11ο ΚΡΗΤΟ-ΚΥΠΡΙΑΚΟ
ΣΥΜΠΟΣΙΟ ΡΕΥΜΑΤΟΛΟΓΙΑΣ

Η ΡΕΥΜΑΤΟΛΟΓΙΑ ΣΗΜΕΡΑ
ΠΡΑΚΤΙΚΑ ΠΡΟΒΛΗΜΑΤΑ ΤΗΣ ΚΑΘΗΜΕΡΙΝΗΣ ΚΛΙΝΙΚΗΣ ΠΡΑΞΗΣ

ΞΕΝΟΔΟΧΕΙΟ HILTON PARK | ΛΕΥΚΩΣΙΑ | ΚΥΠΡΟΣ

20 - 22 ΣΕΠΤΕΜΒΡΙΟΥ 2019

Large vessel vasculitis: Recent advances in pathogenesis and management

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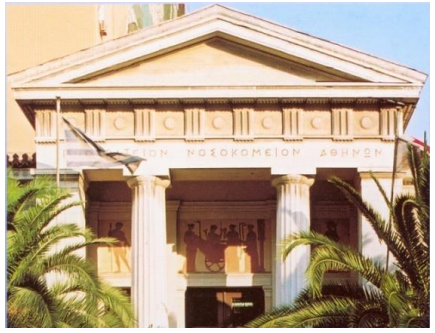


2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

PRIMARY

Large vessel (LVV)

- Giant cell arteritis (GCA)
- Takayasu arteritis (TAK)

Medium vessel (MVV)

- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small vessel (SVV)

- ANCA-associated (AAV)
  - GPA (Wegener)
  - MPA
  - EGPA (Churg-Strauss)
- Immune complex SVV
  - IgA vasculitis (HSP)
  - Cryo vasculitis
  - Anti-GBM
  - Hypocomplementemic Urticarial Vasculitis (HUV)

Variable vessel vasculitis (VVV)

- Behçet's disease (BD)
- Cogan's syndrome (CS)

Single-organ vasculitis (SOV)

- Cutaneous leucocytoclastic angiitis
- Cutaneous arteritis
- Primary CNS vasculitis
- Isolated aortitis
- Others

SECONDARY

Vasculitis associated with systemic disease

- Lupus vasculitis (SLE)
- Rheumatoid vasculitis (RA)
- Sarcoid vasculitis (Sarcoidosis)
- Others

Vasculitis associated with probable etiology

- HCV-associated CV
- HBV-associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- --//-- ANCA-associated vasculitis
- Cancer-associated vasculitis

Jennette JC et al, Arthritis Rheumatol 2013

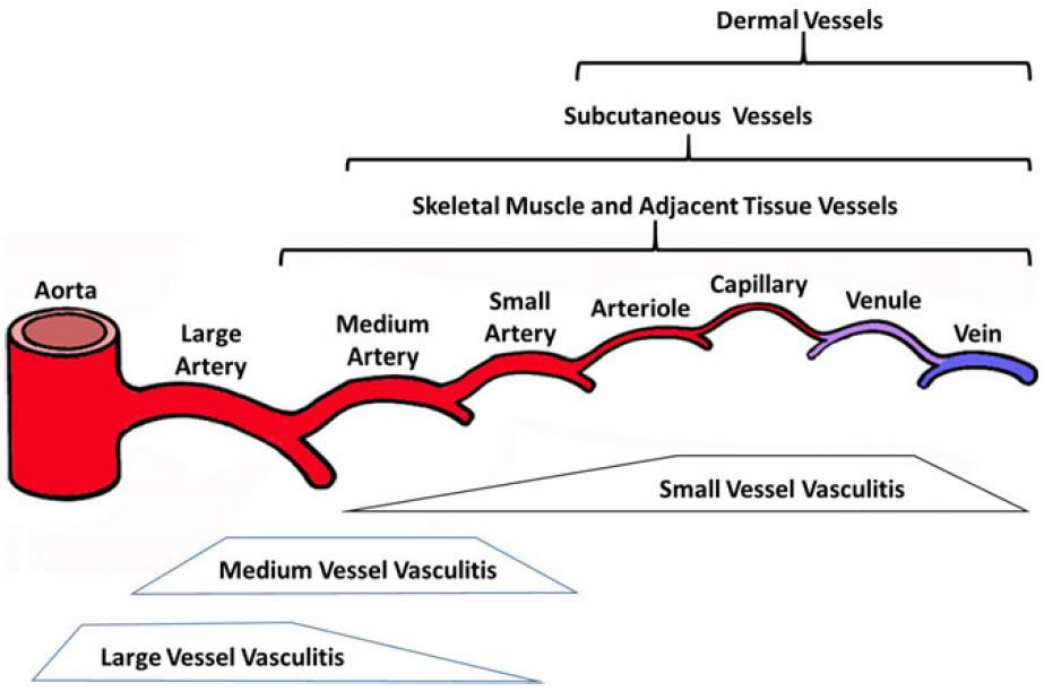
2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 2, February 2018, pp 171–184

Nomenclature of Cutaneous Vasculitis

Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

Cord H. Sunderkötter,[1] Bernhard Zelger,[2] Ko-Ron Chen,[3] Luis Requena,[4] Warren Piette,[5] J. Andrew Carlson,[6] Jan Dutz,[7] Peter Lamprecht,[8] Alfred Mahr,[9] Elisabeth Aberer,[10] Victoria P. Werth,[11] David A. Wetter,[12] Seiji Kawana,[13] Raashid Luqmani,[14] Camille Frances,[15] Joseph Jorizzo,[16] J. Richard Watts,[17] Dieter Metze,[18] Marzia Caproni,[19] Erkan Alpsoy,[20] Jeffrey P. Callen,[21] David Fiorentino,[22] Peter A. Merkel,[23] Ronald J. Falk,[24] and J. Charles Jennette[24]



SKIN

What has been added?

Cutaneous Single-organ vasculitis (SOV)

- **IgG/IgM immune complex vasculitis**
  - Non-IgA immune complex vasculitis of post-capillary venules (old names: *Hypersensitivity vasculitis, idiopathic LCV….)*
- **Nodular vasculitis *(erythema induratum of Bazin)***
  - Panniculitis + Vasculitis of the panniculus
- **Normocomplementemic urticarial vasculitis**
- **Erythema elevatum et diutinum**
- **Recurrent macular vasculitis in hypergammaglobulinemia**

Takayasu arteritis (TAK)

When to think about it?

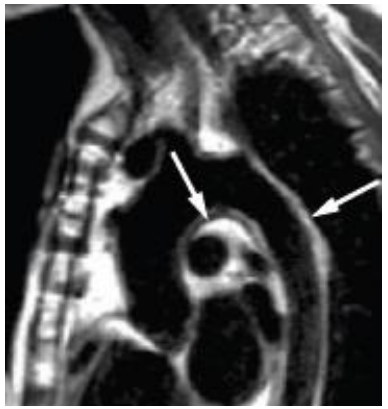
Box 1 | ‘Red flags’ for Takayasu arteritis

In patients under 40 years of age there are a number of clinical findings that might indicate a diagnosis of Takayasu arteritis:

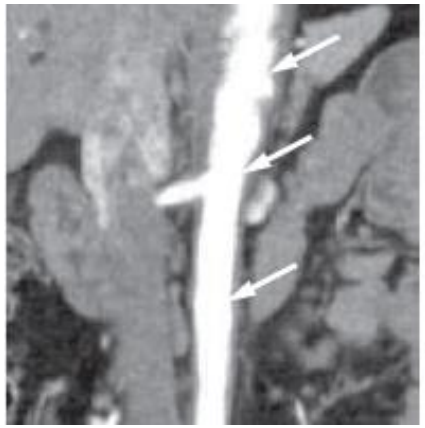
- An unexplained acute phase response (raised erythrocyte sedimentation rate or C-reactive protein levels, or both)
- Carotidynia
- Hypertension
- Discrepant blood pressure between the arms (>10 mmHg)
- Absent or weak peripheral pulse(s)
- Limb claudication
- Arterial bruit
- Angina

Mason JC , Nat Rev Rheumatol 2010

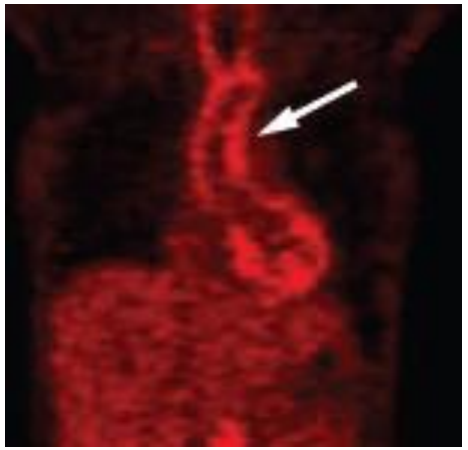
“Imaging” diagnosis



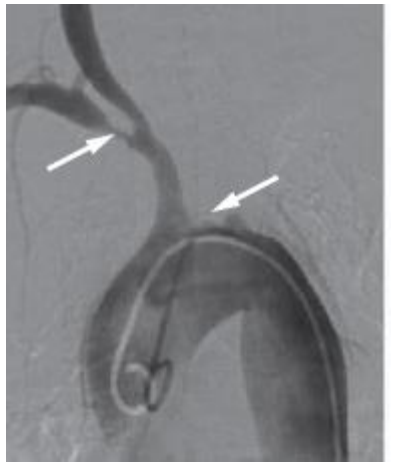
MRA (preferred method)



CTA



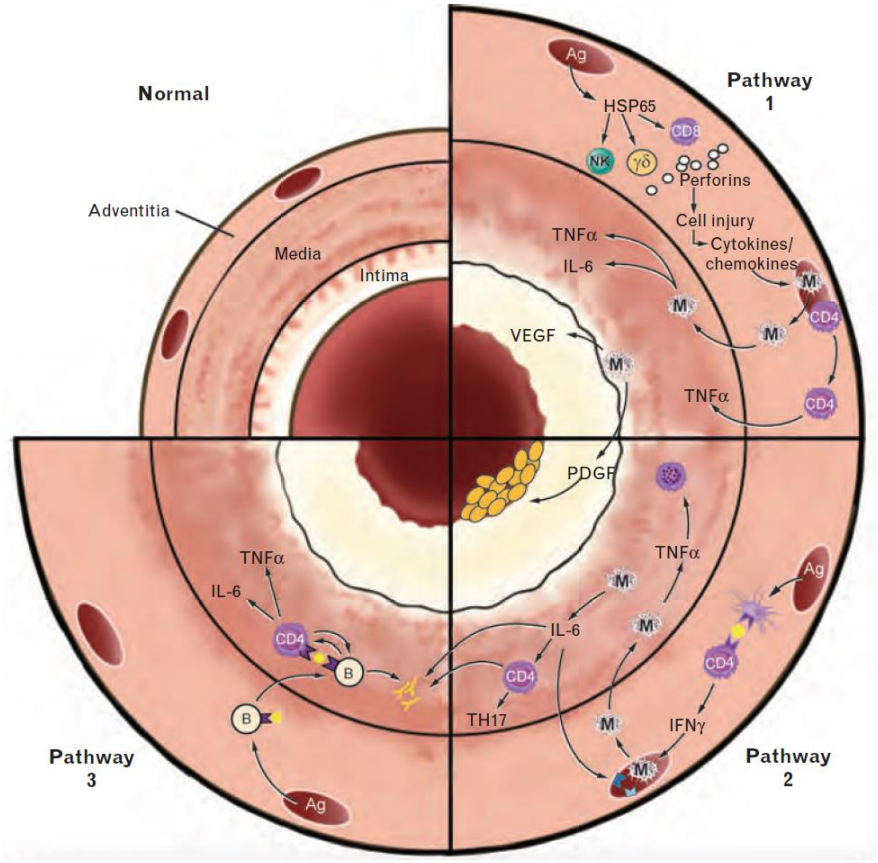
PET-CT



Angiography

Dejaco C , Ann Rheum Dis 2018 (EULAR Guidelines for Imaging)

Takayasu arteritis (TAK): Pathogenesis



Clifford A et al, Curr Opin Rheumatol 2016

- **Granulomatous panarteritis of aorta/ branches of young ♀ (< 40 yrs)**
- **HLA-class I associated disease (B/MICA)**

Renauer PA et al, Arthritis Rheumatol 2015
Saruhan-Direskeneli G et al, Am J Hum Genet 2013

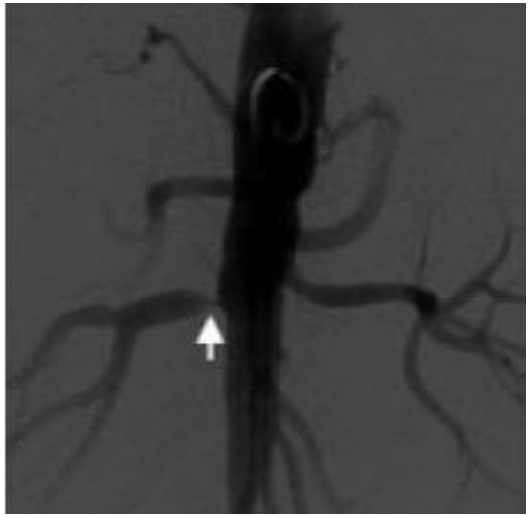
- **Th1/Th17 mediated disease**

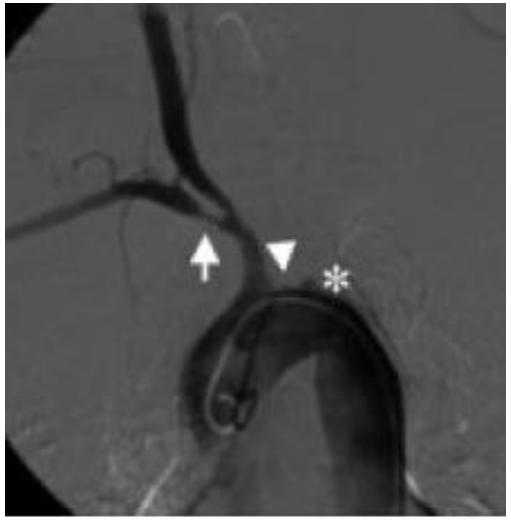
Saadoun D et al, Arthritis Rheumatol 2015

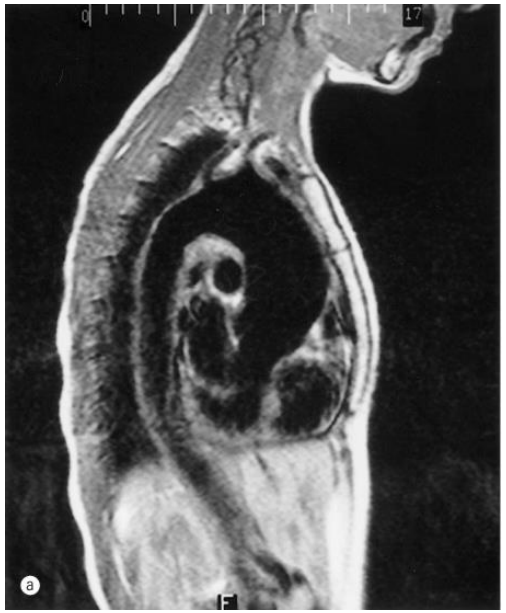
- **Central role for cytokines such as:**
  - **IL6**
  - **IFNγ**
  - **TNFa**

Clifford A et al, Curr Opin Rheumatol 2016

Takayasu arteritis (TAK): Natural course - Monitoring







Relapse rate: 70%

~ 40%: Vascular complications
(stenoses/aneurysms)

Comarmond C et al, Circulation 2017

Monitoring

1st year	q1-3 months
>1 year	q3-6 months

How?

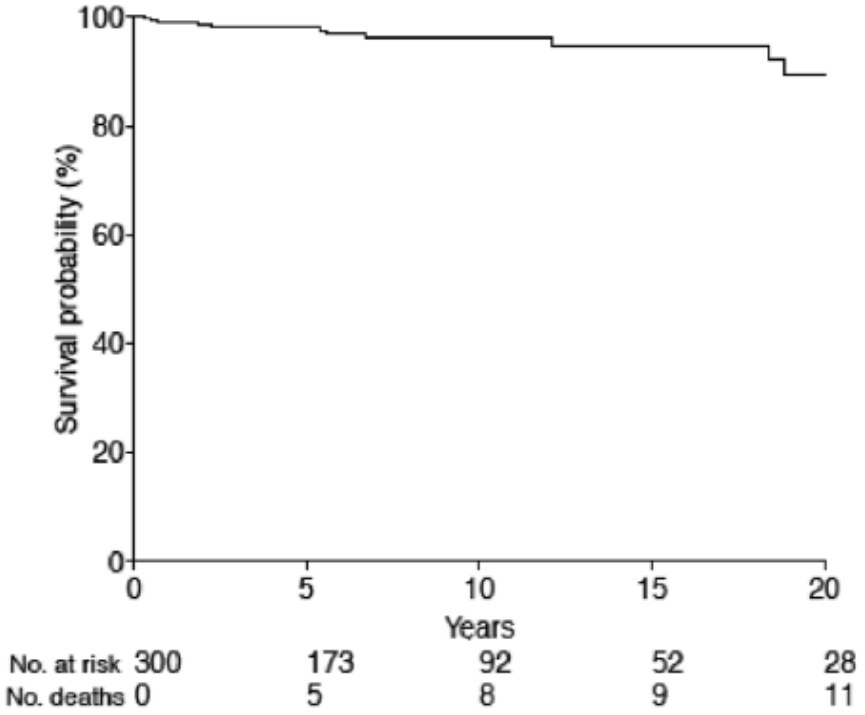
- Clinically (symptoms/signs)
- ESR/CRP
- Imaging (MRA, CTA, US)

Takayasu arteritis (TAK): Mortality

n=318

Age at dx: 36 yrs

Mortality: 5%



Miruse A et al, J Autoimmun 2019
(French Takayasu Network)

Death causes:

- **80% Cardiovascular complications**
  (mesenteric ischemia, aneurysm rupture)
- **20% Infections**

Takayasu arteritis (TAK): Initial GC therapy

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

		LoE	SoR	FV (%)	LoA (0–10)
4	High dose glucocorticoid (GC) therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active TAK+	+5	+D	+100	9.8±0.5
	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 ≤10 mg/day (for TAK)	5	D	87	9.5±0.9
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

Need from combined therapy **at diagnosis**:

GC

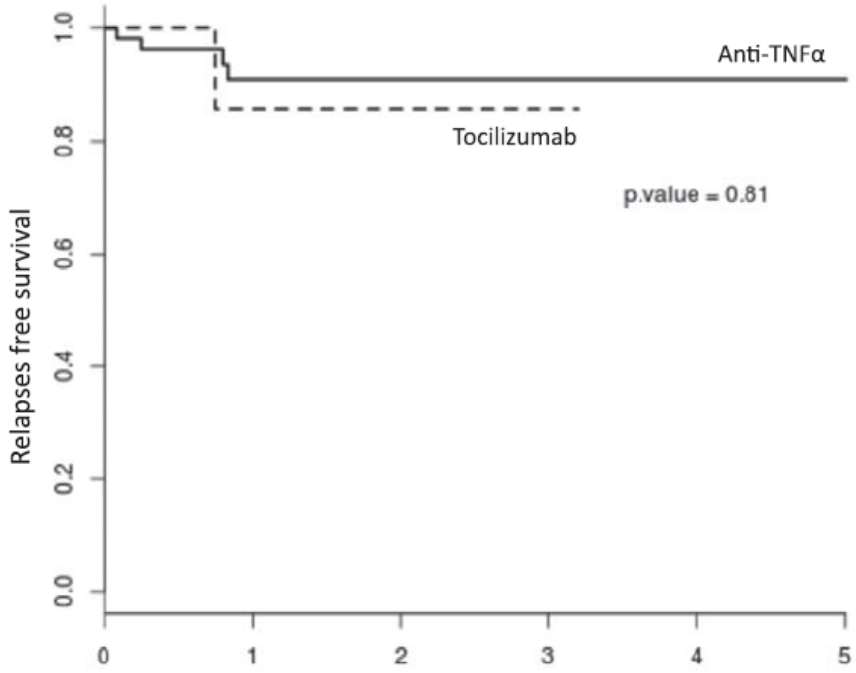
+

Steroid-sparing

(methotrexate/mycophenolate mofetil/leflunomide/azathioprine)

Since TAK targets primarily women with childbearing potential and is a chronic and usually not acutely life threatening disease (unlike AAV), the use of cyclophosphamide should be limited to patients where other treatments have failed or are not tolerated.

Takayasu arteritis (TAK): Anti-TNF vs. TCZ



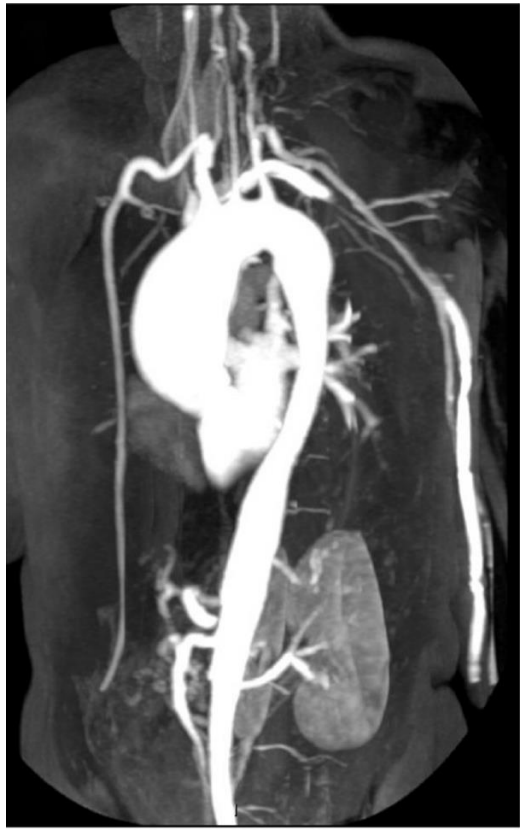
Mekinian A et al, Circulation 2015

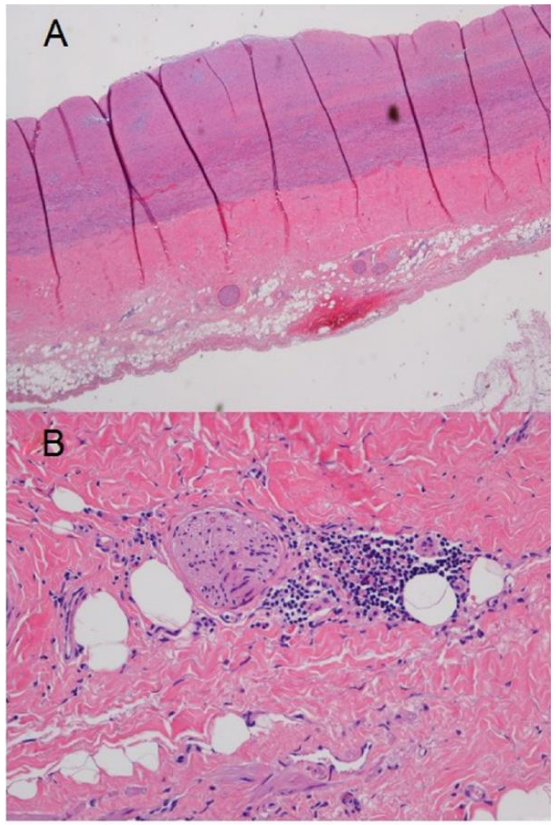
Relapse rate: 70%

- A TNF-inhibitor or TCZ can be used as second line agents in case of **relapsing disease**.

- The choice of a specific immunosuppressive agent should be based on patient **comorbidities** or **contraindications**.

TAK: Progression on TCZ with nl ESR/CRP





Muratore F, Salvarani C. Ann Rheum Dis 2019

25-year-old ♀ with TAK (carotid arteries, thoracic descending and infrarenal abdominal aorta and **dilatation of the ascending aorta 40 mm**)

- Induction Rx: **PRE** (1 mg/kg/day) + **MTX** (20 mg/week).
- On low dose PRE + MTX: **Relapse** (Symptoms + ↑ CRP/ESR + ↑ PET uptake in thoracic-abdominal aorta)
- Start **TCZ** (8 mg/kg/mo IV) → No symptoms – nl ESR-CRP – Normal PET
- **18 mo later on TCZ**:
  MRA = **Dilatation of the ascending aorta 54 mm**,
  Stenosis of descending thoracic and infrarenal abdominal aorta
- Sx: Ascending aorta and proximal hemiarch replacement
- Pathology: Adventitial **fibrosis and mural thickening** (A)
  Adventitial **small vessel vasculitis** (B)
- Switch to **infliximab** + **high-dose steroids**
- **Remission**

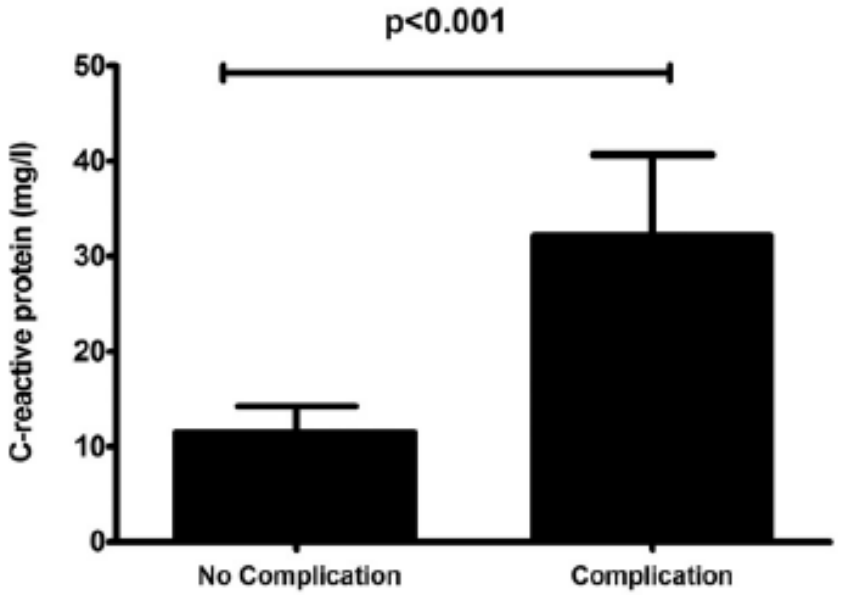
Takayasu arteritis (TAK): Non-medical treatment

Vascular complications
(stenoses/aneurysms)

	Open Surgery*	Endovascular intervention* (angiopalsty ± stent)
Relapses:	**21-40%**	**48-78%**

Perrera AH et al, BJS 2014
Saadoun D et al, Circulation 2012
Fields CE et al, J Vasc Surg 2006
Ham SW et al, J Vasc Surg 2011
Cong XL et al, Clin Rheumatol 2010
Maksimowicz-McKinnon K et al, Arthritis Rheum 2007

*** Better results during remission**

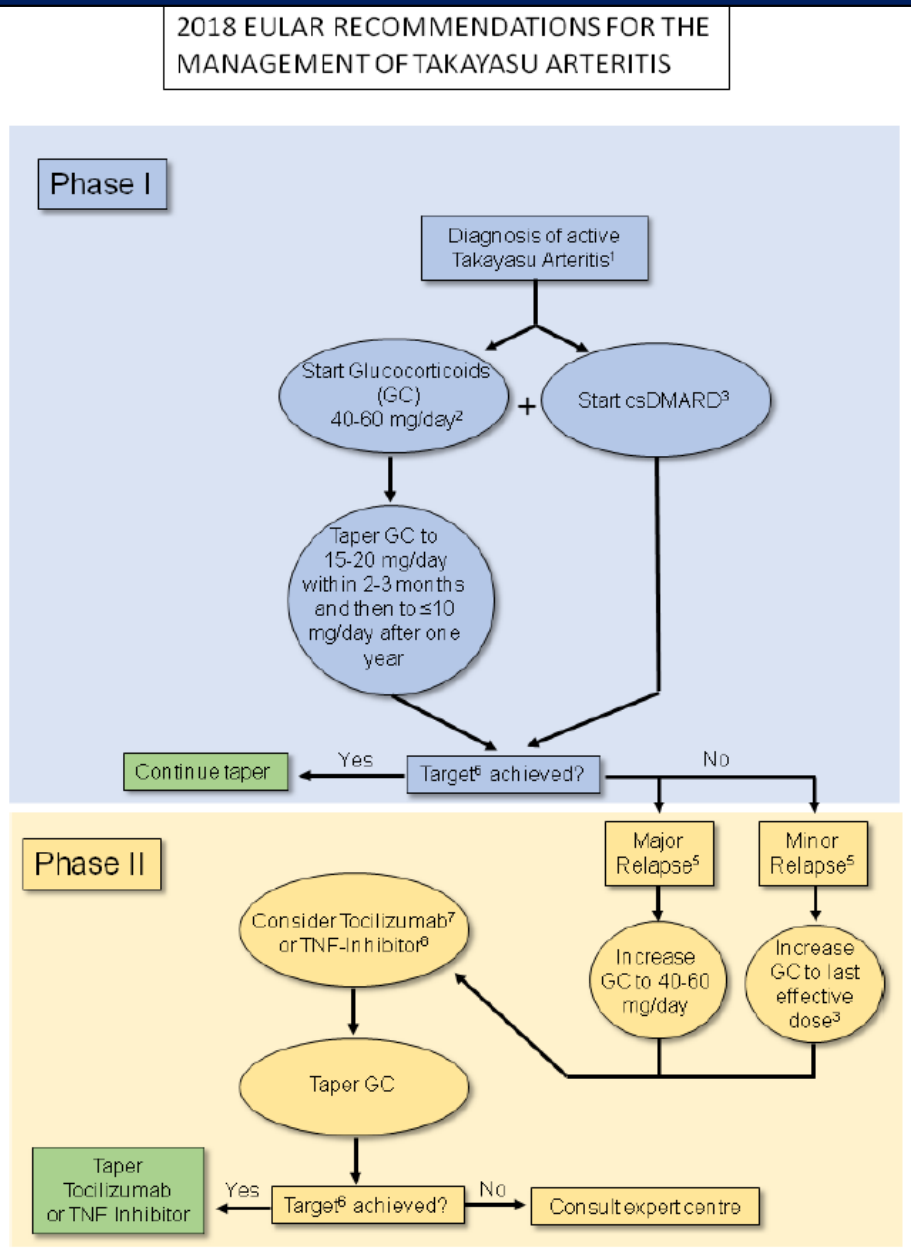


Saadoun D et al, Circulation 2012

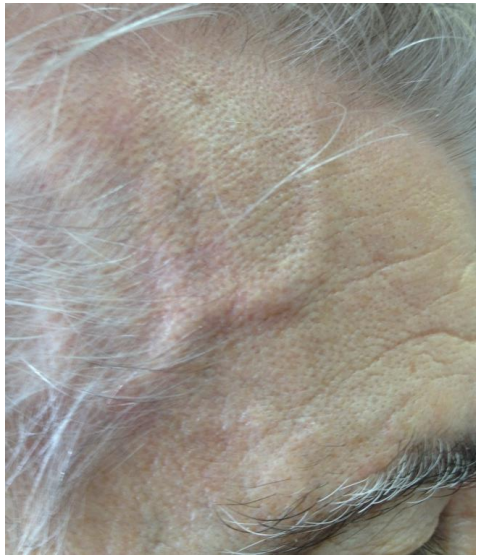
Table 3 EULAR recommendations for the management of LVV—2018 update

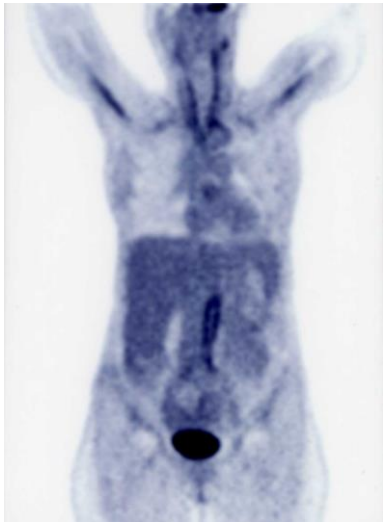
		LoE	SoR	FV (%)	LoA (0–10)
9	In LVV, elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. However, arterial vessel dissection or critical vascular ischaemia requires urgent referral to a vascular team	4	C	95	9.8±0.5

Takayasu arteritis: EULAR Recs 2018



Giant cell arteritis (GCA)

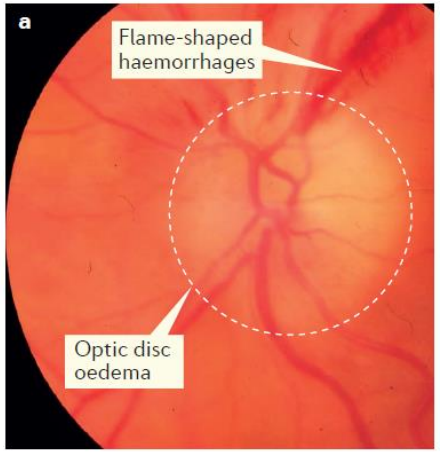




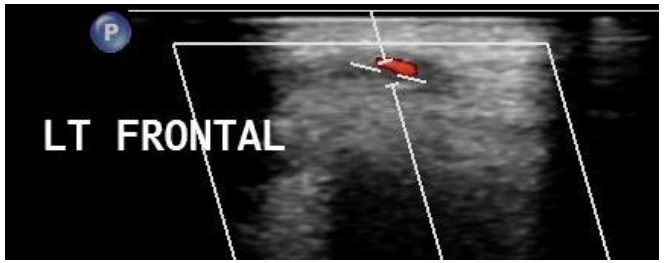
- Most common systemic vasculitis in adults **> 50 yrs**
- Lifetime risk: ♀ **1%** / ♂: **0.5%**

Crowson Cs et al, Arthritis Rheum 2011

- 2 main forms: **Cranial** and **large vessel** GCA
- **10-15%** risk of blindness (close to diagnosis)
- Major advances in earlier diagnosis by **non-invasive imaging** of **cranial** and **large arteries** (U/S, PET-CT, CTA, MRA)

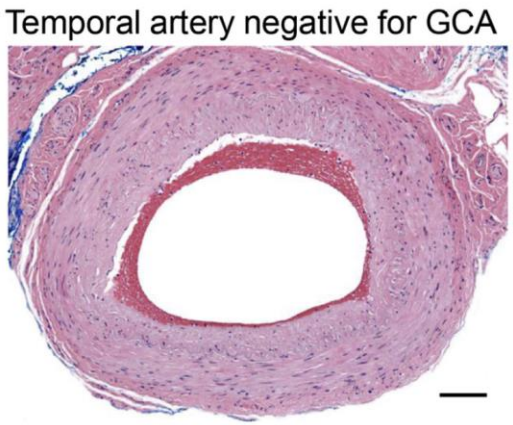


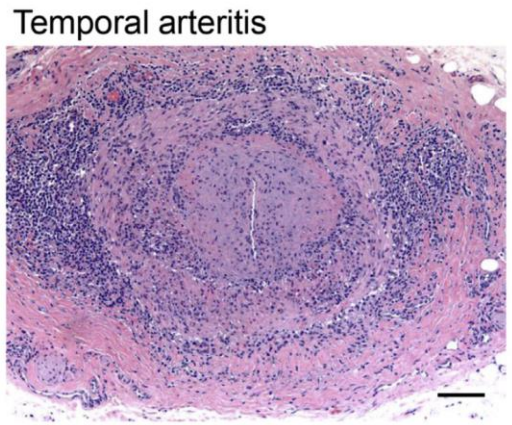
Soriano A et al, Nat Rev Rheumatol 2017

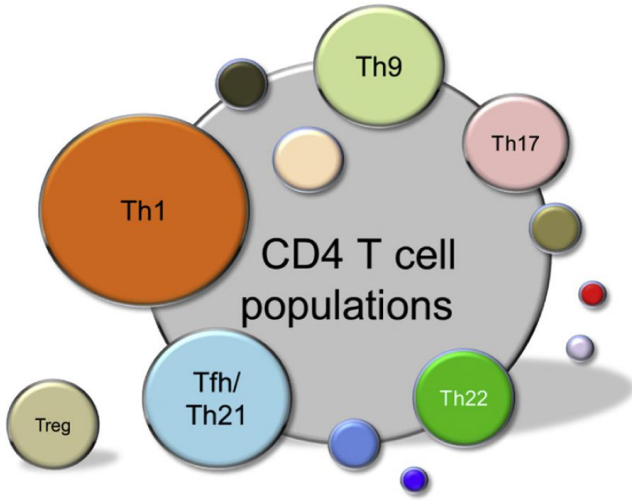


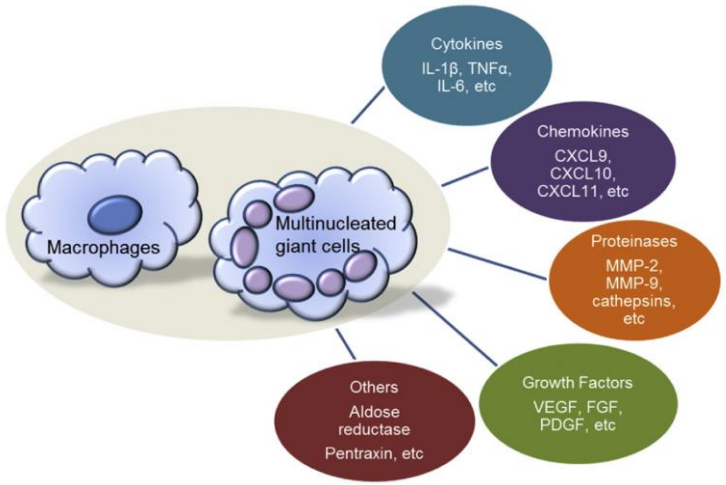
Courtesy G. Skountzos

Giant cell arteritis (GCA): Pathogenesis









Weyand CM, Clin Immunol 2019

- **HLA-class II associated disease**
  (DR-A/B1, DQ-A1/A2)

Carmona D et al, Am J Human Gen 2015
Carmona D et al, Am J Human Gen 2017

Arterial wall layer	Cell types	Process
Adventitia	ECs vasDC T cells (macrophages)	Entrance into the vessel wall T cell-EC interaction Neoangiogenesis T cell antigen recognition
Media	T cells (vasDC) macrophages multinucleated giant cells VSMC	T cell-macrophage interaction Elastic lamina destruction Macrophage effector functions
Intima	Myofibroblasts T cells Macrophages ECs	Intimal hyperplasia neoangiogenesis

Dysfunctional pathways

- ↓ **PD-1/PD-L1** (↑ **T cell activation**)
- ↑ **JAK/STAT**

Zhang H et al, PNAS 2016
Zhang H et al, Circulation 2018

Giant cell arteritis (GCA): Role of PD/PD-L1

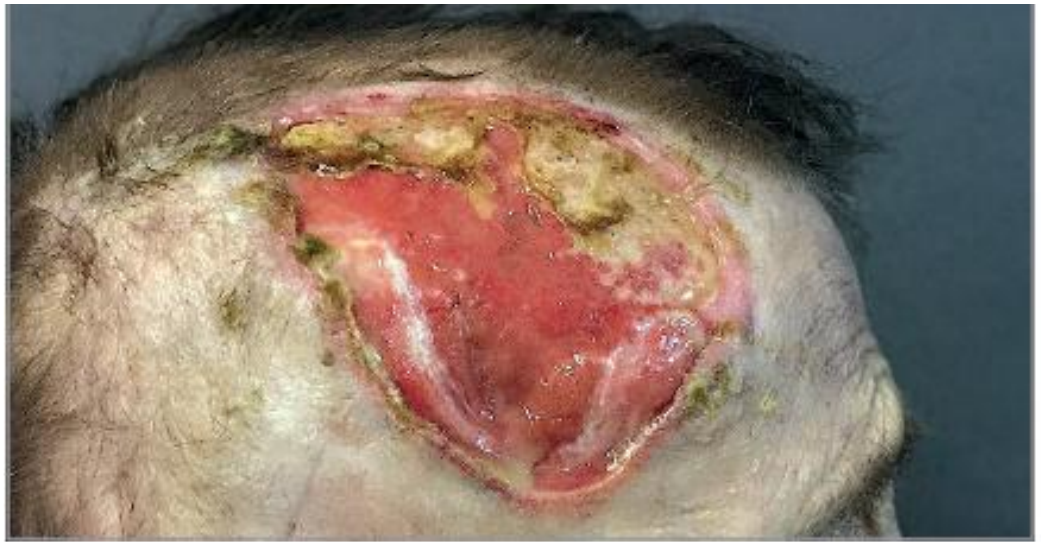
Letters

OBSERVATION

Nivolumab-Associated Giant Cell Arteritis With Scalp Necrosis

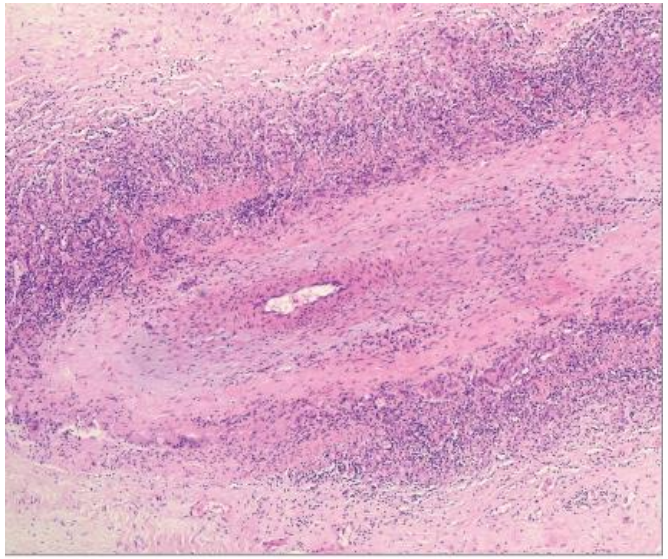
JAMA Dermatology Published online July 17, 2019

Alexander Kreuter, MD
Bijan Koushk-Jalali, MD
Antonino Cusenza, MD
Frank Oellig, MD
Christian Tigges, MD



60-year-old ♀ with resistant to chemo metastatic lung Ca

- Started Nivolumab (PD-1 inhibitor)
- 2 wks later: Unilateral temporal headache, jaw claudication, blurred vision R
- 6 weeks later: Scalp necrosis
- ↑ CRP/ESR



- Started GCs – taper – improvement
- No improvement in sight
- Stopped nivolumab
- 4 mo later: Complete Ca remission

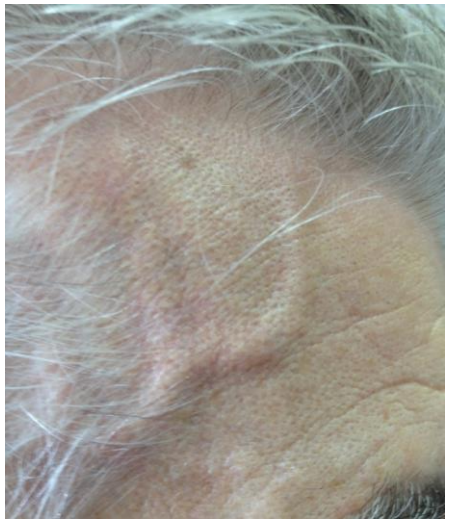
GCA: What is changing in its treatment?

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]

GCA: What is changing in its treatment?



A 70 yrs old ♂ with history of hypertension presents with a 2 week history of daily temporal headache, fatigue and low grade fever.

Labs: Hb= 12 g/dl, PLT = 456.000/uL , CRP= 35 mg/L (<5)**, TKE= 86 mm/h**

What would be your initial therapy?

A. **Methylprednisolone 1000 mg IV pulse x 3 days followed by 32 mg/day pos**
B. **Methylprednisolone 32 mg/day pos with taper over 6 months**
C. **Methylprednisolone 32 mg/day pos with taper over 12 months**
D. **Methylprednisolone 32 mg/day pos + Methotrexate 15 mg/wk SC**
E. **Methylprednisolone 32 mg/day pos + Tocilizumab 162 mg SC q wk**

± Aspirin

LVV [GCA - Takayasu arteritis (TAK)]: Definitions

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.

GCA: What is the initial scheme of GC?

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

		LoE	SoR	FV (%)	LoA (0–10)
4	High dose glucocorticoid (GC) therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA[&]	[&]4	[&]C	[&]100	9.8±0.6

- **No evidence that Pre > 60 mg/d is superior to < 60 mg/d**

  (no need for weight adjusted schemes…1 mg/Kg…)

- **Limited evidence to support IV pulses in pts without visual symptoms**

GCA: Would you use an anti-platelet agent?

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

		LoE	SoR	FV (%)	LoA (0–10)
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

Anti-platelet therapy

- **No good data to support its use**
- **Risk of harm (bleeding) important**

GCA: Would you use a steroid-sparing agent and when?

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

		LoE	SoR	FV (%)	LoA (0–10)
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

Steroid – sparing: TCZ (MTX)

- **Not from the beginning for every patient**

ONLY for those:

- who have already **developed/**have an **increased risk** of developing **GC-related side effects or complications** (osteoporosis, diabetes, cardiovascular disease, glaucoma)

- for **relapsing patients** (irrespective of other risk factors)

- **refractory patients**

- **TCZ** is the preferred agent **(vs. MTX)** – based on the available studies

GCA: How fast to taper GCs?

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

	LoE	SoR	FV (%)	LoA (0–10)
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)	5	D	87	9.5±0.9

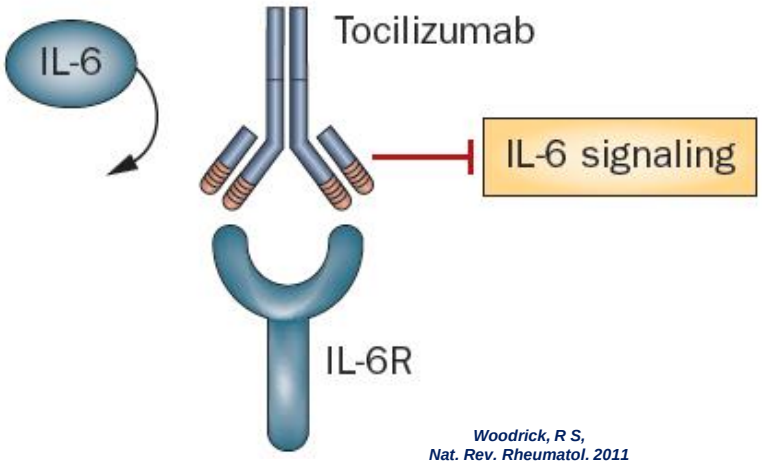
Relapse rate: 34-75%

GC Tapering Scheme

Initial	**40-60 mg/d**
2-3 months	**15-20 mg/d**
1 year	**≤ 5 mg/d**
When to stop?	**≥ 2 yrs**

- **GC alone** — **Slow taper** (no rapid taper: 6 mo Usually up to 2 yrs)
- **GC + GC-sparing agents** — **Faster taper** (TCZ: 6 months)

GCA therapy: Tocilizumab



Woodrick, R S,
Nat. Rev. Rheumatol. 2011

- **Only approved biologic agent for GCA by FDA (05/2017) and EMA (09/2017)**

- **Already approved for:**
  - **RA**
  - **Systemic JIA (sJIA)**
  - **Juvenile Idiopathic polyarthritis (pJIA)**
  - **Cytokine Release Syndrome (CAR T-cell induced, FDA)**

- **Indications**

  - Indicated for the treatment of **Giant Cell Arteritis (GCA) in adult patients.**

  - Dosing:

  - **TCZ: 162 mg SC qweek** in combination with a **tapering course of glucocorticoids.**

  - Can be used **alone** following **discontinuation of glucocorticoids** but should not be used as monotherapy for the treatment of acute relapses

  - **Treatment beyond 52 weeks** should be guided by disease activity, physician discretion, and patient choice.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000955/human_med_001042.jsp&mid=WC0b01ac058001d124

GCA - Tocilizumab: Can we stop after 1 year?

Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial

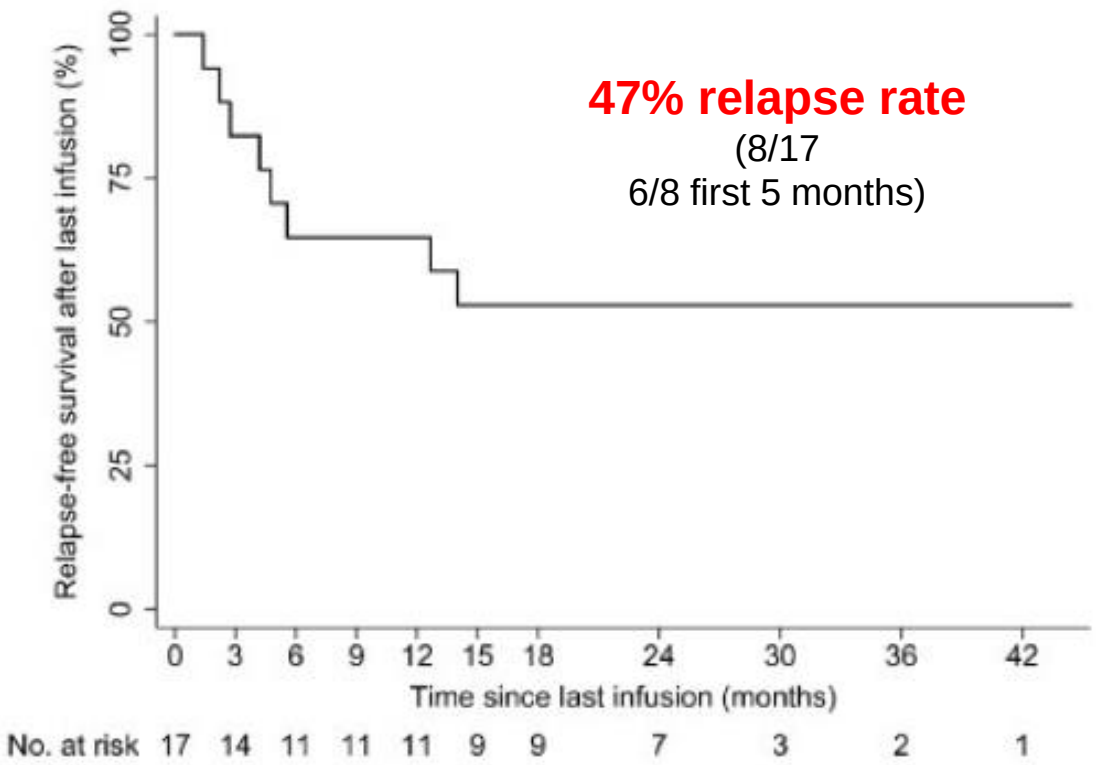
Peter M Villiger*, Sabine Adler*, Stefan Kuchen, Felix Wermelinger, Diana Dan, Veronika Fiege, Lukas Bütikofer, Michael Seitz, Stephan Reichenbach

Lancet 2016; 387: 1921–27

17/20 pts treated for 1 year

with TCZ (IV qmo) - in remission

STOPPED TCZ



47% relapse rate
(8/17
6/8 first 5 months)

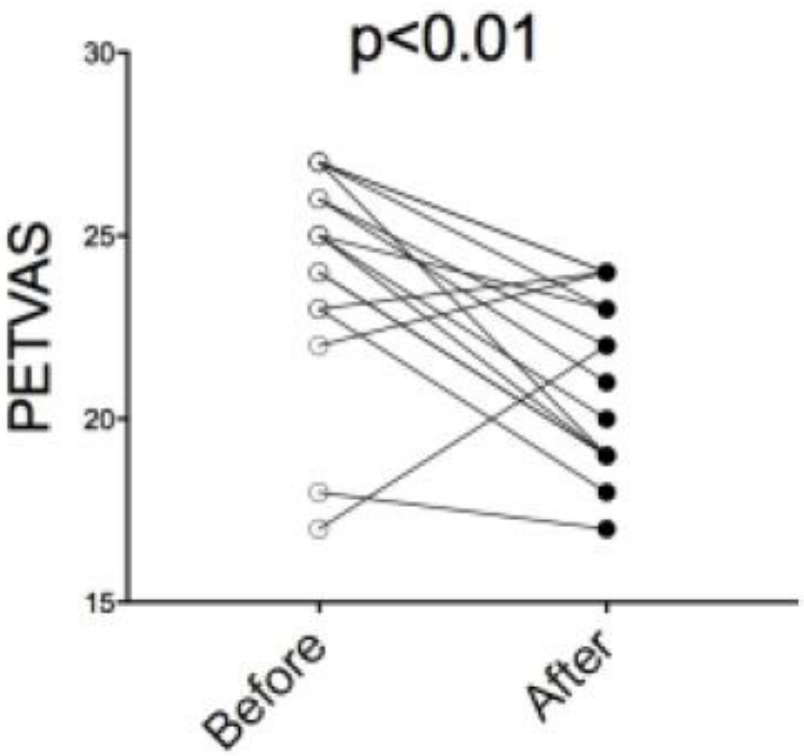
- **No predictors of relapse** (except younger age)
- **All** patients in **remission** had **MRA enhancement**

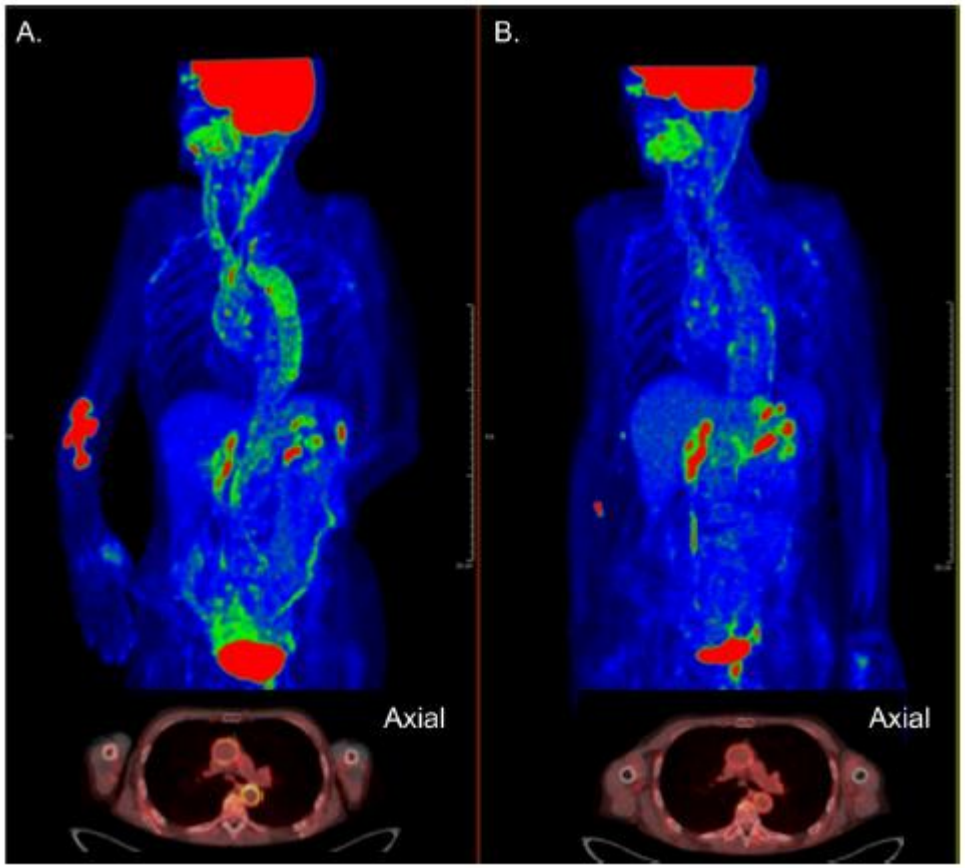
Adler S et al, Rheumatology 2019

GCA - Tocilizumab: Does the PET improves after TCZ therapy?

n=17 treated with TCZ

- **Clinical remission:** 14/17 **(82%)**
- Significant improvement in PET but…
- Only in 3/17 **(18%)** had **Normal PET**





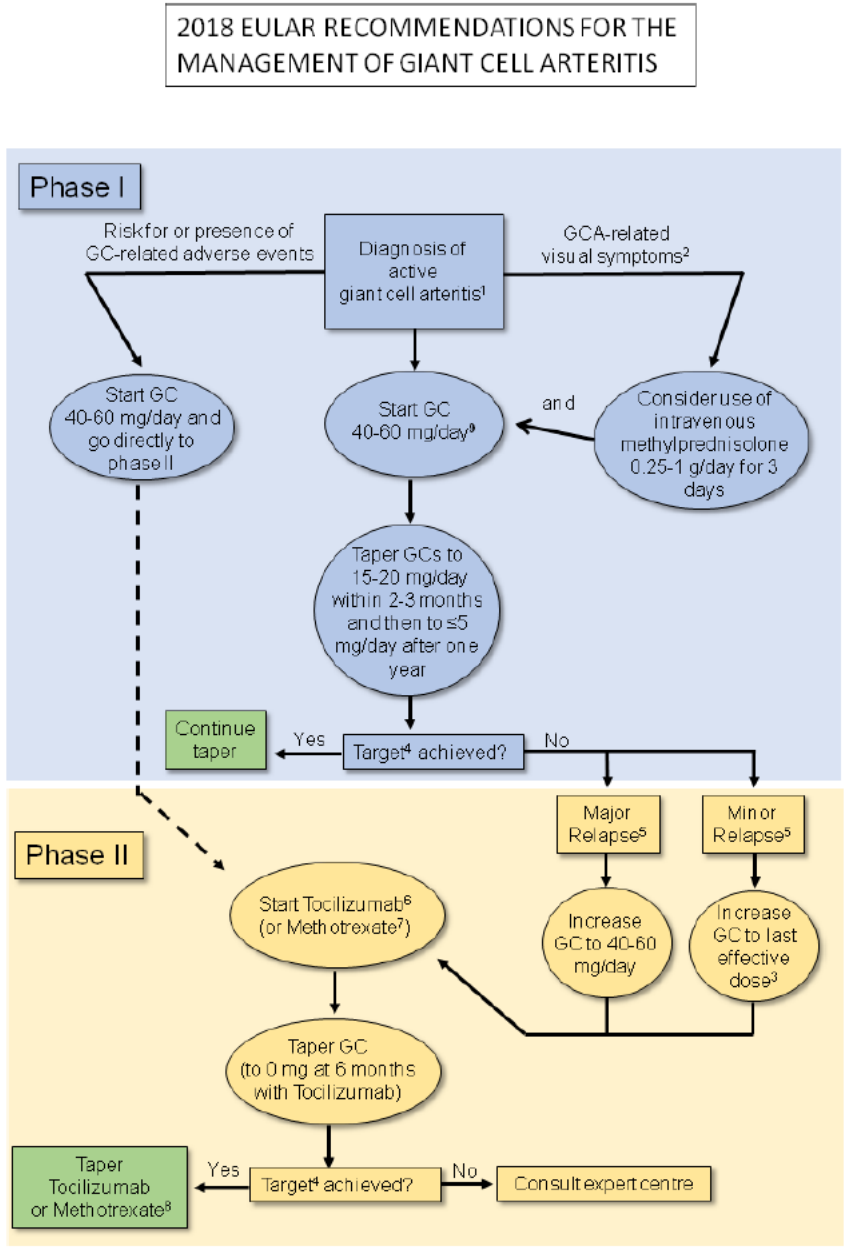
Banerjee S et al, J Rheum 2019

GCA: EULAR Recs 2018

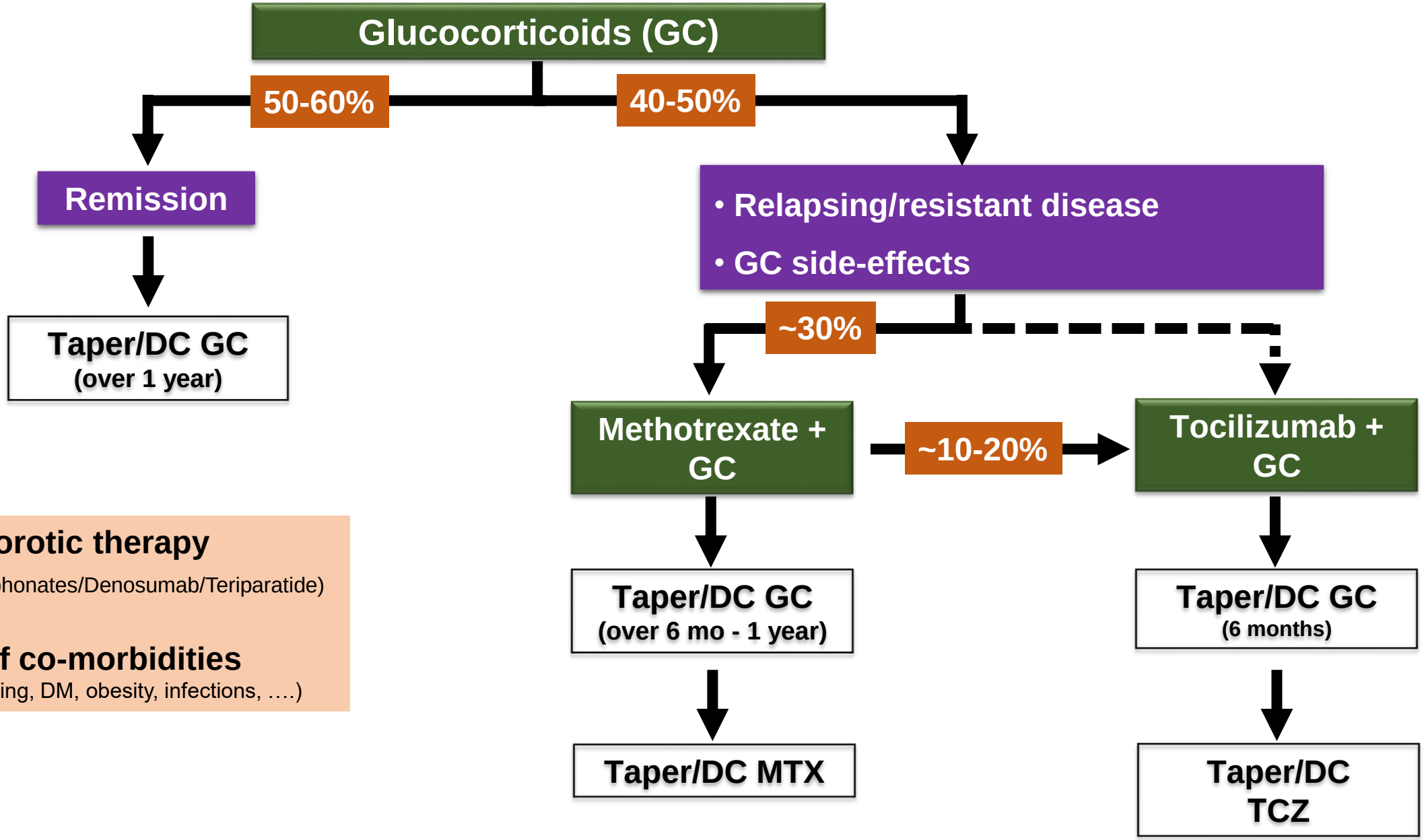
Recommendation

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]



GCA: Therapeutic algorithm



- **Anti-osteoporotic therapy**
  (Ca^{++}/Vit.D/Biphosphonates/Denosumab/Teriparatide)
- **Treatment of co-morbidities**
  (HTN, ↑ Chol, Smoking, DM, obesity, infections, ….)

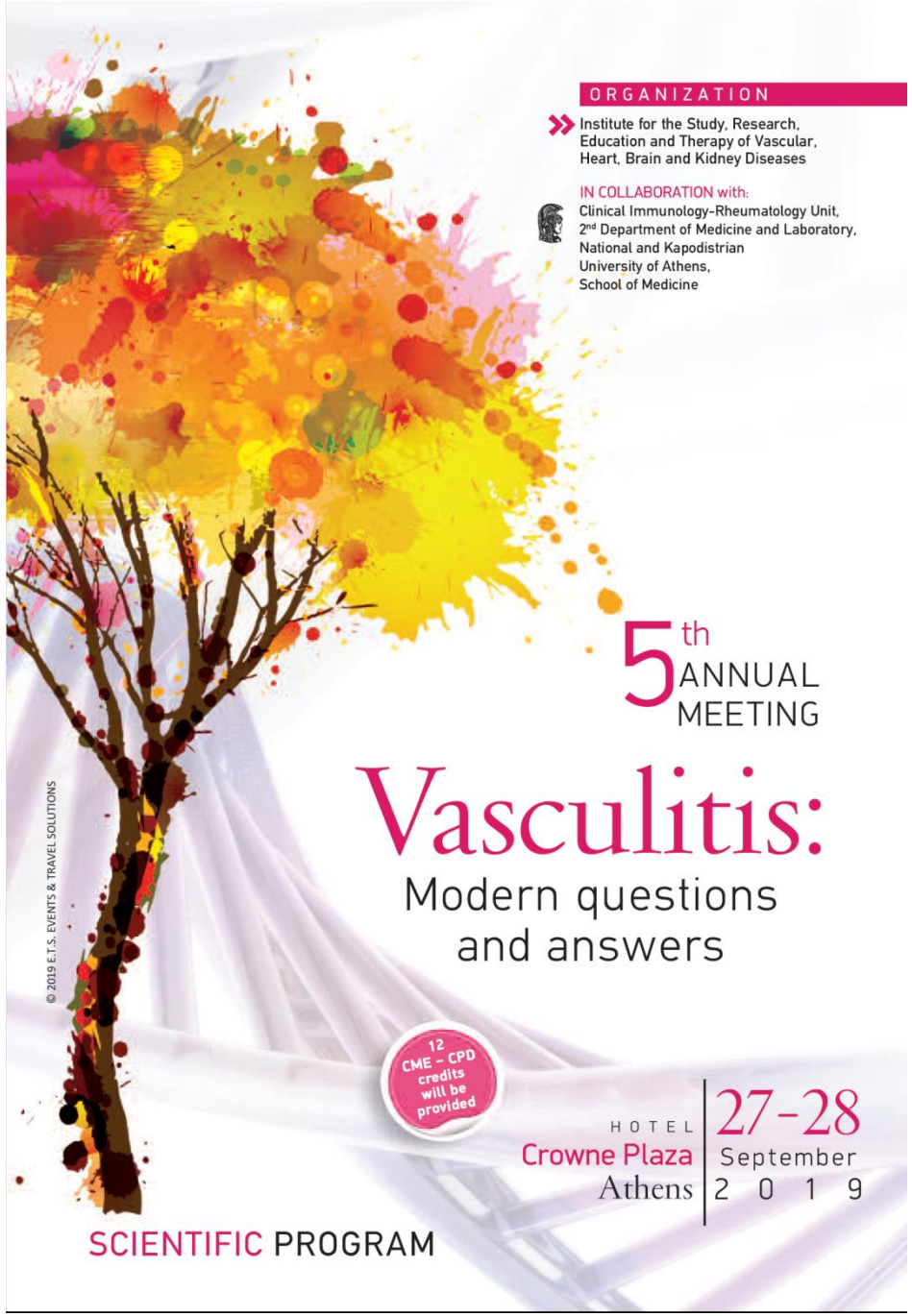
GCA-TAK: Major points

TAKAYASU ARTERITIS

- Combination therapy (GC+MTX) from the begining
- Slow taper of GCs (~10 mg/d at 1 year)
- TCZ or anti-TNFs for refractory patients
- No CYC (unless others failed or not tolerated)

GCA

- No IV pulses for non-visual involvement
- No ASA to all patients
- Steroid-sparing patients ONLY for relapsing/refractory patients and those with established of high risk for GC-related side effects
- Slow-taper for GC monotherapy (~5 mg/d at 1 year, most likely > 2years)
- TCZ the preferred agent over MTX as steroid-sparing agent



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