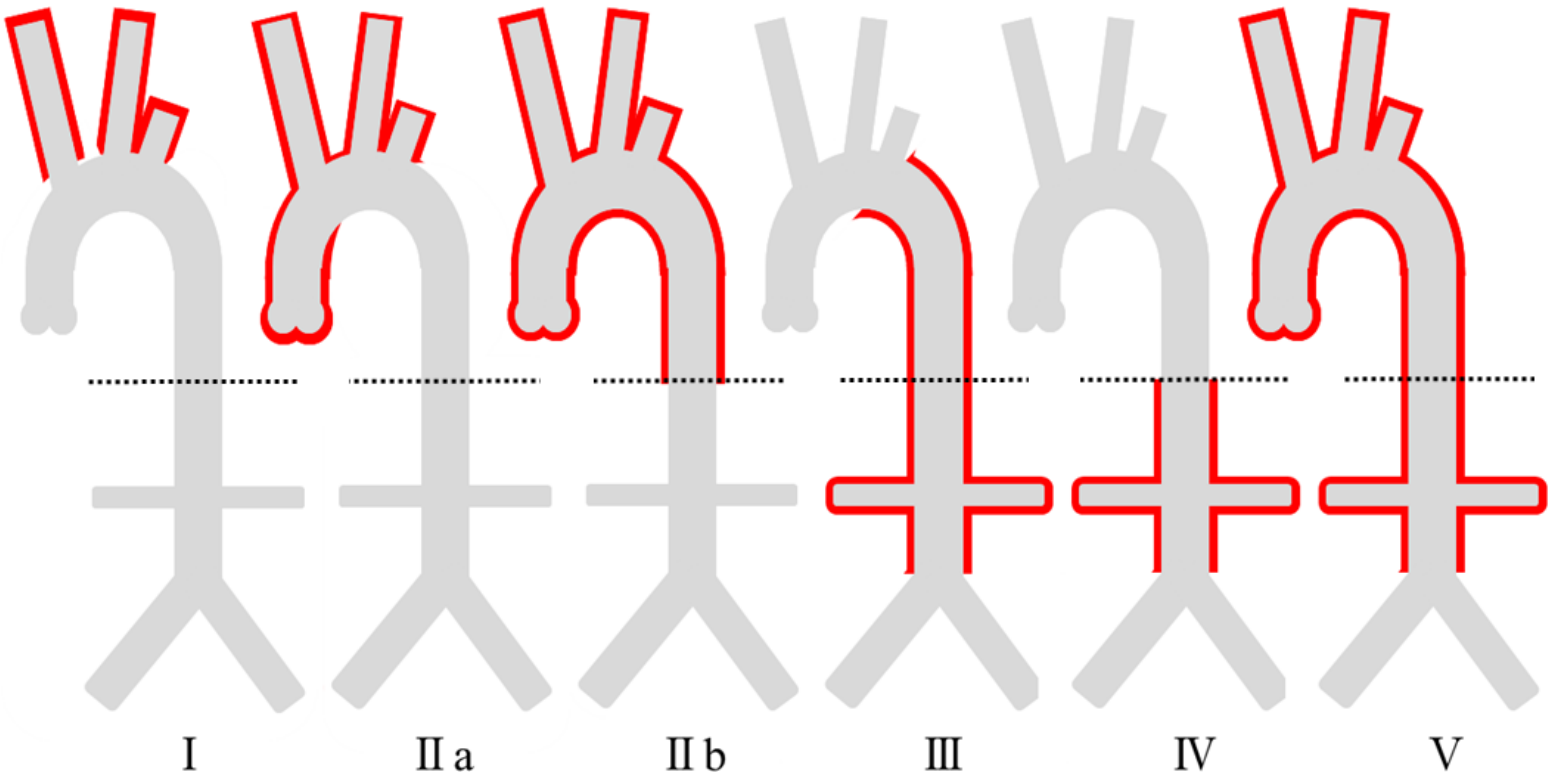
TAKAYASU Αρτηρίτιδα-Νεότερα δεδομένα

Γερολυμάτου Ναυσικά
Επικουρική Ρευματολόγος
Ρευματολογική Κλινική- ΠΓΝ Ιωαννίνων

Αρτηρίτιδα Takayasu

- Κοκκιωματώδης φλεγμονή μεγάλου και μέσου μεγέθους αγγείων (αορτής και κύριων κλάδων της)
- Άσφυγμη νόσος
- Σύνδρομο αορτικού τόξου

Αρτηρίτιδα Takayasu



Angiographic classification of Takayasu arteritis

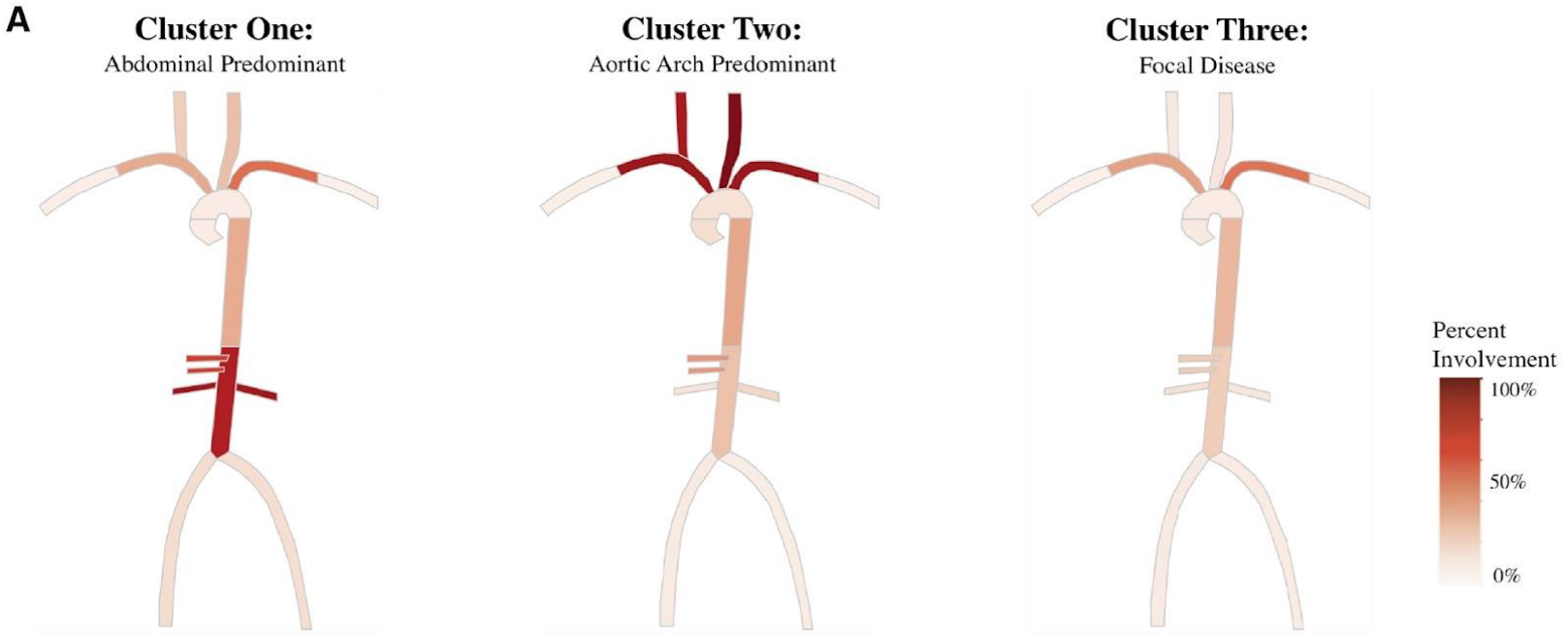
Kato Y, Terashima M, Ohigashi H, Tezuka D, Ashikaga T, Hirao K, et al. (2015). PLoS ONE 10(12): e0145855.

Αρτηρίτιδα Takayasu

ARTERY	Potential Clinical Manifestations
Subclavian	Arm claudication, Raynaud's phenomenon
Common carotid	Visual changes, syncope, transient ischemic attacks, stroke
Abdominal aorta[a]	Abdominal pain, nausea, vomiting
Renal	Hypertension, renal failure
Aortic arch or root	Aortic insufficiency, congestive heart failure
Vertebral	Visual changes, dizziness
Coeliac axis[a]	Abdominal pain, nausea, vomiting
Iliac	Leg claudication
Pulmonary arteries	Dyspnea, chest pain, hemoptysis
Coronary arteries	Chest pain, myocardial infarction

Mason JC. Nat Rev Rheumatol 2010;6:406-415

Αρτηρίτιδα Takayasu-Classification



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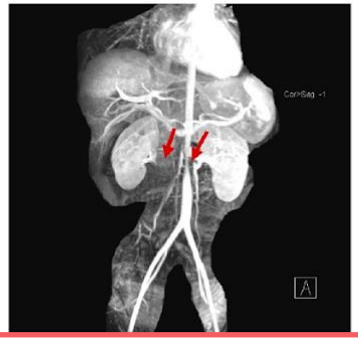
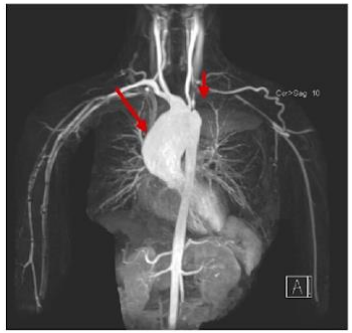


hypertension
lower limb claudication
mesenteric ischemia
childhood onset of disease

C

carotidynia
stroke
upper limb claudication
lightheadedness

D

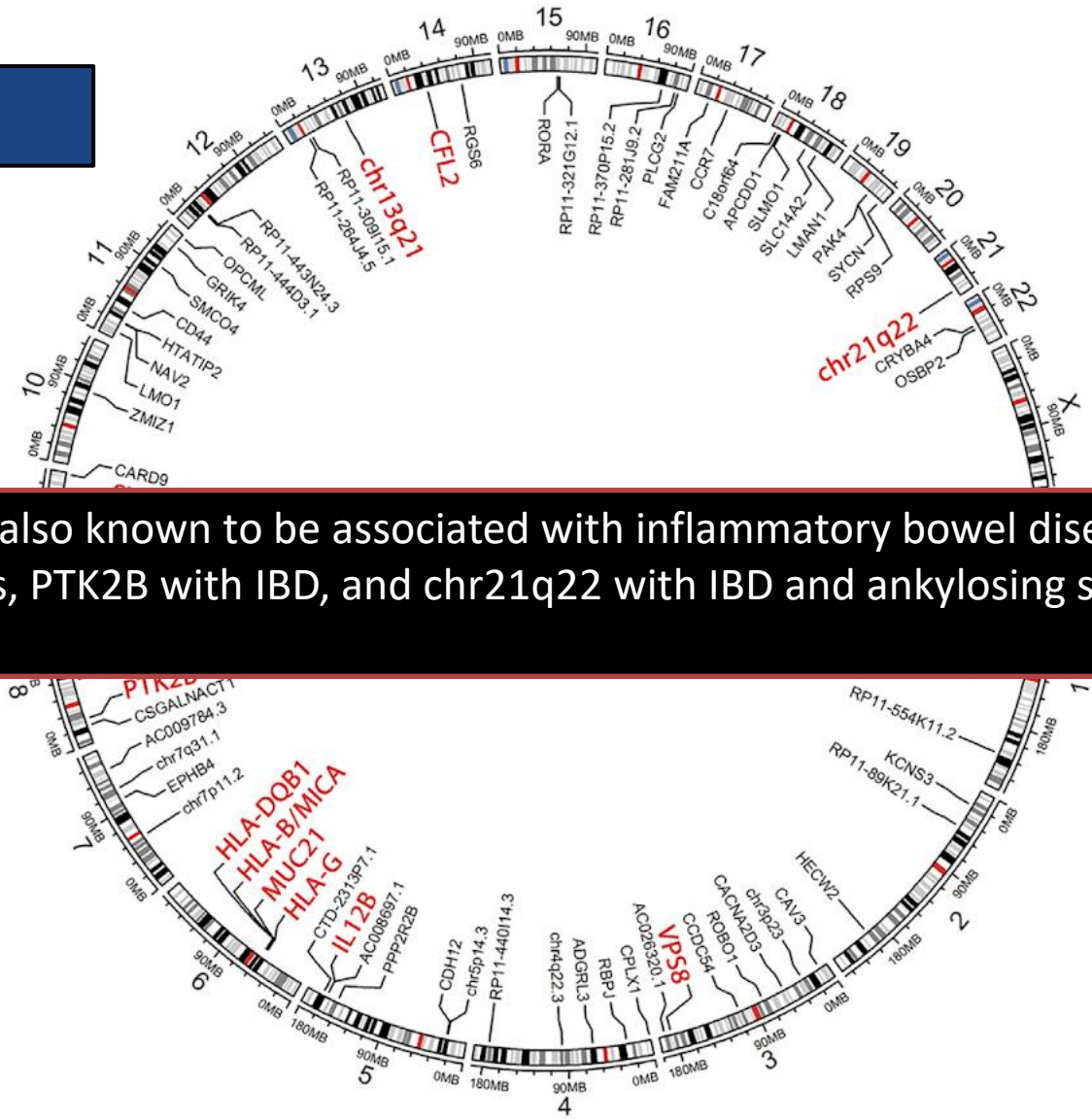


focal disease with a lower number of involved arteries and are less likely to have arterial occlusions

Αρτηρίτιδα Takayasu

the first genome-wide association study conducted in five diverse TAK populations

HLA-B52:01



IL12B is also known to be associated with inflammatory bowel disease (IBD) and psoriasis, PTK2B with IBD, and chr21q22 with IBD and ankylosing spondylitis

Ortiz-Fernandez L, Saruhan-Direskeneli G, Alibaz-Oner F, et al. Am J Hum Genet 2021; 108:84–99.

Αρτηρίτιδα Takayasu- Παθογενετικοί μηχανισμοί

- Cellular immune reactions: T cells, Macrophages (Granulomatous vasculitis)
- Involvement of B cells and autoantibodies has been described
- Autoantibodies targeting *human heat-shock protein (HSP), endothelial cells (AECA), and annexin V* (a protein that induces apoptosis in vascular endothelial cells) have been detected in TAK patients. Whether they have a pathogenetic role or are an epiphenomenon is unclear

Mutoh, T., Shirai, T., Ishii, T. *et al. Nat Commun* **11,** 1253 (2020)

Αρτηρίτιδα Takayasu- Παθογενετικοί μηχανισμοί

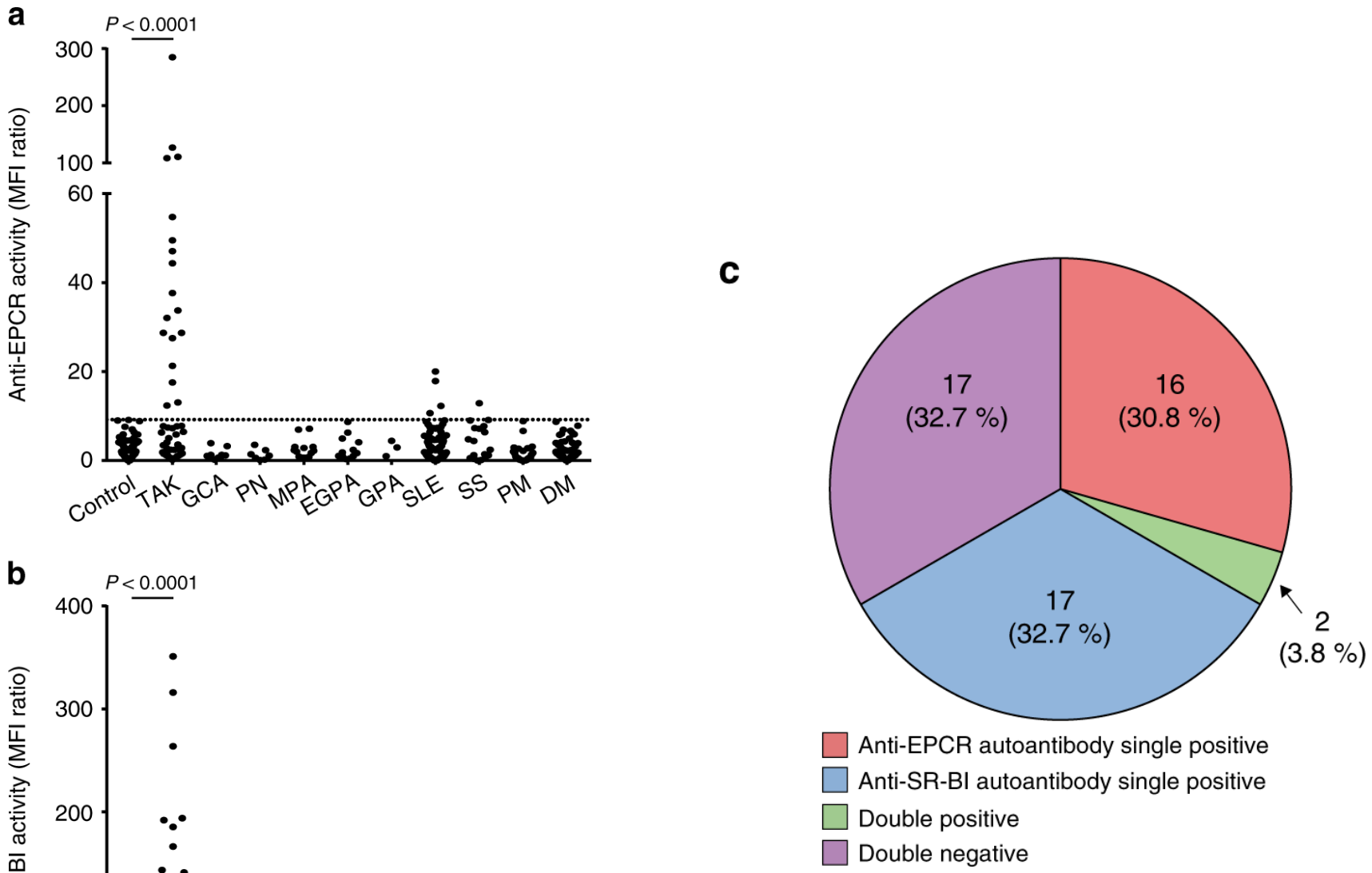
ARTICLE

https://doi.org/10.1038/s41467-020-15088-0 OPEN

nature COMMUNICATIONS

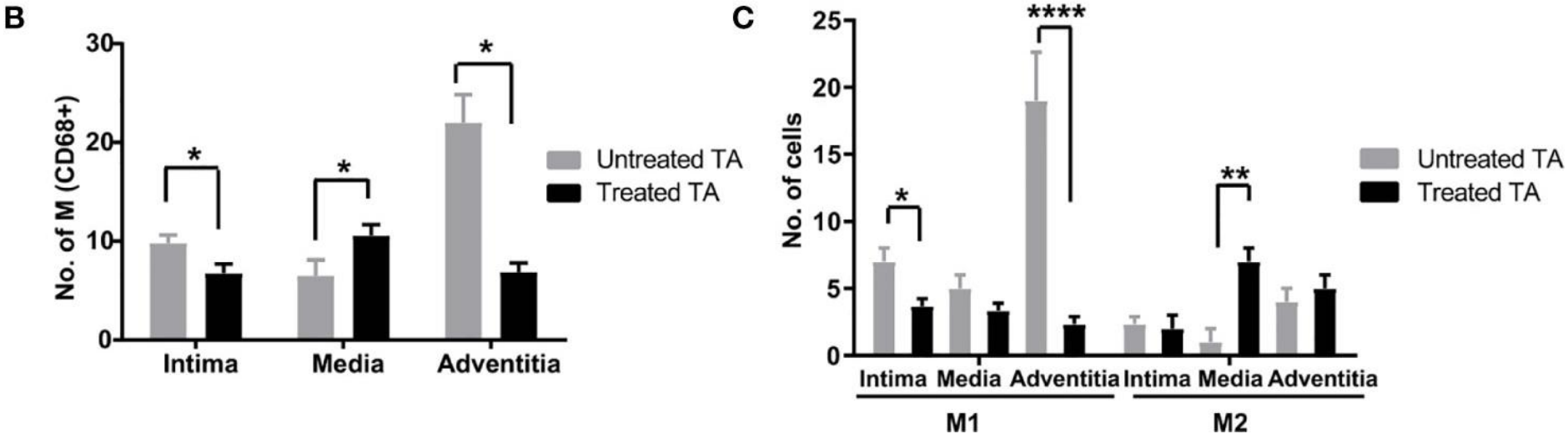
Identification of two major autoantigens negatively regulating endothelial activation in Takayasu arteritis

- Identification of **cell-surface autoantigens** using an expression cloning system.
- **Endothelial protein C receptor (EPCR) and scavenger receptor class B type 1 (SR-BI)** are identified as endothelial autoantigens, detected in 34.6% and 36.5% of cases, respectively, with minimal overlap (3.8%).
- EPCR and SR-BI function as *negative regulators of endothelial activation.* EPCR has also an effect on human T cells and *impair Th17 differentiation*.
- Autoantibodies against EPCR and SR-BI block the functions of their targets, thereby promoting pro-inflammatory phenotype


a
P < 0.0001
Anti-EPCR activity (MFI ratio)
300
200
100
60
40
20
0
Control
TAK
GCA
PN
MPA
EGPA
GPA
SLE
SS
PM
DM
b
P < 0.0001
Anti-SR-BI activity (MFI ratio)
400
300
200
100
0
Control
TAK
GCA
PN
MPA
EGPA
GPA
SLE
SS
PM
DM
c
17
(32.7 %)
16
(30.8 %)
17
(32.7 %)
2
(3.8 %)
Anti-EPCR autoantibody single positive
Anti-SR-BI autoantibody single positive
Double positive
Double negative

Potential Role of Macrophage Phenotypes and CCL2 in the Pathogenesis of Takayasu Arteritis

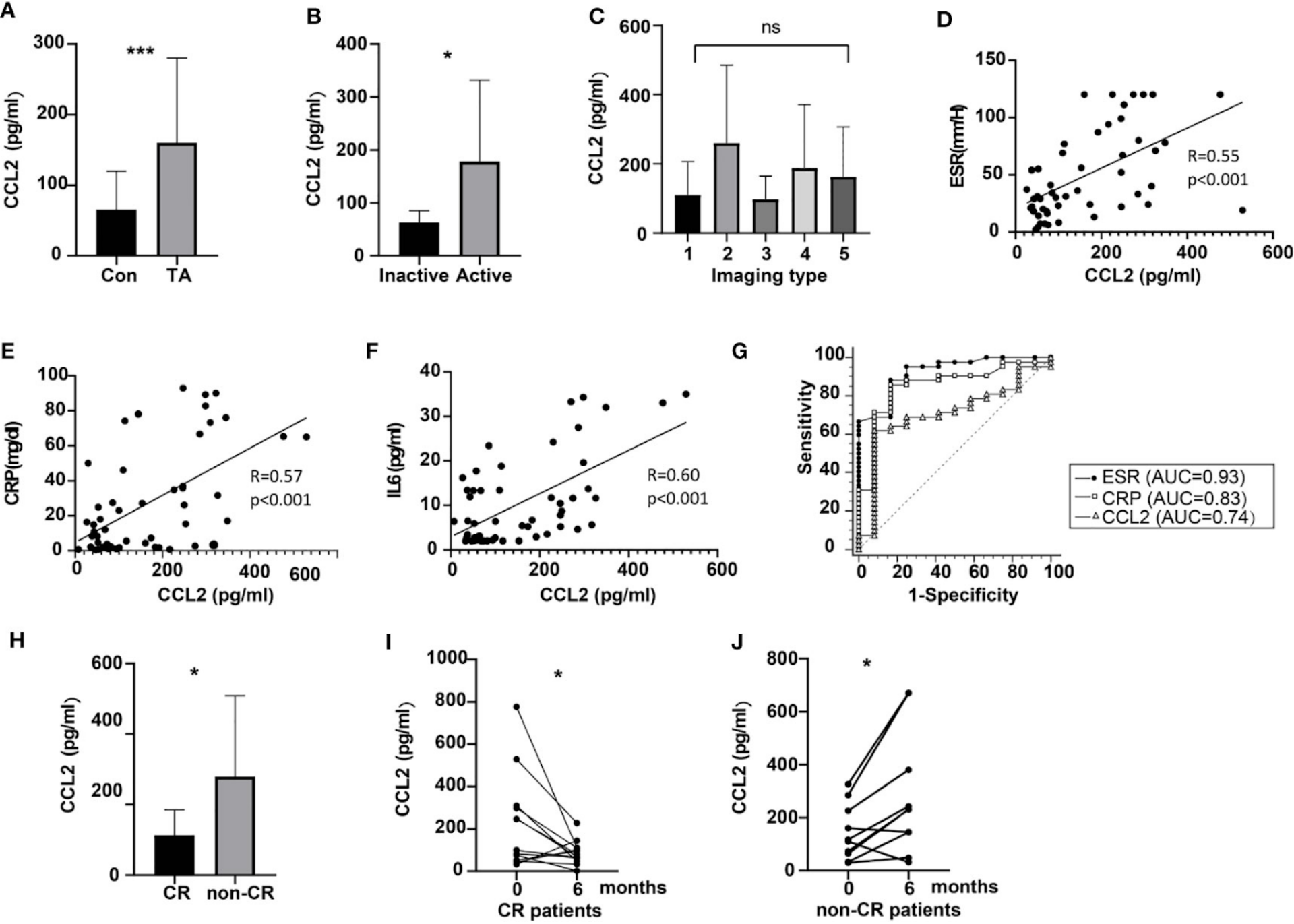
frontiers in Immunology



M1 subset: **pro-inflammatory** role by secreting IL-1, IL-6 and tumor necrosis factor-α (TNF-α)

M2 subset: promote **tissue fibrosis** by producing pro-fibrotic factors such as transformation growth factor-β (TGF-β)

The distribution pattern and phenotype of macrophages and CCL2 expression in vascular tissue of patients with TA indicated that macrophage presented a *phenotype shift (M1 to M2) and distribution change (adventitia to media) as the disease progressed from an active to an inactive phase*.



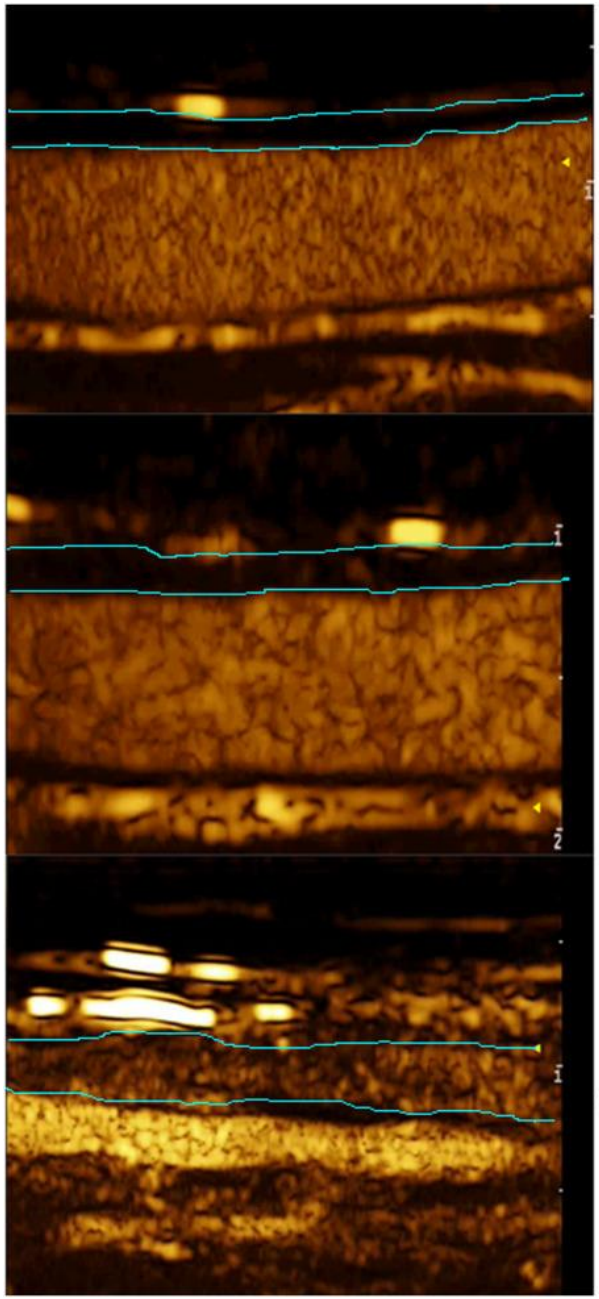
Kong, Xiufang et al. Front Immunol. 2021 May 17;12:646516.

Αρτηρίτιδα Takayasu-Απεικόνιση

Imaging modality	Advantages	Disadvantages
Conventional angiography	Gold standard to show luminal changes such as narrowing or occlusion of the affected vessels	Invasive High radiation exposure Risk of ischemic complications Not useful for early diagnosis due to its inability to detect early vasculitic lesions Inadequate vessel wall assessment Need for intravenous contrast injection
Ultrasonography	Visualization of vessel walls and luminal changes Useful for early diagnosis Noninvasive Widely accessible Short time requirement Limited cost Avoids radiation exposure No need for intravenous contrast injection	Highly operator dependent Inability to visualize the thoracic descending aorta Inability to show the extent of vascular involvement at once
Computed tomography angiography	Visualization of vessel walls and luminal changes Useful for early diagnosis Noninvasive	High radiation exposure Need for intravenous contrast injection
Magnetic resonance angiography	Visualization of vessel walls and luminal changes Useful for early diagnosis Noninvasive Avoids radiation exposure	Poor visualization of calcifications Need for intravenous contrast injection Cost
18F-fluorodeoxyglucose-positron emission tomography/computed tomography	Combination of anatomical and metabolic imaging Useful for early diagnosis even before detectable findings on the other imaging modalities Noninvasive Assessment of multiple arteries at once Useful to exclude malignancies and infections	High radiation exposure Need for intravenous contrast injection Cost Limited availability Inability to detect intracranial arteries False positives (atherosclerosis)

Esatoglu and Hatemi. Curr Opin Rheumatol 2022, 34:18 – 24

Αρτηρίτιδα Takayasu- Contrast Enhanced U/S

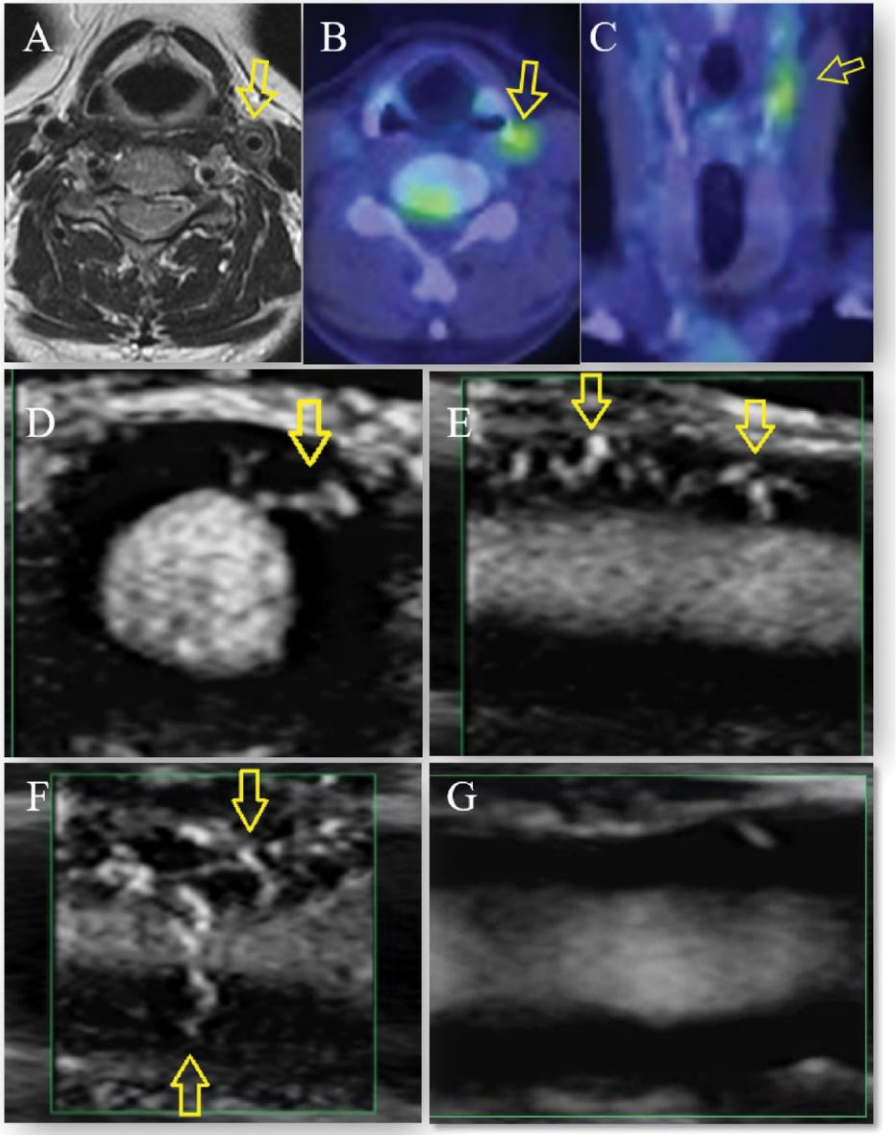


Contrast-enhanced ultrasonography (CEUS) is able to assess vascular wall *neovascularization*.

Carotid CEUS vascularization grade has been shown to be *correlated with the grade of vascular inflammation in 18FDG-PET and disease activity*

Wang Y, Wang YH, Tian XP, et al. Clin Rheumatol 2020; 39:1229 – 1235
Germano G, Macchioni P, Possemato N, et al. Arthritis Care Res (Hoboken) 2017; 69:143 – 149

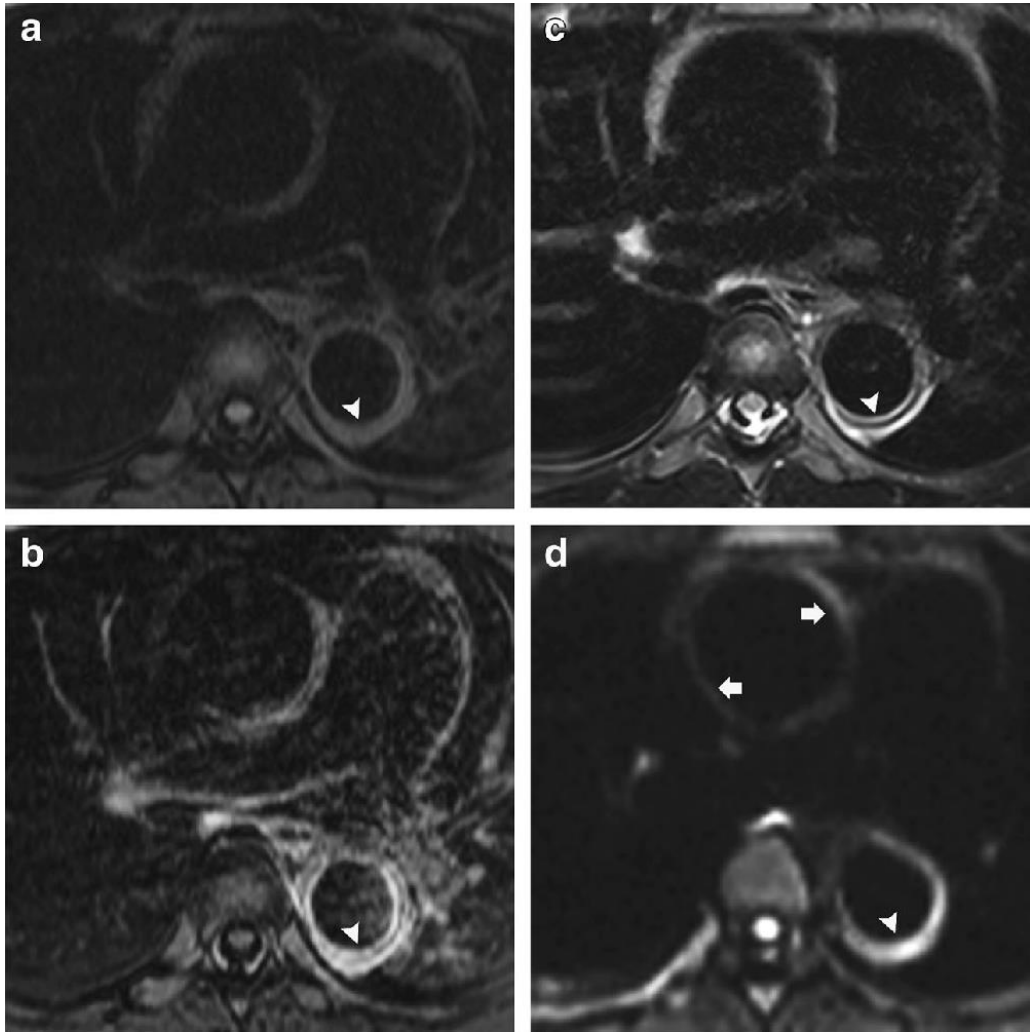
Αρτηρίτιδα Takayasu- SMI



Superb microvascular imaging (SMI), [Aplio; Canon Medical Systems] reveals microvessels & arterial wall neovascularization without contrast medium

Sato W et al. Eur Heart J Cardiovasc Imaging. 2019 Jun 1;20(6):719.

Αρτηρίτιδα Takayasu- DWI

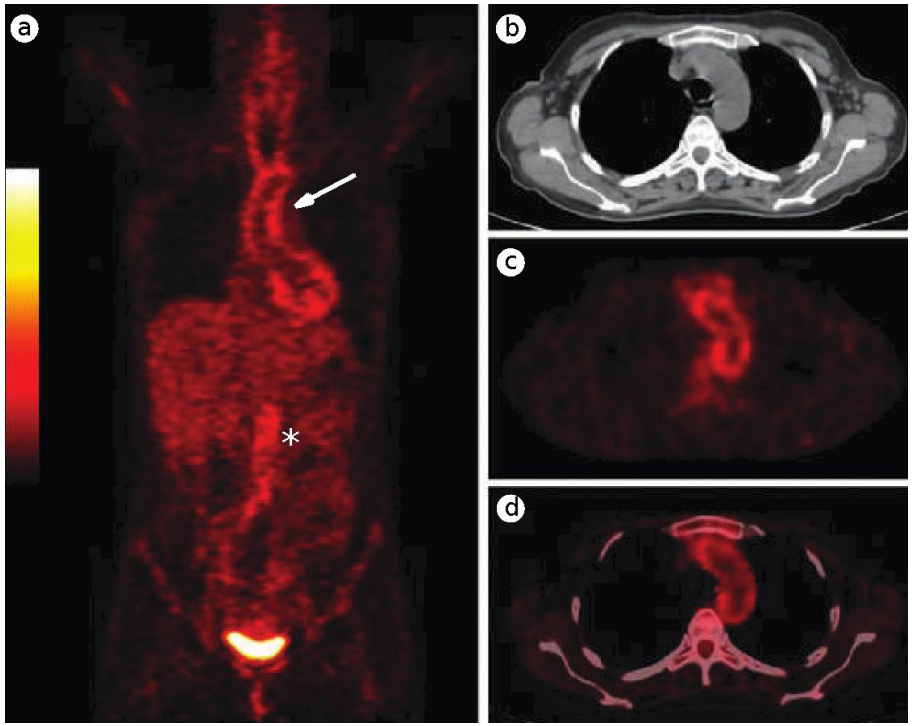


Low b-value diffusion-weighted imaging (DWI), a noncontrast MRI technique, was studied as an alternative imaging modality to contrast-enhanced MRA in identifying mural inflammation

DWI was found to be noninferior to contrast enhanced MRA but was superior to T2WI.

Yang H, Lv P, Zhang R, et al. Eur Radiol 2021; 31:6666 – 6675

Αρτηρίτιδα Takayasu- PET-CT



However, PET–CT did detect active inflammation in 58% of patients who were in clinically determined remission, suggesting either an *inability to distinguish active disease from vascular remodelling and atherosclerosis or the presence of low-grade disease*.

One study investigated PET–CT as a **disease monitoring tool** in 56 patients with LVV and a control group consisting of 59 individuals, including healthy volunteers, disease mimics and patients with hyperlipidaemia. They found *a sensitivity of 85% and specificity of 83% for distinguishing active vasculitis from comparators*.

Αρτηρίτιδα Takayasu- Treatment

	EULAR recommendations	ACR/VF guideline
Remission induction therapy		
Initial glucocorticoid therapy	Initiate a dose of 40–60 mg/day prednisone-equivalent	Initiate a dose of 1mg/kg/day up to 80 mg prednisone-equivalent
csDMARDs/non- glucocorticoid immunosuppressive agent	Start methotrexate, azathioprine, mycophenolate mofetil, leflunomide or cyclophosphamide[b]	Start methotrexate, azathioprine, or a tumor necrosis factor alpha inhibitor
Treatment of relapse	Major relapse: Initiate a glucocorticoid dose of 40–60 mg/day prednisone-equivalent and consider initiating tumor necrosis factor alpha inhibitors or tocilizumab	Not stated
	Minor relapse: Increase the glucocorticoid dose to 5–15 mg above the last effective dose and consider initiating tumor necrosis factor alpha inhibitors or tocilizumab	
Treatment of refractory disease	Consider initiating tumor necrosis factor alpha inhibitors or tocilizumab	Consider switching the initial agent to another non- glucocorticoid immunosuppressive agent (methotrexate, azathioprine, tumor necrosis factor alpha inhibitors, or tocilizumab) Tumor necrosis factor alpha inhibitors are recommended over tocilizumab
Treatment of patients during remission	Consider tapering the biologic agent in patients in remission for at least 6 months and in those who achieved the individual target glucocorticoid dose	Consider tapering glucocorticoids in patients who are in remission for at least 6–12 months
Antiplatelet or anticoagulant therapy	Do not routinely use antiplatelet or anticoagulant therapy unless indicated for other cardiovascular conditions	Consider adding an antiplatelet therapy in patients with active disease and critical cranial or vertebrobasilar involvement
Timing for endovascular or surgical interventions	Perform either intervention, once remission is achieved (with the exception of vascular complications requiring an emergent surgery)	Perform either intervention, once remission is achieved

Effectiveness and safety of leflunomide compared with cyclophosphamide as induction therapy in Takayasu's arteritis: an observational study

Xiaomin Dai*, Xiaomeng Cui*, Ying Sun, Lili Ma and Lindi Jiang
and the East China Takayasu's Arteritis (ECTA) Collaboration Group

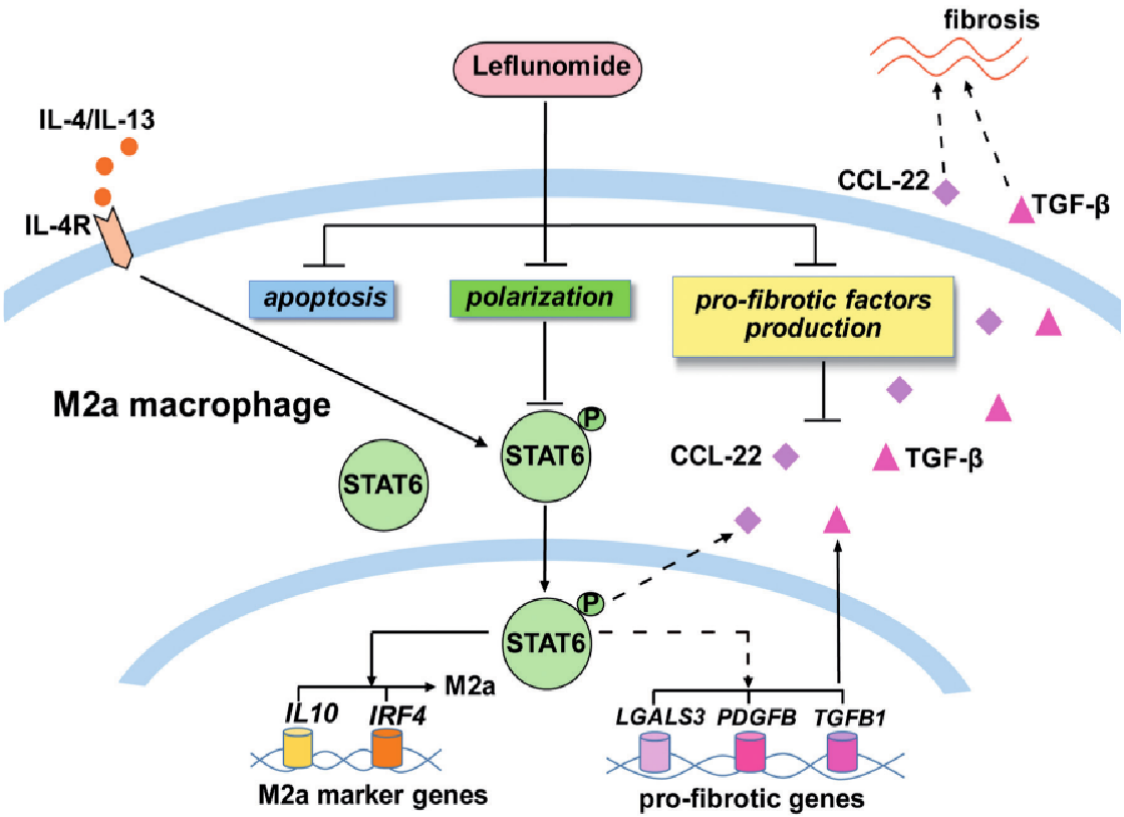
- Comparative observational study
- LEF was superior to CYC for remission induction with a lower adverse event rate

	Before matching			After matching		
	LEF group (*n* = 52)	CYC group (*n* = 78)	*P*	LEF group (n = 23)	CYC group (n = 54)	*P*
CR % (95% CI)	84.6 (74.5–94.8)	59.0 (47.8–70.1)	0.002*	95.7 (86.6–100.0)	63.0 (49.7–76.3)	0.003*
RR (95% CI)	1	0.3 (0.1–0.6)		1	0.1 (0.0–0.6)	
PR % (95% CI)	9.6 (1.3–17.9)	15.4 (7.2–23.6)	0.339	4.3 (0–13.4)	20.4 (9.3–31.5)	0.095
RR (95% CI)	1	1.7 (0.6–5.2)		1	5.6 (0.7–46.4)	
ER % (95% CI)	94.2 (87.7–100.0)	74.4 (64.5–84.3)	0.004*	100 (100–100)	83.3 (73.1–93.6)	0.037*
RR (95% CI)	1	0.2 (0.1–0.6)		1	0.8 (0.3–2.1)	

The potential role of leflunomide in inhibiting vascular fibrosis by down-regulating type-II macrophages in Takayasu's arteritis

X. Cui[1], X. Kong[1], R. Chen[1], L. Ma[1,2], L. Jiang[1,2]

Potential role of LEF in vascular fibrosis / X. Cui et al.



Cui X, Kong X, Chen R, et al.. Clin Exp Rheumatol 2020; 38 Suppl 124:69 – 78

RHEUMATOLOGY

doi:10.1093/rheum
Advance Access publication 1

Concise report

Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study

- Open-label extension study
- 28 patients were treated with tocilizumab for 96 weeks
- Endpoints of the extension: steroid-sparing effects of tocilizumab, imaging data, patient-reported outcomes (36-Item Short Form Health Survey) and safety
- At week 96, 13 **(46%) patients reduced their glucocorticoid dose to <0.1mg/kg/ day**, and the improvement in the patient reported outcomes maintained over time.
- Eighteen relapses were observed in 14 (50%) patients.
- Imaging evaluations indicated that most patients' disease was improved (17.9%) or stable (67.9%) after 96 weeks compared with baseline
- 36-Item Short Form Health Survey scores improved from baseline and maintained over 96 weeks
- 9/36 (25%) severe adverse events occurred, infections being the most common (7/36, 17%). None of the infections led to tocilizumab discontinuation.

RESEARCH ARTICLE Open Access

Tocilizumab in treatment-naïve patients with Takayasu arteritis: TOCITAKA French prospective multicenter open-labeled trial

Arthritis Research & Therapy

- Prospective open-labeled trial in naïve patients with TAK (N=13)
- Received steroids at the dose of 0.7 mg/kg/ day and 7 infusions of 8mg/kg/month of tocilizumab.
- Primary endpoint was the number of patients who discontinued steroids after 7 infusions of tocilizumab .
- Secondary endpoints included disease activity & number of relapses during 18-month follow-up.
- Six (54%) patients met the primary endpoint
- Relapse occurred among 5 patients (45%) out of 11 in which achieved remission after 6 months of tocilizumab

Conclusion: Tocilizumab seems an effective steroid sparing therapy in TAK, but maintenance therapy is necessary.

Mekinian A, Saadoun D, Vicaut E, et al. Arthritis Res Ther 2020; 22:218.

Treatment efficacy and safety of tofacitinib versus methotrexate in Takayasu arteritis: a prospective observational study

BMJ Full Text

- 1st observational study of a Janus-kinase (JAK) inhibitor
- TOFA (n=27) was compared to MTX (n=26) for remission induction
- Tofacitinib led a higher complete remission rate at months 6 and 12 (23/27, 85% vs. 16/26, 61%, P=0.07; 23/26, 88% vs. 13/23, 56%, P=0.02, respectively)
- TOFA had a longer median relapse-free duration and a similar adverse event rate

Kong X, Sun Y, Dai X, et al. Ann Rheum Dis 2021. annrheumdis-2021-220832

Αρτηρίτιδα Takayasu- Ongoing studies

TAK

- An open-label, randomized study comparing MTX with the JAK1/3 inhibitor tofacitinib in patients with mild-to-moderate Takayasu arteritis (TAK)[306].
- A phase III, multicentre RCT of the efficacy of the JAK1 inhibitor upadacitinib[307].
- A phase III RCT targeting the IL-12/23p40 subunit with ustekinumab; proposed following promising case series results[308].
- A multicentre phase II RCT comparing tocilizumab with infliximab in patients with refractory or relapsing TAK (not yet recruiting)[309]; this study will hopefully provide clarification regarding the efficacy of different biologic therapies in this patient group.

Pugh, D., Karabayas, M., Basu, N. *et al.* Large-vessel vasculitis. *Nat Rev Dis Primers* **7,** 93 (2021)

Αρτηρίτιδα Takayasu- Key points

- Early diagnosis in TAK remains a challenge.
- Different new imaging modalities (CEUS, SMI, DWI) have been tried in the assessment of arterial inflammation with promising results.
- Novel autoantigens/autoantibodies have been identified, but they need to be verified in large-sample studies.
- Three novel clusters based on angiographic findings were identified.
- Beyond TNF-a inhibitors and tocilizumab, Janus kinase inhibitors & Leflunomide may be a new therapeutic agent in the management of TAK.