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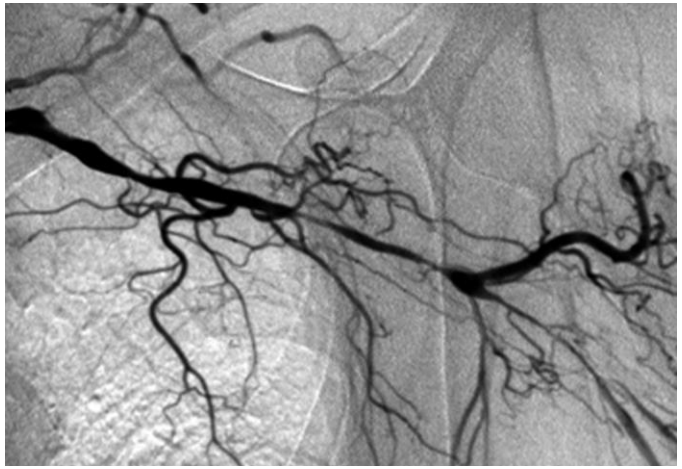
Systemvaskulitiden



Stephan Blüml

KIMIII/Rheumatologie

MUW

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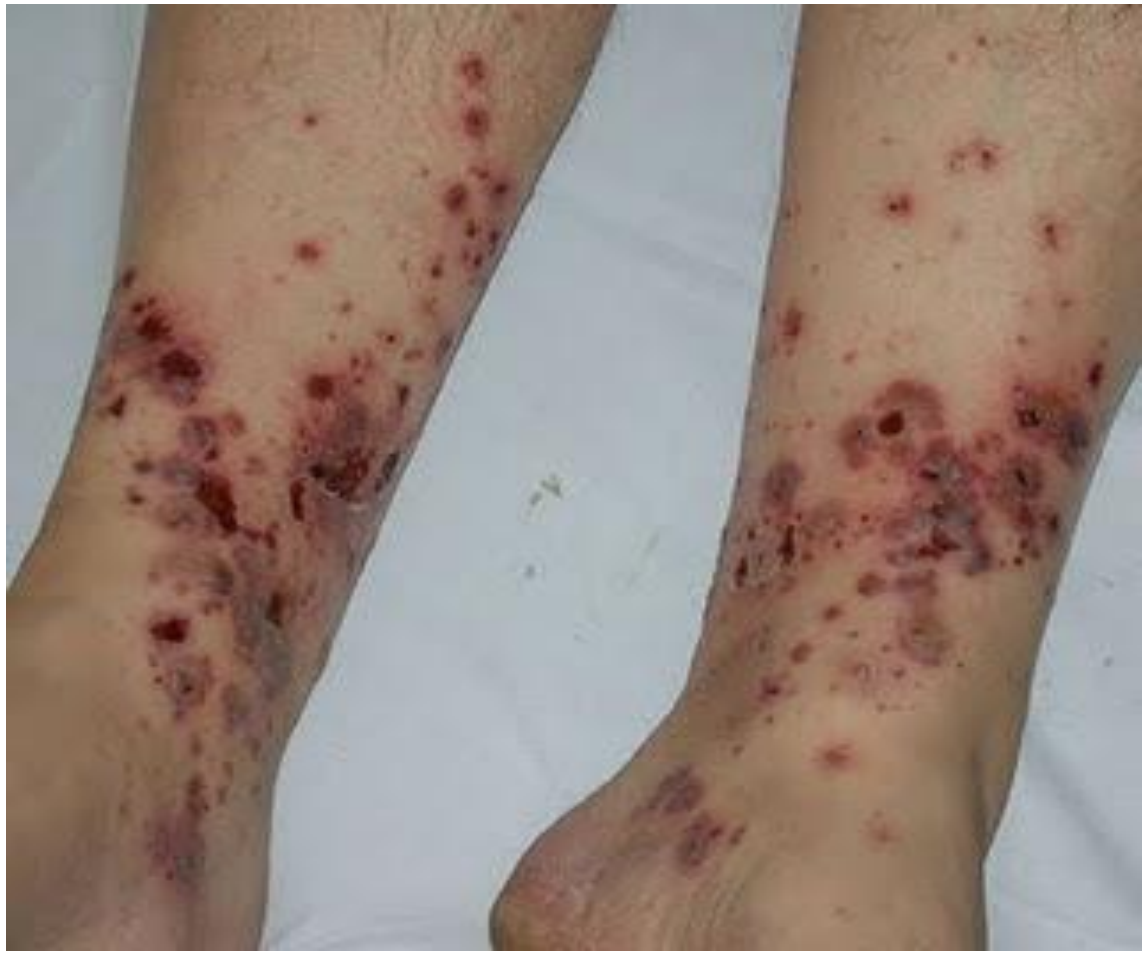
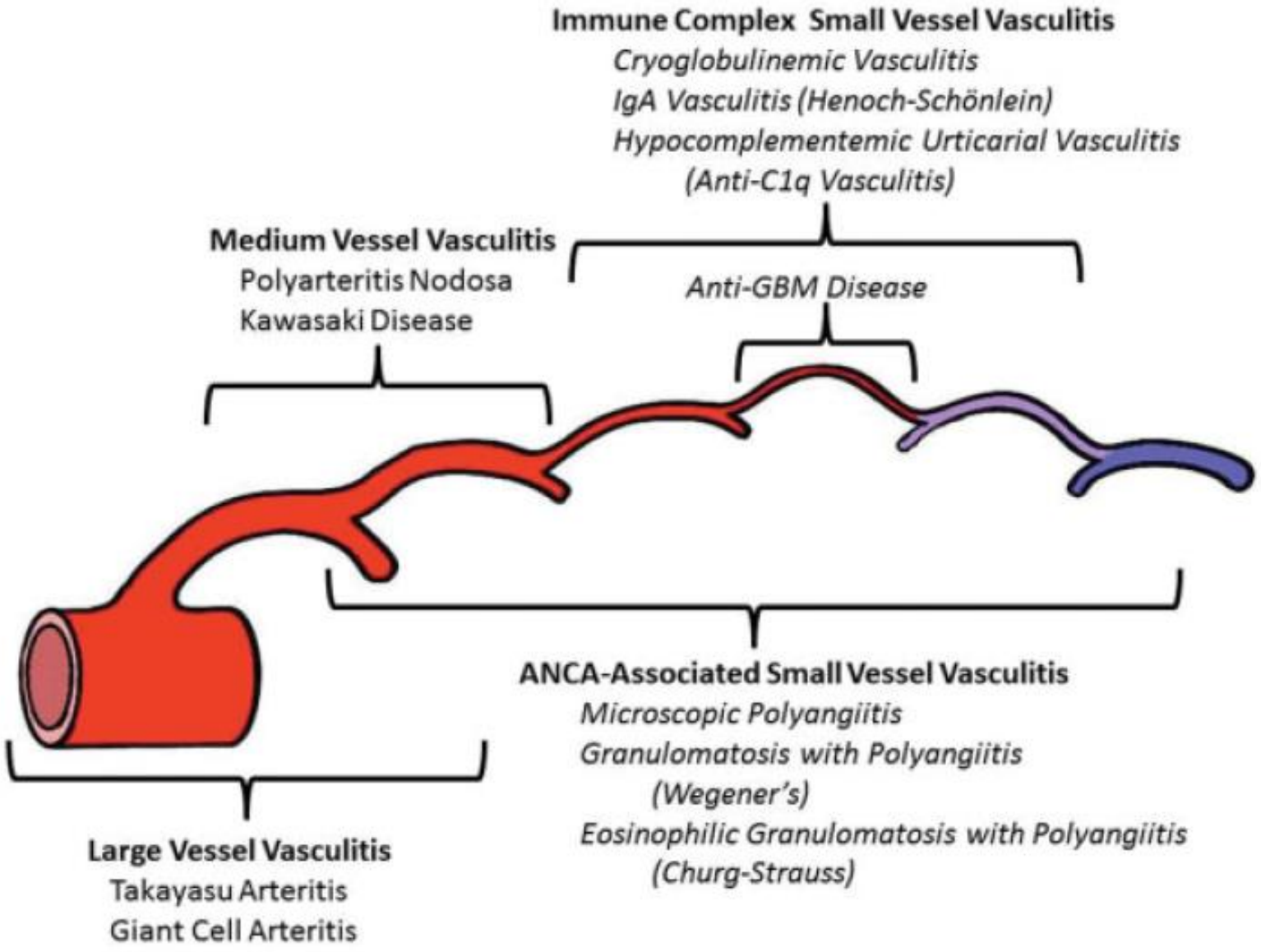
Vaskulitis:

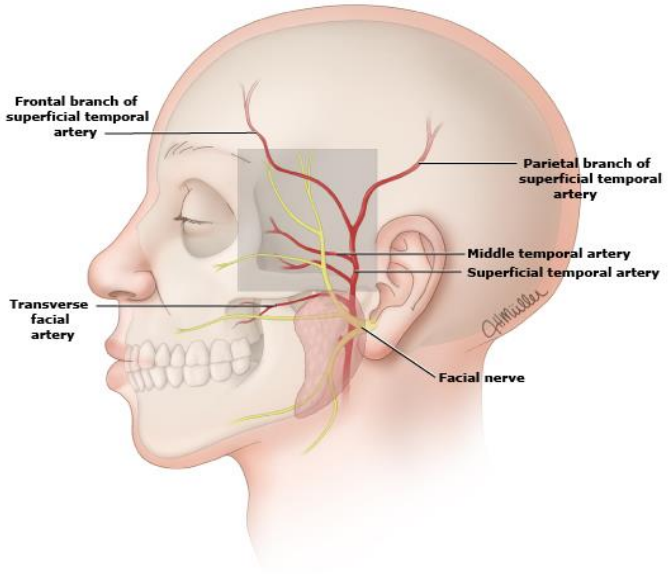
-inflammatory destruction of blood vessels
-presence of inflammatory cells in the vessel wall

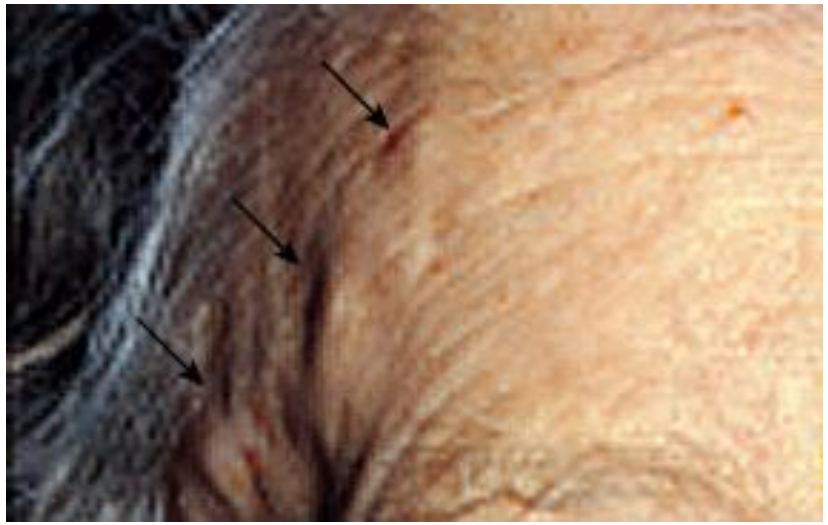


Chapel Hill Consensus Conference (2012) Nomenclature



Riesenzellarteriitis (RZA, GCA, M. Horton)





Druckschmerz, verminderte Pulsation, Arterien knotig verdickt, verhärtet

Beteiligung der Aorta: bis zu 45 %

Symptome der Riesenzellarteriitis

Kopfschmerz, lokalisiert
Sehstörung, einseitiger Visusverlust, transient od. permanent
Claudicatio masticatoria
Fieber unklarer Ursache
Gewichtsverlust, Krankheitsgefühl, Müdigkeit
BSG, CRP, Anämie

Crowson CS, et al. Arthritis Rheum 2011;63:633

Klinische Manifestationen und Subtypen der Riesenzellarteriitis

Polymyalgia rheumatica ~ 50 %

proximal: Arthritis und Periarthritis der großen Gelenke

distal: RS3PE (remitting seroneg., symmetrical synovitis, pitting edema)

Kranielle RZA, Visusverlust ~ 15 %

vordere oder hintere ischämische Optikusneuropathie (AION, PION)

Verschluss der A. centralis retinae

Extra-kranielle RZA, Beteiligung der Aorta und der großen Äste

Aortenaneurysma, Aortendissektion, Armclaudicatio,

ischämischer Insult (~ 3%)

Dejaco C et al., Rheumatology 2017;56:506

The ACR 1990 criteria for the classification of GCA

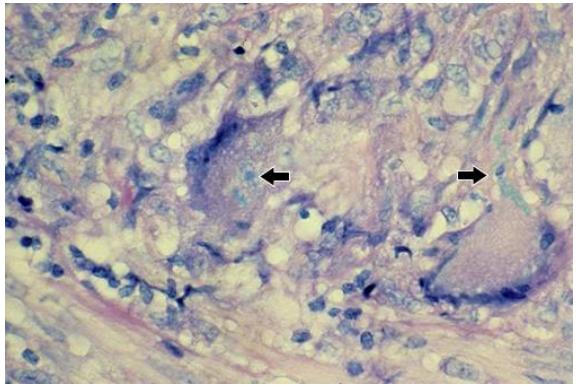
Hunder GG, et al., Arthritis Rheum 1990; 33:1122

- Age ≥ 50 years
- Localized head pain (Sehstörung, PMR, Allgemeinsymptome, Claudicatio)
- Tenderness or decreased pulse of the temporal artery
  (Symptome extra-kranieller Gefäßbeteiligung)
- ESR > 50 mm/hour (CRP ≥ 1.0 mg/dl)
- Positive biopsy (auffällige Bildgebung)

3 out of 5

Sensitivity: 94%

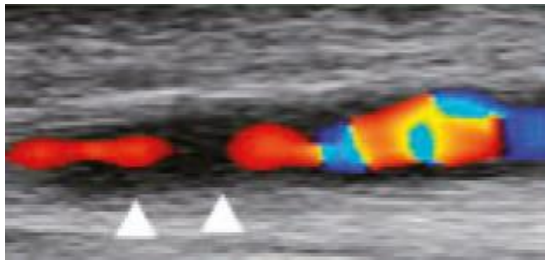
Specificity: 91%



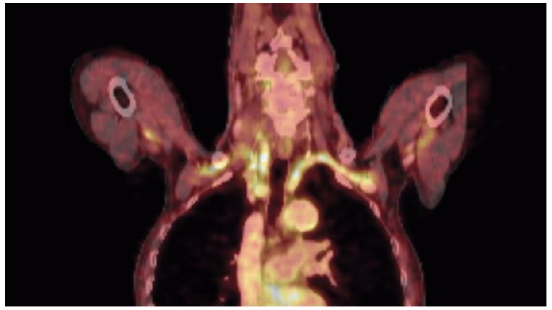
Dejaco C et al., Rheumatology 2017;56:506

Diagnose der Riesenzellarteriitis - Bildgebung

- Farb-Duplex Sonografie
  - temporal + axillary arteries
  - Sensitivity similar to MRI
  - Specificity similar to MRI



- MRT-Angiographie
  - Sensitivity similar to US
  - Specificity similar to US



- CT-Angiographie
  - Not for cranial artery involvement

- FDG PET/PET-CT For the evaluation of large vessels,
  - sensitivity/specificity similar to MRI, not for cranial arteries

Glucocorticoid treatment

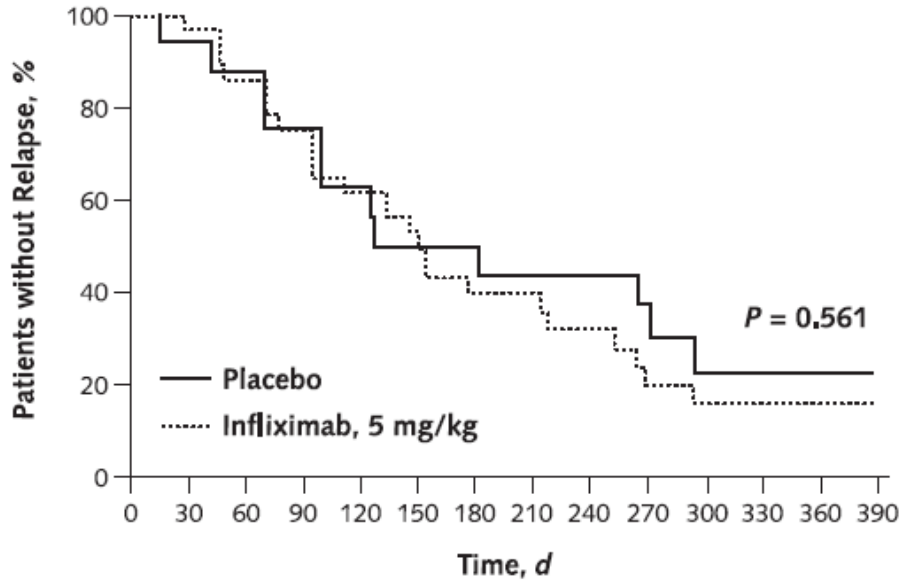
- Instituted promptly once the diagnosis of GCA is suspected strongly
- Negative biopsy, suspicion of GCA is high – continue
  (false neg. results in ~ 9%)
- Initial dose, pulse glucocorticoids for patients with visual loss
- Tapering (~ 2 – 3 a)
- Monitoring (ESR)
- Low dose aspirin, retrospective cohort studies, not part of latest recommendations

- Monitoring for development of aortic aneurysm (chest x-ray)

1) Side effects
2) Not effective in maintaining remission
   ~ 50% relapses/flares

TNF-Inhibitoren wirken nicht

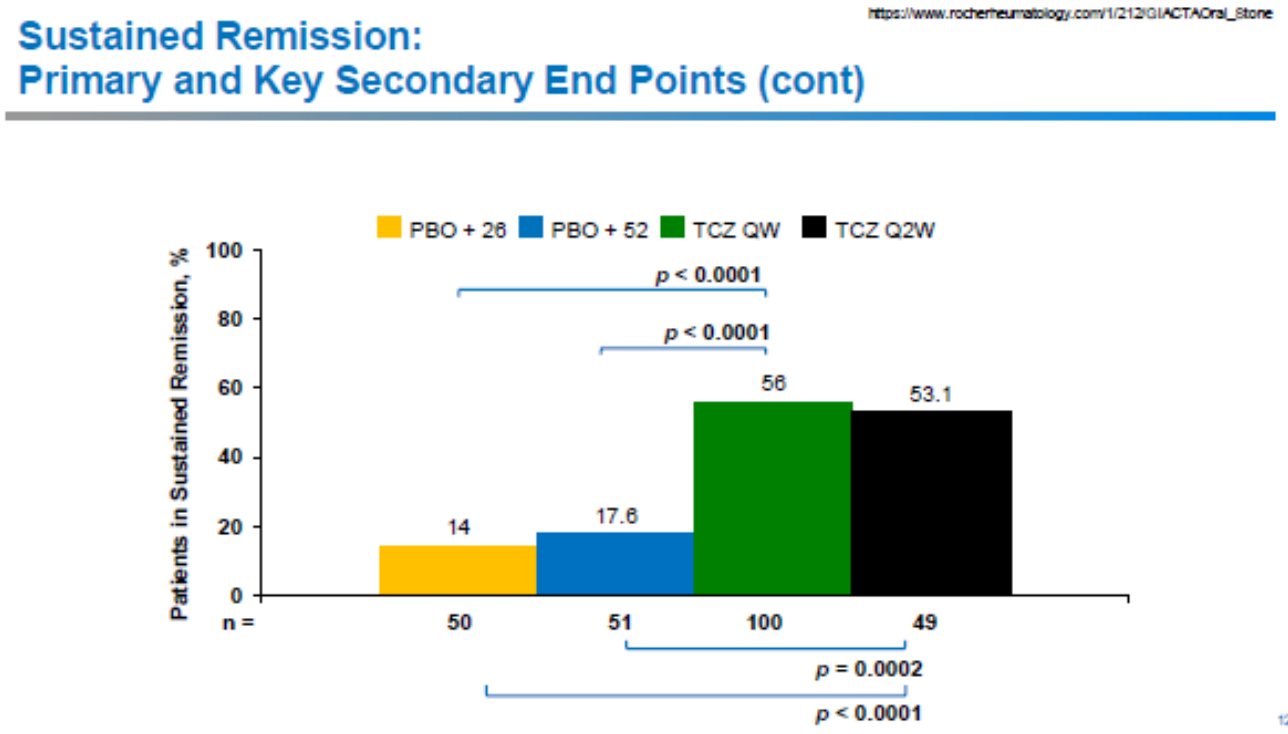
Patients: 44 patients with newly diagnosed giant cell arteritis that was in glucocorticosteroid-induced remission.



Patients at risk, *n*							
Infliximab	28	28	27	27	26	16	9
Placebo	16	16	16	16	16	13	4

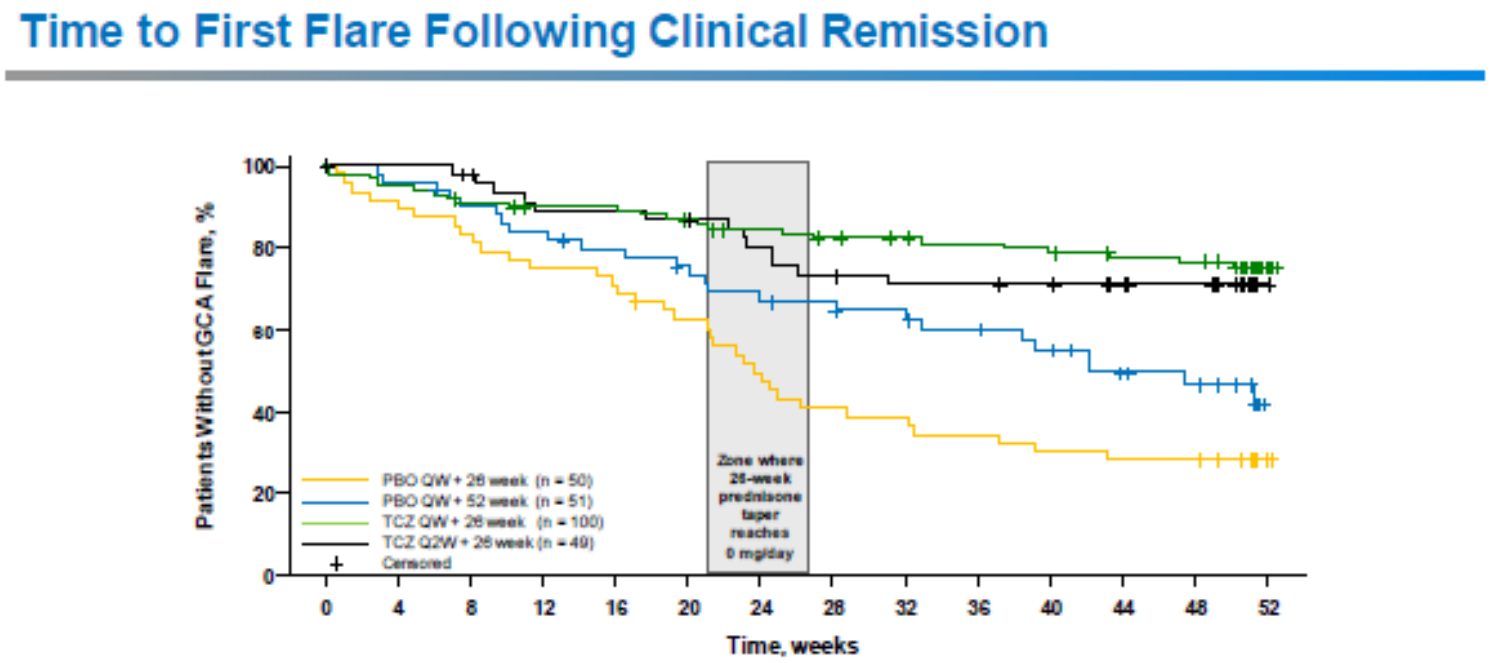
Hoffmann et al., AIM 2007

Tocilizumab (Roactemra) in A. temp. schon



Stone et al. NEJM 2016

Tocilizumab (Roactemra) in A. temp.



Stone et al. ACR 2016

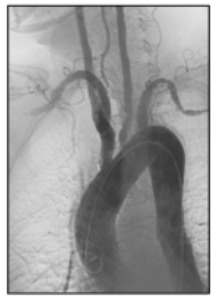
Takayasu arteritis

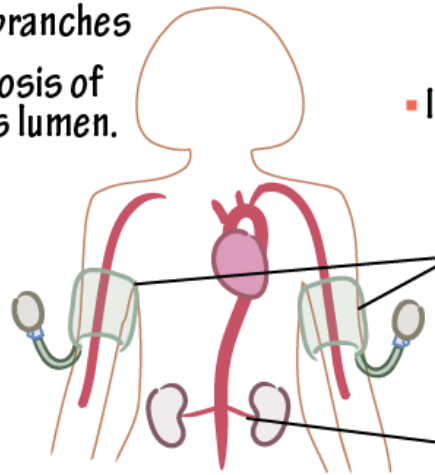
(aka, Pulseless disease)

Granulomatous Disease

✓Aorta and its large branches

- Thickening and fibrosis of vessel wall narrows lumen.



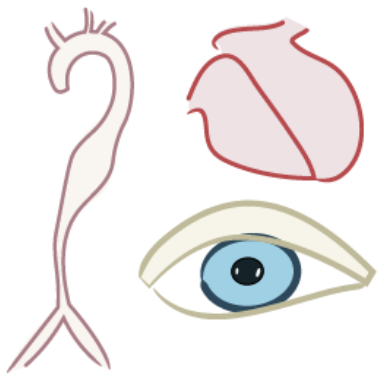


- Ischemia produces:
  - "Pulseless disease" Weak/absent pulse.
  - Different pressures in upper extremities.
  - Claudication in limbs, chest pain.
  - Poss. hypertension (renal art. stenosis)

- Nonspecific symtpoms assoc. with inflammation:
  - Weakness, fatigue, fever, weight loss, arthralgia.

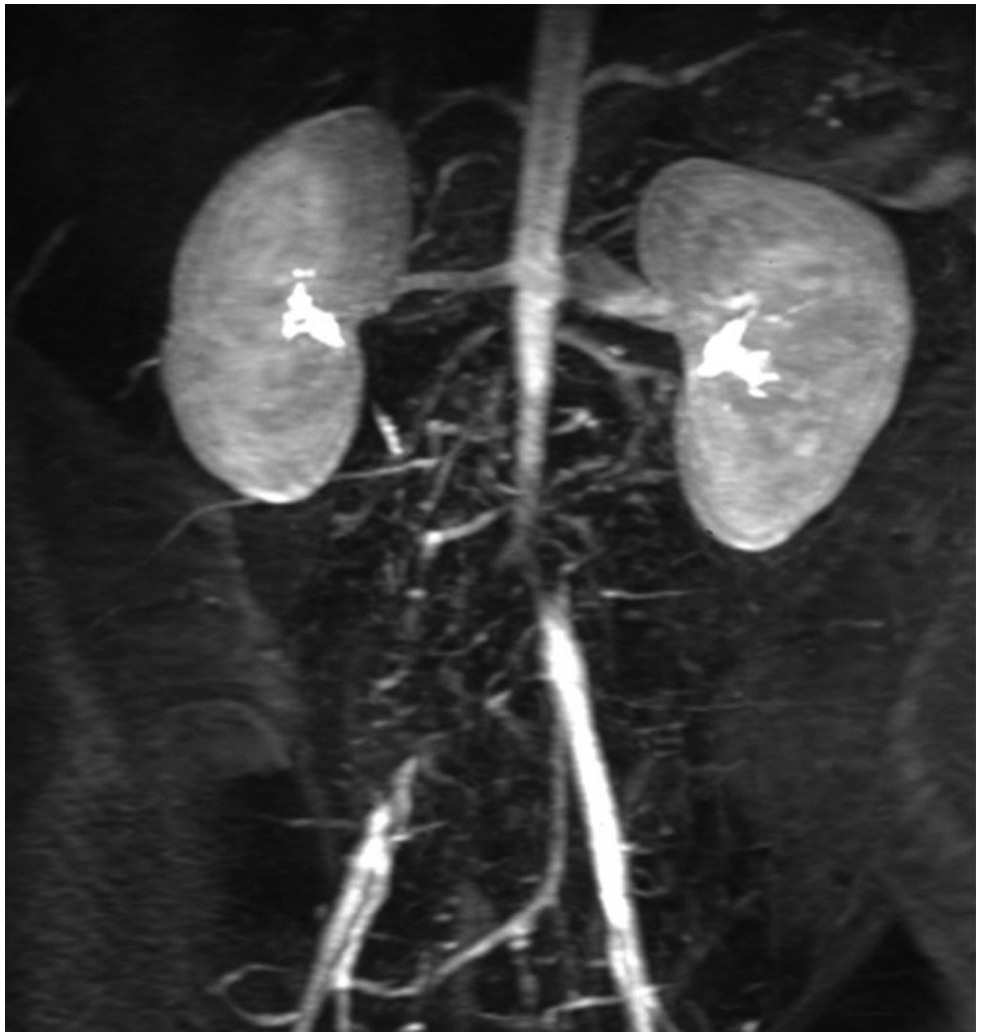
✓Poss. complications:

- Aneurysm, aortic regurgitation, retinopathy.



✓Most common in women < 40 y. o.; esp. Asian ancestry.

https://drawittoknowit.com/course/pathology/glossary/pathophysiologic-disorder/takayasu-arteritis



Restrepo C S et al. Radiographics 2011;31:435-451

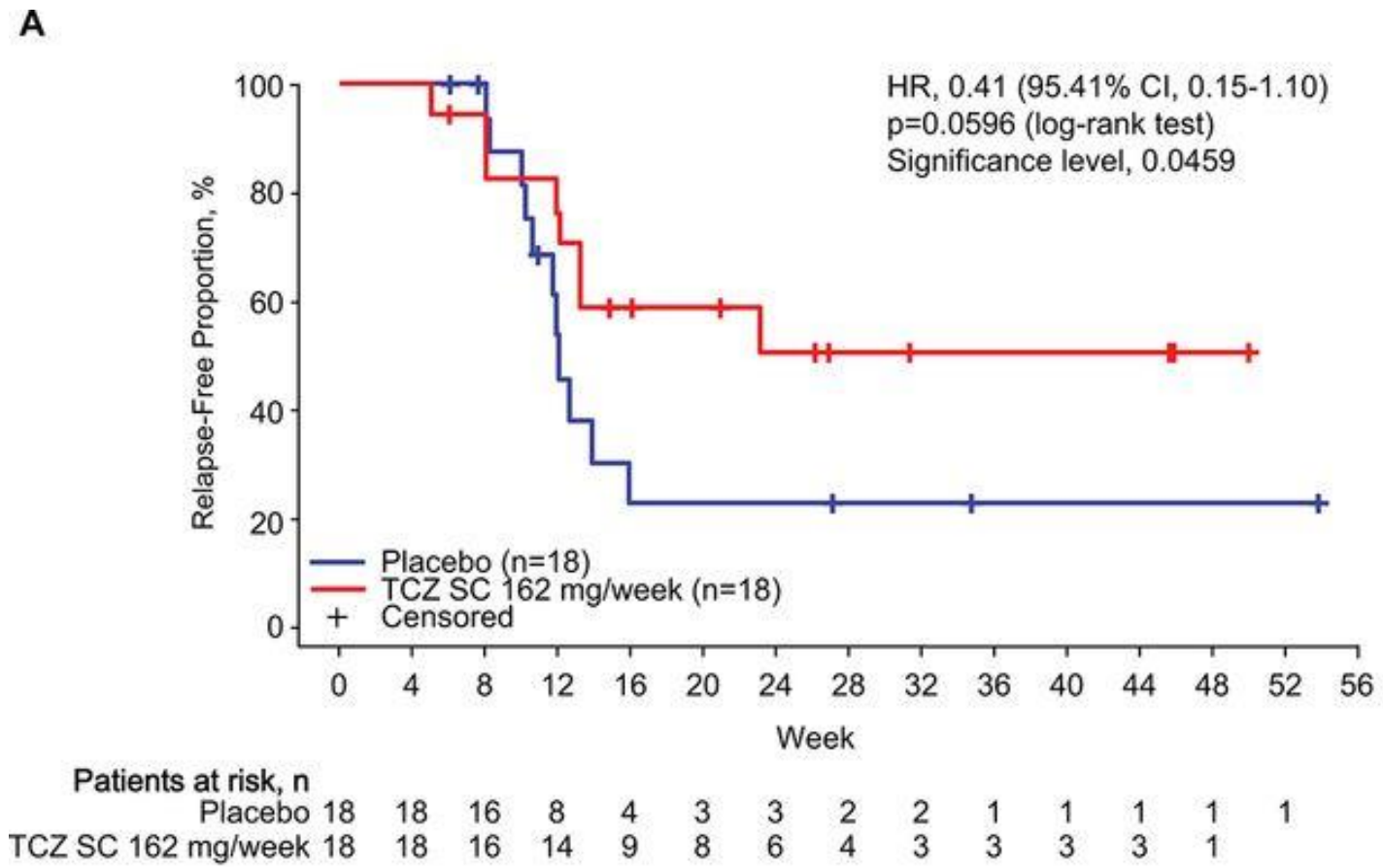
RadioGraphics

Distinguishing features of giant cell versus Takayasu arteritis

Finding	Giant cell arteritis	Takayasu arteritis
Female-to-male ratio	3:2	7:1
Age at onset	>50 years	<40 years
Ethnic ancestry	European	Asian
Histopathology	Granulom. inflam.	Granulom. inflam.
Primary vessels involved	External carotid artery branches	Aorta and branches
Renovascular hypertension	Rare	Common
HLA association	HLA-DR4	HLA-Bw52
Course	Self-limited	Chronic
Response to corticosteroids	Excellent	Excellent
Surgical intervention needed	Rare	Common

Michel, BA, Arend, WP, Hunder, GG.
Clinical differentiation between giant cell arteritis and Takayasu's arteritis.
J Rheumatol 1996; 23:106.

Tocilizumab in Takayasu arteriitis



Nakaoka et al ARD 2018

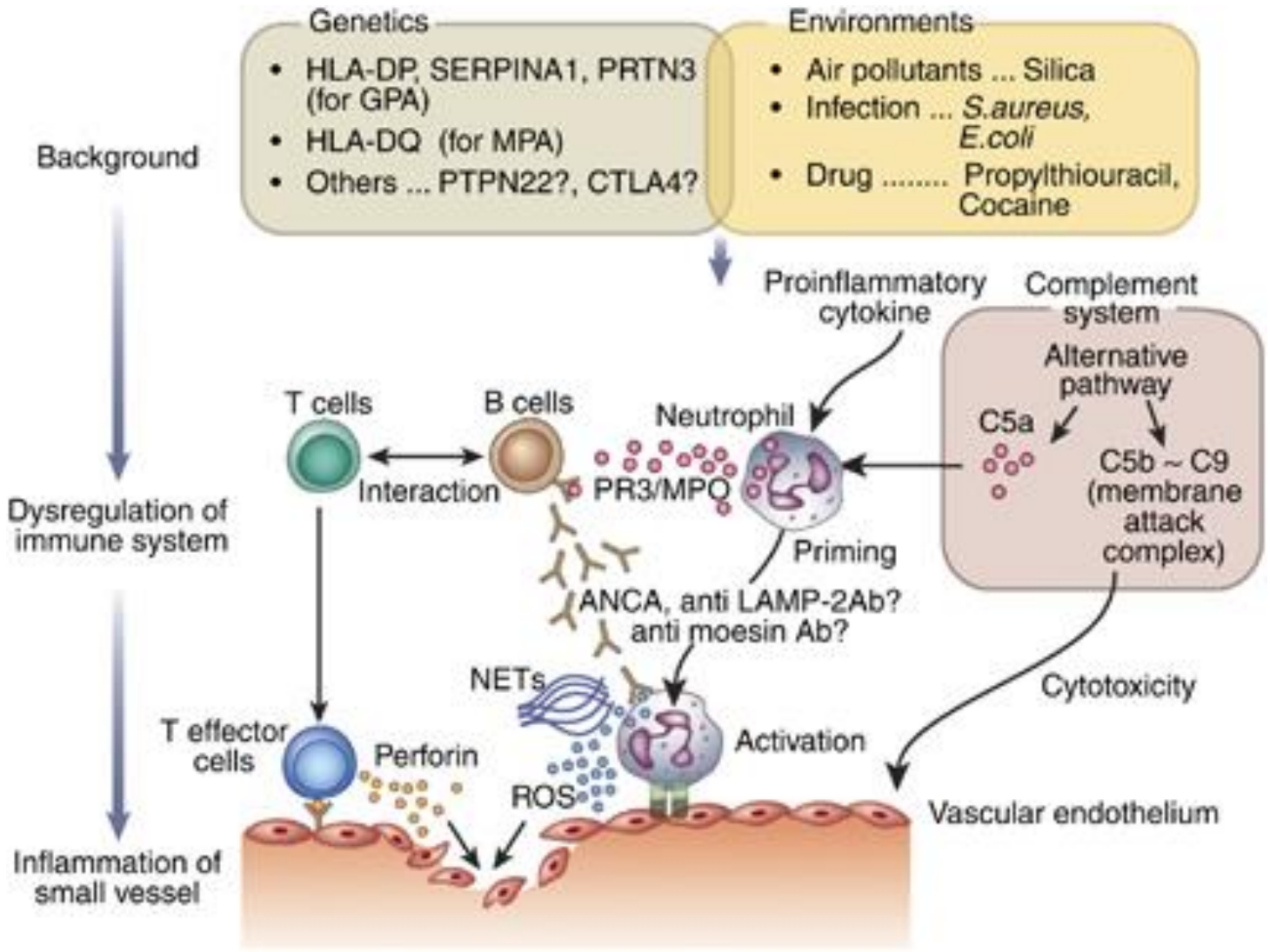
Eular recommendations:

Statement	Level of evidence	Median final vote
We recommend a thorough clinical and imaging assessment of the arterial tree when a diagnosis of Takayasu arteritis is suspected	3	C
A temporal artery biopsy should be performed whenever a diagnosis of giant cell arteritis is suspected, but this should not delay the treatment; a contralateral biopsy is not routinely indicated	3	C
We recommend early initiation of high-dose glucocorticoid therapy for induction of remission in large vessel vasculitis	3	C
We recommend that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjunctive therapy	1A for GCA	B for GCA
	3 for TAK	C for TAK
Monitoring of therapy for large vessel vasculitis should be clinical and supported by measurement of inflammatory markers	3	C
We recommend the use of low-dose aspirin in all patients with giant cell arteritis	3	C
Reconstructive surgery for Takayasu arteritis should be performed in the quiescent phase of disease and should be undertaken at expert centres	3	C

Anca-assoziierte Systemvasculitiden

- Granulomatose mit Polyangiitis, GPA (früher: Morbus Wegener)
- Mikroskopische Panarteritis nodosa (microPAN)
- Eosinophile Garnulomatose mit Polyangiitis, EGPA (früher: Churg-Strauss-Vasculitis)

Pathogenesis: current concepts



Furuta et al. Kidney Int 2013

J. clin. Path. (1963), **16,** 215

Wegener's granulomatosis: report of a patient surviving four and a half years

D. W. EVANS AND J. B. W. HALLEY

From the Queen Elizabeth Hospital, Birmingham, and the Department of Pathology, University of Birmingham

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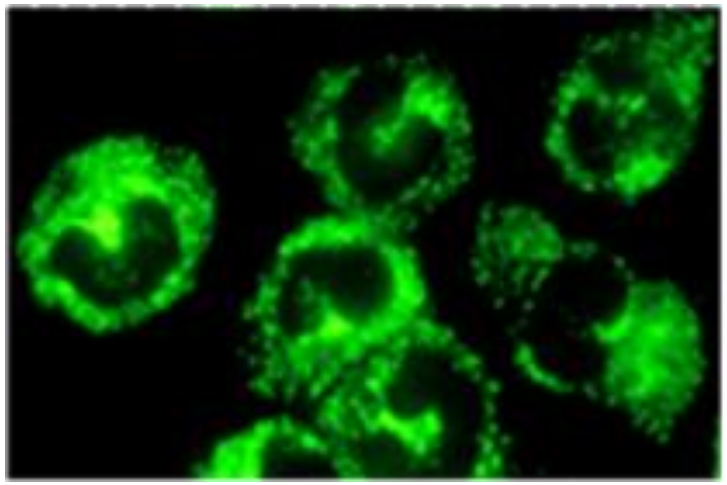
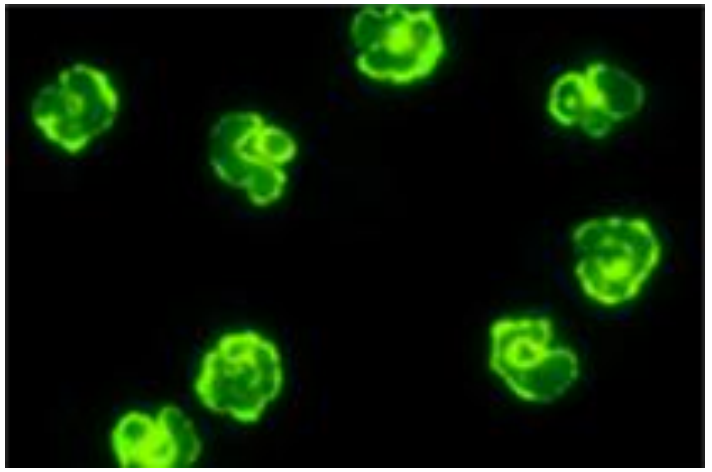
ANCA

- Anti Neutrophile Cytoplasmatische Antikörper
- Cytoplasmatische cANCA gegen PR-3 typisch für Morbus Wegener
- perinucleäre pANCA gegen MPO typisch für mikroskopische PAN, aber auch andere (IBD,…)





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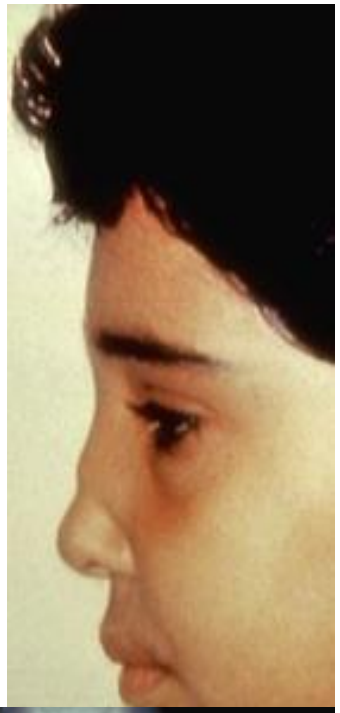
Organmanifestationen AAVs

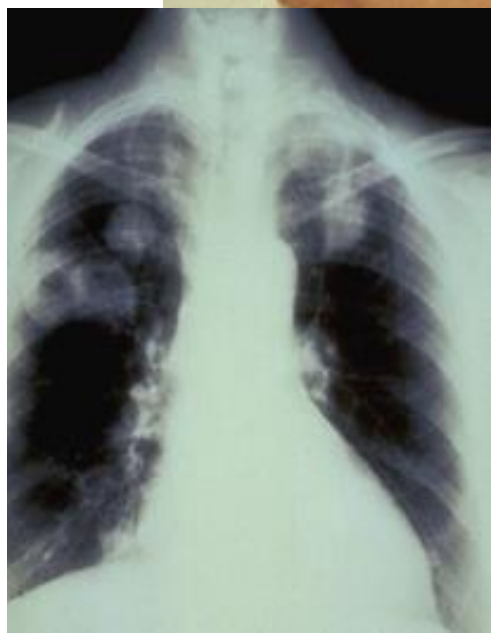
Tab.: Organbeteiligungen bei AAV in Prozent

Organ	GPA (%)	MPA (%)	EGPA (%)
Oberer Respirationstrakt	95	2	48
Unterer Respirationstrakt	65	76	91
Asthma bronchiale	k. A.	k. A.	91
Niere	70	81	22
Herz	12	8	27
Muskuloskelettale Symptome	75	83	38
Haut	25	18	40
ZNS	9	4	5
Peripheres Nervensystem	41	42	55
GI-Trakt	5	5	23
ANCA-Positivität	95	95	31

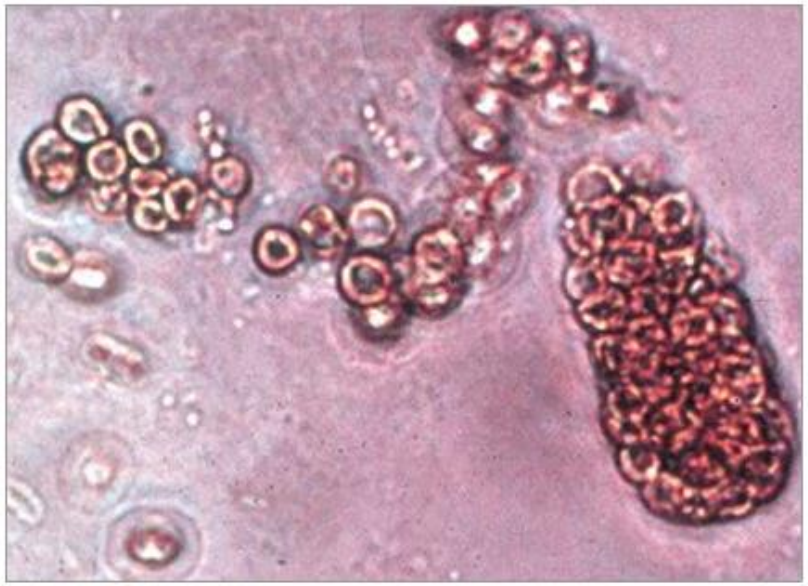
k. A. = keine Angabe

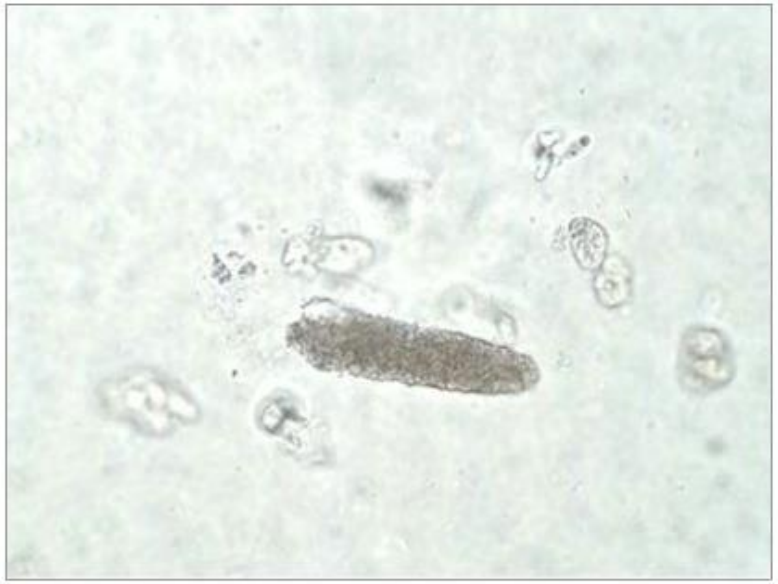
Adaptiert nach: https://dgn.org/leitlinien/ll-030085-zerebrale-vaskulitis-2018

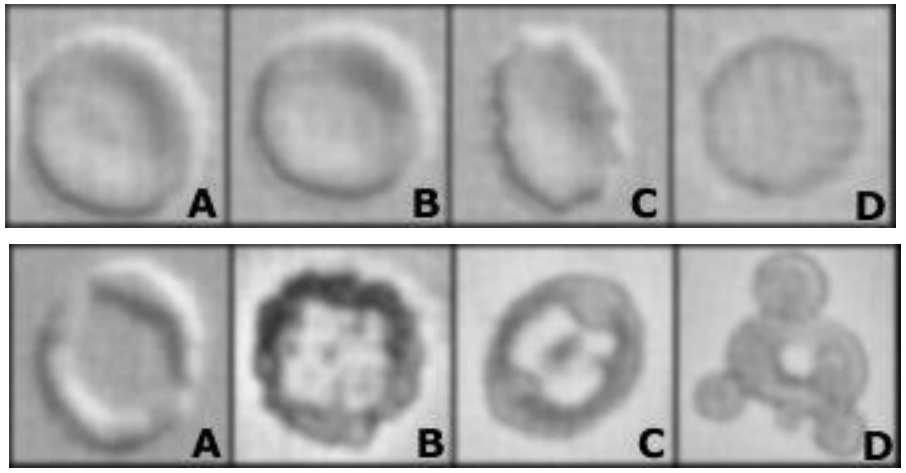




Harnsediment







Neue ACR/Eular Klassifikationskriterien

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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.

Robson et al., ARD 2022

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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

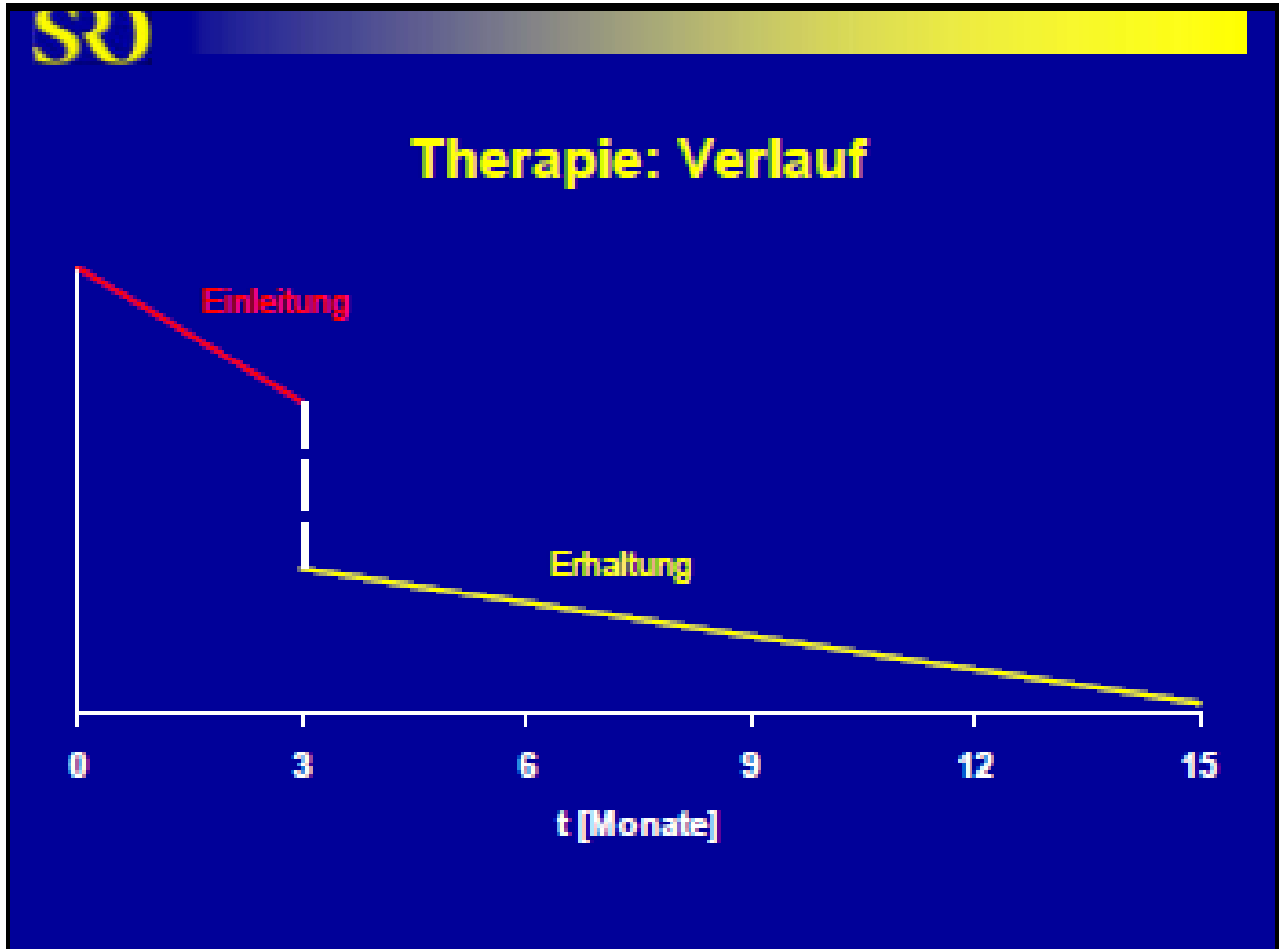
LABORATORY, IMAGING, AND BIOPSY CRITERIA

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

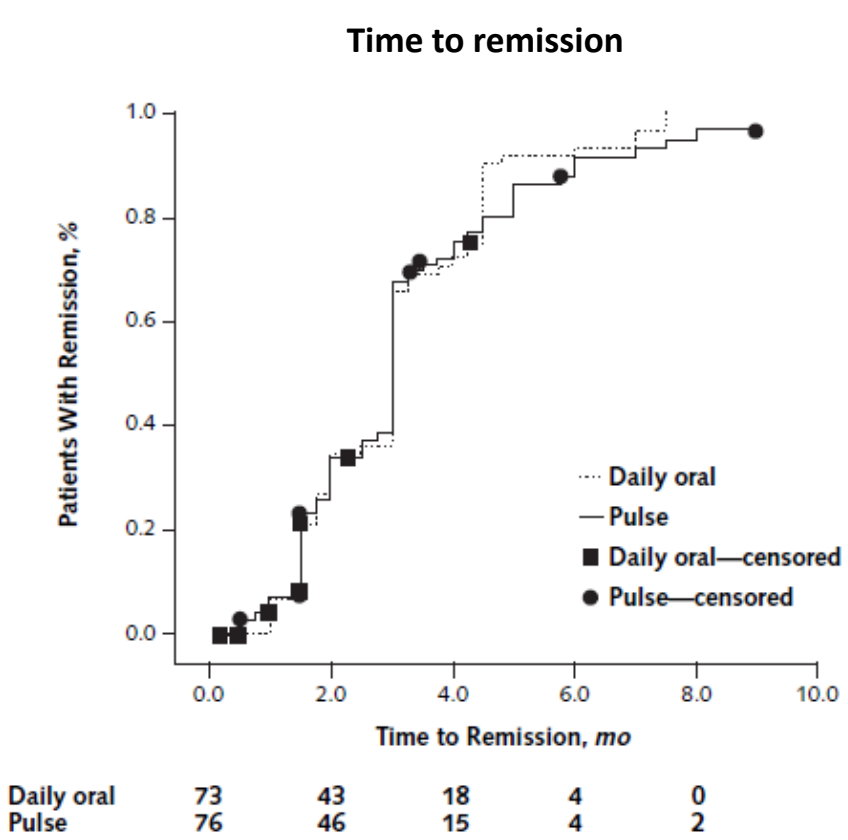
Sum the scores for 6 items, if present. A score of ≥ 5 is needed for classification of MICROSCOPIC POLYANGIITIS.

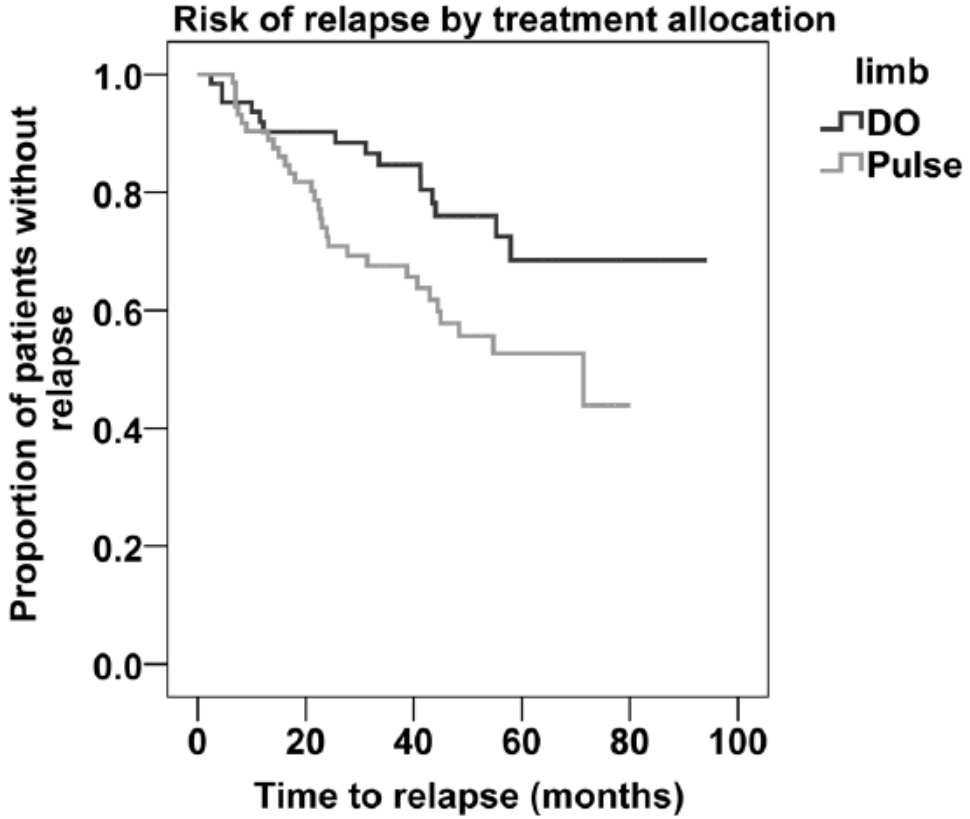
Suppiah et al., ARD 2022

Therapiekonzept Induktionstherapie



Cyclophosphamide for treatment of AAV





De Groot et al AIM 2008

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What causes death in AAV patients?

Table 3 Causes of death within and after the first year of follow-up, respectively

	<1 Year		>1 Year		Total (%)	
Cause of death	**Primary cause**	**Contributing factor**	**Primary cause**	**Contributing factor**	**Primary cause**	**Contributing factor**
Active vasculitis	11 (18.6)	17 (28.8)	6 (8.1)	7 (9.5)	17 (12.8)	24 (18.0)
Pulmonary haemorrhage	6		2		8	
Infection	28 (47.5)	31 (52.5)	15 (20.3)	23 (31.1)	43 (32.3)	54 (40.6)
Pneumonia	15		8		23	
Sepsis	8		7		15	
CMV	2				2	
PCP	3				2	
Cardiovascular	9 (15.3)	11 (18.6)	19 (25.7)	21 (28.4)	28 (21.1)	32 (24.1)
Myocardial infarction	2		4		6	
Cerebrovascular accident	2		2		4	
Pulmonary embolus	2				2	
Sudden death	1		3		4	
Malignancy	0 (0)		16 (21.6)	18 (24.3)	16 (12.0)	18 (13.5)
Solid organ			12		12	
Haematological			4		4	
Miscellaneous	6 (10.2)		9 (12.2)		15 (11.3)	
Pulmonary fibrosis	3		3		6	
Unknown	5 (8.5)		9 (12.2)		14 (10.5)	
Total	59		74		133	

Primary cause: Number of patients where specific factor was main factor of death.
Contributing factor: All patients where specific cause contributed to death (including primary cause).
CMV, cytomegalovirus infection; PCP, *Pneumocystis jiroveci* pneumonia.

Flossmann ARD 2011

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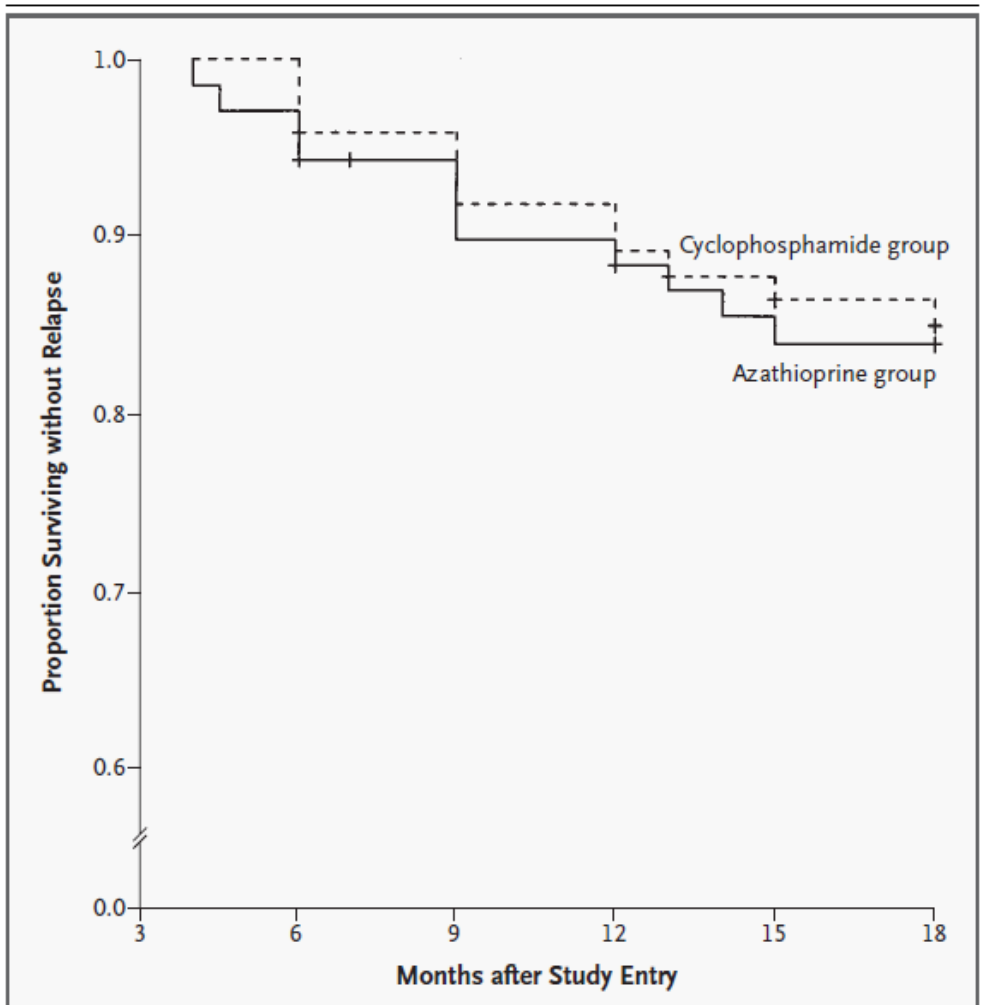
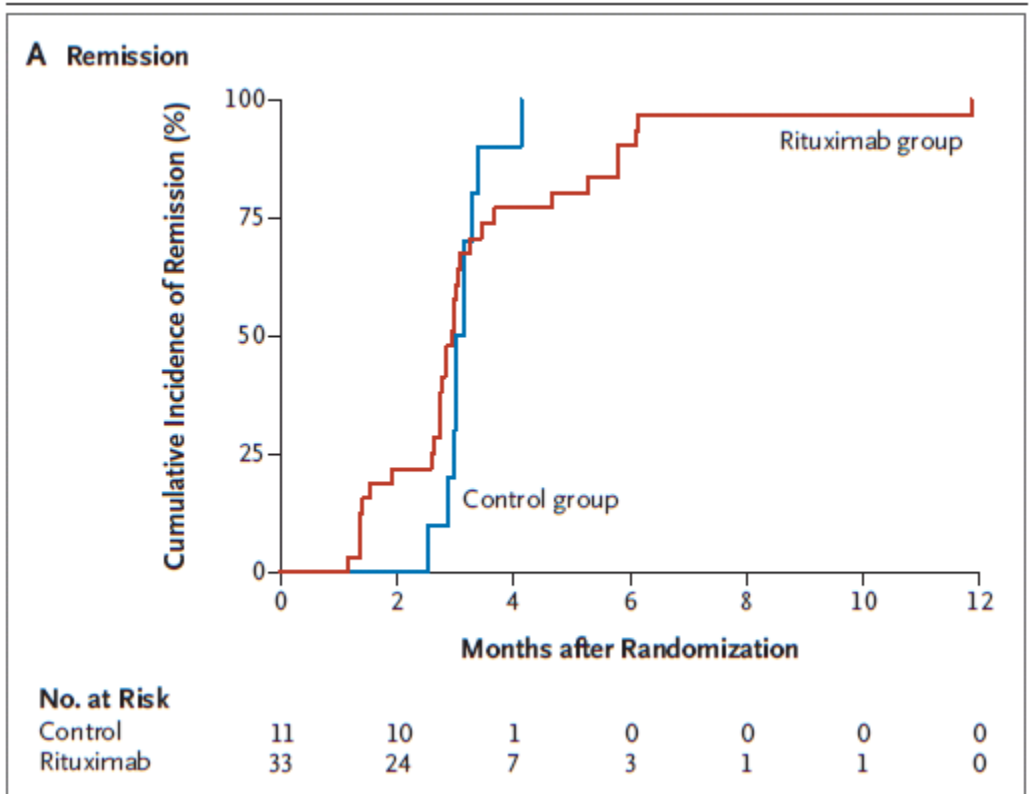
Maintenance mit weniger toxischen Medikamenten



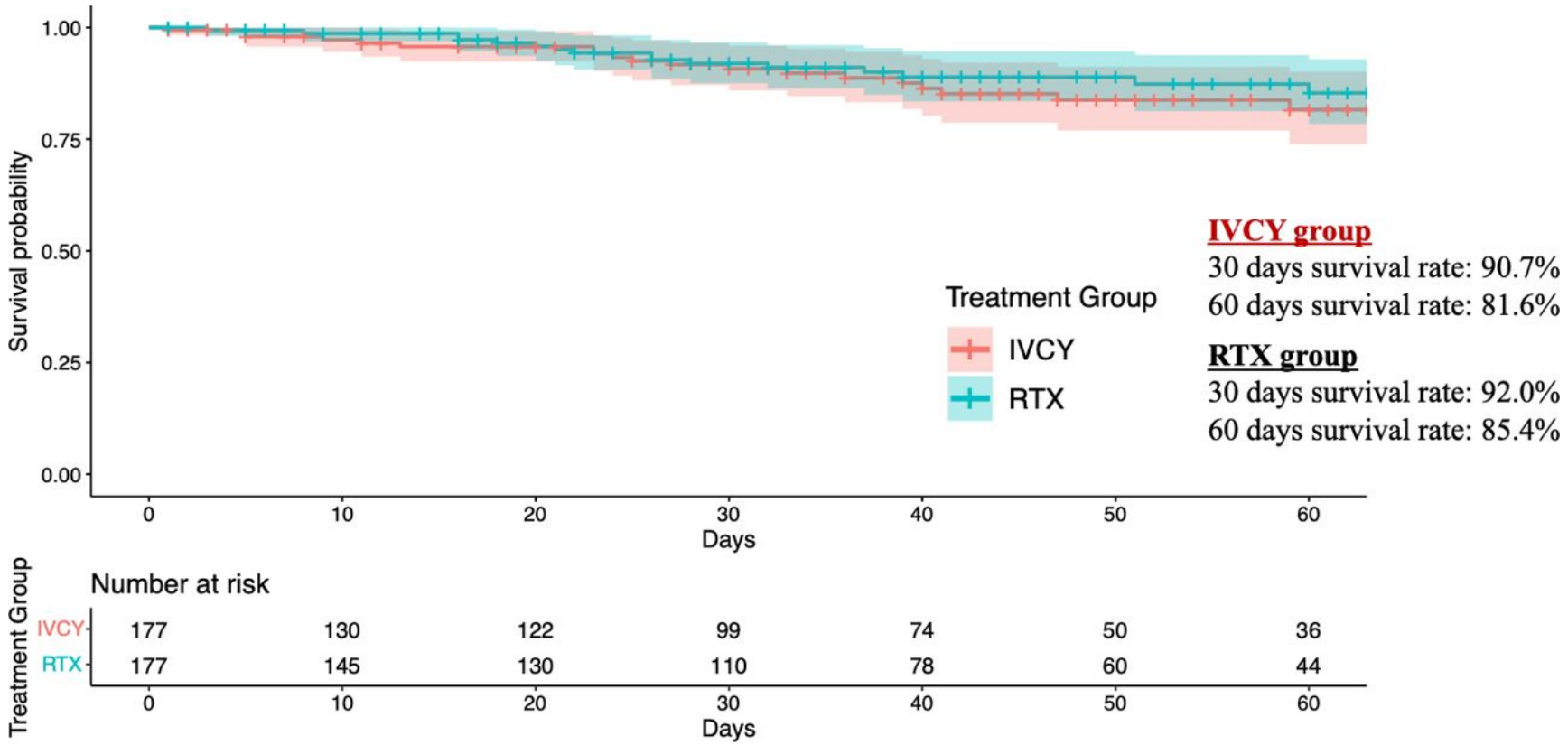
Jayne NEJM 2003

B Zell Depletion mit Rituximab als Alternative zu Cyc



Jones et al. NEJM 2010

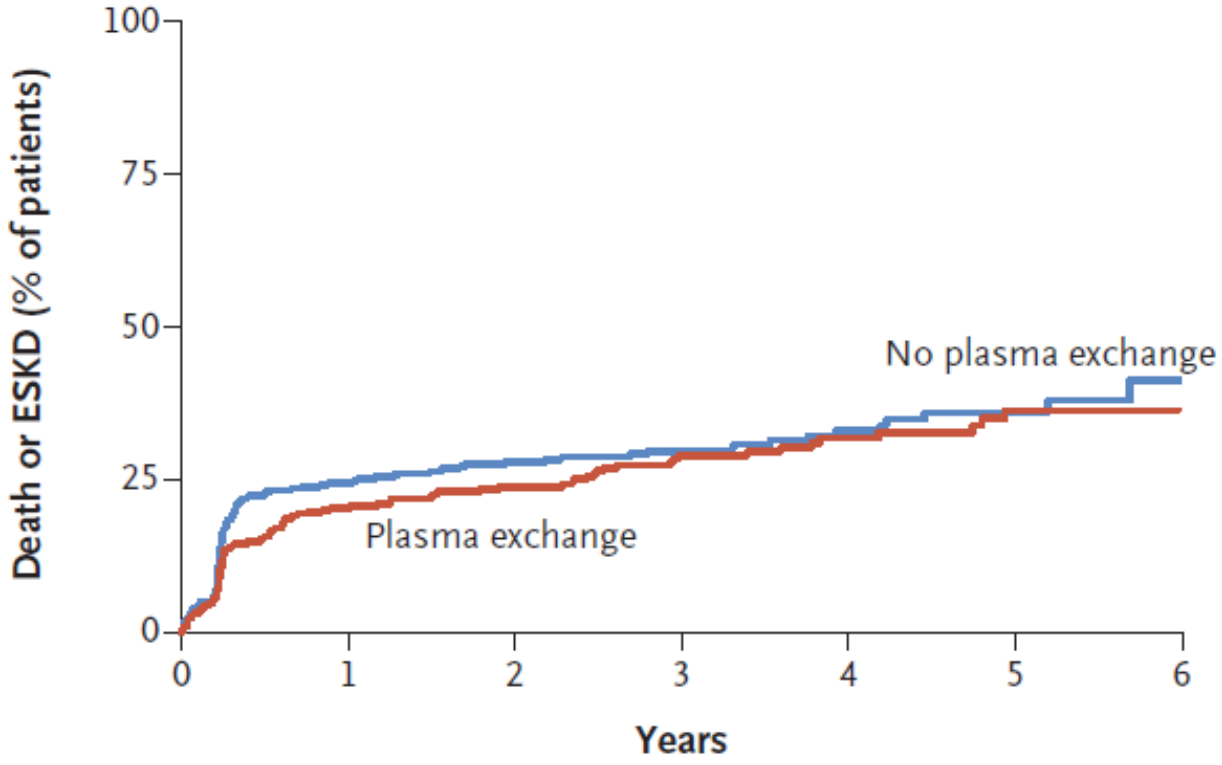
Short-term effectiveness and safety of rituximab versus cyclophosphamide for life-threatening ANCA-associated vasculitis



Ishikava et al., ARD 2023

Plasma exchange? No.

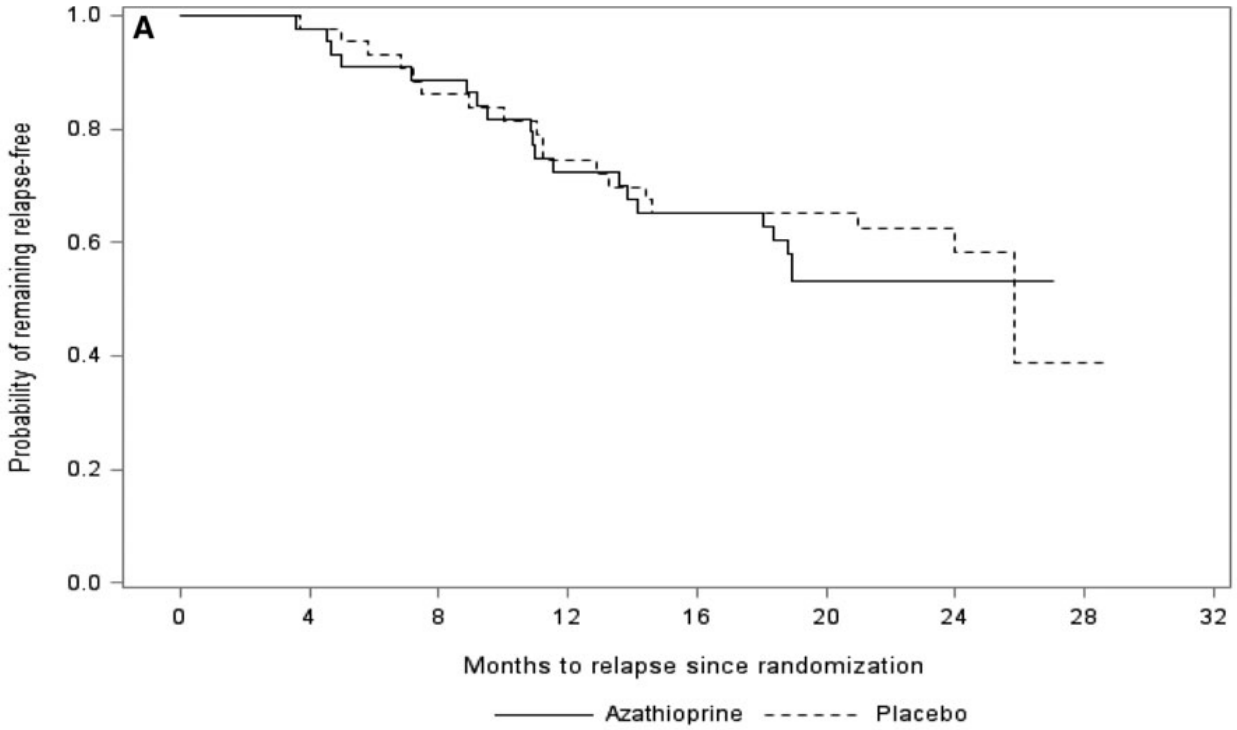
A Primary Outcome According to Plasma Exchange

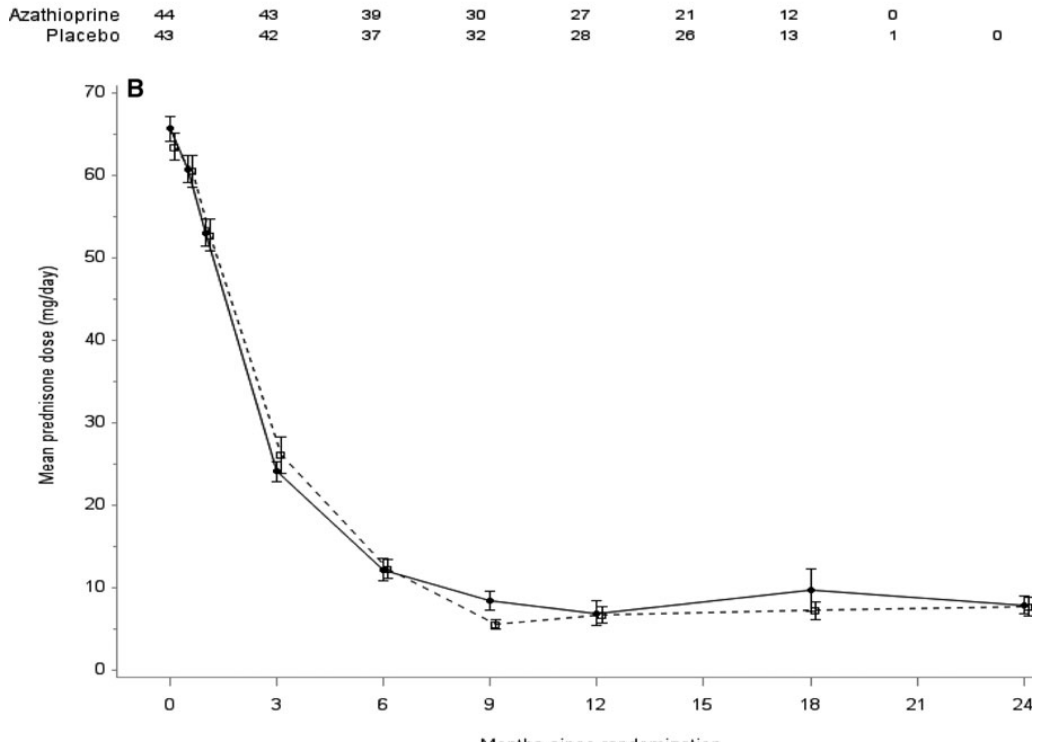


No. at Risk							
No plasma exchange	352	244	183	136	82	44	10
Plasma exchange	352	252	186	135	82	43	10

Walsh et al. NEJM 2020

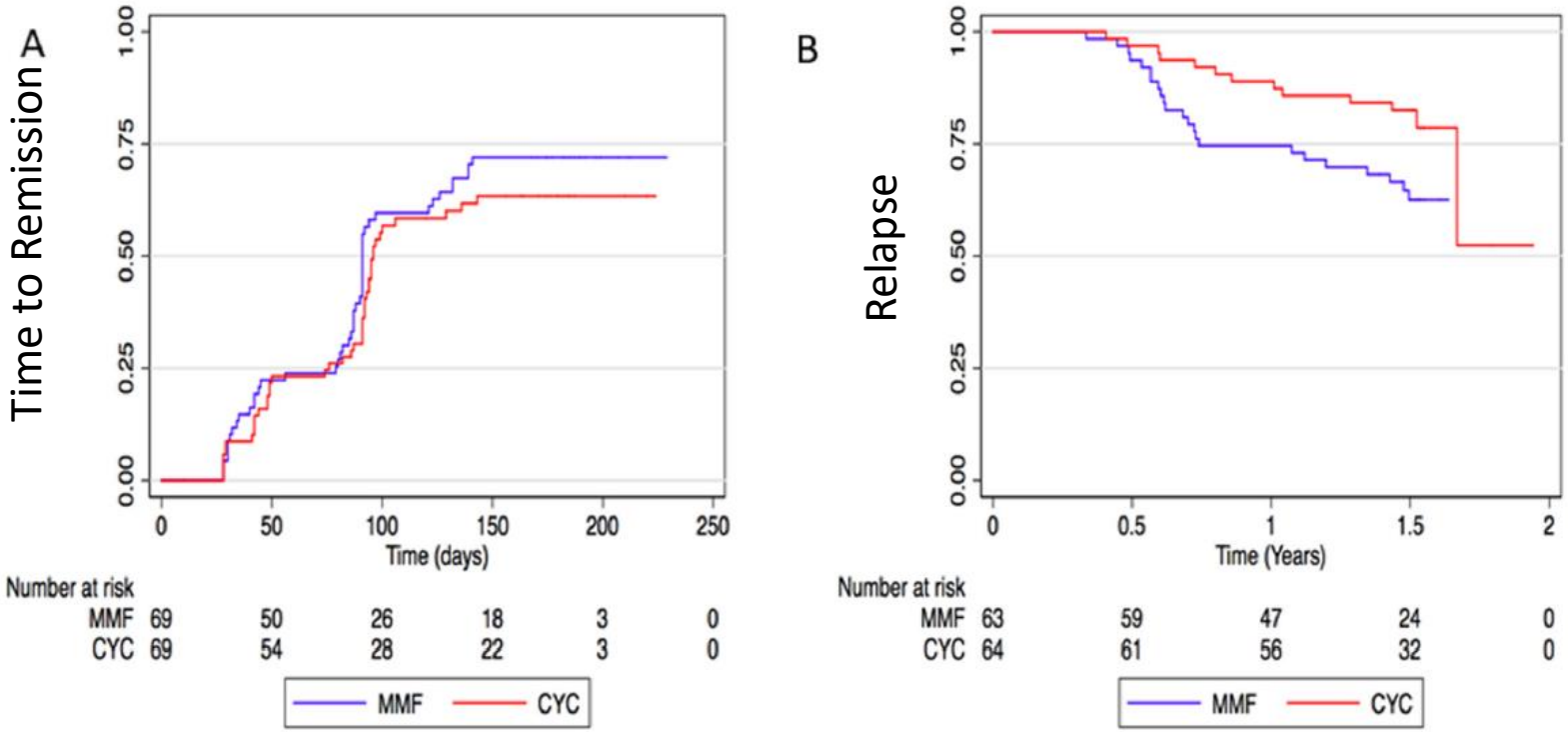
Azathioprin is not suitable for remission induction





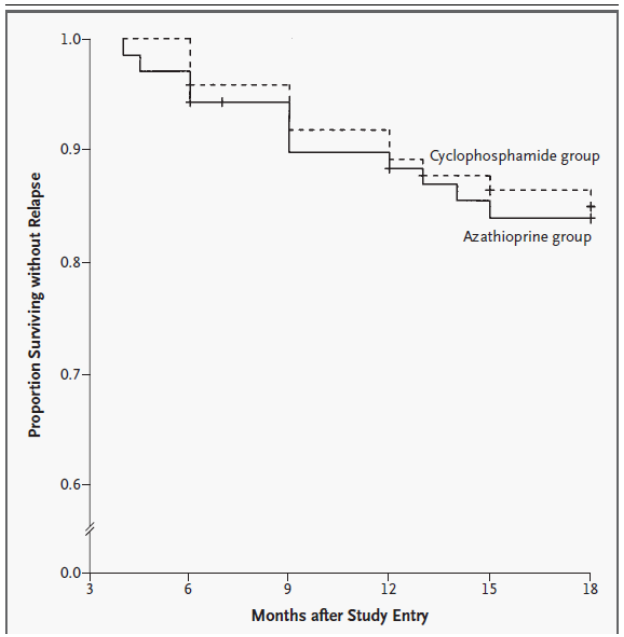
Puechal et al. A&R 2017

MMF is!

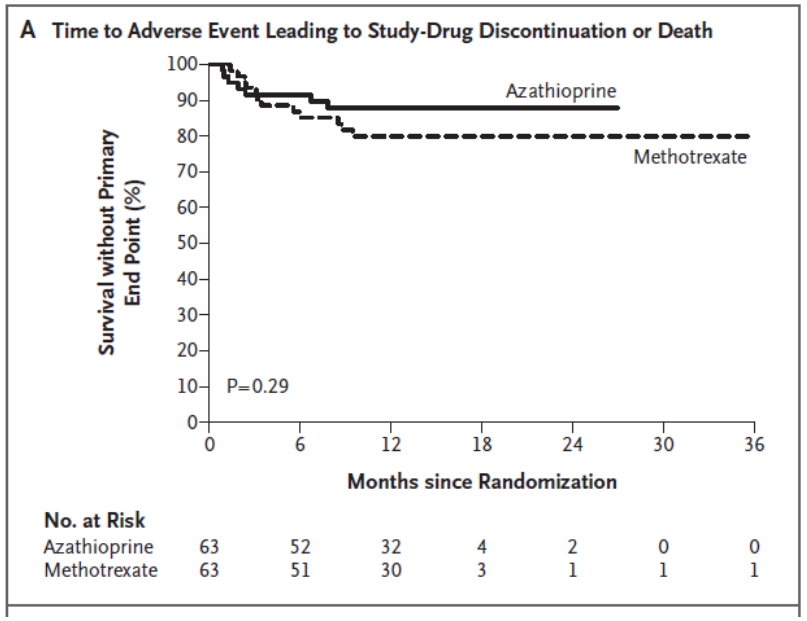


Jones et al. ARD 2019

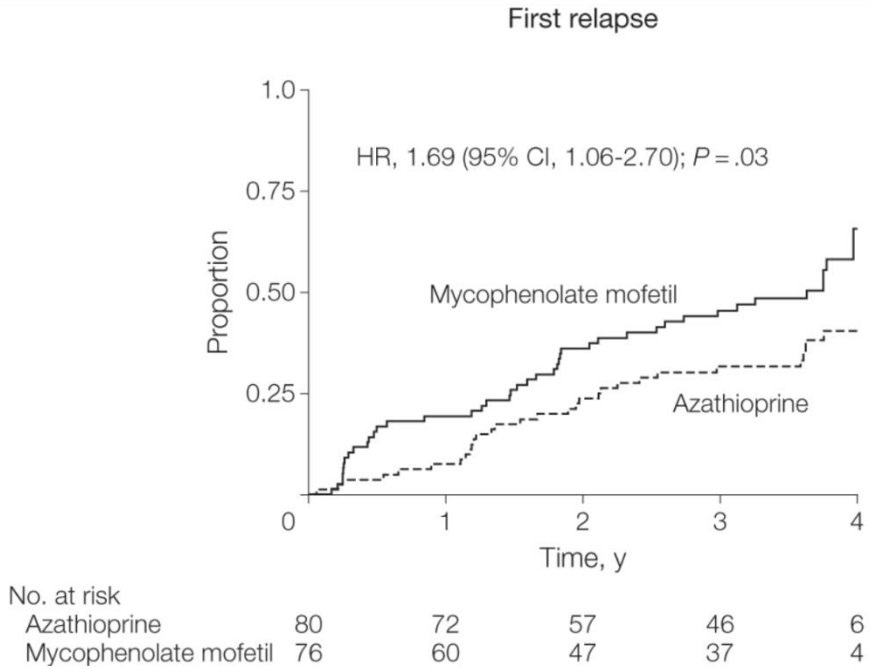
Maintenance therapy: AZA, MTX, (MMF)



Jayne NEJM 2003

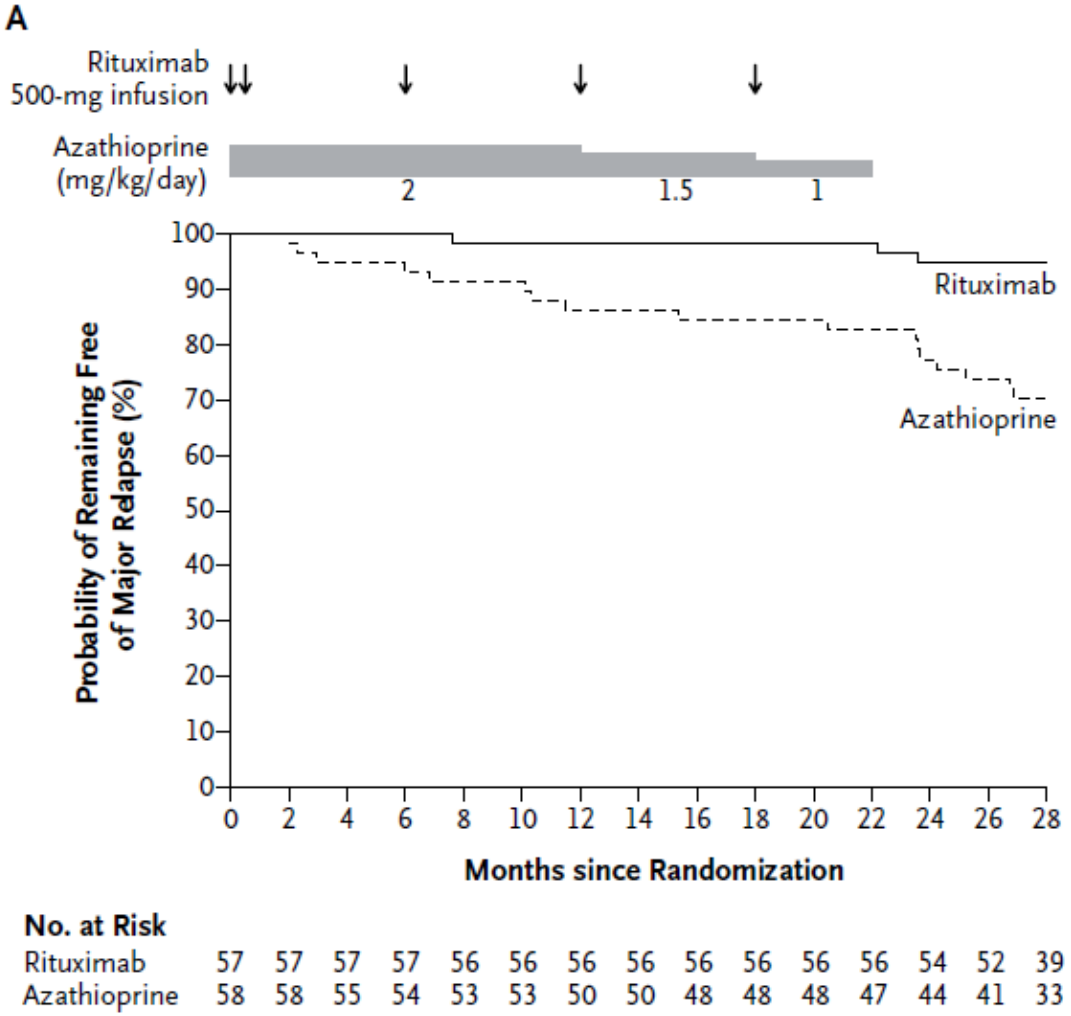


Pagnoux et al. NEJM 2008

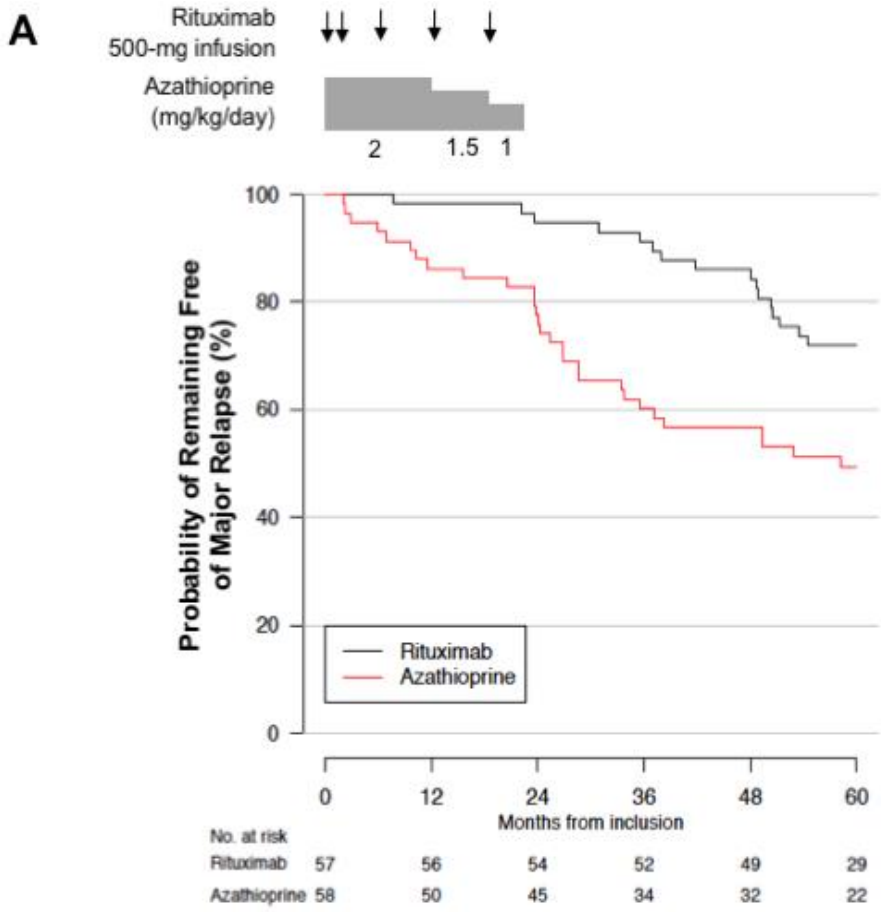


JAMA. 2010;304(21):2381-2388.
doi:10.1001/jama.2010.1658

RTX is superior to Aza in remission maintenance

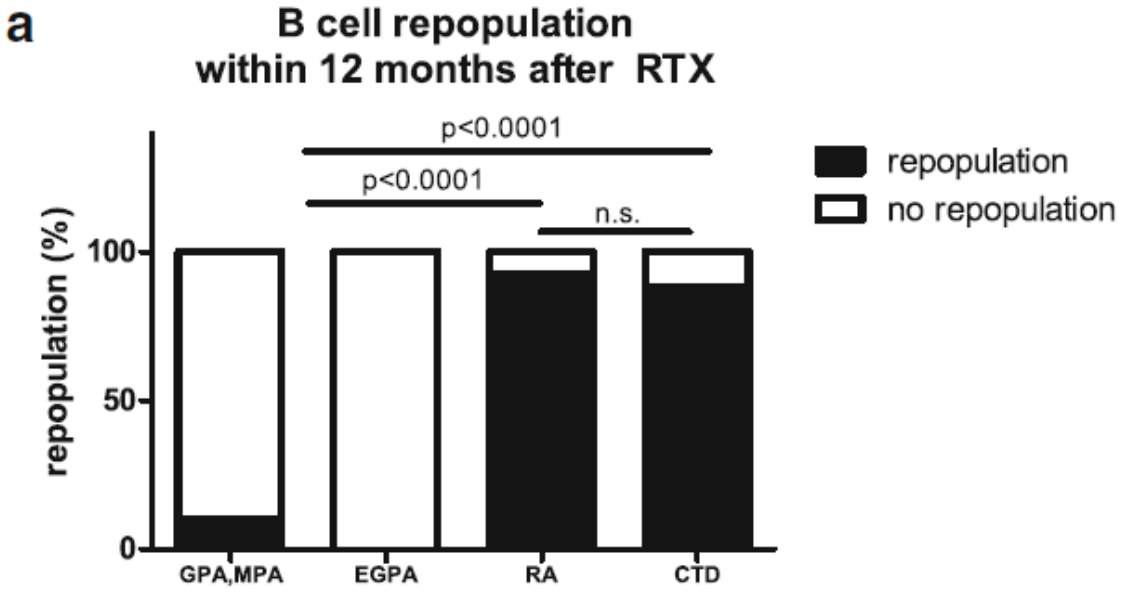


Guillevin et al. NEJM 2014

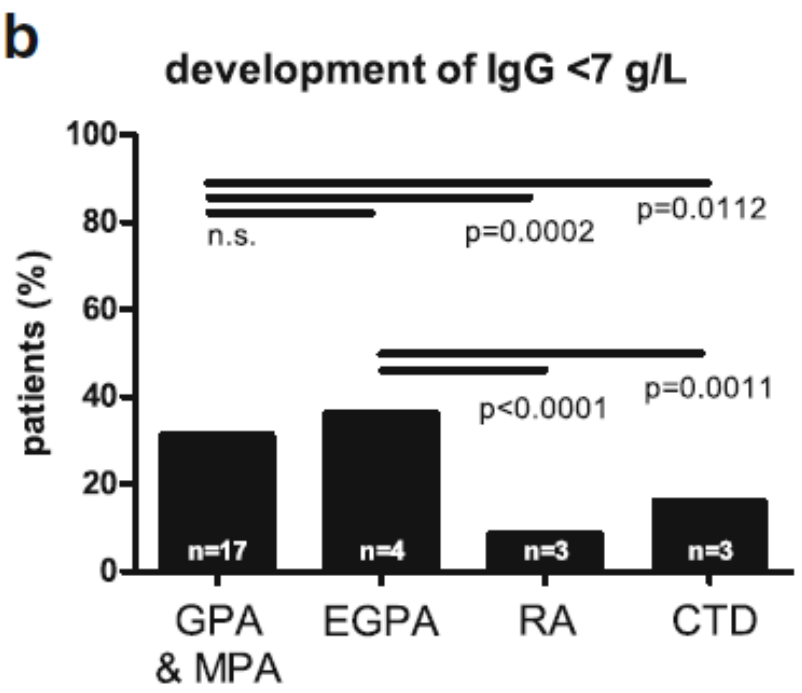


Terrier et al. ARD 2018

B cell depletion differs between diseases!



repopulation	4	0	25	15
no repopulation	39	10	2	2

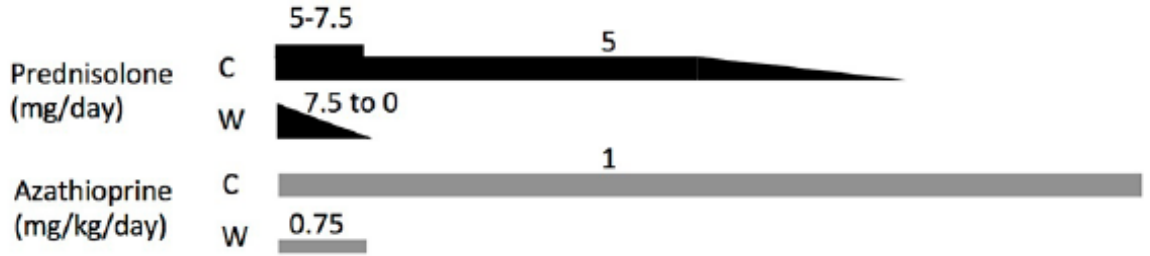


Thiel J., Arthritis Res. Ther. 2017

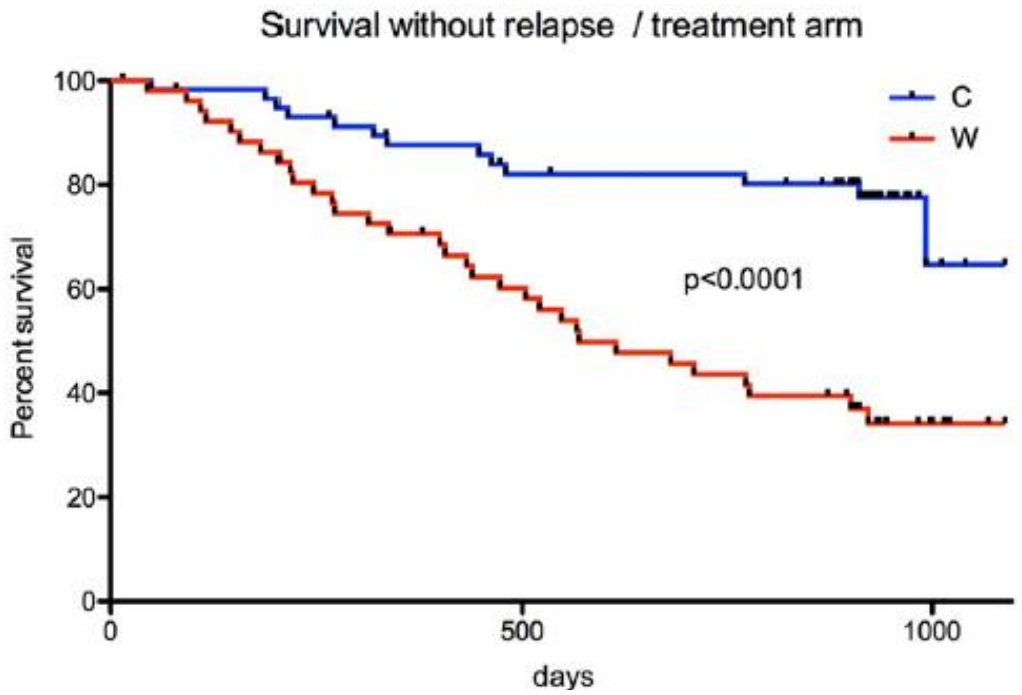
MEDIZINISCHE UNIVERSITÄT WIEN

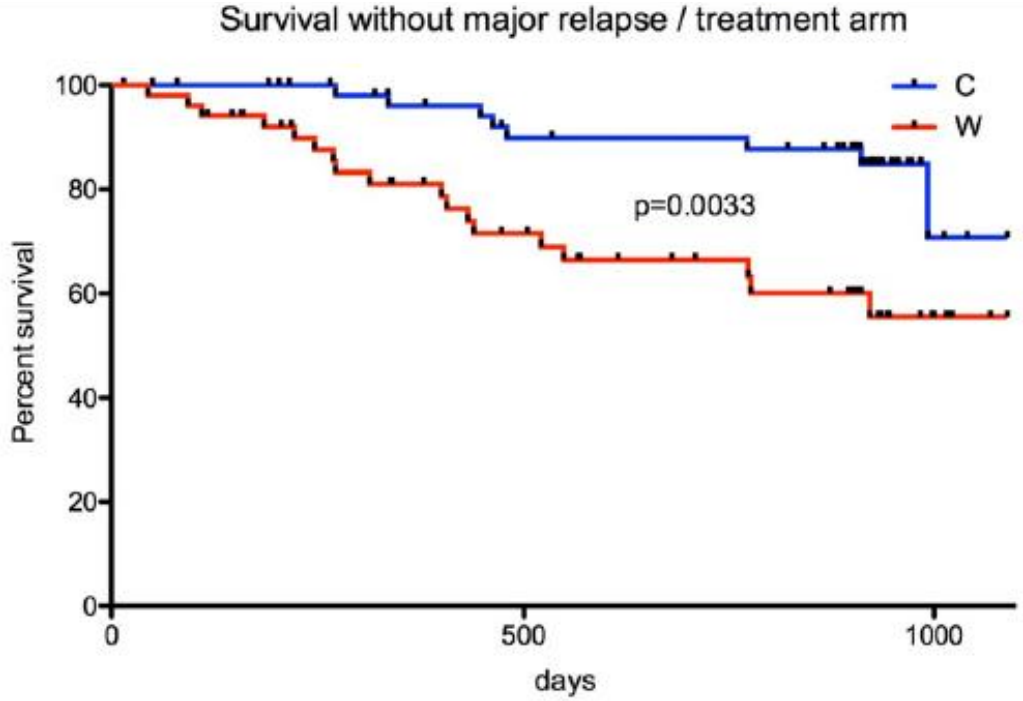
Maintenance Therapy: How long?

Inclusion: 18-24 months after diagnosis and stable remission after induction with Cyclophosphamide and maintenance on Aza

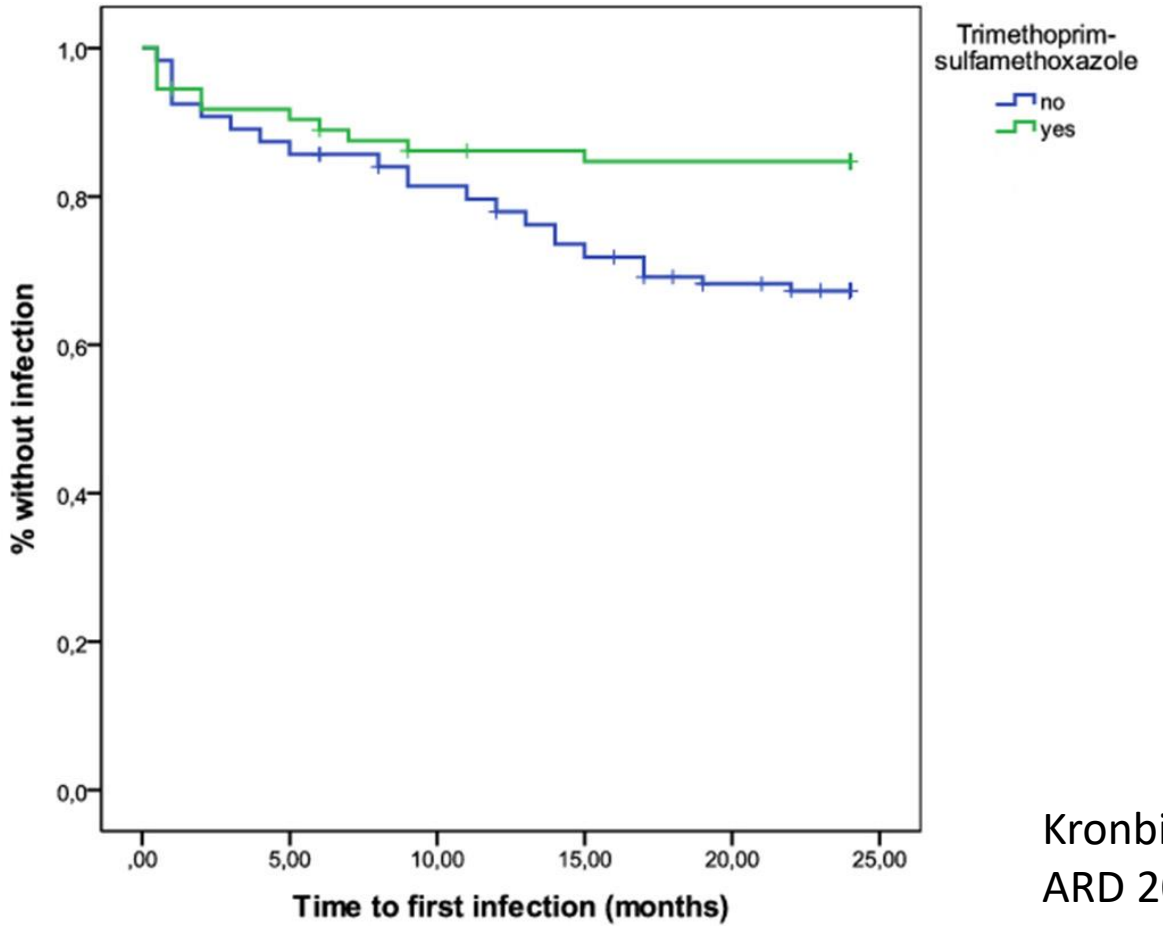


Karras et al., Annals of Rheum. Diseases 2017





Trimethoprim–sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab



Kronbichler et al.
ARD 2018

Glococorticoids, how much?

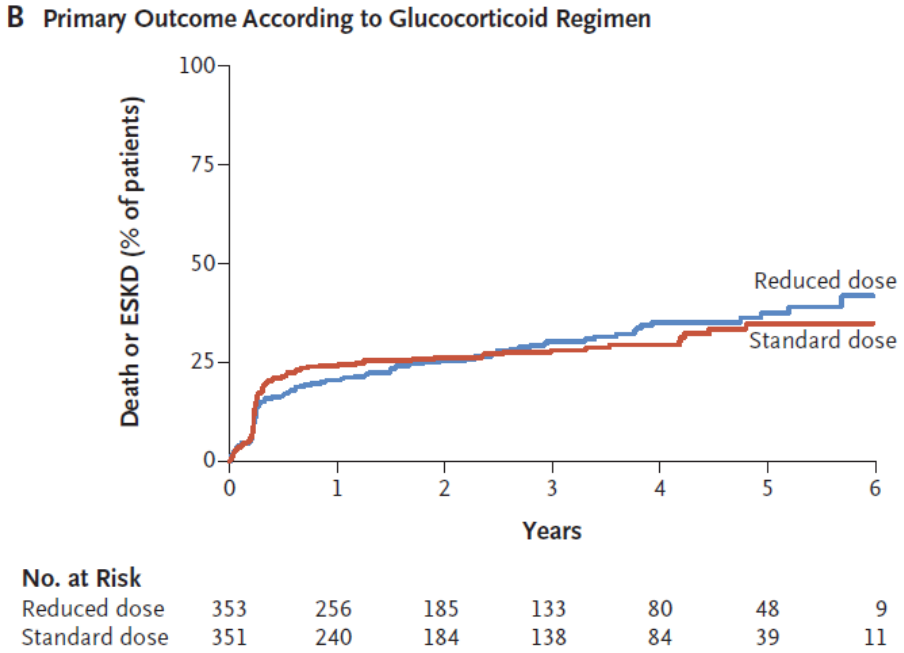
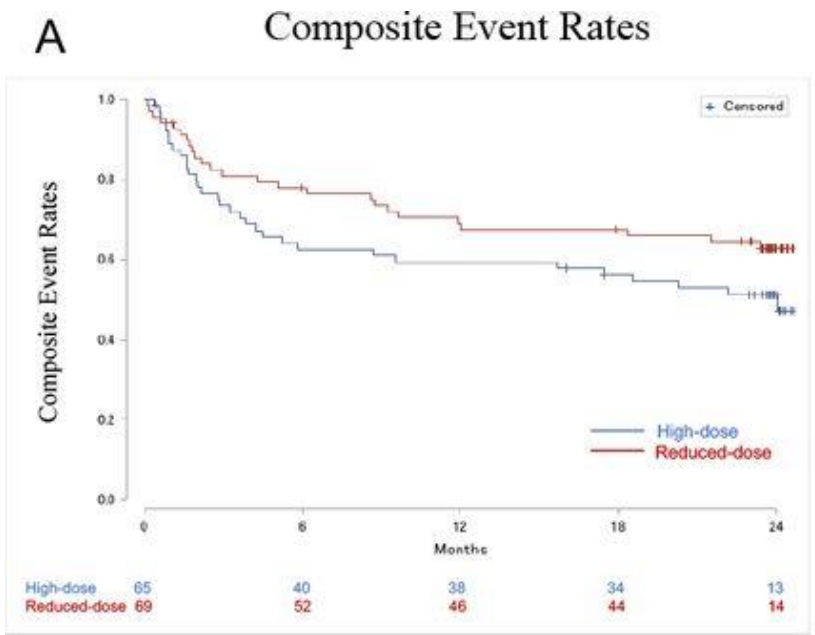


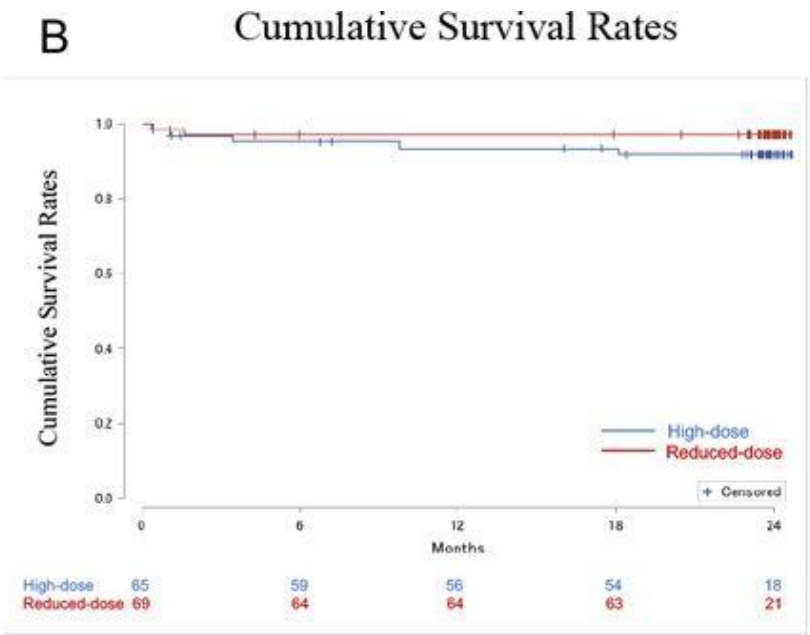
Table 1 Dosing for oral Glucocorticoids in the standard and reduced dose limbs from trial start

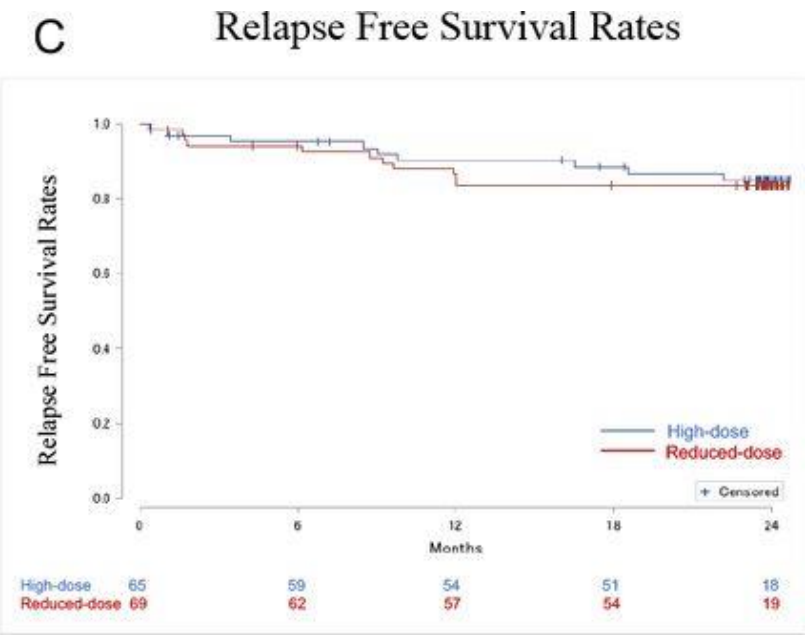
Week	Standard			Reduced Dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	pulse	pulse	pulse	pulse	pulse	pulse
1-2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12	15	20
9-10	20	25	30	10	12	15
11-12	15	20	25	7	10	12
13-14	12	15	20	6	7	10
15-16	10	10	15	5	5	7
17-18	10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

Walsh et al. NEJM 2020

similar results in japanese study

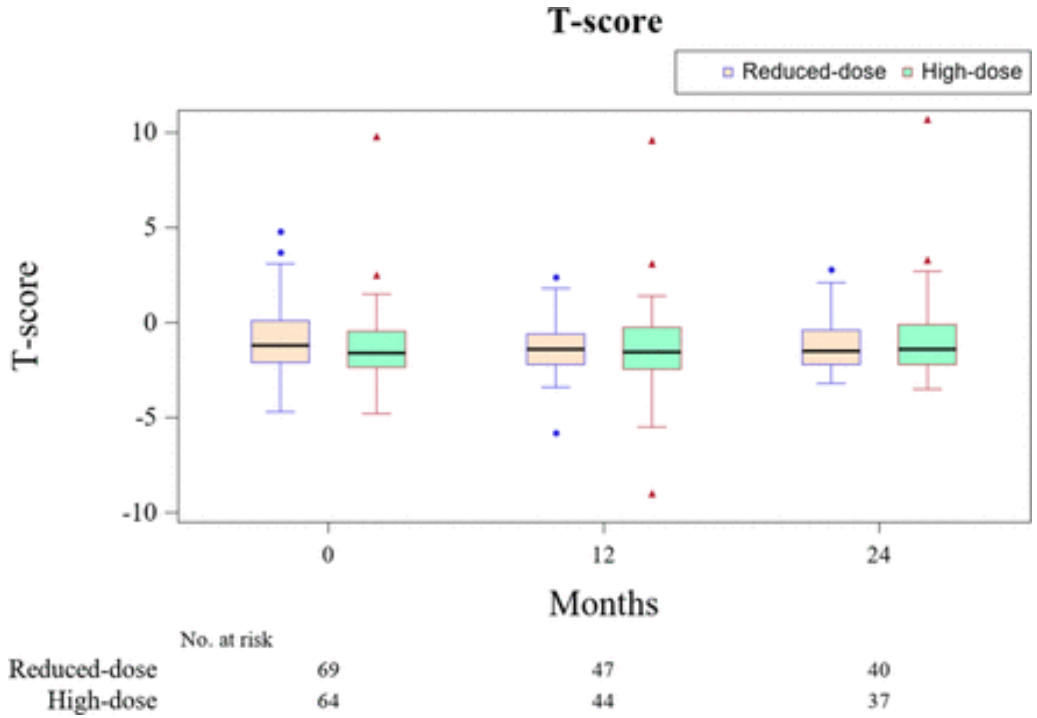






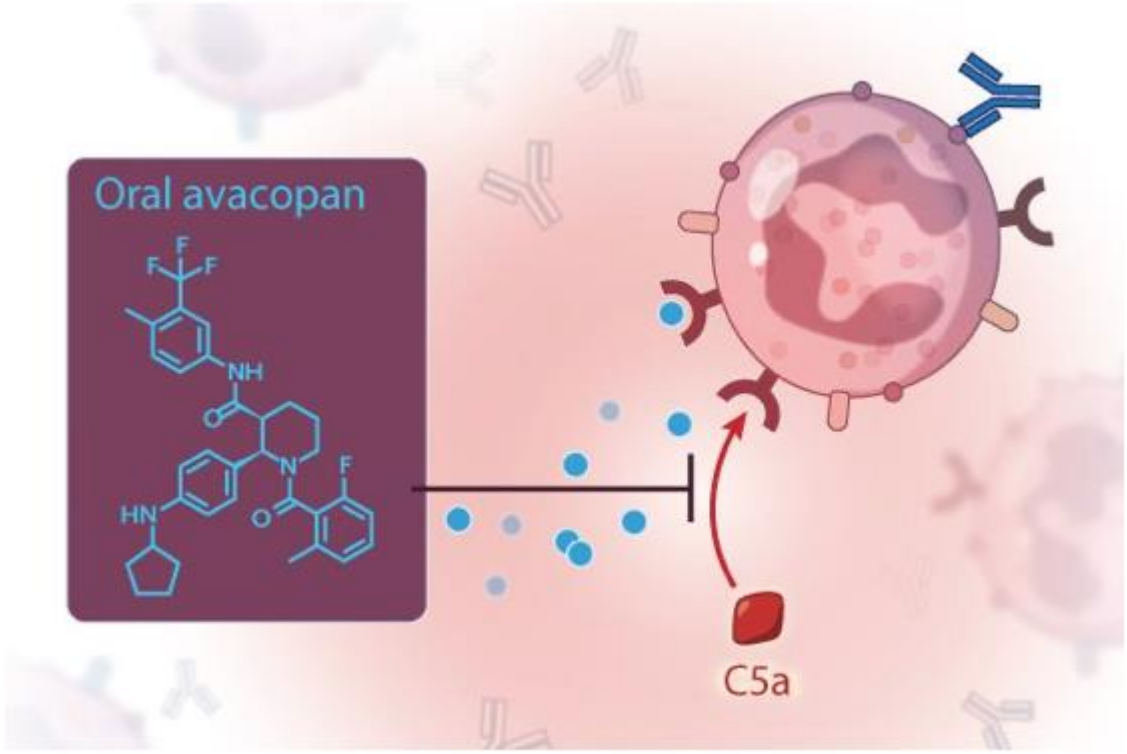
Furuta et al, ARD 2023

T score not different beween the groups, however



Furuta et al, ARD 2023

New avenues: complement inhibition

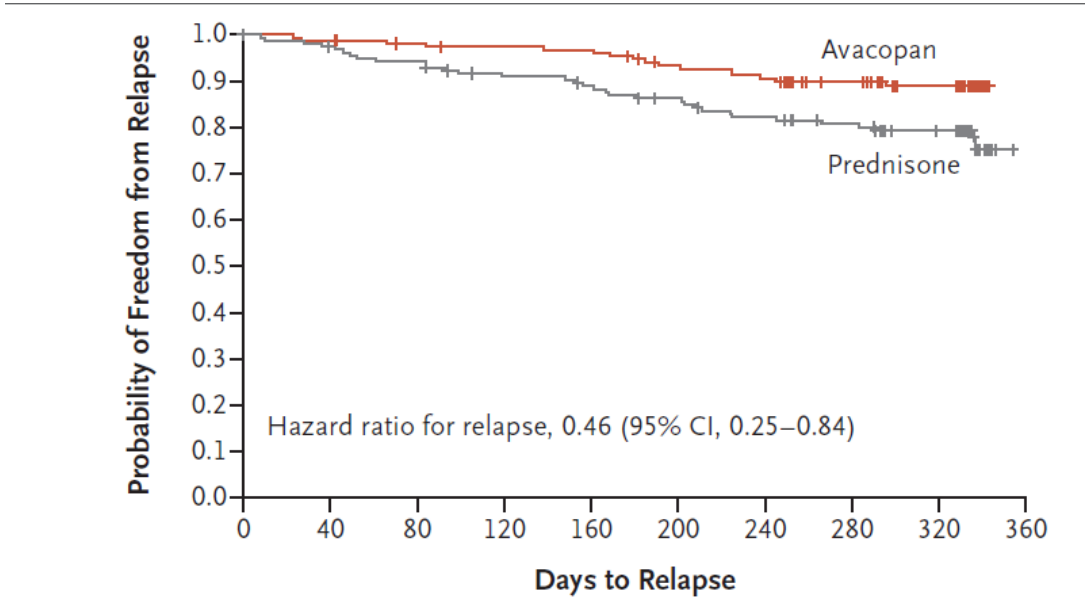


Jayne et al., NEJM 2021

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Avacopan (N=166)	Prednisone (N=1
Age — yr	61.2±14.6	60.5±14.5
Sex — no. (%)		
Male	98 (59.0)	88 (53.7)
Female	68 (41.0)	76 (46.3)
Race — no. (%)†		
White	138 (83.1)	140 (85.4)
Asian	17 (10.2)	15 (9.1)
Black	3 (1.8)	2 (1.2)
Other	8 (4.8)	7 (4.3)
Body-mass index‡	26.7±6.0	26.8±5.2
Median duration of ANCA-associated vasculitis (range) — mo	0.23 (0–362.3)	0.25 (0–212.5)
Vasculitis disease status — no. (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA status — no. (%)		
Antiproteinase 3 positive	72 (43.4)	70 (42.7)
Antimyeloperoxidase positive	94 (56.6)	94 (57.3)
Renal	134 (80.7)	134 (81.7)
General	111 (66.9)	114 (69.5)
Ear, nose, and throat	75 (45.2)	69 (42.1)
Chest	71 (42.8)	71 (43.3)
Nervous system	38 (22.9)	31 (18.9)
Mucous membranes or eyes	26 (15.7)	40 (24.4)
Cutaneous	24 (14.5)	23 (14.0)
Cardiovascular	6 (3.6)	3 (1.8)
Abdominal	4 (2.4)	1 (0.6)

C5a inhibitor can replace prednisone



No. at Risk										
Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

Jayne et al., NEJM 2021

Safety:

Table 3. Safety Results.*

Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event		
No. of patients (%)	164 (98.8)	161 (98.2)
No. of events	1779	2139
Severe adverse event†		
No. of patients (%)	39 (23.5)	41 (25.0)
No. of events	71	94
Life-threatening adverse event		
No. of patients (%)	8 (4.8)	14 (8.5)
No. of events	8	22
Death — no. (%)	2 (1.2)	4 (2.4)
Any serious adverse event‡		
No. of patients (%)	70 (42.2)	74 (45.1)
No. of events	116	166
Any serious event related to vasculitis worsening§		
No. of patients (%)	17 (10.2)	23 (14.0)
No. of events	18	36
Any adverse event potentially related to glucocorticoids as assessed by the investigators — no. (%)	107 (64.5)	131 (79.9)
Any serious adverse event potentially related to prednisone as assessed by the investigators — no. (%)	11 (6.6)	24 (14.6)

Jayne et al., NEJM 2021

Danke für die Aufmerksamkeit