GCA (and LVV) teaching slide set CanVasc

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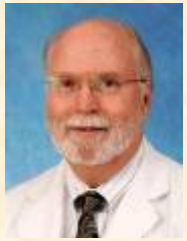
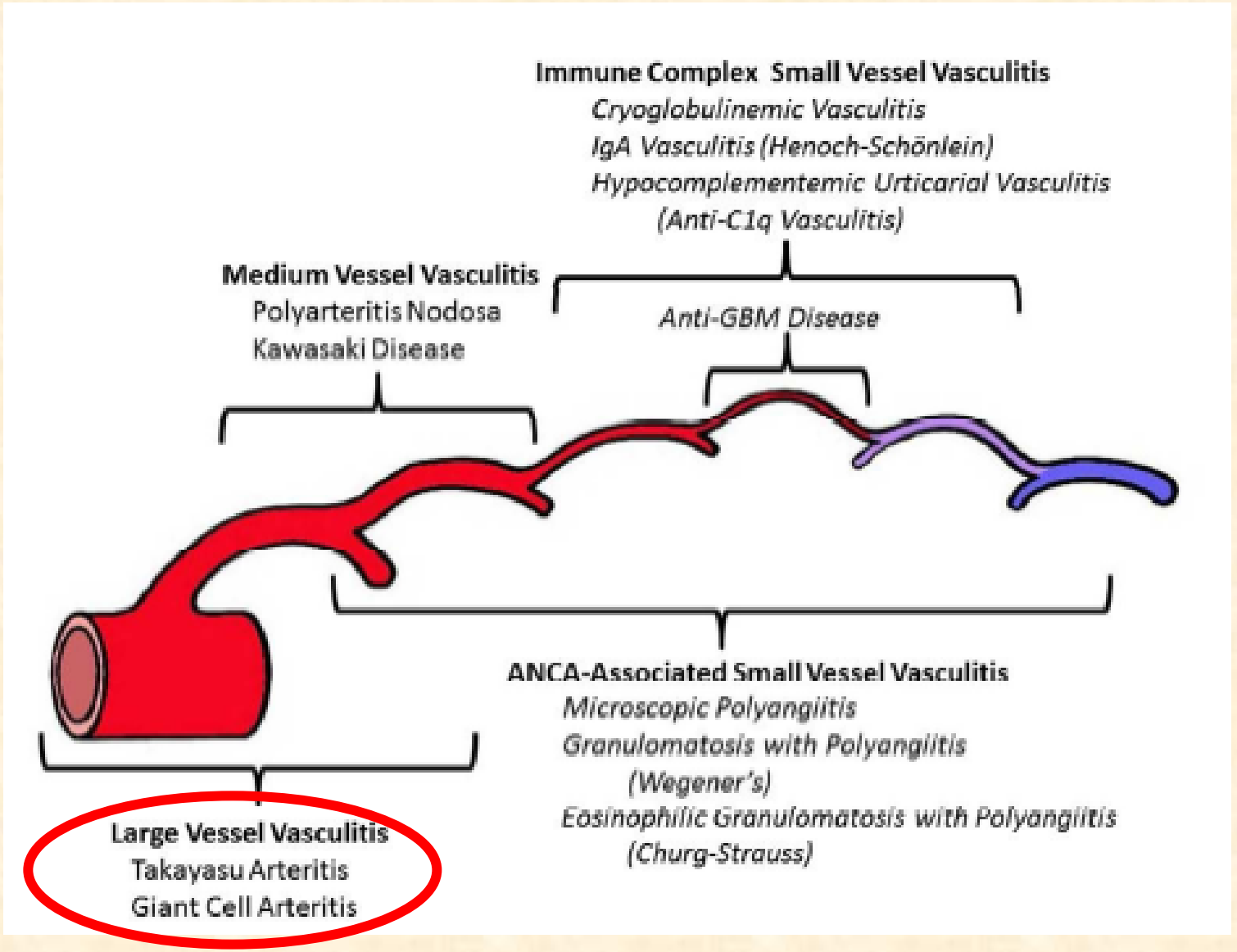
Objectives

- List the official (and unofficial) LVV
- Review the main characteristics and mainstays of the management of GCA and aortitis

- Be aware of the future developments in the management of LVV

2012 Chapel hill Nomenclature





Jennette et al. Arthritis Rheum. 2013

2012 Chapel hill Nomenclature

- Vasculitis affecting large arteries more often than other vasculitides.
- Large arteries are the aorta and its major branches. Any size artery may be affected.

Jennette et al. Arthritis Rheum. 2012 Oct 8.

The other “unofficial LVV”

- Overlap between GCA and TAKA
- Asymptomatic inflammation in the aorta in patients who had aortic surgery
- Periaortitis/retroperitoneal fibrosis

Luqmani et al. Curr Opin Cardiol. 2012

Arthritis Care & Research
Vol. 62, No. 3, March 2010, pp 316–322
DOI 10.1002/acr.20095

ORIGINAL ARTICLE

IgG4-Related Systemic Disease Accounts for a Significant Proportion of Thoracic Lymphoplasmacytic Aortitis Cases

JOHN H. STONE, AREZOU KHOSROSHAHI, VIKRAM DESHPANDE, AND JAMES R. STONE

Objective. **IgG4-related systemic disease, a disorder recognized only recently, can cause lymphoplasmacytic inflammation in the thoracic aorta. The percentage of cases caused by IgG4-related systemic disease is not known. We aimed to determine the percentage of noninfectious thoracic aortitis cases that are associated with IgG4-related systemic disease and to establish pathologic criteria for identifying involvement of the thoracic aorta by this disorder.**

Methods. **We searched our Pathology Service database to identify patients with noninfectious thoracic aortitis who underwent resection over a 5-year time span. The histologic features of these cases were reviewed. All cases of lymphoplasmacytic aortitis and representative cases of giant cell aortitis and atherosclerosis were stained by immunohistochemistry for IgG4 and for the plasma cell marker CD138. We determined the fraction of plasma cells that stained for IgG4.**

Results. **Of 638 resected thoracic aortas, 33 (5.2%) contained noninfectious aortitis. Four of these cases (12% of all patients with noninfectious aortitis) had histologic features of lymphoplasmacytic aortitis. Three of those 4 cases (9% of the noninfectious aortitis cases) demonstrated pathologic involvement by IgG4-related systemic disease, with an elevated proportion of plasma cells staining for IgG4 (mean ± SD 0.82 ± 0.08) compared with cases of giant cell aortitis (0.18 ± 0.13) and atherosclerosis (0.19 ± 0.08; $P < 0.00001$).**

The other “LVV”

- Overlap between GCA and TAKA
- Asymptomatic inflammation in the aorta in patients who had aortic surgery
- Periaortitis/retroperitoneal fibrosis
- IgG4-RD/aortitis/aortic aneurysm

Luqmani et al. Curr Opin Cardiol. 2012

Vasculitis	Prevalence (per million)	Remarks	Annual Incidence (per million)	Remarks
GCA	1,400-16,000 (of population >50 y-o)	Crude estimates (no specific study)	100-300 (of population >50 y-o)	Down to 5 in Israel in late 1960s; Up to 370 in Norway in mid 1990s; 20 in subjetcs <60 and up to 520 in those >80 y-o in Minnesota
Takayasu	4-8	4.7 to 7 in the UK in early 2000s; Up to 40 in Japan (no epidemiological data for India, but probably at least the same)	1-2	Down to 0.4 in Germany; Up to 2.6 in Minnesota in late 1970s, and 3.3 in Kuwait
PAN	22-31 (in the late 1990s)	HBV-related PAN almost disappeared	0.9- 6.8	Up to 8 in the UK, 16 in Kuwait in the late 1990s, and 77 in Alaska in late 1980s (HBV endemy)
Kawasaki	-	Acute disease (in general, but damage)	100-500 (of children <5 y-o)	Down to 16 in Czech republic in late 1990s; Up to 2,180 in Japan; in US, 91 in Caucasian vs. 320 in Asian children in early 2000s
GPA	50-90	Down to 23 in Paris in 2000, 30 in NYC in 1990; Up to 160 in Sweden in 2007	5-10	Down to almost 0 in Japan, 2.9 in Spain; Up to 11 in Australia and Minnesota
MPA	25-50	Down to 25 In Paris in 2000; Up to 94 in Sweden in 2007	5-10	Down to 2.7 In Germany;Up to 15 in Japan, and 24 in Kuwait
CSS	10-15	Down to 7 in Germany in 1994; Up to 22 in Australia in 2004	1-2	Down to 0 in Japan; Up to 2.7 in the UK in late 1990s, and 4 in Minnesota in late 1970s
Behçet	10-500	Extremely wide ethnic variations (from 6 in the UK in late 1970s to 4,200 in Turkey in 2000); 100-300 in US , mainly in immigrants; 24 in European-descent vs. 175 in Asian-descent vs 350 in North-African- descent French population	-	No precise estimation (chronic disease and wide geographical differences); around 4 in Minnesota in mid 2000s
CNS-V				ota

→ 2,000 to 15,000 in Canada

Lugo (Spain)

Gonzales-Gay et al., Ann Rheum Dis 2001

VCRC

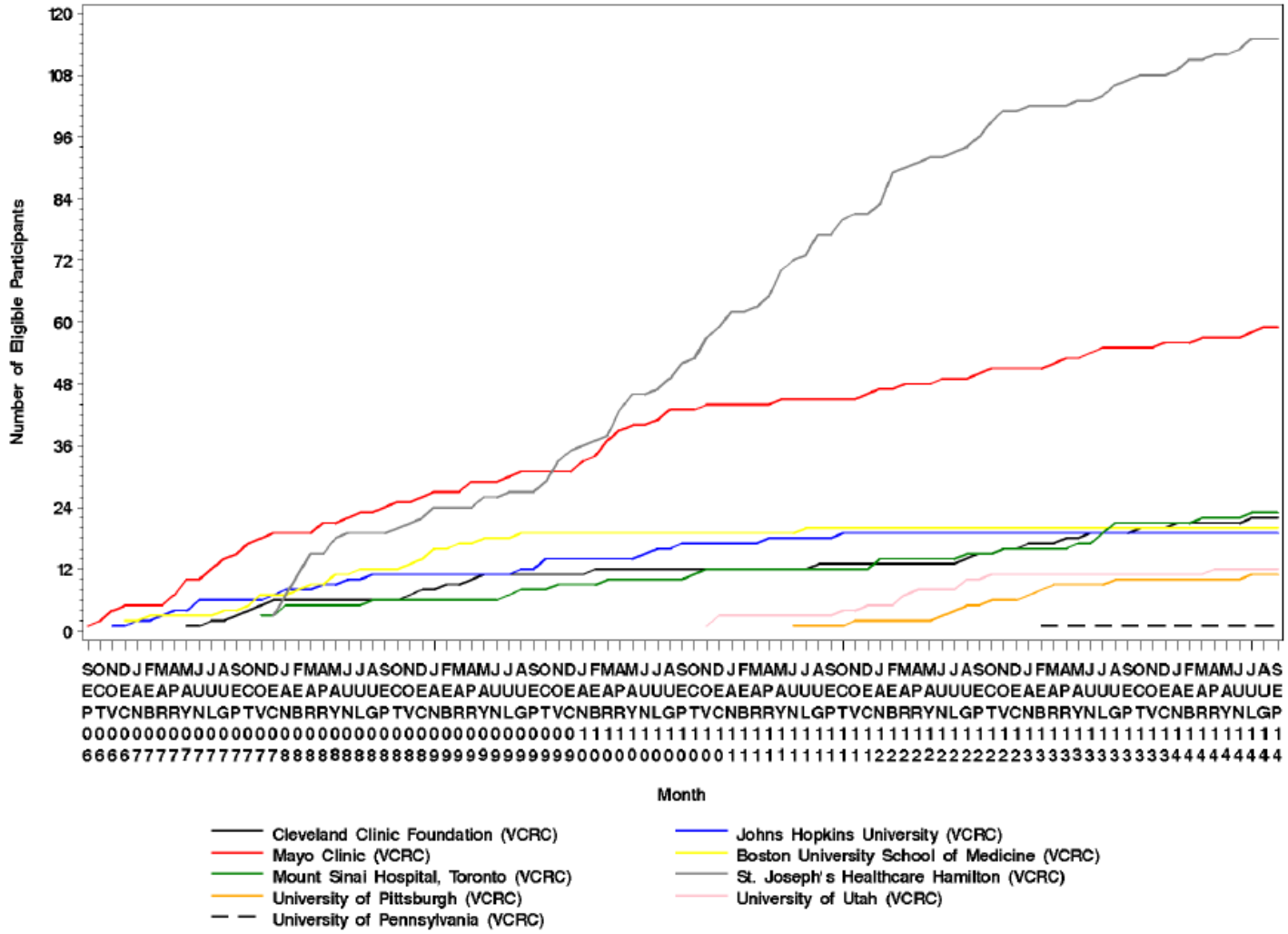
GEN.II.07

Consortium Summary Report (VCRC)

Accrual by Protocol: Number of Eligible Participants Overtime

Data Current as of September 1, 2014

Protocol: 5502 - VCRC Longitudinal Protocol for Giant Cell Arteritis



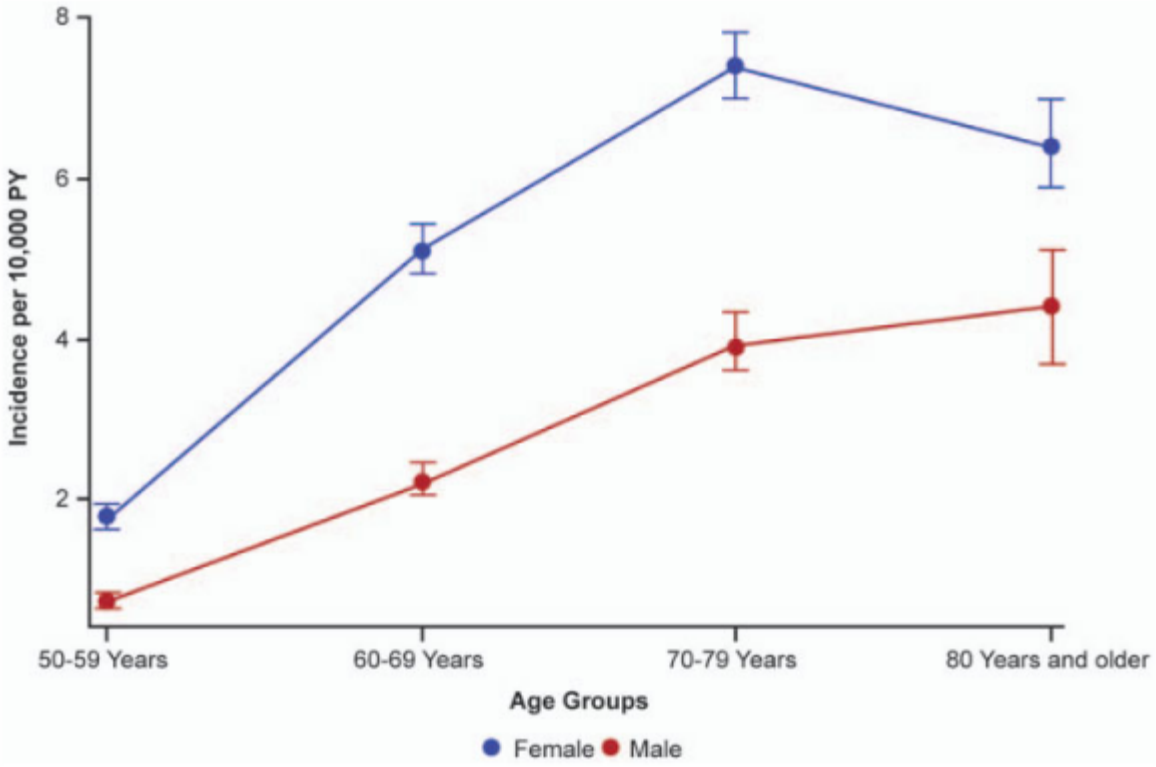
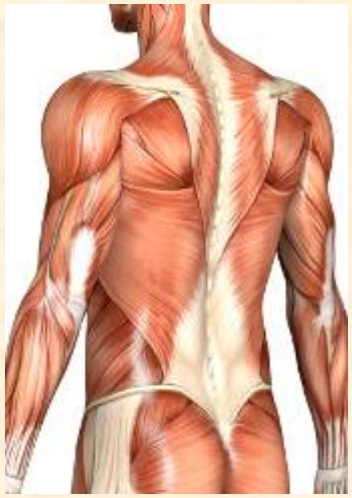


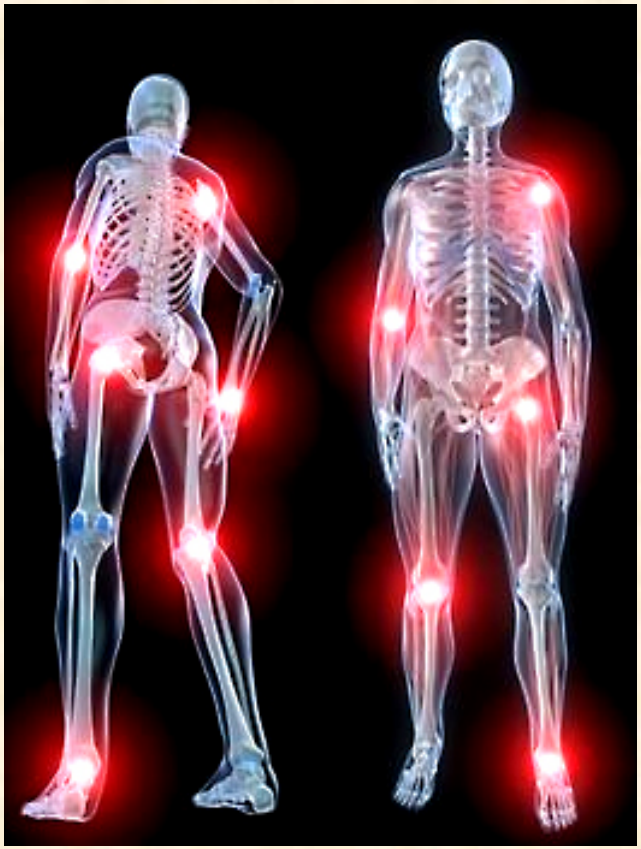
Figure 1. Incidence of giant cell arteritis per 10,000 person-years with 95% confidence intervals (patients treated with corticosteroids). PY = patient-years.

Petri H et al., Arthritis Care & Research 67(3), March 2015

Clinical case

- Mrs. T. A. aged **65 years**
- History:
  - Lung emphysema (past smoker)
  - High blood pressure (amlodipine 5 mg OD)
  - Overweight BMI 31
- Diffuse **headaches** for 2 weeks, neck pain, some jaw pain when starting chewing/meals, then had 3 episodes of bilateral blurry vision for 30 seconds each within the past 2 days
- On examination, some bilateral **temporal tenderness**, left TA less palpable than the right one, no bruits. Peripheral pulses present, but left radial pulse possibly weaker. BP 132/70 on R arm and 128/72 on L arm, regular HR 81/min. No neurological deficit.

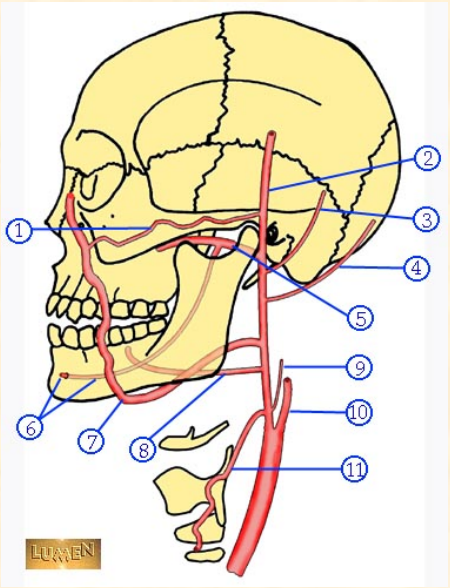




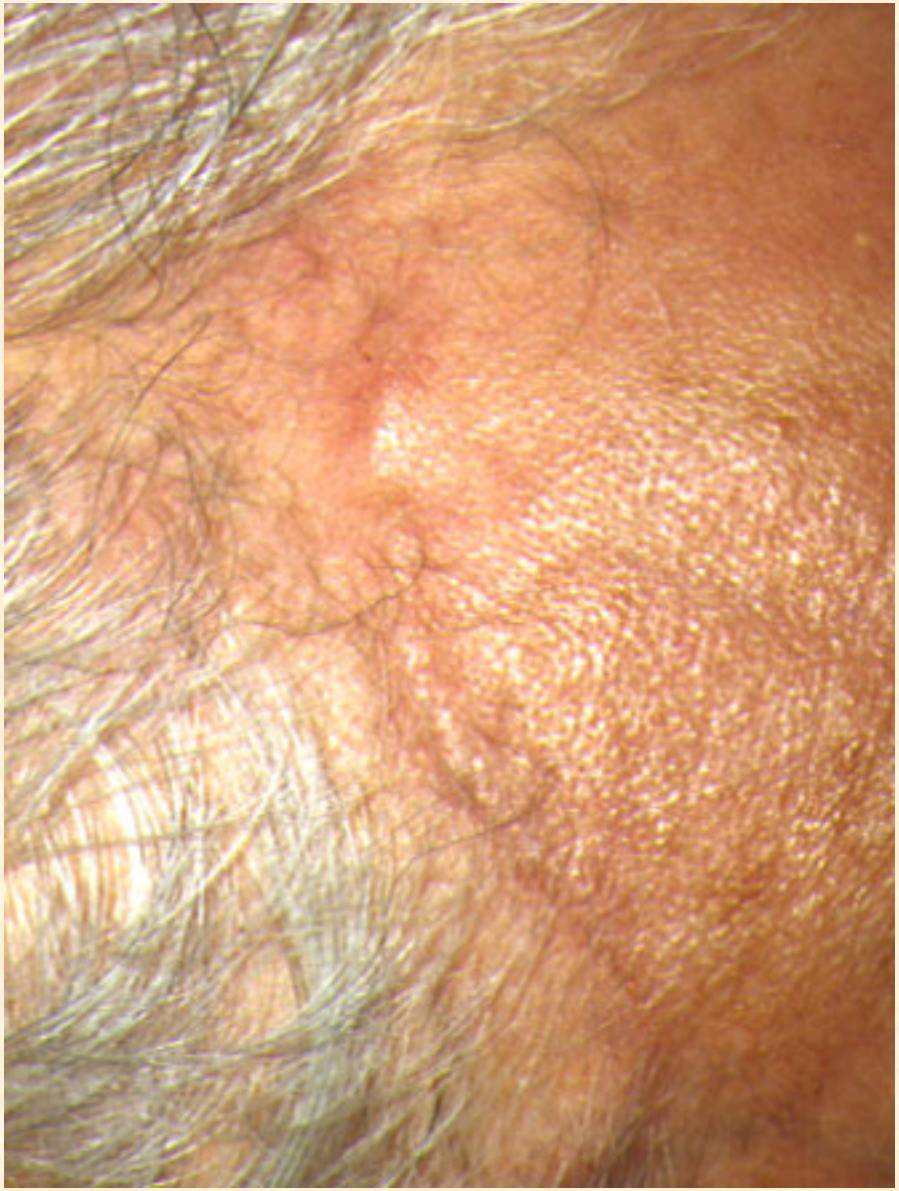
Constitutional symptoms

Links with PMR

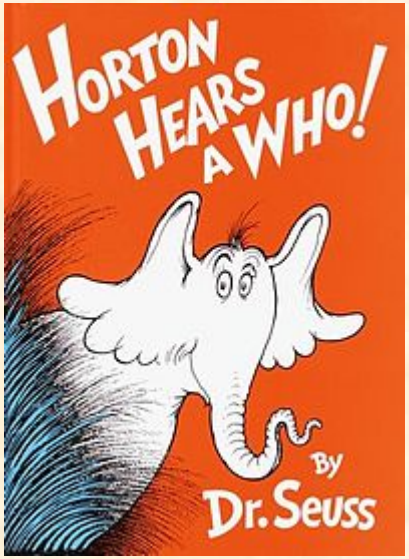
Giant cell / Temporal arteritis



External carotid branches



GCA = Horton disease



Horton Bayard Taylor, Magath TB, Brown GE. An undescribed form of arteritis of the temporal arteries. Proc Staff Meet **Mayo Clin 1932**; 7: 700-701.

ACR criteria (1990)

1. Age at disease onset >=50 years

Development of symptoms or findings beginning at age 50 or older

2. New headache

New onset of or new type of localized pain in the head

3. Temporal artery abnormality

Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries

4. Elevated erythrocyte sedimentation rate

Erythrocyte sedimentation rate >=50 mm/hour by the Westergreen method

5. Abnormal artery biopsy

Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

* For purposes of classification, **≥3 criteria** with a **sensitivity of 93.5% and a specificity of 91.2%**

Hunder et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122---8.

So, what's next?

1. Ophthalmological examination? urgent?
2. Blood work? ESR and/or CRP?
3. Brain imaging? urgent?
4. TA biopsy? directly? which side? bilateral?
5. Other imaging? TA Doppler-US? MRI? angioCT? Supra-aortic vessels? Other arteries?
6. Corticosteroids first? then, think about investigations?

Inflammation

- Increased C-reactive protein
- Increased Sedimentation rate
- Increased WBC (neutrophils)

CRP and ESR

- 119 patients with TAB+ (Baltimore)
- ESR Se=76-86% and CRP Se=97.5%
- But
  - **1 (0.8%) with normal ESR and CRP**
  - **2 (1.7%) with an elevated ESR but normal CRP**

Parikh et al, Ophthalmology 2006 Oct;113(10):1842-5

- 459 TAB+ / 3001 patients who had TAB (CA, US)
- Odds of a TAB+
  - 1.5 times greater with an ESR of 47 to 107 mm/hr
  - 5.3 times greater with a CRP >2.45 mg/dL
  - 4.2 times greater with platelets >400 000/µL.

Walwick et al, Ophthalmology 2011 Jan [Epub ahead of print]
Hayreh et al, Am J Ophthalmol 1997;123:285-96

CRP and ESR

- All patients undergoing TAB between 2000 and 2008 and with both ESR and CRP at the time of TAB
- 764 patients (65% women), age 72.7 ±9.2) years
- TAB consistent with GCA in 177 patients (23%)
- Elevated CRP sensitivity for a TAB+ of 86.9% > elevated ESR sensitivity of 84.1%
- 7 patients (4%) with a TAB+ had a normal ESR and CRP at diagnosis

Kermani et al. Semin Arthritis Rheum. 2012;41(6):866-71

Human Ferritin heavy chain antibodies as a marker of GCA/PMR?

- Protein array technology on 6 GCA sera
  - 37,830 proteins (cDNA fetal brain tissue expressed in E. coli)
  - Candidate Abs → confirmation by ELISA (3 ELISAs: N human heavy chain, internal; N27-Staph.)
- 64 GCA, 47 PMR, 31 GC/PMR, 40 SLE, 36 RA, 70 fever >38.5, 180 blood donors, B-NHL 48
- Protein array for ferritine heavy chain Abs
  - 14% GCA, 19% PMR, 17% both (22% before CS)
  - 3% SLE, 0% RA, 12% fever, 0% BD
- ELISA (N-term 27 AAs of ferritin heavy chain)
  - 55% all with GCA and/or PMR (92% before CS)
  - GCA/PMR 13% in remission vs. 69% during flares
  - 29% SLE, 3% RA, 1% BD

Baerlecken et al. (Hanover) #790

Ferritin IgG autoAb in GCA/PMR

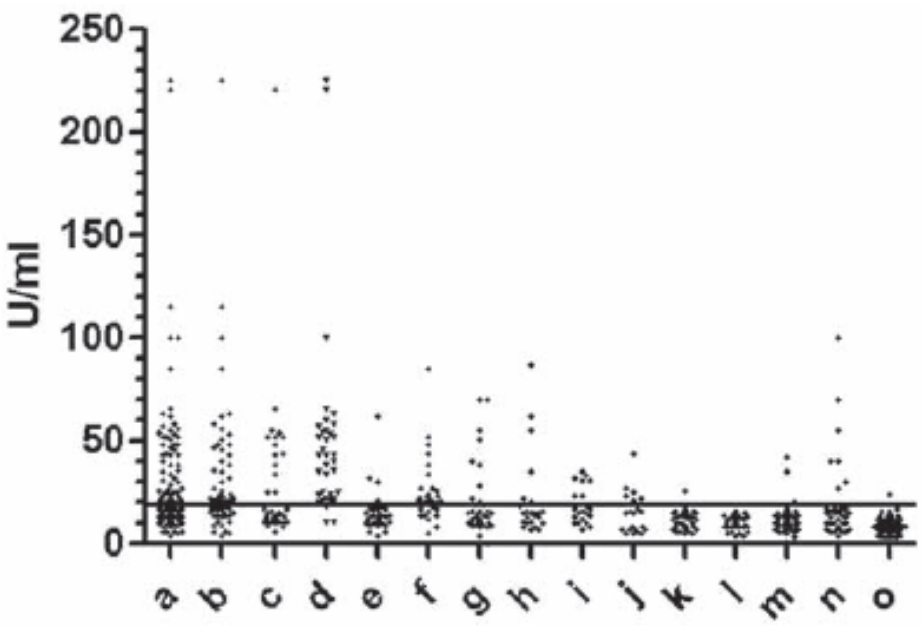


Figure 2 Concentration of antibodies against the N-terminal 27 amino acids of the human ferritin heavy chain in the following groups: (A) GCA and PMR, (B) GCA, (C) PMR, (D) untreated GCA and PMR at first diagnosis, (E) GCA/PMR in remission, (F) GCA/PMR with disease flare in spite of steroid treatment, (G) active SLE, (H) GPA, (I) CSS, (J) MPA, (K) active RA, (L) LORA, (M) B-NHL, (N) fever, (O) blood donors. CO, cut off.

ELISA using the **human** ferritin peptide,

- **Se = 92% in 36 GCA and/or PMR before CS**
- Se = 69% in 32 patients with disease flares
- Se = 55% in 117 treated
- and inactive GCA/PMR patients

In controls, false positive rate

- **29 % (11/38) SLE**
- 3% (1/36) RA
- 0% (0/31) late onset RA
- 6.5% (3/46) B-NHL
- 1% (1/100) blood donors

ELISA using the ferritin peptide of *S epidermidis*

- Se = 89% in 27 untreated GCA/PMR

Baerlecken NT et al, Ann Rheum Dis 2012:71:943–947

Ferritin IgG autoAb in GCA

- Se 82% in TAB+ patients
- 34% in diseases such as vasc, SLE
- 3% in HC

Regent et al, Ann Rheum Dis 2013:72:1269-70

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 7, July 2015, pp 1913–1921
DOI 10.1002/art.39130

14-3-3 in Thoracic Aortic Aneurysms

Identification of a Novel Autoantigen in Large Vessel Vasculitis

Ritu Chakravarti,[1] Karishma Gupta,[1] Mamuni Swain,[1] Belinda Willard,[1] Jaclyn Scholtz,[1] Lars G. Svensson,[1] Eric E. Roselli,[1] Gosta Pettersson,[1] Douglas R. Johnston,[1] Edward G. Soltesz,[1] Michifumi Yamashita,[2] Dennis Stuehr,[1] Thomas M. Daly,[1] and Gary S. Hoffman[1]

Objective. **Large vessel vasculitides (LVV) are a group of autoimmune diseases characterized by injury to and anatomic modifications of large vessels, including the aorta and its branch vessels. Disease etiology is unknown. This study was undertaken to identify antigen targets within affected vessel walls in aortic root, ascending aorta, and aortic arch surgical specimens from patients with LVV, including giant cell arteritis, Takayasu arteritis, and isolated focal aortitis.**

Methods. **Thoracic aortic aneurysm specimens and autologous blood were acquired from consenting patients who underwent aorta reconstruction procedures. Aorta proteins were extracted from both patients with LVV and age-, race-, and sex-matched disease controls with noninflammatory aneurysms. A total of 108 serum samples from patients with LVV, matched controls, and controls with antinuclear antibodies, different forms of vasculitis, or sepsis were tested.**

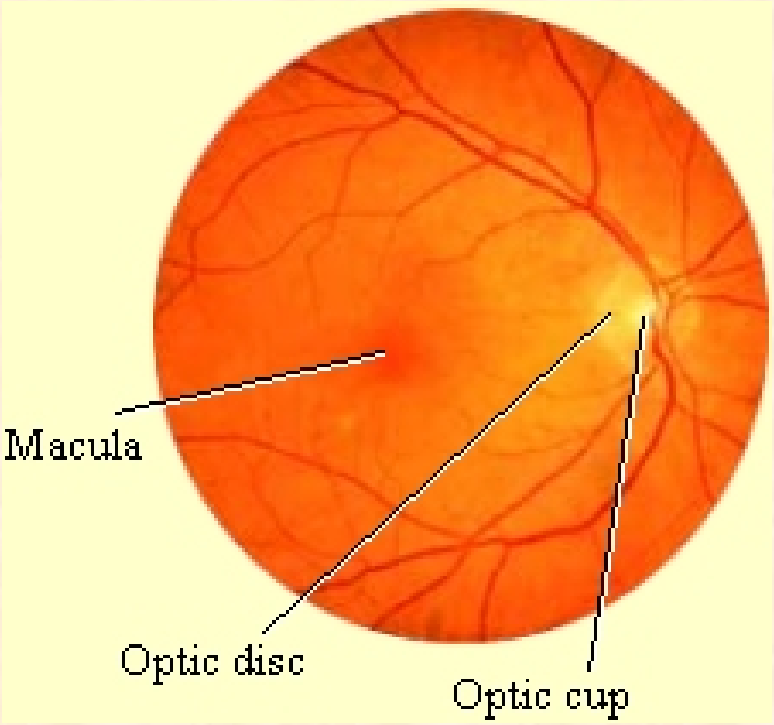
Results. **Evaluation of 108 serum samples and 22 aortic tissue specimens showed that 78% of patients with LVV produced antibodies to 14-3-3 proteins in the aortic wall (93.7% specificity), whereas controls were less likely to do so (6.7% produced antibodies). LVV patient sera contained autoantibody sufficient to immunoprecipitate 14-3-3 protein(s) from aortic lysates. Three of 7 isoforms of 14-3-3 were found to be upregulated in aorta specimens from patients with LVV, and 2 isoforms (ϵ and ζ) were found to be antigenic in LVV.**

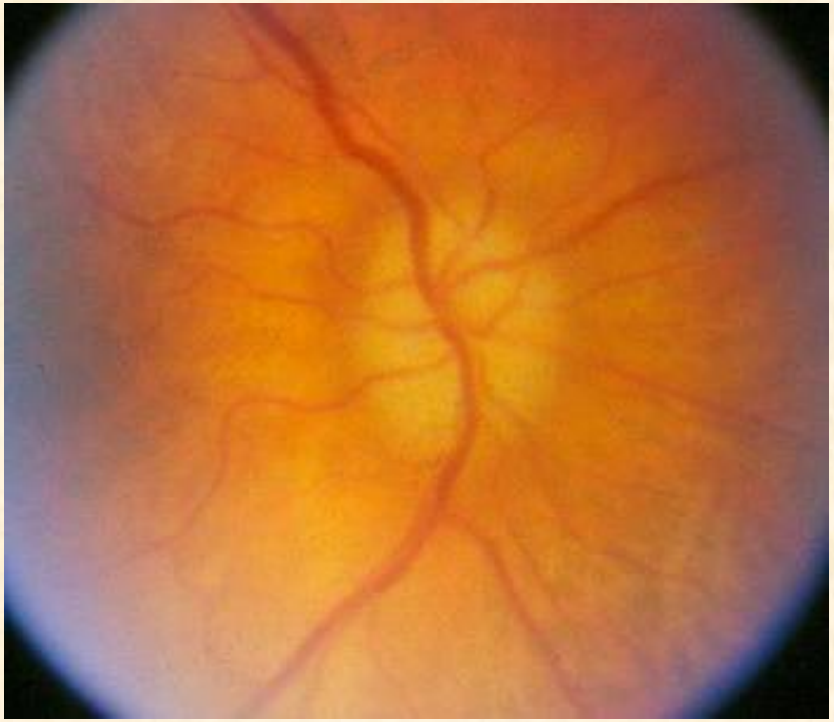
Conclusion. **This is the first study to use sterile, snap-frozen thoracic aorta biopsy specimens to identify autoantigens in LVV. Our findings indicate that 78% of patients with LVV have antibody reactivity to 14-3-3 protein(s). The precise role of these antibodies and 14-3-3 proteins in LVV pathogenesis deserves further study.**

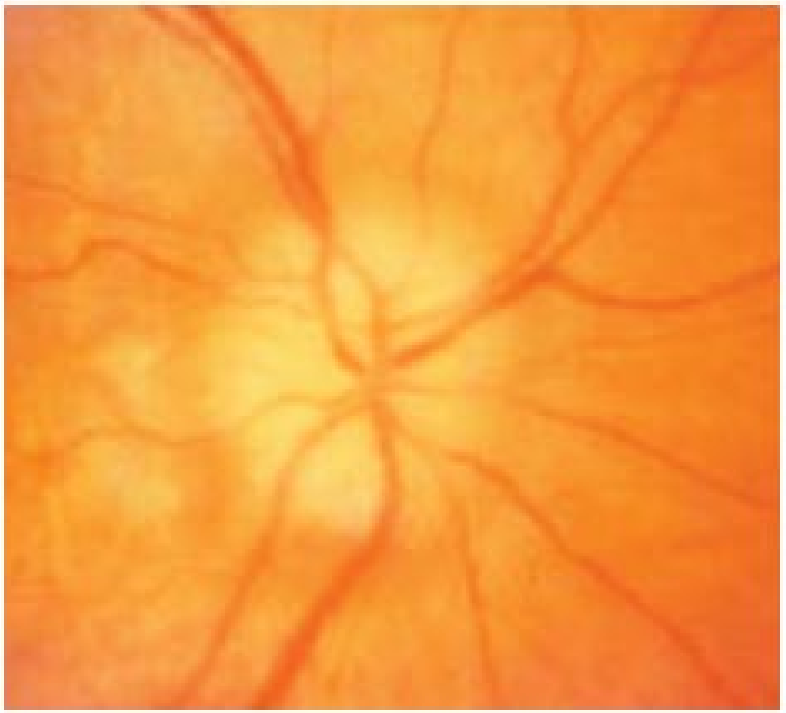
Ophthalmological examination

- **50%** [6-70] of the patients have visual symptoms/signs (older, less headaches, lower ESR)
- Amaurosis fugax (26.8%) is the main symptom (alone in 9.8%), diplopia (8%)
- Mainly **ANTERIOR** ischemic optic neuropathy (lateral or medial posterior ciliary artery circulation) >80%; bilateral in 30% → chalky white optic disk edema
- Central RA occlusion 14%, posterior ION 7% (optic atrophy+)

Hayreh et al, Am J Ophthalmol 1998;125:509-520

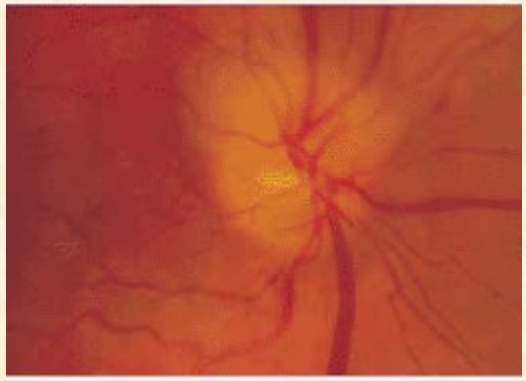

Macula
Optic disc
Optic cup





14. Arteritic anterior ischemic optic neuropathy. Note the pallid swelling.

Non-arteritic AION



small cup

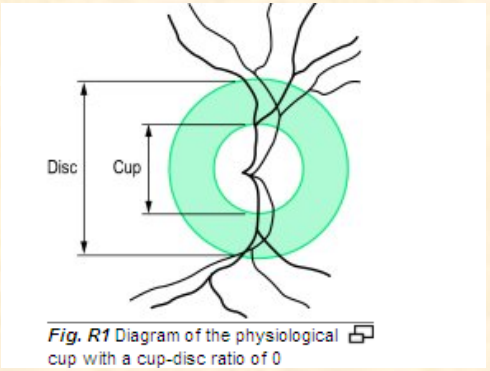
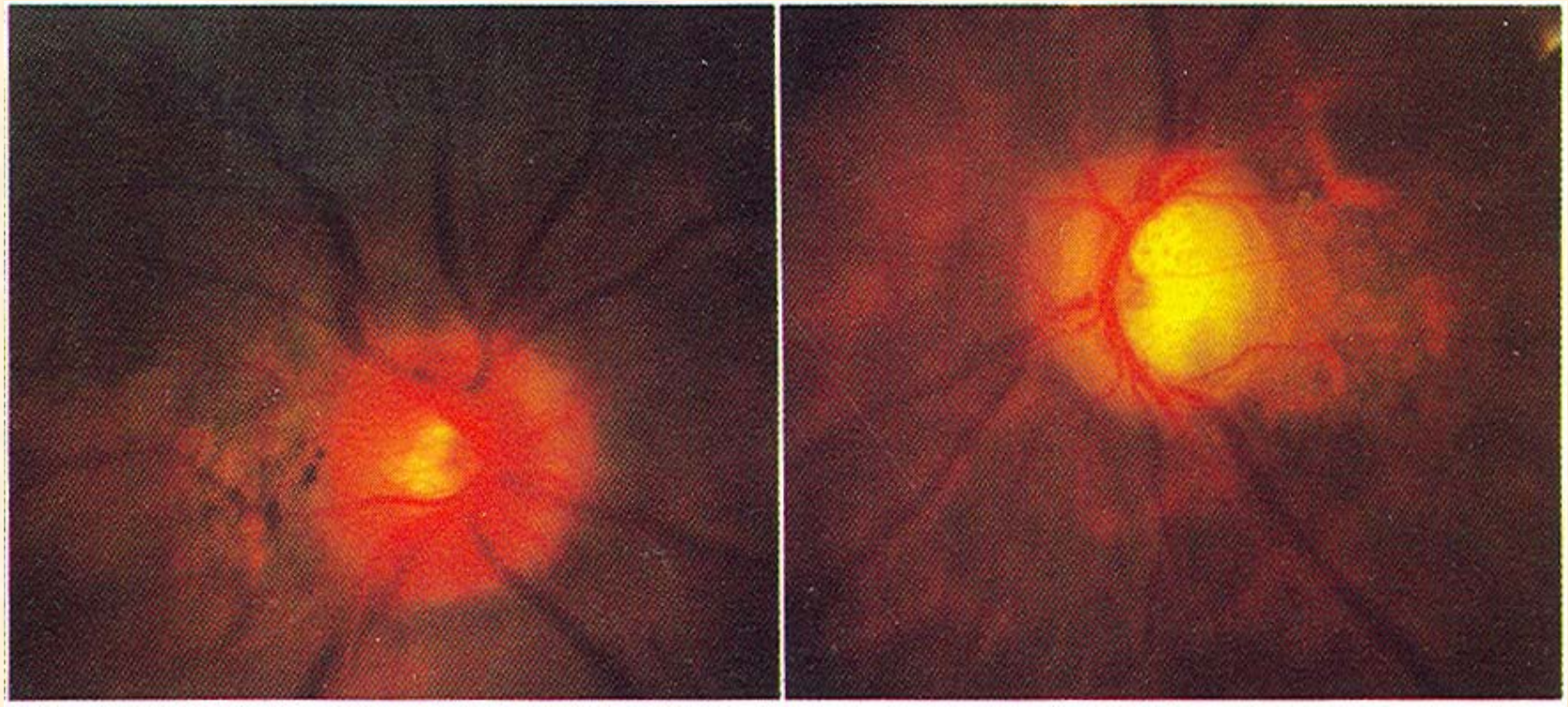


Fig. R1 Diagram of the physiological cup with a cup-disc ratio of 0

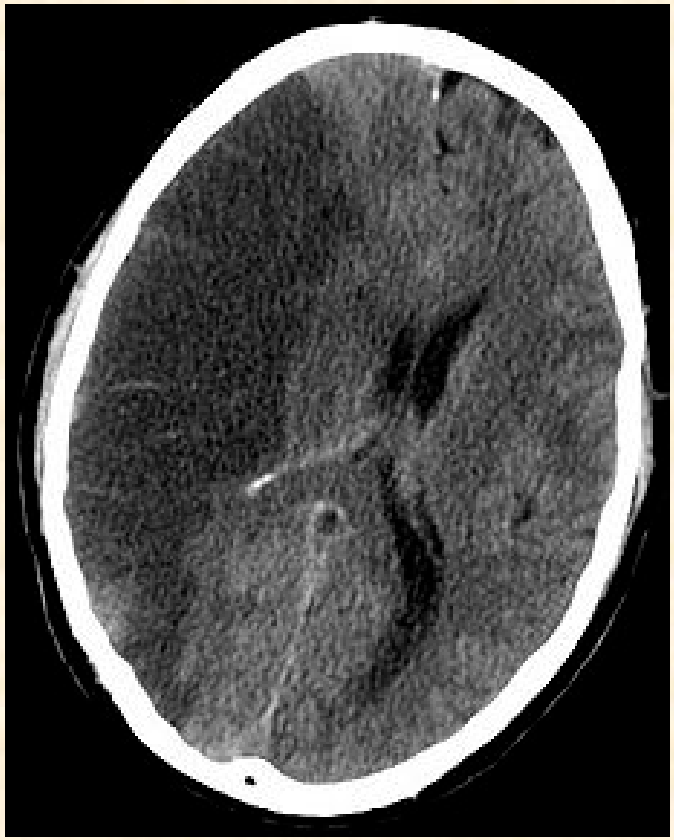
Large/average-sized cupping of the optic disc

Denise Goodwin, Review of Optometry

Normal small cup / markedly large cup in GA



Sebag et al, Ophthalmology 1986; 93:357-61

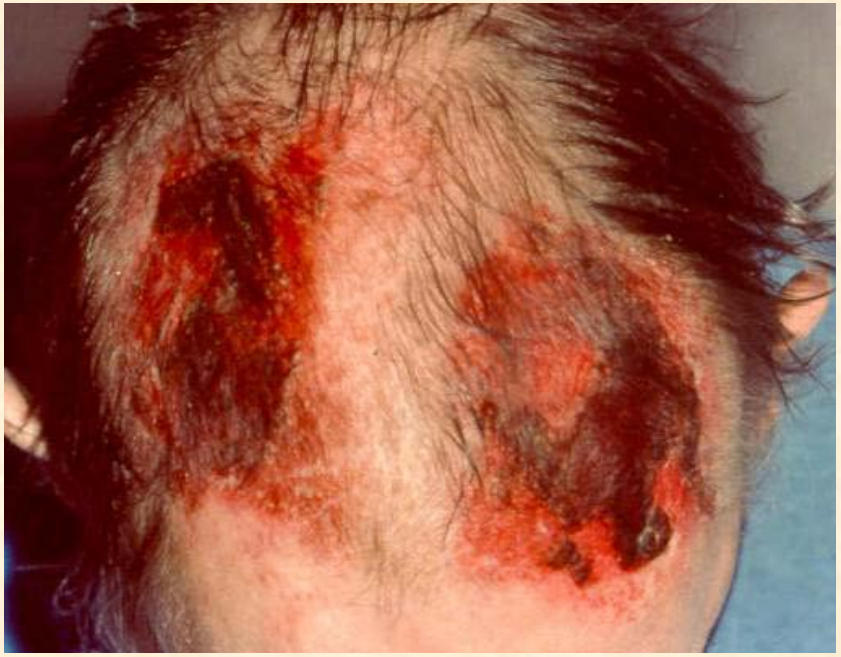


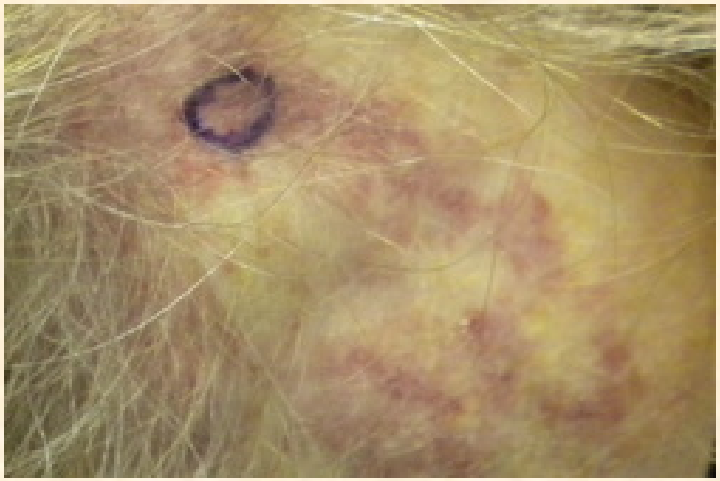
Stroke 2-4%

Brain imaging

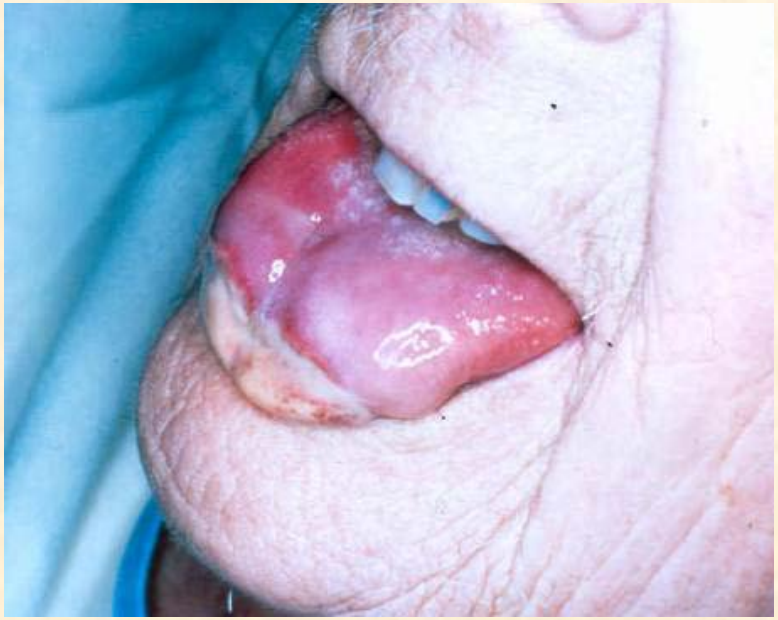
- **Strokes in GCA**
  - 287 patients with TBA+ GCA over a 27 years in Spain
  - 8 **(2.8%)** patients had strokes (1 in the carotid and 7 in the **vertebrobasilar territory**) between the onset of GCA symptoms and 4 weeks after; 6 were men
  - In most cases, stroke occurred **after the onset of corticosteroids**
  - Smoking history was more common (OR, 5.22), **permanent visual loss** (OR, 5.42) and arterial hypertension (OR, 5.06). **Reduced risk in anemic** patients (OR, 0.13).

Gonzalez-Gay et al, Medicine (Baltimore) 2009;88:227-35





Uffelmann et al, Dermatology Online Journal 18 (6): 6



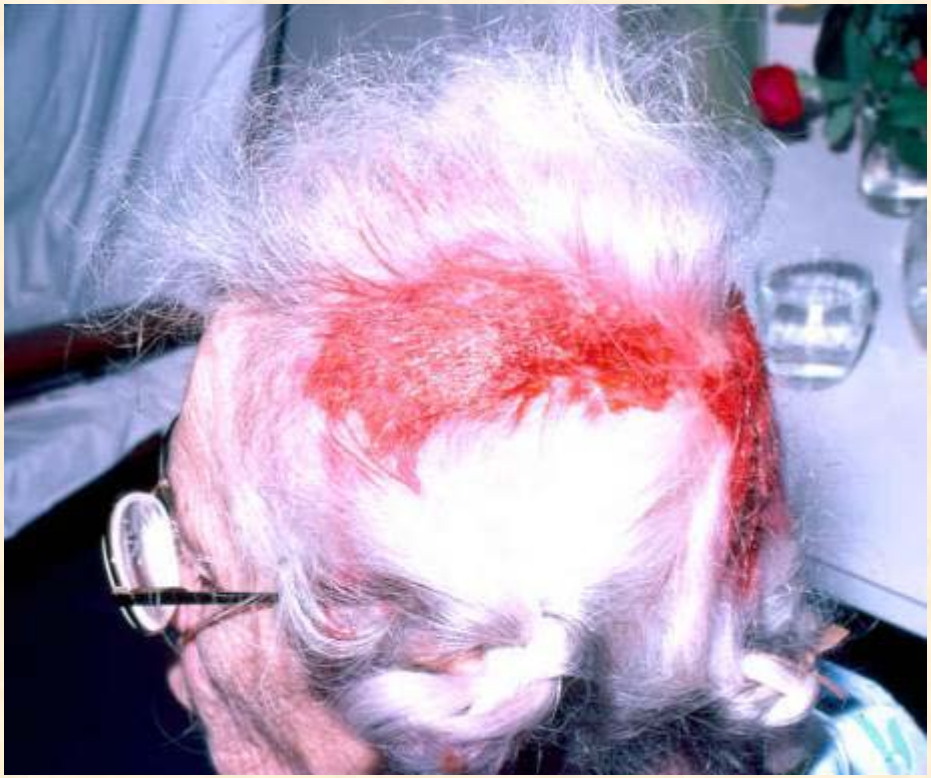


Figure 1 Cumulative incidence for venous thromboembolism (upper panel), pulmonary embolism (middle panel) and deep venous thrombosis (bottom panel) in the 909 cases with incident giant cell arteritis (GCA) as compared with the 9288 age-matched, sex-matched and entry-time-matched non-GCA subjects.

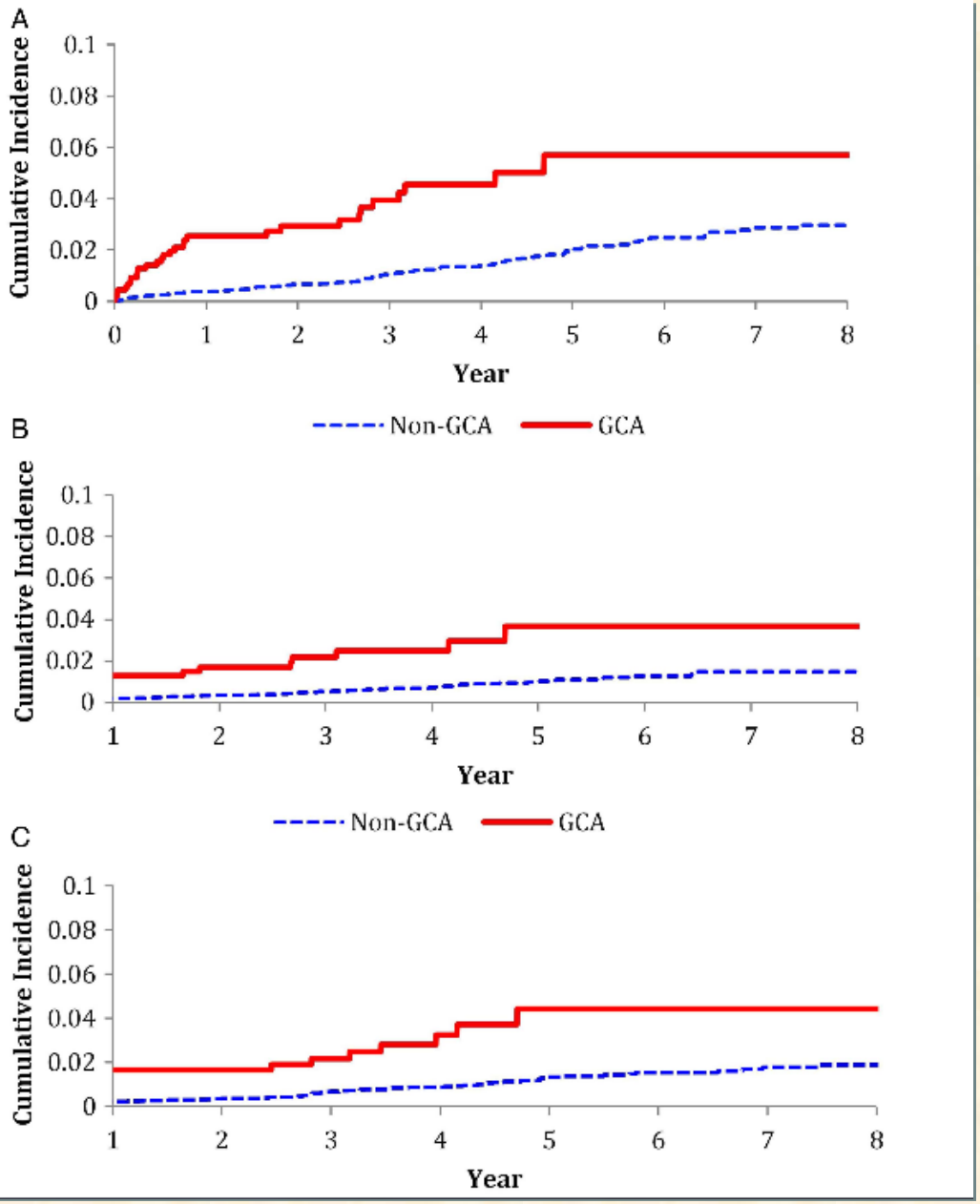


Table 2 Risk of incident VTE, PE and DVT according to GCA status

	GCA N=909	Non-GCA* N=9288
VTE (PE or DVT)		
Cases, n	31	121
Incidence rate/1000 person-years	13.3	3.7
Incidence rate ratio (95% CI)*	3.58 (2.33 to 5.34)	1.0
PE		
Cases, n	18	63
Incidence rate/1000 person-years	7.7	1.9
Incidence rate ratio (95% CI)*	3.98 (2.22 to 6.81)	1.0
DVT		
Cases, n	20	73
Incidence rate/1000 person-years	8.5	2.2
Incidence rate ratio (95% CI)*	3.82 (2.21–6.34).	1.0

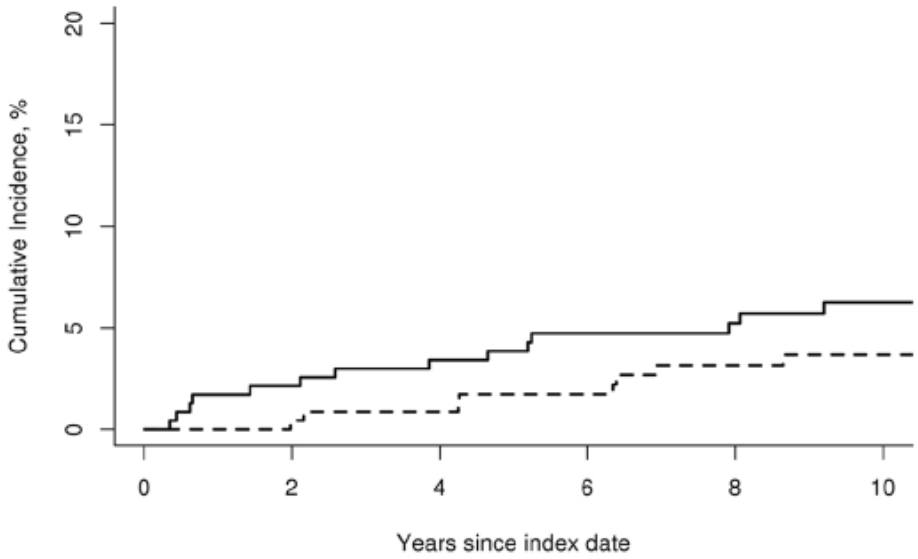
*Age-matched, sex-matched and entry-time-matched.
DVT, deep vein thrombosis; GCA, giant cell arteritis; PE, pulmonary embolism; VTE, venous thromboembolism.

Aviña-Zubieta et al. Ann Rheum Dis, Sept 2014

RESEARCH ARTICLE

Venous Thromboembolism and Cerebrovascular Events in Patients with Giant Cell Arteritis: A Population-Based Retrospective Cohort Study

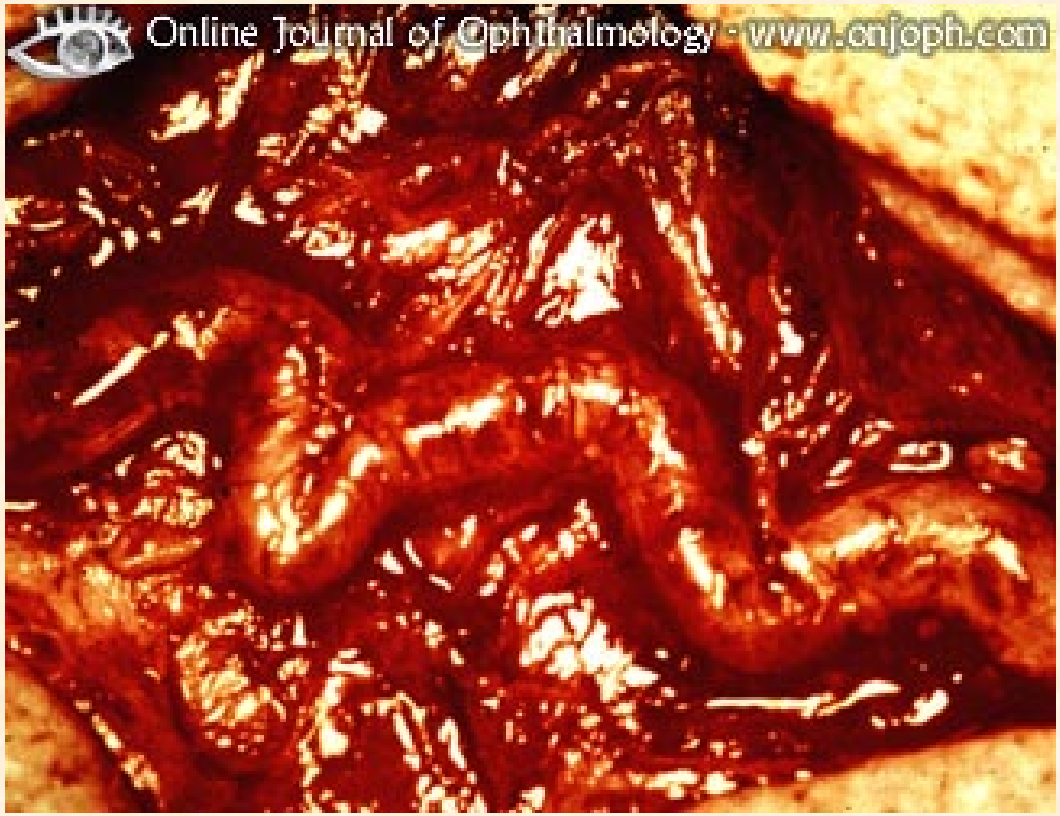
Alberto Lo Gullo[1☯], Matthew J. Koster[2☯*], Cynthia S. Crowson[2,3], Ashima Makol[2], Steven R. Ytterberg[2], Antonino Saitta[1], Carlo Salvarani[5], Eric L. Matteson[2,4], Kenneth J. Warrington[2]



P=0.22

Fig 1. Cumulative incidence of venous thromboembolic events. Cumulative incidence (%) of venous thromboembolism in 244 patients with incident GCA in the period 1950–2009 (solid line) compared to 240 subjects without GCA (dashed line).

PLOS One 2016



TAB in GCA

TAB in GCA

- False negative >40% = **low Se**

Temporal artery biopsy

- 278 TAB (**28.4% were +;** 19% of TBA- still considered GCA)
  - headache (RR 3.6), jaw claudication (RR 2.9) and **abnormal TA on palpation** (RR 2.5) associated with GCA+ (whereas anemia is with a RR 0.35)

Marí et al, Eur J Intern Med 2009;20:533-6

- TAB+ if constitutional syndrome (OR = 6.1), **abnormal TA on palpation** (OR = 3.2) and visual signs (OR = 4.9), but <u>not</u> headaches

Gonzalez-Gay et al, Semin Arthritis Rheum 2001;30:249-56

Predictors of positive TAB

- Hayreh et al.: 368 p = 106 Bx+ vs. 257 Bx-

	OR
• Jaw claudication	9.0
• Neck pain	3.4
• ESR 47-107 mm/h	2.0
• CRP ≥ 24.5 mg/l	3.2
• Age ≥ 75 years	2.0

Ophthalmology. 2008 Feb;115(2):298-305

Predictors of positive TAB

- González-López et al.: 335 p with GCA suspicion, 2001-2010
  - temporal cutaneous hyperalgesia (OR = 10.8; p < 0.001)
  - jaw claudication (OR = 4.6; p = 0.001)
  - recent-onset headache (OR = 4.4; p = 0.001)
  - decreased temporal pulse (OR = 2.8; p = 0.02)
  - pain and stiffness in neck and shoulders (OR = 2.3; p = 0.05)
  - unintentional weight loss (OR = 1.33; p = 0.003)
  - age (OR = 1.085; p = 0.004).

  - length of the surgical specimen (OR = 1.079; p = 0.028)
  - erythrocyte sedimentation rate (OR = 1.042; p < 0.001)

  - total accumulated dose of previous GC (p = 0.043) but not with number of days of previous GC (p = 0.146).

Acta Ophthalmol. 2013 Dec;91(8):763-8

TAB in GCA

- False negative >40% = low Se
- How to increase Se?
  - Serial cuts, full length study
  - TAB length?
  - Early TAB?
  - Bilateral TAB?
  - Imaging-guided TAB?

- Alternative to TAB → imaging?

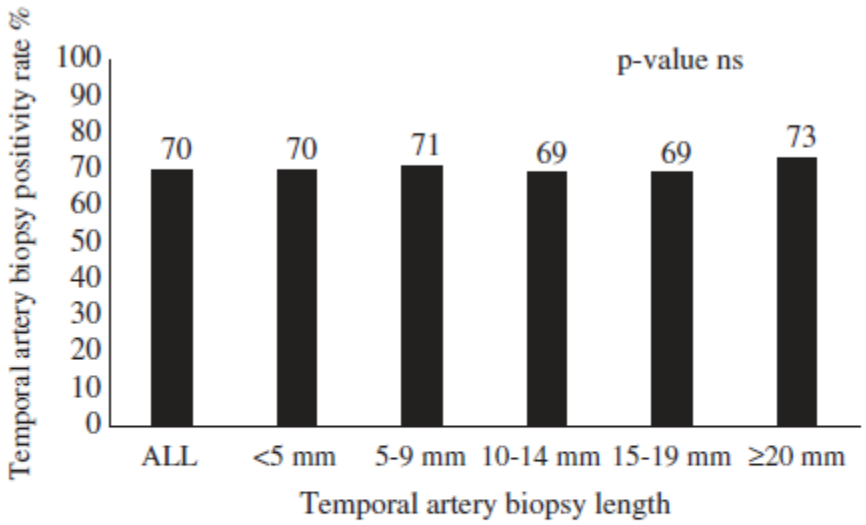
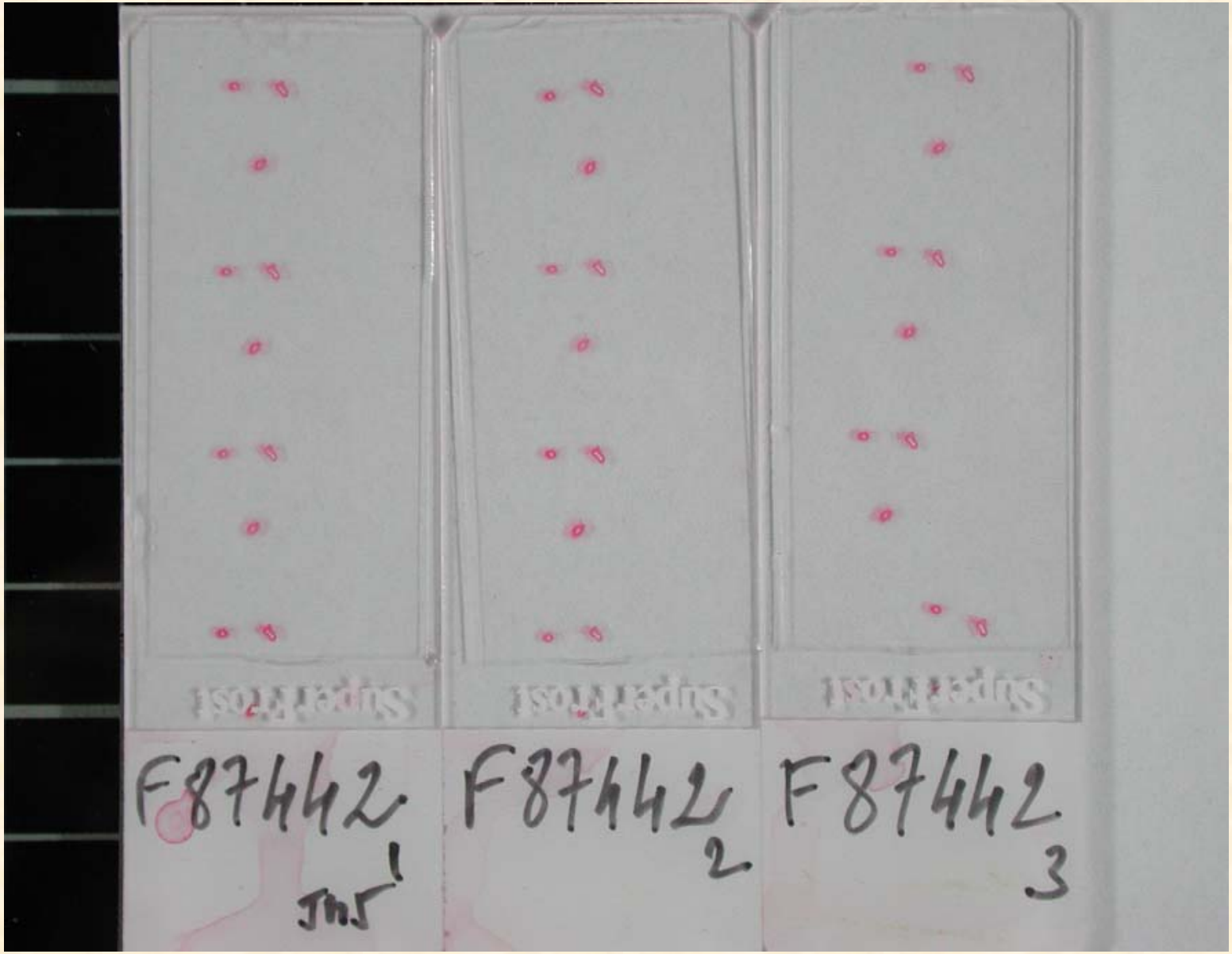


Figure 1. Overall rate of temporal artery biopsy (TAB) positivity among patients diagnosed with giant cell arteritis (GCA) and according to biopsy specimen length.

Grossman et al. Scand J Rheum 2016
260 patients: 88 GCA (60 TABx+)
Mean length 1.15mm → no difference (*only 11 with >2cm*)

Serial cuts (HES)



Bilateral TAB?

- Unilateral TAB+ among bilateral:
  - 1/91 (1%) (Pless et al.)
  - 6/186 (3,2%) (Boyev et al.)
  - 3/60 (5%) (Danesh-Meyer et al.)
  - 41/234 (18%) (Hall et al.)
  - 22/42 (52%) (Ponge et al.)

- Bilaterally = would detect 12% of more GCA
  (13/51 bilateral Bx are positive on 1 side only)

Breuer et al, J Rheumatol 2009;36:794-6

Temporal artery biopsy

- TAB+ in GCA patients
  - 78% when CS < 2 weeks
  - 65% when CS for 2-4 weeks
  - 40% when CS > 4 weeks

- In PMR who develop GCA, TAB+ under CS for 6 months (mean 7.5 mg/d) in 88% of the patients

Narváez et al, Semin Arthritis Rheum 2007;37:13-9

- TAB+ in GCA patients 31% before CS
- TAB+ in GCA patients 35% after CS
  - 43% when CS, 1 week
  - 30% between 1 and 2 weeks
  - 28% when > 2 weeks

Achkar et al, Ann Intern Med 1994;120:987-92

Rheumatology Advance Access published June 17, 2014
RHEUMATOLOGY 262, 273

Concise report

doi:10.1093/rheumatology/keu241

Is colour duplex sonography-guided temporal artery biopsy useful in the diagnosis of giant cell arteritis? A randomized study

Giuseppe Germanò[1], Francesco Muratore[1], Luca Cimino[2], Alberto Lo Gullo[3], Niccolò Possemato[1], Pierluigi Macchioni[1], Alberto Cavazza[4], Nicolò Pipitone[1], Luigi Boiardi[1] and Carlo Salvarani[1]

Abstract

Objective. The aim of this study was to assess the usefulness of colour duplex sonography (CDS)-guided temporal artery biopsy (TAB) for the diagnosis of GCA in patients with suspected GCA.

Methods. From September 2009 through December 2012, 112 consecutive patients with suspected GCA were randomized to undergo CDS-guided TAB or standard TAB. All patients underwent temporal artery physical examination and temporal artery CDS prior to TAB. CDS of the temporal artery was performed by the same ultrasonographer, who was unaware of the patient's clinical data, and all TABs were evaluated by the same pathologist. Seven patients in whom biopsy failed to sample temporal artery tissue were excluded from the analysis.

Results. Fifty patients were randomized to undergo CDS-guided TAB and 55 patients to standard TAB. Except for a younger age in patients who underwent standard TAB ($P = 0.026$), no significant differences were observed between the two groups. There were no significant differences in the frequencies of positive TAB for classic transmural inflammation (28% *vs* 18.2%) or for periadventitial small vessel vasculitis and/or vasa vasorum vasculitis (6% *vs* 14.5%) between the two groups. No significant differences in the frequency of positive TAB in the two groups were observed when we excluded the patients treated with glucocorticoids and when we stratified the patients of the two groups for the presence or absence of the halo sign.

Conclusion. Our study showed that CDS-guided TAB did not improve the sensitivity of TAB for diagnosing GCA.

Key words: colour duplex sonography, giant cell arteritis, halo sign, guided temporal artery biopsy, randomization, temporal artery physical examination, transmural vasculitis, periadventitial small vessel vasculitis, vasa vasorum vasculitis, glucocorticoid therapy.

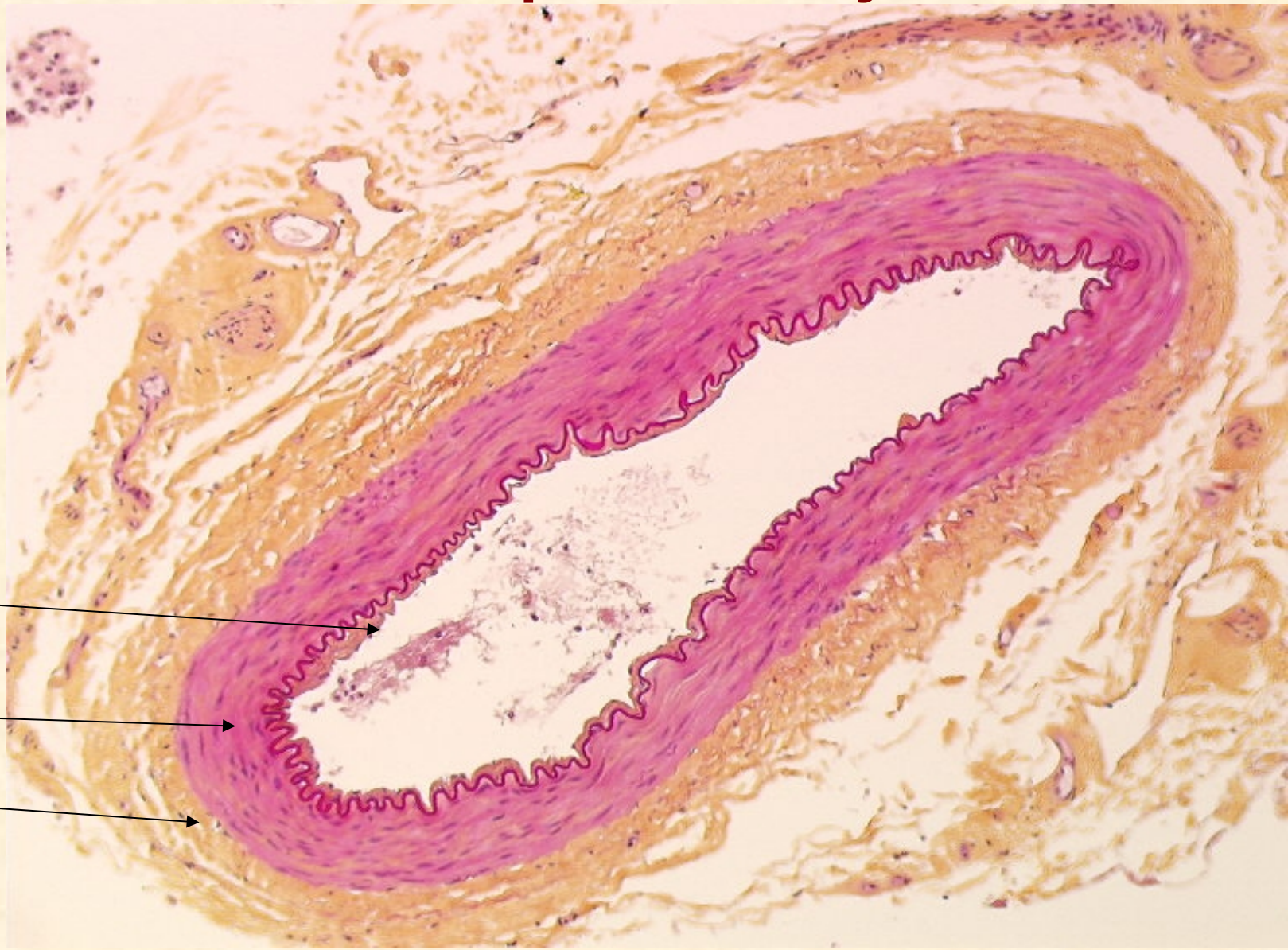
US-guided TABx is not better…

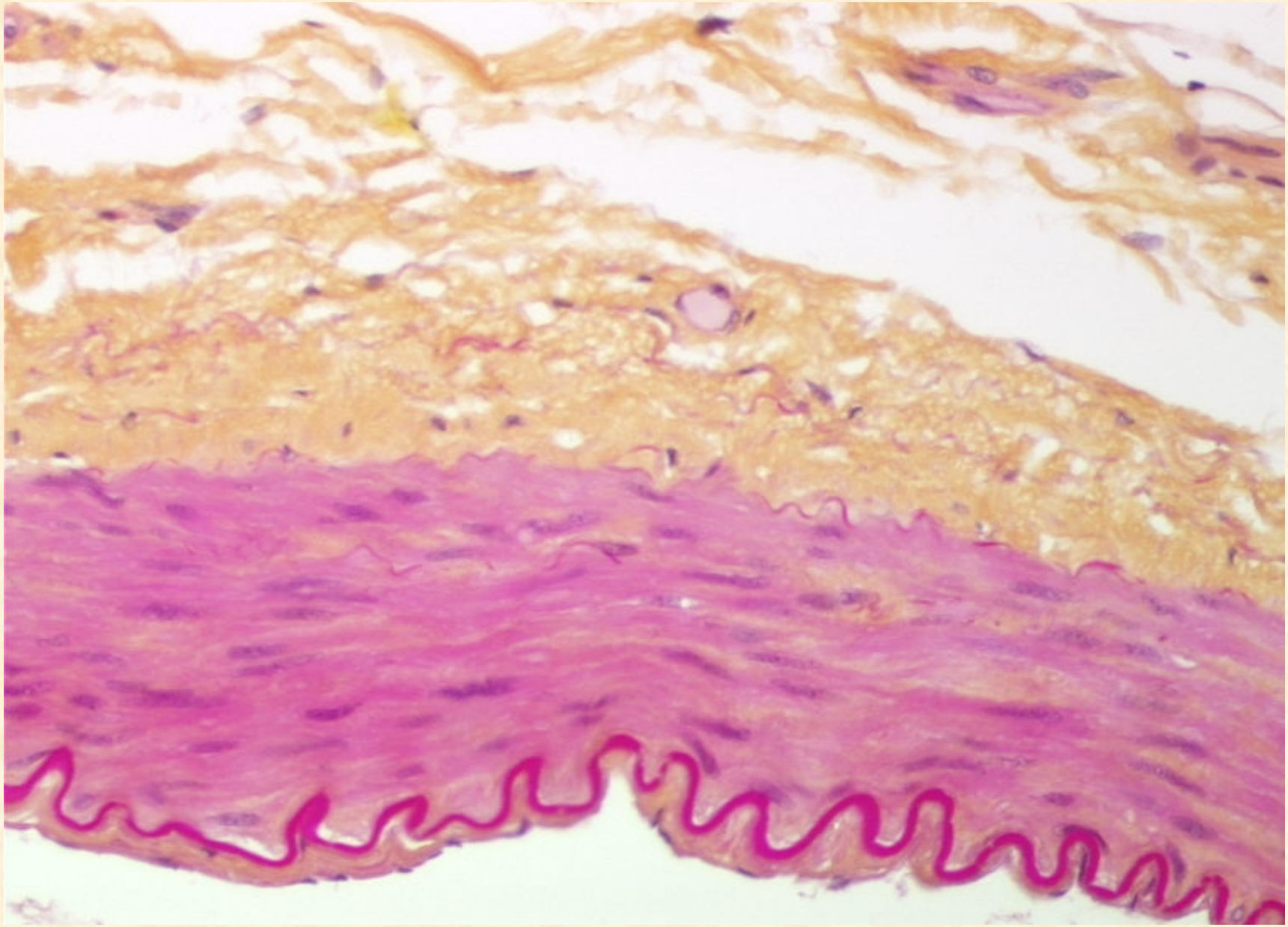
TABLE 2 Comparison of TAB histological findings in the two study groups and in different study subgroups

Histological findings	CDS-guided TAB	Standard TAB	*P*-value[a]
All patients			0.230
Classic transmural GCA	14/50 (28)	10/55 (18.2)	
SVV and/or VVV	3/50 (6)	8/55 (14.5)	
Negative	33/50 (66)	37/55 (67.3)	
Patients not on glucocorticoid therapy			0.088
Classic transmural GCA	8/20 (40)	5/25 (20)	
SVV and/or VVV	1/20 (5)	7/25 (28)	
Negative	11/20 (55)	13/25 (52)	
Patients with evidence of halo on CDS			0.453
Classic transmural GCA	13/23 (56.5)	9/20 (45)	
SVV and/or VVV	1/23 (4.3)	3/20 (15)	
Negative	9/23 (39.1)	8/20 (40)	
Patients with bilateral halo on CDS			0.130
Classic transmural GCA	10/17 (58.8)	6/14 (42.9)	
SVV and/or VVV	0/17 (0)	3/14 (21.4)	
Negative	7/17 (41.2)	5/14 (35.7)	
Patients without evidence of halo at CDS			0.692
Classic transmural GCA	1/27 (3.7)	1/35 (2.9)	
SVV and/or VVV	2/27 (7.4)	5/35 (14.3)	
Negative	24/27 (88.9)	29/35 (82.9)	

Values are the number of patients who were positive/number of total patients (%). [a]*P*-values refer to the intergroup comparisons. TAB: temporal artery biopsy; CDS: colour duplex sonography; SVV: small-vessel vasculitis; VVV: vasa vasorum vasculitis.

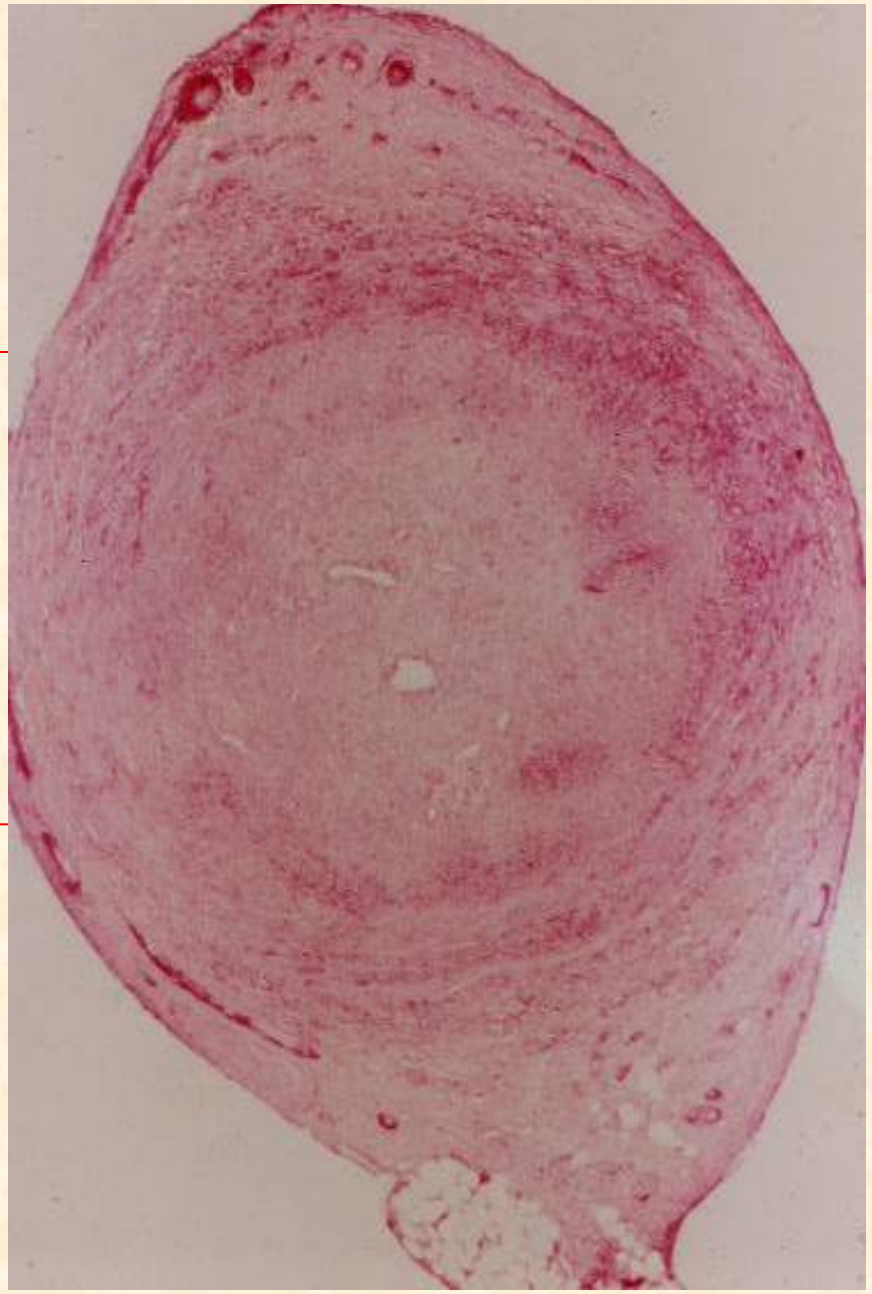
Normal temporal artery

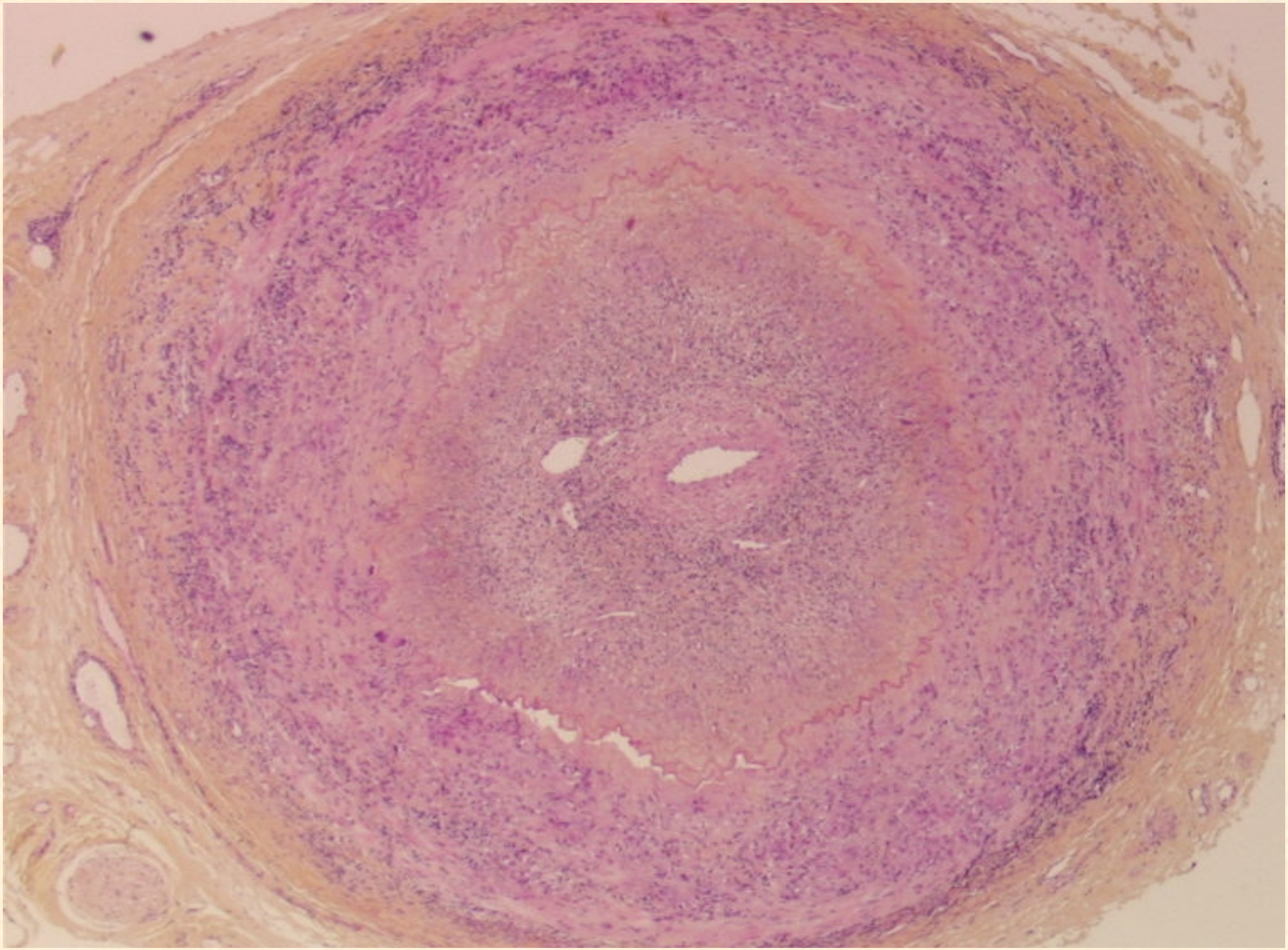


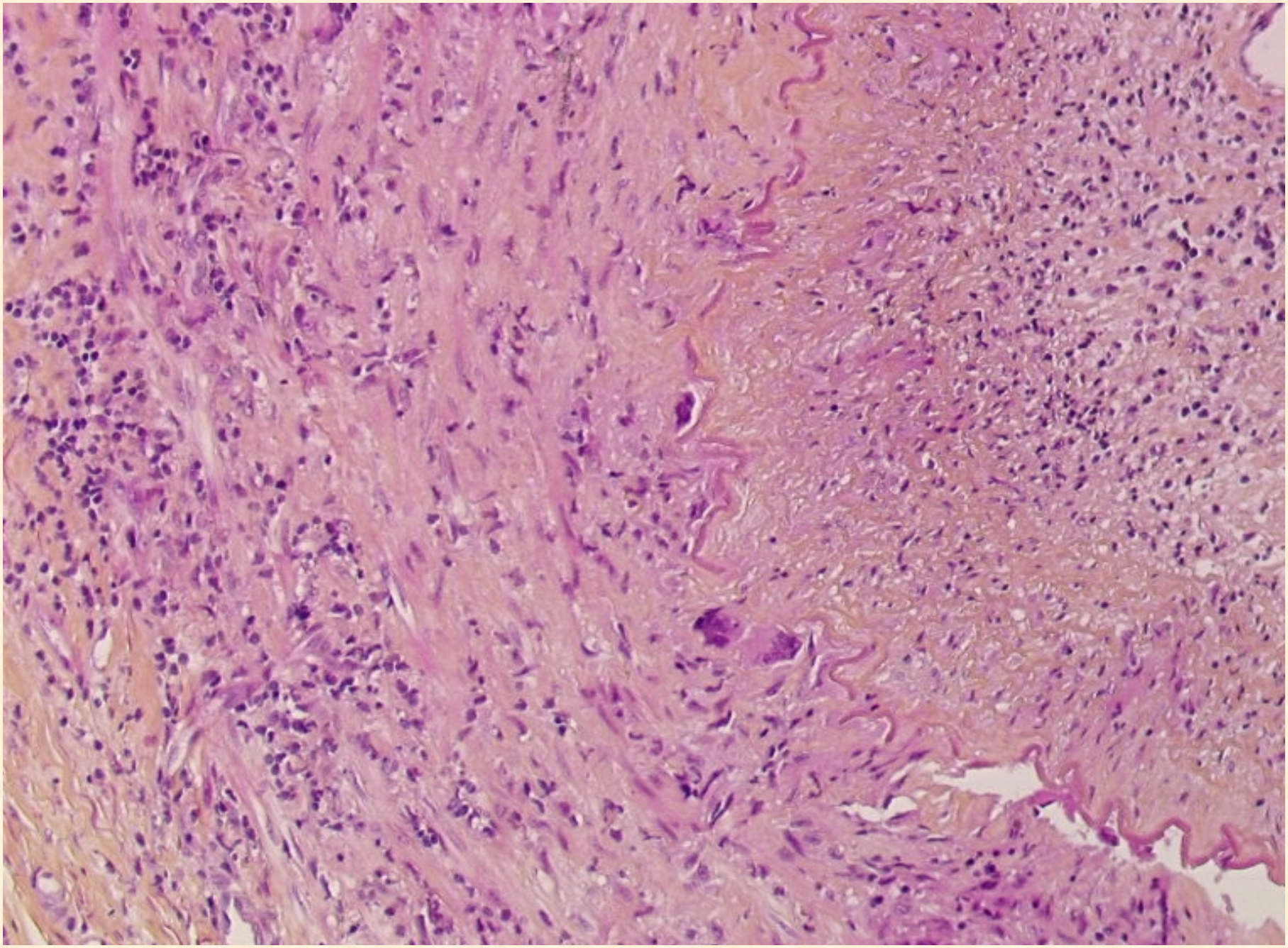

EEL
IEL

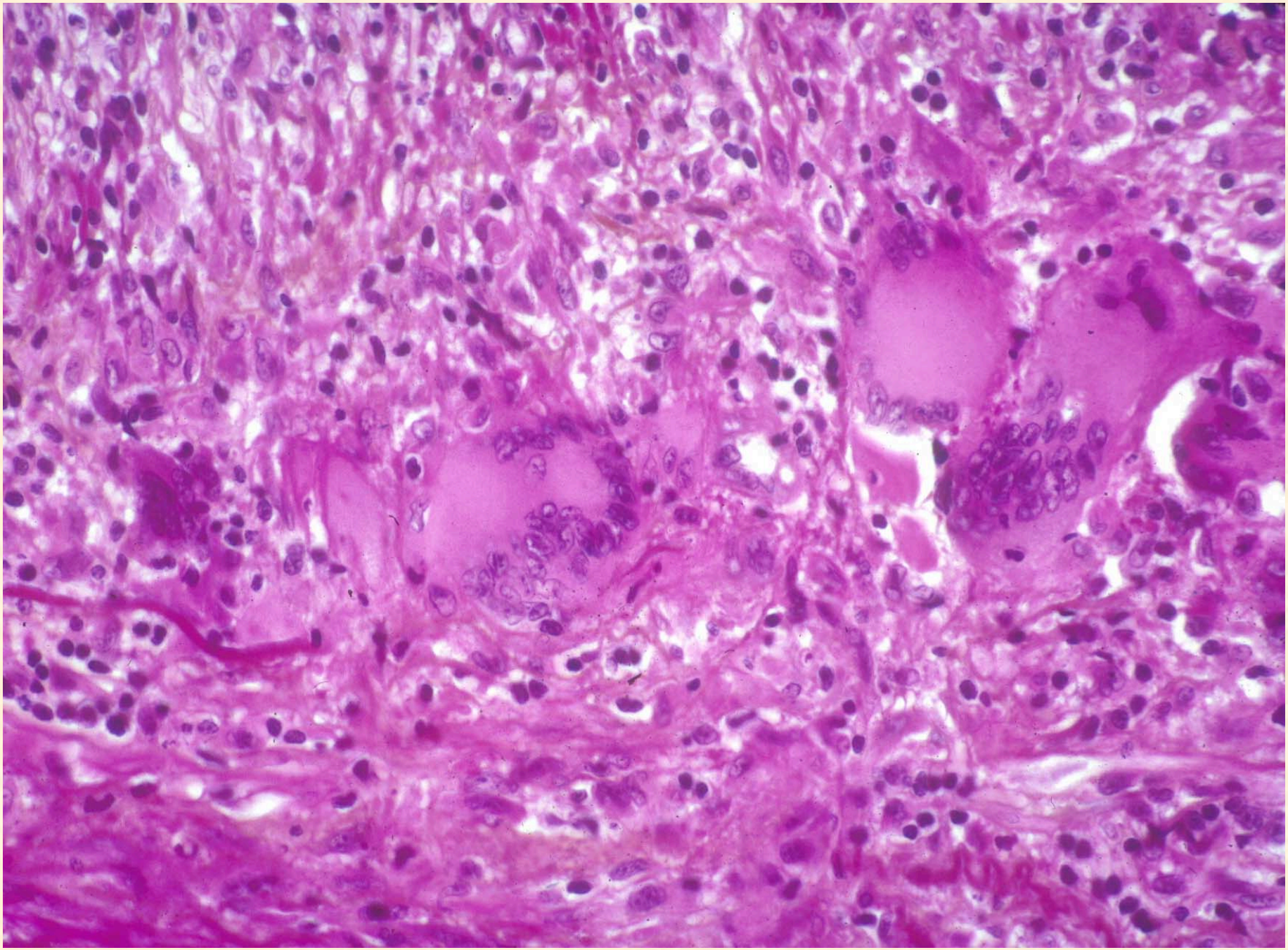
GCA

- Arteritis of the 3 layers
- Granuloma (lympho-plasma-histiocytes, no necrosis)
- Giant multinucleated cells



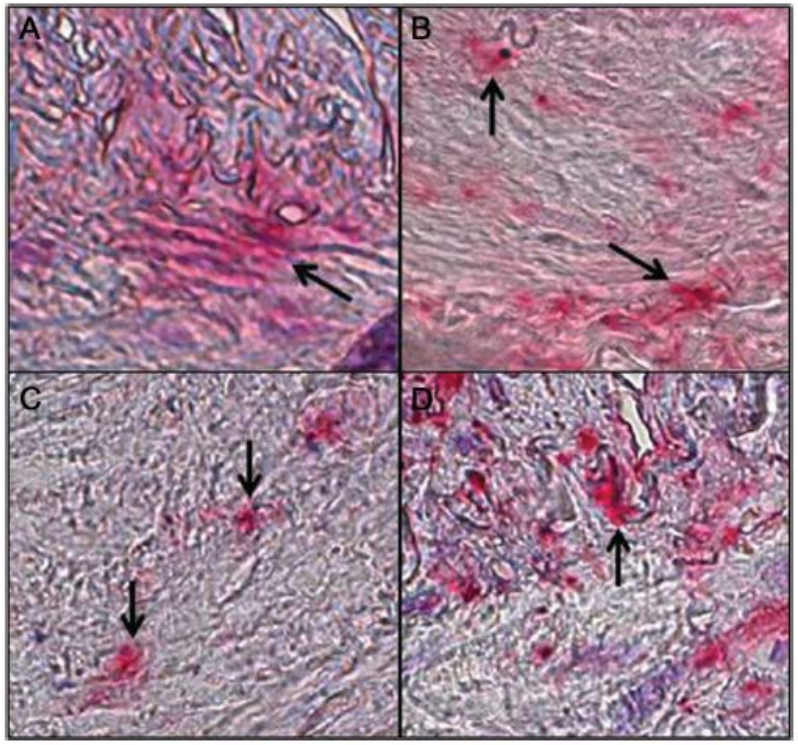






Is biopsy needed?

Figure 2 Multiple areas of VZV antigen in a biopsy-negative temporal artery of a subject with clinically suspected giant cell arteritis



In a temporal artery that was found to contain VZV antigen, 95 consecutive 5-μm sections from that artery were further stained to determine how many sections contained VZV antigen. Arrows show 4 positive areas along a 500-μm length of temporal artery at position 20, 160, 250, and 480 μm (A-D, respectively). Original magnification ×600. VZV = varicella-zoster virus.

Five (21%) / 24 TAB-negative GCA patients revealed VZV
(but not HSV-1)

Nagel et al. Neurology 2013

Multifocal VZV vasculopathy with temporal artery infection mimics giant cell arteritis

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Alexander Choe, BA
April Rempel
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Don Gilden, MD

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ABSTRACT

Objective: To address the incidence of varicella-zoster virus (VZV) infection in patients with biopsy-negative giant cell arteritis (GCA), we examined archived biopsy-negative temporal arteries from subjects with clinically suspected GCA for the presence of VZV antigen.

Methods: Formalin-fixed, paraffin-embedded temporal arteries that were pathologically negative for GCA and normal temporal arteries were analyzed immunohistochemically for VZV and herpes simplex virus-1 (HSV-1) antigen.

Results: Five (21%) of 24 temporal arteries from patients who were clinically suspect but biopsy negative for GCA revealed VZV but not HSV-1 by immunohistochemical analysis. Thirteen normal temporal arteries did not contain VZV or HSV-1 antigen. All 5 subjects whose temporal arteries contained VZV antigen presented with clinical and laboratory features of GCA and early visual disturbances.

Conclusion: Multifocal VZV vasculopathy can present with the full spectrum of clinical features and laboratory abnormalities characteristically seen in GCA. *Neurology*® 2013;80:2017-2021

GLOSSARY

AION = anterior ischemic optic
formalin-fixed, paraffin-embedde
saline; **TA** = temporal artery; **VZ**

Giant cell arteritis (GCA)
tenderness, jaw or tongue

Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis

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ABSTRACT

Objective: Varicella-zoster virus (VZV) infection may trigger the inflammatory cascade that characterizes giant cell arteritis (GCA).

Methods: Formalin-fixed, paraffin-embedded GCA-positive temporal artery (TA) biopsies (50 sections/TA) including adjacent skeletal muscle and normal TAs obtained postmortem from subjects >50 years of age were examined by immunohistochemistry for presence and distribution of VZV antigen and by ultrastructural examination for virions. Adjacent regions were examined by hematoxylin & eosin staining. VZV antigen–positive slides were analyzed by PCR for VZV DNA.

Results: VZV antigen was found in 61/82 (74%) GCA-positive TAs compared with 1/13 (8%) normal TAs ($p < 0.0001$, relative risk 9.67, 95% confidence interval 1.46, 63.69). Most GCA-positive TAs contained viral antigen in skip areas. VZV antigen was present mostly in adventitia, followed by media and intima. VZV antigen was found in 12/32 (38%) skeletal muscles adjacent to VZV antigen–positive TAs. Despite formalin fixation, VZV DNA was detected in 18/45 (40%) GCA-positive VZV antigen–positive TAs, in 6/10 (60%) VZV antigen–positive skeletal muscles, and in one VZV antigen–positive normal TA. Varicella-zoster virions were found in a GCA-positive TA. In sections adjacent to those containing VZV, GCA pathology was seen in 89% of GCA-positive TAs but in none of 18 adjacent sections from normal TAs.

Conclusions: Most GCA-positive TAs contained VZV in skip areas that correlated with adjacent GCA pathology, supporting the hypothesis that VZV triggers GCA immunopathology. Antiviral treatment may confer additional benefit to patients with GCA treated with corticosteroids, although the optimal antiviral regimen remains to be determined. *Neurology*® 2015;84:1948-1955

Research

Original Investigation

Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis

Maria A. Nagel, MD; Teresa White, BS; Nelly Khmeleva, BS; April Rempel, BS; Philip J. Boyer, MD, PhD; Jeffrey L. Bennett, MD, PhD; Andrea Haller, MD; Kelly Lear-Kaul, MD; Balasurbramaniyam Kandasmy, MD; Malena Amato, MD; Edward Wood, MD; Vikram Durairaj, MD; Franz Fogt, MD; Madhura A. Tamhankar, MD; Hans E. Grossniklaus, MD; Robert J. Poppiti, MD; Brian Bockelman, MD; Kathy Keyvani, MD; Lea Pollak, MD; Sonia Mendlovic, MD; Mary Fowkes, MD, PhD; Charles G. Eberhart, MD, PhD; Mathias Buttmann, MD; Klaus V. Toyka, MD; Tobias Meyer-ter-Vehn, MD; Vigdis Petursdottir, MD; Don Gilden, MD

Supplemental content at jamaneurology.com

IMPORTANCE Giant cell arteritis (GCA) is the most common systemic vasculitis in elderly individuals. Diagnosis is confirmed by temporal artery (TA) biopsy, although biopsy results are often negative. Despite the use of corticosteroids, disease may progress. Identification of causal agents will improve outcomes. Biopsy-positive GCA is associated with TA infection by varicella-zoster virus (VZV).

OBJECTIVE To analyze VZV infection in TAs of patients with clinically suspected GCA whose TAs were histopathologically negative and in normal TAs removed post mortem from age-matched individuals.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study for VZV antigen was performed from January 2013 to March 2015 using archived, deidentified, formalin-fixed, paraffin-embedded GCA-negative, GCA-positive, and normal TAs (50 sections/TA) collected during the past 30 years. Regions adjacent to those containing VZV were examined by hematoxylin-eosin staining. Immunohistochemistry identified inflammatory cells and cell types around nerve bundles containing VZV. A combination of 17 tertiary referral centers and private practices worldwide contributed archived TAs from individuals older than 50 years.

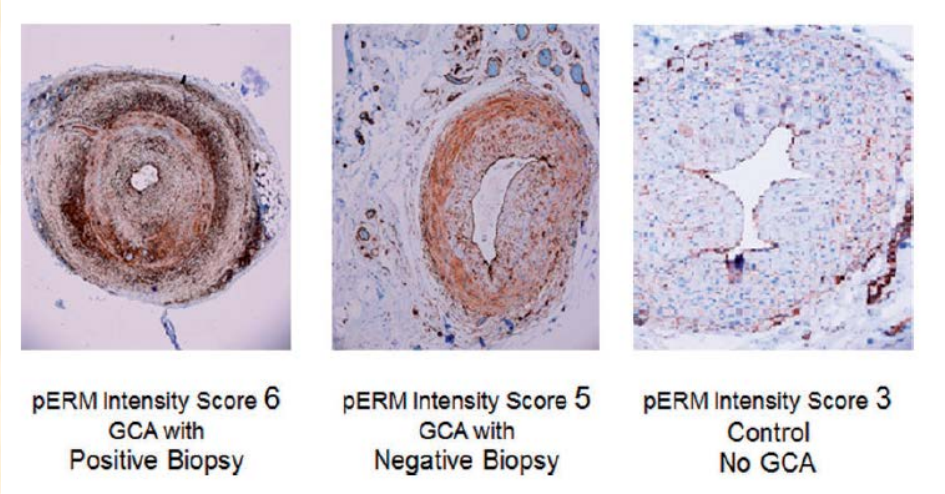
MAIN OUTCOMES AND MEASURES Presence and distribution of VZV antigen in TAs and histopathological changes in sections adjacent to those containing VZV were confirmed by 2 independent readers.

RESULTS Varicella-zoster virus antigen was found in 45 of 70 GCA-negative TAs (64%), compared with 11 of 49 normal TAs (22%) (relative risk [RR] = 2.86; 95% CI, 1.75-5.31; $P < .001$). Extension of our earlier study revealed VZV antigen in 68 of 93 GCA-positive TAs (73%), compared with 11 of 49 normal TAs (22%) (RR = 3.26; 95% CI, 2.03-5.98; $P < .001$). Compared with normal TAs, VZV antigen was more likely to be present in the adventitia of

Rho kinase activity in TAB

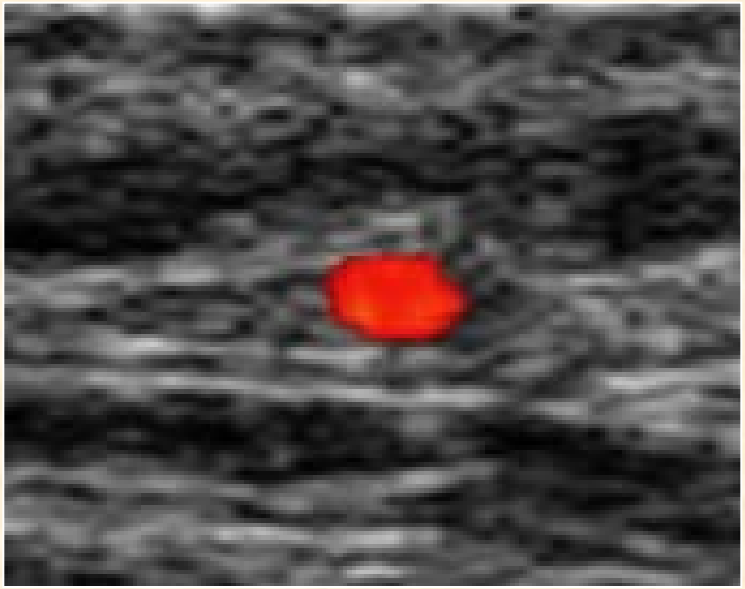
- Staining for pERM (phosphorylated ezrin/radixin/moesin), surrogate of ROCK activity
- 19 GCA TAB+, 17 GCA TAB-, 18 nonGCA TAB-
- Se = 90%, NPV = 91%

  (compared to Se 51% for histology)

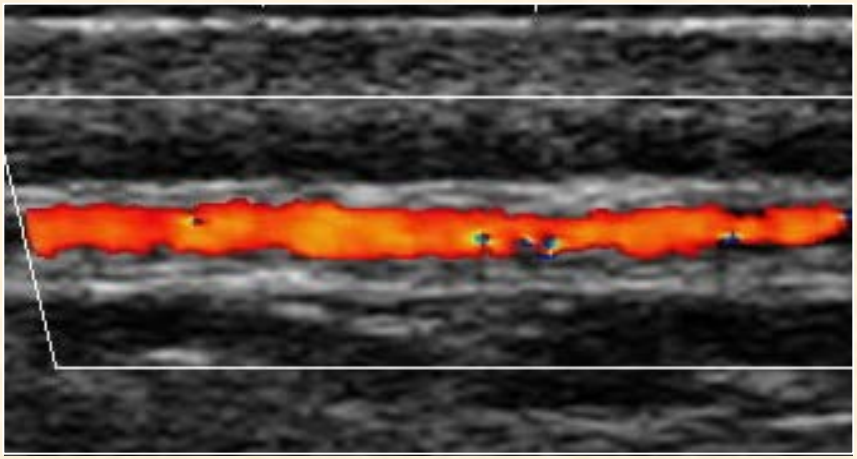


Lally et al. Rheumatology 2014: Sept

From Mahr A.

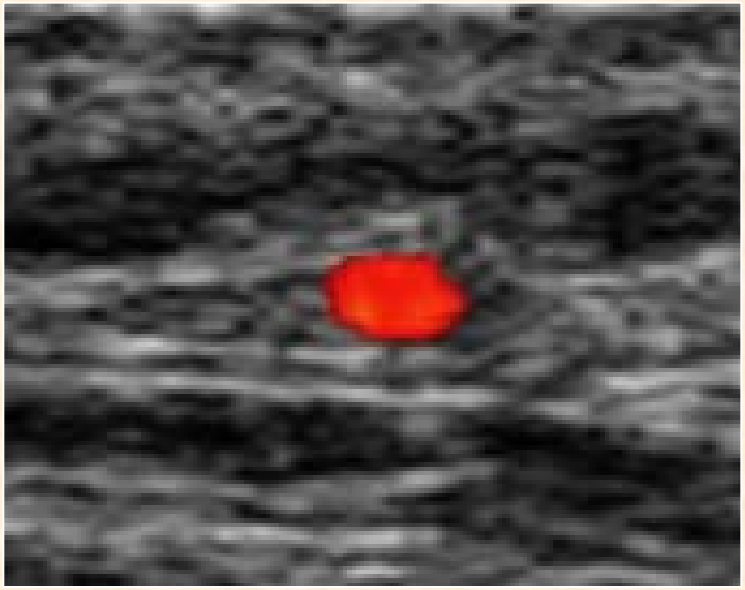


TA normal

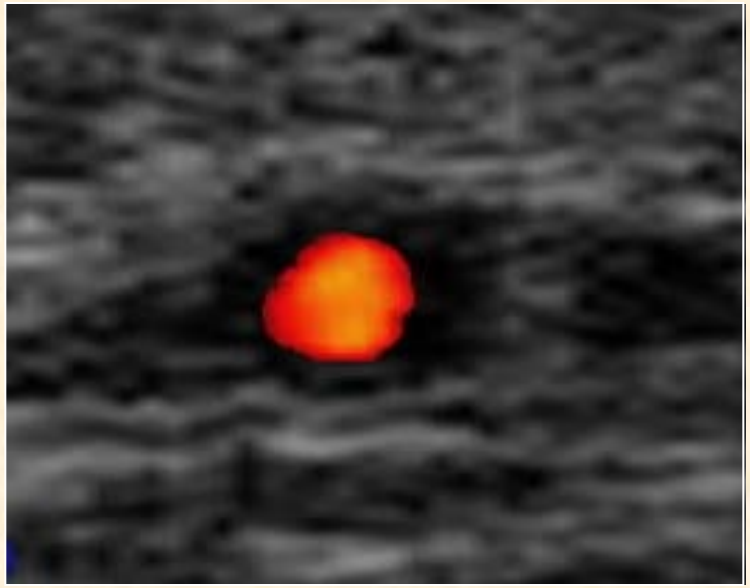


TA normal

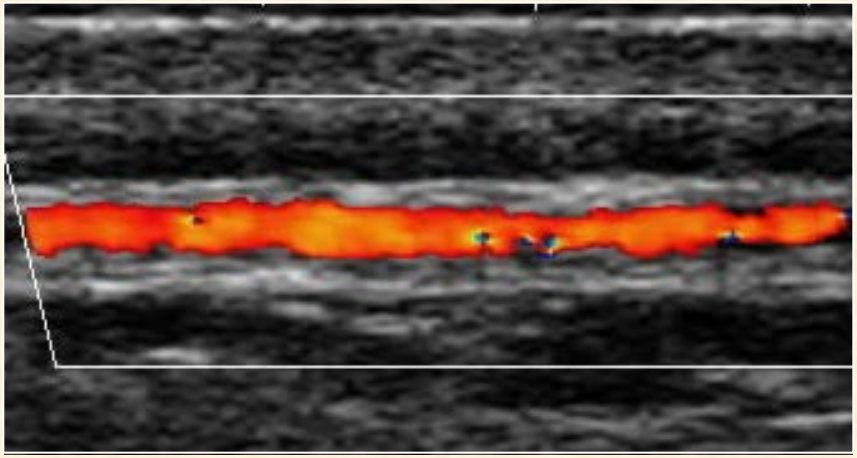
From Mahr A.



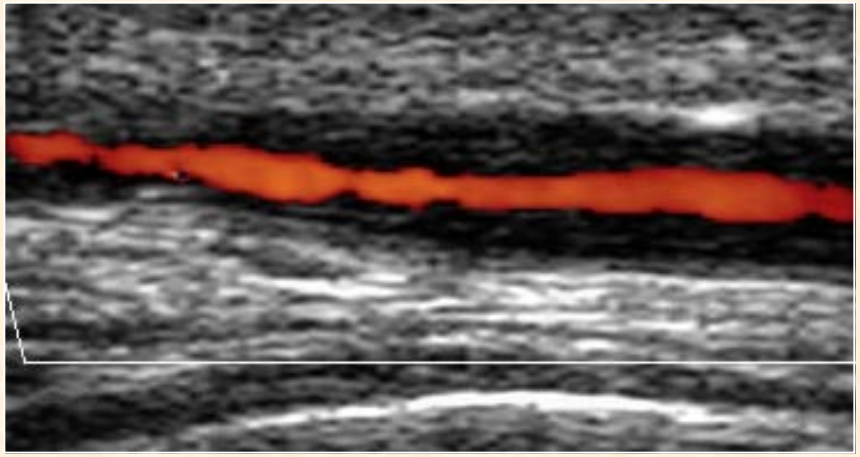
TA normal



TA GCA



TA normal

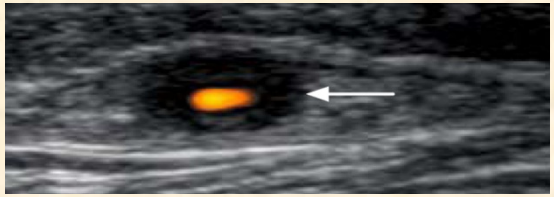


TA GCA

GCA and halo on Doppler-US

	Se	Sp
Salvarani et al.	40%	93%
Nesher et al.	50%	78%
Schmid et al.	50%	100%
Reinhard et al.	73%	93%
Schmidt et al.	76%	92%
Pfadenhauer et al.	83%	89%
Le Sar et al.	86%	92%
Romero-Villegas et al.	95%	91%
Venz et coll.	100%	86%

From Mahr A.



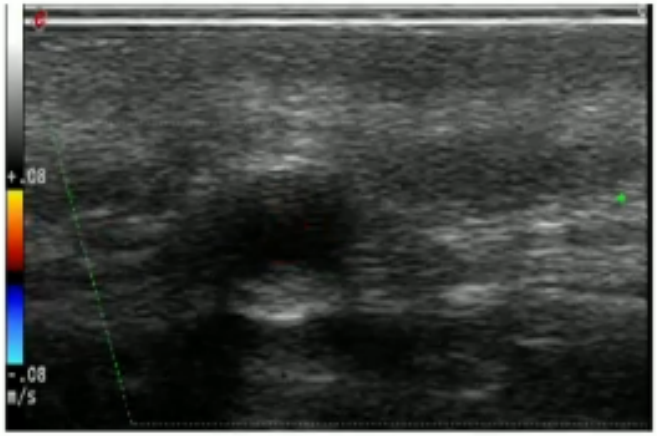
TA imaging

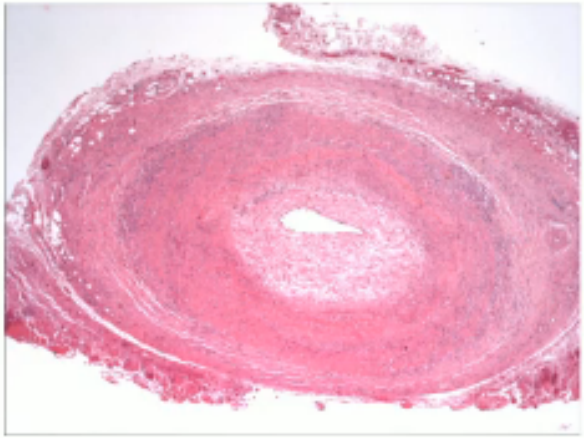
- Doppler-US of the orbital vessels (late 1970s)
- Became trendy ++
- Periluminal hypoechogenic halo; segmental stenosis or occlusion
- Interexaminer variability seems huge!
  - Se/Sp 100% → **75% / 83%** → 40-69% / 57-59%
  - **halo = most specific, but variable Se…**
- Ophthalmic complications more frequent if US+

Maldini et al, J Rheumatol. 2010;37:2326-30
Schmidt et al, Rheumatology 2009;48:383-5
Salvarani et al, Ann Intern Med 2002;137:232-8

Ball et al, Br J Surg 2010;97:1765-71
Suelves et al, Clin Ophthalmol 2010;4:1383-4

The Role of Ultrasound vs Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis: A Diagnostic Accuracy and Cost-Effectiveness Study





R Luqmani, E Lee, S Singh, M Gillett, W A Schmidt, M Bradburn, B Dasgupta, A P Diamantopoulos, W Forrester-Barker, W Hamilton, S Masters, B McDonald, E McNally, C T Pease, J Piper, J Salmon, A Wailoo, K Wolfe, A Hutchings and the TABUL Study Group

NHS National Institute for Health Research

UNIVERSITY OF OXFORD

TABUL – n=399 patients with suspected GCA

Luqmani et al. ACR 2015

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 90 NOVEMBER 2016
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The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study

Raashid Luqmani, Ellen Lee, Surjeet Singh, Mike Gillett, Wolfgang A Schmidt, Mike Bradburn, Bhaskar Dasgupta, Andreas P Diamantopoulos, Wulf Forrester-Barker, William Hamilton, Shauna Masters, Brendan McDonald, Eugene McNally, Colin Pease, Jennifer Piper, John Salmon, Allan Wailoo, Konrad Wolfe and Andrew Hutchings

Strategy	Sensitivity	Specificity	% having ultrasound	% having biopsy
Biopsy only (all patients)	39%	100%	0%	100%
Ultrasound only (all patients)	54%	81%	100%	0%
Biopsy & ultrasound (both in all patients)	65%	81%	100%	100%
Ultrasound followed by biopsy if US negative	65%	81%	100%	57%
Ultrasound followed by biopsy if high risk	94%	77%	100%	2%
Ultrasound followed by biopsy if medium or high risk	95%	77%	100%	13%

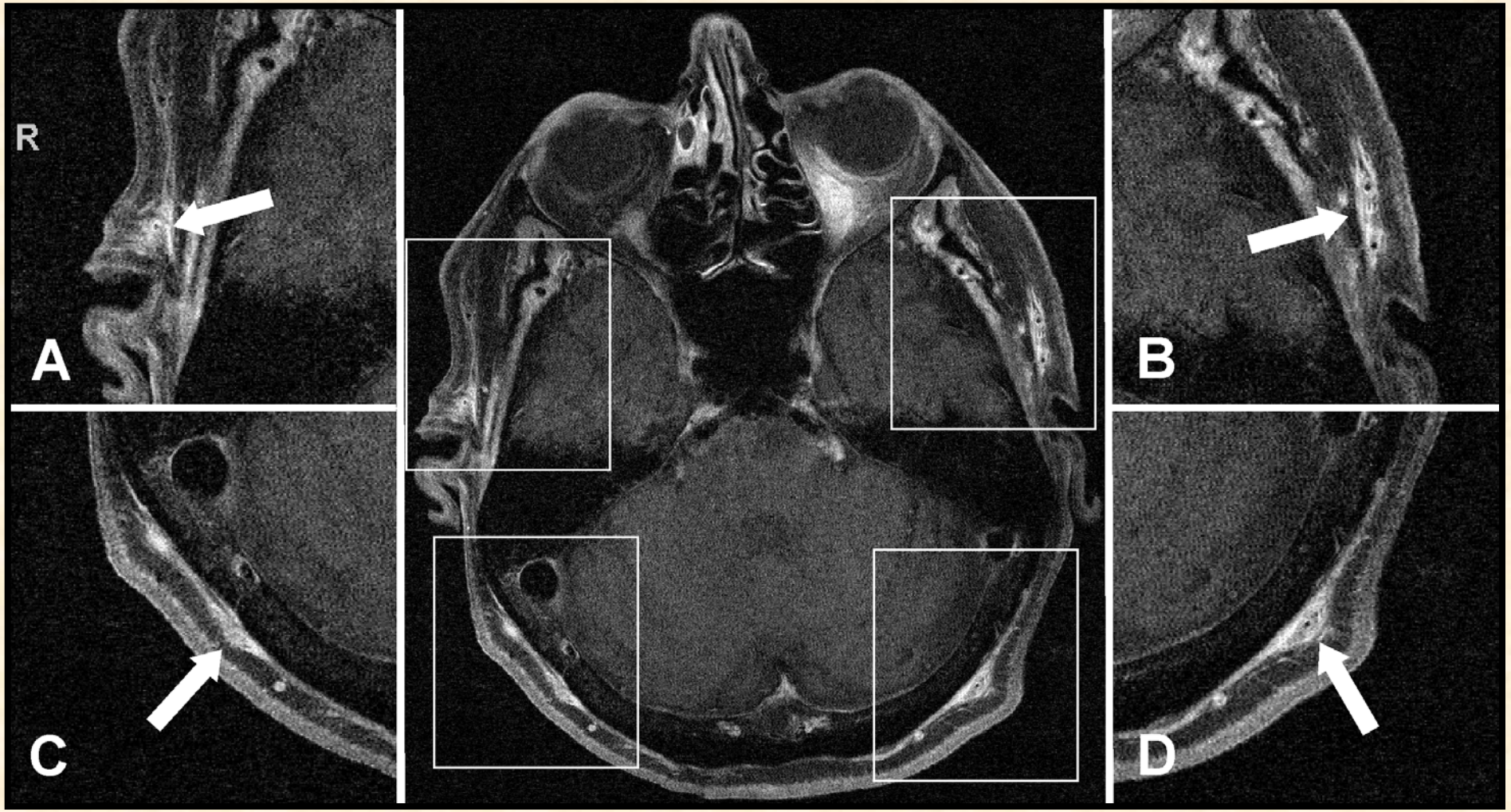
Luqmani et al. ACR 2015

B0565 DiamantopouloS ET AL – SONOVAS, NORWAY

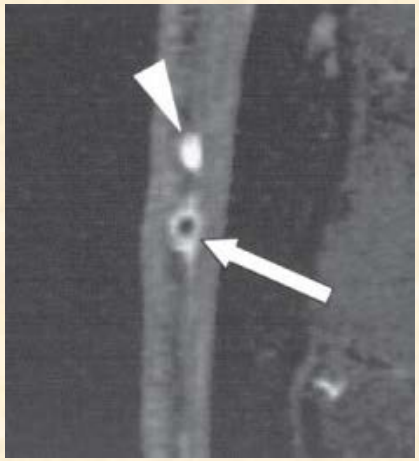
CAN COLOR DOPPLER ULTRASOUND BE USED TO MONITOR TREATMENT RESPONSE IN LARGE VESSEL GIANT CELL ARTERITIS?

- 10 patients (9 women, 63 +/- 25 years) with new onset (2) or relapsing (8) GCA (positive US of the TA and typical clinical picture) and with axillary arteritis
- Intima media complex (IMC) thickness of the axillary artery
- On CDUS examinations between the active phase and remission 3.1 +/- 4.1 months later
- → Mean reduction of IMC thickness of 0.6 mm (95% CI; 0.2-1.0, p=0.004) in the R axillary and 0.7 mm (95% CI; 0.2-1.2, p=0.009) in the L axillary arteries

GCA and MRI (3 Tesla)

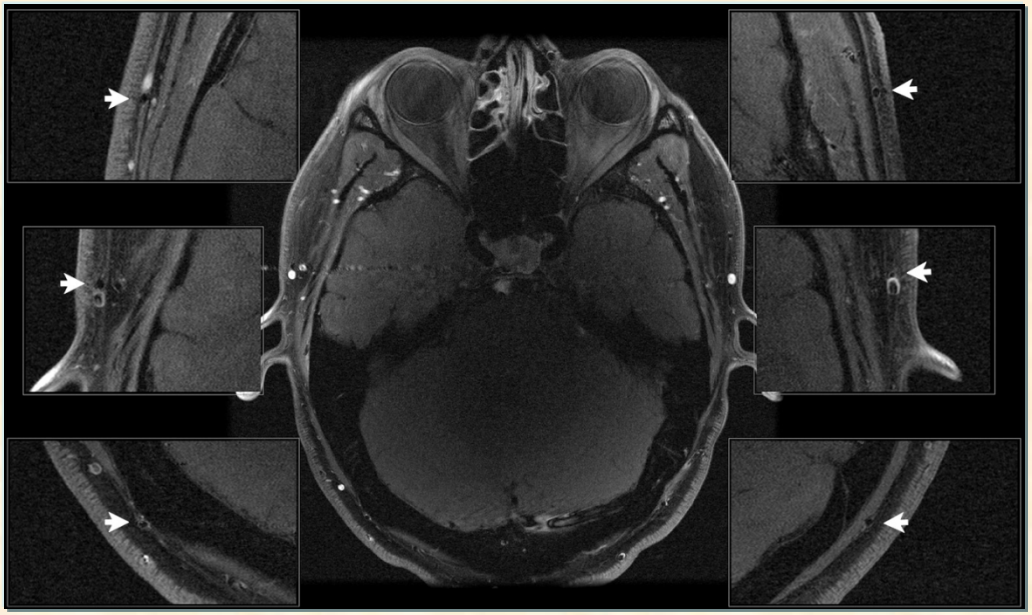


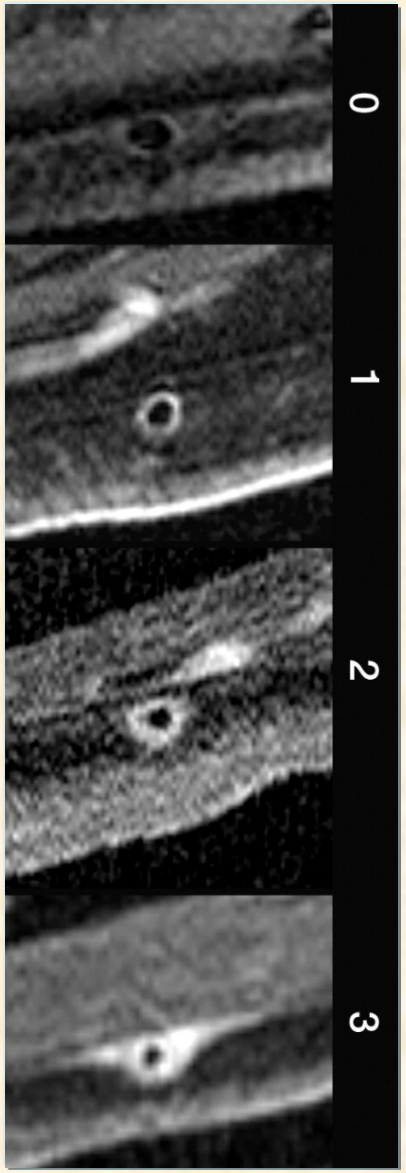
TA imaging

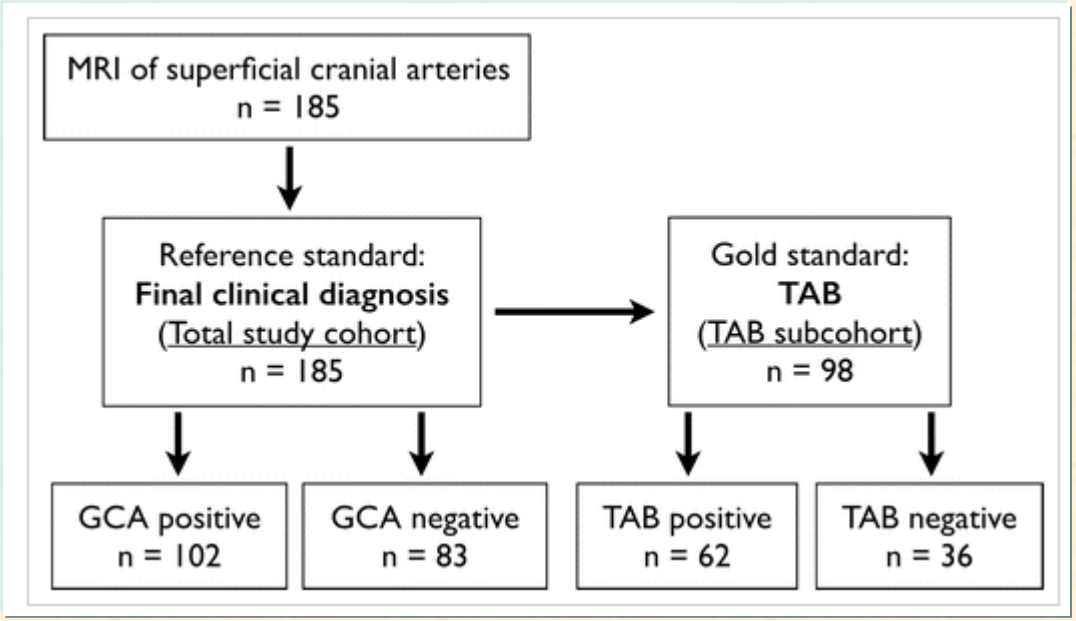


- **MRI** (3T)
- Under investigation
- In TA+ GCA (59 patients, 36 with GCA, 24 TAB+)
  - Se of MRI 83% vs. US 79%
  - Sp of MRI 71% vs. US 59%
  - PPV of MRI 80% vs. US 73%
  - **NPV of MRI 75%** vs. US 67%

Bley et al, Arthritis Rheum 2008;58:2574-8







Klink et al. Radiology. 2014 Aug 6 [Epub ahead of print]

Group and Observer	No. of Patients	TP Results	TN Results	FP Results	FN Results	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*
All patients, total study cohort									
Observer 1	185	85	71	12	17	83.3 (74.7, 90.0)	85.5 (76.1, 92.3)	87.6 (79.4, 93.4)	80.7 (70.9, 88.3)
Observer 2	185	80	75	8	22	78.4 (69.2, 86.0)	90.4 (81.9, 95.8)	90.9 (82.9, 96.0)	77.3 (67.7, 85.2)
Patients with TAB, TAB subcohort									
Observer 1	98	58	27	9	4	93.6 (84.3,98.2)	75.0 (57.8, 87.9)	86.6 (76.0, 93.7)	87.1 (70.2, 96.4)
Observer 2	98	55	27	9	7	88.7 (78.1, 95.3)	75.0 (57.8, 87.9)	85.9 (75.0, 93.4)	79.4 (62.1, 91.3)
Patients without TAB but with a final clinical diagnosis									
Observer 1	87	24	46	6	11	68.6 (50.7, 83.2)	88.5 (76.6, 95.7)	80.0 (61.4, 92.3)	80.7 (68.1, 90.0)
Observer 2	87	21	49	3	14	60.0 (42.1,76.1)	94.3 (84.1, 98.8)	87.5 (67.6, 97.3)	77.8 (65.5, 87.3)

MR imaging signs of vasculitis decreased <u>after >5 days of GC</u>
(ROC curves decrease from 0.944 to 0.804; P = 0.08)

Klink et al. Radiology. 2014 Aug 6 [Epub ahead of print]

ACR and CRA 2012 → ACR 2014

77 patients (69 ACR+, 39 MRI+, 17 TAB+)

Comparison	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
MRI vs ACR	53%	67%	90%	
Biopsy vs ACR	19.64%	100%	100%	15%
MRI vs Biopsy	**100%**	**68%**	**40%**	**94%**

St. Joseph's Healthcare Hamilton

McMaster University

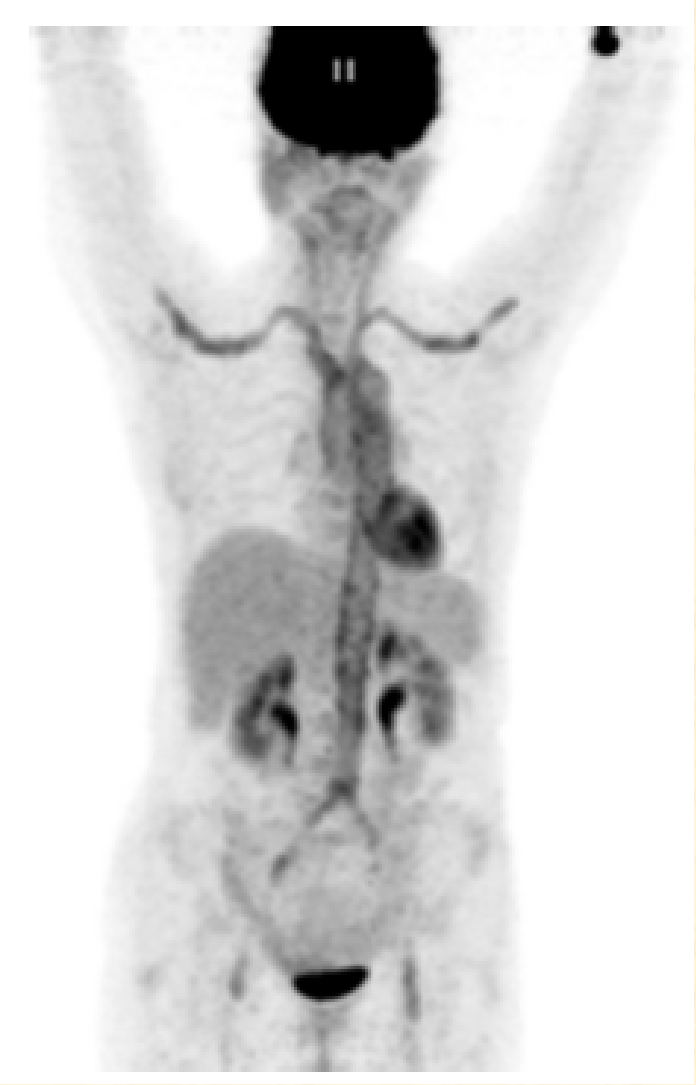
→ **177 patients**

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 1, January 2017, pp 161–168
DOI 10.1002/art.39824

High-Resolution Magnetic Resonance Imaging of Scalp Arteries for the Diagnosis of Giant Cell Arteritis

Results of a Prospective Cohort Study

Maxime Rhéaume,[1] Ryan Rebello,[2] Christian Pagnoux,[3] Simon Carette,[3] Marie Clements-Baker,[4] Violette Cohen-Hallaleh,[2] David Doucette-Preville,[2] B. Stanley Jackson,[2] Samih Salama Sargious Salama,[2] George Ioannidis,[2] and Nader A. Khalidi[2]



Daumas et al. La Revue de médecine interne 35 (2014) 4–15

AB0597 Just et al. Denmark

FDG PET-CT VERSUS TEMPORAL ARTERY BIOPSY IN PATIENTS PRESENTING WITH GCA/PMR: A RETROSPECTIVE CROSS-SECTIONAL STUDY

• Cross-sectional retrospective study on 19 PMR and 13 GCA who had both FDG PET-CT scan and temporal artery biopsy at presentation

	Vasculitis in biopsy	Normal biopsy	Total
PET-CT with vasculitis pattern	7	5	12
Normal PET-CT or isolated PMR pattern	2	18	20
Total	9	23	32

• 3 TAB+ had received GC before PET-CT = 1 with vasculitis, 2 PMR pattern or normal

• PET-CT FDG vasculitis uptake sensitivity = 78% (7/9) and specificity = 78% (18/23); **PPV 58%, NPV 90%**

cf. at supraaortic vessels, Se 81% and Sp 79% *(n=32 vs 20 cancer)*

at the aorta, Se 58% and Sp 90%

Prieto-González et al. Ann Rheum Dis 2014; 73:1388–92

Observational Study

Medicine

OPEN

^{18}F-fluorodeoxyglucose positron emission tomography and the risk of subsequent aortic complications in giant-cell arteritis

A multicenter cohort of 130 patients

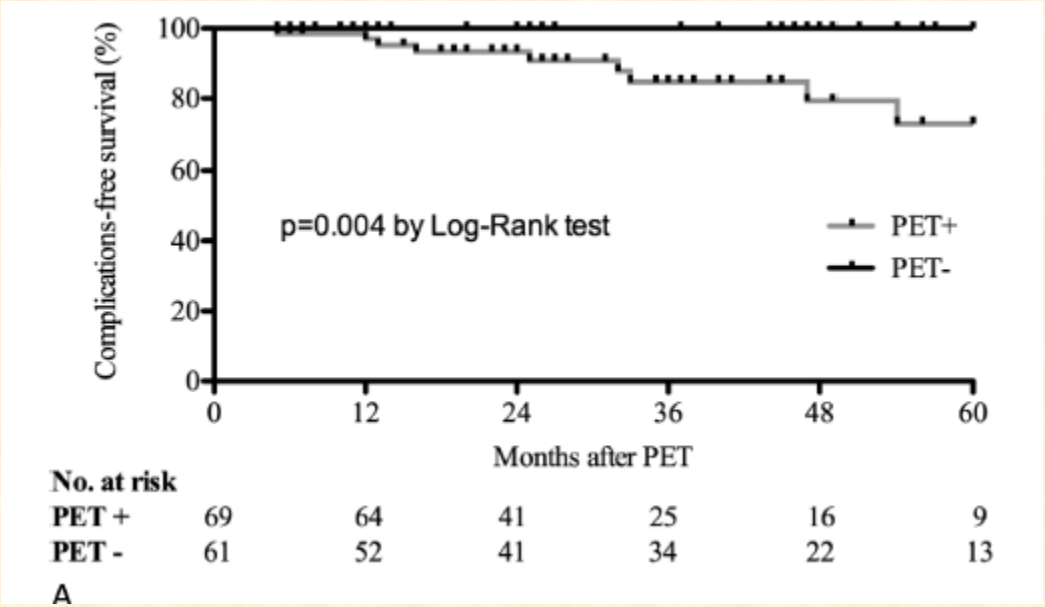
Hubert de Boysson (MD, MSc)[a,*], Eric Liozon (MD)[b], Marc Lambert (MD, PhD)[c], Jean-Jacques Parienti (MD, PhD)[d], Nicolas Artigues (MD)[e], Loïk Geffray (MD)[f], Jonathan Boutemy (MD)[a], Yann Ollivier (MD)[a], Gwénola Maigné (MD)[a], Kim Ly (MD)[b], Damien Huglo (MD, PhD)[g], Eric Hachulla (MD, PhD)[c], Pierre-Yves Hatron (MD, PhD)[c], Achille Aouba (MD, PhD)[a], Alain Manrique (MD, PhD)[h], Boris Bienvenu (MD, PhD)[a]

Table 2

PET/CT findings in patients with positive scan (n=69).

Number of affected vascular territories	**4 [1–8]**
Localization of vascular uptakes	
Thoracic aorta	54 (78)
Abdominal aorta	38 (55)
Subclavian arteries	50 (72)
Carotid arteries	34 (49)
Axillary arteries	27 (39)
Upper limb arteries	12 (17)
Iliac arteries	25 (36)
Lower limb arteries	8 (12)

CT = computed tomography, PET = positron emission tomography.
All results are numbers (percentage) or medians [range].



N=130
Bx + in 59%
FDG+ at Dx 60%,
FDG+ f-up 46%
9% aortic complication
After mean 33 months

→ Postive FDG associated with risk of aortic complications

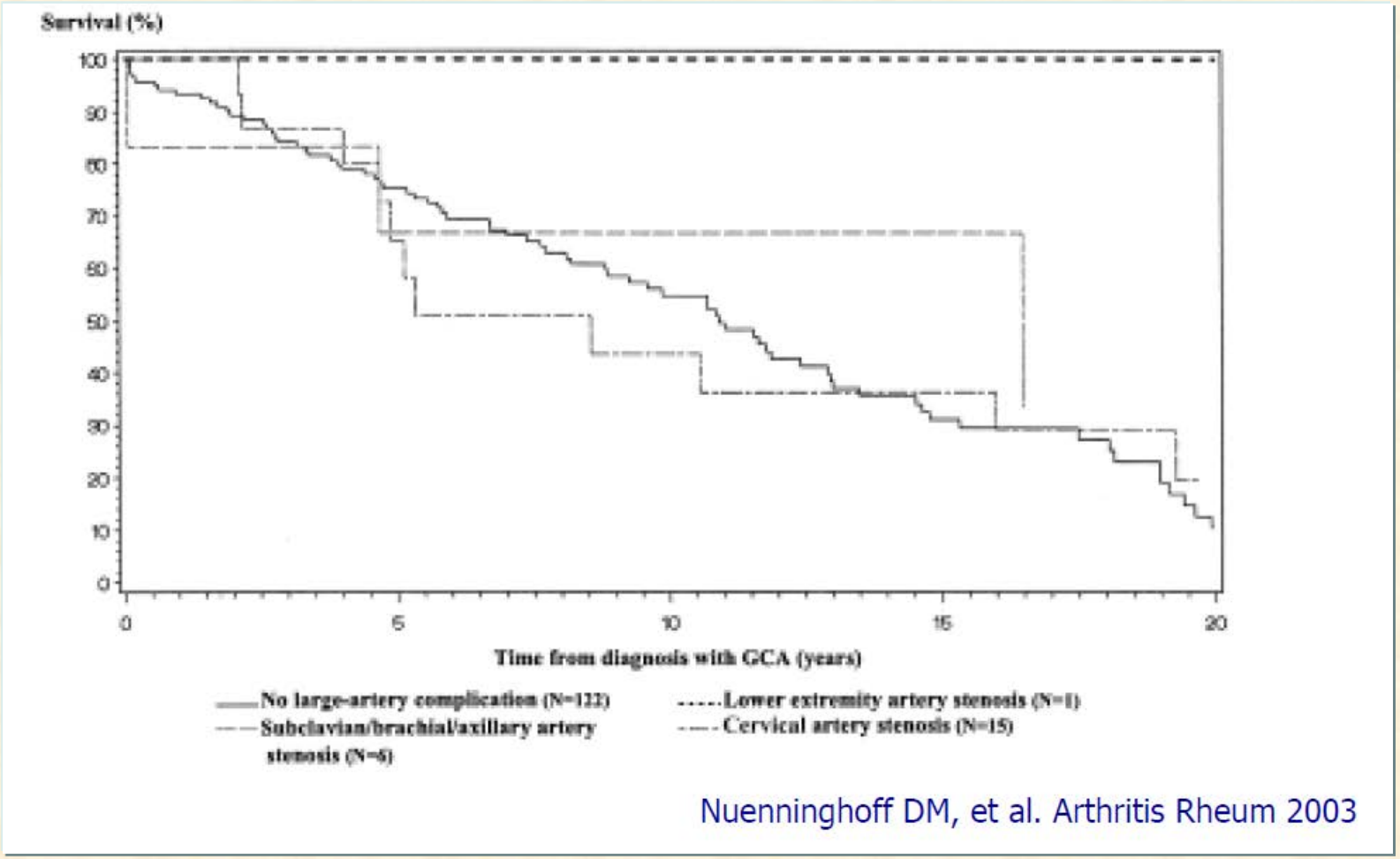
Upper/lower extremity vasculitis involvement

- On US, **up to 30%** (53/176)
  - bilateral in 79%
  - mainly axillary arteries on upper arms
  - more female (83 vs 65%) and younger subjects (mean 66 vs 72 yrs)

Schmidt et al, Rheumatology (Oxford) 2008;47:96-101
Aschwanden et al, Rheum Dis 2010;69:1356-9

- Presentation and outcomes
  - precedes GCA 20%
  - in association with GCA 36%
  - after GCA 44%
  - upper extremity alone 58%, lower extremity alone 19%, both 23%
  - aortic localization is common (69% of these patients)
  - disappearance or improvement of clinical manifestations (88%), deterioration (11%).

Assie et al, Medicine (Baltimore) 2011;90:40-51



Nuenninghoff DM, et al. Arthritis Rheum 2003

No influence on survival of extra-temporal (non-aortic) involvement

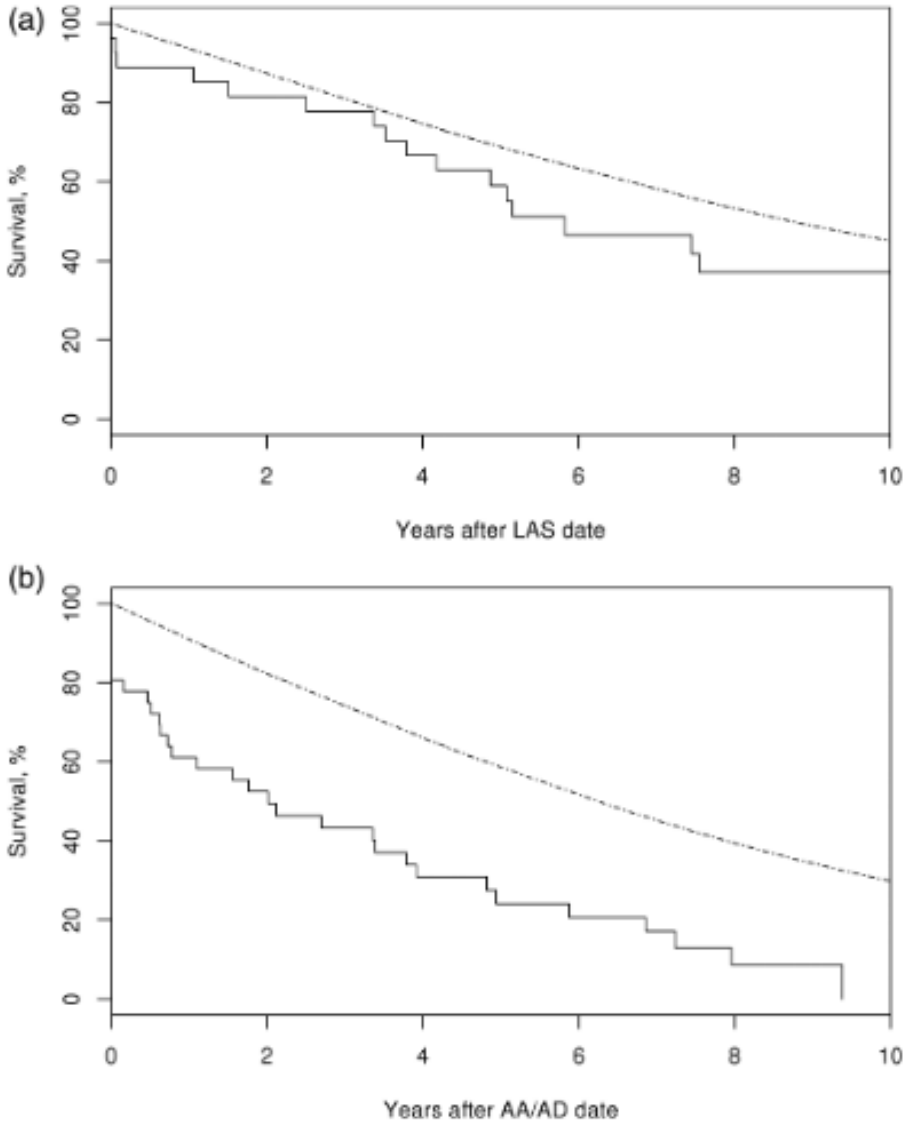


Figure 2 Survival in patients with giant cell arteritis (solid line) who develop large-artery stenosis (LAS) (top panel) log-rank p=0.11, or, aortic aneurysm/dissection (AA/AD) (bottom panel) compared with the general population (dotted line), log-rank p<0.001.

204 patients GCA
Median follow-up 8.8 years

Any LV at 10 years
24.9% for Dx >1980
8.3% for Dx <1980

The incidence of aortic aneurysm or dissection increased 5 yrs after GCA Dx

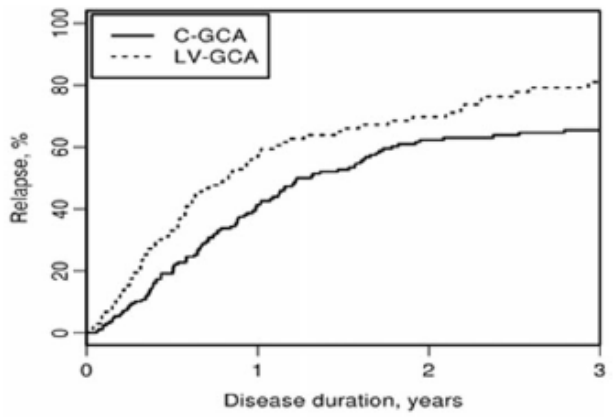
Aortic manifestations → increased mortality (HR=3.4; 95% CI 2.2 to 5.4)

Aortic aneurysm/dissection → mortality (SMR) 2.63 (95% CI, 1.78 to 3.73)

Large-artery stenosis → SMR 1.44 (95% CI, 0.87 to 2.25)

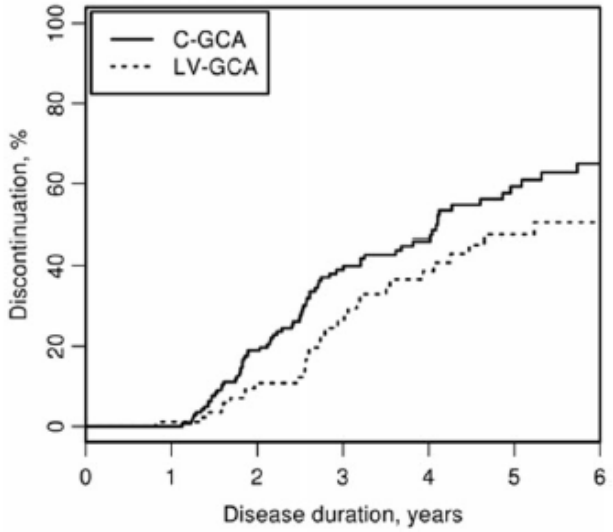
Kermani et al, ARD 2013;72 (12):1989-94

Fig. 1 Percentage of patients with at least one relapse by disease duration in patients with LV-GCA and C-GCA



Log-rank *P*-value = 0.006. C-GCA: cranial GCA; LV-GCA: large-vessel GCA.

Fig. 2 Percentage of patients who discontinued steroids for at least 6 months by disease duration in patients with LV-GCA and C-GCA



Log-rank *P*-value = 0.023. C-GCA: cranial GCA; LV-GCA: large-vessel GCA.

Mayo Clinic, Dx between 1999-2008

212 Cranial TAB+ GCA vs. 120 LV-GCA (s/clav)
Only 39% of LV-GCA satisfied ACR criteria
Median follow-up 4.6 vs. 3.6 years

LV- GCA were younger (68 vs 75 yr)
had more Hx of PMR (26% vs 15%)
had LESS visual loss (4% vs 11%)
relapsed MORE and sooner
had more Ao. aneur. at 5 yrs (15% vs 3%)
received more prednisone total
received more IS (52% vs 16%)

Muratore, Kermany et al, Rheumatology Sept 2014 E-pub

Aortic involvement

- Large-vessel GCA
- **Aortic involvement**
  - **aortitis in 3 to 18% of GCA patients**
  - FDG-TEP scanner → **up to 50%**
  - predominant involvement of the **thoracic aorta**
  - at diagnosis 85%, later 15%
  - resolution or improvement under Rx 53% (back to normal 9%)
  - **increased risk of aneurysm (RR=17, women+, ascending ao+)**, even **(mainly) after treatment** discontinuation (5-11 years later)

→ chest X-ray, echocardiogram, abdomen Doppler-US

or → CT scan of the chest and abdomen

YEARLY??

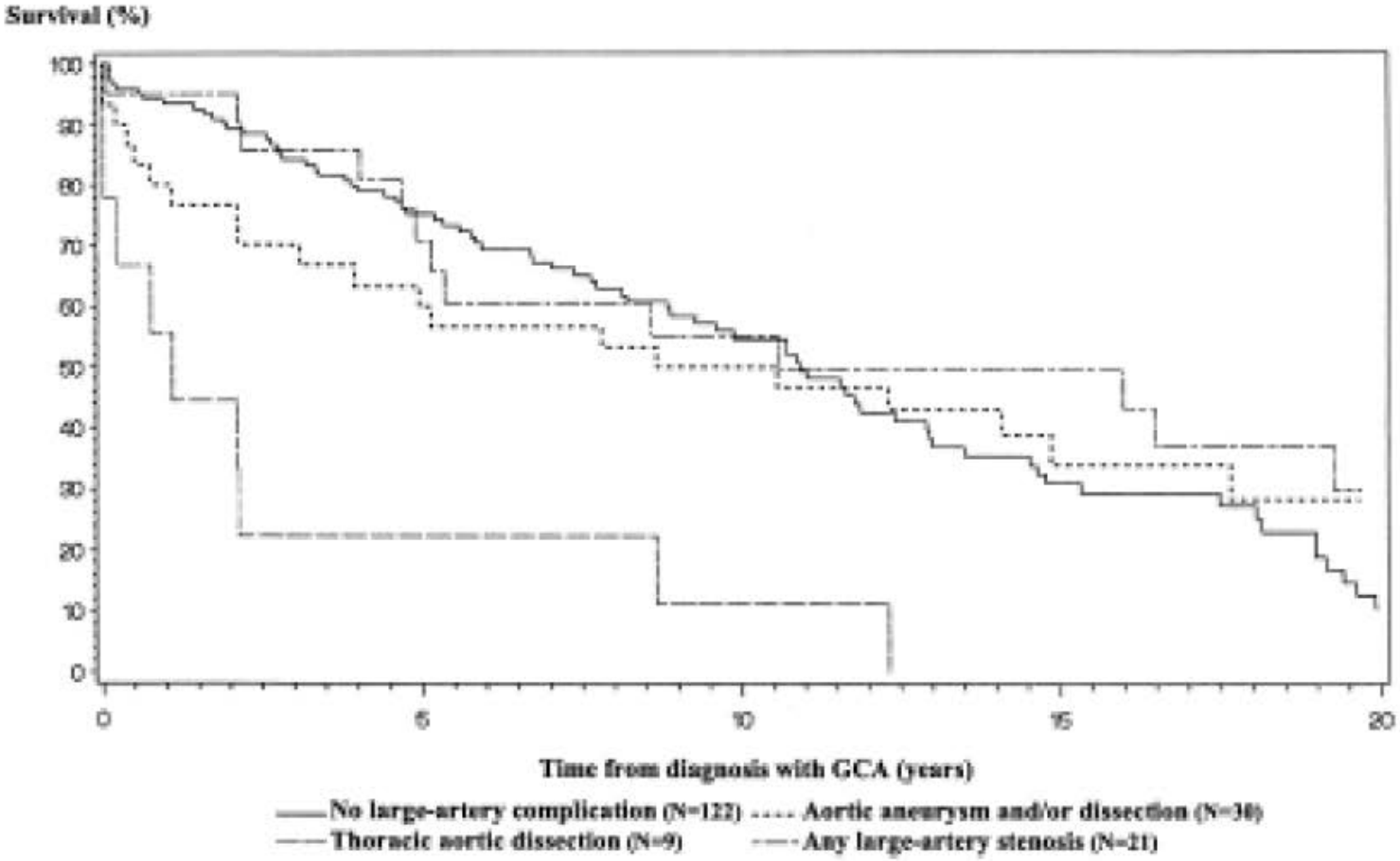
Marie et al, Medicine (Baltimore) 2009;88:182-92

Table 2. Large vessel involvement (LVI) in patients with giant cell arteritis (GCA) and reference subjects.

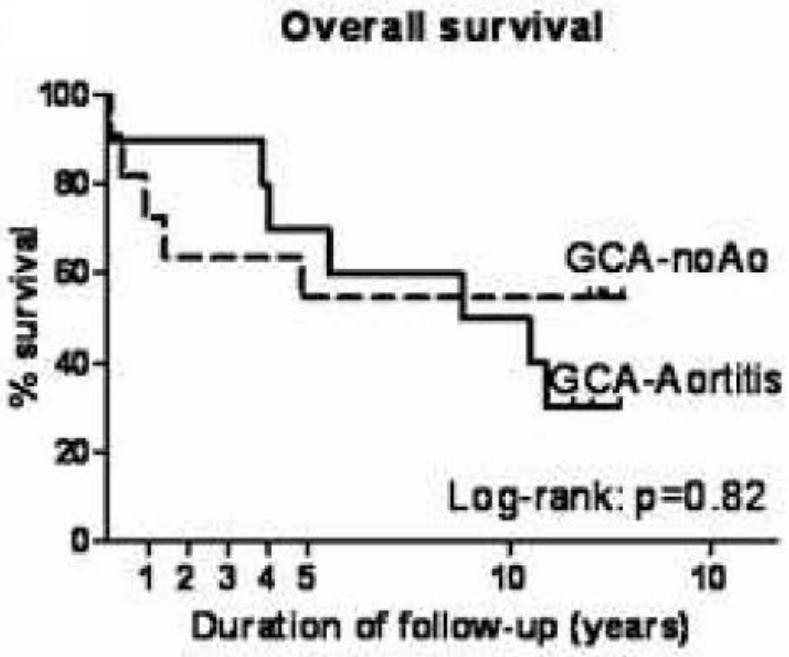
	Main analysis		Sensitivity analysis†	
	GCA patients n = 164	Reference subjects n = 330	GCA patients n = 169	Reference subjects n = 332
Incident LVI total, % (n)	14.6 (24)	10.9 (36)	17.1 (29)	11.4 (38)
Incident LVI aorta, % (n)	9.8 (16)	5.4 (18)	11.8 (20)	6.0 (20)
Incident LVI tributary, % (n)	8.3 (14)	6.6 (22)	8.9 (15)	6.6 (22)
Prevalent LVI, % (n)	3.0 (5)	0.6 (2)	na	na
Gender: female, % (n)*	71 (17)	61 (22)	69 (20)	61 (23)
Age at LVI (years), mean (sd)	81.1 (6.3)	81.1 (6.3)	79.0 (7.6)	81.3 (6.2)

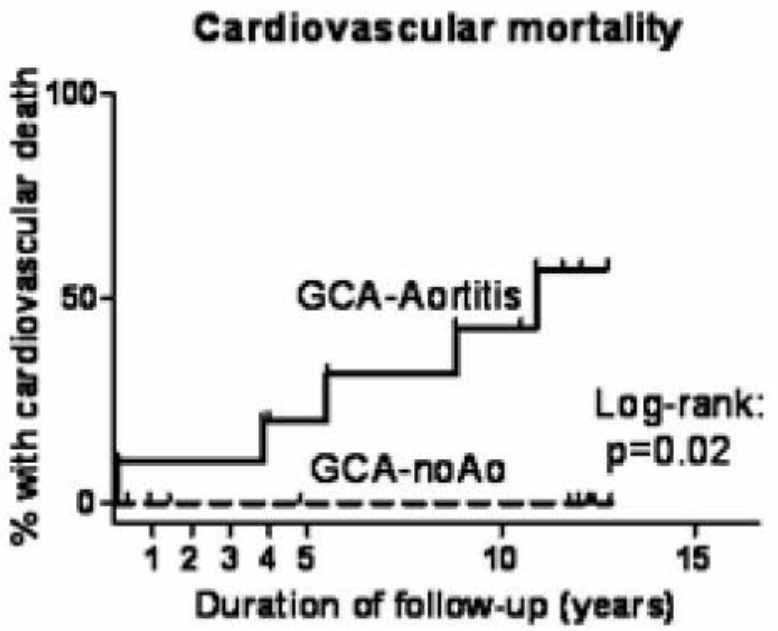
na, Non-applicable; sd, standard deviation.
*Among those with LVI.
†The sensitivity analysis also includes subjects with LVI more than 1 year before GCA diagnosis or the corresponding dates in reference subjects.

Naderi et al. Scand J Rheum 2016
Routine clinical practice
164 Patients in Sweden 1997-2004
LVV detected after a median of 3.7 years AFTER GCA Dx



Nuenninghoff DM, et al. Arthritis Rheum 2003

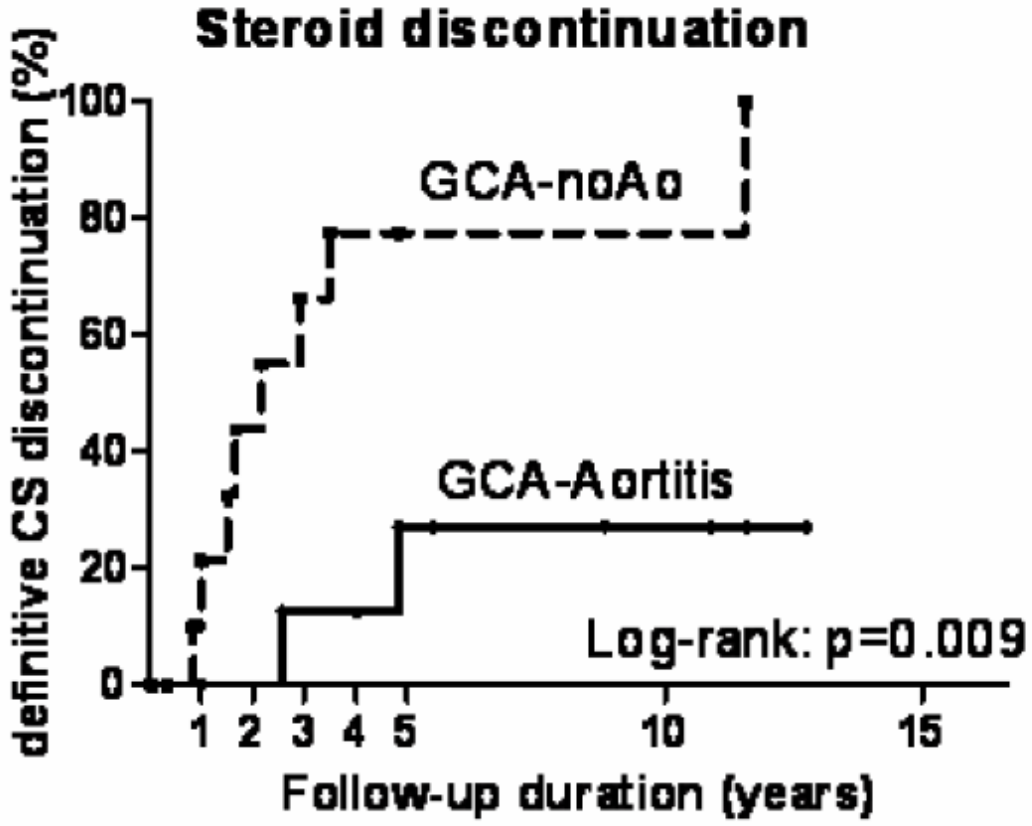




Espitia O, et al. J Rheumatol 2012

	GCA-Ao (n=10)	GCA-noAo (n=12)	p
Aortic complications	3 (30)	1 (9)	0.29
Thoracic aortic dissection	1 (10)	0 (0)	0.47
Ruptured abdominal aortic aneurysm	1 (10)	0 (0)	0.47
Uncomplicated abdominal aortic aneurysm	1 (10)	1 (9)	0.94
Stage III/IV obliterating arteriopathy	4 (40)	1 (9)	0.12
Stroke	**4 (40)**	**0 (0)**	**0.03**
Coronary artery disease	2 (20)	1 (9)	0.57

Espitia O, et al. J Rheumatol 2012



Espitia O, et al. J Rheumatol 2012

What about treatment?

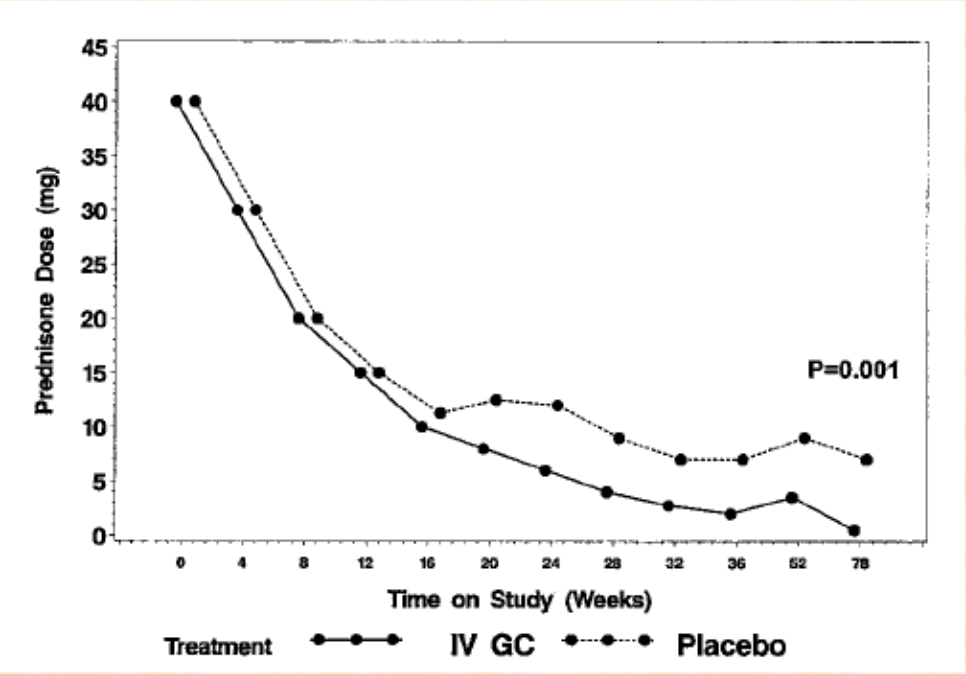
- IV corticosteroid pulses?

What about treatment?

- IV corticosteroid pulses?

- Chevalet et al. *J Rheumatol* 2000
  - 1992-1996
  - 164 patients received
    - a 240 mg IV MP then 0.7 mg/kg/day oral prednisone (Group 1)
    - 0.7 mg/kg/day prednisone without IV MP (Group 2, controls)
    - A 240 mg IV MP then 0.5 mg/kg/day oral prednisone (Group 3)
  - Cumulative CS doses at 1 year were identical in all groups (p=0.39)
  - No differences in the time to normalization of CRP, CS-resistance (13.5%) and CS-related AEs (39% of patients; p=0.37).
  - **MP pulses have no significant long term or CS sparing effects** in the treatment of simple forms of GCA

Initial IV methylprednisolone?



- **<u>Double blind</u>** RCT on 27 TAB+
- 10/14 IV GC (**15mg/kg D1 +/- 2 and 3**) vs 2/13 **placebo** taking ≤ 5mg/d prednisone at 36 weeks (P = 0.003)
- higher number of sustained remissions after discontinuation of GC in the IV GC group at 78 weeks (P<0.001)
- **median cumulative prednisone dose** of 5,636 mg in the IV GC group vs. 7,860 mg (P = 0.001)
- 21 **relapses/flares** in 14 IV-GC patients vs 37 in 13 placebo patients (P = 0.03)

Mazlumzadeh et al, Arthritis Rheum 2006;54:3310-8

What about treatment?

- Aspirin (clopidogrel)

Aspirin (or clopidogrel) in GCA

- **EULAR**: “We recommend the use of low dose aspirin in all patients with giant cell arteritis” - level 3/C
- Retrospective study (x 2 positive)
  - 175 patients, 36 on aspirin prior to GCA
  - 43 strokes: **3 (8%) on aspirin vs. 40 (29%, *P*=0.01)**
    OR=0.22 [95% CI, 0.06-0.80]
  - >3 months = 3% on aspirin vs. 13% (*P*=0.02)
- **No** effect on 121 patients, 37 on aspirin or clopidogrel prior to GCA (1 x negative)*

Mukhtyar et al, EULAR Ann Rheum Dis 2009;68:318-23
Nesher et al, Arthritis Rheum 2004;50:1332-7
Lee et al, Arthritis Rheum 2006;54:3306-9
**Narváez et al, Clin Exp Rheumatol 2008;26:S57-62*

Aspirin (or clopidogrel) in GCA

- Negative: Berger et al, Rheumatology, 2009; 48(3):258-61
  - 85 patients, 22 on ASA at Dx → **no** differences in severe or non-severe ischemic events (32% and 68% vs 34% and 73% for all 85 patients)

- Negative: Salvarani et al, Rheumatology 2009; 48(3):250-3
  - 180 patients, 26 with ASA/anticoag at Dx → more likely to suffer cranial ischemic events than those without (P=0.03)!!

Aspirin as adjunctive treatment for giant cell arteritis (Protocol)

Mollan SP, Marrone M, Burdon MA, Levin LA, Denniston AK

THE COCHRANE COLLABORATION®

July 2013…

Sept. 2014

Selection criteria

We planned to include only randomised controlled trials (RCTs) comparing outcomes of GCA with and without concurrent adjunctive use of low-dose aspirin.

Data collection and analysis

Two authors independently assessed the search results for trials identified by the electronic searches.No trials met our inclusion criteria, therefore we undertook no assessment of risk of bias or meta-analysis.

Original article

Management of giant cell arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA)

B. Bienvenu[a], K.H. Ly[b], M. Lambert[c], C. Agard[d], M. André[e], Y. Benhamou[f], B. Bonnotte[g], H. de Boysson[a], O. Espitia[d], G. Fau[h], A.-L. Fauchais[b], F. Galateau-Sallé[i], J. Haroche[j], E. Héron[k], F.-X. Lapébie[b], E. Liozon[b], L.B. Luong Nguyen[l], J. Magnant[m], A. Manrique[n], M. Matt[b], M. de Menthon[h], L. Mouthon[o], X. Puéchal[o], G. Pugnet[p], T. Quemeneur[q], A. Régent[o], D. Saadoun[r], M. Samson[g], D. Sène[s], P. Smets[e], C. Yelnik[c], L. Sailler[p], A. Mahr[l,*], for the "Groupe d'étude français des artérites des gros vaisseaux (GEFA)", under the aegis of the "Filière des maladies auto-immunes et auto-inflammatoires rares (FAI²R)"

Low-dose aspirin (75–300 mg/day) should be considered for every patient with newly-diagnosed GCA upon benefit–risk assessment; for GCA with ophthalmic involvement, prescribing low-dose aspirin should be advised

The systematic prescription of an anticoagulant or a statin is not recommended

Warfarin?

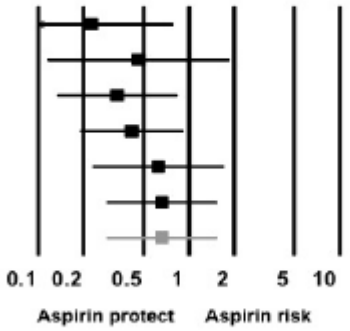
	Ischemic event	No ischemic event	*P*
Age, years	71.1	73.3	0.15
Female, %	67.4	80.4	0.10
ESR, mm/hour	66.3	85.5	0.03
Platelet count, $\times 10^3/mm^3$	392	383	NS
Biopsy-proven diagnosis, %	76.1	71.1	NS
Cerebrovascular risk factors, %	67.4	69.1	NS
Aspirin at time of event, %	17.4	48.5	<0.0005
Warfarin at time of event, %	4.4	13.2	0.04†
Clopidogrel at time of event, %	2	1	NS

* Except where indicated otherwise, values are the mean. An ischemic event represents vision loss or hemispheric stroke secondary to GCA. See Table 1 for definitions.
† By multivariate logistic regression analysis.

Lee et al. Arthritis Rheum 2006

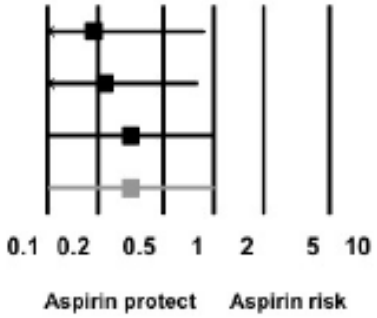
Aspirin/anticoag **BEFORE** GCA

Study name	Cumulative statistics		
	Point	Lower limit	Upper limit
Nesher G	0.225	0.065	0.776
Gonzalez-Gay MA	0.462	0.115	1.846
Lee MS	0.333	0.134	0.830
Narvaez J	0.419	0.191	0.918
Salvarani C	0.625	0.229	1.703
Berger CT	0.661	0.287	1.520
Random	0.661	0.287	1.520



Severe ischemic complications

	Cumulative statistics		
	Point	Lower limit	Upper limit
Nesher G	0.190	0.041	0.879
Lee MS	0.221	0.061	0.807
Narvaez J	0.318	0.101	0.996
Random	0.318	0.101	0.996

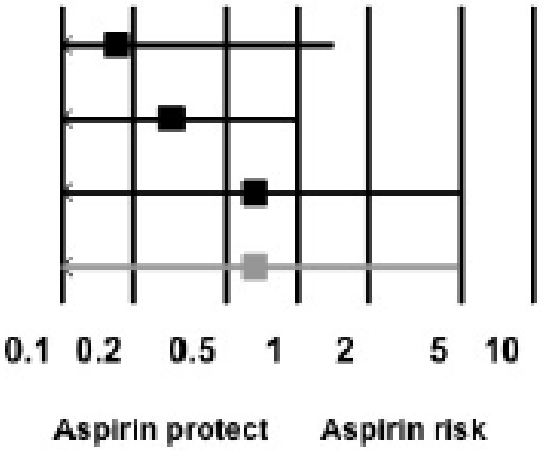


Aspirin/anticoag **AFTER** GCA

Martínez-Taboada et al. Autoimm Rev 2014

Bleeding complication AFTER diagnosis

St…	Cumulative statistics			Cumulative odds ratio (95% CI)
	Point	Lower limit	Upper limit	
Nesher G	0.171	0.021	1.420	
Lee MS	0.291	0.087	0.974	
Narvaez J	0.658	0.089	4.856	
Random	0.658	0.089	4.856	



Statins?

Table 3. Results of Cox proportional hazard regression model investigating the effect of statins and other variables on the probability of maintenance on a low prednisone dose (< 5 mg/day) during more than 6 months in giant cell arteritis.

Variables	Hazard Ratio (95% CI)	p
Age	1.0 (0.64–1.54)	0.98
Sex	0.95 (0.55–1.62)	0.83
GCA with PMR	0.84 (0.54–1.3)	0.43
First prednisone dose	1.0 (0.99–1.01)	0.98
Cardiovascular comorbidity	0.94 (0.6–1.47)	0.78
Diabetes mellitus	1.21 (0.38–3.85)	0.75
Platelet aggregation inhibitors	0.89 (1.0–1.76)	0.97
Antihypertensives	0.91 (0.58–1.42)	0.67
Statins at baseline	1.9 (1.16–3.15)	0.011
Statins at maintenance on low prednisone dose	1.6 (0.97–2.72)	0.067
Time-dependent statin exposure from index date		
No exposure	1	
1 to12 mos	4.5 (2.15–9.55)	< 0.0001
12 to 20 mos	3.8 (1.69–8.44)	0.00012
> 20 mos	0.8 (0.41–1.61)	0.56
Cumulative statin exposure from index date		
No exposure	1	
1 to 160 DDD	4.88 (2.32–10.28)	< 0.0001
160 to 261.1 DDD	2.36 (1.10–5.09)	0.027
> 261.1 DDD	0.89 (0.45–1.75)	0.73

The hazard ratios displayed are from the univariate analysis. DDD: defined daily dose; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

103 GCA patients

28 on statins before
+ 5 after diagnosis

→ No impact on Dx
→ May favor GC tapering

Pugnet et al, J Rheum 2015; 42:316-22

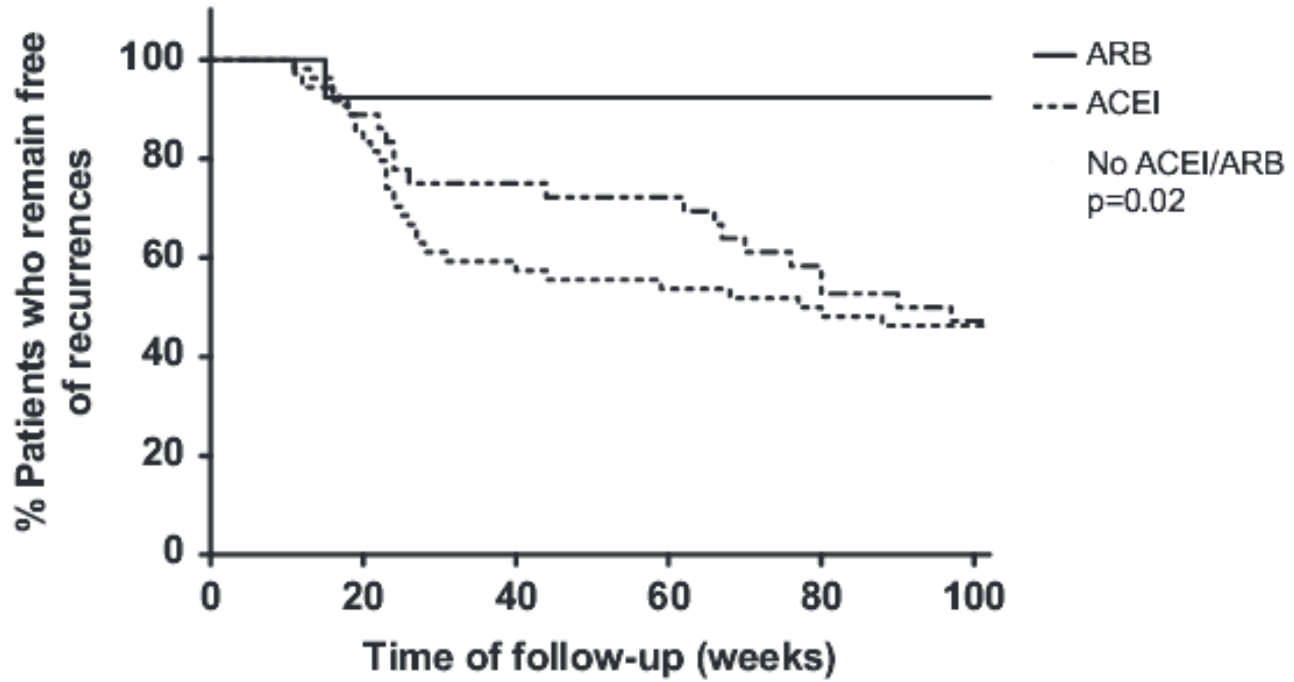


Fig. 1. Kaplan–Meier estimate of the probability of relapse depending on treatment with ACEI, ARB, or no ACEI/ARB.

adjusted HR for relapses with ARB 0.32 (95% CI: 0.12–0.81, p=0.017)

Alba et al. Semin Arthritis Rheum 43 (2014) 772-7

What about treatment?

- Prednisone dose/duration?
- **Risk of relapse?**

Relapses in GCA

- VCRC cohort
- 128 GCA (80% women, 69.9 years, follow-up 21.4 months)
- At baseline, 39% had experienced a previous relapse

During follow-up, 59 relapses in 44 patients (34%)

– 24% in the 69 newly Dx within 1 year post-diagnosis

– 10 (8%) had ≥2 relapses

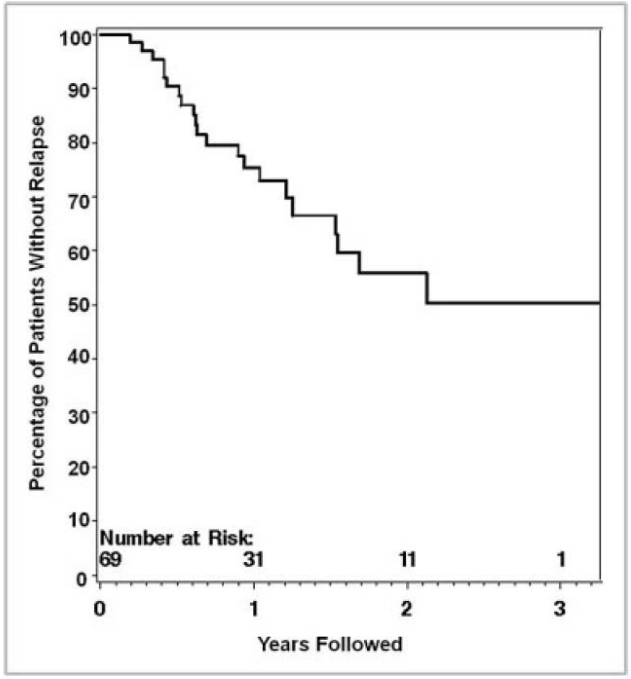
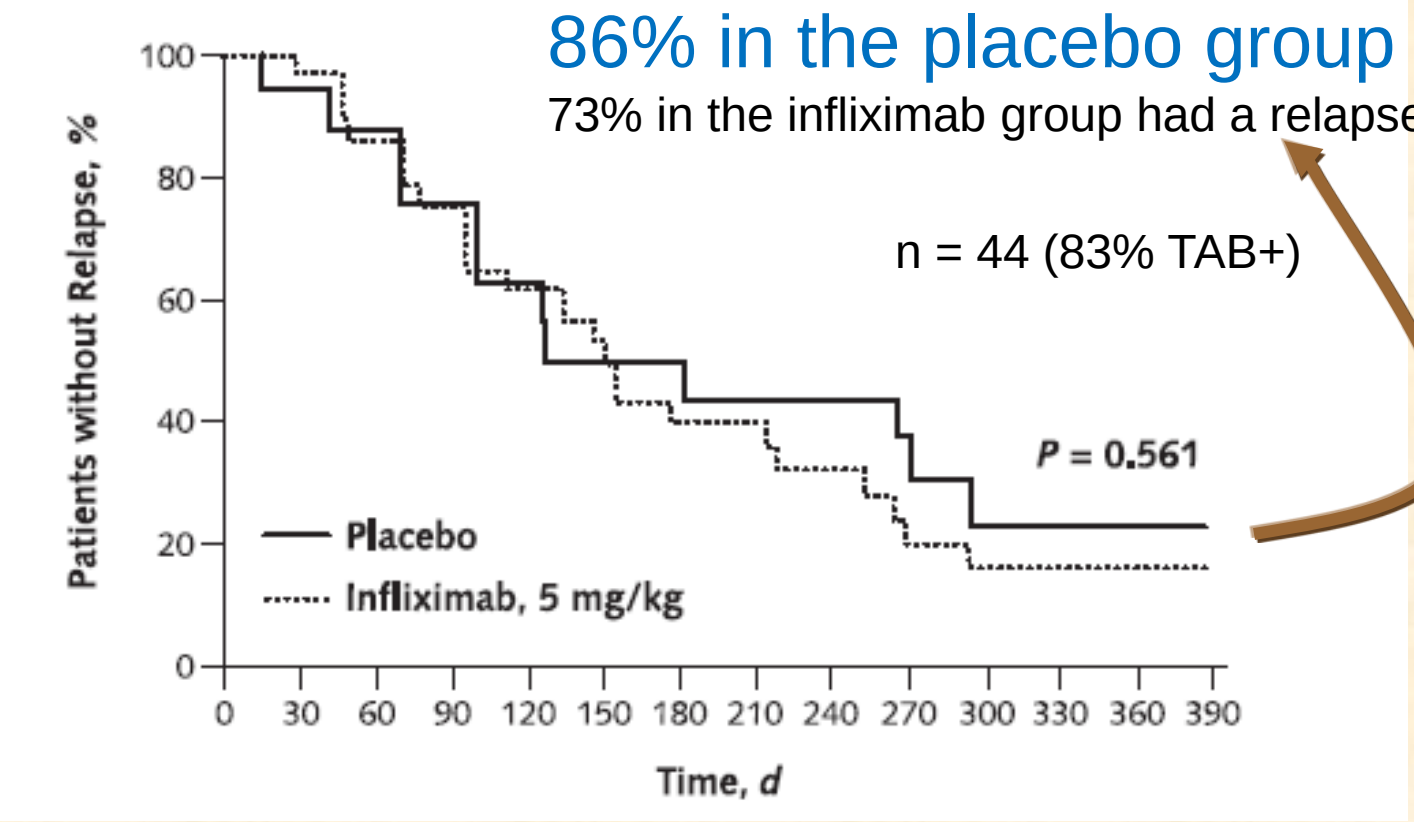


Figure. Time from diagnosis to first relapse in 69 patients with newly-diagnosed GCA

Kermani et al. (Mayo, VCRC) #1513

Relapse rate of GCA



CS to be stopped at 6 months

Hoffman et al, Ann Intern Med 2007;146:621-630.

Relapse rate of GCA

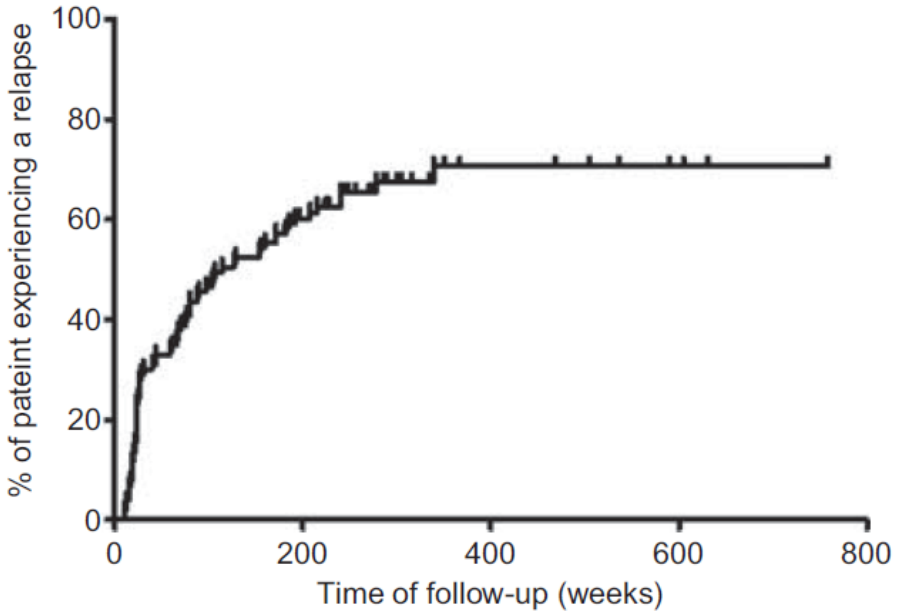


FIGURE 1. Kaplan-Meier plot of the entire series showing the probability of relapse over time.

Spanish cohort
106 TAB+ patients
F/up 7.6 +/- 3.3 years

→ 64% relapsed (at median 51 weeks)
→ rarely with vision loss

→ weak predictors: scalp tenderness, PMR symptoms, high SIR (haptoglobin)

→ *LV-GCA?*

→ *40% to 85% in other studies*

Alba et al, Medicine 2014;93:194-201

What about treatment?

- Place of methotrexate?
- Alternative treatments?
  - LEF, CYC, AZA, MMF
  - TNFα blockers
  - CTLA4-Ig (abatacept)
  - anti-IL6RA
  - Others (ustekinumab)?
  - Immune checkpoint modulators?

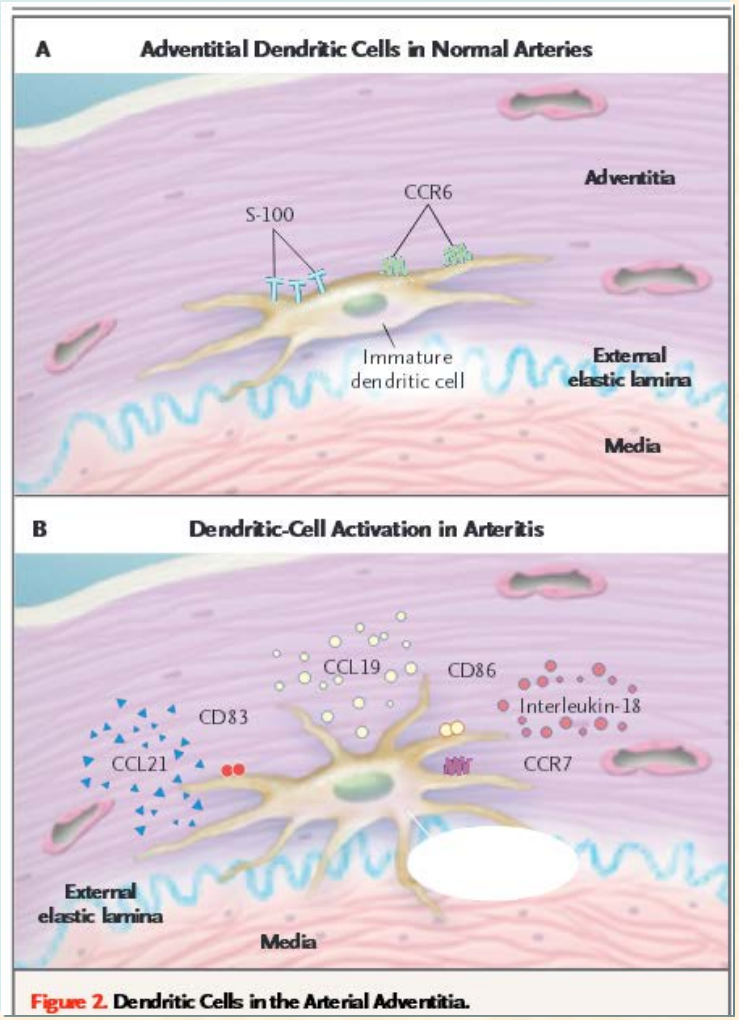
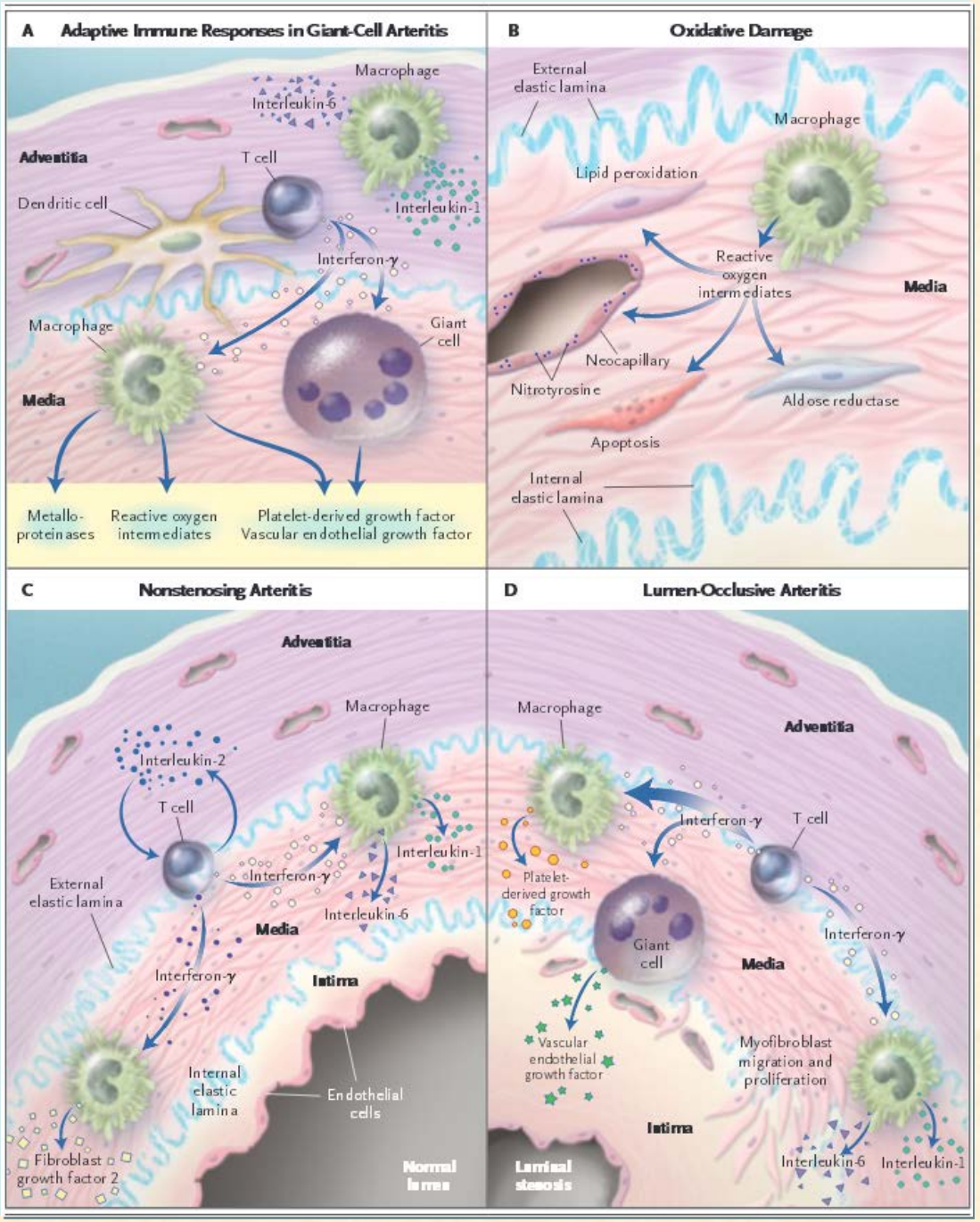
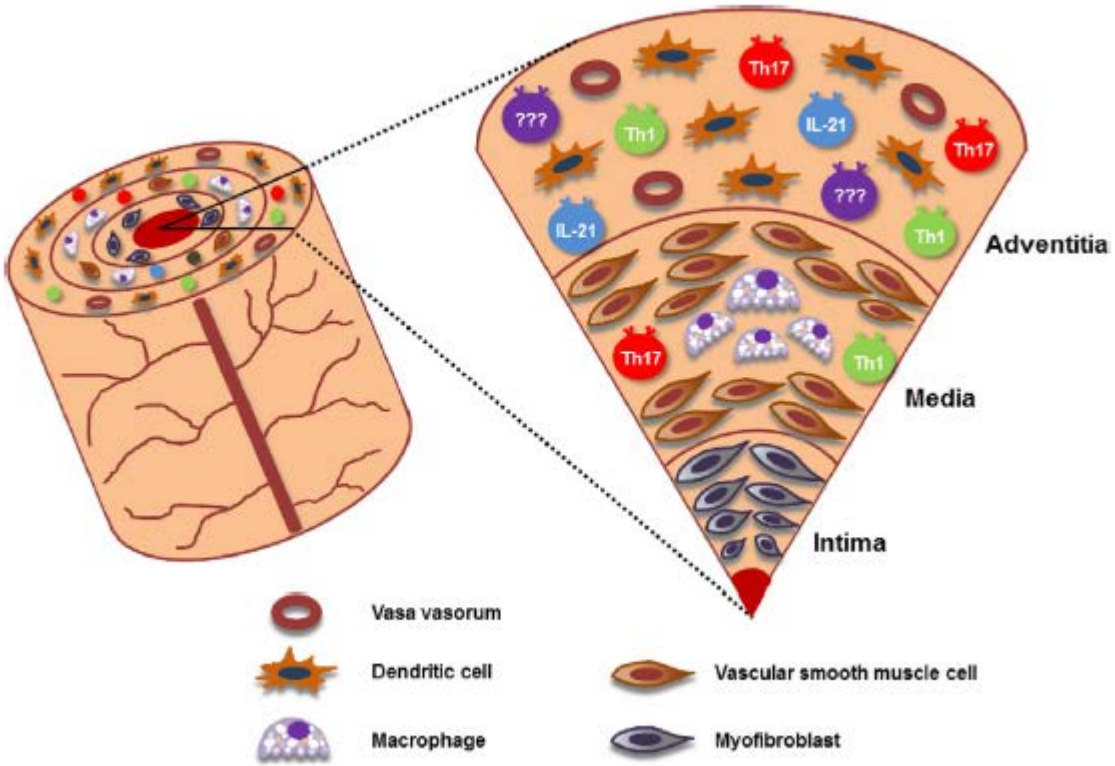


Figure 2. Dendritic Cells in the Arterial Adventitia.



Weyand, NEJM 2012
Gorgonzy, Nat Rev Rheum 2013


Th17
???
Th1
IL-21
Th17
???
IL-21
Th1
Adventitia
Th17
Th1
Media
Intima
Vasa vasorum
Dendritic cell
Macrophage
Vascular smooth muscle cell
Myofibroblast

ARD Online First, published on June 11, 2014 as 10.1136/annrheumdis-2014-205261

CONCISE REPORT

Influence of the *IL17A locus* in giant cell arteritis susceptibility

A Márquez,[1] J Hernández-Rodríguez,[2] M C Cid,[2] R Solans,[3] S Castañeda,[4] M E Fernández-Contreras,[5] M Ramentol,[3] I C Morado,[6] J Narváez,[7] C Gómez-Vaquero,[7] V M Martínez-Taboada,[8] N Ortego-Centeno,[9] B Sopeña,[10] J Monfort,[11] M J García-Villanueva,[12] L Caminal-Montero,[13] E de Miguel,[14] R Blanco,[8] Spanish GCA Consortium, O Palm,[15] O Molberg,[15] J Latus,[16] N Braun,[16] F Moosig,[17] T Witte,[18] L Beretta,[19] A Santaniello,[19] G Pazzola,[20] L Boiardi,[20] C Salvarani,[20] M A González-Gay,[8] J Martín[1]

Table 3 Conditional logistic regression analysis for the *IL17A* polymorphisms considering the four populations as covariates

	GCA vs Controls			
	p Value	p Value add to rs4711998	p Value add to rs2275913	p Value add to rs7747909
rs4711998	0.0591	N/A	0.080	0.064
rs2275913	**1.85E−03**	**8.30E−03**	N/A	**0.022**
rs7747909	**8.49E−03**	**0.042**	0.782	N/A

Significant p values are shown in bold.
GCA, giant cell arteritis.

- 266 biopsy-proven GCA patients
- 3779 healthy controls from 4 European populations (Spain, Italy, Germany and Norway)

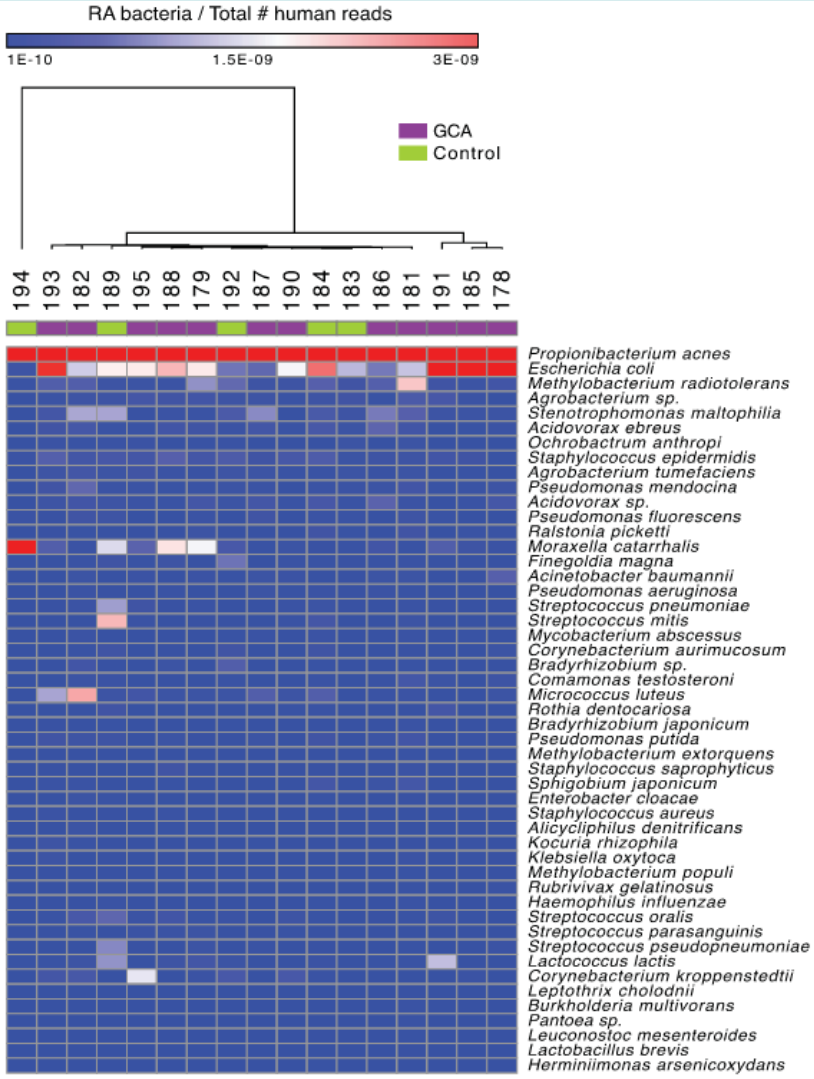


Figure 2. Heatmap representation of the most abundant organisms in the temporal artery tissue microbiome of patients with giant cell arteritis (GCA) and non-GCA controls. Whole-genome sequencing of the temporal artery biopsy specimens was followed by microbial taxonomic classification of the reads using the PathSeq computational platform. As demonstrated, PathSeq analysis of the GCA microbiome does not show an enrichment of candidate pathogens or other microbes in cases compared to controls. The 49 most abundant organisms in cases and controls are shown in the heatmap. The heatmap indicates the relative abundance (RA) value (with values normalized to the total number of human reads per

DNA sequencing of TAB specimens from GCA, in comparison with non-GCA controls, showed no evidence of previously identified candidate GCA pathogens

Bhatt et al, Arthritis Rheumato l 2014;66(7): 1939–44

Journal of Human Genetics (2015), 1–6

www.nature.com/jhg

REVIEW

Revisited HLA and non-HLA genetics of Takayasu arteritis—where are we?

Chikashi Terao[1,2,3,4,5]

Takayasu arteritis (TAK) is an immune-mediated vasculitis affecting large arteries first reported in 1908 from Japan. Case reports of familial onset of TAK from Japan and other countries indicated genetic contribution to TAK onset beyond ethnicity. Genetic studies of TAK have been performed mainly addressing the human leukocyte antigen (HLA) locus. HLA genetic studies of TAK that have previously been reported are reviewed in this manuscript. HLA-B*52:01 is associated with TAK beyond population. Many of the associations other than HLA-B*52:01 can be explained by a haplotype with HLA-B*52:01. HLA-B*67:01 is a novel susceptibility HLA-B allele to TAK confirmed in the Japanese population. Further independent associations are suggested in the HLA locus. Involvement of the 171st and 67th amino acid residues with TAK onset has been indicated. The 67th amino acid may explain the difference in susceptibility effects to TAK and Behçet's disease between HLA-B*52:01 and *51:01. HLA-B*52:01 is associated not only with TAK susceptibility but also with clinical phenotypes. Recent genome-wide association studies of TAK revealed multiple non-HLA susceptibility genes. In particular, the IL12B region seems to have a central role in TAK onset and its progression. Whether TAK and giant cell arteritis (GCA), the other vasculitis affecting large arteries, are the same disease is an interesting question to address in spite of different clinical manifestations between the two diseases. GCA is associated with HLA-DR4, which is not associated with TAK. GCA is not associated with HLA-Bw52. These two diseases seem not to share non-HLA susceptibility loci based on the recent genetic studies.
Journal of Human Genetics advance online publication, 16 July 2015; doi:10.1038/jhg.2015.87

A Large-Scale Genetic Analysis Reveals a Strong Contribution of the HLA Class II Region to Giant Cell Arteritis Susceptibility

F. David Carmona,[1,54,*] Sarah L. Mackie,[2,54] Jose-Ezequiel Martín,[1,54] John C. Taylor,[3] Augusto Vaglio,[4] Stephen Eyre,[5] Lara Bossini-Castillo,[1] Santos Castañeda,[6] María C. Cid,[7] José Hernández-Rodríguez,[7] Sergio Prieto-González,[7] Roser Solans,[8] Marc Ramentol-Sintas,[8] M. Francisca González-Escribano,[9] Lourdes Ortiz-Fernández,[9] Inmaculada C. Morado,[10] Javier Narváez,[11] José A. Miranda-Filloy,[12] Spanish GCA Group, Lorenzo Beretta,[13] Claudio Lunardi,[14] Marco A. Cimmino,[15] Davide Gianfreda,[16] Daniele Santilli,[17] Giuseppe A. Ramirez,[18] Alessandra Soriano,[19] Francesco Muratore,[20] Giulia Pazzola,[20] Olga Addimanda,[20] Cisca Wijmenga,[21] Torsten Witte,[22] Jan H. Schirmer,[23] Frank Moosig,[23] Verena Schönau,[24] Andre Franke,[25] Øyvind Palm,[26] Øyvind Molberg,[26] Andreas P. Diamantopoulos,[27] Simon Carette,[28] David Cuthbertson,[29] Lindsy J. Forbess,[30] Gary S. Hoffman,[31] Nader A. Khalidi,[32] Curry L. Koening,[33] Carol A. Langford,[31] Carol A. McAlear,[34] Larry Moreland,[35] Paul A. Monach,[36] Christian Pagnoux,[28] Philip Seo,[37] Robert Spiera,[38] Antoine G. Sreih,[34] Kenneth J. Warrington,[39] Steven R. Ytterberg,[39] Peter K. Gregersen,[40] Colin T. Pease,[41] Andrew Gough,[42] Michael Green,[43] Lesley Hordon,[44] Stephen Jarrett,[45] Richard Watts,[46] Sarah Levy,[47] Yusuf Patel,[48] Sanjeet Kamath,[49] Bhaskar Dasgupta,[50] Jane Worthington,[5] Bobby P.C. Koeleman,[51] Paul I.W. de Bakker,[51,52] Jennifer H. Barrett,[3] Carlo Salvarani,[20] Peter A. Merkel,[34] Miguel A. González-Gay,[53,55] Ann W. Morgan,[3,55] and Javier Martín[1,55]

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[54]These authors contributed equally to this work
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http://dx.doi.org/10.1016/j.ajhg.2015.02.009.

Time to 1st and 2nd Relapse

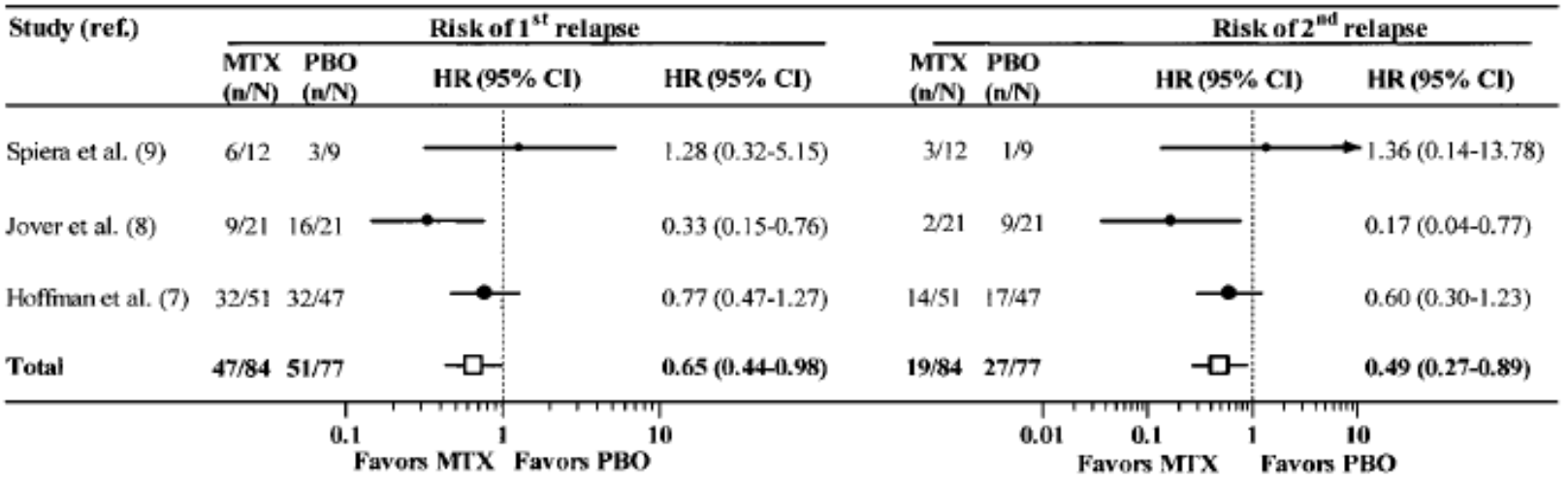
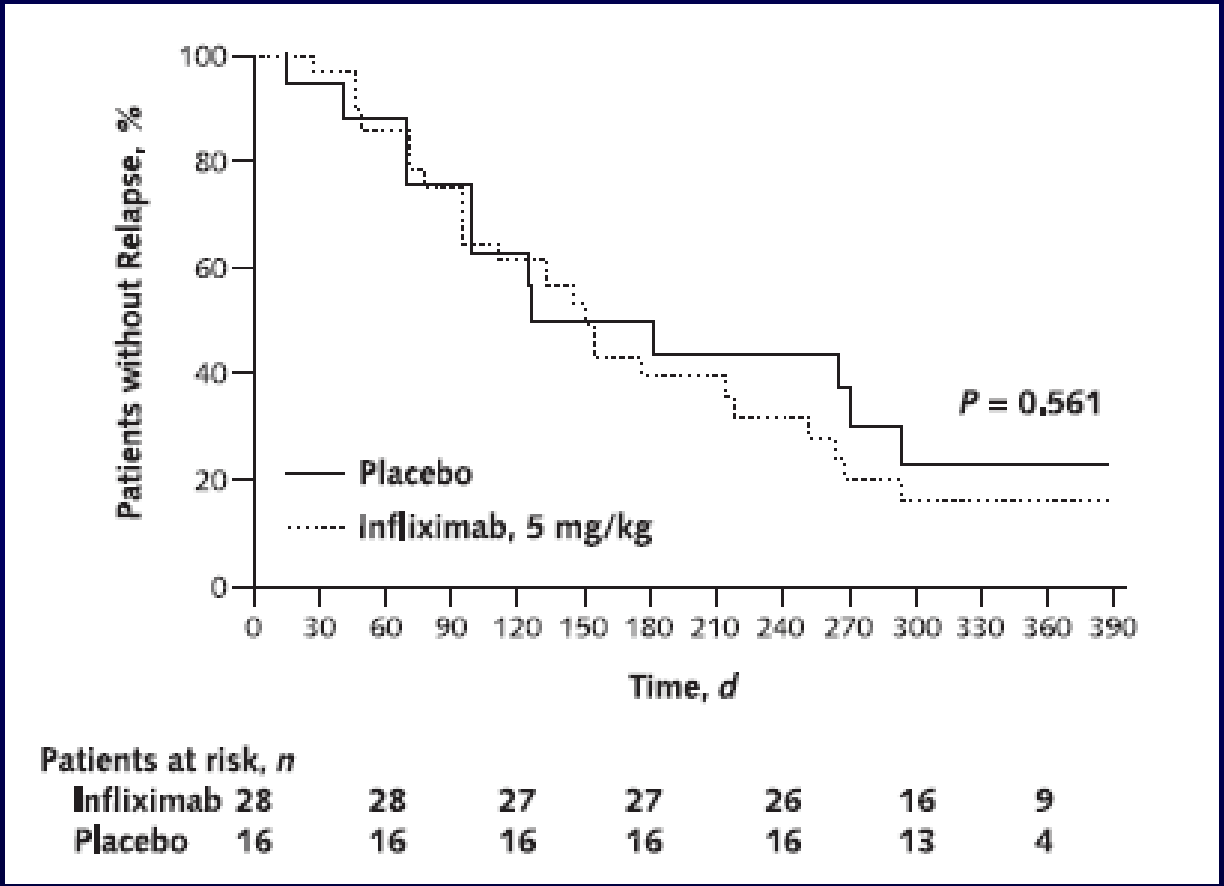


Figure 1. Hazard ratios (HRs) for the occurrence of a first or second relapse of giant cell arteritis in patients receiving adjunctive methotrexate (MTX) versus those receiving placebo (PBO). Values under each treatment group are the number of events (n) among the total number of subjects exposed (N). 95% CI = 95% confidence interval.

Mahr et al Arthritis Rheum. 2007 Aug;56(8):2789-97

ANTI-TNF: infliximab



Hoffman et al. Ann Intern Med 2007

Etanercept and GCA

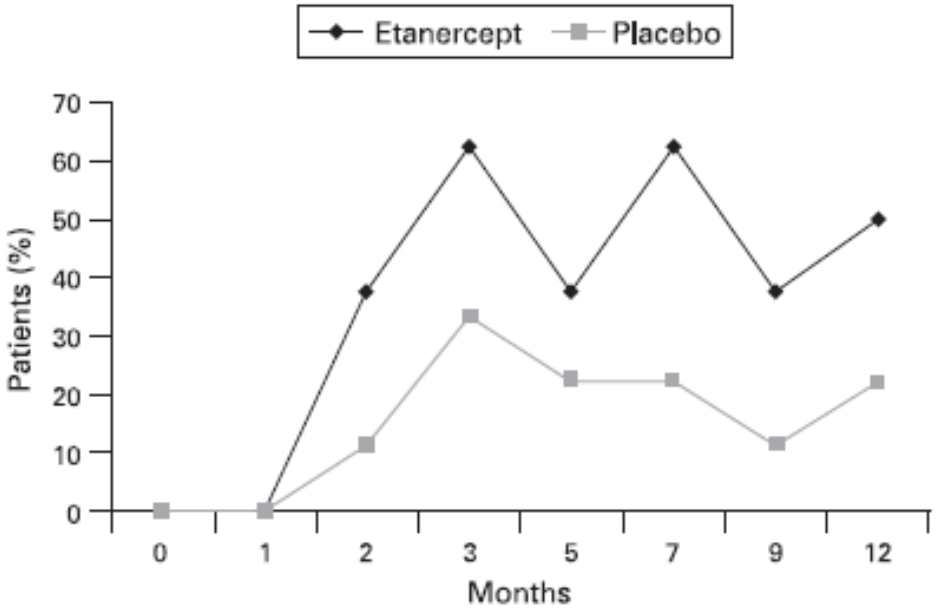


Figure 2 Patients with giant cell arteritis (GCA) without corticosteroid therapy during phase I of the study. At the end of the 12 months of the double-blind phase of the study, 50% of the patients in the etanercept group compared to 22.2% in the placebo group were able to control disease activity without corticosteroid treatment (p value not significant).

Martínez-Taboada et al. Ann Rheum Dis. 2008 May;67(5):625-30

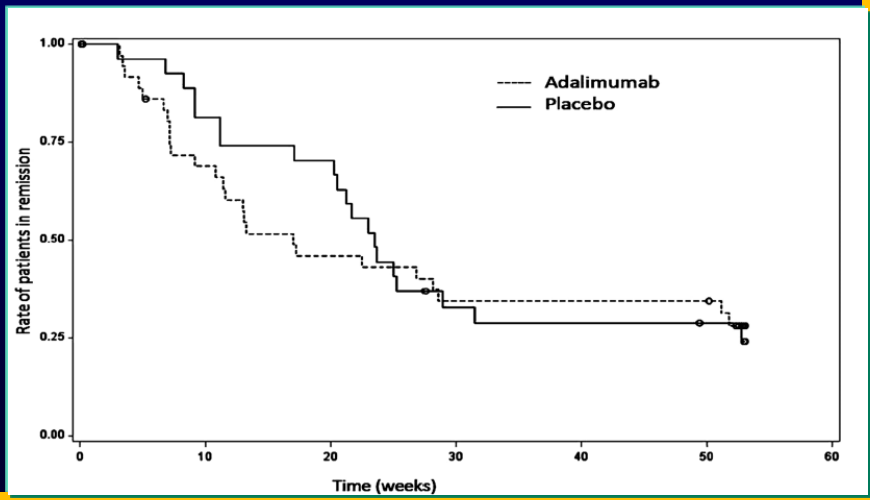
RCT of adalimumab for GCA

- CS 0.7 mg/kg/d + ADA (SQ, W0, 2, 4, 6, 8, 10) or placebo (dble blind)
- Primary EP = % of patients with PDN <0.1 mg/kg/d at W26

- *aimed to enroll 100 (started in 2006)*
- 34 ADA, 36 Placebo (74 yrs, CRP 16-85, ESR 45-100, Hb 10.7-12.7)
-
- Primary EP achieved in 50.0% ADA vs. 58.9% Placebo (NS)

- SAEs 14.7% ADA vs. 47.2% Placebo

- Dose of PDN similar in both arms

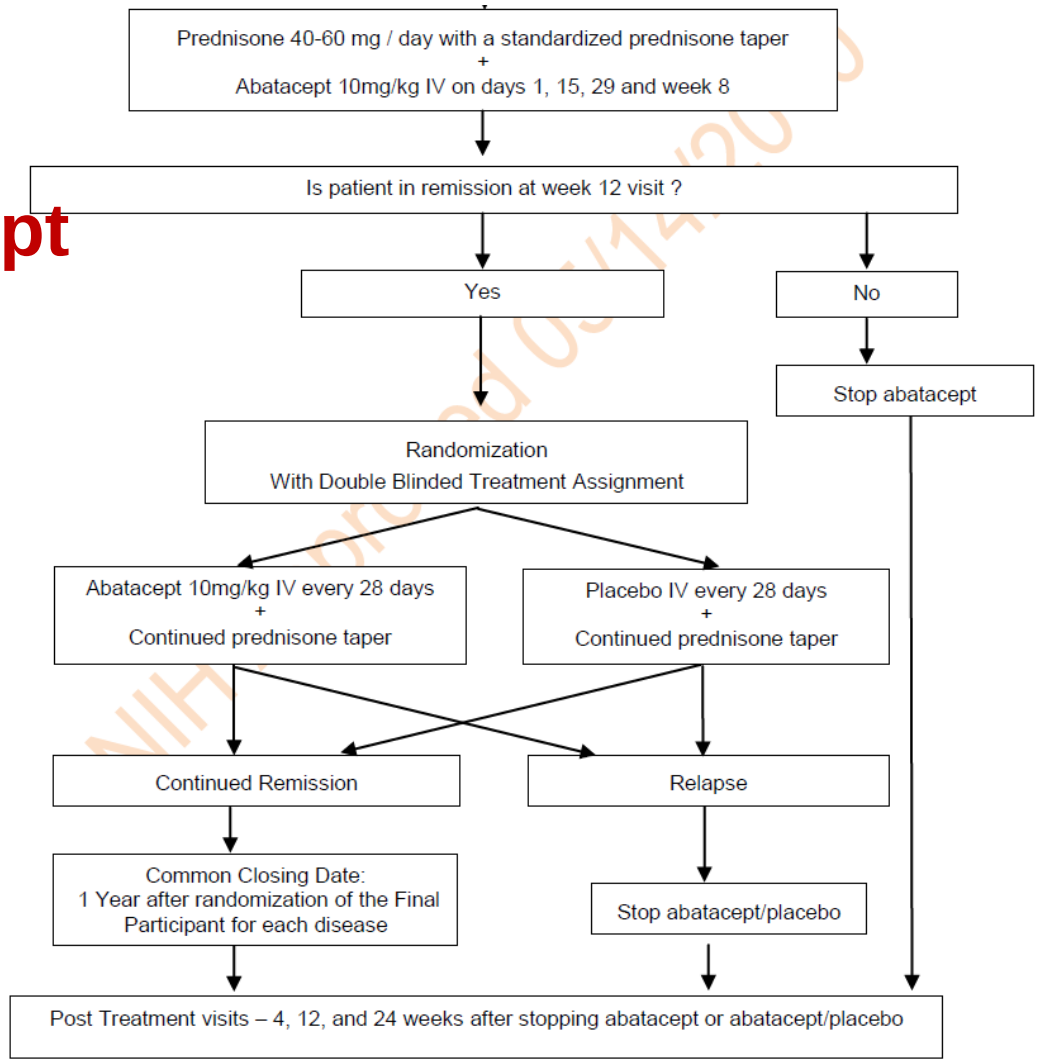


Seror et al. Ann Rheum Dis. 2013 Jul 29. Epub

AGATA LVV

- VCRC 5523
- CTLA4-Ig / abatacept

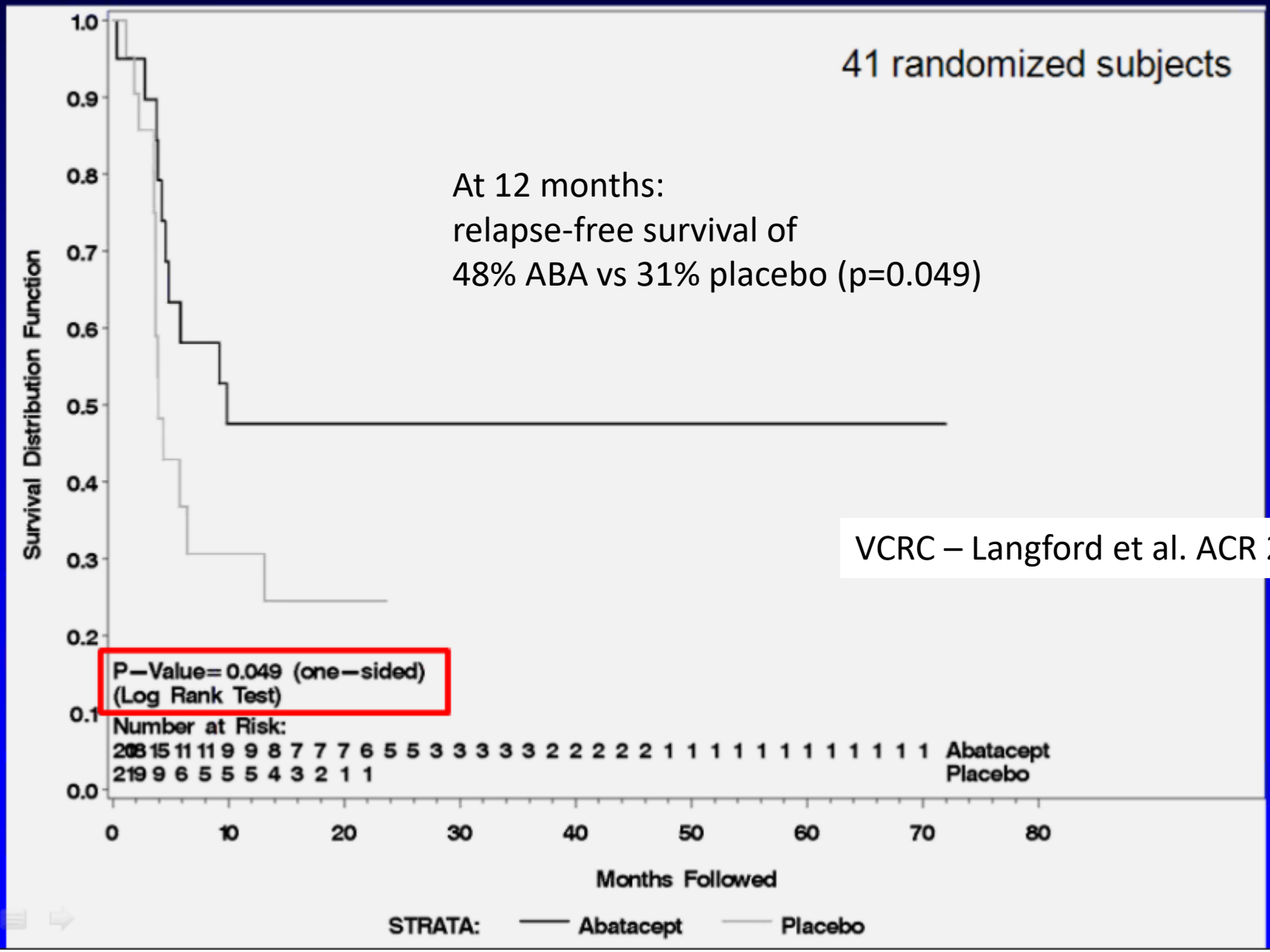
- 15 Hamilton
- 11 Toronto



VCRC – Langford et al. ACR 2015

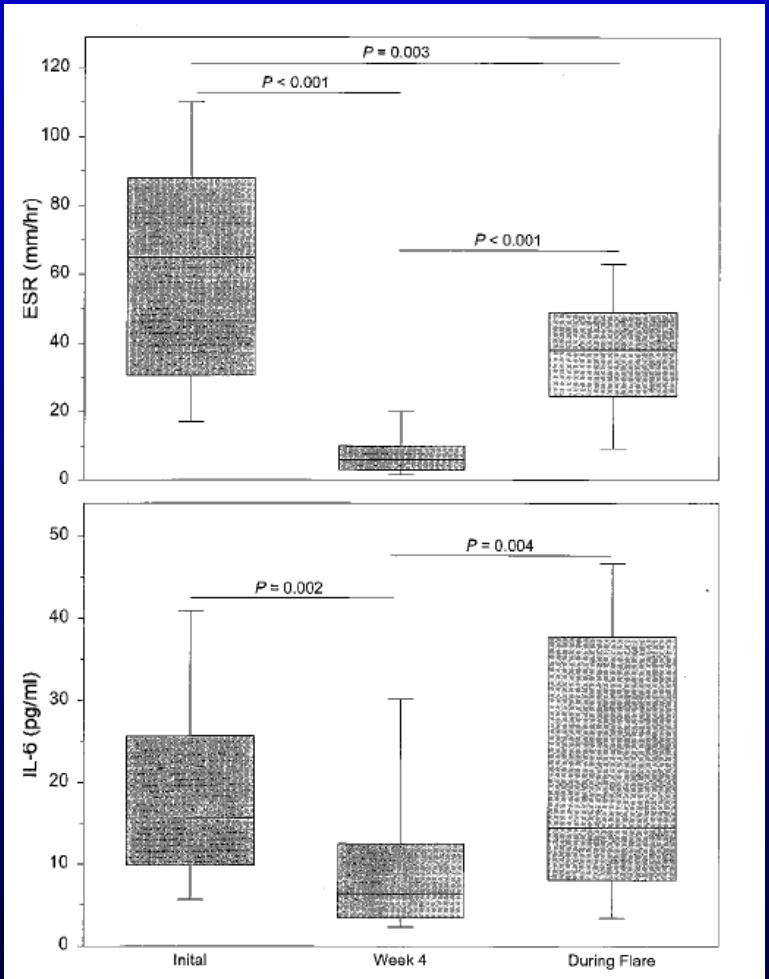
Abatacept in Giant Cell Arteritis

Primary Endpoint - Intent-to-Treat - Kaplan-Meier Plot



VCRC – Langford et al. ACR 2015

IL6 in GCA



- Increased serum IL-6 (but not TNFα) level in PMR or GCA, in correlation with clinical symptoms… since late 1980s
- Corticosteroids rapidly decrease IL-6 but not totally (Roche et al. 1993, then Weyand et al.)

Dasgupta et al, Br J Rheumatol 1990;29:456-8
García-Martínez et al, Arthritis Care Res 2010;62:835-41
Roche et al, Arthritis Rheum 1993;36:1286-94
Weyand et al, Arthritis Rheum 2000;43:1041-8

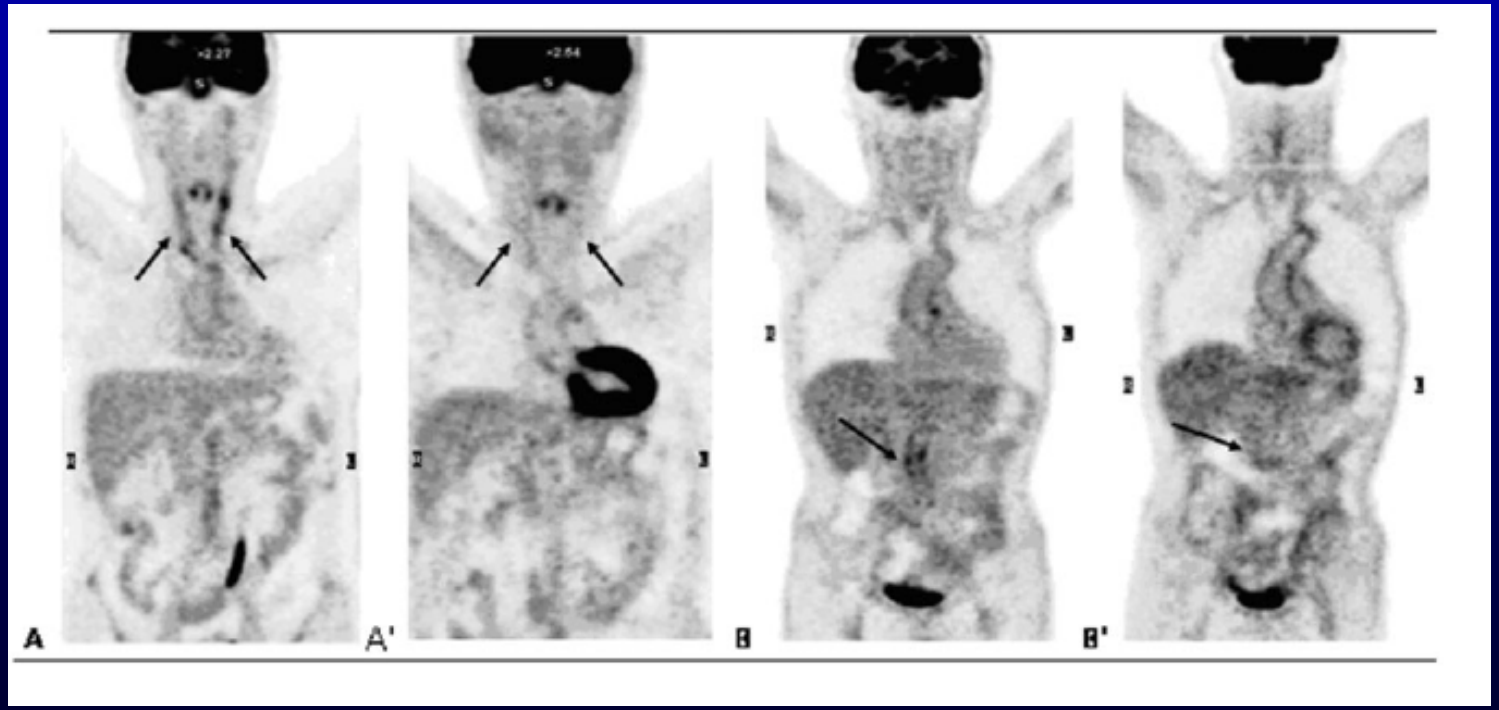
Tocilizumab and GCA–TA
IL6 Receptor inhibitor

- **Sietz et al, 2011**
  - 5 GCA (+ 2TA)
  - 8 mg/kg/week for 1 month, then monthly (2 without CS!)
  - At month 8, all in remission
    - 3 still under TCZ, but no CS
    - 2 stopped TCZ after 7 months, with no immediate relapse

Sietz et al, Swiss Med Wkly 2011;141:w13156

Tocilizumab for LVV

- 8 mg/kg/month for 6 months
- 2 GCA (+ 2 TAK)
- Effective in both on ESR, CRP, Kerr and/or ITAN scores
- 1/2 relapsed 7 months after cessation of TCZ



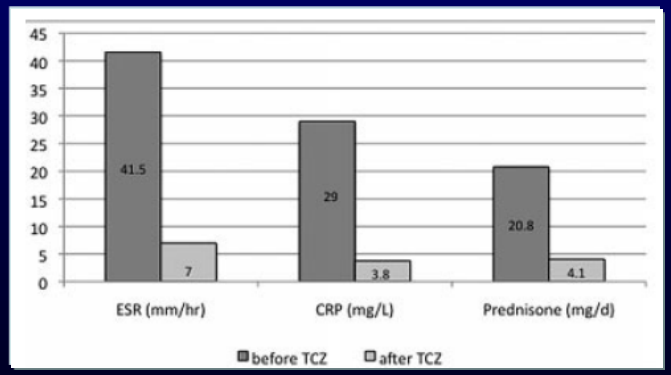
Salvarani et al. Rheumatology (Oxford). 2012;51(1):151-6

Tocilizumab for LVV

- **GCA (7),** TA (2), and PMR (1)
- TCZ for a mean of 7.8 months (range 4–12 months)

- 2.4 flares/year before → **All entered remission during therapy**
- PDN 20.8 mg/day (7–34.3) → 4.1 mg/day (0–10.7)
- AE: mild neutropenia (4) and transaminitis (4)

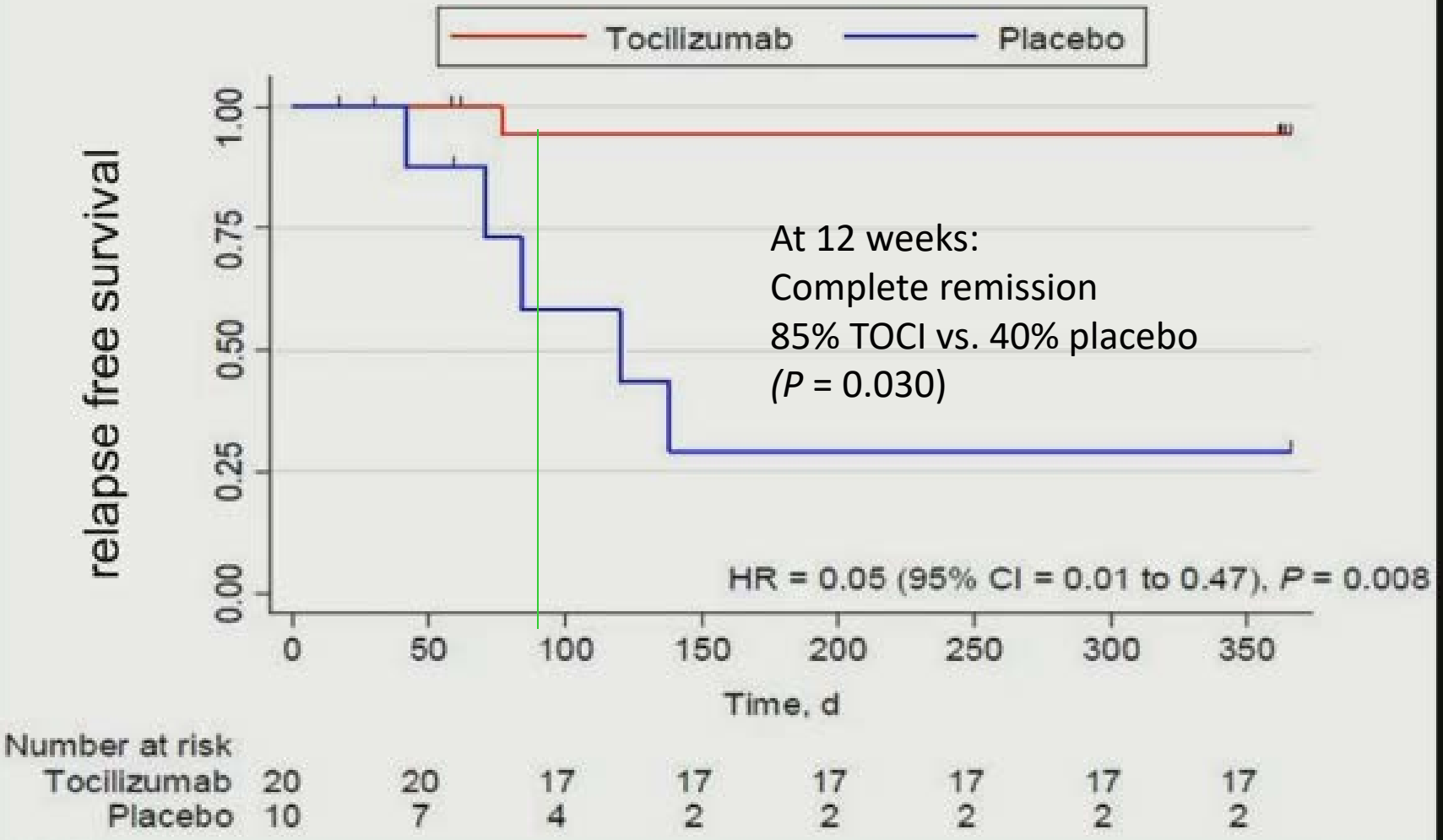
- 1 flared 2 months after TCZ discontinuation
- 1 died from a postop MI (elective surgery) → persistent vasculitis of large and medium-sized arteries on autopsy



Unizony et al. Arthritis Rheum. 2012;64(11):1720-9

Time to first Relapse

TCZ (8 mg/kg IV)



Adler et al. ACR 2015

Safety *Serious Adverse Events (SAE)*

	TCZ (n=20)	Placebo (n=10)
SAE	7/20	10/10
characteristics		
cardiovascular	1	3
gastrointestinal	3	1
osteoporotic fracture	0	2
back pain	0	2
glucocorticoid related	1	2
infection	1	0
other	1	0

Adler et al. Lancet 2016

GiACTA Study

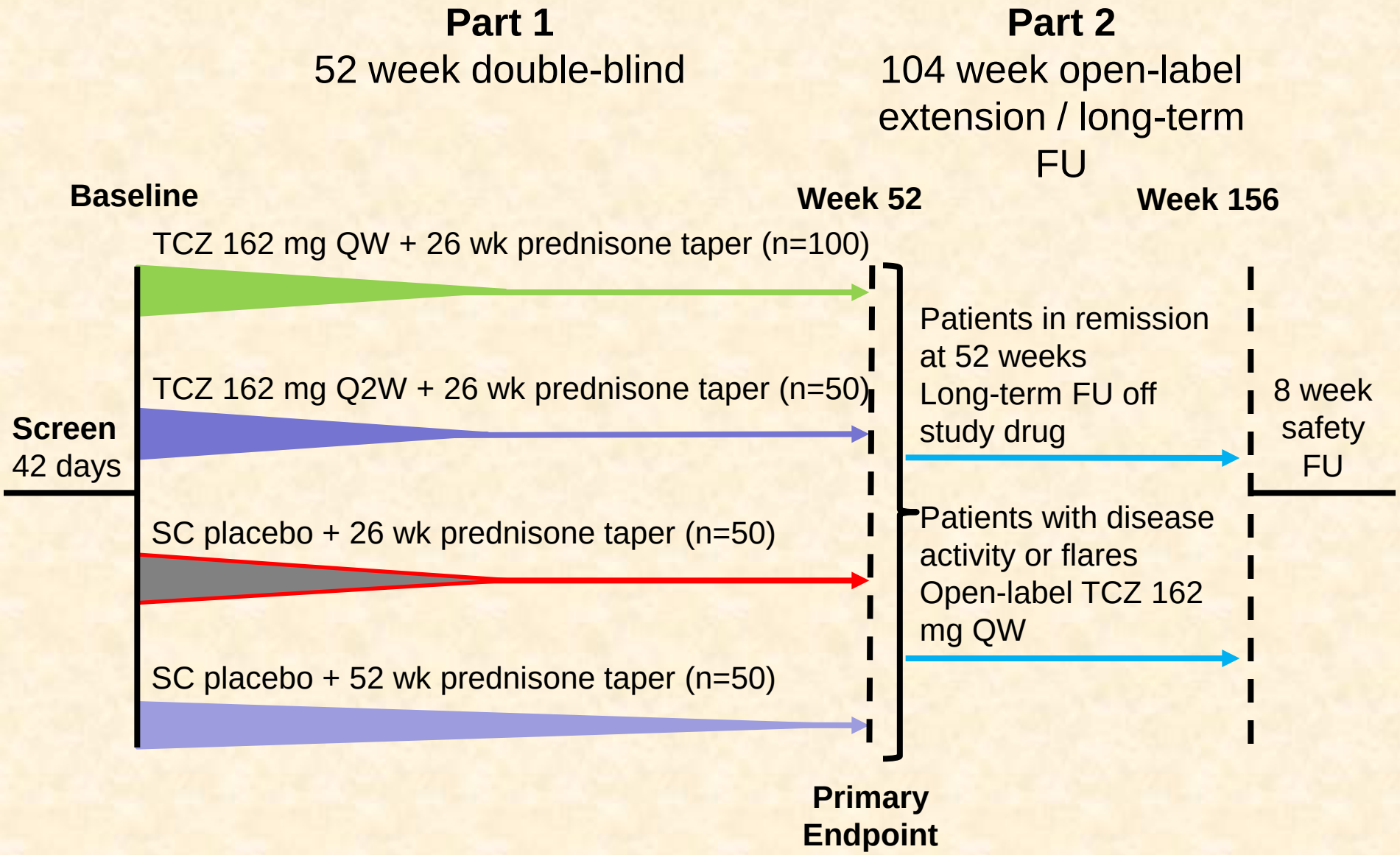
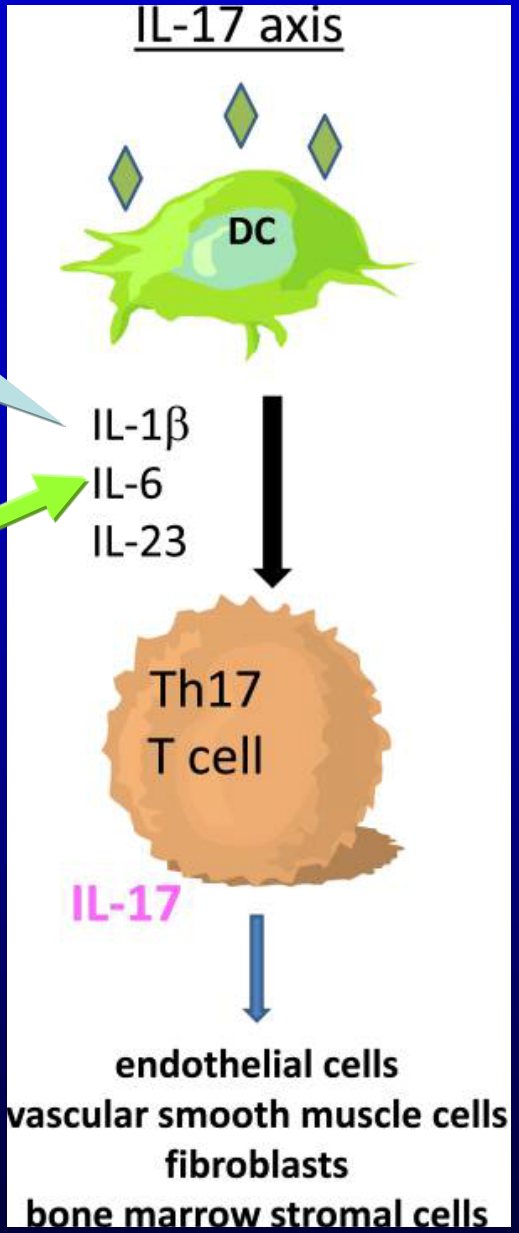


Table. Efficacy and Safety During GiACTA Part 1				
	A) Short-course prednisone n = 50	**B) Long-course prednisone n = 51**	**C) Weekly SC TCZ n = 100**	**D) Every other week SC TCZ n = 49**
Patients in sustained remission at 52 weeks, n (%)	7 (14.0)	9 (17.6)	56 (56.0)	26 (53.1)
TCZ groups vs short-course prednisone Unadjusted difference in proportion of responders (99.5% CI)	—	—	42.0 (18.0, 66.0) $p < 0.0001$	39.1 (12.5, 65.7) $p < 0.0001$
TCZ groups vs long-course prednisone[a] Unadjusted difference in proportion of responders (99.5% CI)	—	—	38.4 (17.9, 58.8) $p < 0.0001$	35.4 (10.4, 60.4) $p = 0.0002$
Cumulative CS dose, median (min-max)	3296.00 932.0-9777.5	3817.50 822.5-10697.5	1862.00 630.0-6602.5	1862.00 295.0-9912.5
AEs Patients with event, n (%)	48 (96.0)	47 (92.2)	98 (98.8)	47 (95.9)
Withdrawals Patients withdrawn from study, n (%)	6 (12.0)	5 (9.8)	15 (15.0)	9 (18.4)
Withdrawals due to an AE, n (%)	2 (4.0)	0	7 (7.0)	3 (6.1)
SAEs Patients with event, n (%)	11 (22.0)	13 (25.5)	15 (15.0)	7 (14.3)
Infection SAEs Patients with event, n (%)	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)

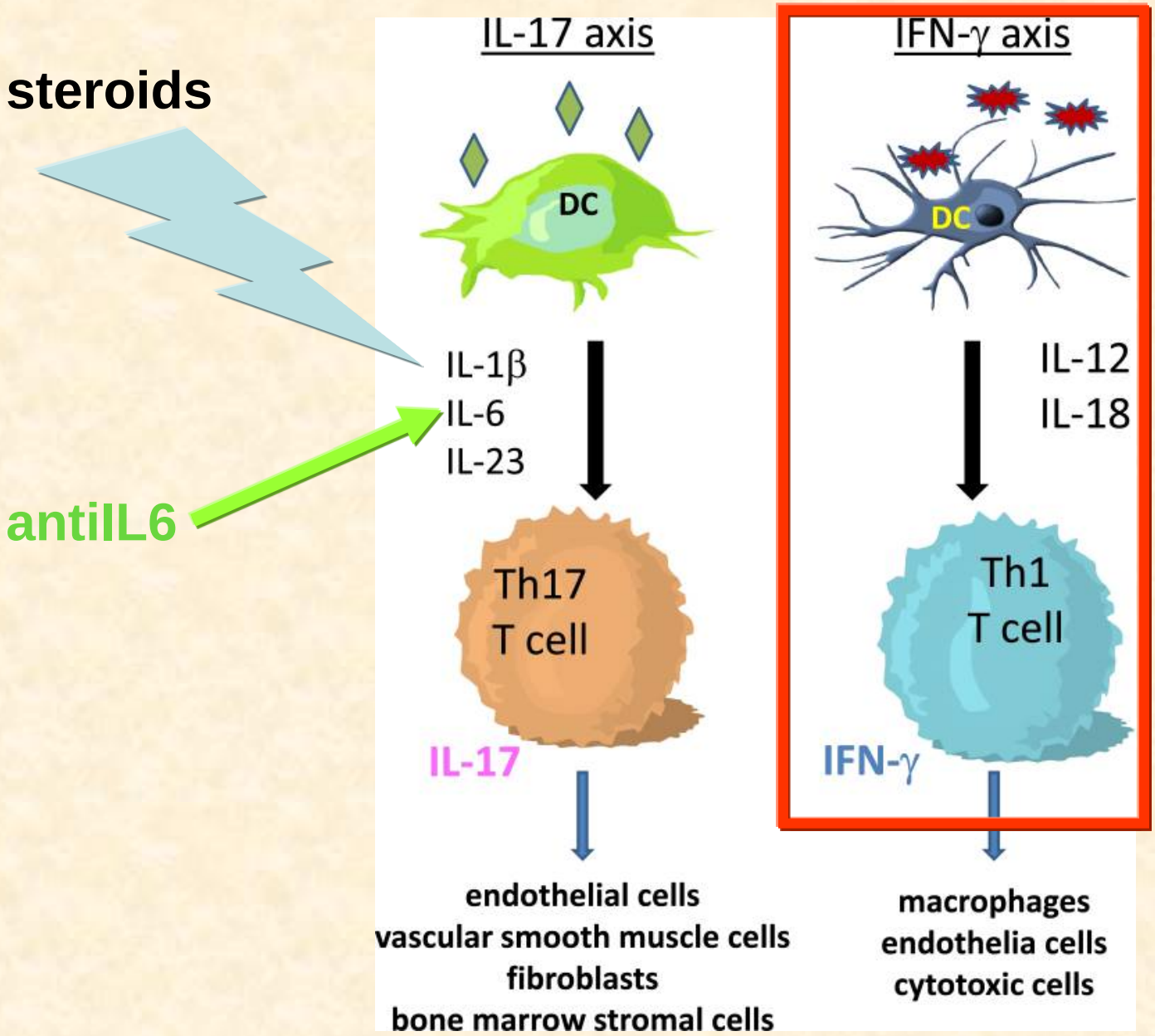
AE, adverse event; CI, confidence interval; SAE, serious adverse event.

steroids

antiIL6



Weyand CM et al. Curr Opin Rheumatol. 2011; 23(1): 43–49



Weyand CM et al. Curr Opin Rheumatol. 2011; 23(1): 43–49

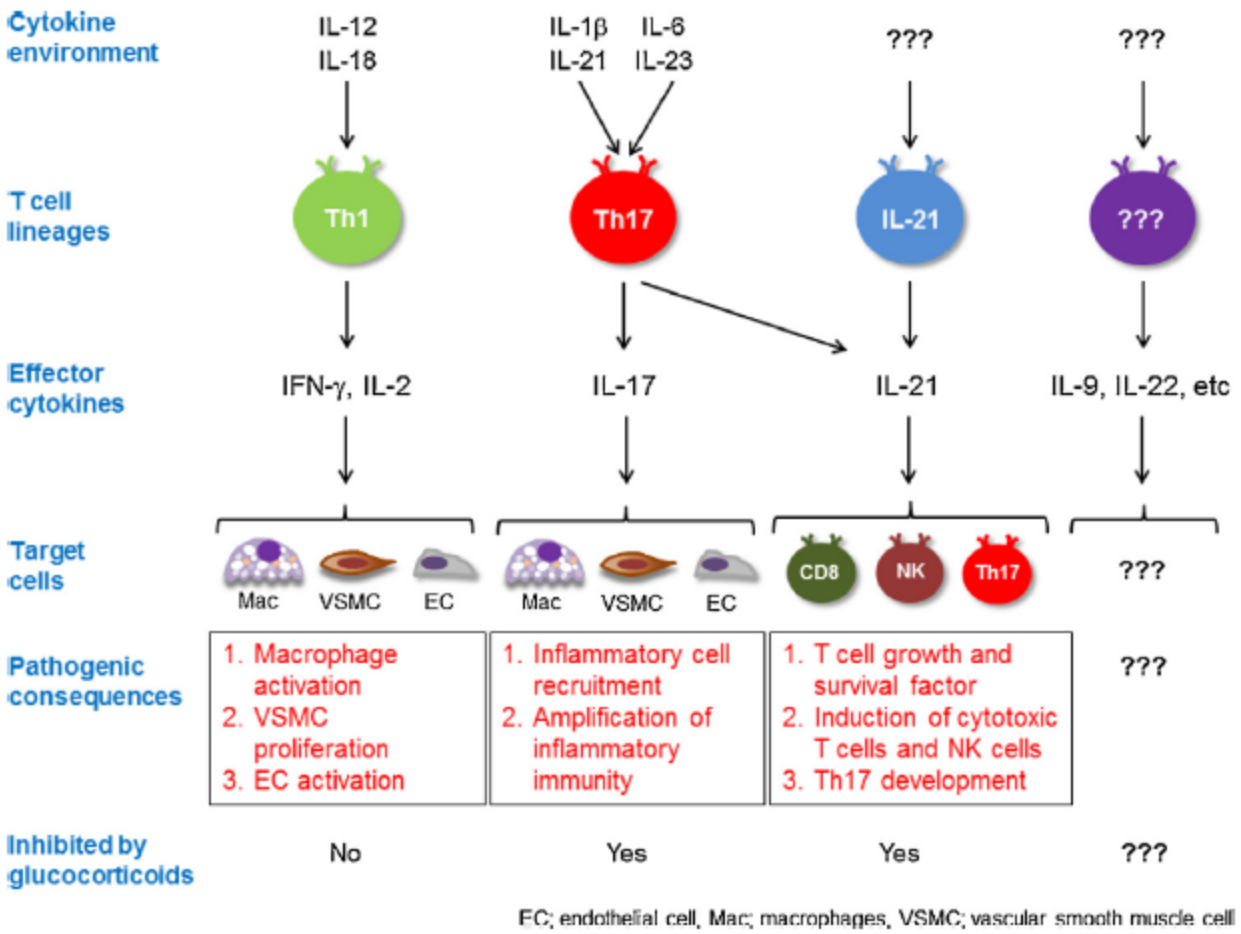
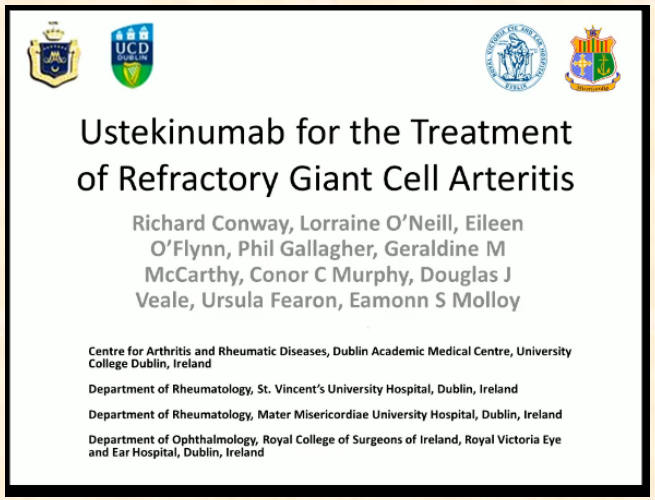


Fig. 2. Pro-inflammatory T cells in GCA. T cells accumulating in the granulomatous infiltrates of GCA are functionally diverse. Based on their cytokine production profile, such lesional T cells are able to interact with selected immune and non-immune target cells and promote distinct pathogenic pathways. The best understood pathways are outlined. Available data suggest that additional T cell dependent pathogenic cascades are operational in the inflamed arterial wall.



Ustekinumab for the Treatment of Refractory Giant Cell Arteritis

Richard Conway, Lorraine O'Neill, Eileen O'Flynn, Phil Gallagher, Geraldine M McCarthy, Conor C Murphy, Douglas J Veale, Ursula Fearon, Eamonn S Molloy

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IL-12/23 monoclonal

Open label study, monocentric
N = 14 with refractory GCA (≥2 relapses)

USTK 90mg SQ D0, M1 then q3months

Median f-up 10.5 months
→ No relapse
→ 4 stopped GC
→ Improvement of wall thickening 7/7

→ 3 stopped / AE
(hair loss, LRTIs, paresthesia)

Conway et al. ARD 2016

ABSTRACT NUMBER: 876

Long Term Efficacy of Ustekinumab for the Treatment of Giant Cell Arteritis

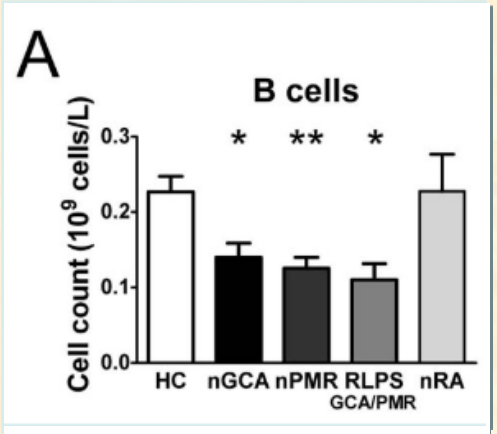
Richard Conway[1], Lorraine O'Neill[2], Phil Gallagher[3], Eileen O'Flynn[4], Geraldine M. McCarthy[5], Conor Murphy[6], Douglas J. Veale[7], Ursula Fearon[8] and Eamonn S. Molloy[9], [1]CARD Newman Research Fellow, University College Dublin, Dublin, Ireland, [2]Rheumatology, St. Vincent's University Hospital, Dublin, Ireland, [3]St. Vincent's University Hospital, Department of Rheumatology, Dublin, Ireland, [4]Rheumatology, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [5]Div of Rheumatology, Mater Misericordiae University Hospital, Dublin, Ireland, [6]Department of Ophthalmology, Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [7]Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin 4, Ireland, [8]Trinity College Dublin, Department of Molecular Rheumatology, Trinity College Dublin, Dublin, Ireland, [9]Rheumatology, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, St Vincent's University Hospital, Dublin, Ireland

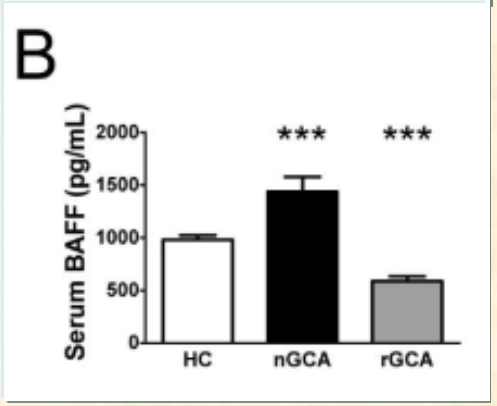
Meeting: 2016 ACR/ARHP Annual Meeting

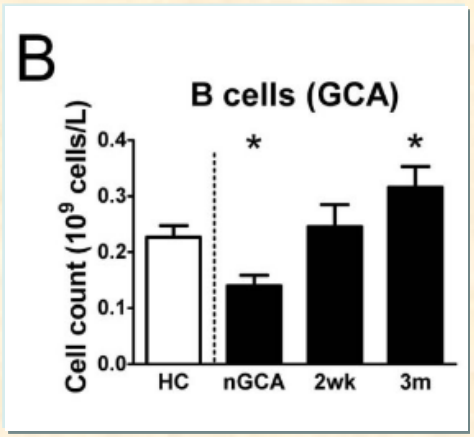
Date of first publication: September 28, 2016

Keywords: Biologic agents, giant cell arteritis and steroids

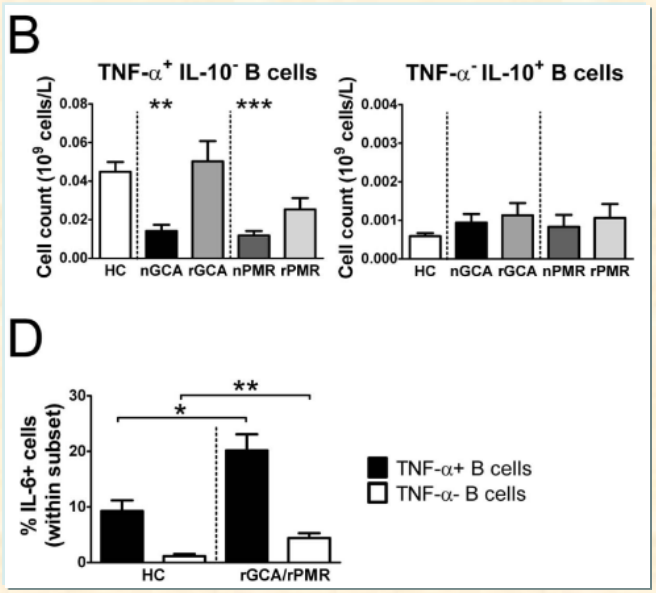
25 patients having failed to taper GC and a median of 1 other IS
Median duration of ustekinumab 15 (6, 22) months
Median GC reduced from 15mg (5, 20) to 5mg (3.8, 10) (p=0.002)
20% stopped GC
7 with LVV had improvement on follow-up imaging
No relapse of GCA during ustekinumab
11 AE (2 RTI, 1 each pancreatitis, Bell palsy, thyroid goitre, alopecia, paresthesia, tinea pedis, UTI, dental abscess, and cold extremities)
3 patients discontinued ustekinumab due to AE, 2 subsequently flared of PMR







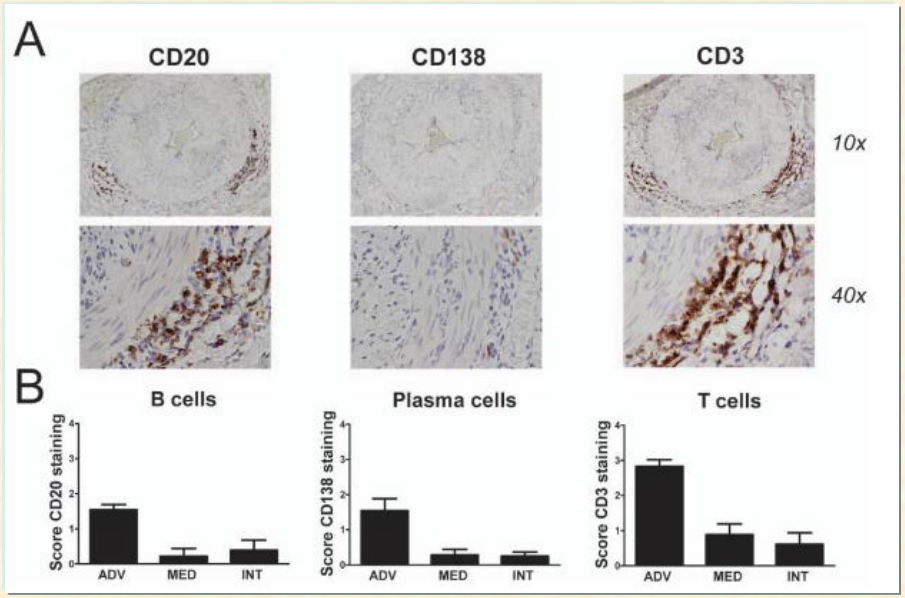
B cell numbers recovers rapidly in treated GCA in remission



- TNF alpha + B eff cells, but not IL-10+ B reg cells are decreased in newly diagnosed GCA
- Following treatment, circulating numbers of B eff cells normalizes and have enhanced production of IL-6

GCA patients have decreased numbers of circulating B cells, inversely correlated with ESR, CRP and serum BAFF levels

Few B cells are in TAB



van der Gees et al. Arthritis Rheum 2014; 6(7):1927–38

Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis

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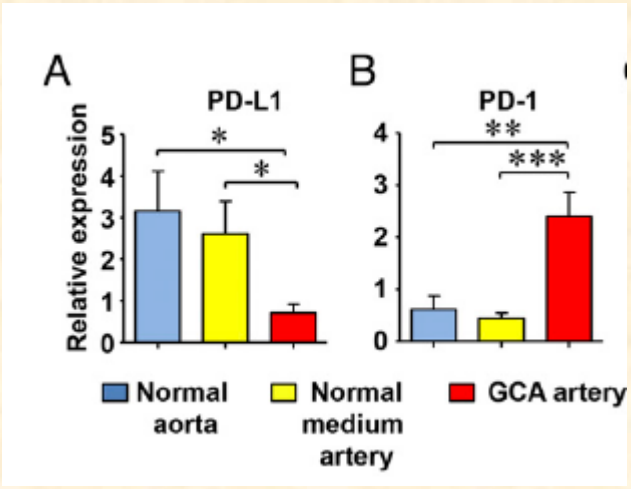
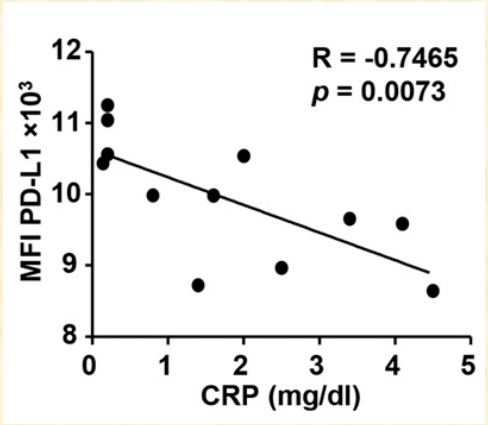
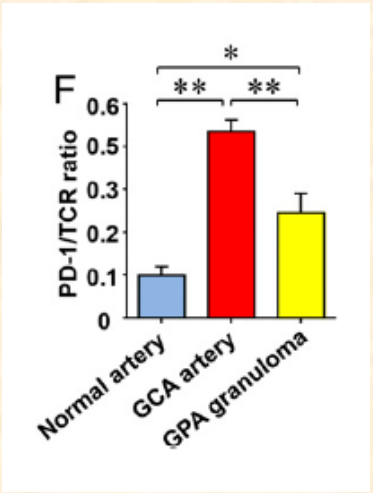
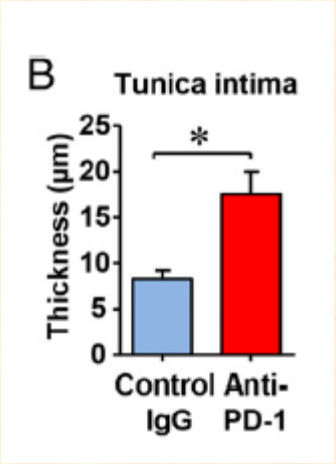








GCA: low expression of the coinhibitory ligand programmed death ligand-1 (PD-L1) concurrent with enrichment of the programmed death-1 (PD-1) receptor.
DC from GCA patients were PD-L1lo, majority of vasculitic T cells are PD-1+
→ inefficiency of the tissue-immunoprotective PD-1/PD-L1 immune checkpoint
In human artery-SCID chimeras, PD-1 blockade exacerbated vascular inflammation, IFN-γ, IL-17, and IL-21, microvascular neoangiogenesis and hyperplasia of intimal layer

Conclusions: more questions than answers…

- Diagnostic challenge
  - TAB and CRP/ESR remain unsatisfactory
  - Place of imaging versus biopsy?
  - C-GCA vs. LV-GCA and need to investigate

BIS: extra-cranial involvement

- Large-vessel GCA
- **Aortic involvement**
  - **aortitis in 3 to 18% of GCA patients**
  - FDG-TEP scanner → **up to 50%**
  - predominant involvement of the **thoracic aorta**
  - at diagnosis 85%, later 15%
  - resolution or improvement under Rx 53% (back to normal 9%)
  - **increased risk of aneurysm**, even **(mainly) after treatment** discontinuation

→ chest X-ray, echocardiogram, abdomen Doppler-US

or → CT scan of the chest and abdomen

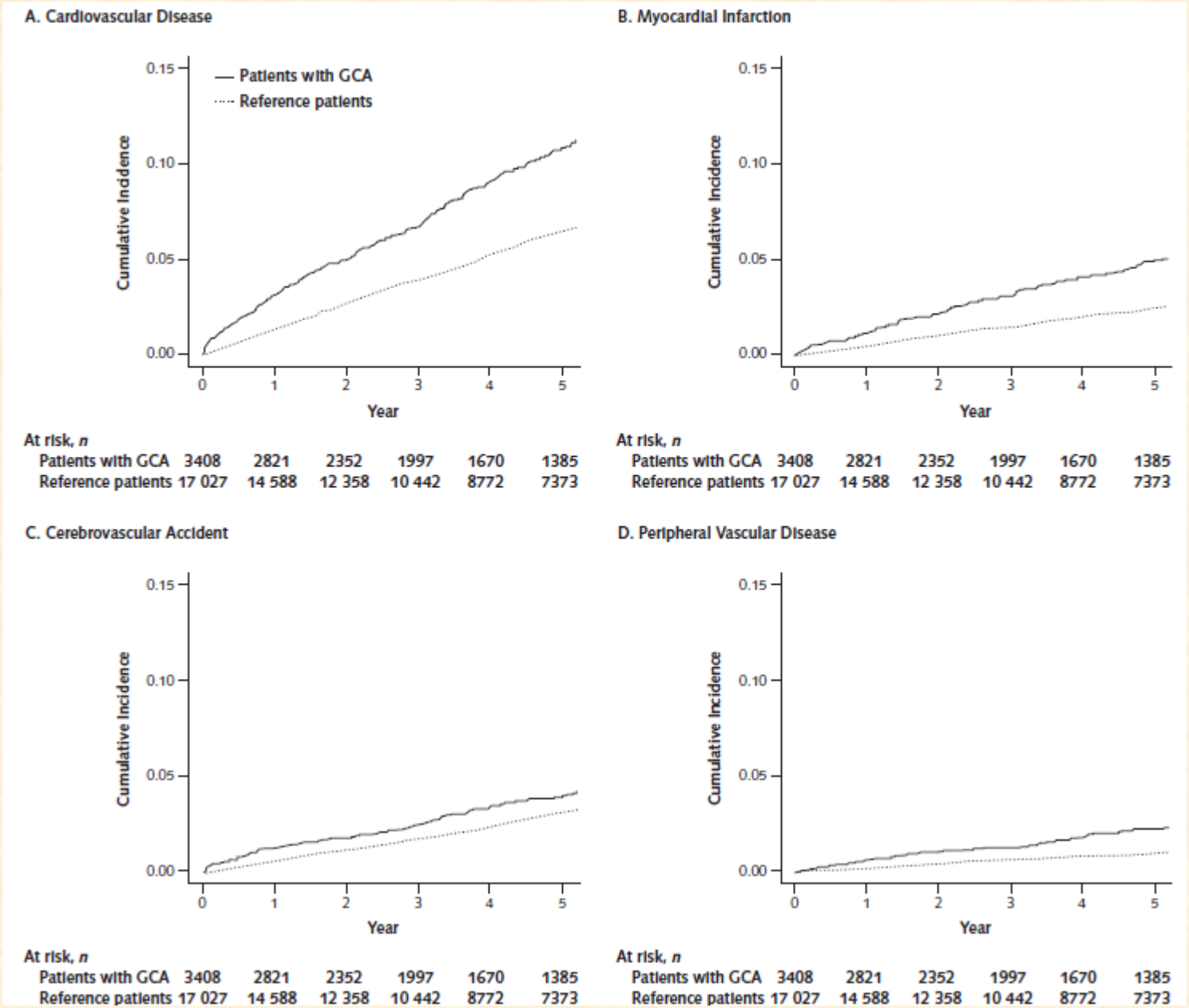
YEARLY??

Marie et al, Medicine (Baltimore) 2009;88:182-92

Conclusions: more questions than answers…

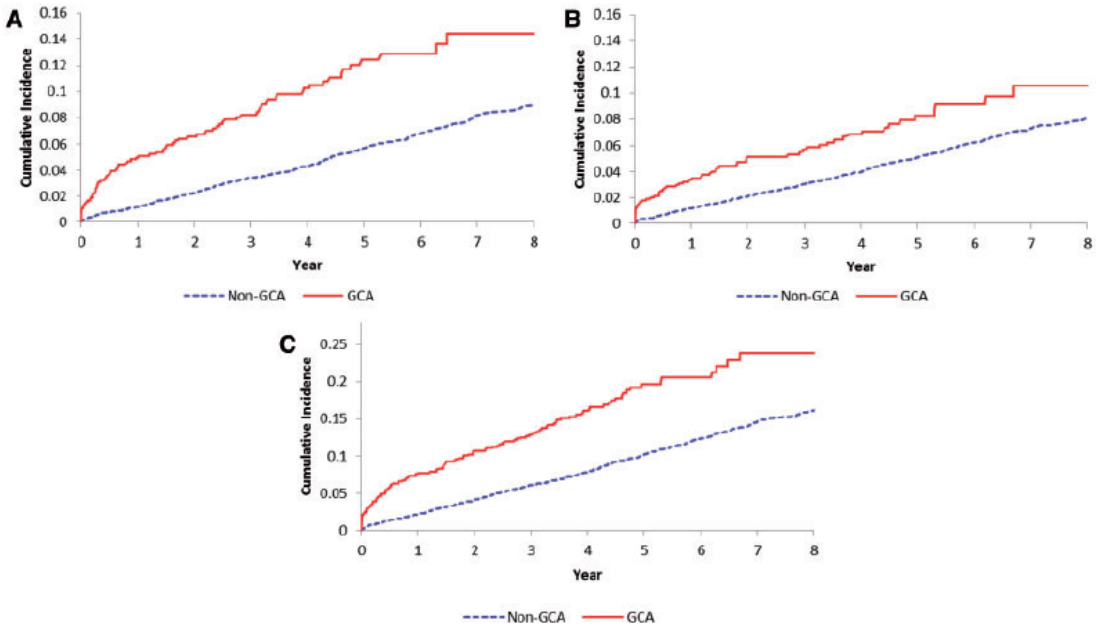
- Diagnostic challenge
  - TAB and CRP/ESR remain unsatisfactory
  - Place of imaging versus biopsy?
  - C-GCA vs. LV-GCA and need to investigate

- Frequent need for additional treatments
  - Need/benefits for ASA/anticoagulants?
  - Optimal duration of treatment?
  - Efficacy / place of biologics?
  - Continuous need for (therapeutic) studies



Tomasson et al, Ann Interne Med 2014;160:73-80.

FIG. 1 Cumulative incidence of cardiovascular disease in GCA



Cumulative incidence for myocardial infarction (**A**), stroke (**B**) and overall cardiovascular disease (**C**) in the cases with incident GCA compared with non-GCA subjects.

Amiri et al, Rheumatology 2016 (UBC database)

Case-matched cohort

TABLE 3 Age- and sex-adjusted Cox HRs for MI, stroke or MI/stroke in GCA according to follow-up period

Time after diagnosis, years	MI HR (95% CI)	Stroke HR (95% CI)	MI/stroke HR (95% CI)
<1	4.76 (3.29, 6.88)	3.20 (2.11, 4.87)	3.92 (2.91, 5.28)
<2	3.56 (2.60, 4.86)	2.93 (2.09, 4.13)	3.17 (2.47, 4.06)
<3	3.14 (2.37, 4.16)	2.38 (1.72, 3.28)	2.71 (2.15, 3.40)
<4	3.16 (2.44, 4.11)	2.30 (1.70, 3.11)	2.70 (2.19, 3.35)
<5	3.11 (2.43, 3.99)	2.36 (1.77, 3.14)	2.73 (2.23, 3.34)
Total follow-up	2.75 (2.16, 3.50)	2.21 (1.68, 2.91)	2.48 (2.04, 3.01)

MI: myocardial infarction; HR: hazard ratio.

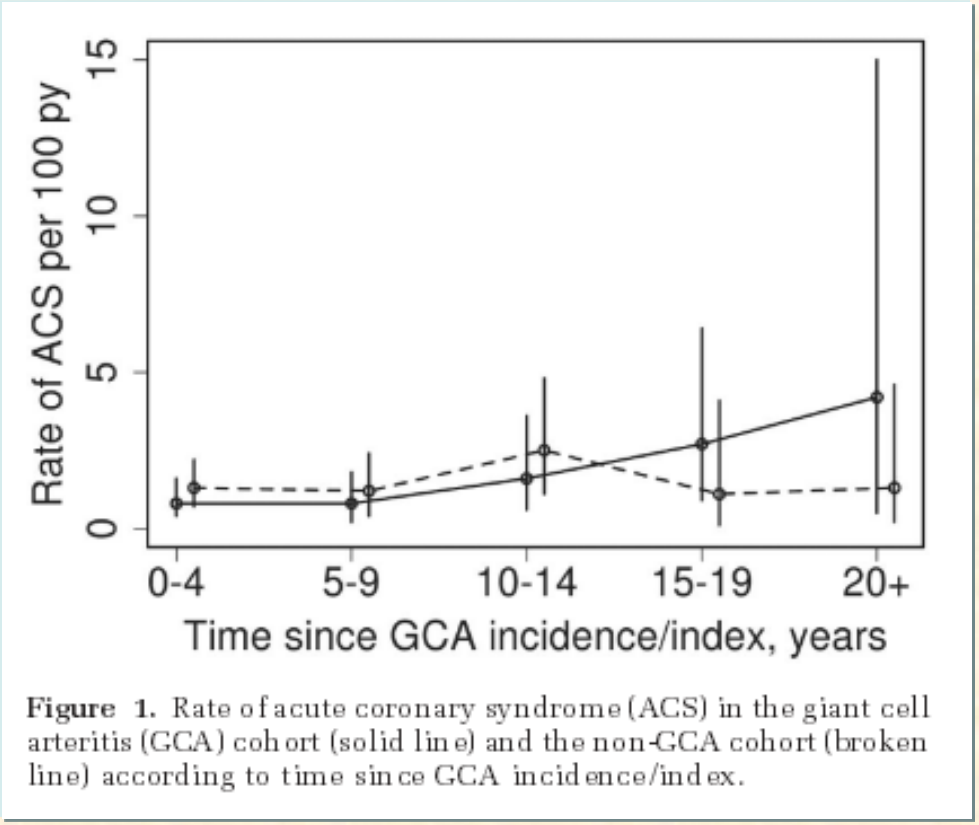


Figure 1. Rate of acute coronary syndrome (ACS) in the giant cell arteritis (GCA) cohort (solid line) and the non-GCA cohort (broken line) according to time since GCA incidence/index.

No difference in another study in ACS

UDAYAKUMAR et al, Arthritis Care & Research Vol. 67, No. 3, March 2015, pp 396–402.

RESEARCH ARTICLE

Venous Thromboembolism and Cerebrovascular Events in Patients with Giant Cell Arteritis: A Population-Based Retrospective Cohort Study

Alberto Lo Gullo[1☯], Matthew J. Koster[2☯*], Cynthia S. Crowson[2,3], Ashima Makol[2], Steven R. Ytterberg[2], Antonino Saitta[1], Carlo Salvarani[5], Eric L. Matteson[2,4], Kenneth J. Warrington[2]

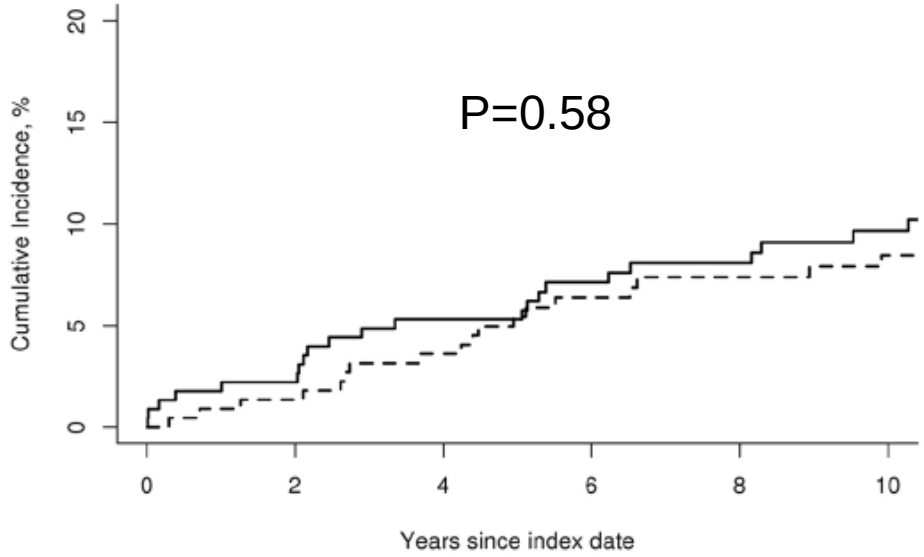


Fig 2. Cumulative incidence of cerebrovascular events. Cumulative incidence (%) of cerebrovascular events in 244 patients with incident GCA in the period 1950–2009 (solid line) compared to 240 subjects without GCA (dashed line).

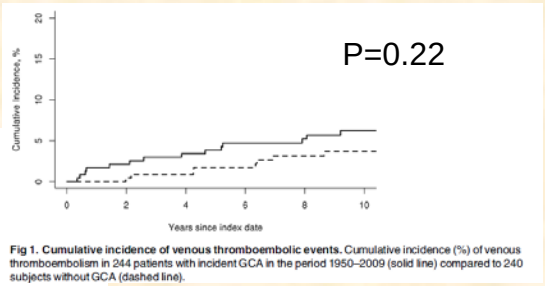


Fig 1. Cumulative incidence of venous thromboembolic events. Cumulative incidence (%) of venous thromboembolism in 244 patients with incident GCA in the period 1950–2009 (solid line) compared to 240 subjects without GCA (dashed line).

PLOS One 2016

Other primary LVV-mimickers

- Infections: TB, syphilis, HIV, bacterial (salmonella etc)
- Other non-LVV vasculitides: ANCA, Behcet, Cogan, RA, relapsing PC, SPA
- Atherosclerosis
- Thromboembolic
- Genetic: Marfan, Loeys-Dietz, Grange
- Congenital: aortic coarctation, Turner, Williams
- Unknown etiology: FMD, segmental arterial mediolysis
- Inflammatory: IgG4 or non-IgG4 related