L'ARTERITE GIGANTOCELLULARE

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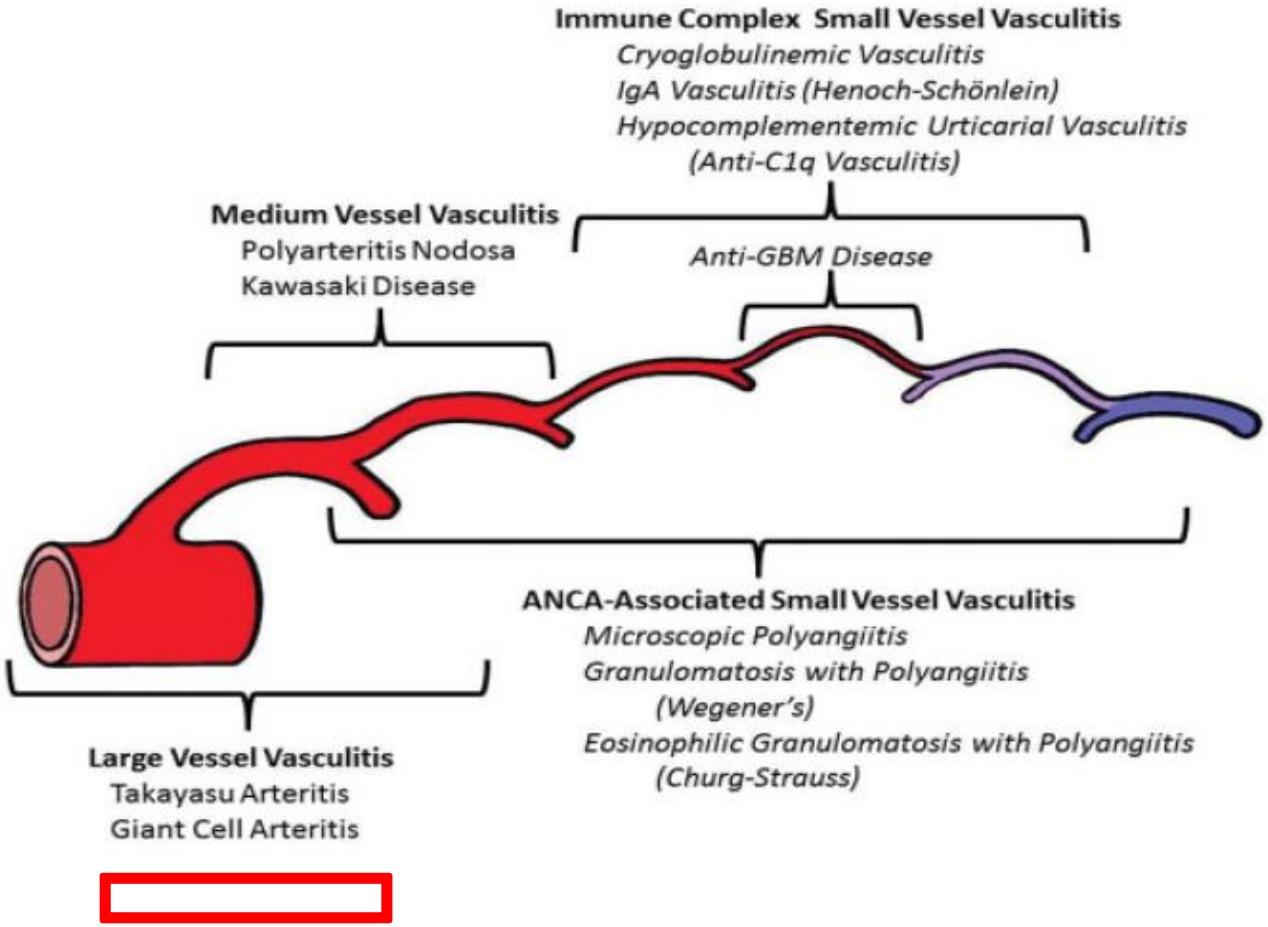
Vasculiti



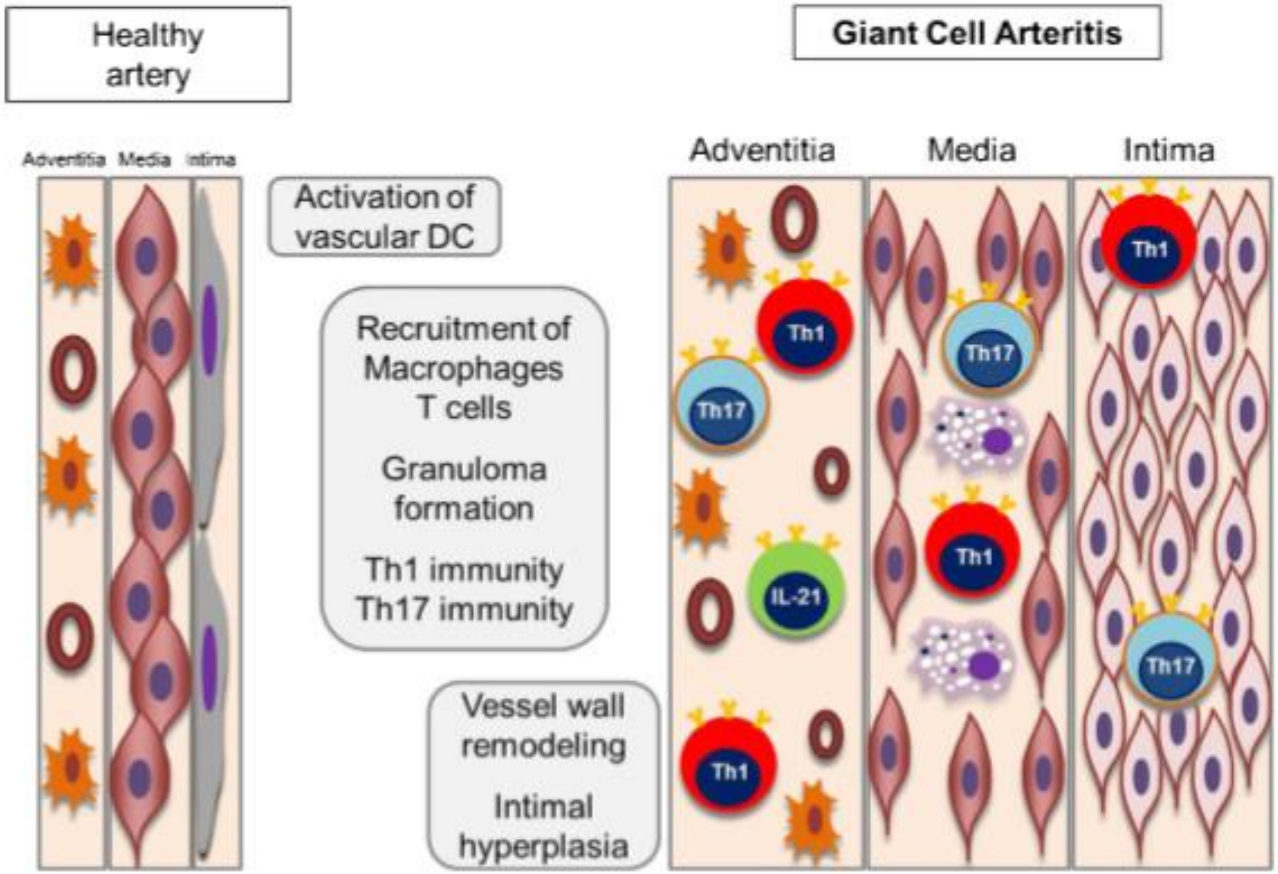
Jenette et al., Arthritis and Rheumatism, 2012

AGC: epidemiologia

- La più comune forma di vasculite in soggetti sopra i 50 anni
- Più frequente nelle popolazioni caucasiche
- Due volte più frequente nelle donne rispetto ai maschi
- Incidenza massima nei Popoli del Nord (Scandinavia e Minnesota): 15-35:100.000 >50 anni
  - Background genetico

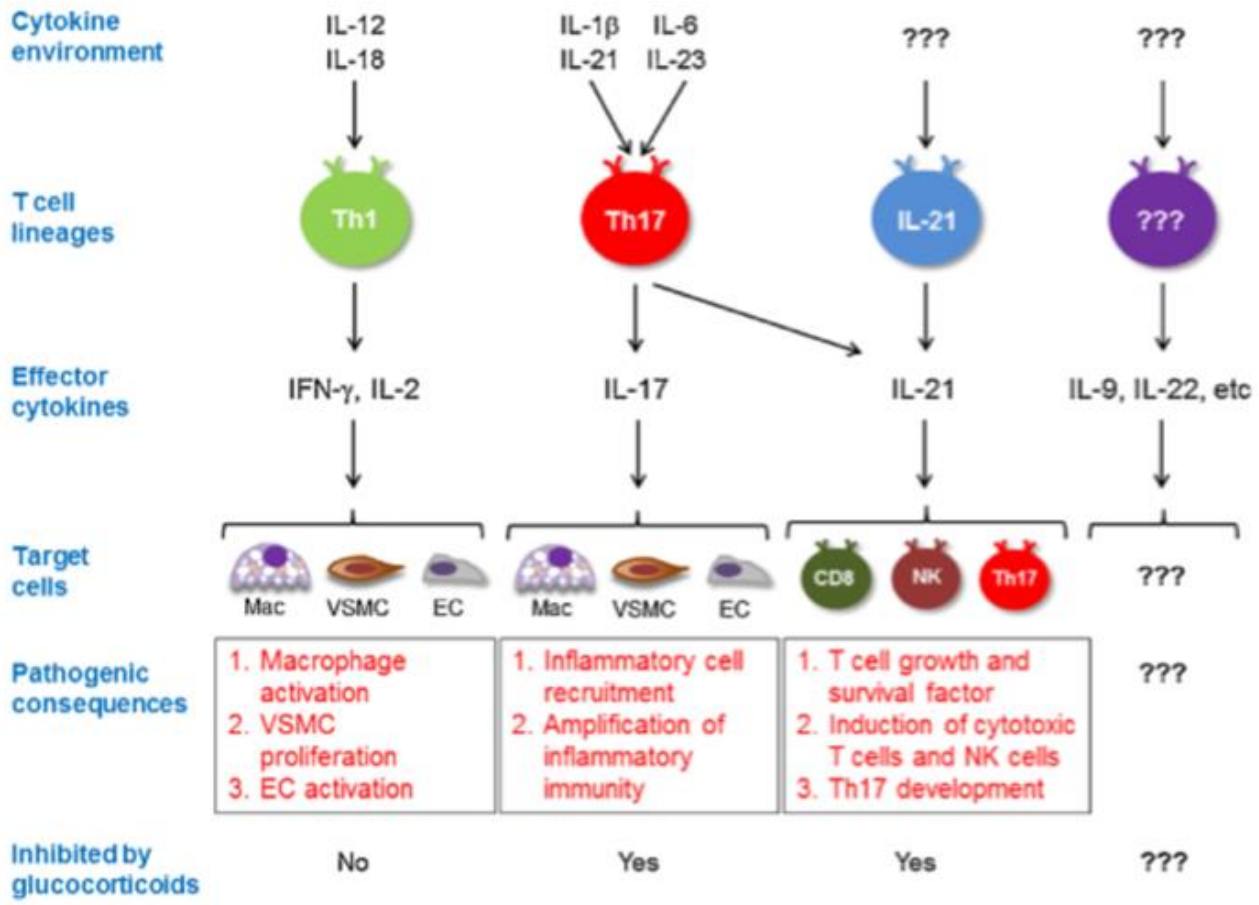
Watts R.A., Rheumatology 2014
Smeeth L. et al., Ann Rheum Dis, 2006

AGC: patogenesi



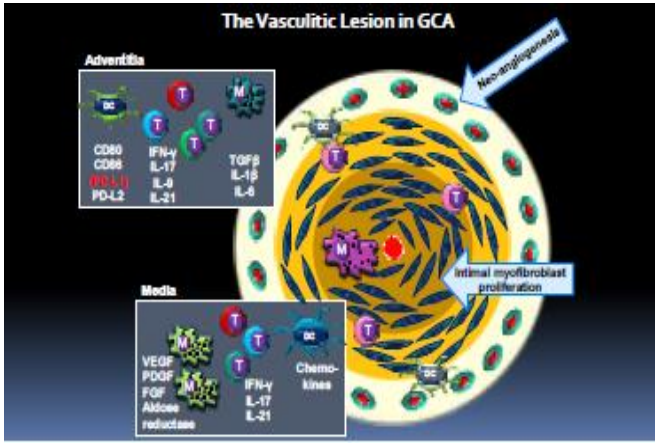
Watanabe R. et al., Curr Treatm Opt Rheumatol, 2016

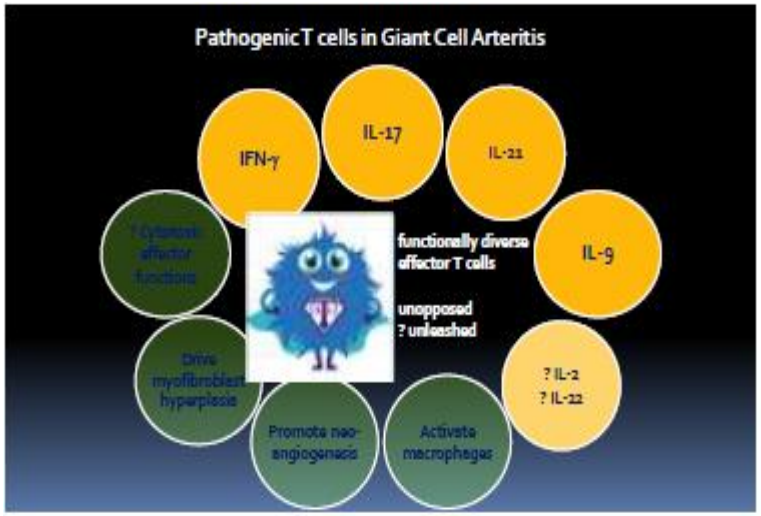
Patogenesi

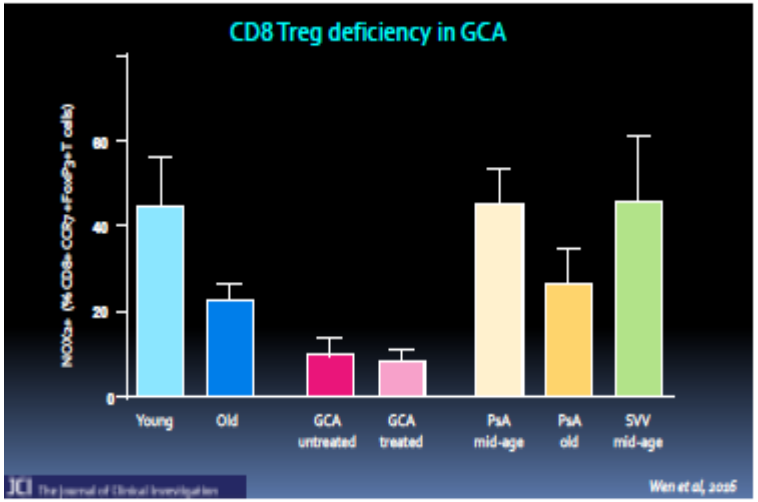


Watanabe R. et al., Joint Bone Spine, 2017

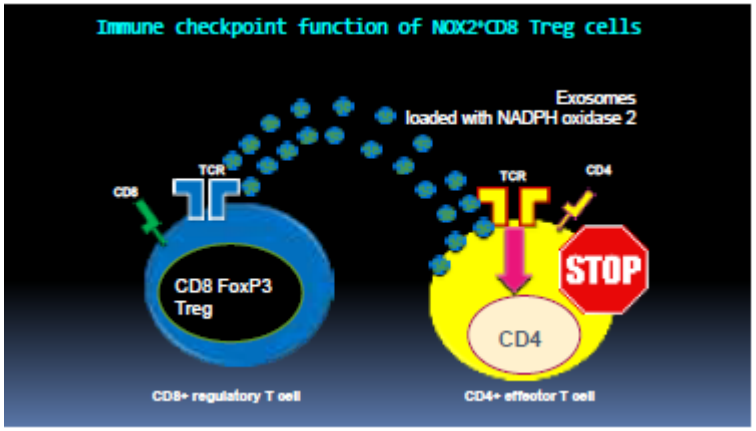
Patogenesi (Weyand C. ACR 2017)







Patogenesi:immune checkpoint (Weyand C. 2017)

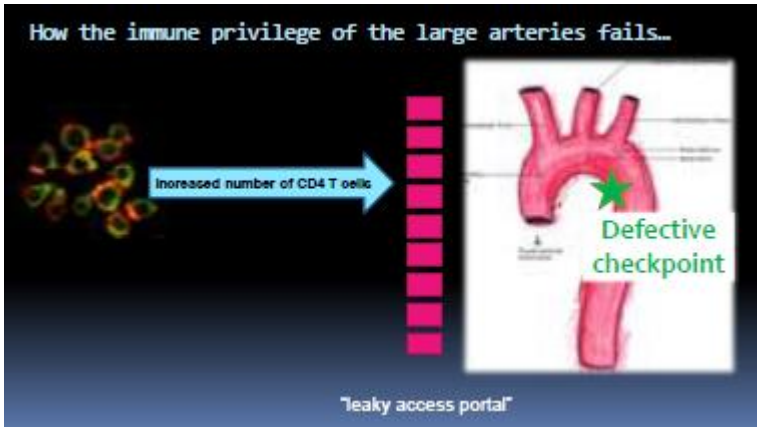


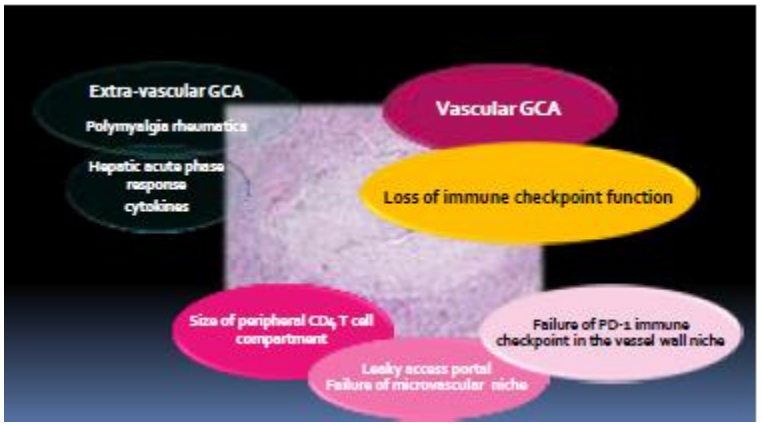
Checkpoint inhibition unleashes T cell immunity

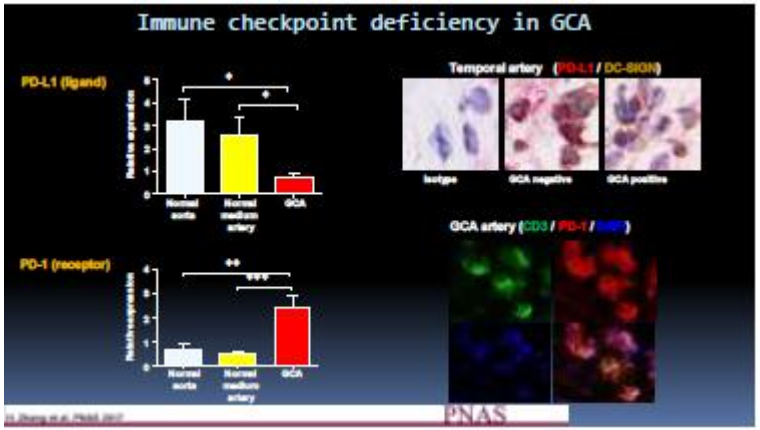
Checkpoint inhibition accelerates tissue cytokine production

The PD-1 checkpoint controls intimal hyperplasia

The PD-1 checkpoint controls microvascular angiogenesis



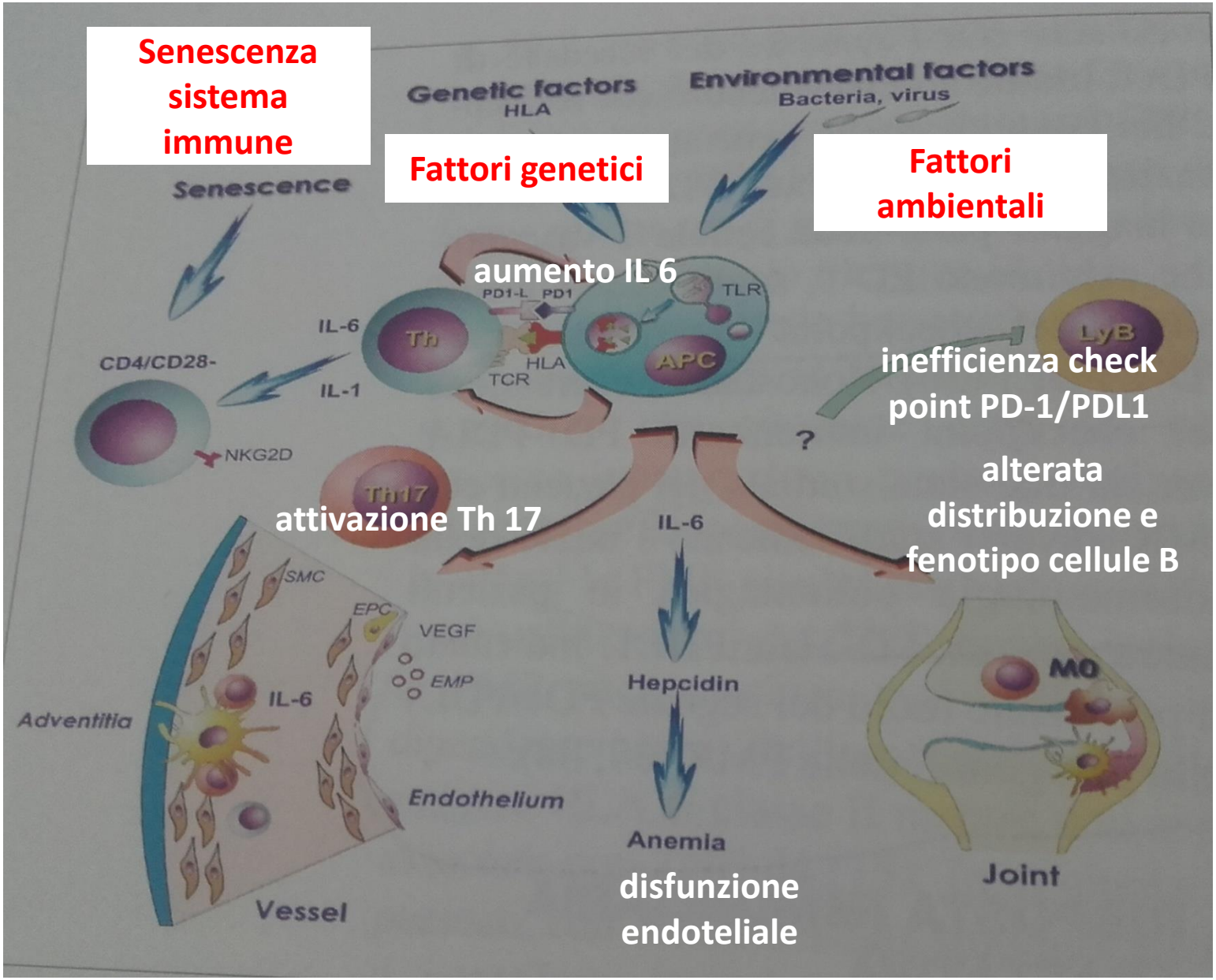




Nature Review Rheum, vol. 13, March 2017

Patogenesi PMR

Interazione tra fattori ambientali e sistema immune in soggetti geneticamente predisposti



Patogenesi: sintesi

- Meccanismo T cell/CD4 dipendente, cellule dentritiche/macrofagi
- Attivazione Th1-Th17 e citochine correlate
- Ruolo INFgamma (attività citotossica, stimolo miofibroblasti, neoangiogenesi, aumento macrofagi)
- **Difetto checkpoint nella parete grandi vasi** (PD1 correla con attività; rottura tolleranza immunitaria in parete vasale con stimolo citochinico di parete e sistemico)

Diagnosi e Classificazione

CLASSIFICAZIONE

Table 3
The American College of Rheumatology 1990 GCA classification criteria.

(1)	Age at onset ≥50 years
(2)	A new headache
(3)	Temporal artery abnormality such as tenderness to palpation or decreased pulsation
(4)	Erythrocyte sedimentation rate ≥ 50 mm/h
(5)	Abnormal artery biopsy showing vasculitis with mononuclear cell or granulomatous inflammation, usually with giant cells.

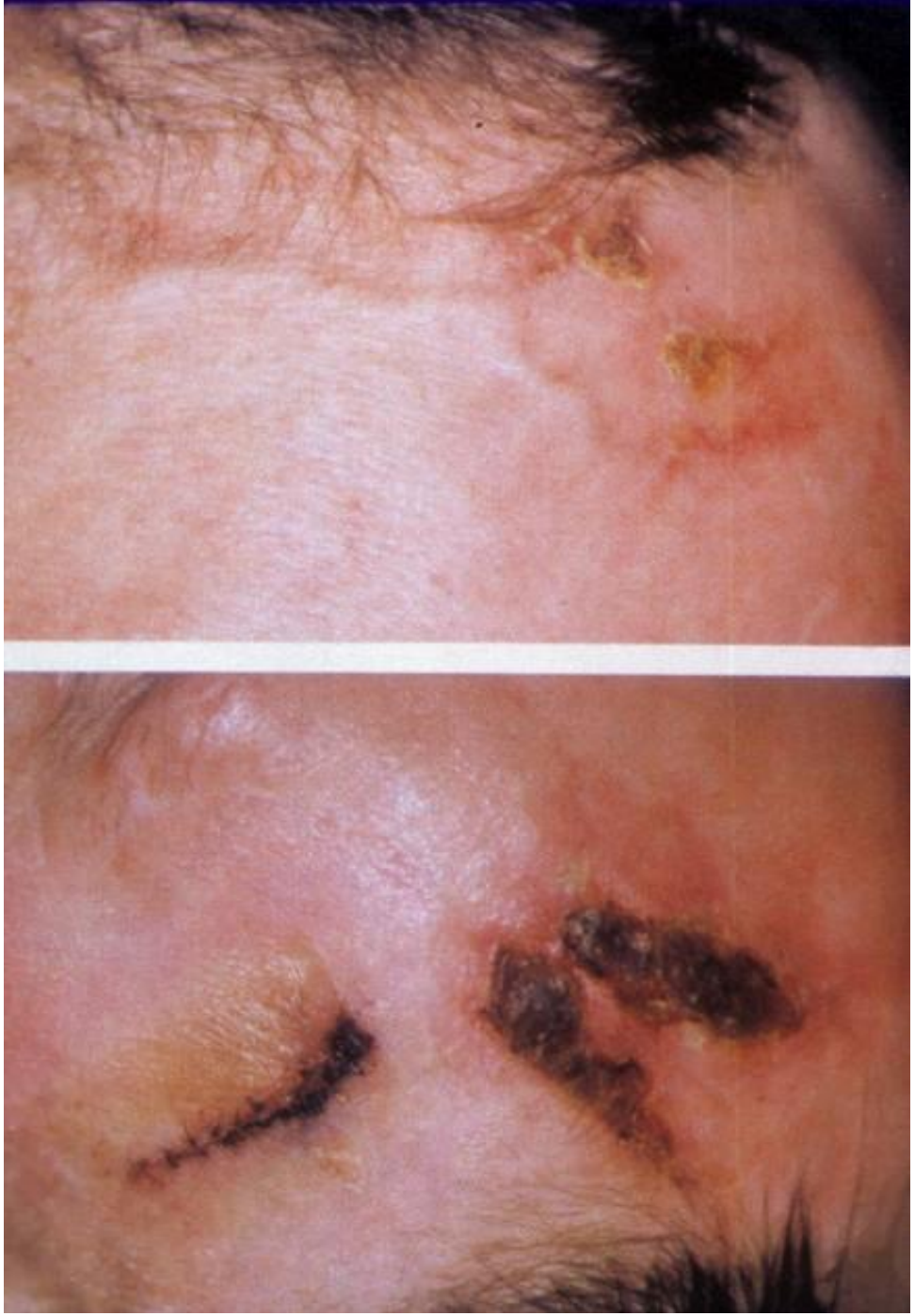
At least three of the five parameters must be present, which yields a sensitivity of 93% and a specificity of 91%, in relation to controls with other vasculitides.

DIAGNOSI

- Elementi clinici
- Laboratoristici
- Strumentali
- Dati istologici

Arterite gigantocellulare (GCA)
Diagnosi

- cefalea temporale intensa mono o bilaterale irradiata a regioni parietali o frontali
- dolore non responsivo ad analgesici
- possibile presenza di calo del visus, claudicatio mandibolare, iperestesia cuoio capelluto
- complicanza più severa: neuropatia ottica ischemica anteriore con rischio cecità (20% casi)
- possibile interessamento intracranico di tipo ischemico: interessamento arterie vertebrobasilari o carotidi
- interessamento grandi vasi (succlavia, ascellare, aorta e ramificazioni): 20% casi, spesso silente



Alterazioni arteria temporale superficiale

Arterite gigantocellulare (GCA)
Diagnosi

Eco arterie temporali

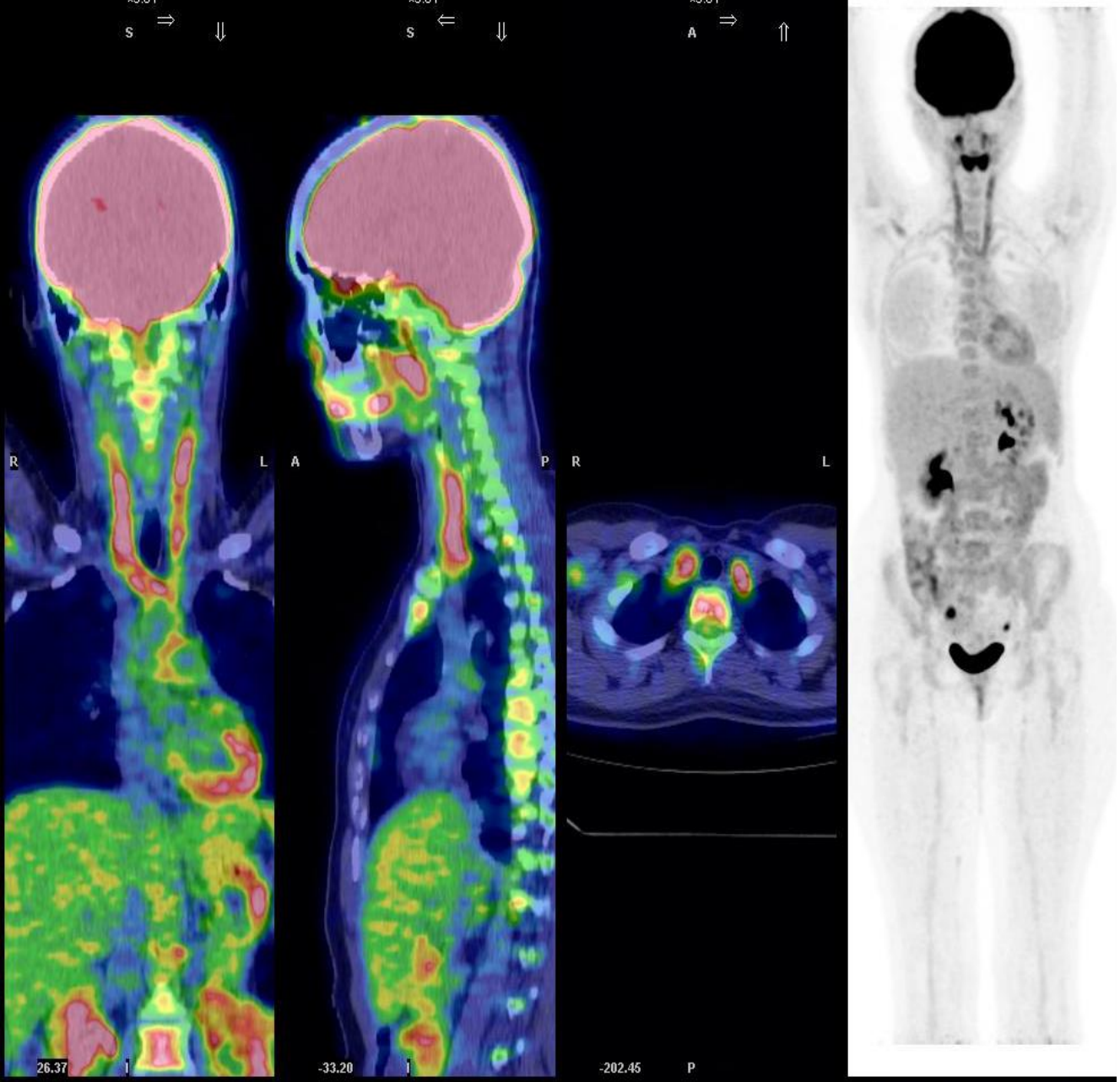
- *halo sign* (sensibilità 75% e specificità 83%, bilaterale 100%)
- test compressione positivo

Biopsia arteria temporale

- falsi negativi nel 10-20% casi senza terapia steroidea
- **negativizza con steroide nel 20% casi dopo 2 settimane di steroide** e nel **40% dopo 4 settimane**

PET-TC

- se dubbio di interessamento grandi vasi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S
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I
-33.20
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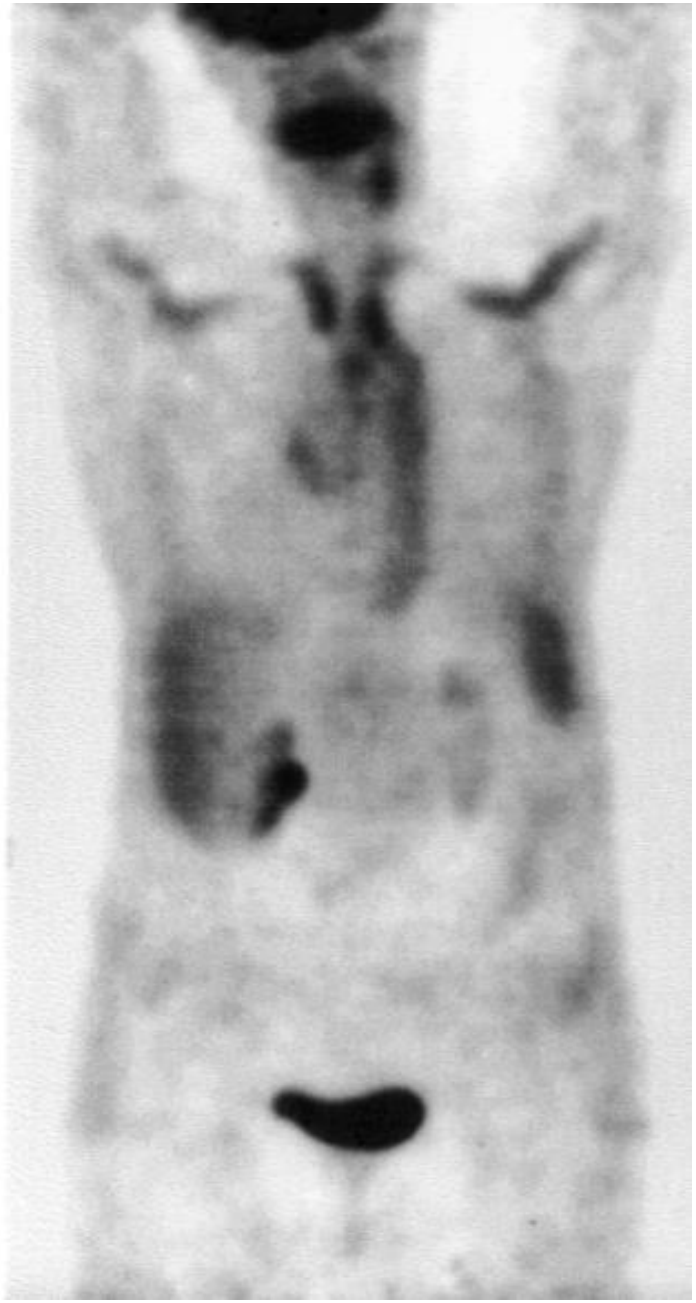
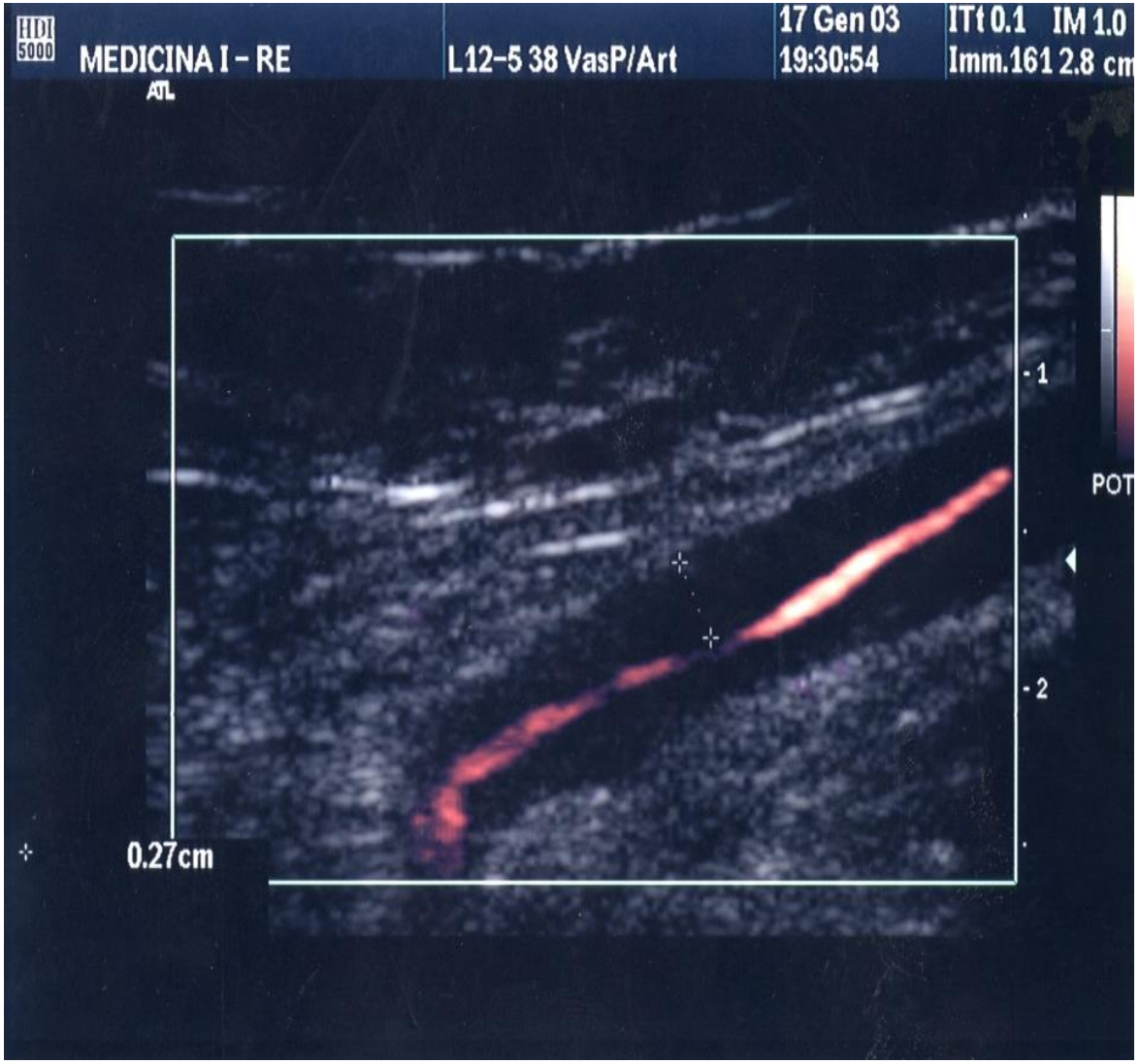
-202.45
P
Fused Coronals
Fused Sagittals
Fused Transaxials
MIP Navigate

AGC




HDI 5000
MEDICINA I – RE
ATL
L12-5 38 VasP/Art
17 Gen 03
19:30:54
ITt 0.1 IM 1.0
Imm.161 2.8 cm
1
2
POT
0.27cm

Arterite gigantocellulare (GCA)

Diagnosi (US/PET/angioRMN)

- **US** con sensibilità 75%, 95% se bilaterale
- Alone 80% se flogosi a tutto spessore, meno se flogosi solo avventiziale
- Aiuta poco a biopsia
- Se eco negativa e clinica di sospetto: biopsia
- US: fare anche le ascellari
- US con contrasto per parete
- **PET**: molto sensibile, grandi vasi; considerare gradiente 2 o 3 (=/> fegato)
- **RMN** temporali: problematiche tecniche/costo

A suspected diagnosis of LVV should be confirmed by imaging (ultrasound or MRI for temporal or other cranial arteries, ultrasound, CT, positron-emission-tomgraphy (PET)T-CT or MRI for the aorta/ extracranial arteries) or histology (TAB)

22 January 2018

Recommendation

EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

- Ultrasound of temporal—axillary arteries is recommended as the first imaging modality ('halo' sign).
- High resolution MRI of cranial arteries to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.
- CT and PET are not recommended for the assessment of inflammation of cranial arteries.
- Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA.

In patients in whom there is a **high clinical suspicion of GCA and a positive imaging test**, the diagnosis of GCA may be made **without an additional test** (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts towards a diagnosis are necessary.

Draft ACR/EULAR class,criteria for GCA

Established diagnosis of vasculitis and age ≥40 years ≥ 6

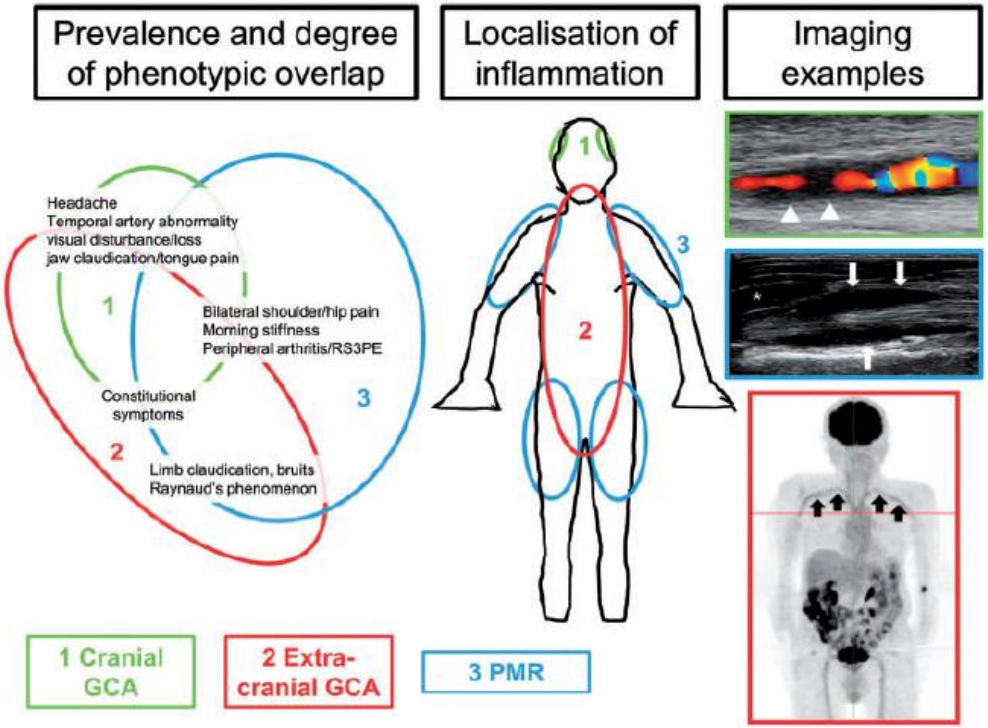
Clinical features		
	Morning stifness in shoulders or neck	2
	Sudden visual loss	2
	Jaw or tongue claudication	**2**
	New temporal headache	2
	Scalp tenderness	2
Temporal artery findings	Reduced pulse or tenderness of TA	1
	ESR ≥ 50mm/h ore CRP≥10mg/dl	3
	Temporal artery biopsy positive	5
Imaging findings	Ultrasound halo sign TA	5
	Ultrasound bilateral artery involvement	3
	FDG-PET positive	3

Rhematology 2018;58:kez08.017 (abstract 077)

.. tutto così chiaro e semplice?

Fenotipi di malattia

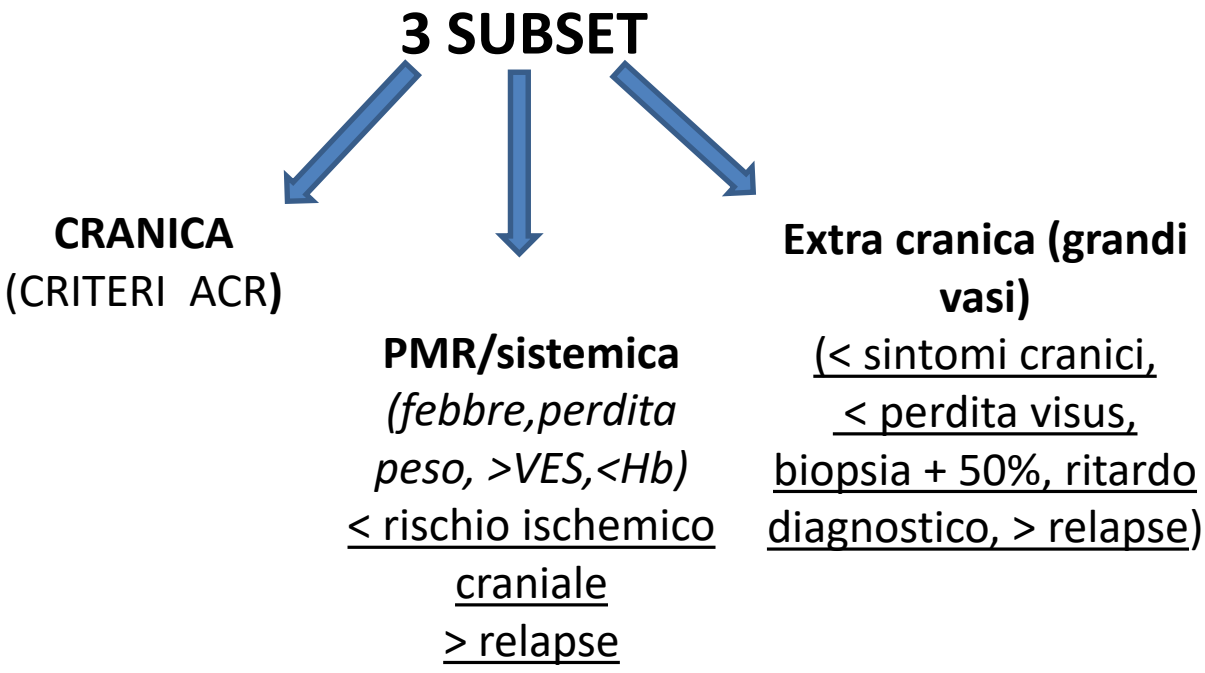
Disease spectra of cranial, large-vessel GCA and PMR



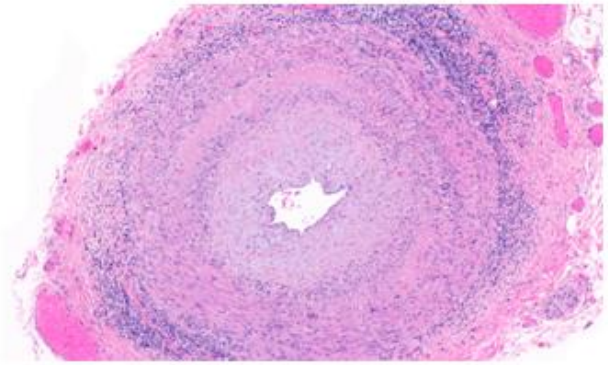
Left: prevalence and phenotypic overlap. The size of the circles reflects the estimated incidence of each condition (relative to each other, not indicating absolute values), and the overlapping areas correspond to the proportion of the phenotypic overlap. At the crossing of the curves, characteristic clinical symptoms of the respective diseases are depicted. Middle: main localization of inflammation in each disease. Right: imaging findings. Green box: US image of a patient with cranial GCA showing the halo sign (arrowhead). Blue box: US image of a PMR patient. White arrows point to biceps tenosynovitis, the asterix depicts subdeltoid bursitis. Red box: ^{18}F-FDG PET image of a patient with large-vessel-GCA. Black arrows indicate FDG uptake in supra-aortic large arteries.

Dejaco C. et al., Rheumatology 2016

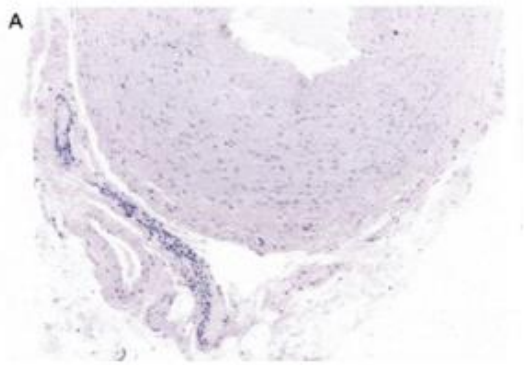
AGC


3 SUBSET
CRANICA
(CRITERI ACR)
PMR/sistemica
(febbre,perdita peso, >VES,<Hb)
< rischio ischemico craniale
> relapse
Extra cranica (grandi vasi)
(< sintomi cranici, < perdita visus, biopsia + 50%, ritardo diagnostico, > relapse)

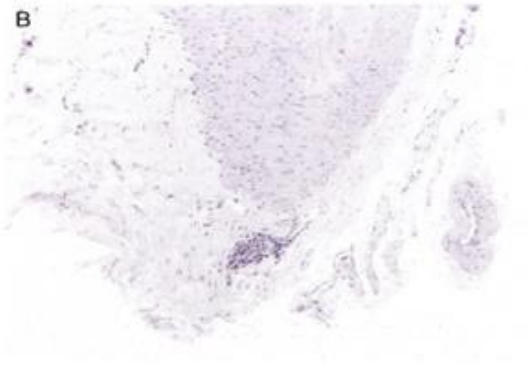
Fenotipi istologici



Transmural inflammation



Inflammation restricted to periadventitial small vessels (SVV)



Inflammation restricted to vasa vasorum (VVV) anche linfocitario

<u>Rischio ischemico oculare = nei tre pattern</u>

SVV con < sintomi craniali, minore flogosi, >sinoviti

Restuccia G. et al., Arthritis & Rheumatism, 2012

Fenotipi di malattia ed tipo di interessamento istologico

Table 2. Characteristics of the patients with SVV and/or VVV, SVV, isolated VVV, and classic GCA*

	SVV and/or VVV (n = 39)	SVV (n = 16)	Isolated VVV (n = 18)	Classic GCA (n = 39)	*P*, SVV and/or VVV vs. GCA	*P*, SVV vs. GCA	*P*, SVV vs. VVV	*P*, VVV vs. GCA
No. (%) men/women	16 (41)/23 (59)	9 (56.3)/7 (43.7)	3 (16.7)/15 (83.3)	12 (30.8)/27 (69.2)	0.479	0.126	0.030	0.342
Age at disease onset, mean ± SD years	74 ± 7	77 ± 6	71 ± 8	75 ± 7	0.418	0.298	0.027	0.095
Headache	16/39 (41.0)	5/16 (31.3)	9/18 (50)	26/39 (66.7)	0.040	0.030	0.315	0.256
Scalp tenderness	1/38 (2.6)	0/15 (0)	1/18 (5.6)	9/37 (24.3)	0.007	0.040	1.000	0.140
Abnormalities of the temporal arteries	8/18 (44.4)	2/7 (28.6)	5/8 (62.5)	23/27 (85.2)	0.007	0.007	0.315	0.312
Visual loss	6/39 (15.4)	3/16 (18.8)	2/18 (11.1)	7/39 (17.9)	1.000	1.000	0.648	0.704
Jaw claudication	2/39 (5.1)	0/16	2/18 (11.1)	11/39 (28.2)	0.013	0.030	0.487	0.191
Systemic signs/symptoms†	22/39 (56.4)	7/16 (43.8)	12/18 (66.7)	29/39 (74.4)	0.153	0.059	0.300	0.545
PMR	23/39 (59.0)	11/16 (68.8)	10/18 (55.6)	18/39 (46.2)	0.365	0.149	0.497	0.576
Peripheral synovitis	9/39 (23.1)	5/16 (31.3)	3/18 (16.7)	3/39 (7.7)	0.114	0.040	0.429	0.368
ESR, mean ± SD mm/hour	81 ± 32	70 ± 29	93 ± 27	102 ± 22	0.005	0.001	0.030	0.372
CRP, mean ± SD mg/dl‡	6.2 ± 6.5	6.0 ± 6.2	5.2 ± 3.2	10.4 ± 5.7	0.001	0.010	0.813	0.002
Hemoglobin, mean ± SD gm/dl§	11.2 ± 1.5	11.6 ± 1.5	10.9 ± 1.3	10.6 ± 1.2	0.039	0.020	0.164	0.488
Initial prednisone dosage, mean ± SD mg/day¶	29.5 ± 17.3	24.2 ± 19.5	34.0 ± 15.0	68.1 ± 92.9	0.0001	0.0001	0.053	0.0001
Duration of prednisone therapy, mean ± SD months#	29.4 ± 35.5	27.7 ± 32.7	32.8 ± 41.6	32.1 ± 49.1	0.478	0.591	0.483	0.974
Cumulative prednisone dose, mean ± SD gm**	5.462 ± 7.641	3.180 ± 3.323	7.834 ± 10.264	8.681 ± 7.480	0.007	0.004	0.093	0.236
Duration of followup, mean ± SD months††	67.4 ± 50.7	53.1 ± 41.7	75.3 ± 54.4	44.5 ± 39.5	0.040	0.470	0.260	0.040
Interval between first symptoms and diagnosis, mean ± SD days	63 ± 52	55 ± 44	78 ± 59	81 ± 59	0.135	0.100	0.211	0.891
Relapses/recurrences	7/23 (30.4)	1/8 (12.5)	3/11 (27.3)	11/34 (32.4)	1.000	0.402	0.603	1.000
Death	14/39 (35.9)	8/16 (50)	3/18 (16.7)	14/37 (37.8)	1.000	0.545	0.060	0.133

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Systemic signs/symptoms†	22/39 (56.4)	7/16 (43.8)	12/18 (66.7)	29/39 (74.4)	0.153	0.059	0.300	0.545
PMR	23/39 (59.0)	11/16 (68.8)	10/18 (55.6)	18/39 (46.2)	0.365	0.149	0.497	0.576
Peripheral synovitis	9/39 (23.1)	5/16 (31.3)	3/18 (16.7)	3/39 (7.7)	0.114	0.040	0.429	0.368
ESR, mean ± SD mm/hour	81 ± 32	70 ± 29	93 ± 27	102 ± 22	0.005	0.001	0.030	0.372
CRP, mean ± SD mg/dl‡	6.2 ± 6.5	6.0 ± 6.2	5.2 ± 3.2	10.4 ± 5.7	0.001	0.010	0.813	0.002
Hemoglobin, mean ± SD gm/dl§	11.2 ± 1.5	11.6 ± 1.5	10.9 ± 1.3	10.6 ± 1.2	0.039	0.020	0.164	0.488
Initial prednisone dosage, mean ± SD mg/day¶	29.5 ± 17.3	24.2 ± 19.5	34.0 ± 15.0	68.1 ± 92.9	0.0001	0.0001	0.053	0.0001
Duration of prednisone therapy, mean ± SD months#	29.4 ± 35.5	27.7 ± 32.7	32.8 ± 41.6	32.1 ± 49.1	0.478	0.591	0.483	0.974
Cumulative prednisone dose, mean ± SD gm**	5.462 ± 7.641	3.180 ± 3.323	7.834 ± 10.264	8.681 ± 7.480	0.007	0.004	0.093	0.236
Duration of followup, mean ± SD months††	67.4 ± 50.7	53.1 ± 41.7	75.3 ± 54.4	44.5 ± 39.5	0.040	0.470	0.260	0.040
Interval between first symptoms and diagnosis, mean ± SD days	63 ± 52	55 ± 44	78 ± 59	81 ± 59	0.135	0.100	0.211	0.891
Relapses/recurrences	7/23 (30.4)	1/8 (12.5)	3/11 (27.3)	11/34 (32.4)	1.000	0.402	0.603	1.000
Death	14/39 (35.9)	8/16 (50)	3/18 (16.7)	14/37 (37.8)	1.000	0.545	0.060	0.133

Restuccia G. et al., Arthritis & Rheumatism, 2012

Presentazioni cliniche

SINTOMI

- Sintomi costituzionali (30-60%)
- Cefalea (70-85%)
- Dolore al cuoio capelluto (20-40%)
- Claudicatio masticatoria(30-40%)
- Sitomi visivi (15-45%)
- Claudicatio degli arti (5-20%)
- Sindrome polimialgica(20-65%)
- Altri (FUO, tosse stizzosa, altri)

SEGNI

- Anormalità-palpatorie/visive dell'arteria temporale (30-60%)
- Incremento di VES e PCR (>95%)
- Anemia/trombocitemia reattive (30-65%)
- Anormalità del fundus oculi/ fluorangiografia/ campo visivo/ attività visiva

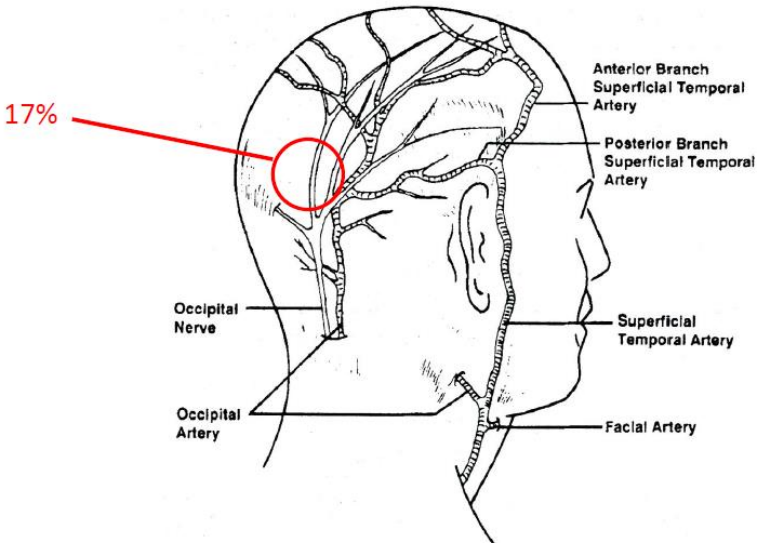
COMPLICANZE

- Perdita della vista
- Aneurismi/dissezioni di vasi di medio e grosso calibro
- Impegno ischemico cerebrale

Nesher G. ET AL., *Medicine* (Baltimore), 2004.
Weyand CM. et al., *New England Journal of Medicine,* 2014.

Cefalea atipica: cervicalgia, nucalgia e cefalea occipitale

NERVO OCCIPITALE



Jundt JW. et al, Arthritis &Rheumatism, 1991

ARTERIA OCCIPITALE

First author	Year of publication	Type of paper	Number of patients assessed	
Jese [11]	2017	Case study	93 GCA patients	31%
Pfadenhauer [9]	2003	Case study	78, 27 GCA patients	63%
Salvarani [12]	2002	Case study	86, 20 GCA patients	0%
Schmidt [10]	2002	Case-control study	33 GCA patients, 33 age and sex matched controls	9%

Pinnel J. et al, Clinical Rheumatology, 2018

Coinvolgimento oculare

- Offuscamento della vista
- Diplopia 1-19%
- Difetto visivo settoriale
- Perdita transitoria della vista 8-30%
- Perdita permanente della vista 8-28%

TABLE I
Visual symptoms in patients with visual impairment due to GCA

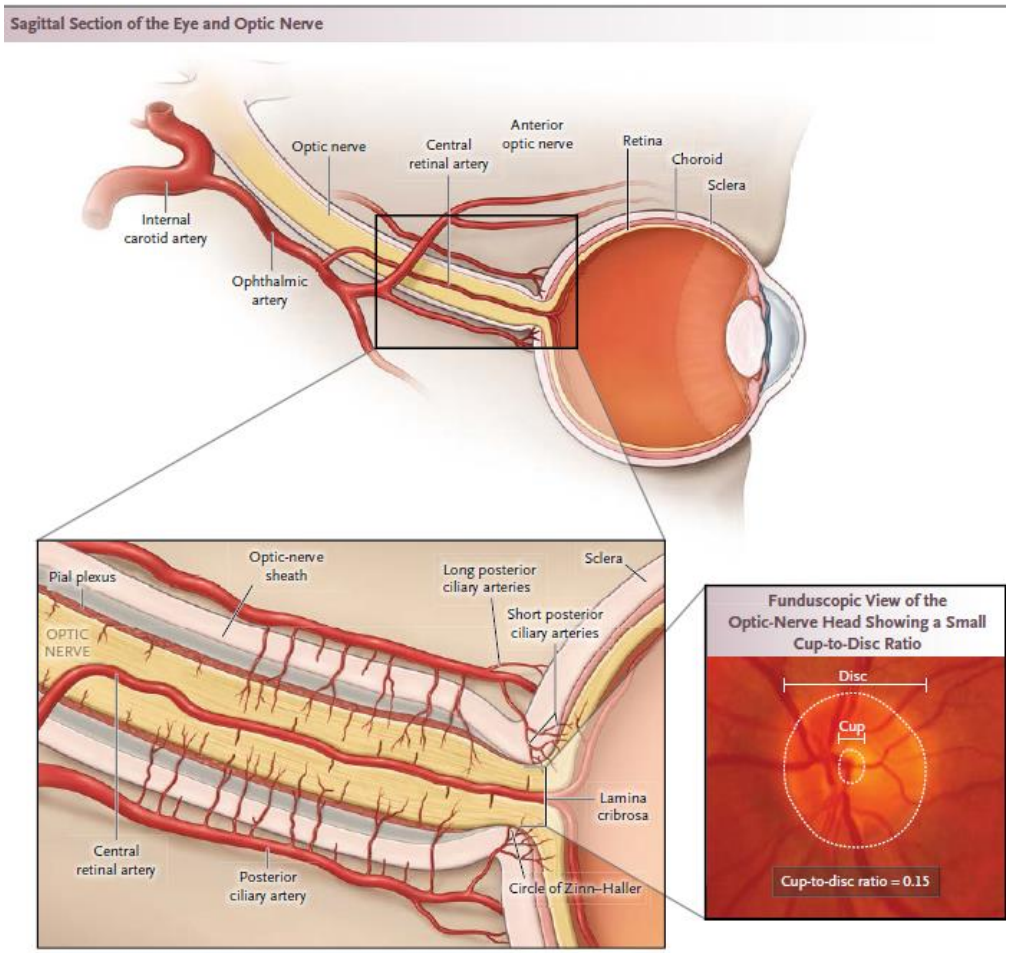
Visual loss	*N*	Premonitory symptoms	(*N*)
Monocular	12		
Sudden	8	amaurosis fugax	4
		diplopia	1
Progressive	4	blurry vision	3
		inferior hemifield loss	2
Binocular	7		
Sudden	2	blurry vision	1
Progressive		blurry vision	4
		amaurosis fugax	1
		diplopia	1
		inferior hemifield loss	1
Visual fields defect	4		
Sudden	3	amaurosis fugax	2
		blurry vision	1

N, number of patients.

Biousse V. et al, N Engl J Med, 2015
Font C. et al, *Br J Rheumatol* 1997.
Vodopivec I., et al, Rheumatology 2018

Coinvolgimento oculare

- AION 90%
  - **Ischemia anteriore del nervo ottico**
  - **Arteria ciliare posteriore**
  - Al fundus: disco pallido ed edematoso
  - All'angiografia: ipoperfusione corioidea
- CRAO (central retina artery occlusion) <8%
  - Al fundus: cherry red spots + segmentazione dell'apporto sanguigno
- Stroke occipitale <7%
  - MRI
- PION (posterior ischemic optic neuropathy) <4%
  - Ischemia della porzione retrobulbare del nervo ottico
  - **Alterazioni del fundus dopo 6-8 settimane**



Biousse V. et al, N Engl J Med, 2015
Font C. et al, *Br J Rheumatol* 1997.
Vodopivec I., et al, Rheumatology 2018

Coinvolgimento oculare: come distinguere un AION infiammatorio da un AION NON-infiammatorio?

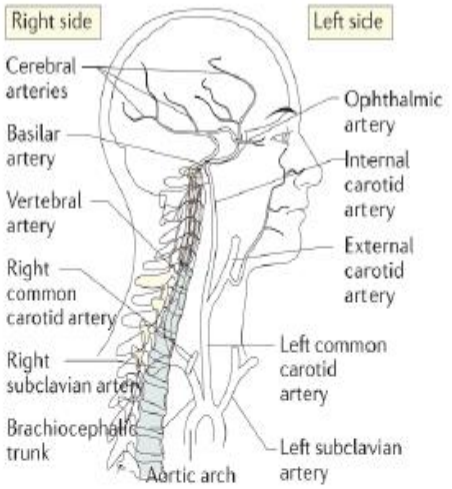
	Not inflammatory AAION	Arteritic AAION
Age	> 50 years	> 65 years
Sex distribution	M=F	F>M
Side	unilateral	uni or bilateral
Vision loss	sudden	sudden
Pain	pain occasionally noted	headache
Vision deficit	upper part	complete
Disc	hyperemic>segmental pale	Pale, swelling, cotton wool spots
Prognosis	variable	severe
Associated diseases	Hypertension, Diabetes	AGC
ESR and CRP	normal	increased

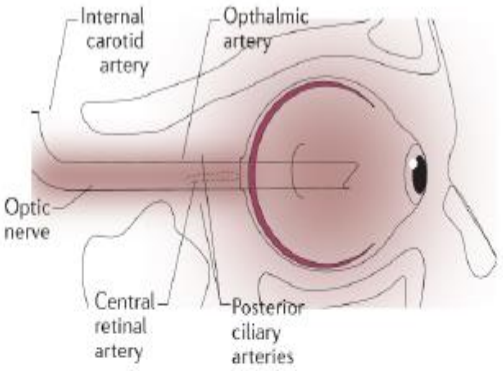
Coinvolgimento oculare: quali sono i fattori di rischio per sviluppare cecità?

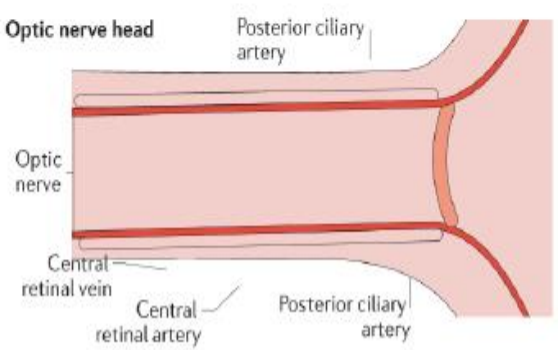
Studio	Tipo di studio	Risk factors					Livello di evidenza
		Sintomi visivi	Assenza di sintomi costituzionali	PCR e VES non elevate	Claudicatio masticatoria	FR CV/ PVD	
Cid et al. Arthritis Rheum 1998	Retrospective study of 32 Pts						2
Gonzalez-Gay et al. Arthritis Rheum 1998	Retrospective study of 239 Pts	✓	✓	✓			2
Hayreh et al. Ophthalmology 1998	Prospective study of 85 Pts	✓	✓		✓		2
Liozon *et al.* Am J of Med 2001	Prospective study of 87 Pt		✓	✓		✓	
Salvarani et al. Rheumatology 2009	Retrospective study of 180 Pts	✓	✓	✓		✓	2
Yates et al. Rheumatology 2017	Observational study of 433 Pts			✓		✓	2

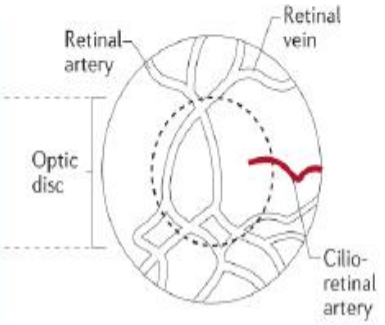
Impegno ischemico oculare: sintesi

- **Sempre precoce** (entro 5 gg da steroide, entro 4 sett da inizio sintomi)
- 1 paziente su 6**, raro dopo steroide** (1%)
- **Monolaterale** nel 67-70%, **possibile progressione bilaterale** se non trattamento
- Legato a **neuropatia ischemica anteriore del n.ottico** nella maggior parte dei casi
- **Fattori di rischio**: fattori rischio CV, genetica (PLA A1-2 polimorfismo), istologia, iperplasia intimale, calcificazioni), risposta infiammatoria, clinica ischemica precedente (amaurosi fugax, eventi visivi, claudicatio masseteri.)









AGC: impegno ischemico cerebrale

- **Stroke (>) e TIA** nel 1.5-7%; anche come esordio, in genere primo mese da inizio sintomi
- **Rari dopo steroide**
- Da eventi occlusivi **arterie extradurali**: vertebrobasilari (70%) e carotidi
- **Raro** impegno intracranico **intradurale** (vasi senza vasa vasorum e lamina elastica) con stenosi a corona rosario + dilatazioni aneurismatiche intradurali
- **Maggiore mortalità** rispetto ad atero
- **Atteggiamento terapeutico aggressivo** se intramurale

Fattori di rischio per eventi ischemici: ipertensione arteriosa, tradizionali fattori di rischio CV, precedente cardiopatia ischemica, basso livello di infiammazione (< angiogenesi)

Esistono GCA ad indici di flogosi negativi?

Studio	Tipo di studio	Risultato	Sì/ No	Livello di evidenza
Parikh et al. Ophtalmology 2006	Studio retrospettivo su 119 pazienti	2-3% delle biopsy-proven-GCA aveva indici di flogosi negativi	☑	2
Kermani et al. Semin Arthritis Rheum 2012	Studio retrospettivo su 764 pazienti	2-3% avevano indici di flogosi negativi	☑	2
Abha et al. J Rheumatol 2015	Studio retrospettivo su 204 pazienti	4% delle biopsy-proven-GCA aveva indici di flogosi negativi	☑	2

Arterite a cellule giganti: un'emergenza reumatologica.

Agisci immediatamente!

1	2	3	4
età >50 anni (solitamente >65)	PCR/VES elevate	≥1 sintomo della ACG (vedi tabella*)	Insorgenza acuta/sub-acuta

Criteri 1-4 presenti

A Prednisone (equivalente) 50mg p.o. immediatamente

B **Invio urgente dal reumatologo (appuntamento entro 1-2 giorni lavorativi)**
- In caso di disturbi visivi invio immediato in pronto soccorso per valutazione oculistica
- In caso di TIA/ictus invio immediato in pronto soccorso per valutazione neurologica

C Continua la terapia (Prednisone(equivalente) 50mg p.o./die) fino alla visita reumatologica

***Sintomi della ACG**
- Cefalea di nuova insorgenza
- Peggioramento acuto della vista (es. restrizione del campo visivo, amaurosis fugax)
- Claudicatio della mandibola / lingua
- Anormalità dell'arteria temporale
- Claudicatio degli arti

Spesso legati a
- Polimialgia reumatica
- Sintomi costituzionali (es. febbre, sudorazioni notturne, calo ponderale)

gruppo vasculiti
C. Deiaco (2019)

I pazienti con ACG possono raramente presentare VES o PCR normali. Il percorso in questi casi è uguale a quello dei pazienti con VES/PCR elevate.
I disturbi visivi e i sintomi neurologici rappresentano un'emergenza medica. I sintomi elencati sopra possono essere causati anche da malattie diverse che però necessitano ugualmente di una valutazione specialistica urgente.

Arterite gigantocellulare (GCA): fast track
H Santa Chiara Trento

Fast – track

In considerazione della importanza di una diagnosi precoce per evitare le temibili complicanze dell'arterite gigantocellulare i paziente che presentano le **caratteristiche di sospetto possono accedere al nostro servizio** per **eseguire ecodoppler dei vasi extracranici** tramite **fast trak .**

Tale accesso ha già dimostrato in studi di essere in grado di ridurre i casi di cecità permanente

(Clinc Exp. Rheum 33 (2suppl.89) S 103-S106 (2014) e Rheumatology (Oxford) 55, 66-70 (2016) e dati di real life (Vasculitis Philadelphia 2019)

MANAGEMENT

Received 6 May 2019
Revised 10 June 2019
Accepted 10 June 2019

Recommendation

2018 Update of the EULAR recommendations for the management of large vessel vasculitis

Bernhard Hellmich,[1] Ana Agueda,[2] Sara Monti,[3] Frank Buttgereit,[4] Hubert de Boysson,[5] Elisabeth Brouwer,[6] Rebecca Cassie,[7] Maria C Cid,[8] Bhaskar Dasgupta,[9] Christian Dejaco,[10,11] Gulen Hatemi,[12] Nicole Hollinger,[13] Alfred Mahr,[14] Susan P Mollan,[15,16] Chetan Mukhtyar,[17] Cristina Ponte,[18,19] Carlo Salvarani,[20] Rajappa Sivakumar,[21] Xinping Tian,[22] Gunnar Tomasson,[23] Carl Turesson,[24] Wofgang Schmidt,[25] Peter M Villiger,[26] Richard Watts,[27] Chris Young,[28] Raashid Ahmed Luqmani[29]

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Focus sulla terminologia

Table 2 EULAR consensus definitions for disease activity states in GCA and other types of LVV

Activity state	EULAR consensus definition
Active disease	1. The presence of typical signs or symptoms of active LVV (table 4). 2. At least one of the following: a. Current activity on imaging or biopsy. b. Ischaemic complications attributed to LVV. c. Persistently elevated inflammatory markers (after other causes have been excluded).
Flare	We do not recommend use of this term
Relapse	We recommend use of the terms major relapse or minor relapse as defined below
Major relapse	Recurrence of active disease with either of the following: a. Clinical features of ischaemia* (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication). b. Evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis or dissection.
Minor relapse	Recurrence of active disease, not fulfilling the criteria for a major relapse
Refractor'y	Inability to induce remission (with evidence of reactivation of disease, as defined above in 'Active disease') despite the use of standard care therapy
Remission	Absence of all clinical signs and symptoms attributable to active LVV and normalisation of ESR and CRP; in addition, for patients with extracranial disease there should be no evidence of progressive vessel narrowing or dilatation (frequency of repeat imaging to be decided on an individual basis)
Sustained remission	1. Remission for at least 6 months. 2. Achievement of the individual target GC dose.
Glucocorticoid-free remission	Sustained remission Discontinued GC therapy (but could still be receiving other immunosuppressive therapy)

*Some symptoms listed are typical only for GCA and may require further diagnostic work-up if present in other types of LVV.
GC, glucocorticoid; GCA, giant cell arteritis; LVV, large vessel vasculitis.

2018 Update of the EULAR recommendations for the management of large vessel vasculitis

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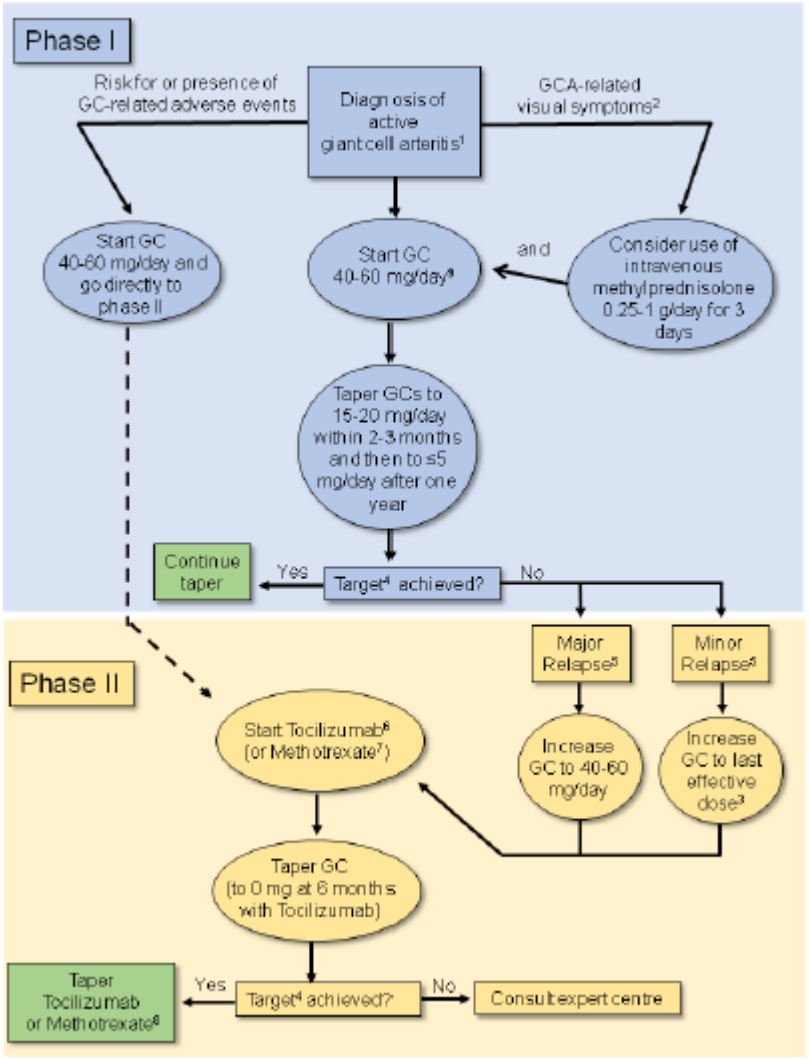
RACCOMANDAZIONI

Table 3 EULAR recommendations for the management of LVV—2018 update

		LoE	SoR	FV (%)	LoA (0–10)
	Overarching principles				
A	Patients with LVV should be offered best care which must be based on a shared decision between the patient and the rheumatologist, considering efficacy, safety and costs	n.a.	n.a.	n.a.	9.7±0.7
B	Patients should have access to education focusing on the impact of LVV, it's key warning symptoms and its treatment (including treatment-related complications)	n.a.	n.a.	n.a.	9.7±0.7
C	Patients with LVV should be screened for treatment-related and cardiovascular comorbidities. We recommend prophylaxis and life-style advice to reduce cardiovascular risk and treatment-related complications	n.a.	n.a.	n.a.	9.8±0.7
	Recommendations				
1	All patients presenting with signs and symptoms suggestive of GCA should be urgently referred to a specialist team for further multidisciplinary diagnostic work-up and management	2b	C	91	9.2±2.1
2	All patients presenting with signs and symptoms suggestive of TAK should be referred to a specialist team for multidisciplinary diagnostic work-up and management	5	D	100	9.6±0.9
3	A suspected diagnosis of LVV should be confirmed by imaging (ultrasound* or MRI§ for temporal or other cranial arteries, ultrasound, CT, PET-CT or MRI for the aorta/extracranial arteries#) or histology (TAB*)	*1b §2b #3	*A §B #C	*100 §100 #100	9.5±0.9 9.3±1.2 9.6±0.8
4	High dose glucocorticoid (GC) therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA& or TAK+ Once disease is controlled, we recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day (for GCA) and to ≤10 mg/day (for TAK)	&4 +5 5	&C +D D	&100 +100 87	9.8±0.6 9.8±0.5 9.5±0.9
5	Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using tocilizumab**. Methotrexate may be used as an alternative§§	**1b §§1a-	**A §§A	**100 §§100	9.4±0.8 9.4±0.8
6	Non-biologic disease modifying agents should be given in combination with GC in all patients with TAK#. Tocilizumab or TNF-inhibitors can be considered in case of relapsing or refractory disease despite conventional DMARD therapy#	4	C	100	9.4±1.2
7	In case of major relapse (either with signs or symptoms of ischaemia or progressive vascular inflammation) we recommend reinstitution or dose escalation of GC therapy as recommended for new onset disease.## For minor relapses we recommend an increase in GC dose at least to the last effective dose.* Initiation or modification of adjunctive therapy should be considered particularly after recurrent disease relapses&&	##2b &&1b	##C &&A	##95 &&95	9.5±1.0 9.6±1.0
8	Antiplatelet or anticoagulant therapy should not be routinely used for treatment of LVV unless it is indicated for other reasons (eg, coronary heart disease or cerebrovascular disease etc). In special situations such as vascular ischaemic complications or high risk of cardiovascular disease, these might be considered on an individual basis	4	C	100	9.4±0.8
9	In LVV, elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. However, arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team	4	C	95	9.8±0.5
10	Regular follow-up and monitoring of disease activity in patients with LVV is recommended, primarily based on symptoms, clinical findings and ESR/CRP levels	3b	C	100	9.6±0.6

The LoE was determined for different parts of each recommendation (referred to with different signs such as * or §). The level of agreement was computed on a 0–10 scale. DMARD, disease modifying anti-rheumatic drug; FV, final vote (% of expert panel members that agreed to the recommendation); LVV, large vessel vasculitis; LoA, level of agreement; LoE, level of evidence; NA, not applicable; SoR, strength of recommendation; TAB, temporal artery biopsy; TAK, Takayasu arteritis; TNF, tumour necrosis factor.

High dose GC therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA or TAK. Once disease is controlled, we recommend tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months and after 1 year to ≤5 mg/day (for GCA) and to ≤10 mg/day (for TAK)



- Dose fissa e non in base al peso
- 0.25-1 g di equivalente prednisonico solo nei pazienti con sintomi visivi
- Tapering dello steroide fino a 15-20 mg/die in 2-3 mesi e poi a $\leq$ 5 mg dopo un anno
- Sospensione in circa 2 anni
- Tapering e sospenzione più rapidi se utilizzato uno steroido-risparmiatore
- Differenziare tra minor e major relapse

Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

- Attualmente non disponiamo di predittori di relapse alla diagnosi (né clinici né istologici)

Steroide-risparmiatore da riservare a pazienti selezionati (effetti collaterali da GC, comorbidità, relapse ricorrenti..)

Tocilizumab e Methotrexate

Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

TOCILIZUMAB

Minori relapses, minori flares, minor dose di steroide, non miglior outcme comlicanze ischemiche

!!!! Inibisce la sintesi di PCR a livello epatico !!!!! -> Difficoltà nel monitoraggio

Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

METHOTREXATE

ARTHRITIS & RHEUMATISM
Vol. 56, No. 8, August 2007, pp 2789–2797
DOI 10.1002/art.22754

Adjunctive Methotrexate for Treatment of Giant Cell Arteritis

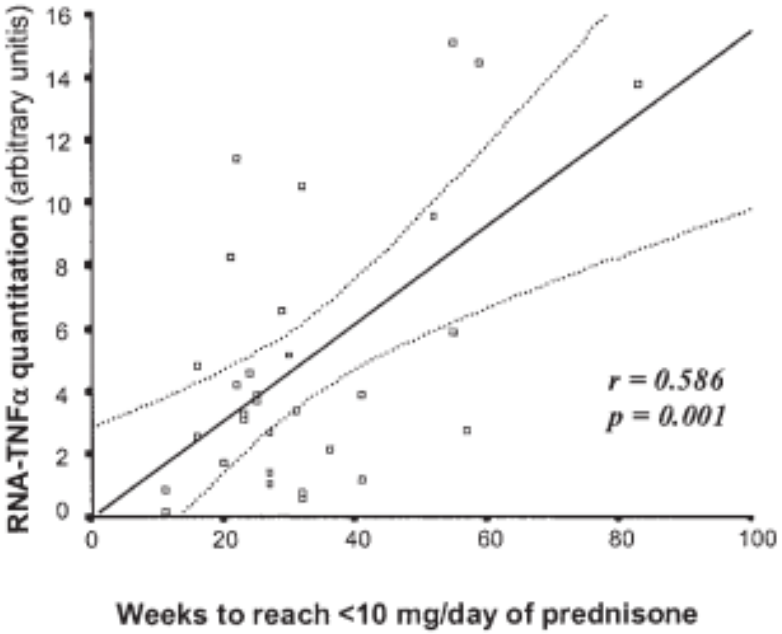
An Individual Patient Data Meta-Analysis

Alfred D. Mahr,[1] Juan A. Jover,[2] Robert F. Spiera,[3] César Hernández-García,[2] Benjamin Fernández-Gutiérrez,[2] Michael P. LaValley,[4] and Peter A. Merkel[1]

"In GCA, adjunctive treatment with MTX lowers the risk of relapse and reduces exposure to corticosteroids. These findings indicate that MTX could be considered as a therapeutic option in addition to standard-of-care treatment with corticosteroids for patients with GCA."

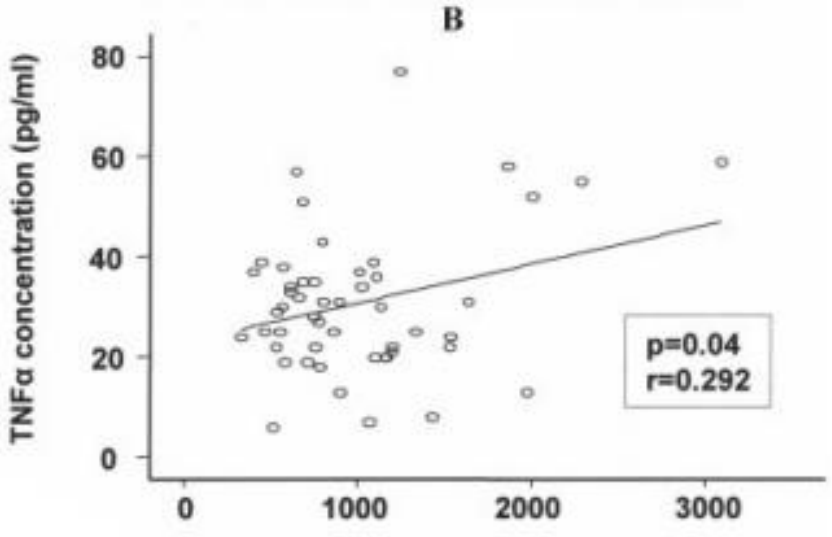
Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

Altri immunosoppressori: C'è un razionale per l'utilizzo degli anti-TNF?



GCA patients with a strong systemic inflammatory response, who have been previously shown to be more resistant to corticosteroid therapy, have elevated tissue expression of proinflammatory cytokines IL-1b, TNFa and IL-6. High production of TNFa is associated with longer corticosteroid requirements

Hernandez-Rodriguez J. et al, Rheumatology 2004

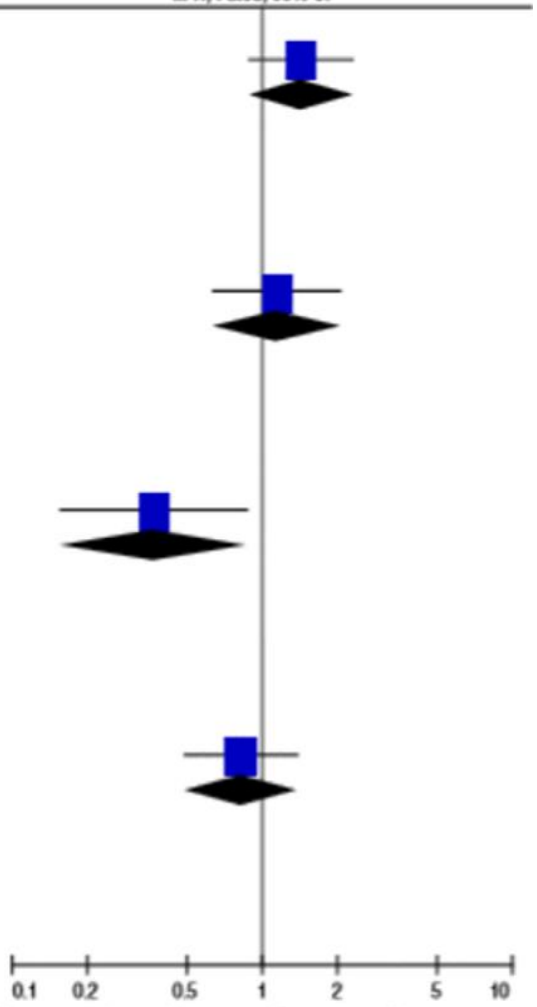


Garcia-Martinez A, et al., Arthritis Care & Research 2010

Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

Altri immunosoppressori: C'è un razionale per l'utilizzo degli anti-TNF?

Study or Subgroup	Immunosuppressant Events	Total	Prednisolone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Hydroxychloroquine						
Sailer 2009	20	32	14	32	100.0%	1.43 [0.89, 2.30]
Subtotal (95% CI)		32		32	100.0%	1.43 [0.89, 2.30]
Total events	20		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.1.3 Infliximab						
Hoffman 2007	16	28	8	16	100.0%	1.14 [0.64, 2.05]
Subtotal (95% CI)		28		16	100.0%	1.14 [0.64, 2.05]
Total events	16		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.1.6 Dapsone						
Liozon 1993	5	24	13	23	100.0%	0.37 [0.16, 0.87]
Subtotal (95% CI)		24		23	100.0%	0.37 [0.16, 0.87]
Total events	5		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						
1.1.7 Adalimumab						
Seror 2013	14	34	18	36	100.0%	0.82 [0.49, 1.38]
Subtotal (95% CI)		34		36	100.0%	0.82 [0.49, 1.38]
Total events	14		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.46)						

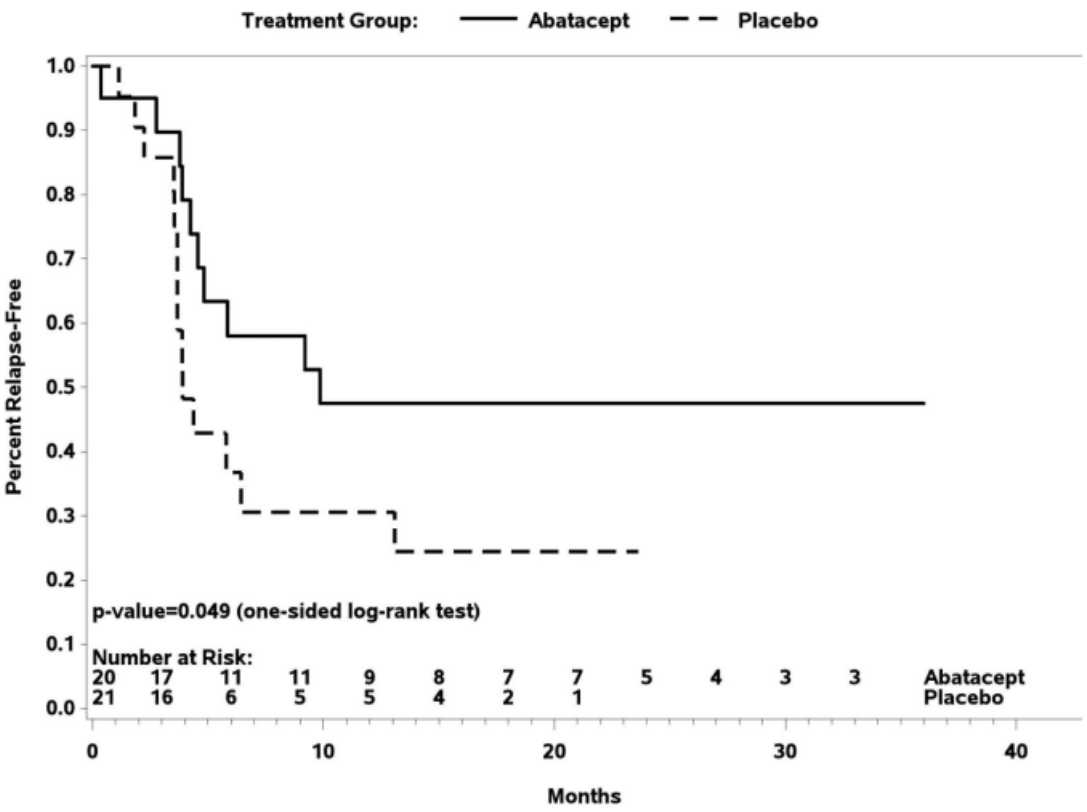


Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

Altri immunosoppressori: Abatacept

A RANDOMIZED, DOUBLE-BLIND TRIAL OF ABATACEPT (CTLA4-IG) FOR THE TREATMENT OF GIANT CELL ARTERITIS

Carol A. Langford, MD MHS[1], David Cuthbertson, MS[2], Steven R. Ytterberg, MD[3], Nader Khalidi, MD[4], Paul A. Monach, MD PhD[5], Simon Carette, MD[6], Philip Seo, MD MHS[7], Larry W. Moreland, MD[8], Michael Weisman, MD[9], Curry L Koening, MD[10], Antoine Sreih, MD[11], Robert Spiera, MD[12], Carol A. McAlear, MA[11], Kenneth J. Warrington, MD[3], Christian Pagnoux, MD[6], Kathleen McKinnon, DO[8], Lindsy J. Forbess, MD[9], Gary S. Hoffman, MD MS[1], Renée Borchin[2], Jeffrey P. Krischer, PhD[2], Peter A. Merkel, MD MPH[11], and for the Vasculitis Clinical Research Consortium

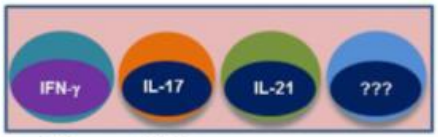
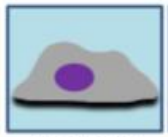
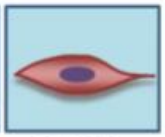


- Relapse-free survival at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo (p=0.049).
- A longer median duration of remission was seen with abatacept (9.9 months) compared to placebo (3.9 months, p=0.023).
- No difference in the frequency or severity of adverse events between treatment arms, including infection.

Dati da confermare in coorti più ampie

ALL'ORIZZONTE

Table 1. Approaching disease complexity with a multipronged and individualized therapeutic strategy

	Innate immunity		Adaptive immunity		Vascular cells	
Cellular players	 *Dendritic cells*	 *Macrophages*	 *Th1* *Th17*		 *Endothelial cells*	 *Smooth muscle cells*
Available therapies	Gluco-corticoids	Gluco-corticoids	Gluco-corticoids	Gluco-corticoids	Gluco-corticoids	
Possible therapies	IL-6 blockade Statins	IL-6 blockade Statins	Abatacept Aspirin Azathioprine Mycophenolate Methotrexate ? Cyclosporine ? Tacrolimus ? (Cyclophosphamide ?)		VEGF blockade Statins	Statins
On the horizon	anti-GM-CSF Blocking signaling pathways (JAK/STAT, NFkB, MAPK) Mesenchymal stem cells Glabridin		Antibodies to T-cell cytokines Blocking co-stimulation Blocking T-cell recruitment Mesenchymal stem cells		Metabolic interference	Blocking smooth muscle cell contraction

Watanabe R. et al, Curr Treatm Opt Rheumatol, 2016

Antiplatelet or anticoagulant therapy should not be routinely used for treatment of LVV unless it is indicated for other reasons (eg, coronary heart disease, cerebrovascular disease, etc). In special situations such as vascular ischaemic complications or high risk of cardiovascular disease, these might be considered on an individual basis

Impact of antiplatelet therapy in the development of severe ischemic complications and in the outcome of patients with giant cell arteritis

J. Narváez, B. Bernad, C. Gómez-Vaquero, C. García-Gómez, D. Roig-Vilaseca, X. Juanola, J. Rodriguez-Moreno, J.M. Nolla, J. Valverde

Rheumatology 2009;48:258–261
Advance Access publication 7 January 2009
doi:10.1093/rheumatology/ken480

Concise Report

High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition

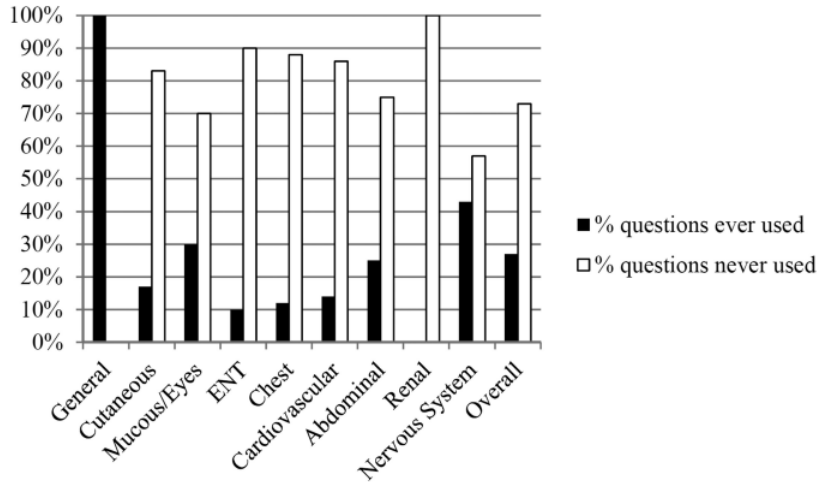
C. T. Berger[1,2], M. Wolbers[3], P. Meyer[4], T. Daikeler[1,5,*] and C. Hess[1,2,*]

AGC: clinimetria unmet need

J Rheumatol. 2016 June ; 43(6): 1078–1084. doi:10.3899/jrheum.151063.

The Birmingham Vasculitis Activity Score as a Measure of Disease Activity in Patients with Giant Cell Arteritis

TA Kermani, MD, MS[1], D Cuthbertson, MS[2], S Carette, MD, FRCPC[3], GS Hoffman, MD, MS[4], NA Khalidi, MD, FRCPC[5], CL Koening, MD, MS[6], CA Langford, MD, MHS[4], K McKinnon-Maksimowicz, DO[7], CA McAlear, MA[8], PA Monach, MD, PhD[9], P Seo, MD, MHS[10], KJ Warrington, MD[11], SR Ytterberg, MD[11], PA Merkel, MD, MPH[8], EL Matteson, MD, MPH[11], and the Vasculitis Clinical Research Consortium



- The BVAS has limited utility in GCA.
- Patients with active GCA can have a BVAS of 0.
- Many important ischemic symptoms attributable to active vasculitis are not captured in the composite score

Necessità di uno strumento specifico per valutare l'attività di malattia

AGC: monitoraggio e follow up

Regular follow-up and monitoring of disease activity is recommended in patients with LVV, primarily based on symptoms, clinical findings and ESR/CRP levels

- **Rivalutazione clinica** e degli indici di flogosi ogni 1-3 mesi nel primo anno, poi ogni 3-6 mesi
- Visita annuale per i pazienti in relapse-free remission
- **NON raccomandato l'uso dell'imaging, a meno di sospetto relapse**
- **Screening per aorta** (dopo 4-5 anni) specie se altri fattori di rischio CV (ipertensione)
- **Considerare rischio CV**: possibile coronaropatia; possibile stroke (40-70% vertebro basilare, spesso primo anno; stenosi/eco con alone, raro arterie intracraniche, ma grave)

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 9, September 2018, pp 1366–1376
DOI 10.1002/art.40520

REVIEW

What Is the Current Evidence for Disease Subsets in Giant Cell Arteritis?

Kornelis S. M. van der Geest, Maria Sandovici, Yannick van Sleen, Jan-Stephan Sanders, Nicolaas A. Bos, Wayel H. Abdulahad, Coen A. Stegeman, Peter Heeringa, Abraham Rutgers, Cees G. M. Kallenberg, Annemieke M. H. Boots, and Elisabeth Brouwer

- Evidence for **distinct GC**A subset based **on clinical features**
- Evidence for distinct GCA subset based **on immunologic features**
  Dendritic cells (DCs) and T lymphocytes and macrophages , VSMC in the inflamed artery.
  B cells and ectopic lymphoid structures in the inflamed artery. Chemokines in the inflamed artery.
- Histologic patterns **in temporal biopsy**
- Targeting factors **associated with cranial ischemic symptoms and relapse and high glucocorticoid requirement**

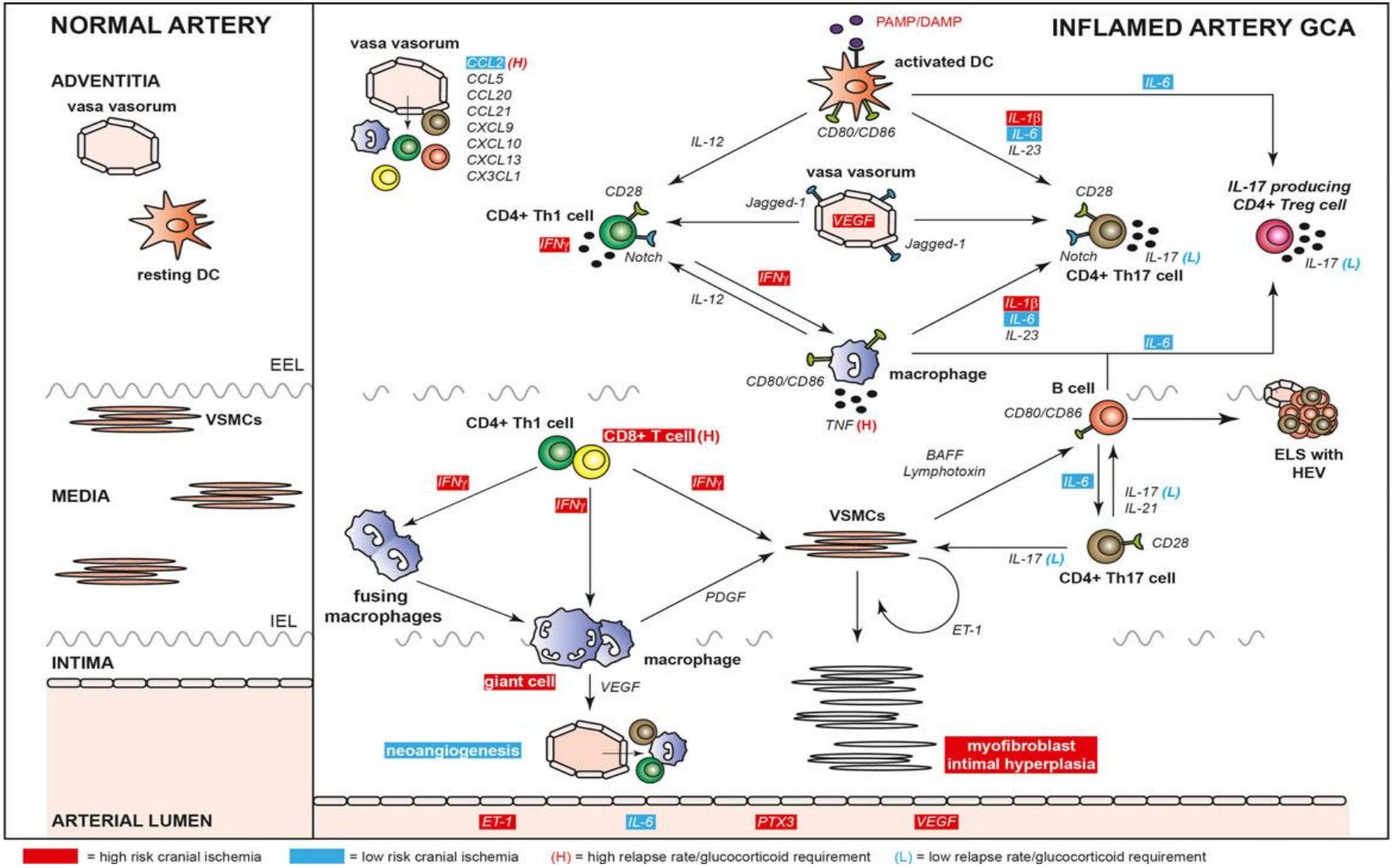


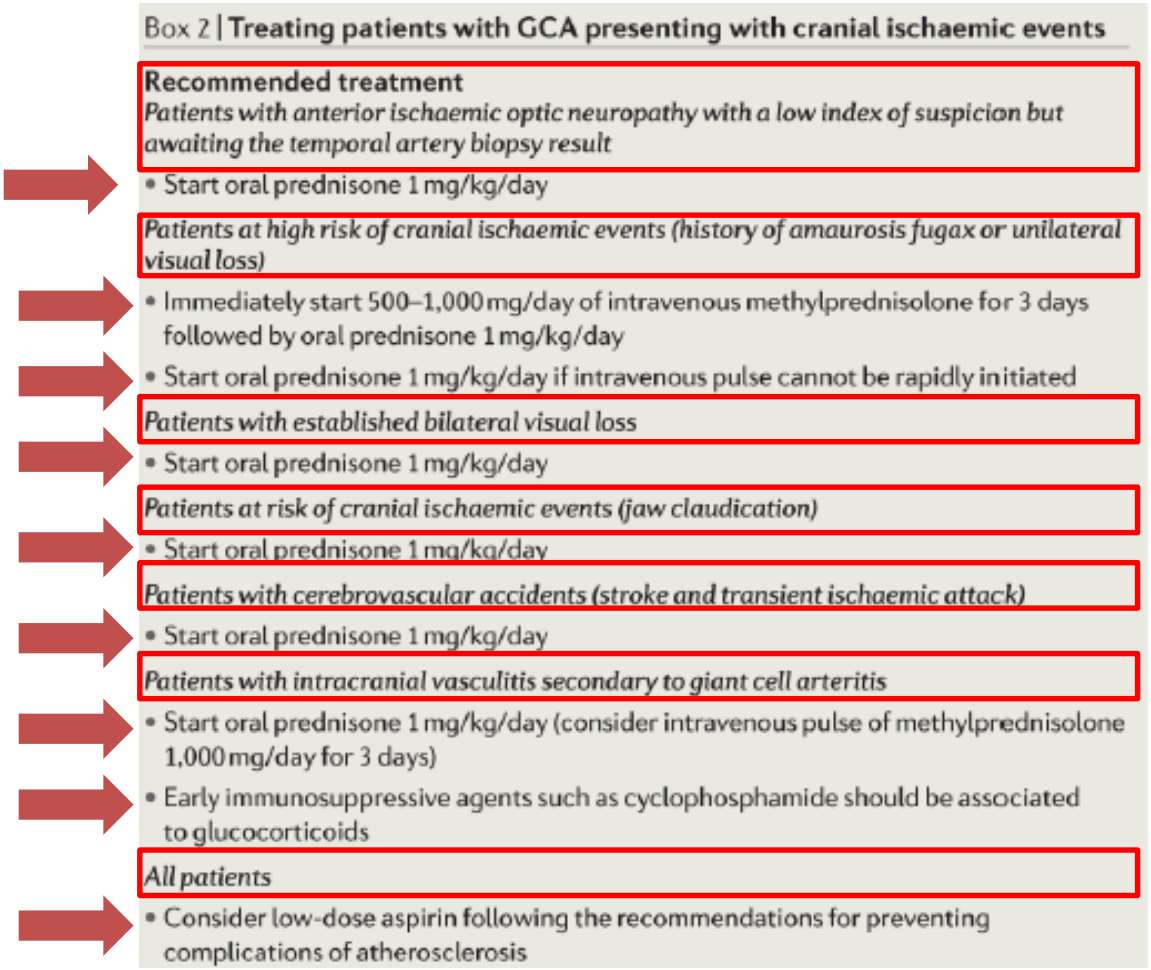
Figure 1. Overview of immune pathology of giant cell arteritis (GCA).

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 9, September 2018, pp 1366–1376

Take home messages: AGC terapia

- **Trattamento precoce** (< danno ischemico, perdita visus)
- PN 40-60 mg die
- MPD boli se deficit visus
- No ASA routinario
- Prevenire danno da steroide (osso)
- MTX conflittuale (NNT 5 per prevenire una relapse, non riduzione EC)
- No altri immunosoppressori (ciclofosfamide in casi rari gravi)
- Leflunomide possibile
- Non anti TNFα
- **Si tocilizumab (GIACTA): recidive, diabete, osteoporosi complicata..?**
- In studio Abatacept, ustekinumab, anti IL17, Jak 2 inibitori

AGC ed impegno ischemico cerebrale: individualizzare terapia in relazione a clinica



Box 2 | **Treating patients with GCA presenting with cranial ischaemic events**

Recommended treatment

Patients with anterior ischaemic optic neuropathy with a low index of suspicion but awaiting the temporal artery biopsy result

- Start oral prednisone 1 mg/kg/day

Patients at high risk of cranial ischaemic events (history of amaurosis fugax or unilateral visual loss)

- Immediately start 500–1,000 mg/day of intravenous methylprednisolone for 3 days followed by oral prednisone 1 mg/kg/day
- Start oral prednisone 1 mg/kg/day if intravenous pulse cannot be rapidly initiated

Patients with established bilateral visual loss

- Start oral prednisone 1 mg/kg/day

Patients at risk of cranial ischaemic events (jaw claudication)

- Start oral prednisone 1 mg/kg/day

Patients with cerebrovascular accidents (stroke and transient ischaemic attack)

- Start oral prednisone 1 mg/kg/day

Patients with intracranial vasculitis secondary to giant cell arteritis

- Start oral prednisone 1 mg/kg/day (consider intravenous pulse of methylprednisolone 1,000 mg/day for 3 days)
- Early immunosuppressive agents such as cyclophosphamide should be associated to glucocorticoids

All patients

- Consider low-dose aspirin following the recommendations for preventing complications of atherosclerosis

NATURE REVIEWS | RHEUMATOLOGY VOLUME 13 | AUGUST 2017 | 479

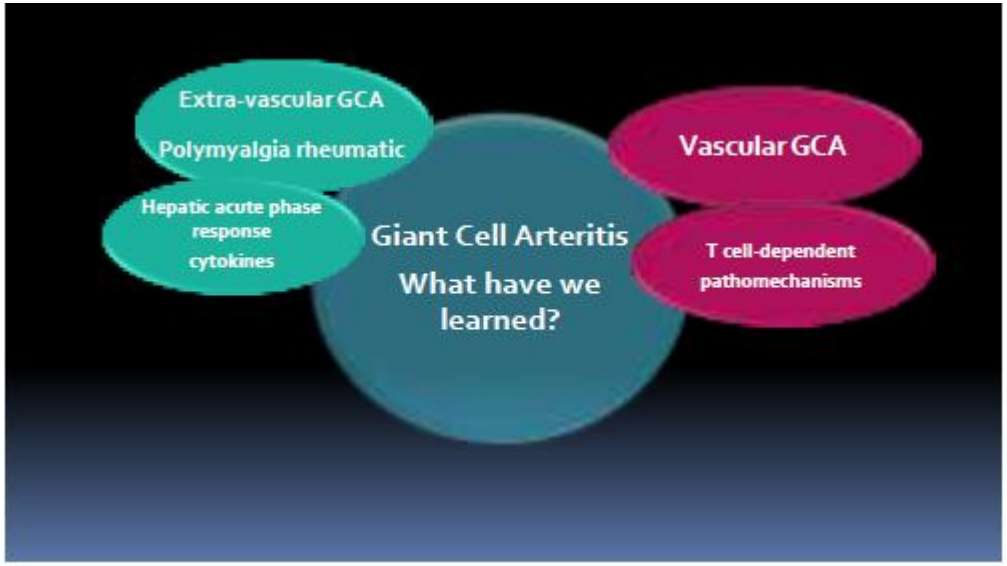
Visual loss and other cranial ischaemic complications in giant cell arteritis

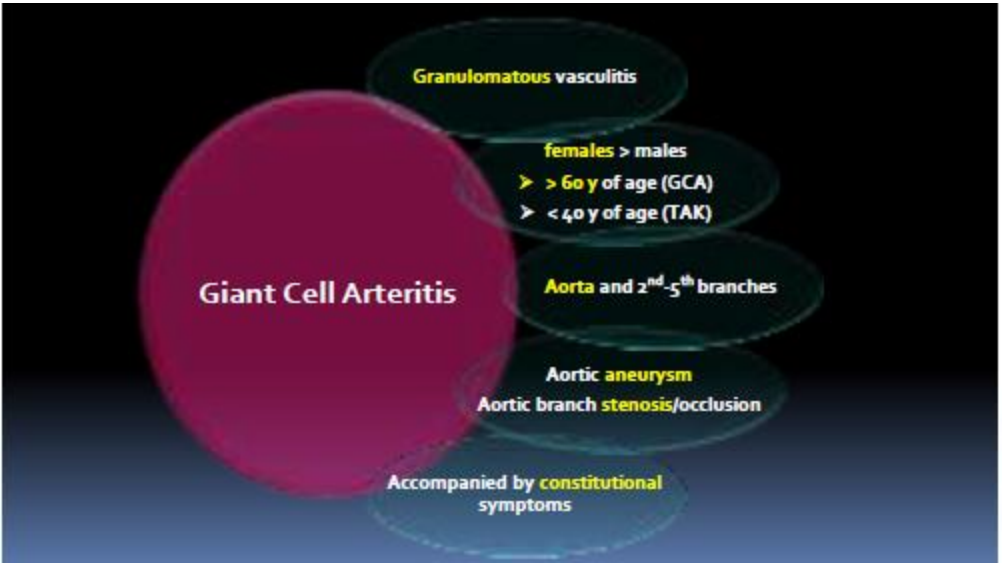
Alessandra Soriano[1,2], Francesco Muratore[1,3], Nicolò Pipitone[1], Luigi Boiardi[1], Luca Cimino[4] and Carlo Salvarani[1,3]

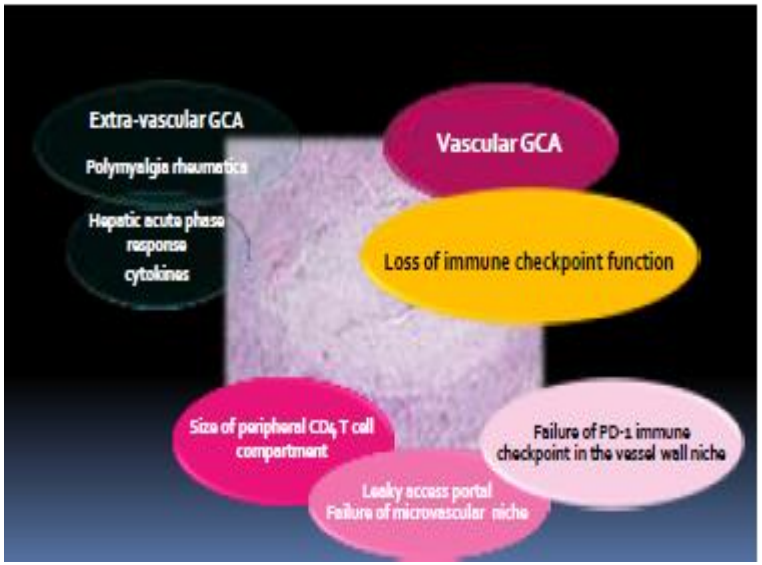
Key points

- Visual loss is the most feared manifestation of giant cell arteritis (GCA) and occurs in up to 20% of patients before glucocorticoid therapy is commenced
- Anterior ischaemic optic neuropathy (AION) owing to arteritis of the posterior ciliary arteries is the most common cause of visual loss in GCA and must be differentiated from non-arteritic AION
- Cerebrovascular accidents — stroke and transient ischaemic attack — occur in 1.5–7% of patients with GCA and are caused by stenosis or occlusion of the extradural vertebral or carotid arteries
- A previous ischaemic event in GCA is the strongest predictor for a subsequent event; patients with traditional cardiovascular risk factors and a lower inflammatory response are more likely to develop ischaemic manifestations
- Adequate doses of glucocorticoids in GCA largely prevent further cranial ischaemic events, but are scarcely effective at improving established visual loss
- Fast-track clinics for the diagnosis of GCA might substantially reduce the occurrence of permanent sight loss by reducing diagnostic delay.

Arterite gigantocellulare: cosa abbiamo imparato?







RINGRAZIAMENTI

OSPEDALE SANTA CHIARA TRENTO
U.O. di Reumatologia

Roberto Bortolotti

Francesco Cavatorta

Susanna Peccatori

Lorenzo Leveghi

Milena Bond

Sara Tonetta

Giovanni Barausse

Alvise Berti

Abdel Jaber Masen

Si ringrazia inoltre tutto il personale infermieristico, assistenziale e amministrativo con cui lavoriamo ogni giorno

Grazie per l'attenzione!