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Disease stratification in giant cell arteritis and polymyalgia rheumatica

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2-2-2024

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Rheumatology and Clinical Immunology

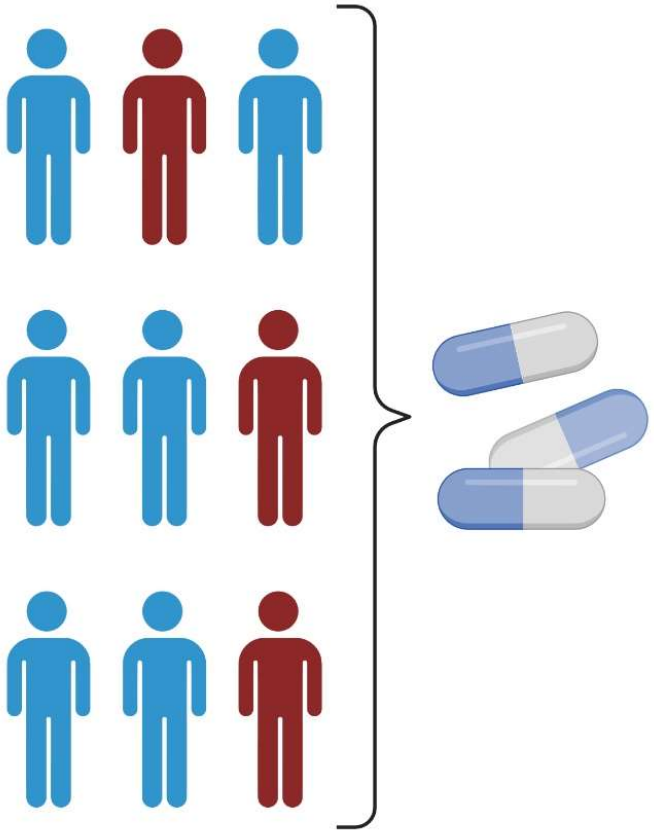
Disclosures

Conflict of interests	See below
Relevant relationship with companies	Companies
• Sponsoring or research money • Fee or other reimbursement • Shareholder • Other relationship, namely …	• AbbVie, Siemens, Roche • None • None • None

Overview

- **Disease stratification**
- Disease stratification in giant cell arteritis (GCA)
- Disease stratification in polymyalgia rheumatica (PMR)
- GCA/PMR Spectrum Disease (GPSD)

Traditional approach: *one size fits all*



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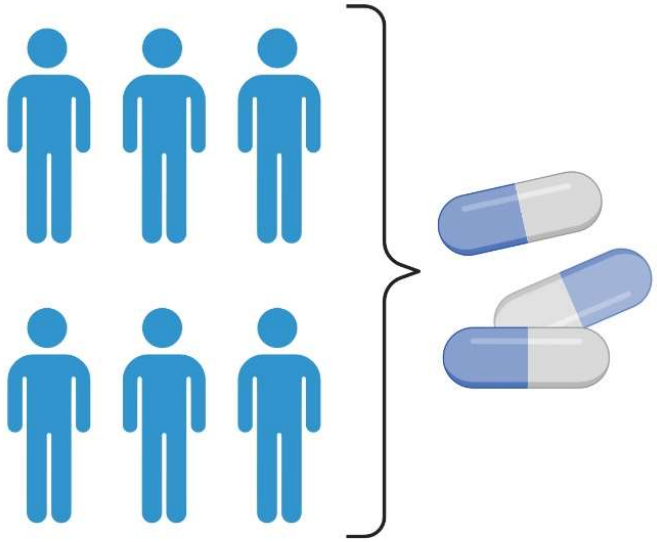
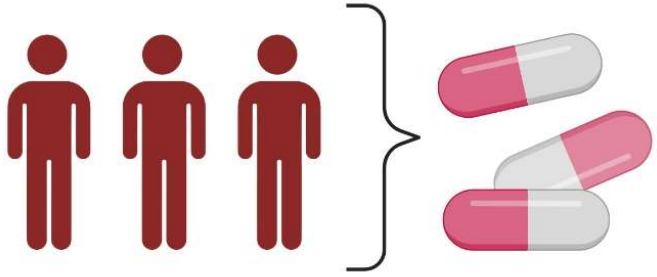
Disease stratification

Disease subset A



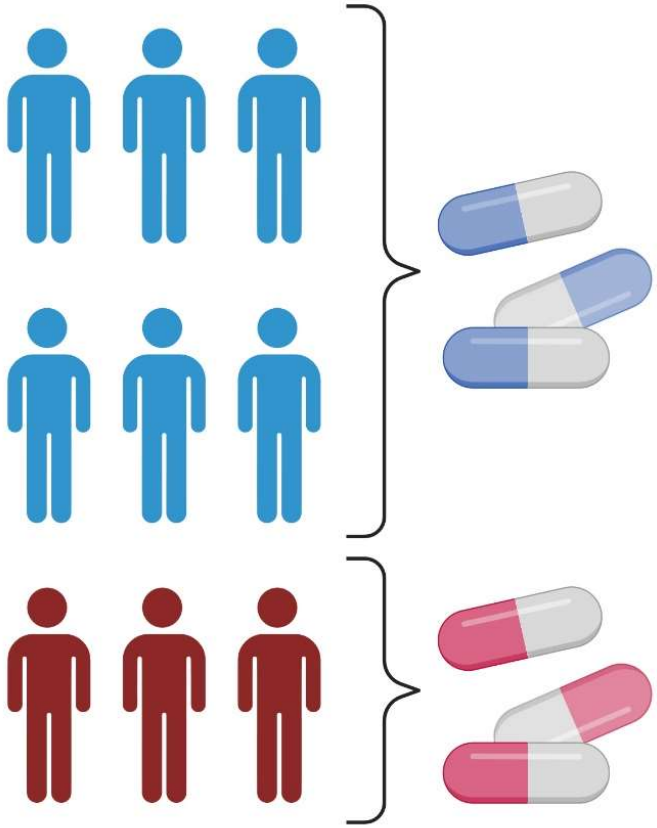
Disease subset B



Disease stratification

Patient factors
- *Demographics*
- *Co-morbidities*
- *Genetics*

Disease factors
- *Symptoms*
- *Laboratory markers*
- *Imaging*

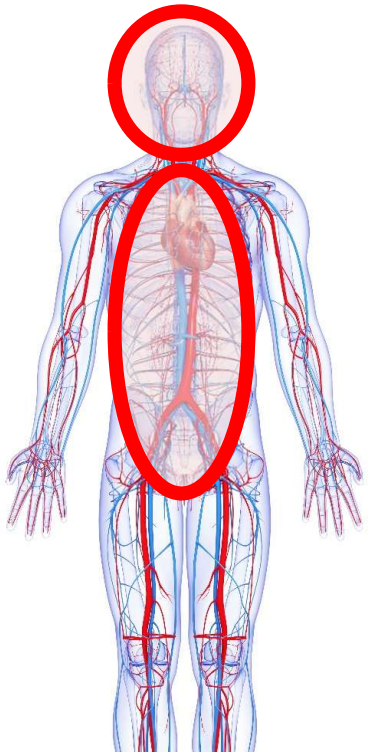


Overview

- Disease stratification
- **Disease stratification in giant cell arteritis (GCA)**
- Disease stratification in polymyalgia rheumatica (PMR)
- GCA/PMR Spectrum Disease (GPSD)

Giant cell arteritis (GCA)

- Autoimmune disease
  - Large and medium arteries
- Age ≥ 50
- Women > Men



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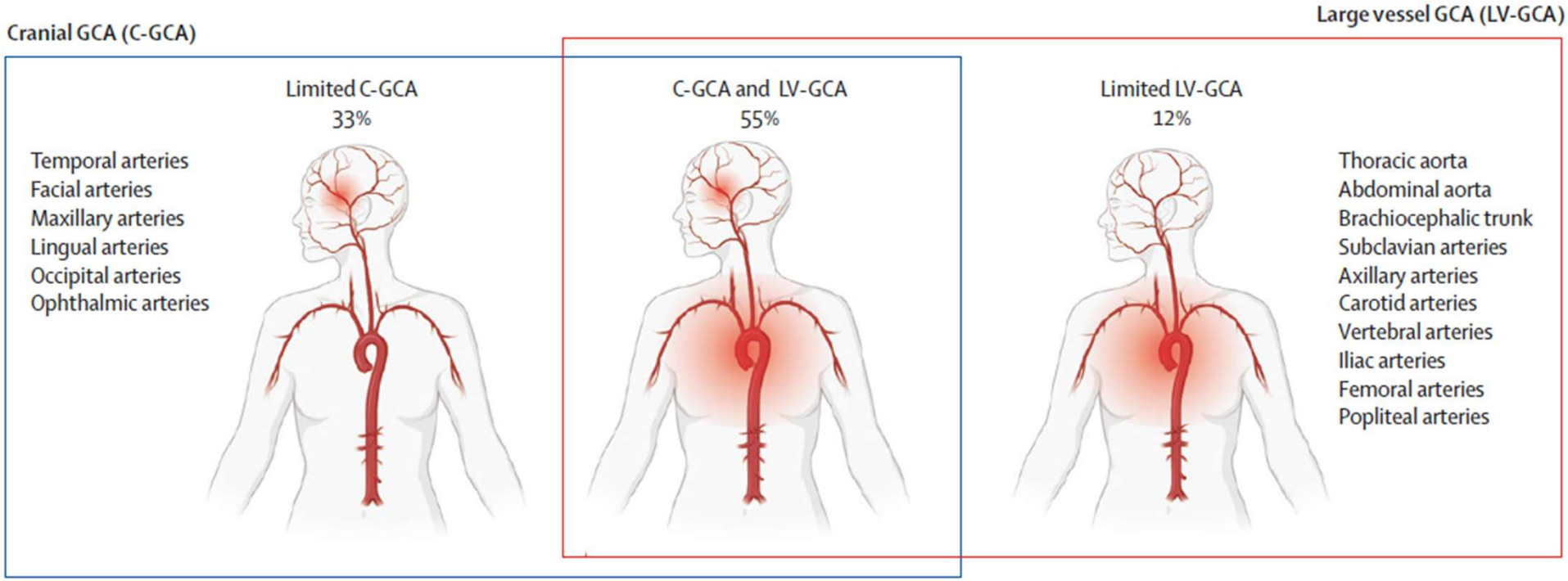
Cranial and *large vessel* GCA subsets



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Van der Geest et al. Lancet Rheumatology (in press)

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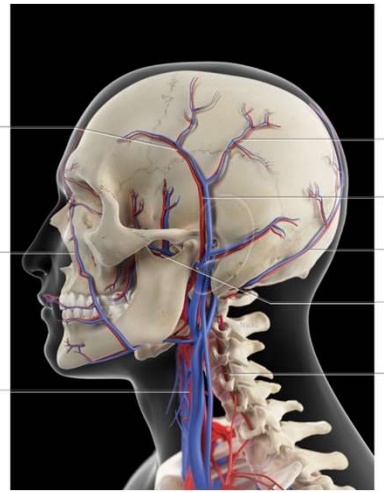
Cranial GCA

Headache (72%)

Scalp tenderness (39%)



Tongue claudication (3%)

Abnormal temporal Artery (53%)

Jaw claudication (38%)

Weight loss, fever, night sweats

Main complication (early in disease)

Ischaemic sight loss (24%)

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Van der Geest et al. JAMA Internal Medicine 2020

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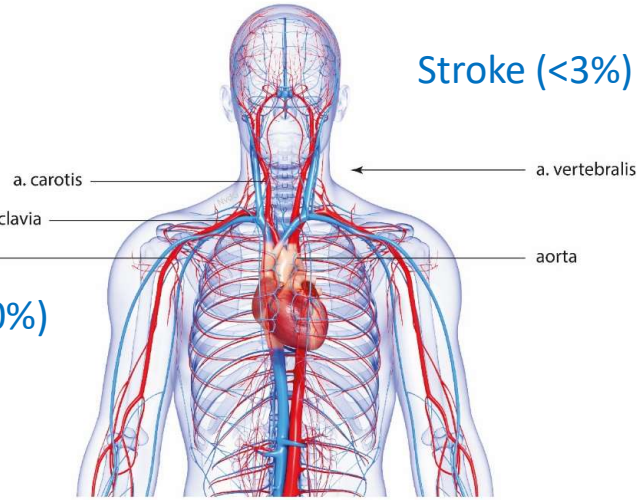
Large vessel GCA

Bruits (17%)
BP difference (18%)

Arm claudication (20%)



Stroke (<3%)

Weight loss, fever, night sweats

Main complication (late in disease)
Aortic aneurysm (23-30%)
Aortic dissection (0-2%)

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Van der Geest et al. JAMA Internal Medicine 2020 | Moreel et al. Ann Int Med 2023
Van der Geest et al. Lancet Rheumatology (in press)

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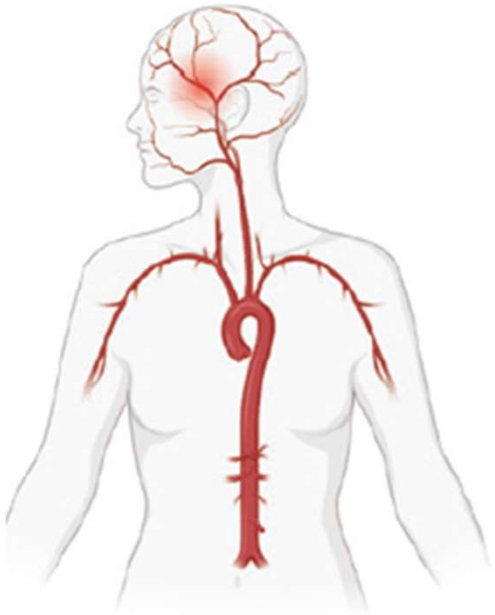
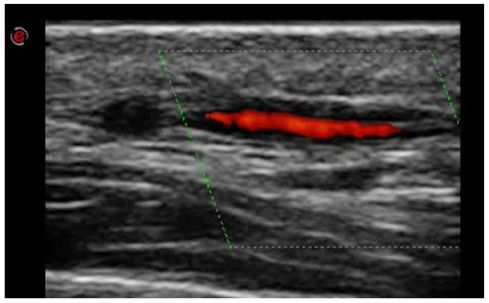
Cranial GCA: diagnostic approach

Cranial GCA



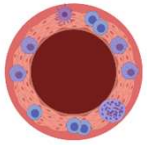
Temporal artery ultrasound



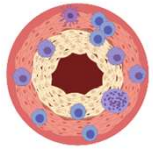
Temporal artery biopsy

Heterogeneity: temporal artery thickness

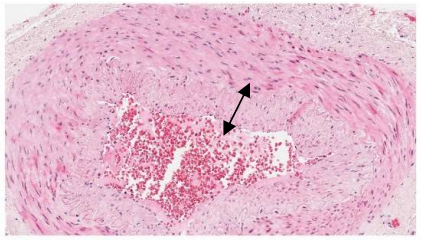
Non-GCA
Immune cells: -
Intima hyperplasia: -



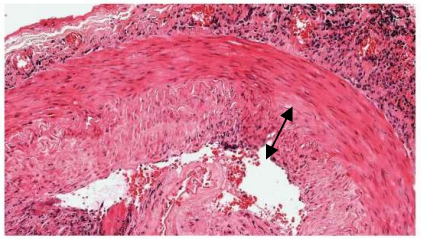
GCA
Immune cells: +
Intima hyperplasia: -



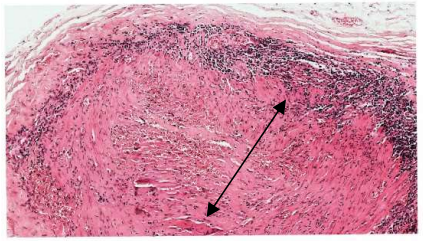
GCA
Immune cells: +
Intima hyperplasia: +



TMI- IntHyp-

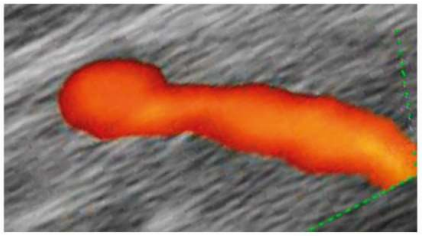


TMI+ IntHyp-

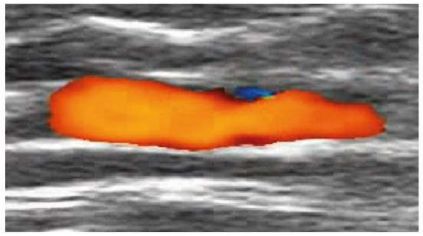


TMI+ IntHyp+

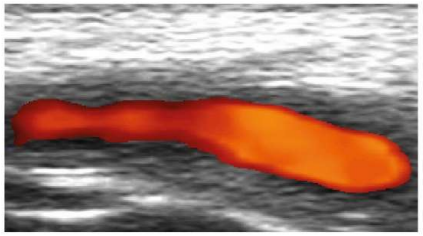
Biopsy



Halo Score = 0



Halo Score = 1



Halo Score = 16

Ultrasound

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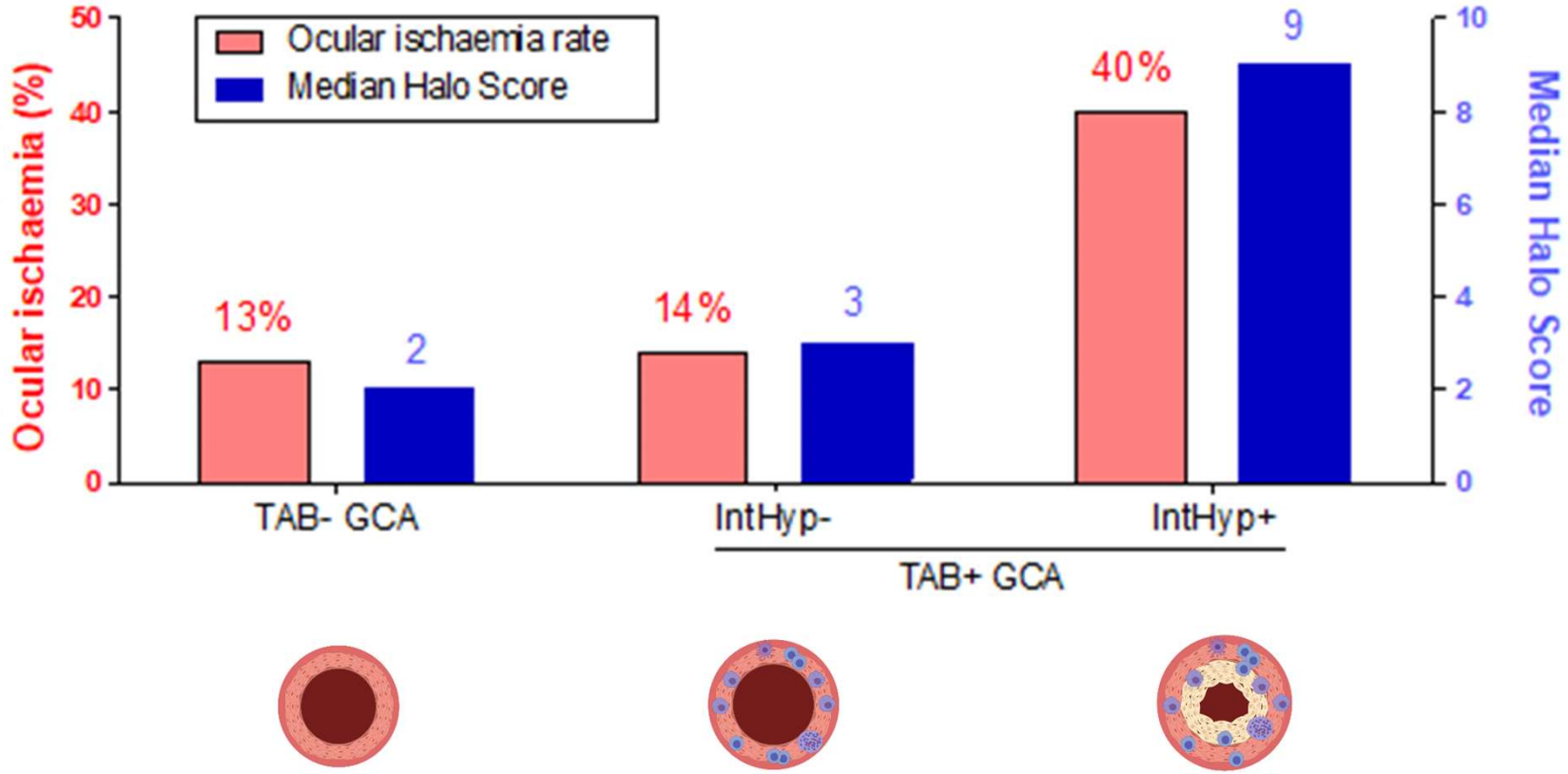
Temporal artery thickness and ischaemic sight loss



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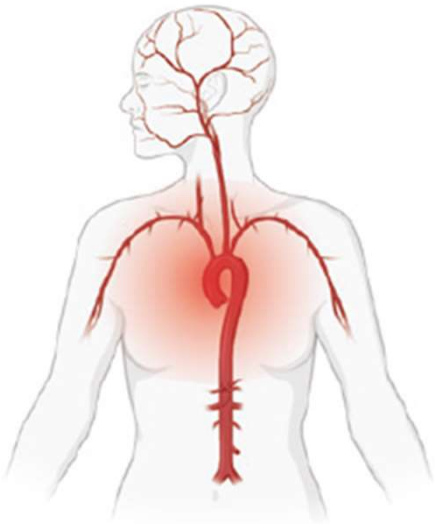
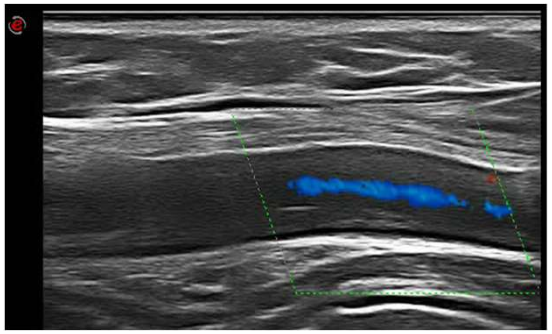
Large vessel GCA: diagnostic approach

Large vessel GCA



Axillary artery ultrasound



^{18}F-FDG-PET/CT

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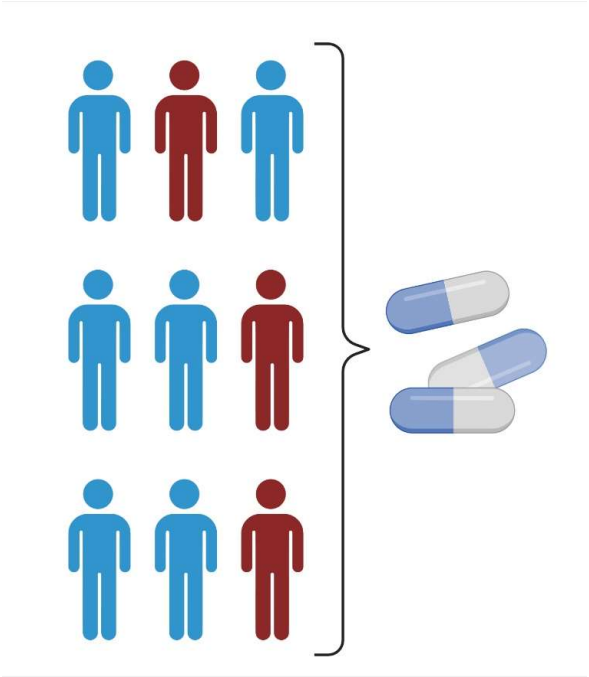
GCA standard therapy: one size fits all

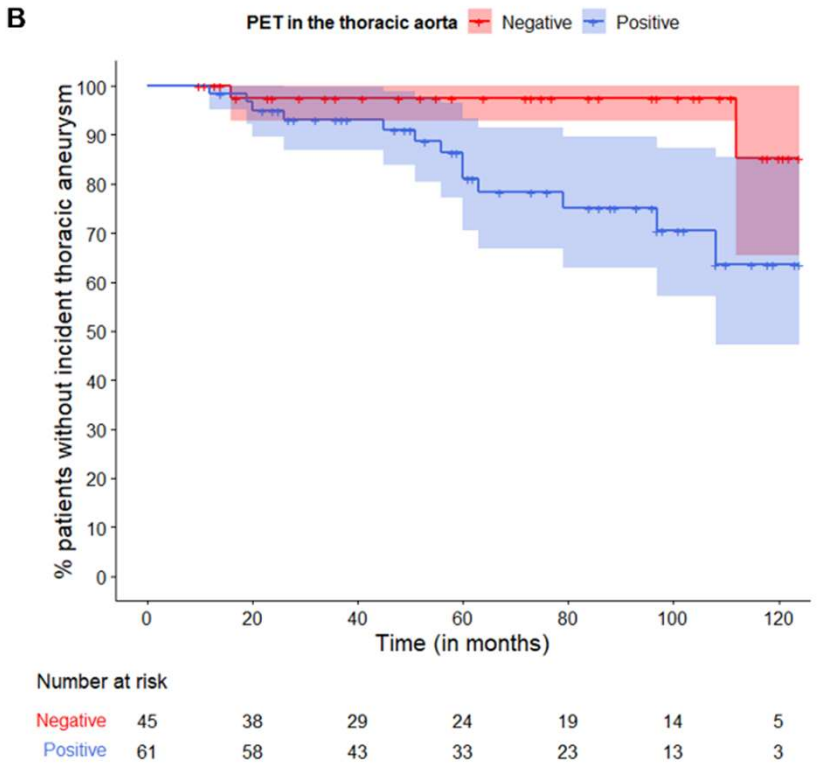


- Prednisolone 40-60 mg/day
- Taper within 12-18 months
- DMARDs
  - Methotrexate, tocilizumab
  - If contra-indication for prednisolone
  - If toxicity of prednisolone

Large vessel GCA: outcomes during follow-up

Study (no. of patients)	Relapse risk	Glucorticoid requirement	Aortic dilatation / aneurysm
Blockmans et al. 2008 (n=46)			Increased
Schmidt et al. 2008 (n=106)		No effect	
Espitia et al. 2012 (n=22)	Increased	Increased	
Muratore et al. 2014 (n=332)	Increased	Increased	Increased
Czihal et al. 2015 (n=43)	Increased	No effect	
de Boysson et al. 2016 (n=130)			Increased
de Boysson et al. 2017 (n=80)	No effect	No effect	
Samson et al. 2018 (n=20)	Increased		
de Boysson et al. 2019 (n=288)	Increased	Increased	
Dumont et al. 2019 (n=326)	Increased	Increased	
Muratore et al. 2019 (n=93)			Increased
Bellan et al. 2020 (n=19)	No effect		
Muratore et al. 2020 (n=121)	No effect	No effect	
Sammel et al. 2020 (n=21)	No effect		
Sugihara et al. 2020 (n=119)	Increased		

Thoracic aorta ^{18}F-FDG uptake at diagnosis: thoracic aneurysm



Test: FDG uptake ≥ 2 in thoracic aorta

Outcome: thoracic aneurysm

- Sensitivity: 87% (60-98)
- Specificity: 47% (37-58)
- Positive likelihood ratio 1.64 (1.13-2.12)
- Negative likelihood ratio 0.28 (0.08-0.83)

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Moreel et al. Annals of Internal Medicine 2023

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New treatment approach

	Muratore et al. 2024 Rheumatology
GCA type	Large vessel
GCA stage	New-onset or relapsing
Therapy	Methylprednisolone 500 mg for 3 days + tocilizumab for 1 year (SC)
Outcome	8/17 (47%) patients in relapse-free remission at week 52 (primary outcome)
Specific concerns	4 patients (24%) with aortic dilatation at diagnosis: aortic diameter further increased by ≥ 5 mm

New treatment approach: for LV-GCA only?

	Muratore et al. 2024 Rheumatology	Christ et al. 2021 Lancet Rheum
GCA type	Large vessel	Large vessel and/or cranial
GCA stage	New-onset or relapsing	New-onset
Therapy	Methylprednisolone 500 mg for 3 days + tocilizumab for 1 year (SC)	Methylprednisolone 500 mg for 3 days + tocilizumab for 1 year (IV 1x, then SC)
Outcome	8/17 (47%) patients in relapse-free remission at week 52 (primary outcome)	13/18 (72%) patients in relapse-free remission at week 52 (secondary outcome)
Specific concerns	4 patients (24%) with aortic dilatation at diagnosis: aortic diameter further increased by ≥ 5 mm	**Ischaemic sight loss in 1 patient (15 days after methylprednisolone)**

Disease stratification in GCA

	Cranial GCA	Large vessel GCA
Diagnostic pathway:	Ultrasonography Temporal artery biopsy	Ultrasonography ^{18}F-FDG-PET/CT
Main concern	**Ischaemic sight loss (early)**	**Aortic aneurysm (late)** **More relapses?**
Standard therapy	Prednisolone 60 mg * Start urgently upon suspicion Taper in 12-18 months	Prednisolone 40-60 mg Start after diagnosis Taper in 12-18 months *Early DMARD introduction?*
Ultrashort glucocorticoid therapy with anti-IL-6 receptor therapy	*No*	*Yes?*
Screening for aortic damage:	*No?*	*Yes?*

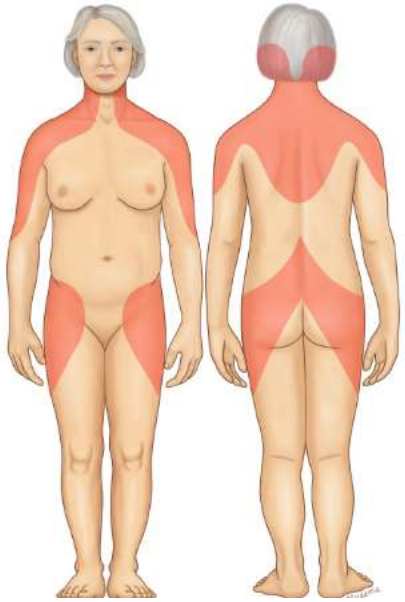
** Methylprednisolone 500-1000 mg IV for 3 days in case of ischaemic sight loss*

Overview

- Disease stratification
- Disease stratification in giant cell arteritis (GCA)
- **Disease stratification in polymyalgia rheumatica (PMR)**
- GCA/PMR Spectrum Disease (GPSD)

Polymyalgia rheumatica (PMR)

- Autoimmune disease
  - Bursae, tendons, joints
  - Shoulders, hips, spine
- Age ≥ 50
- Women > men



Pain and stiffness

Weight loss, fever, night sweats

Clinical disease subsets in PMR

- Severity of inflammation (ESR, CRP) at diagnosis
  - Not predictive of disease course

- Peripheral joint involvement
  - More relapse
  - Prolonged glucocorticoid treatment

- Subclinical GCA

Van Sleen et al. Rheumatology 2020| Salvarani et al. Arthr Care Res 2005
Tomelleri & van der Geest et al. Nat Rev Rheum 2023

Peripheral joint involvement: trully PMR?

	Lumpers	Splitters
Shoulder and pelvic girdle pain and stiffness	PMR	PMR
Hand arthritis	**PMR**	**NOT PMR***
Wrist arthritis	**PMR**	**NOT PMR***
Knee arthritis	**PMR**	**NOT PMR***

Peripheral joint involvement: trully PMR?

	Lumpers	Splitters
Shoulder and pelvic girdle pain and stiffness	PMR	PMR
Hand arthritis	**PMR**	**NOT PMR***
Wrist arthritis	**PMR**	**NOT PMR***
Knee arthritis	**PMR**	**NOT PMR***

** NOT PMR: seronegative rheumatoid arthritis, spondyloarthritis*

Synovial hypertrophy, erosions, secundary osteoarthritis ≠ PMR

PMR subset with subclinical GCA

- 346 patients with new-onset PMR without GCA symptoms

- 79 (23%) cases of subclinical GCA by ultrasonography
  - Limited large vessel GCA 31 (9%)
  - Mixed large vessel/cranial GCA 26 (8%)
  - Limited cranial GCA 22 (6%)

PMR with subclinical GCA: relapsing disease course

Table 1 Demographic, relapses and treatments in pure PMR and PMR with subclinical GCA

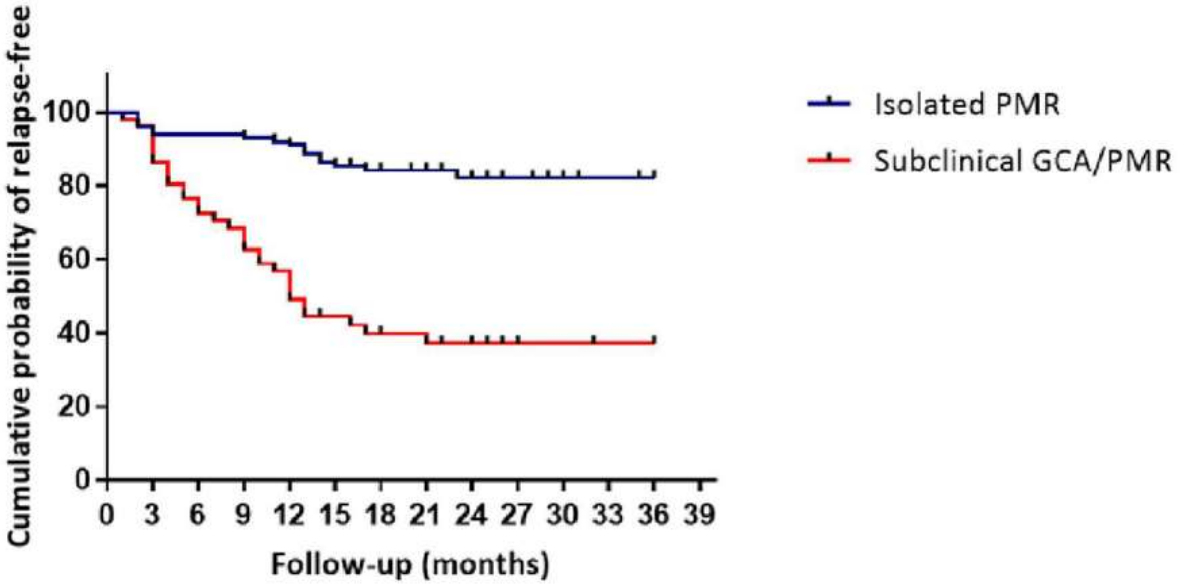
	Isolated PMR (n=100)	Subclinical GCA/PMR (n=50)	P value
Age, mean±SD years	72.1±8.8	74.1±7.8	0.080
Female sex, n (%)	62 (59%)	25 (50%)	0.216
CRP, mean±SD mg/L	55.3±52.4	47.5±40.7	0.336
ESR, mean±SD mm/hour	63.2±31.2	62.7±33.1	0.936
Patients who relapse, n/n total (%)			
Total	16/100 (16.0%)	31/50 (62.0%)	0.001
Minor	16/100 (16.0%)	30/50 (60.0%)	0.001
Major	0	1 (2.0%)	

Test: presence of subclinical GCA
Disease outcome: relapse
Sensitivity: 66% (51-79)
Specificity: 82% (73-89)
Positive likelihood ratio 3.58 (2.29-5.65)
Negative likelihood ratio 0.42 (0.27-0.60)

De Miguel et al. Ann Rheum Dis 2023

PMR with subclinical GCA: low relapse-free survival

Prednisolone starting dose (median)
Isolated PMR: 20 mg
PMR with subclinical GCA: 37 mg



Number at risk:

Time (months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Isolated PMR	100	96	94	94	92	76	72	66	25	11	4	2	1	0
Subclinical GCA	50	48	38	34	28	18	15	14	10	4	3	2	2	0

De Miguel et al. Ann Rheum Dis 2023

Disease stratification PMR

- Peripheral arthritis
  - Reconsider diagnosis (rheumatoid arthritis, spondyloarthritis)

- Subclinical GCA
  - Treat as GCA
  - Early introduction of other immunosuppressive therapy

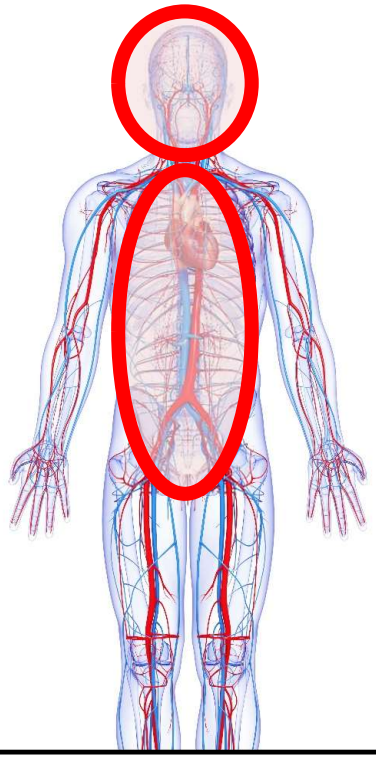
Overview

- Disease stratification
- Disease stratification in giant cell arteritis (GCA)
- Disease stratification in polymyalgia rheumatica (PMR)
- **GCA/PMR Spectrum Disease (GPSD)**

GCA/PMR overlap

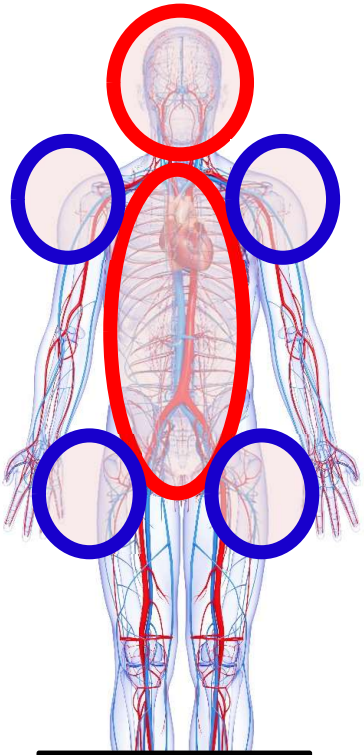
C-GCA

LV-GCA



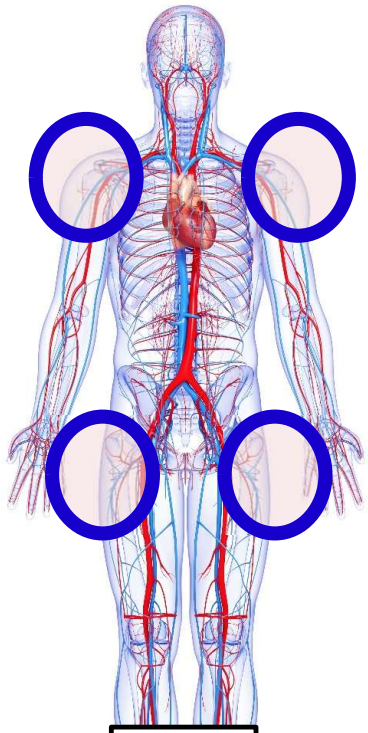
GCA

~20%



GCA/PMR

~20%



PMR

~60%

Alba et al. 2014 Medicine | De Miguel et al. Rheumatology 2024

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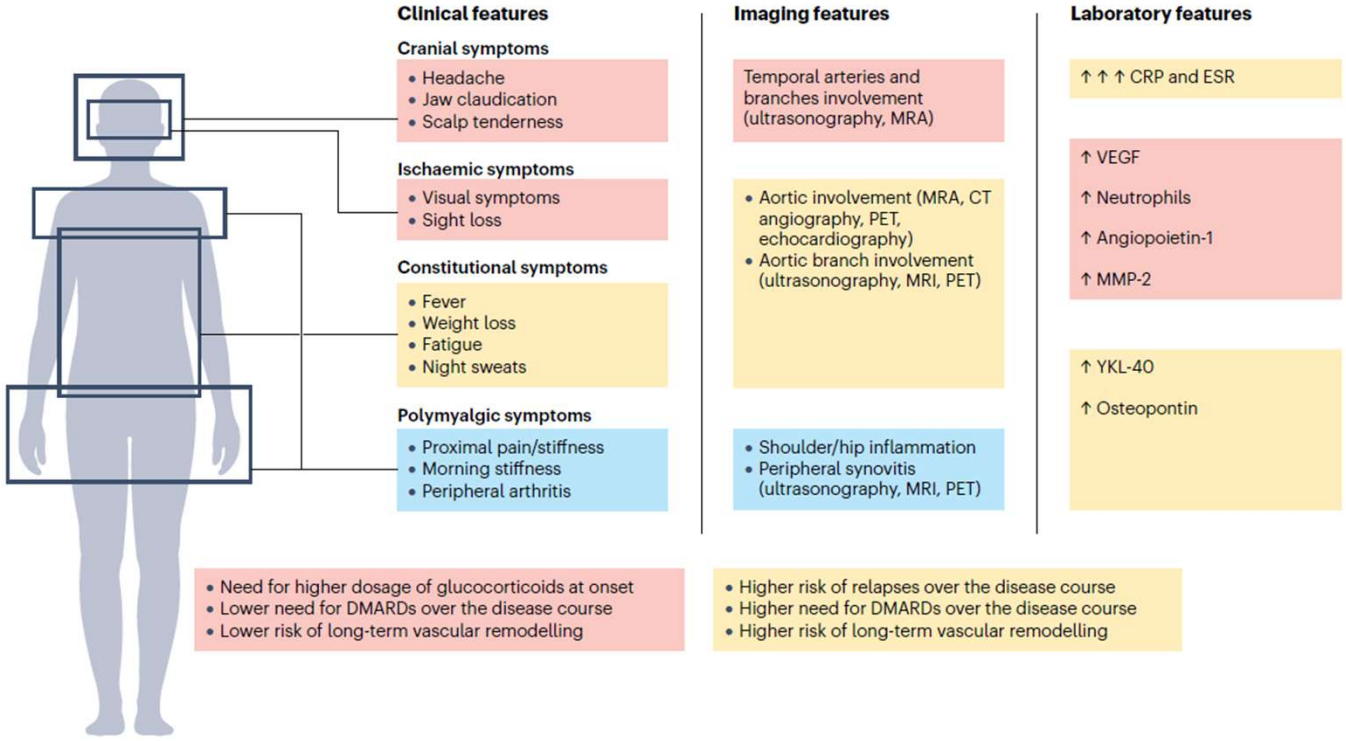
Giant cell arteritis-Polymyalgia Spectrum Disease (GPSD)

The GPSD concept

Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) share a common pathophysiology:

- Age group affected
- Genetics
- Immunology (T helper 1 (T_H1) and T_H17 pathways activated, IL-6 expression)
- Anatomical sites of arterial and musculoskeletal inflammation



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Tomelleri & van der Geest et al. 2023 Nature Reviews Rheumatology

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GPSD concept

- Simplifying GCA/PMR relationship
  - Not two diseases, but one disease affecting multiple tissues
  - *Comparable to other systemic autoimmune diseases*

- Accelerating introduction of new therapies?

Anti-IL-6 receptor therapy in GCA (2017)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2017 VOL. 377 NO. 4

Trial of Tocilizumab in Giant-Cell Arteritis

J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

Approval of tocilizumab for GCA

Anti-IL-6 receptor therapy in PMR (2022-2023)

Tocilizumab in patients with new onset polymyalgia rheumatica (PMR-SPARE): a phase 2/3 randomised controlled trial

Michael Bonelli ,[1] Helga Radner,[1] Andreas Kerschbaumer ,[1] Daniel Mrak ,[1] Martina Durechova,[1] Jutta Stieger,[2] Rusmir Husic,[3] Peter Mandl ,[1] Josef S Smolen,[1] Christian Dejaco ,[3,4] Daniel Aletaha [1]

Ann Rheum Dis 2022

Sarilumab for Relapse of Polymyalgia Rheumatica during Glucocorticoid Taper

Robert F. Spiera, M.D., Sebastian Unizony, M.D., Kenneth J. Warrington, M.D., Jennifer Sloane, M.D., Angeliki Giannelou, M.D., Michael C. Nivens, Ph.D., Bolanle Akinlade, M.D., Wanling Wong, Ph.D., Rafia Bhore, Ph.D., Yong Lin, M.D., Frank Buttgereit, M.D., Valerie Devauchelle-Pensec, M.D., Ph.D., Andrea Rubbert-Roth, M.D., George D. Yancopoulos, M.D., Ph.D., Frederic Marrache, M.D., Ph.D., Naimish Patel, M.D., and Bhaskar Dasgupta, M.D., for the SAPHYR Investigators*

NEJM 2023

JAMA | Preliminary Communication

Effect of Tocilizumab on Disease Activity in Patients With Active Polymyalgia Rheumatica Receiving Glucocorticoid Therapy
A Randomized Clinical Trial

Valérie Devauchelle-Pensec, MD, PhD; Guillermo Carvajal-Alegria, MD; Emmanuelle Dernis, MD, MSc; Christophe Richez, MD, PhD; Marie-Elise Truchetet, MD, PhD; Daniel Wendling, MD, PhD; Eric Toussirot, MD, PhD; Aleth Perdriger, MD, PhD; Jacques-Eric Gottenberg, MD, PhD; Renaud Felten, MD; Bruno Jean Fautrel, MD, PhD; Laurent Chiche, MD, PhD; Pascal Hilliquin, MD, PhD; Catherine Le Henaff, MD; Benjamin Dervieux, MD; Guillaume Direz, MD; Isabelle Chary-Valckenaere, MD, PhD; Divi Cornec, MD, PhD; Dewi Guellec, MD; Thierry Marhadour, MD; Emmanuel Nowak, PhD; Alain Saraux, MD, PhD

JAMA 2022

Still waiting for approval in Europe

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Anti-IL-6 receptor therapy in GCA in GPSD?

Trial of Tocilizumab in ~~Giant-Cell Arteritis~~ GPSD

J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

Can we combine GCA and PMR in single trial?

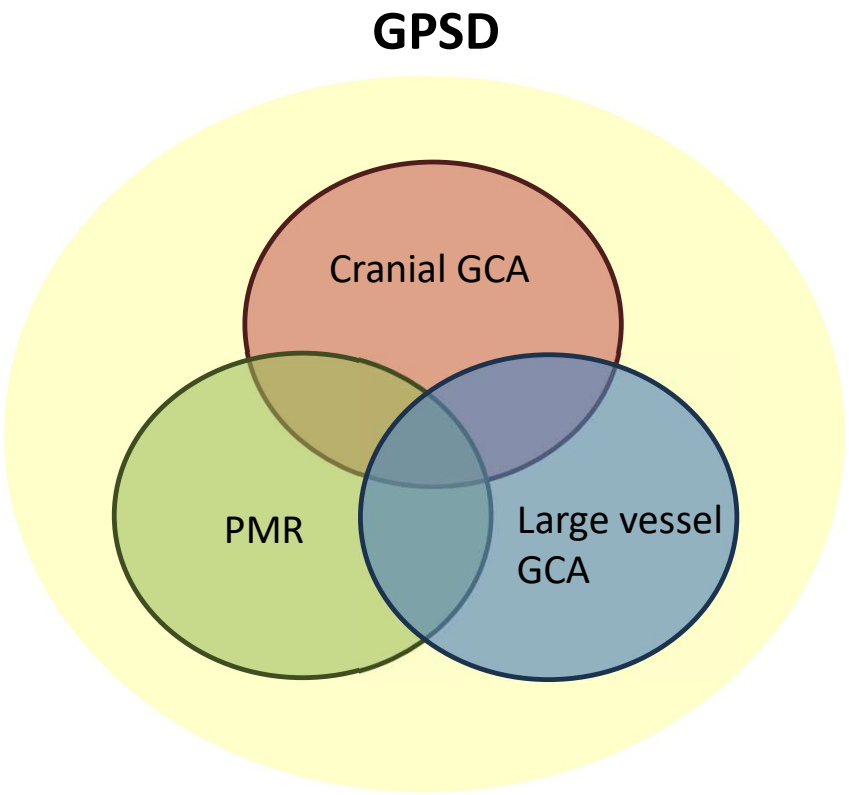
- We already do!

- Trial anti-IL-6R therapy in GCA:
  - 2/3 of patients had PMR

- Trials (n=3) anti-IL-6R therapy in PMR
  - Presence of GCA not evaluated
  - 1/4 of patients likely had GCA

Take home messages

- GCA and PMR are not monolithic diseases
  - Each has intrinsic heterogeneity
- GCA and PMR are part of one disease spectrum (GPSD)
- Further research needed
  - Firmly define disease subsets
  - Establish management strategies for each subset



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GCA systemic inflammation resposne

Table 1. Characteristics predicting cranial ischemia or long-term prognosis in GCA patients*

Characteristic, study	Study design	Cranial ischemia risk	Relapse rate	Glucocorticoid requirement
Strong systemic inflammatory response				
Cid et al, 1998 (12)	Retro	Decreased	NA	NA
Gonzalez-Gay et al, 1998 (13)	Retro	Decreased	NA	NA
Liozon et al, 2001 (14)	Prosp	Decreased	NA	NA
Hernandez-Rodriguez et al, 2002 (15)	Retro	Decreased	Increased	Increased
Gonzalez-Gay et al, 2004 (16)	Retro	Decreased	NA	NA
Salvarani et al, 2005 (17)	Retro	Decreased	NA	NA
Gonzalez-Gay et al, 2005 (18)	Retro	Decreased	NA	NA
Lopez-Diaz et al, 2008 (19)	Retro	Decreased	NA	NA
Nesher et al, 2008 (9)	Retro	No effect	Increased	Increased
Chatelain et al, 2009 (10)	Prosp	No effect	NA	NA
Gonzalez-Gay et al, 2009 (20)	Retro	Decreased	NA	NA
Salvarani et al, 2009 (21)	Retro	Decreased	NA	NA
Martinez-Lado et al, 2011 (29)	Retro	NA	Increased	NA
Muratore et al, 2016 (22)	Retro	Decreased	NA	NA
Liozon et al, 2016 (23)	Prosp	Decreased	NA	NA
Grossman et al, 2017 (24)	Retro	Decreased	NA	NA
Restuccia et al, 2017 (30)	Retro	NA	NA	Increased
De Boysson et al, 2017 (25)	Retro	Decreased	NA	NA
Yates et al, 2017 (11)	Prosp	No effect	NA	NA

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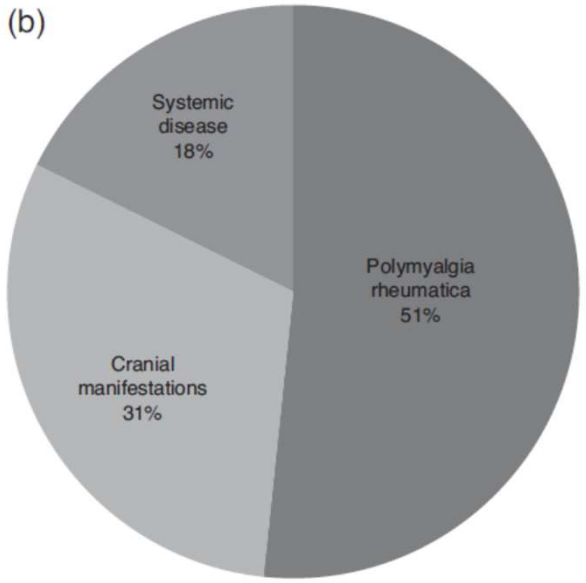
van der Geest et al. 2018 Arthr Rheum

PMR presence in GCA: more relapses

	Relapse rate	
	GCA with PMR	GCA without PMR
Alba et al. 2014 Medicine	40/53 (74%)	28/52 (54%)

Test: presence of PMR
Outcome: relapse
Sensitivity: 59% (46-71)
Specificity: 63 (46-78)
Positive likelihood ratio 1.60 (1.04-2.61)
Negative likelihood ratio 0.65 (0.45-0.96)

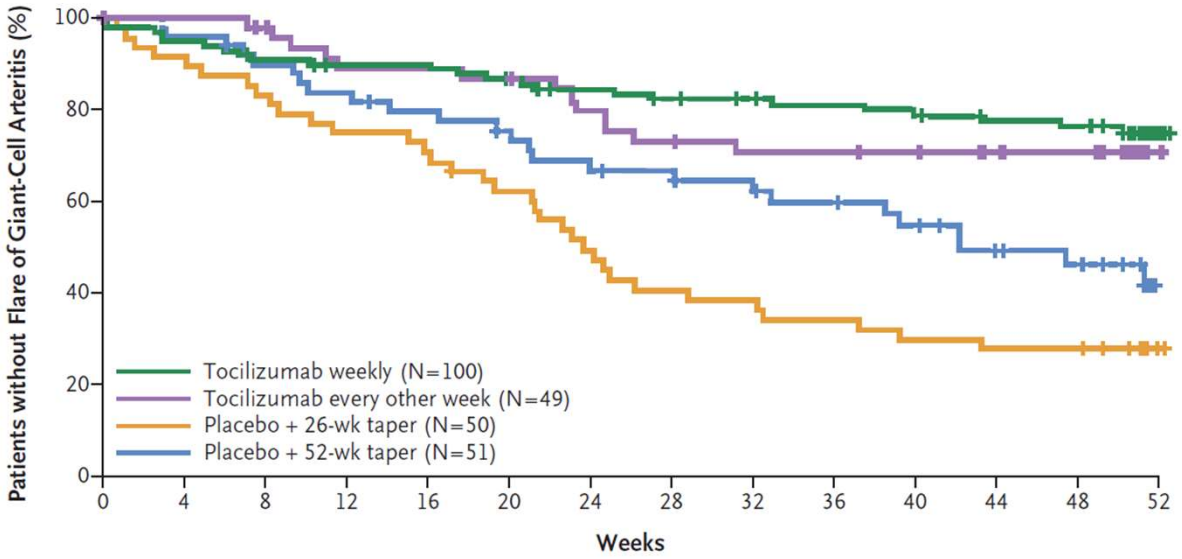
Main symptoms of relapse



Ultrashort glucocorticoid therapy (2)

	Unizony et al. 2023 Lancet Rheum
GCA type	Cranial and/or large vessel
GCA stage	New-onset or relapsing
Therapy	Prednisolone for 8 weeks (start 20-60 mg) + tocilizumab for 1 year (SC)
Outcome	23/30 (77%) patients relapse-free remission at week 52 (primary outcome)
Specific concerns	-

Disease subsets: response to therapy



No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

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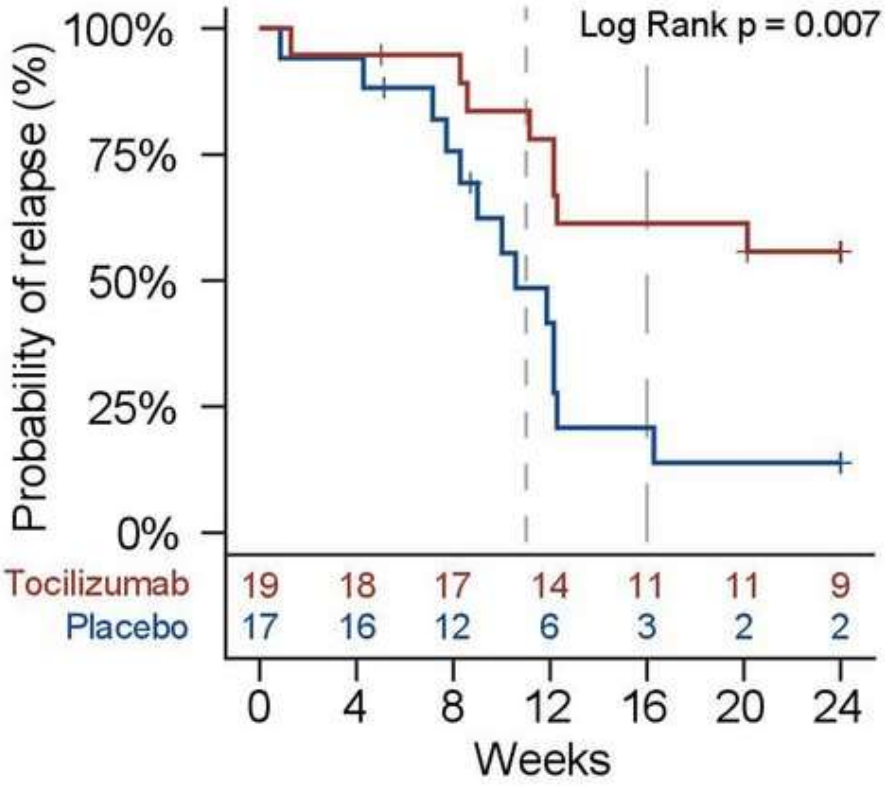
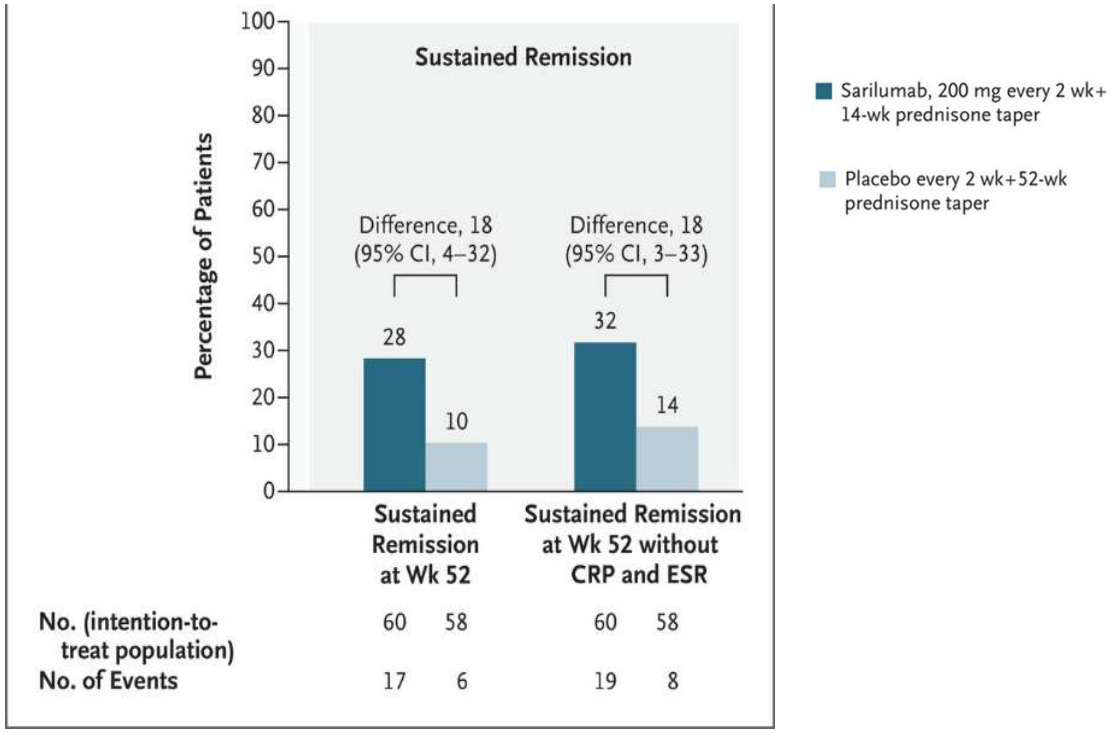
Stone et al. NEJM 2017

Disease subsets: response to therapy





Devauchelle et al. JAMA 2022 | Spiera et al. NEJM 2023