RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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The APP's guide to diagnosing and managing Takayasu's arteritis

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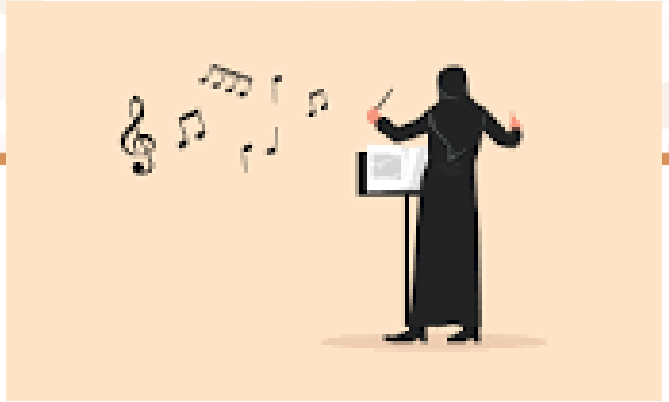
Course Objectives

1. Define and differentiate the epidemiology and pathophysiology of Takayasu and how it varies from GCA.
2. Recognize the disease manifestations in active Takayasu arteritis.
3. Compare the different imaging modalities used to diagnose and evaluate Takayasu's arteritis
4. Recall immunosuppressive therapies that are used to manage Takayasu's

Case Presentation



- **HPI:**

- 18 year old female presents with right arm pain

- High school band director

Develops pain and cramping in her right arm whenever she tries to conduct

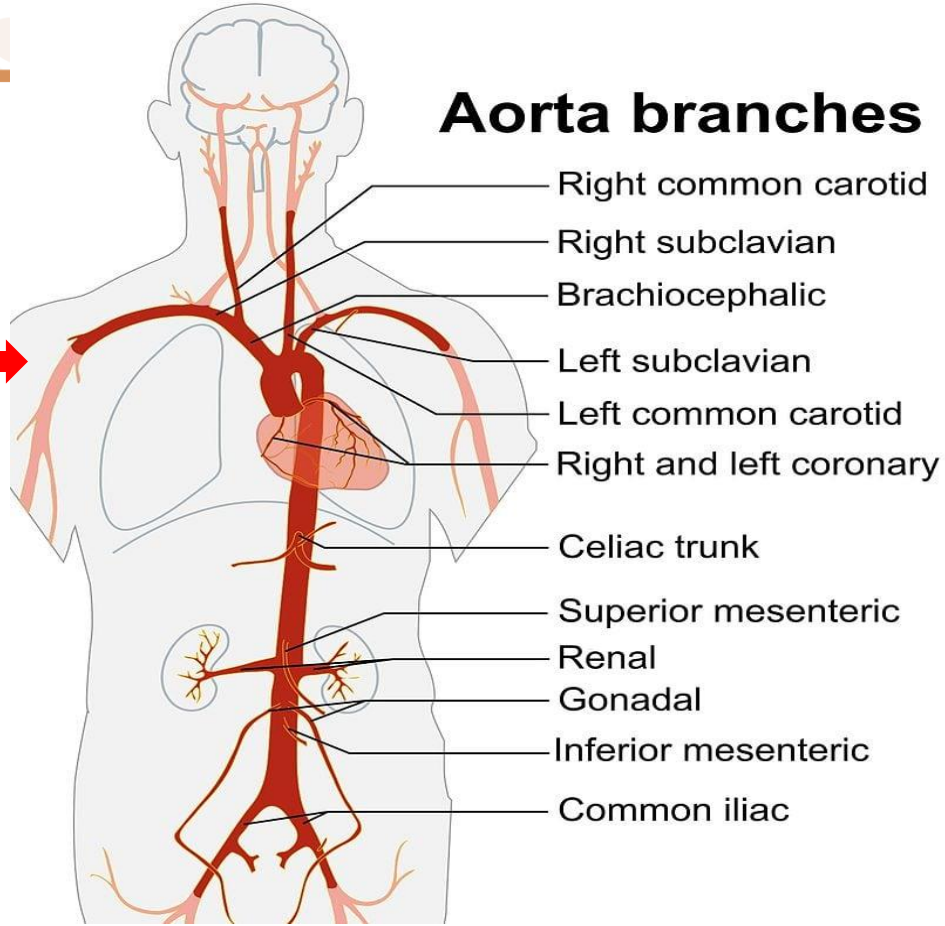
- Orthopedics: rotator cuff tendinopathy

Right radial pulse absent

Case Presentation – Physical exam

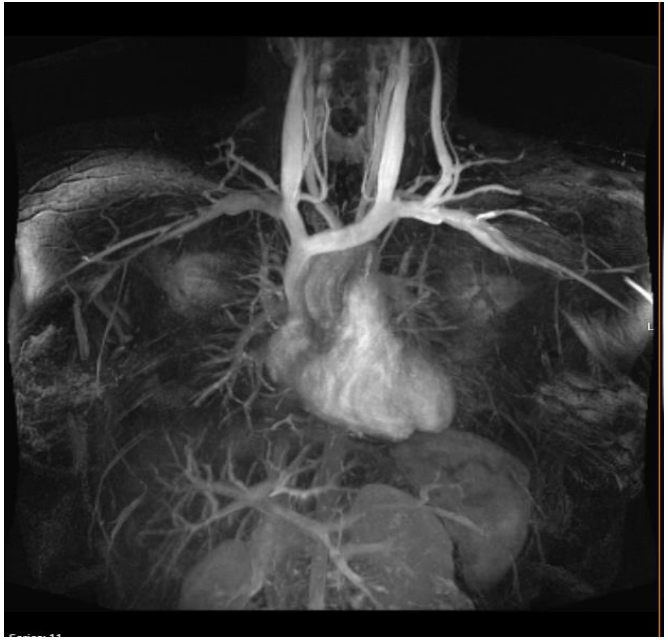
- Well appearing.
- Unable to obtain blood pressure in right arm.
- Heart and lung examinations unremarkable.
- MSK: Full ROM in all joints including right shoulder. No limitations
- Vascular exam:
  - No scalp tenderness. No carotidynia. No carotid bruits.
  - Right subclavian bruit.
  - Right radial pulse absent. Left radial pulse present.
  - Bilateral femoral and pedal pulses present equally.
  - No abdominal bruit.

Right sub-clavian bruit

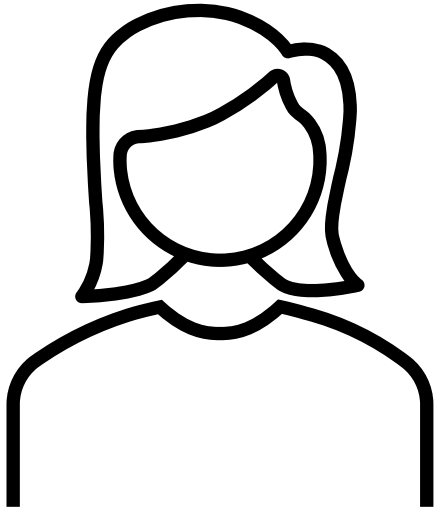


Case Presentation - Imaging

"Redemonstration of near complete occlusion of the right subclavian artery with reconstitution at the level of the right axillary artery as well as 50% stenosis of the proximal right vertebral artery"



Right arm pain/cramping



?

Absent right radial pulse

+ right sub-clavian bruit

Large Vessel Vasculitis - Overview

Affects large vessels

Aorta and main branches

The presence of leukocytes in the vessel walls causing damage to the vessel walls

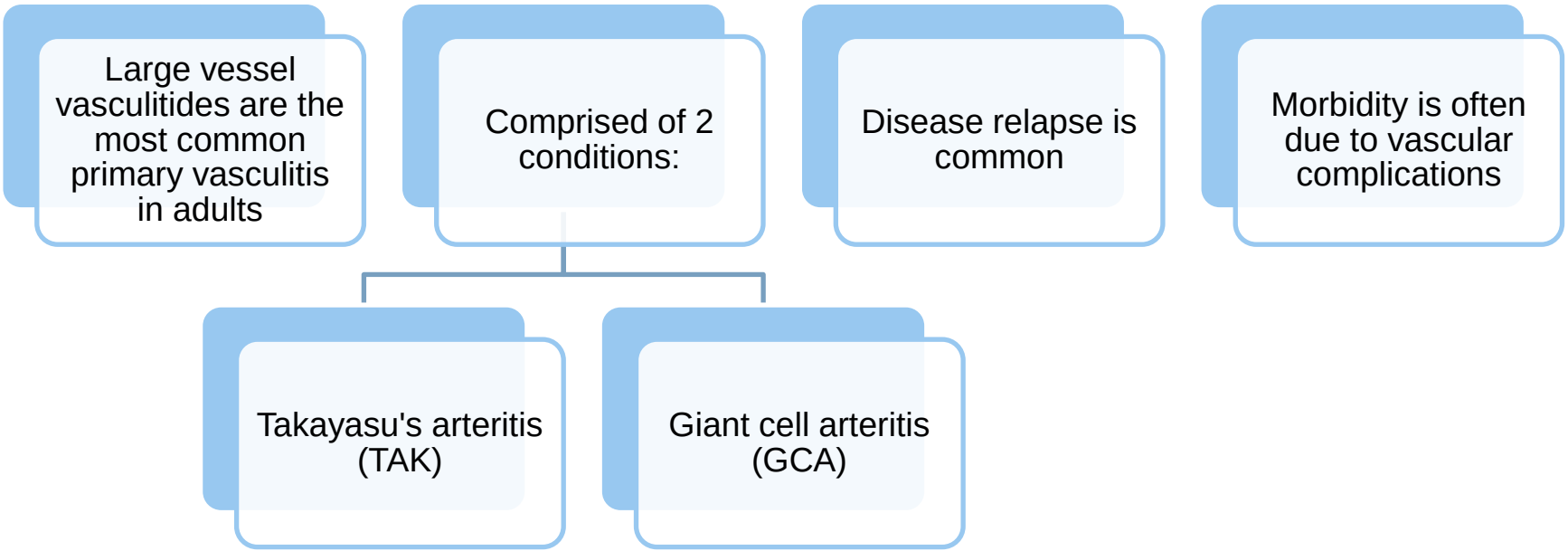
Leads to bleeding

Degradation of the lumen

Can result in tissue ischemia and necrosis

Merkel, P.A. (2022). Overview of and approach to the vasculitides in adults. In K.J. Warrington & P. Seo (Eds.), UptoDate. Available from https://www.uptodate.com/contents/overview-of-and-approach-to-the-vasculitides-in-adults

Large Vessel Vasculitis - Overview



Pugh D, Karabayas M, Basu N, Cid MC, Goel R, Goodyear CS, Grayson PC, McAdoo SP, Mason JC, Owen C, Weyand CM, Youngstein T, Dhaun N. Large-vessel vasculitis. Nat Rev Dis Primers. 2022 Jan 6;7(1):93. doi: 10.1038/s41572-021-00327-5. PMID: 34992251: PMCID: PMC9115766.

Large Vessel Vasculitis - Overview

Rapid diagnosis and treatment improve patient outcome

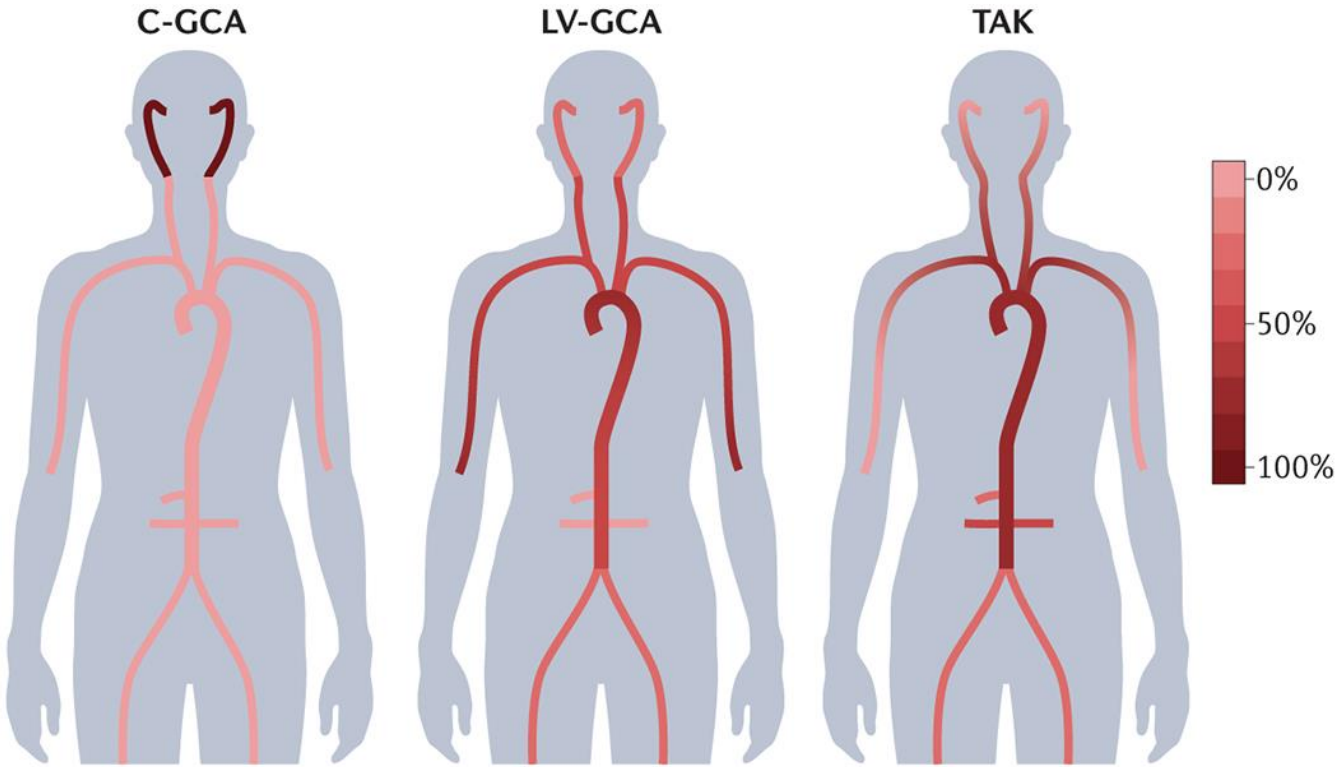
Diagnosis is based on a combination of medical history, physical exam, laboratory tests and imaging modalities.

Treatment options include:

glucocorticoids,
conventional DMARDS
biologic drugs.

Pugh D, Karabayas M, Basu N, Cid MC, Goel R, Goodyear CS, Grayson PC, McAdoo SP, Mason JC, Owen C, Weyand CM, Youngstein T, Dhaun N. Large-vessel vasculitis. Nat Rev Dis Primers. 2022 Jan 6;7(1):93. doi: 10.1038/s41572-021-00327-5. PMID: 34992251; PMCID: PMC9115766.

Arterial involvement in large vessel vasculitis



Pugh D, Karabayas M, Basu N, Cid MC, Goel R, Goodyear CS, Grayson PC, McAdoo SP, Mason JC, Owen C, Weyand CM, Youngstein T, Dhaun N. Large-vessel vasculitis. Nat Rev Dis Primers. 2022 Jan 6;7(1):93. doi: 10.1038/s41572-021-00327-5. PMID: 34992251; PMCID: PMC9115766.

Epidemiology

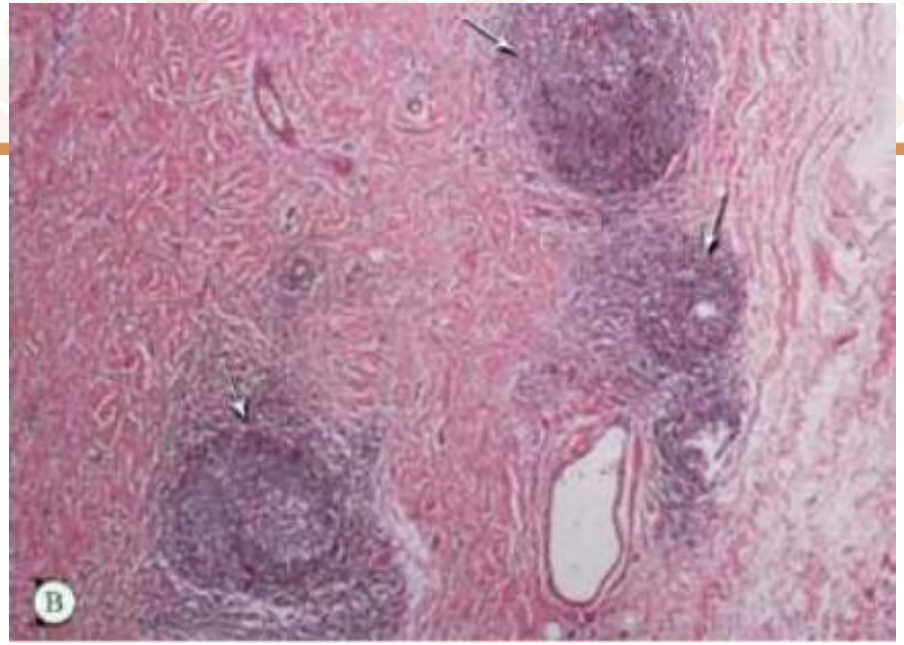
GCA	TAK
Age 50 and older	Age less than 40 at disease onset
Incidence increases with age	Can occur later in life (primarily in Asian descent)
F>M	Primarily occurs in females (12:1 F>M)
Greater prevalence in people of northern European descent (15-25 per 100,000)	Incidence rate highest in Asia (1 per million per year)
6 per 100,000 in southern European descent	Can occur in all races
Rare in blacks and Hispanics (1-2 per 100,000)	

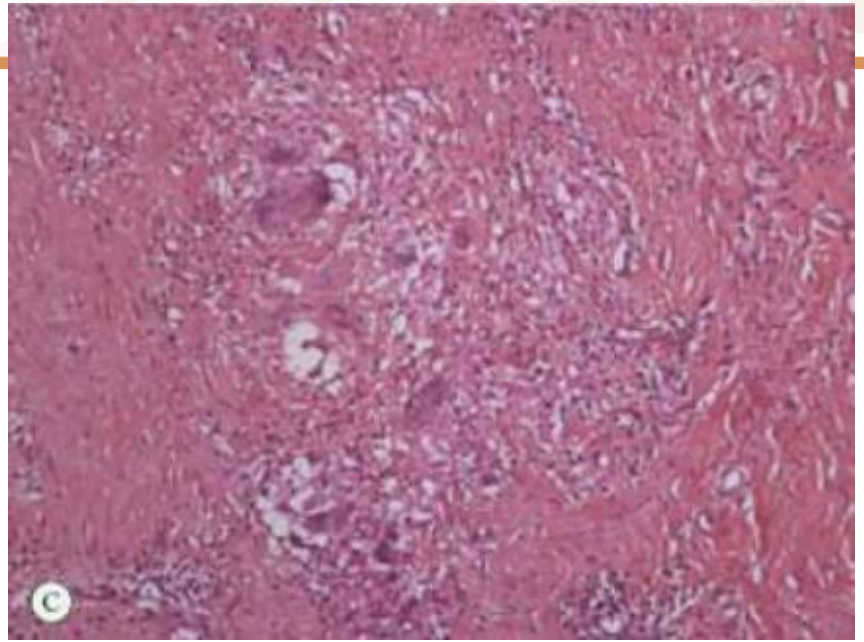
Onen F, Akkoc N. Epidemiology of Takayasu arteritis. Presse Med. 2017 Jul-Aug;46(7-8 Pt 2):e197-e203. doi: 10.1016/j.lpm.2017.05.034. Epub 2017 Jul 26. PMID: 28756072.

Giant cell formation

- After initial insult (autoantigen, injury, trauma, injection, drug etc.) dendritic cells in the adventitia are activated.
- Dendritic cells release:
  - chemokines
    - which attract CD4+ helper T-cells and macrophages into the arterial wall
  - IL-6 and IL-8
    - These activate T-cells and promote IFN-gamma release from the T-cells
      - IFN-gamma promotes inflammation, macrophage activation and granuloma formation.
- The activated macrophages release substances causing endothelial damage, the also bond together forming syncytia (a single cell containing multiple nuclei) aka “giant cell” formation

Ameer MA, Peterfy RJ, Khazaeni B. Temporal Arteritis. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459376/





B) 3 granulomas at the medio-adventitial junction
C) Multinucleated giant cells in granuloma

Sotoudeh Anvari, M., Masoudkabir, F., Abbasi, K., Boroumand, M. A., Zarghampour, M., & Goodarzynejad, H. (2016). Takayasu's Arteritis Presenting with Headache and Peripheral Facial Palsy: A Case Report. *The journal of Tehran Heart Center*, *11*(4), 195–197.

Pathologic examination of the patient's aortic valve in hematoxylin and eosisn (H&E) stain.

TAK pathophysiology

- Unknown etiology
- Granulomatous polyarteritis
- Thickened adventitia with perivascular infiltrates
- “Giant cells” are found in the media of the large elastic arteries.
- The damage to the cell wall leads to dilation of the vessel wall, aneurysm formation and can lead to thrombus

Weyand, C.M. & Goronzy, J.J. (2008) Vasculitides, giant cell arteritis, polymyalgia rheumatica, and Takayasu’s arteritis. In J.H. Kippel (Ed), *Primer on the rheumatic diseases* (13th ed., pp 399-407). Springer.

Clinical Manifestations

	GCA	TAK
Constitutional	Fever, fatigue, weight loss,	Weight loss, low grade fever, fatigue
Head	Headache (2/3 of patients), transient visual loss (curtain effect, unilateral), permanent vision loss (sudden, painless, partial or complete, unilateral or bilateral) Stroke is uncommon, maxillary and dental pain, facial swelling, throat pain, tongue pain and macroglossia	Lightheadedness, vertigo, syncope, orthostasis, headaches, convulsions and stroke. *Visual impairment is a late manifestation of severe disease due to arterial insufficiency
CV	Aortic aneurysms (10-20% of cases), arterial bruits, diminished or absent blood pressures, arm claudication.	Carotidynia (10-30% of patients), absent or diminished peripheral pulses, limb claudication, arterial bruit, HTN, discrepant BP between arms, angina
Pulmonary	Non-productive cough	Chest pain, dyspnea, hemoptysis, pulmonary hypertension
GI		Abdominal pain, post-prandial pain, diarrhea, and GI hemorrhage
Integumentary		Erythema nodosum or pyoderma gangrenosum - uncommon
MSK	Jaw claudication, PMR symptoms, occasionally peripheral synovitis	Arthralgia in 50%, uncommon to be synovitis. Symptoms can be transient or continuous

Wood, P.R. (2020). Large-vessel vasculitis: giant cell arteritis, Takayasu arteritis, and aortitis. In S.G. West & J. Kolfenbach (Eds.)

TAK - Common Clinical Manifestations

Bruits 80%

Decreased pulses 60%

Asymmetric BP 50%

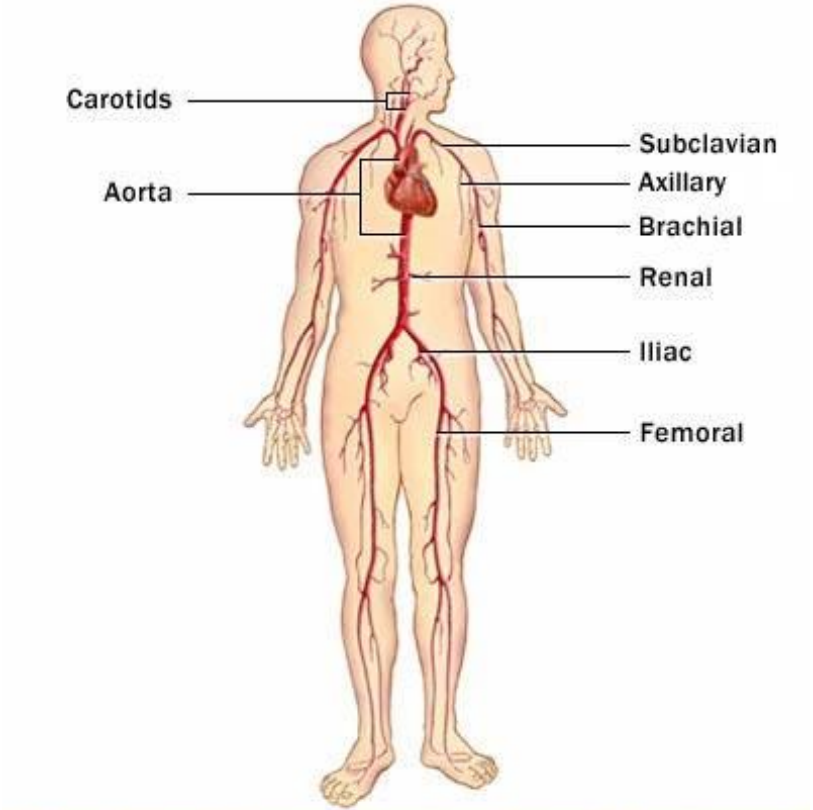
Limb claudication 70% when the subclavian/iliac arteries are involved

Presyncope and headache 30-40% respectively, with carotid and vertebral artery involvement

Pulmonary artery disease 70% (<25% have symptoms of pulmonary hypertension)

Wood, P.R. (2020). Large-vessel vasculitis: giant cell arteritis, Takayasu arteritis, and aortitis. In S.G. West & J. Kolfenbach (Eds.) *Rheumatology Secrets* (4th ed., pp. 227-233). Elsevier.

Bruit



Large Vessel Vasculitis: Diagnosis and Management

Large Vessel Vasculitis: Diagnosis

- No validated diagnostic criteria
- Diagnosis can be challenging and is based on symptoms, physical exam findings, and imaging
- Imaging is **key** in making the diagnosis!

Large Vessel Vasculitis – Imaging Modalities

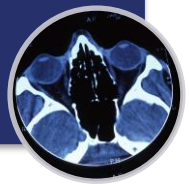
Per 2021 ACR guidelines, MRA, CTA, PET are recommended over catheter-based angiography.

MRI

- No radiation
- Good for serial imaging
- Check renal function before giving contrast

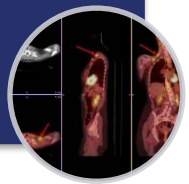
CT

- Not as sensitive in detecting active disease compared to MRA
- Inferior to MRA in detecting wall edema and inflammation

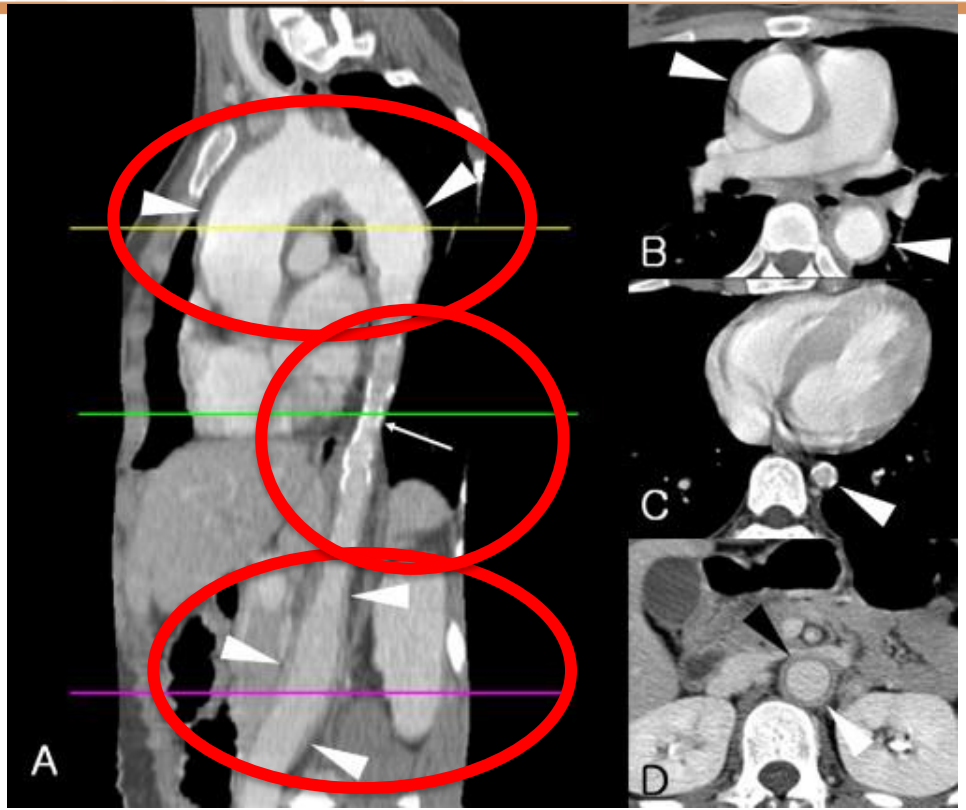


PET/CT

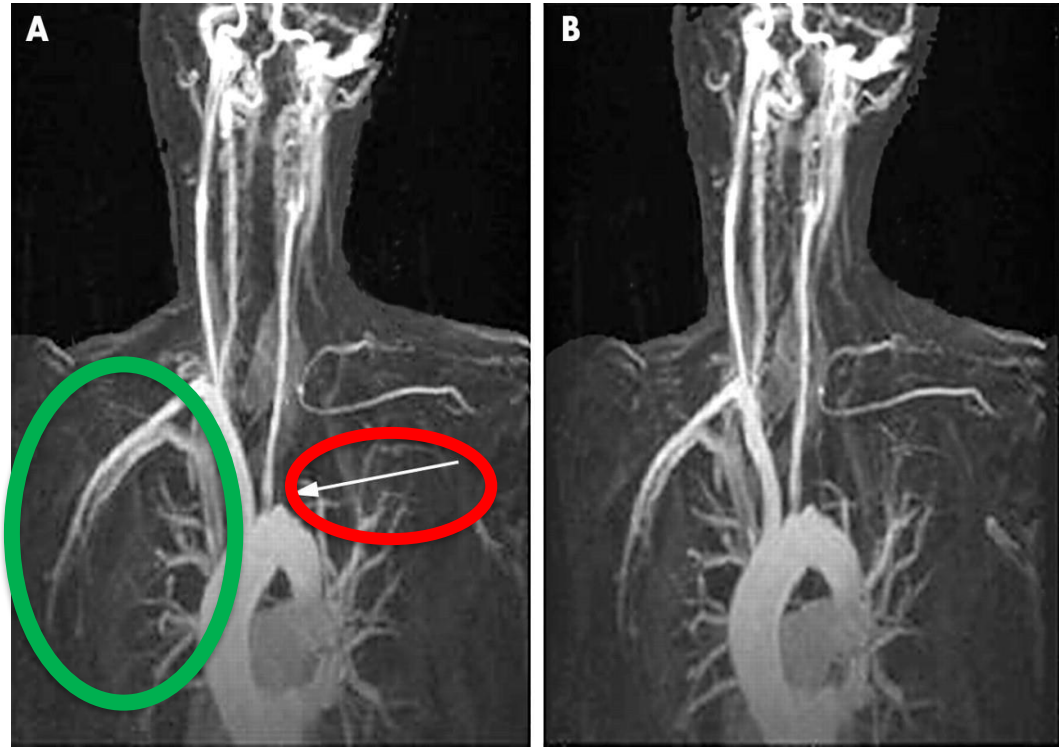
- Helpful in determining if disease is active
- More sensitive to treatment → need to do within a few days of starting prednisone
- Interpretation of results can be challenging



CT angiogram with/without contrast



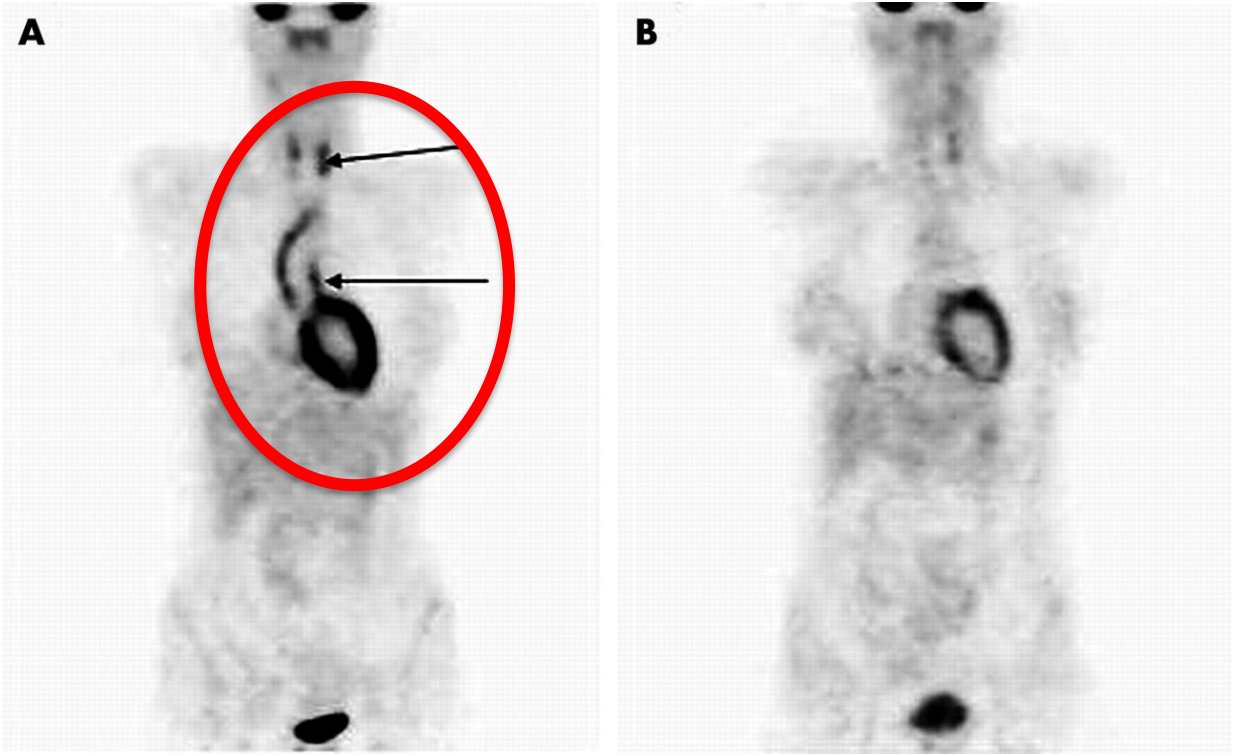
Jin Wook Chung, Hyo-Cheol Kim, Young Ho Choi, Sang Joon Kim, Whal Lee, Jae Hyun Park, Patterns of aortic involvement in Takayasu arteritis and its clinical implications: Evaluation with spiral computed tomography angiography, Journal of Vascular Surgery, Volume 45, Issue 5, 2007, Pages 906-914.



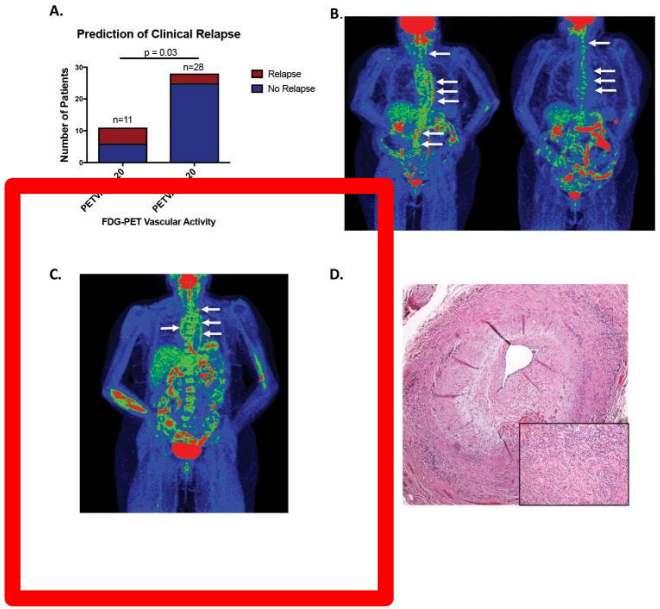
MR angiography in patient with active Takayasu's

Andrews J, Al-Nahhas A, Pennell DJ*, et al*
Non-invasive imaging in the diagnosis and management of Takayasu's arteritis
Annals of the Rheumatic Diseases 2004;**63:**995-1000.

FDG-PET scan of patient 5 with active TA at diagnosis



“Positron Emission Tomography as an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients with Large Vessel Vasculitis”



170 FDG-PET scans:

56 patients - LVV

59 patients - disease mimickers, hyperlipidemia, health controls

PET-CT had 85% sensitivity and 83% specificity for detecting active vasculitis.

Clinical Remission:

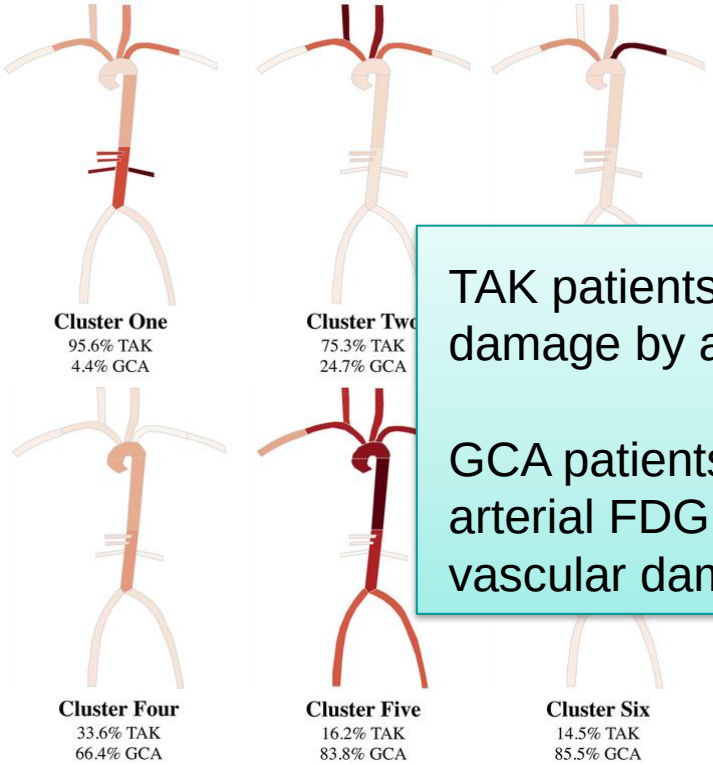
TAK: 48% of PET scan interpreted as active disease

GCA: 62% of PET scans interpreted as active disease

Global burden of arterial uptake much higher in GCA patients compared to TAK patients

Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, Malayeri AA, Merkel PA, Novakovich E, Bluemke DA, Ahlman MA. 18F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. Arthritis Rheumatol. 2018 Mar;70(3):439-449. doi: 10.1002/art.40379. Epub 2018 Feb 6. PMID: 29145713; PMCID: PMC5882488.

Patterns of arterial disease in TAK and GCA



TAK	GCA
Abdominal aorta	Diffuse disease
	ral axillary/sub-clavian es
	al FDG uptake on PET t vascular damage
Vessel wall damage	

TAK patients → more likely to have damage by angiography

GCA patients → More likely to have arterial FDG uptake by PET without vascular damage

Gribbons KB, Ponte C, Carette S, Craven A, Cuthbertson D, Hoffman GS, Khalidi NA, Koening CL, Langford CA, Maksimowicz-McKinnon K, McAlear CA, Monach PA, Moreland LW, Pagnoux C, Quinn KA, Robson JC, Seo P, Sreih AG, Suppiah R, Warrington KJ, Ytterberg SR, Luqmani R, Watts R, Merkel PA, Grayson PC. Patterns of Arterial Disease in Takayasu Arteritis and Giant Cell Arteritis. Arthritis Care Res (Hoboken). 2020 Nov;72(11):1615-1624. doi: 10.1002/acr.24055. PMID: 31444857; PMCID: PMC7035996.

Laboratory Work-up

Baseline work-up
CBC
Comprehensive metabolic panel
ESR
CRP
RPR
Quantiferon
Lipid panel

Additional work-up (dependent on presenting symptoms)
ANA
ANCA
ESR
CRP
RF
CCP antibody
Cryoglobulins
IgG4 levels
SPEP
Hepatitis serologies (rule out PAN)

Patient with suspected Takayasu arteritis: Now what?

Step 1. Does the patient have TAK?

Step 2. If yes – Is the disease active?

Step 1. Does the patient have Takayasu's?

❑What is the story?

- Fevers, night sweats
- Neck tenderness
- Feeling dizzy or lightheaded
- Cramping in the arms or legs with repetitive motions
- Post-prandial pain
- New headaches
- Visual changes

Step 1. Does the patient have Takayasu's?

- ❑ What does the imaging show?
- ❑ Could radiographic images represent something else?

Differential diagnoses:
- Fibromuscular dysplasia
- Polyarteritis nodosa
- Atherosclerotic disease
- Syphilis
- Tuberculosis
- IgG4-related disease

Step 1. Does the patient have Takayasu's?

- What are your physical exam findings?
  - Carotidynia, scalp tenderness
  - Bruits: Carotid, sub-clavian, abdominal, femoral
  - Absent pulses?
  - Joint tenderness
  - Skin findings: erythema nodosum, cool extremities, discoloration

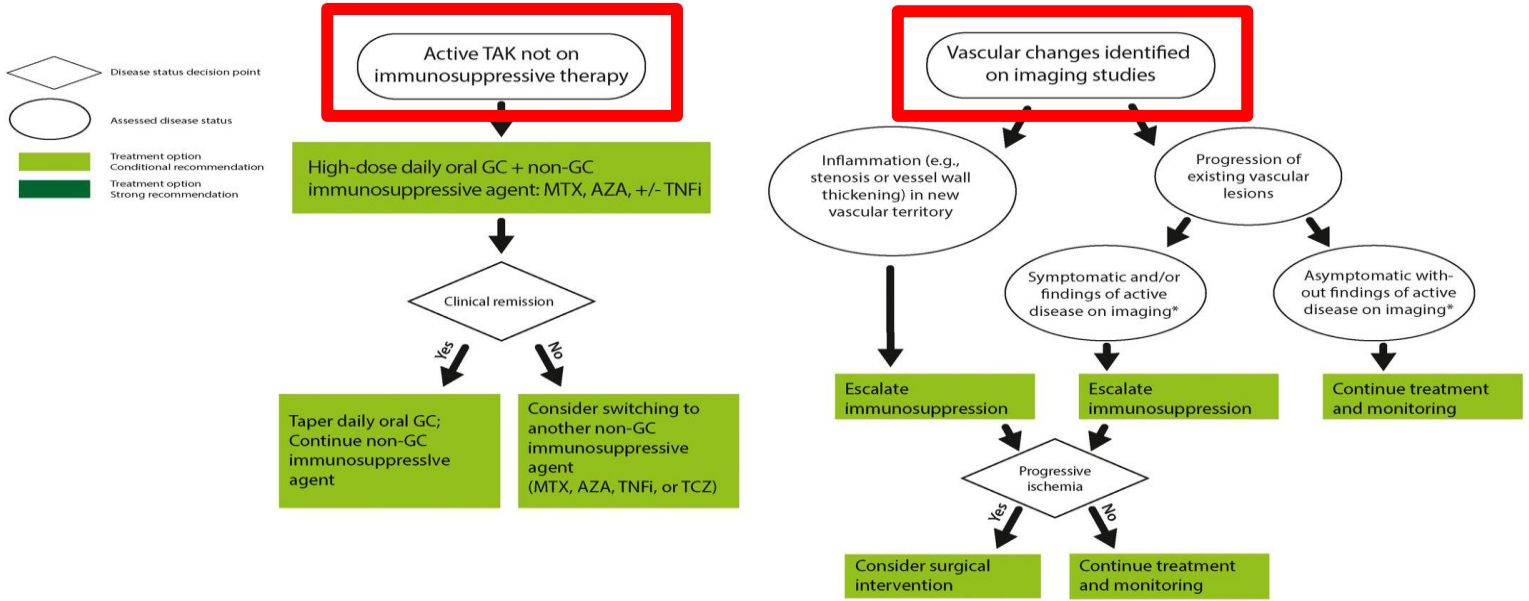
Step 2. Is the disease active?

- ❑ Does the patient have radiographic changes?
  - Helpful to review prior imaging

- ❑ Does the patient have *new* or *worsening* symptoms that could indicate active disease?
  - New constitutional symptoms
  - New claudication in arms or legs
  - More dizziness/lightheadedness
  - Elevated ESR/CRP

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis

Overview of treatment of Takayasu arteritis (TAK) based on clinical and radiographic assessments



AZA = azathioprine; CT = computed tomography; FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; GC = glucocorticoids; MR = magnetic resonance; MTX = methotrexate; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor

* Can be suggested by vascular edema, contrast enhancement, and/or increased wall thickness on MR or CT angiography, or supra-physiologic FDG uptake in the arterial wall on PET imaging

Arthritis & Rheumatology, Volume: 73, Issue: 8, Pages: 1349-1365, First published: 08 July 2021, DOI: (10.1002/art.41774)

Takayasu's: Medication management

- Glucocorticoids: If new/severe disease, recommend 1 mg/kg daily. Max dose 60-80mg x 2-4 weeks, then taper.

- Steroid sparing agents:

First line treatments:

- Methotrexate
- Azathioprine
- TNF inhibitors

Takayasu's: Medication management

Second Line therapy

- Leflunomide
- Myc
- Cyc
  Use
  thre
  thre
- No
  use of one drug ov
  another
- Tocilizumab: Consider if
  disea tory

No FDA approved medications for Takayasu arteritis

Table 1
New targeted therapies in Takayasu Arteritis

Drug	Pathogenetic basis	Evidence in TAK	Recommendations and clinical use
TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol)	**Inhibitors of TNF-α (bDMARDs):** • TNF-α has a major role in the development of TAK granulomatous inflammation • In active TAK higher serum levels of TNF-α and higher mRNA expression and intracellular production by T cells	• Cohort studies and open-label prospective study, showing positive results in TAK patients (clinical improvement, GC sparing effect, higher sustained remission rate compared to cDMARDs) (19–24) • No RCTs • Meta-analysis with 19 observational studies, showing more than 80% of treated patients attaining at least partial clinical response (25) • Good safety profile in cohort studies	• **2018 EULAR recommendations:** TNF-α inhibitors as second line treatment in TAK patients resistant to csDMARD • **2021 ACR guidelines:** TNF-α inhibitors as first line treatment, like methotrexate and azathioprine
Tocilizumab	**Anti-IL-6r (bDMARD)** • IL-6 is a pro-inflammatory cytokine • Higher IL-6 levels in TAK patients compared to HC and in TAK patients with active disease compared to patients with low disease activity	• Cohort studies, showing positive results in TAK patients (clinical improvement, GC sparing effect, higher sustained remission rate compared to cDMARDs) (22, 26–30) • Meta-analysis with 22 observational studies, showing more than 87% of treated patients attaining at least partial clinical response (25) • One RCT (TAKT study): relapse-free survival tended to be improved in treated tients, but no statistical significance. Longer-term open-label extension showed GC aring effect, lower radiological disease progression, better PROs (31, 32) Good safety profile in cohort studies and RCT	• **2018 EULAR recommendations:** tocilizumab as second line treatment in TAK patients resistant to csDMARD • **2021 ACR guidelines:** tocilizumab as second line treatment in patients with inadequate response to other immunosuppressive therapies
JAK-Inhibitors (tofacitinib, upadaci ni)	• block signali interferons, IL- • suppress tiss damage	**facitinib:** ase reports and one prospective observational study, showing positive results in K patients (clinical improvement, lower radiological disease progression, superior to ethotrexate) (33–37) Good safety profile One ongoing RCT (NCT04299971) **adacitinib:** One ongoing RCT (NCT04161898) **o data on other JAK-Inhibitors**	• Only case reports • Not included in 2018 EULAR recommendations or 2021 ACR guidelines
Rituximab	**Anti-CD20 (bI** • In TAK patie of activated B- • Rituximab bl	solated case reports on rituximab in TAK with contradictory results (38–42) lo RCTs, no meta-analysis, no ongoing trial	• Very limited evidence with contradictory results • Only case reports • Not included in 2018 EULAR recommendations or 2021 ACR guidelines
Abatacept	**Soluble fusio** • In TAK patie of activated B- • Abatacept bl	One RCT with 34 TAK patients: abatacept not associated with a longer median ration of remission compared to placebo (43)	• **2021 ACR guidelines**: Abatacept is not recommended in TAK
Ustekinumab	**Anti-p40. IL-12 and IL-23 inhibitor (bDMARD)** • Th17 and Th1 pathways contribute to TAK pathogenesis • Ustekinumab target p40, a common subunit of IL-12 and IL-23 (main cytokines involved in Th17 and Th1 pathways)	• A small prospective observational study (improvement in clinical symptoms but no changes in intramural enhancement on MRA) (44) • One ongoing RCT (NCT04882072)	• Very limited evidence • Not included in 2018 EULAR recommendations or 2021 ACR guidelines

SELECT-TAK
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Upadacitinib in Subjects With Takayasu Arteritis (SELECT-Takayasu)

Regola F, Uzzo M, Toniati P, Trezzi B, Sinico RA, Franceschini F. Novel Therapies in Takayasu Arteritis. Front Med (Lausanne). 2022 Jan 12;8:814075. doi: 10.3389/fmed.2021.814075. PMID: 35096902; PMCID: PMC8790042.

How do I know if my patient is flaring?

It can be extremely difficult to determine if patient is flaring

Any new symptoms warrant further evaluation – often via imaging

Within the correct clinical context, a change in imaging raises concern for active disease:

Should always compare imaging to prior imaging to properly evaluate for evidence of new disease

New symptoms?

dizziness/lightheadedness
claudication
chest pain
constitutional symptoms
Elevated acute inflammatory markers?

New arterial lesions

Enhanced wall thickening

New stenosis

Disease Monitoring

- Routine medical visits to monitor for new/worsening symptoms.

- Serial imaging: No guidelines. We typically repeat imaging every 3-6 months or if there are new symptoms. Can move to less frequent imaging if imaging has been stable

- Acute inflammatory markers: ACR guidelines recommend against treating elevated ESR/CRP in the absence of symptoms and/or imaging changes. Helpful to trend, especially if they rise in the setting of possible disease flare.

Surgical Intervention

- ACR guidelines: Recommends against surgical intervention for patients with limb claudication, unless quality of life is severely impacted

- Recommend surgery only in patients without active disease

- When doing a graft, surgeon will need to ensure that there are no active lesions in the artery where the graft will attach

Summary

“Takayasu’s is the most humbling disease that we treat”
- Dr. Peter Merkel

Summary

- ❑ Refer to a vasculitis specialty center whenever possible
- ❑ Be prepared to deal with uncertainties
  - Do these symptoms represent disease or damage?
- ❑ Get ready to go to bat for your patients
  - Difficult to obtain insurance approval for imaging
  - Currently no FDA approved medications for Takayasu arteritis

Resources for Your Patients With Vasculitis

References

Ameer MA, Peterfy RJ, Khazaeni B. Temporal Arteritis. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459376/

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Which of these men founded Takayasu’s arteritis: