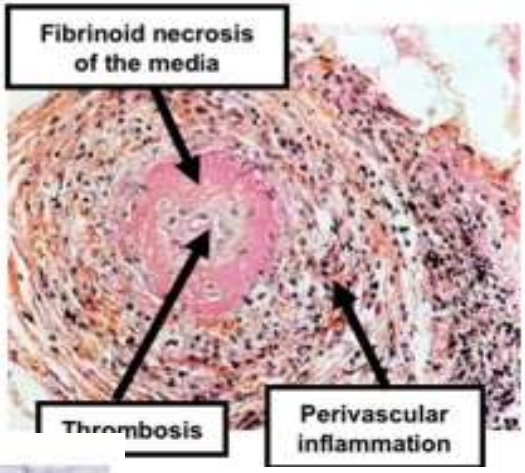


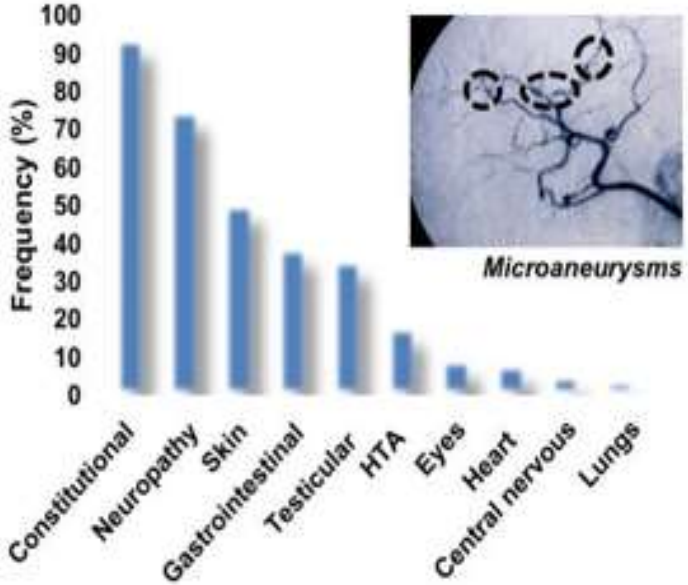


Musculaire arterie duidelijk lamina elastica interna en externa

Polyarteritis Nodosa

Chapel Hill 2012 definition
Necrotizing vasculitis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCA





Microaneurysms

FFS 1996 prognostic score
Proteinuria >1 g/d
Creatinin >140 µmol/L
GI tract involvement
Cardiomyopathy
CNS involvement

Treatment based on FFS 1996

	FFS = 0	FFS ≥ 1
Induction	GCs	GCs ± *pulses MP* + CYC x 6-9
Maint-enance	GCs 18-24 mo.	GCs + AZA/MTX 18-24 mo.

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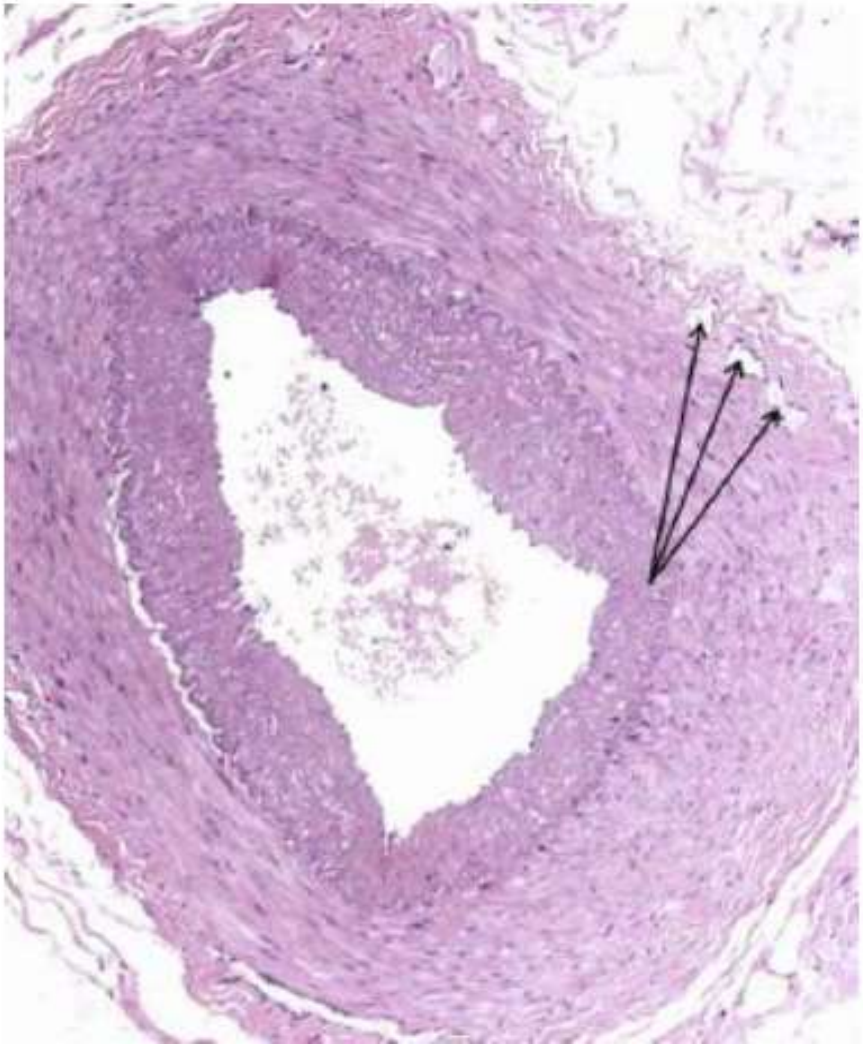
VASCULITIS EXPERTISE CENTER GRONINGEN

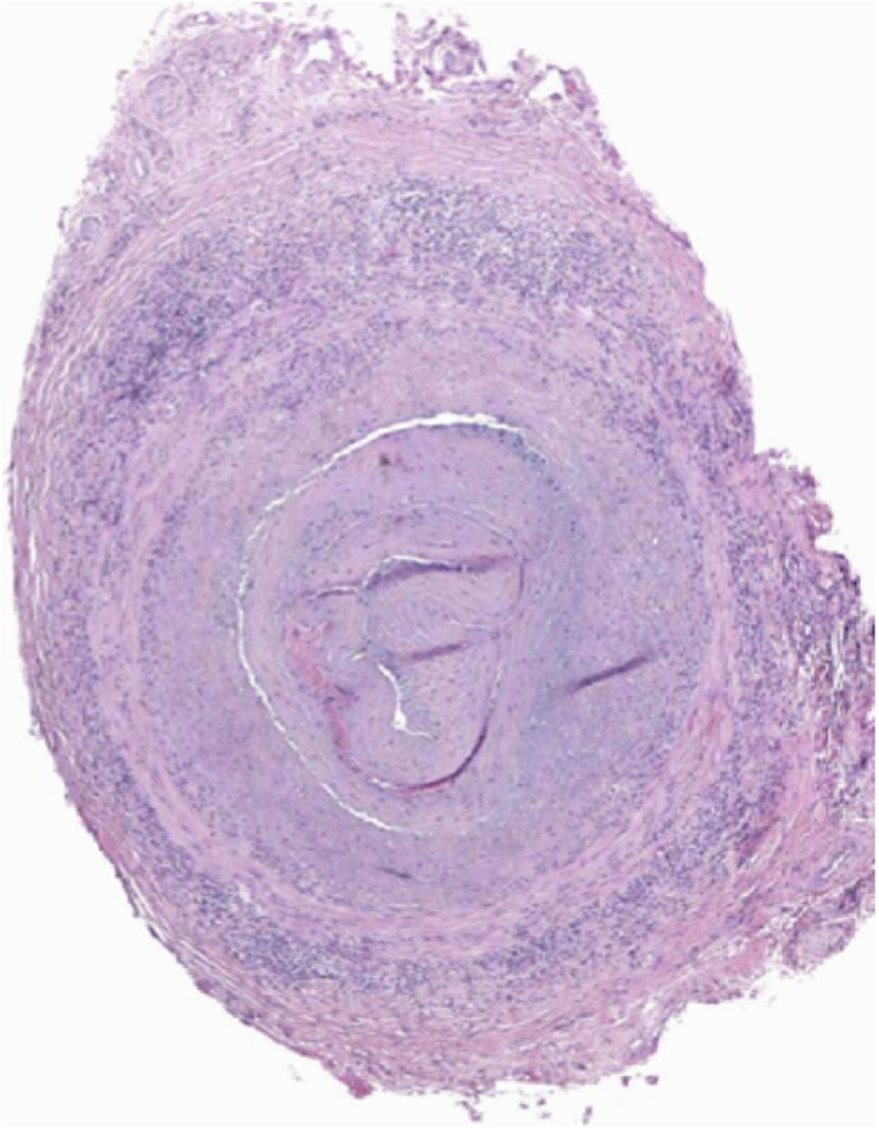
Indeling

- Kleine vaten vasculitis
- Middelgrote vaten vasculitis
- **Grote vaten vasculitis**

Normaal vat

Reuscelarteriitis





ACR 1990 classificatie criteria

Reuscelarteriitis RCA

- Leeftijd ouder dan 50 jaar
- Nieuwe hoofdpijn
- Afwijkende arterie temporalis (pijn / afname pulsaties)
- Verhoogde BSE > 50 jaar
- Bijpassend Biopt mononucleaire of granulomateuze ontsteking

Hunder AR 1990 3/5 sens 93,5 en spec 91,2

Takayasu arteriitis TAK

- Leeftijd jonger dan 40 jaar
- Claudicatio armen en benen
- Afgenomen pulsaties arterie brachialis
- Verschil in bloeddruk > 10 mm Hg tussen beide armen
- Souffle arterie subclavia/aorta
- Vernauwing aorta en / of zijtakken

Arend AR 1990 3/6 sens 80,5 en spec 97,8

2022 ACR / EULAR classificatie RCA

Grote of middelgrote vaten vasculitis is vastgesteld en patiënt is ouder dan 50 jaar

Aanvullende klinische criteria	
Ochtendstijfheid schouders/ nek	+ 2
Plotseling visus verlies	+ 3
Kaak of tong claudicatie	+ 2
Nieuwe temporale hoofdpijn	+ 2
Pijn bij aanraken hoofdhuid	+ 2
Abnormale temporaal arterie	+ 2
Lab imaging en biopsie criteria	
BSE ≥ 50 mm/ uur en CRP ≥ 10 mg/L	+ 2
Positieve TAB of HALO sign bij US	+ 5
Bilaterale axillaire betrokkenheid	+ 2
FDG PET activiteit in hele aorta	+ 2

Score ≥ 6 Classificatie Reuscelarteriitis
Ponte C, Grayson PC, Robson JC, et al. Ann Rheum Dis 2022;81:1647–1653

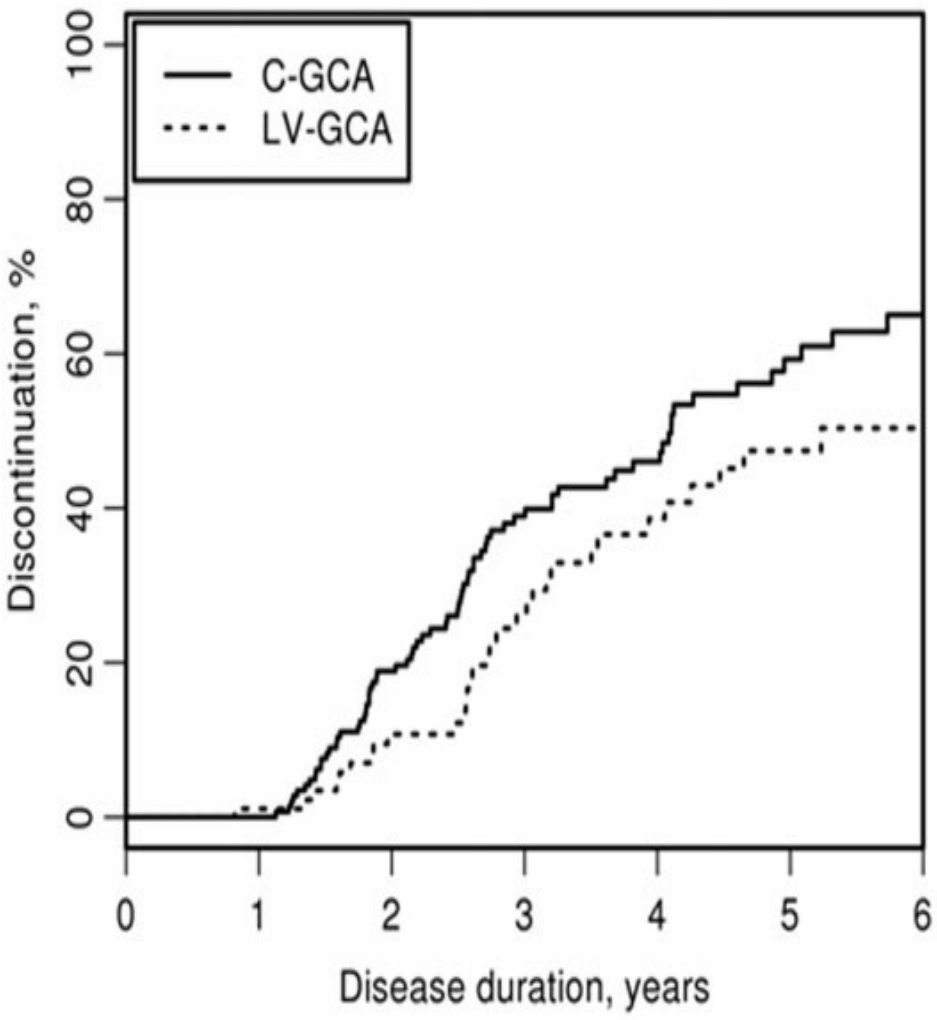
GC Effect on Vessel wall Biopsy

Granuloma ↓ / Medial fibrosis ↑

TAB	Baseline	Follow up
Granulomatous	37/40 (93%)	14/40 (35%)
Giant cells	22/40 (55%)	11/40 (28%)
Lymphocytes	40/40 (100%)	24/40 (60%)
Plasma cells	33/40 (83%)	10/40 (25%)
Non Granulomatous	3/40 (7%)	10/40 (25%)
Medial fibrosis	13/40 (33%)	24/ 40 (60%)

Maleszewski Mod Pathol 2017

Duur prednisolon behandeling



Large-vessel giant cell arteritis: a cohort study
Francesco Muratore, et al Rheumatology 2014

Bewijs voor Methotrexaat

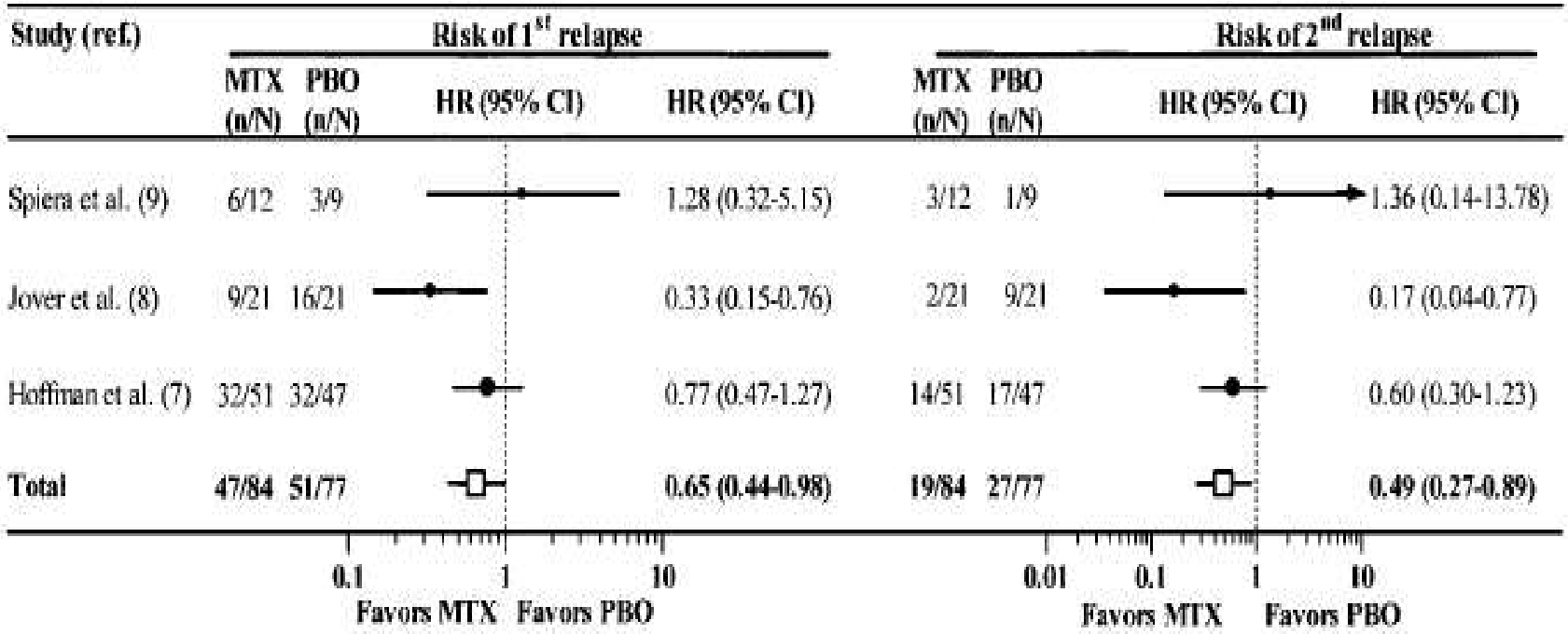


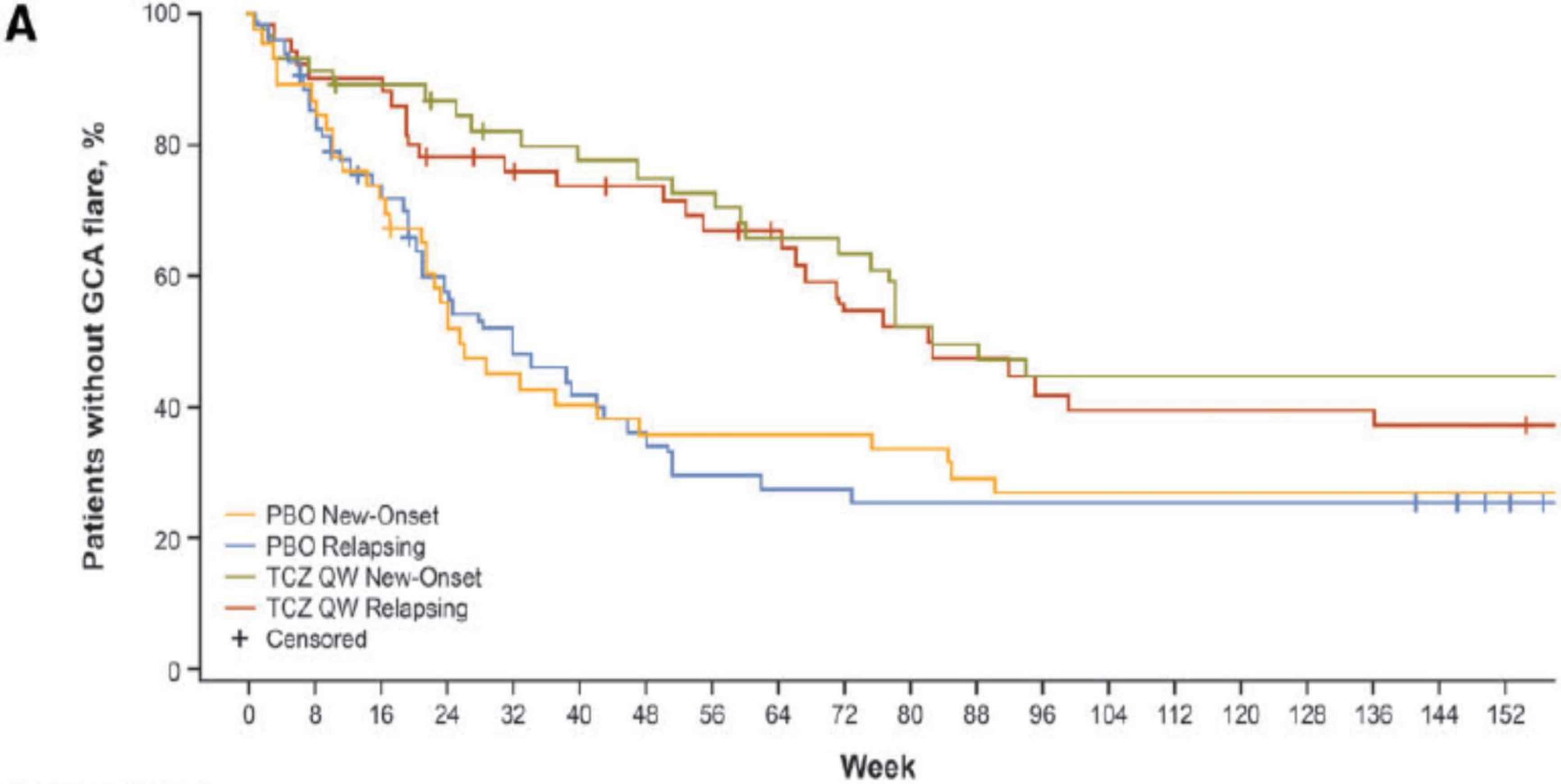
Figure 1. Hazard ratios (HRs) for the occurrence of a first or second relapse of giant cell arteritis in patients receiving adjunctive methotrexate (MTX) versus those receiving placebo (PBO). Values under each treatment group are the number of events (n) among the total number of subjects exposed (N). 95% CI = 95% confidence interval.

Mahr AR 2007

Leflunomide 1 dd 20 mg mogelijk alternatief echter nog geen goed bewijs

GiACTA 3 year Stone et al

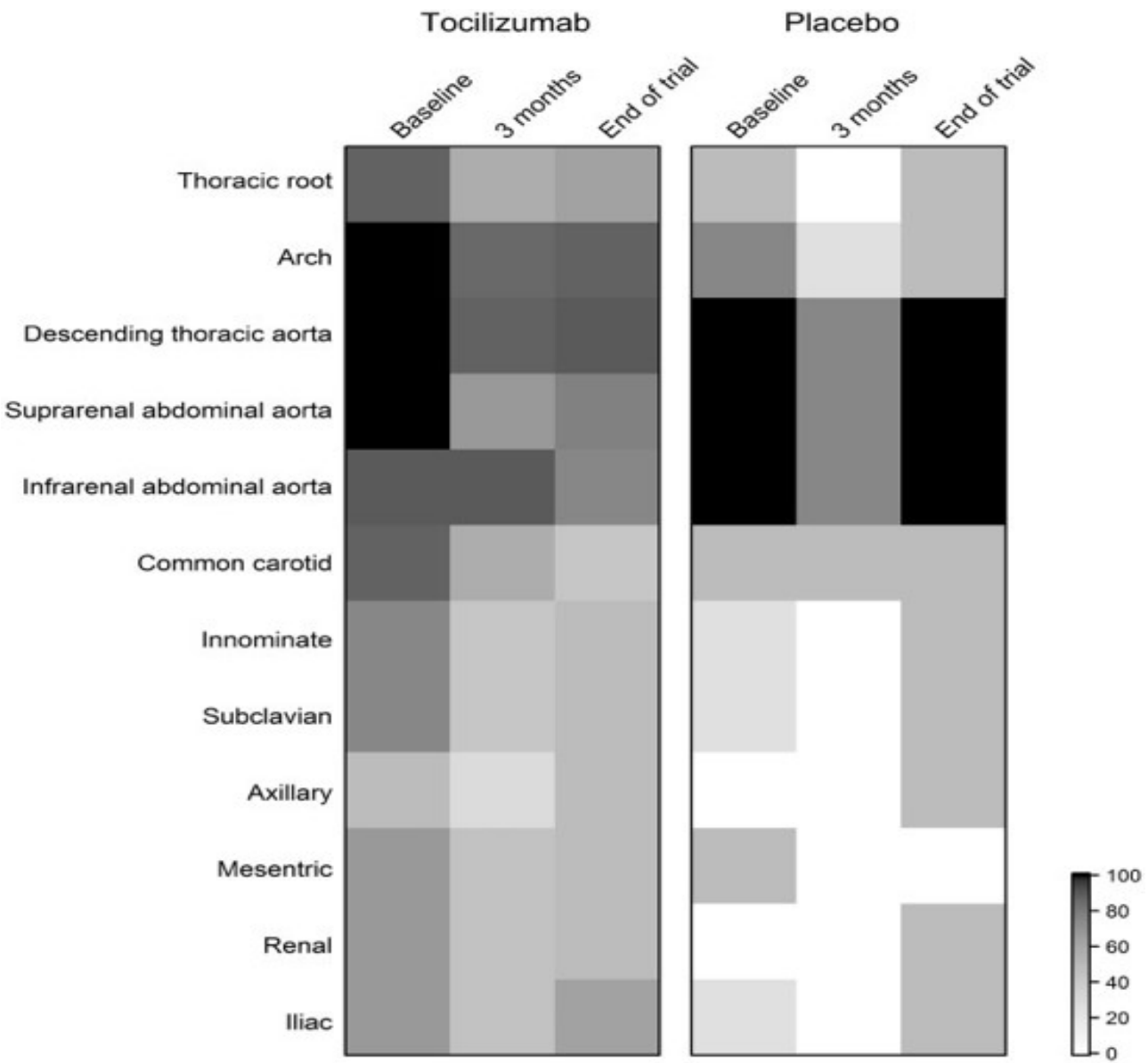
Rheumatology 2022



Number of Patients

PBO New-Onset	46	41	40	35	33	30	25	21	20	19	18	17	16	16	16	16	16	16	16	15	15	15	13	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11
PBO Relapsing	55	52	45	41	38	33	29	27	26	23	21	19	18	14	14	14	13	13	13	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	10	9
TCZ QW New-Onset	47	43	42	40	40	40	38	36	35	34	33	33	32	31	31	29	28	28	27	26	22	21	21	20	19	19	19	19	19	19	19	19	19	19	19	19	19	19	19
TCZ QW Relapsing	53	50	46	45	45	39	37	36	35	34	33	32	32	31	29	28	27	24	22	22	21	19	19	18	17	16	16	16	16	16	16	16	16	16	16	15	15	15	15

Tocilizumab effect on Vessels MRA



Reichenbach Rheumatology 2018

Tocilizumab snelle prednisolon taper

- Prednisolon in 26 weken afbouwen.
- Start 60 mg/dag gedurende 1 week;
- - daarna (mits sprake is van remissie) afbouw met 10 mg per week tot 40 mg/dag;
- - daarna (mits sprake is van remissie) met 5 mg/week tot 15 mg/dag;
- - daarna (mits sprake is van remissie) 2 weken 12,5 mg/dag;
- - daarna (mits sprake is van remissie) 1 week 10 mg dag;
- - daarna (mits sprake is van remissie) af te bouwen tot stop prednison gebruik in tijdspad van 15 weken.

Tocilizumab IL-6 receptor blokkade

	N and diagnosis	Disease activity	treatment	Outcome
Tocilizumab IV Villeger Lancet 2016	N= 27 New Relapsing	Clinic ESR > 30 mm/hr CRP > 10 mg/L	Tocilizumab 8mg/kg every 4 weeks Rapid GC taper 7 mg at week 12	Toci CR wk 12 12/17 85% Placebo CR wk 12 4/10 40%
Tocilizumab GiACTA Stone NEJM 2017	N=252 New Relapsing	Clinic	4 treatment arms	Toci SR wk 52 56/100 56% 26/49 53% Prednisolone 7/50 14% 9/ 51 18%
Tocilizumab GUSTO Trial Christ Lancet Rheum 2021	Open Label N=18 New	Clinic ESR > 30 mm/hr CRP > 10 mg/L	Tocilzumab IV 8 mg/kg day 3 Followed by 162 mg sc weekly 3 days 500 mg IV methylpred	Week 24 14/18 remission Week 52 13/ 18 no relapse 1 AION 1 hepatopathy

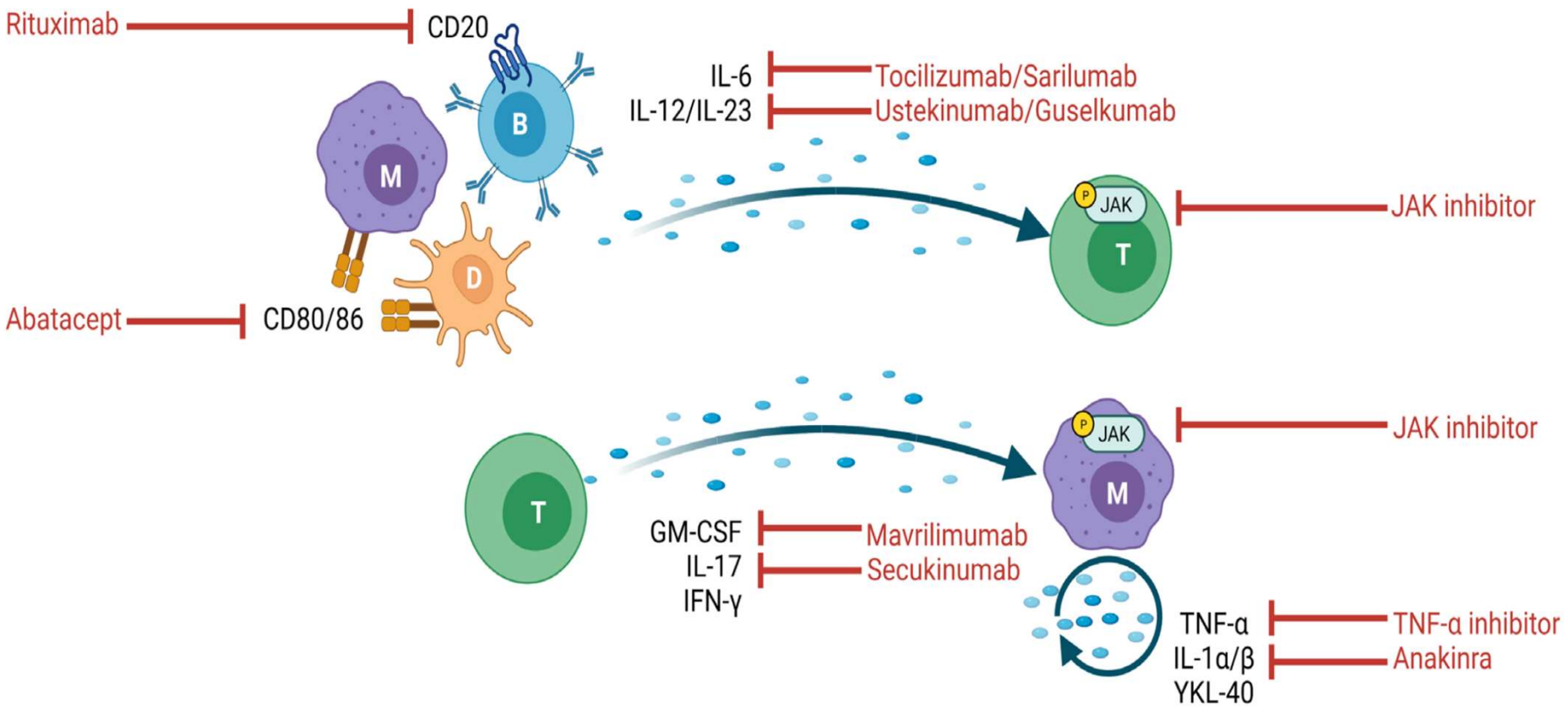
Ts and b DMARDs

	Study design N GCA new/ relapse	Disease activity	Treatment	Outcome
Abatacept CTLA4-Ig Langford AR 2017	Open Label N= 49 New and relapse	Clinic ESR > 40 mm/hr CRP > 10 mg/L	10 mg/kg IV Day 1, 15,29 and 56 GC 40-60 mg 28 wk GC taper	Relapse free survival W28 Positive
Mavrililumab GM-CSF receptor alpha inhibitor Cid ARD 2021	Phase 2 RCT N=70 New and Relapse	Clinic ESR > 30 mm/hr CRP > 10 mg/L	N=42 150 mg mavrilimumab sc eo week N= 28 placebo 26 week GC taper	26 Week remissio 83% Mavrililumab 50% Placebo
Secukinumab IL-17A inhibitor Venhoff Trials 2021	Phase 2 RCT N=50	Clinic ESR > 30 mm/hr CRP > 10 mg/L	1:1 secukinumab 300 mg sc /week 5 doses then 300 mg/ 4 week or placebo 26 week GC taper	52 week 59,3% vs 8% sustained remission

Ts and b DMARDs

	Study design N GCA new/ relapse	Disease activity	treatment	Outcome
Ustekinumab IL-12/IL-23 inhibitor Conway Sem AR 2018	Open Label Relapsing N= 25	Clinic with or without ARP	Ustekinumab 90 mg every 12 weeks GC 5 mg 52 weeks	No relapses Reduction GC dose
Ustekinumab IL-12/IL-23 Matza Inhibitor ACR 2021	Open label New onset Relapsing N= 20	Clinic ESR > 40 mm/hr CRP > 10 mg/L	Ustekinumab 90 mg every 12 weeks 24 week GC taper	N=3 in GC remission at 52 weeks Study prematurely terminated
Baricitinib JAK/Stat inhibitor Koster ARD 2022	Open label N=15 Relapsing	Clinic ESR > 30 mm/hr CRP > 10 mg/L	4 mg tablet per day Accelerated GC taper 15 (10), 19(20), 22 (30)	52 weeks GC 0 1/14 relapse

Nieuwe targets voor behandeling



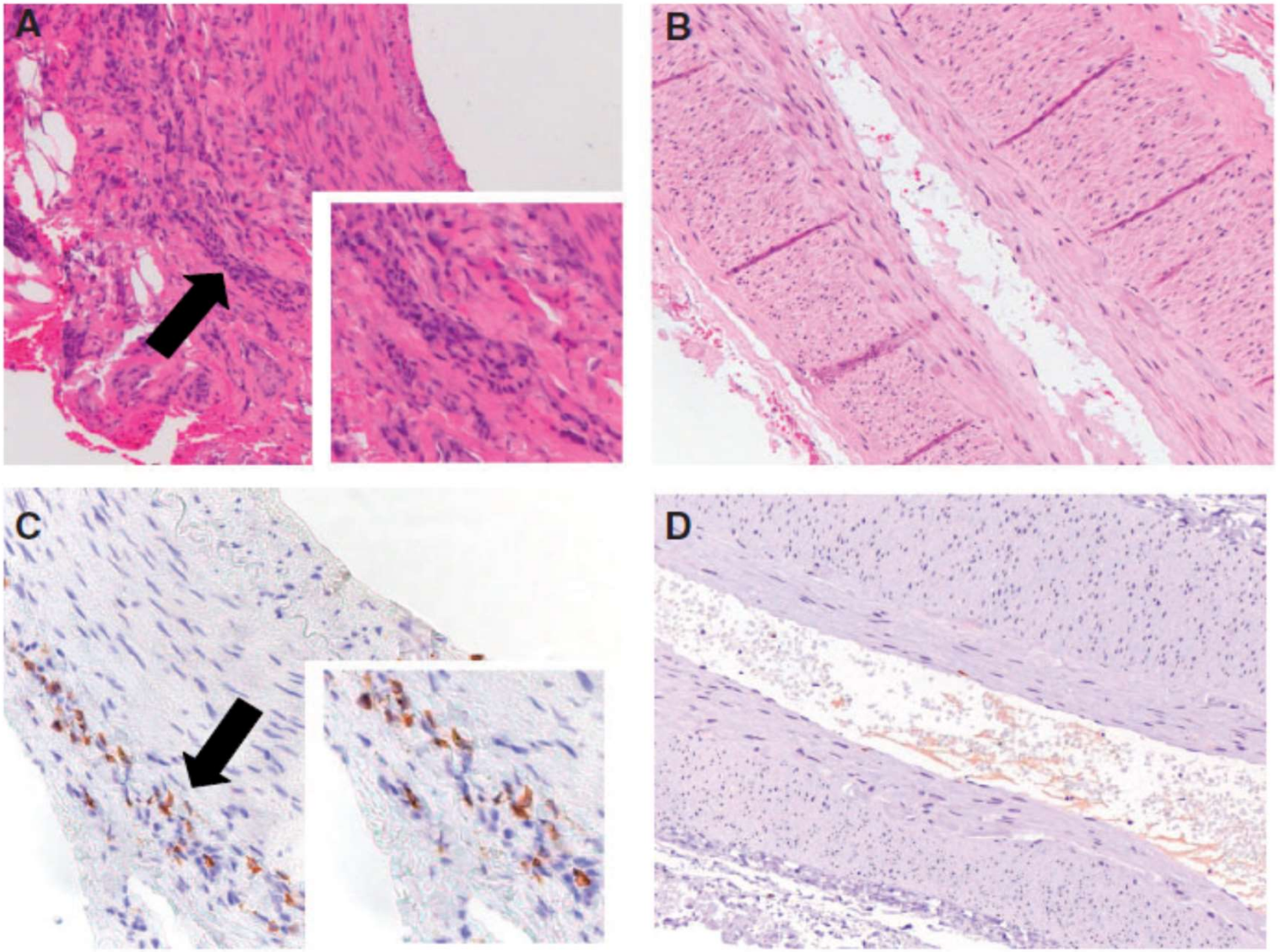
Sandovici M,van der Geest KSM, van Sleen Y,et al. Need and value of targeted immunosuppressive therapy in giant cell arteritis. RMD Open2022;8:e001652. doi:10.1136/rmdopen-2021-001652

Cyclophosphamide in GCA

- Relapse 4/15
- 3 after 24 months of cyclophosphamide cessation
- 6/15 no GC and 9 GC, 5 mg/ day

Luca Quartuccio, Marta Maset, Giovanna De Maglio, Elena Pontarini Martina Fabris, Elisa Mansutti , Laura Mariuzzi, Stefano Pizzolitto, Carlo Alberto Beltrami and Salvatore De Vita Rheumatology 2012;51:16771686

Biopsy Outcome



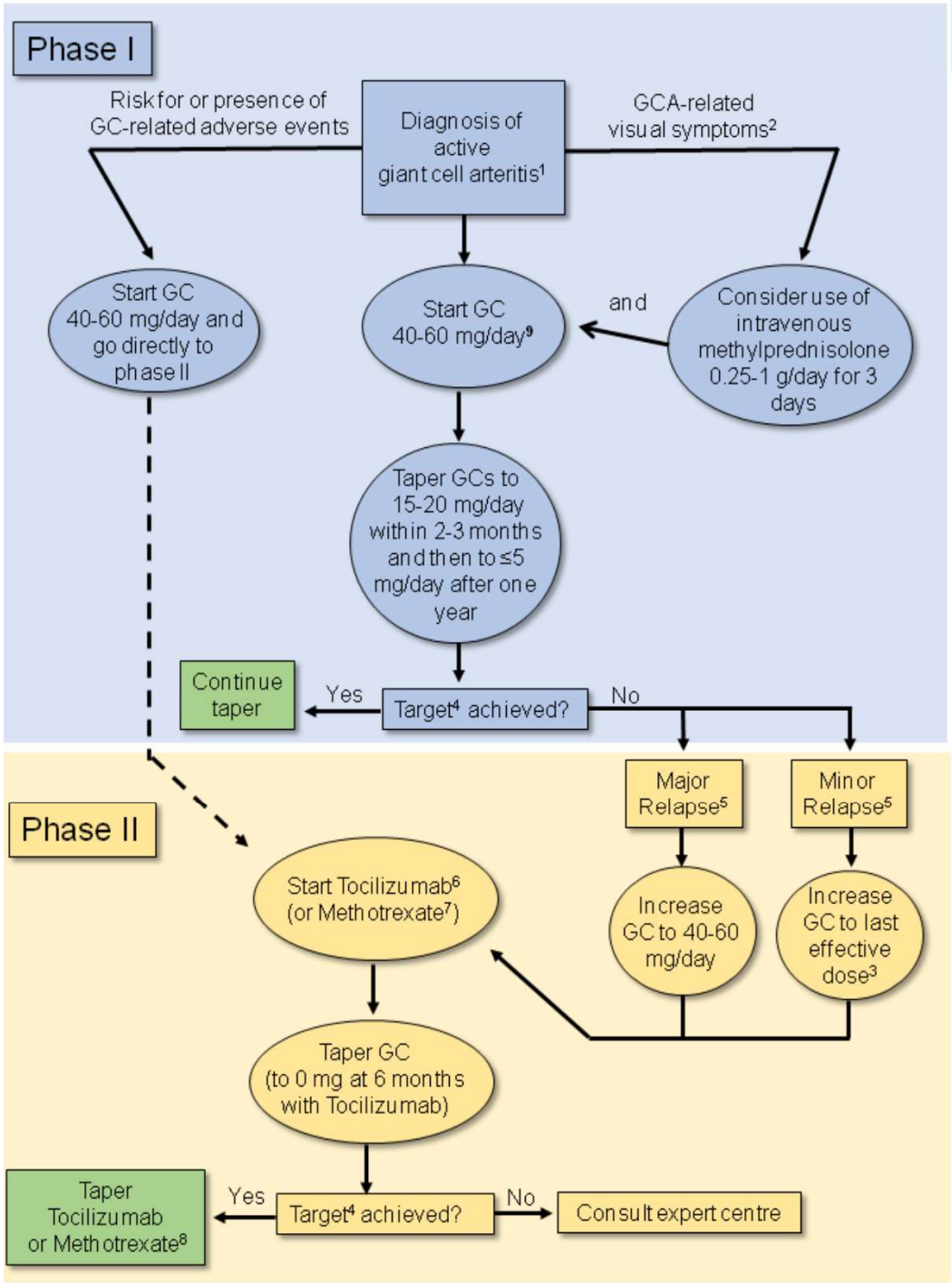
Ongoing trials ClinicalTrials.gov

- Upadacitinib
- Abatacept
- METOGIA France tocilizumab versus MTX
- Secukinumab
- Ustekimumab

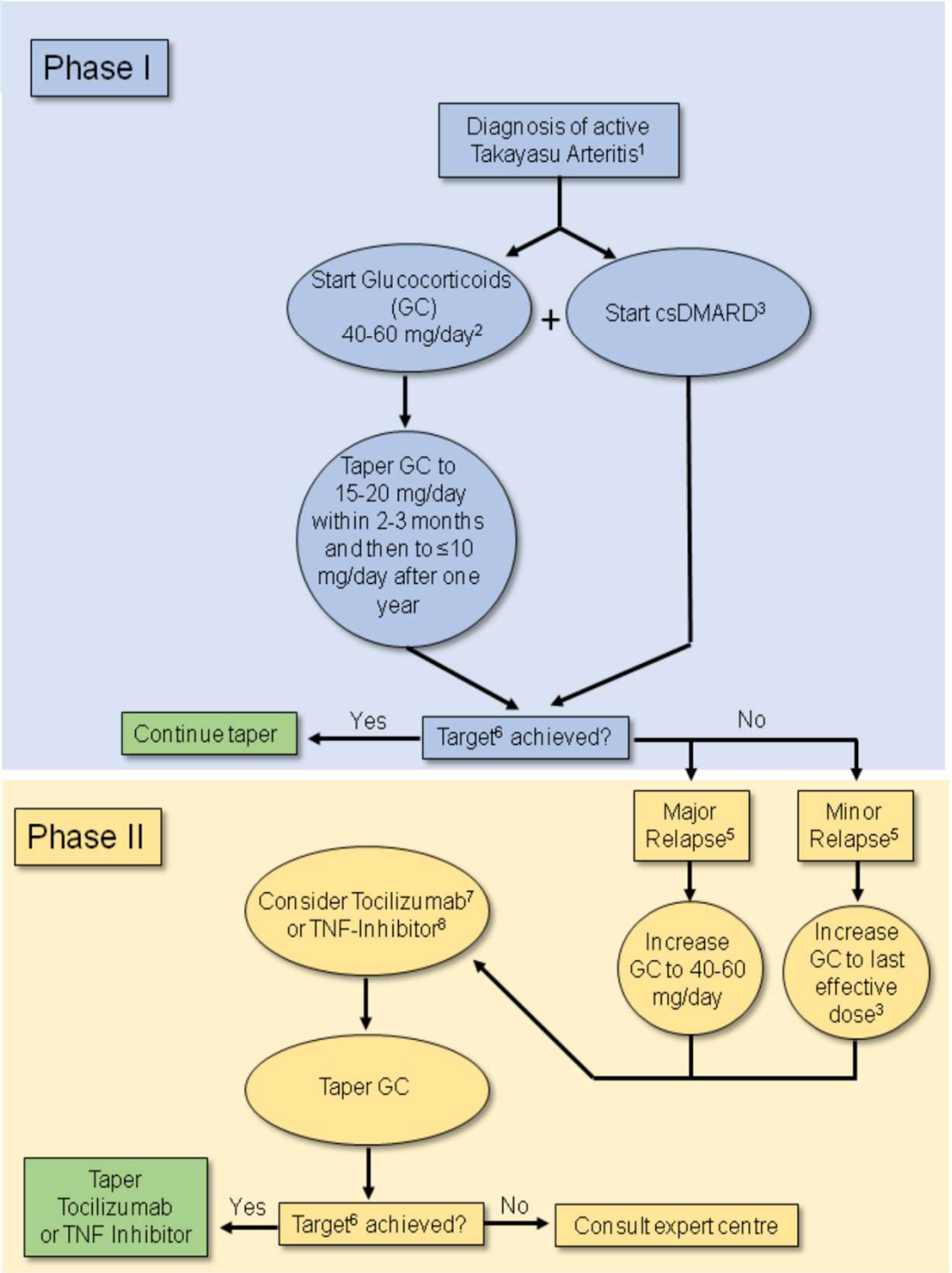
Samenvatting Behandeling RCA

- Start prednisolon 40-60 mg per dag
- Methylprednisolon IV indien visus stoornissen
- Overweeg gelijk te starten met methotrexaat (standpunt NVR) dan wel tocilizumab (beste evidence)
- Monitor RCA patient op basis kliniek
- Relapse meer dan stijgen van BSE/CRP
- Belang vaatwand vervolgen

2018 EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF GIANT CELL ARTERITIS



2018 EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF TAKAYASU ARTERITIS



Take home Messages

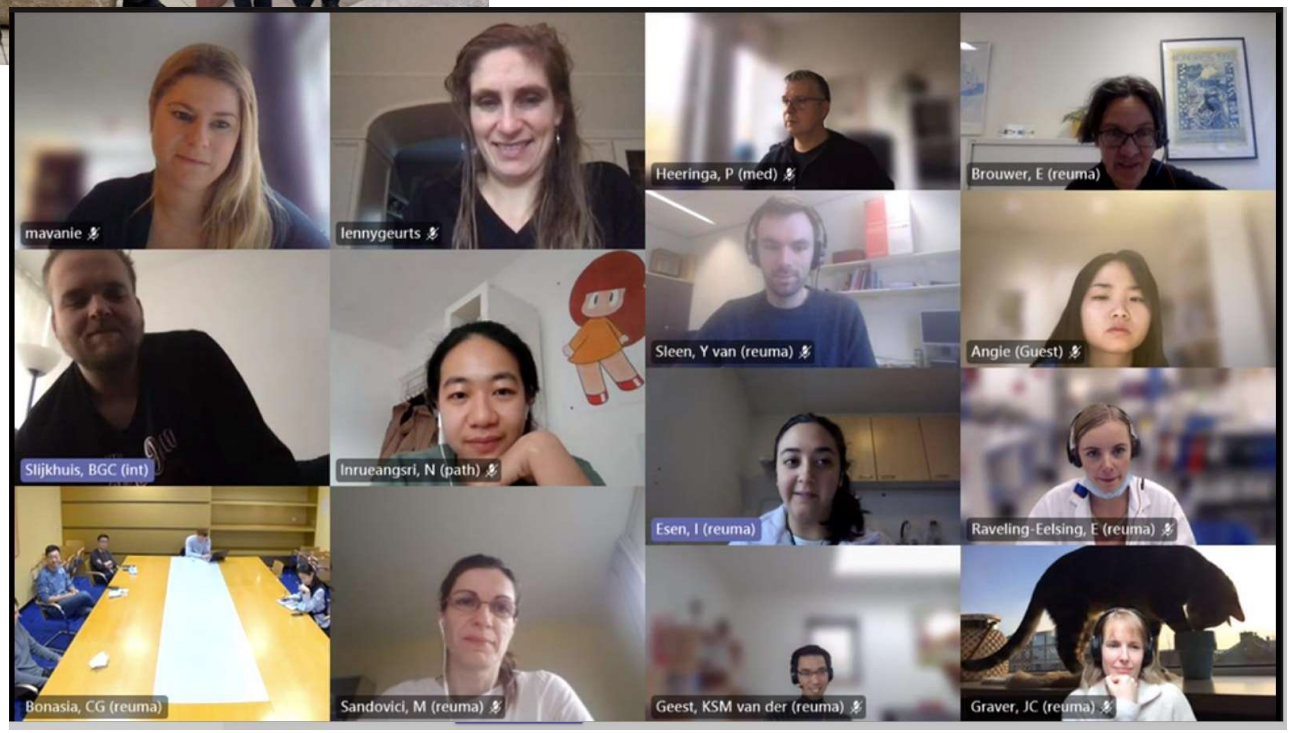
- Weefseldiagnose blijft belangrijk
- Genetisch onderzoek ADA-2 / UBA-1 VEXAS
- Inductie met een effectief middel naast start prednisolon
- meten ziekte activiteit vaten
- Meten orgaan en vaatschade
- Meenemen Patient Reported Outcome

Vasculitis Expertise Centrum Work in Progress

www.vasculitiscentrum.nl ARCH MDO wekelijks

ARCH

Autoimmune Research & Collaboration Hub



University Medical Center Groningen
Rheumatology and Clinical Immunology

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