UNFOLDING NATURE'S ORIGAMI: MEDICAL TREATMENT OF TAKAYASU ARTERITIS AND GIANT CELL ARTERITIS

CanVasc meeting
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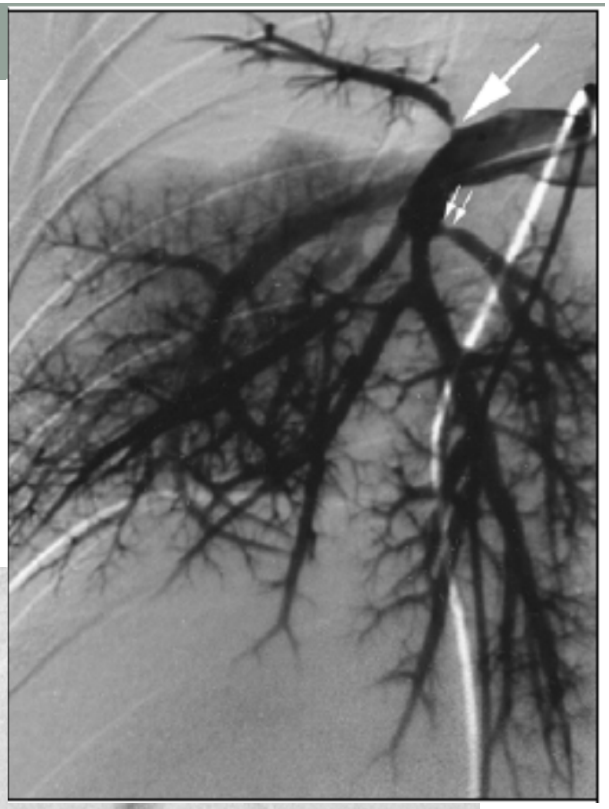
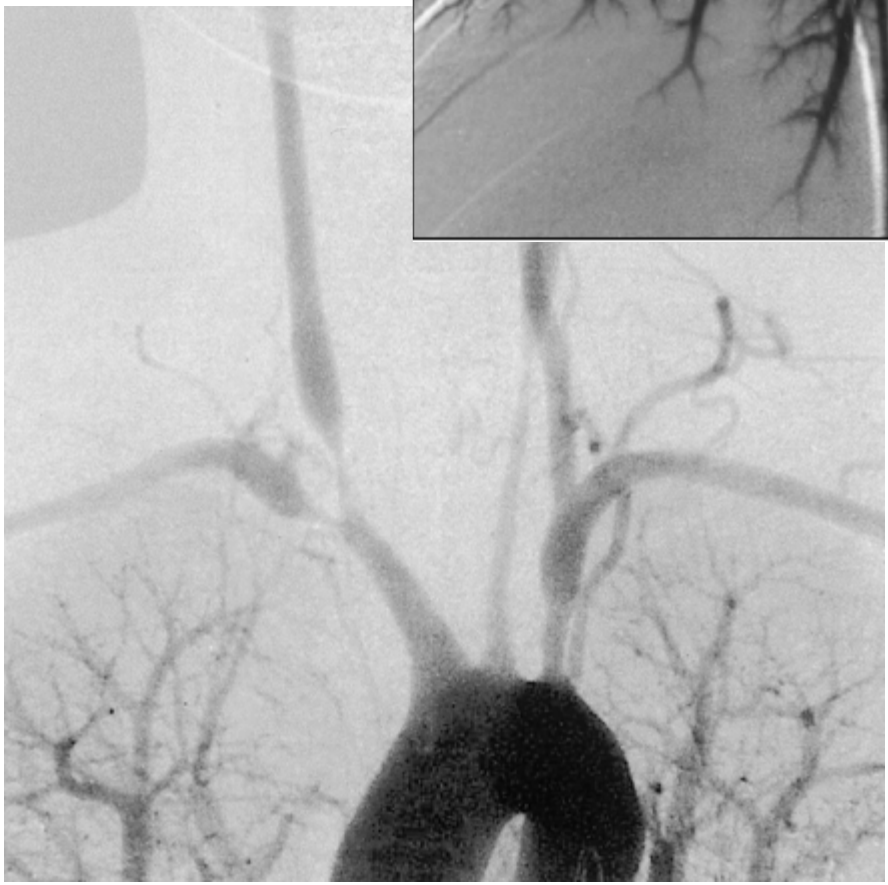
Takayasu arteritis: introduction

- idiopathic, inflammatory
- Granulomatous vasculopathy of the aorta and its main branches. The pulmonary arteries can also be involved in up to 50%
- Stenosis, occlusion, aneurysms





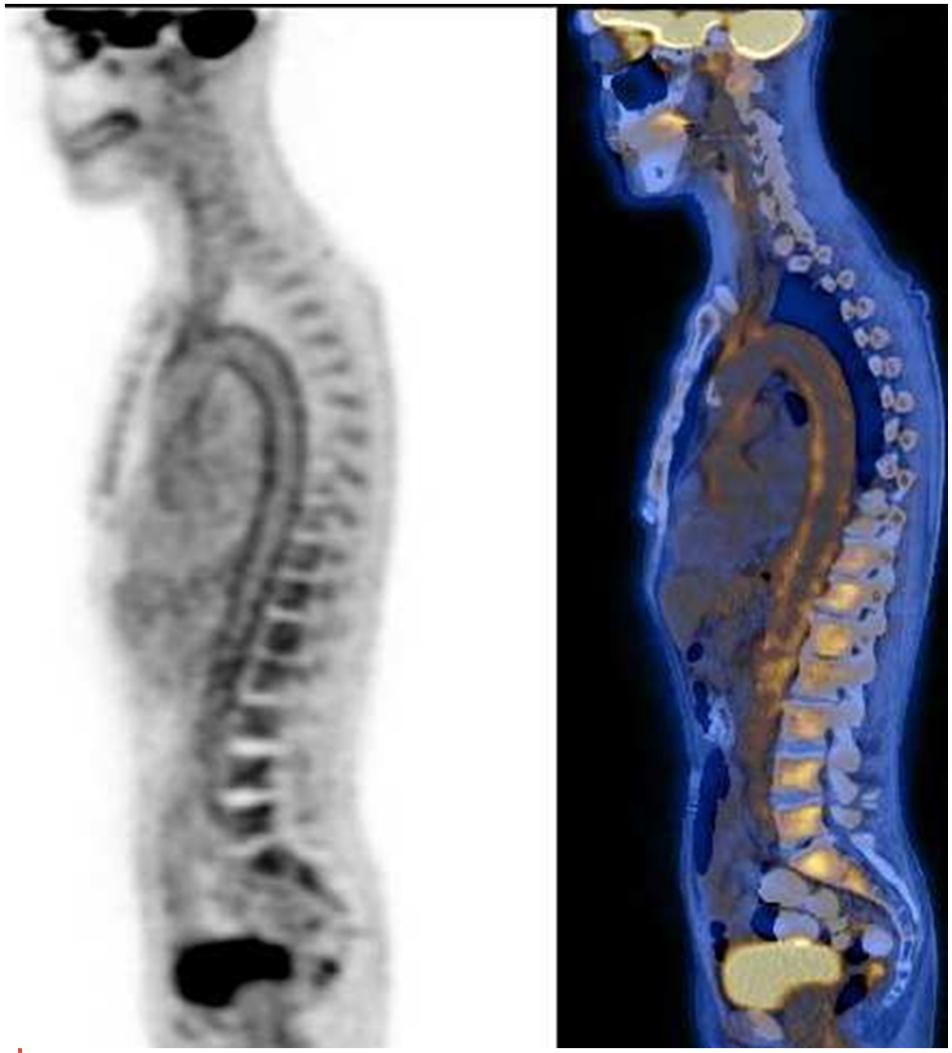
Outcomes:

- Course:
  - Relapsing/remitting or progressive: 80%
  - Monophasic: 20%
  - Implication: disease may not be active at the time of consultation.
- Progressive disease: new lesions, worsening of existing lesions:
  - 33-77%
- Survival:
  - 70-90% at 10 years

Kerr GS, Hallahan CW, Giordano J, et al.: Takayasu arteritis. Ann Intern Med 1994, 120:919–929
Souza Freitas D. Rheumatol Int (2012) 32:703–709
Maksimowicz-McKinnon K. Arthritis Rheum 2007;56:1000–1009
Soto ME. Clin Exp Rheumatology 2008; 26 (suppl 49): S9-S15

When to treat: defining extent and activity

- Systemic symptoms
- Features of vascular insufficiency or inflammation
- Inflammatory markers
- Imaging:
  - Anatomy:
    - MRA, CTA, conventional angiography, ultrasonography
  - ?inflammatory activity:
    - MRA, CTA, PET/CT, ultrasonography

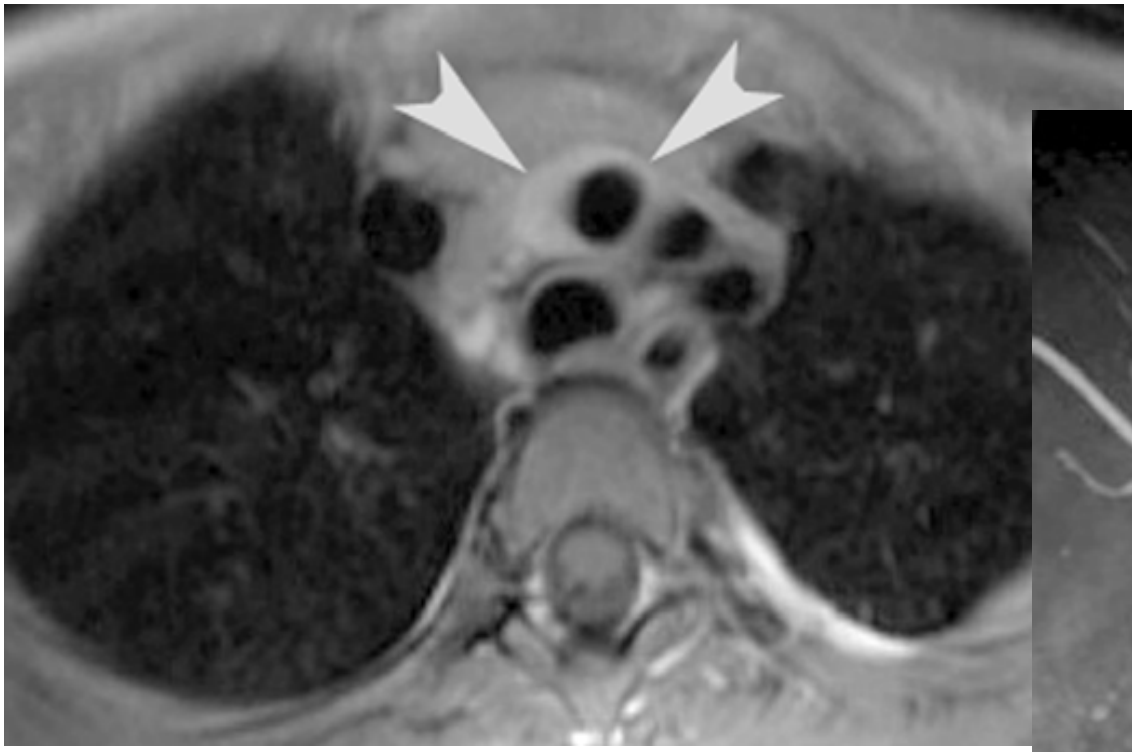


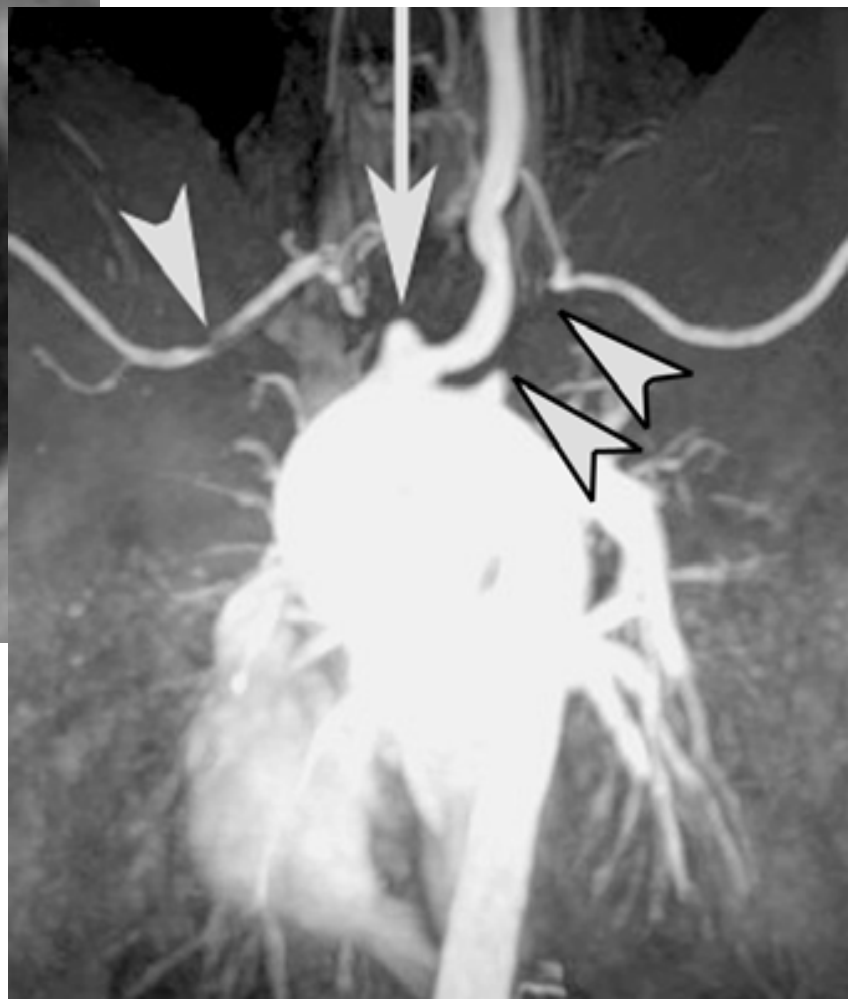
Medical treatment:

- **Corticosteroids**
  - Prednisone 1 mg/kg for 1 month
  - Taper over 1-2 years
  - Improvement/remission: 60%
  - Relapses: 50-80%

Pipitone N. Clin Exp Rheumatology 2012; 30 (suppl 70): S139-S161
JCS Joint Working Group. Circ J 2011; 75: 474 – 503
Mukhtyar C. Ann Rheum Dis 2009;68:318–323
Kerr GS. Takayasu Arteritis. Ann Intern Med 1994;120:919–29.
Souza Freitas D. Rheumatol Int (2012) 32:703–709

Résonance magnétique et angio-IRM





Gotway MB. *AJR 2005;184:1945–1950*

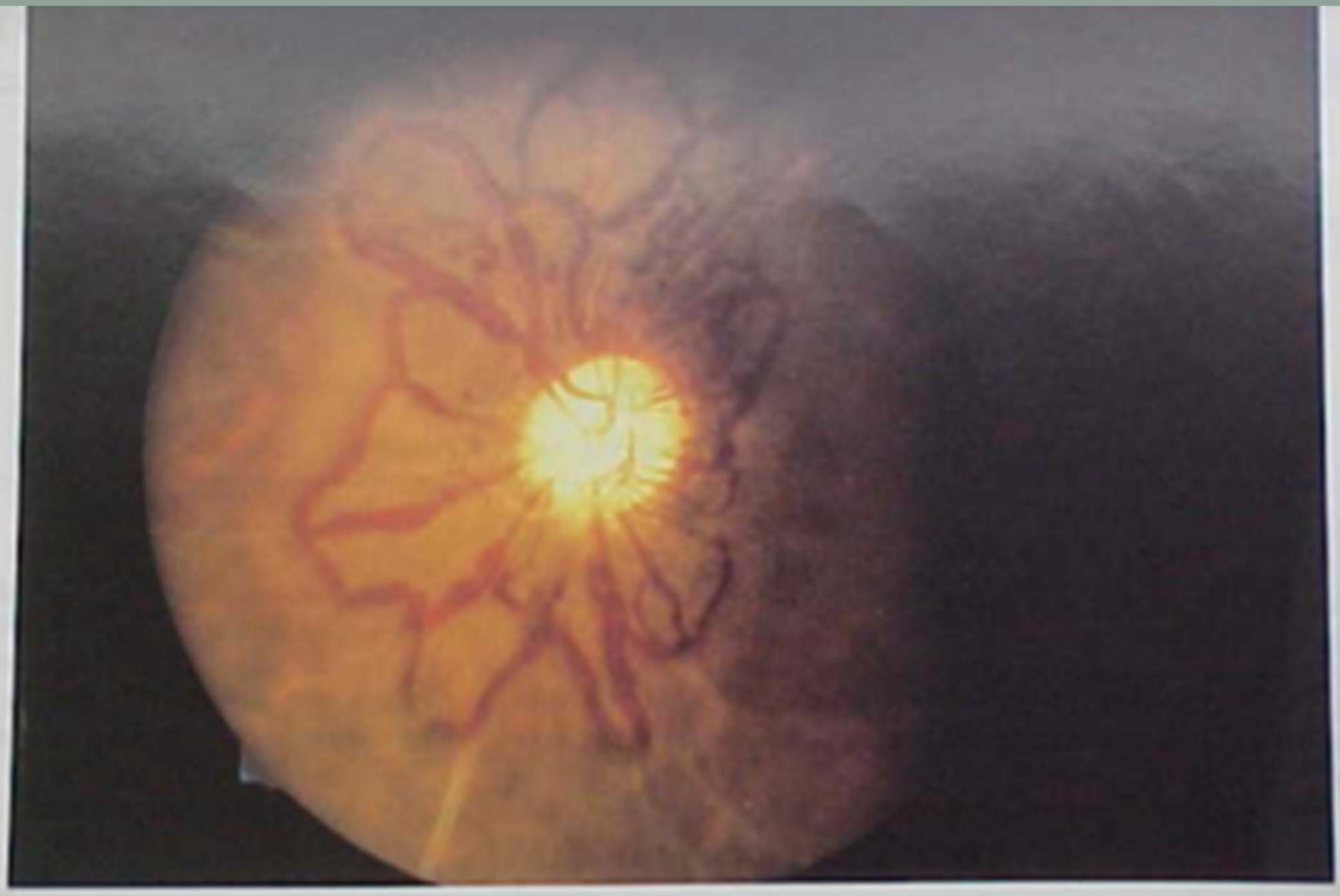


Fig. 1. Coronary anastomosis of the retinal vasculature in Takayasu arteritis.

Medical treatment

- **Methotrexate:**
  - Open label studies or case reports
  - Initial treatment or added in refractory cases
  - Improvement/remission in up to 80%
  - Relapses : ≈ 50-76,7%

Hoffman GS. Arthritis Rheum1994;37:578–82.
Souza Freitas D. Rheumatol Int (2012)
32:703–709

Medical therapy

- **Azathioprine :**
  - steroid sparing (no control group)
  - Valsakumar AK. J Rheumatol 2003, 30:1793–1798.
- **Mycophenolate mofetil:**
  - remission (although not achieved by others)
  - Daina E. Ann Intern Med 1999, 130:422–426.
- **Cyclosporine:**
  - improvement, decrease in prednisone doses
  - Horigome H. Med J Aust 1999, 170:566.
- **Cyclophosphamide:**
  - mixed results, toxicity
  - Kötter I. Clin Exp Rheumatol 2012; 30 (sjppl 70): S114-S129
- **Leflunomide:**
  - case reports describing remission

Biologics in Takayasu arteritis:TNF inhibitors

TABLE 1 Baseline characteristics and infliximab response in 15 patients with TA during a follow-up period of 12 months

Number of evaluable patients	Baseline assessment ($n = 15$)	3-month evaluation ($n = 15$)	6-month evaluation ($n = 13$)	12-month evaluation ($n = 11$)
Clinical response				
Infliximab efficacy (by physician), *n* (%)	–	13 (87)	10 (77)	8 (73)
Disease clinical activity, *n* (%)	11 (73)	3 (20)**	4 (31)*	3 (27)*
Infliximab-associated treatments				
CSs (prednisone), *n* (%)	14 (93)	12 (80)	11 (85)	10 (92)
CSs (prednisone, mg/day)	20 (5–35)	15 (5–20)**	7.5 (5–18)*	6 (2.5–30)*
Steroid dependence, *n* (%)	8 (53)	2 (13)*	0**	1 (9)*
MTX, *n* (%)	7 (46)	8 (53)	6 (46)	7 (64)
MTX, mg/week	15 (7.5–25)	15 (7.5–20)	15 (5–15)	15 (5–20)
AZA, *n* (%)	4 (27)	4 (27)	4 (31)	4 (36)
AZA, mg/day	125 (100–175)	125 (100–175)	100 (100–175)	100 (100–175)
Laboratory data				
Biological activity, *n* (%)	11 (75)	4 (27)*	4 (31)***	4 (42)***
ESR, mm/h	60 (12–100)	15 (6–32)*	10 (4–64)*	8 (2–60)
CRP, mg/l	30 (4–70)	5 (0–57)*	6 (0–50)*	9 (0–100)
Fibrinogen, g/l	5.5 (3–7.5)	3 (1–6.5)*	2.5 (2–6)*	2 (2–4)
Leucocyte count, $10^3/mm^3$	11 (2.4–20)	6 (3.6–15)*	6 (4.2–15) ***	6 (3.8–16)

Values are medians with ranges or frequencies with percentages. Steroid dependence: prednisone $\geqslant 20$ mg/day. Associated treatments were all initiated before infliximab. *$P < 0.05$ *vs* baseline, **$P < 0.005$ *vs* baseline, ***$P = 0.06$.

Mekinian A. Rheumatology 2012;51:882886

Biologics in Takayasu arteritis:TNF inhibitors

Table 1. Effect of TNF inhibitors in difficult-to-treat Takayasu arteritis: comparison of our study with 2 previous studies*

Author, year (ref.)	No. of patients	Type of TNF inhibitor: no.	Remission	Sustained remission	Relapse	New arterial lesion during TNF inhibitor use	CS cessation
Hoffman et al, 2004 (11)	15	Inflix: 8 Etan: 7	14/15 (93)	10/15 (66)		4/14 (28)	10/15 (66)
Molloy et al, 2008 (12)	25	Inflix: 16 Etan: 9	22/25 (88)	15/25 (60)	15/24 (62)	4/24 (16)	15/25 (60)
Present study	20	Inflix: 17 Etan: 1 Ada: 2	18/20 (90)	10/20 (50)	6/18 (33)	0	7/12 (58)

Discontinuation due to adverse event: 20%

* Values are the number/total (percentage) unless otherwise indicated. TNF = tumor necrosis factor; CS = corticosteroids; inflix = infliximab; etan = etanercept; ada = adalimumab.

Schmidt J. Arthritis Care & Research 2012; 64 (7): 1079–1083
Hoffman GS. Arthritis Rheum 2004;50: 2296–304
Molloy ES. Ann Rheum Dis 2008;67:1567–9.

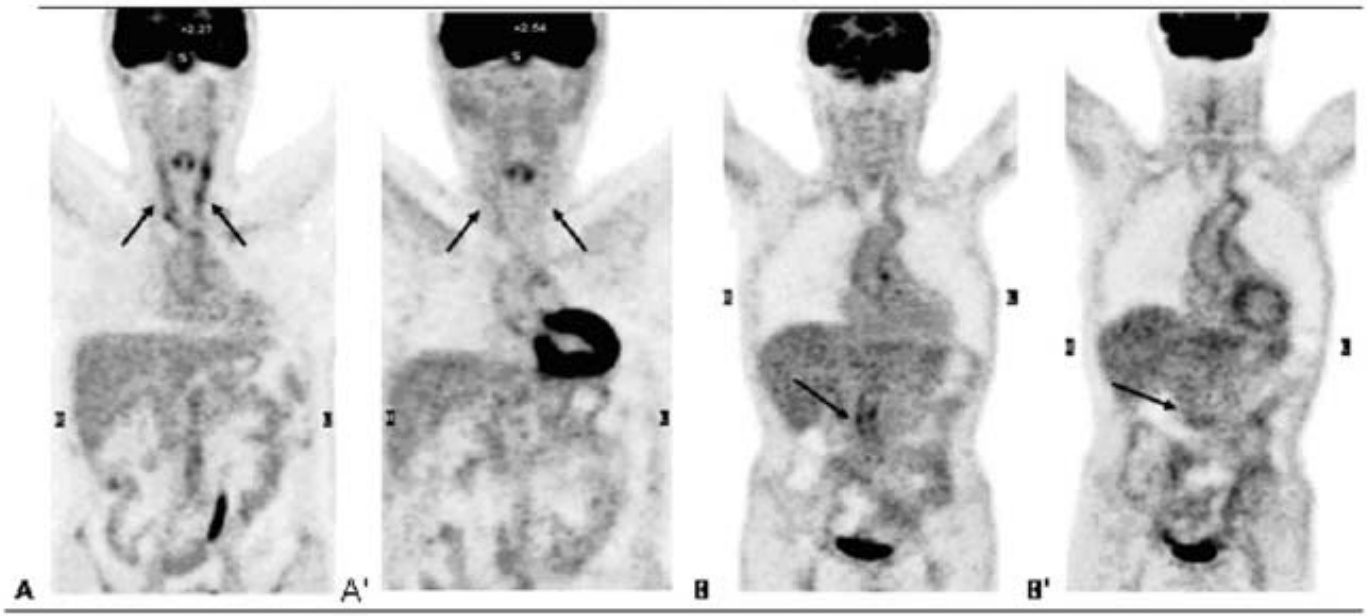
Concise report

Rheumatology 2012;51:151–156

Tocilizumab: a novel therapy for patients with large-vessel vasculitis

Carlo Salvarani[1], Luca Magnani[1], Mariagrazia Catanoso[1], Nicolò Pipitone[1], Annibale Versari[2], Lucia Dardani[1], Lia Pulsatelli[3], Riccardo Meliconi[4] and Luigi Boiardi[1]

FIG. 1 PET/CT scans of Patients 2 and 3 before (**A**, **B**) and after (**A′**, **B′**) TCZ therapy. Patient 2 (**A** and **A′**): bilateral Grade 3 carotid artery FDG uptake before TCZ (→) (**A**). After TCZ therapy, FDG uptake markedly decreases to Grade 1 (**A′**). Patient 3 (**B** and **B′**): Grade 3 FDG uptake in the abdominal aorta before TCZ (→) (**B**). Note the marked decrease to Grade 1 after TCZ therapy (**B′**).



Biologics: Tocilizumab

- Retrospective case series
- 7 patients
- Refractory disease
- Average of 4 immunosuppressive agents prior to tocilizumab (8 mg/kg per infusion)
- 5: no improvement
- 5: progressive vascular lesions

Baldissera E. ACR annual meeting 2012. abstract 2368

Biologics: rituximab

- **Case report**
  - 3 patients
  - Remission proven by PET/CT

Hoyer.Ann Rheum Dis 2012; 71: 75-79

Comorbidities

- Screen for hypertension:
  - 4 limb BP
  - Assess for end organ damage
  - If in doubt, measure central blood pressure
- Atherosclerosis
  - Silent myocardial ischemia may be present in a majority of patients (clinical significance to be determined)
  - ischemic events less prevalent in patients on ASA

De Souza AWS. Circulation J 2010; 74: 1236-1241
Saadoun D. ACR annual meeting 2012. abstract 2365

Takayasu arteritis: Japanese circulation society guidelines

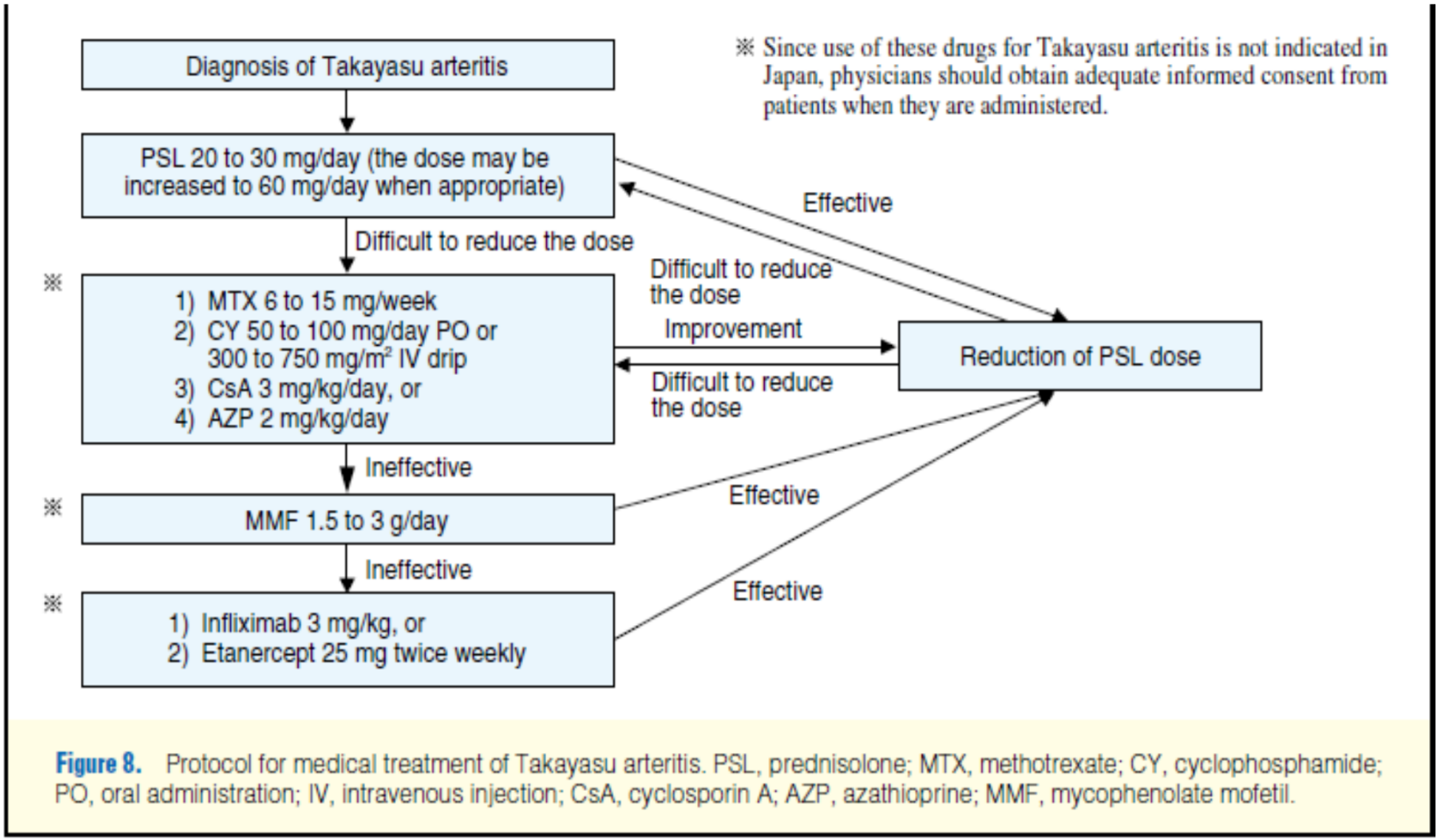


Figure 8. Protocol for medical treatment of Takayasu arteritis. PSL, prednisolone; MTX, methotrexate; CY, cyclophosphamide; PO, oral administration; IV, intravenous injection; CsA, cyclosporin A; AZP, azathioprine; MMF, mycophenolate mofetil.

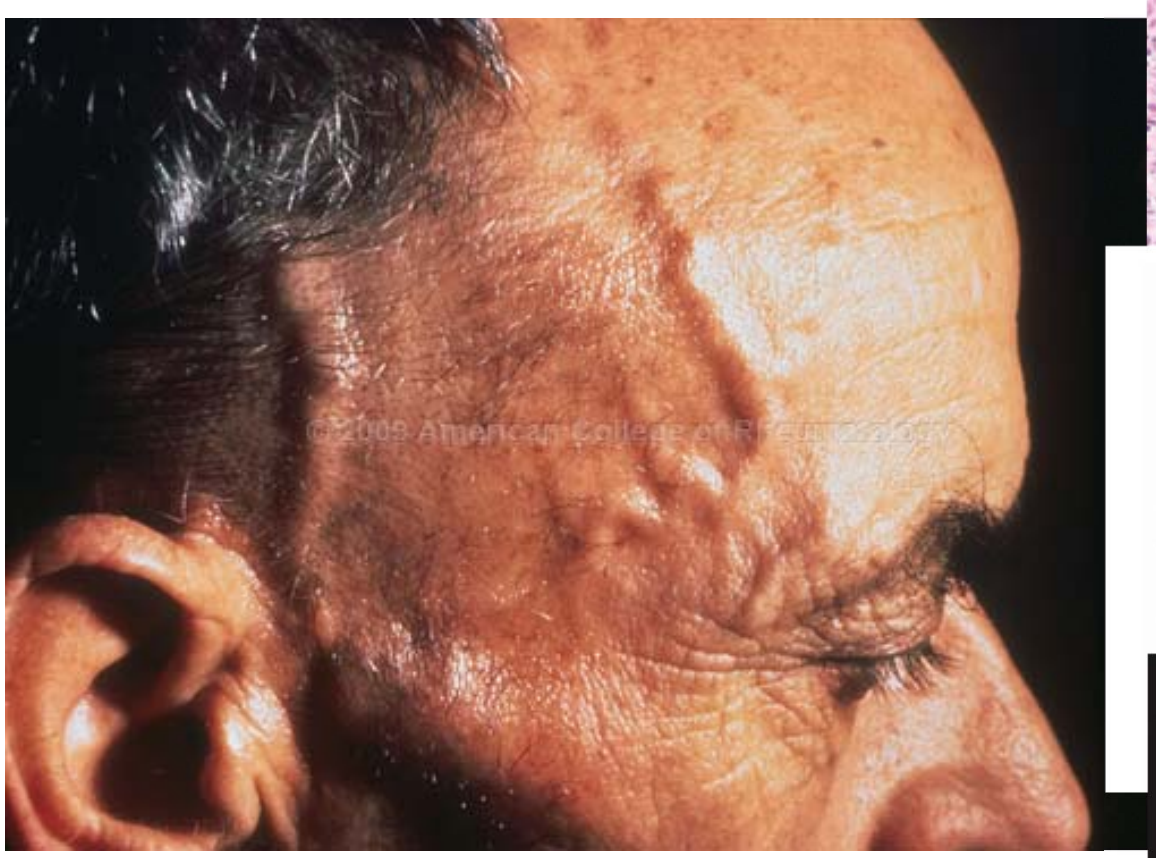
JCS Joint Working Group. Circ J 2011; 75: 474 – 503

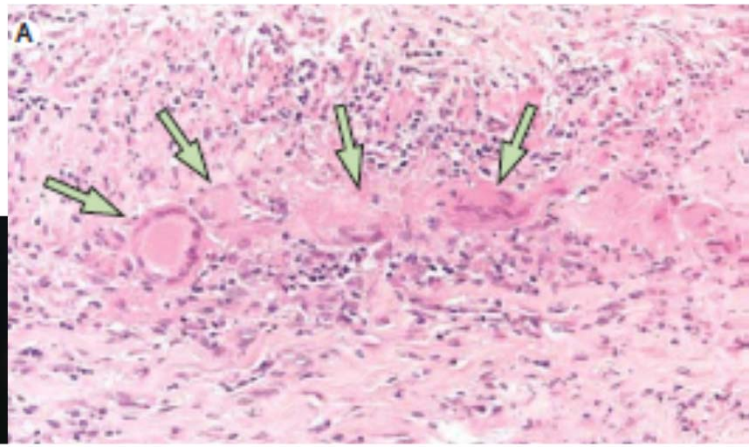
Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents

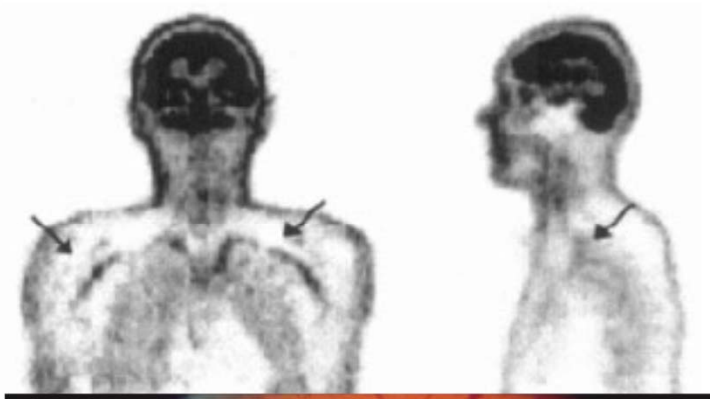
- TNF inhibitors and tocilizumab:
  - May be used with persistently active disease ≥ 6 months or ≥ 2 flares or relapse despite glucocorticoids and ≥ 1 immunosuppressive agent.
  - Assess efficacy within 4 months
- Immunosuppressive agents that may be used:
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil

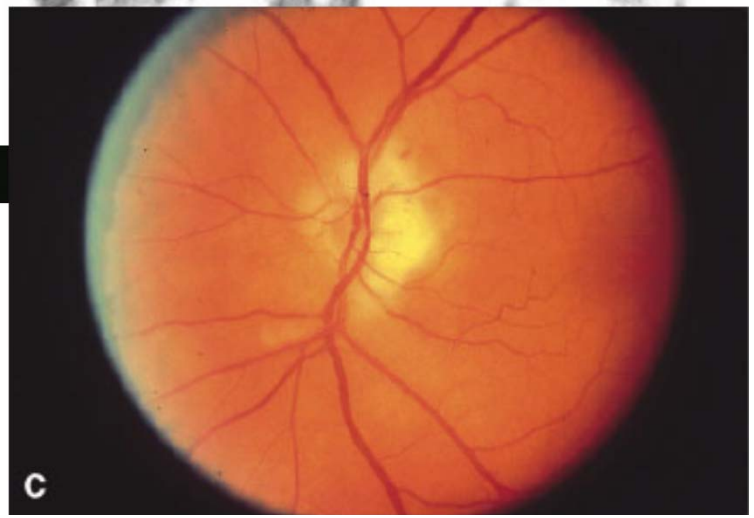
Pipitone N. Clin Exp Rheumatology 2012; 30 (suppl 70): S139-S161)

Giant cell arteritis









GCA: treatment

- Steroids
  - Initial doses: 40-60 mg qd
  - Maintain 1 month before starting taper
  - Do not taper on alternate day schedule: ↑ relapse
  - Plan to be around 10-15 mg qd at 3 months
    - 5-7.5 mg at 12 months
  - Duration: > 1 year
    - 10-15 % cannot decrease to less le 10-15 mg qd
    - 40-50% cannot decrease to less than physiological doses

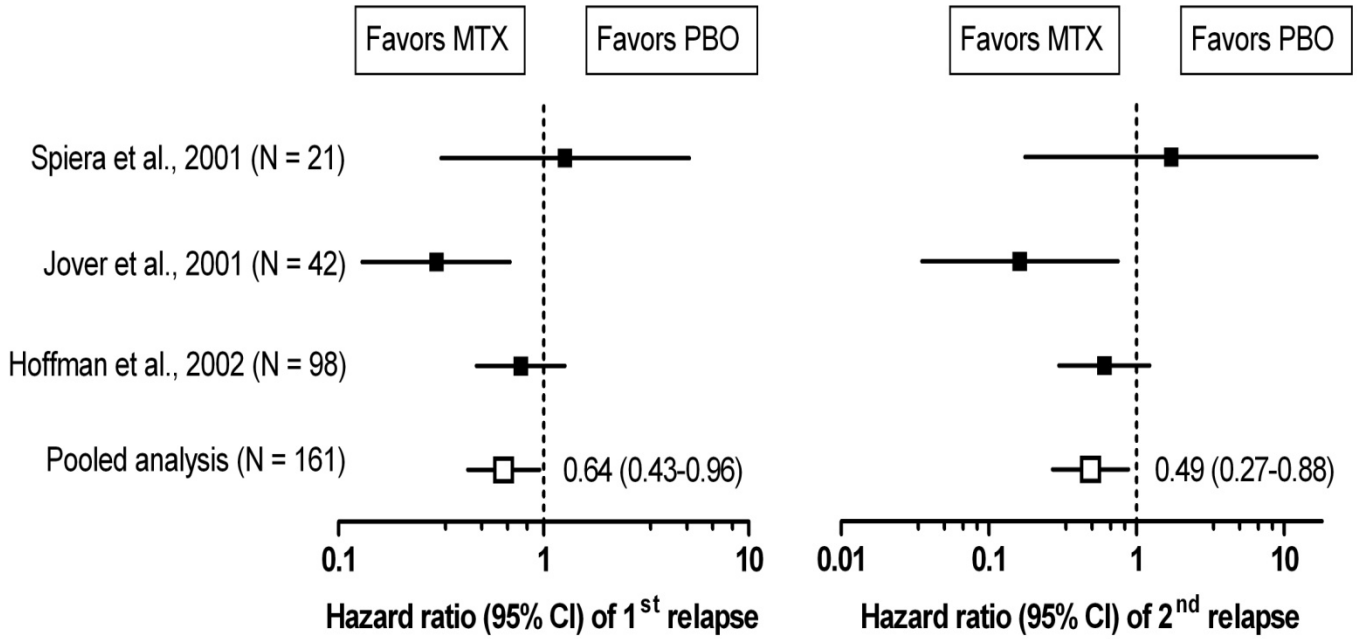
Mukhtyar C. Ann Rheum Dis 2009;68:318–323

GCA: treatment

- Aspirin:
  - Pts on aspirin at the time of diagnosis of GCA have less ischemic complications (stroke, vision loss). (RR: 0.2)
  - Possible prevention of further ischemic complications post Dx
    - 3 vs 13% in one study

Nesher G. Arthritis Rheum (2004) 50: 1332–1337
Lee MS. Arthritis Rheum (2006); 54: 3306-3309

Methotrexate in GCA



Patients on MTX took 800 mg less prednisone

Personal conclusion: possible modest benefit; mtx can be tried for steroid dependent patients

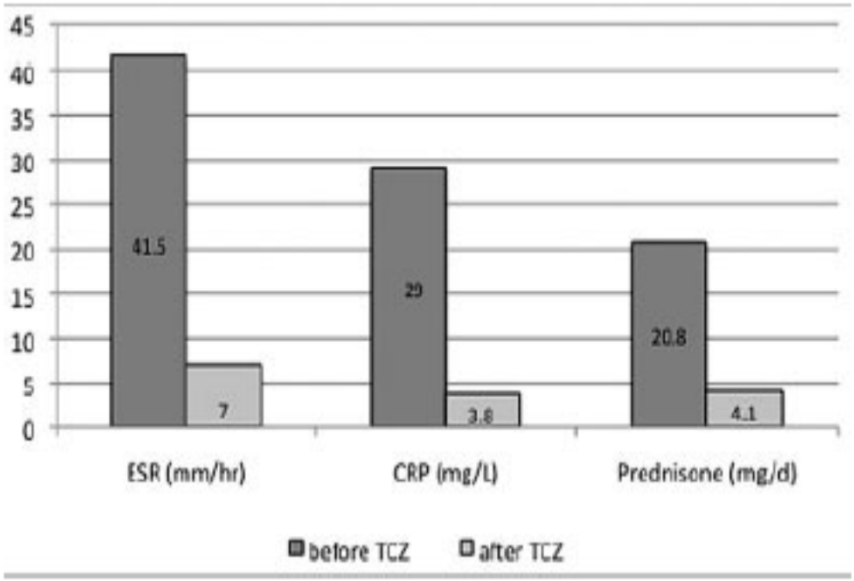
Mahr A. Arthritis Rheum (2007); 56: 2789-97

Tocilizumab for the Treatment of Large-Vessel Vasculitis (Giant Cell Arteritis, Takayasu Arteritis) and Polymyalgia Rheumatica

S. UNIZONY,[1] L. ARIAS-URDANETA,[1] E. MILOSLAVSKY,[1] S. ARVIKAR,[1] A. KHOSROSHAHI,[1] B. KEROACK,[2] J. R. STONE,[1] AND J. H. STONE[1]

Arthritis Care Research 2012; 64: 1720-1729

10 patients: 7 GCA, 2 TA, 1 PMR
2,4 relapses in year preceding tocilizumab
Mean prednisone dose:
before toci: 20 mg/day
after: 4,1 mg/day
All patients: better ≤ 8-12 weeks



Tocilizumab and giant cell arteritis

- ClinicalTrials.gov Identifier: NCT01450137
- **New onset of giant cell arteritis**
- **ACR criteria AND**
  - sedimentation rate> 40 mm/h and a CRP > 20 mg/L
  - AND a biopsy proven GCA OR a large vessel vasculitis assessed by MR Angiography
- randomized, placebo-controlled, double blind, monocentric trial
- **2 arms:**
  - Tocilizumab 8mg/kg every 2 weeks in the first 3 months, thereafter every 4 weeks until week 52 + Glucocorticoids (GCs) vs.
  - Placebo + GCs
- **Outcomes:**
  - Complete remission at 12 weeks
  - Relapses, cumulative steroid doses

VCRC Protocol 5523

Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu's Arteritis to Examine the Safety, Efficacy, and Immunologic Effects of Abatacept (CTLA4-Ig) in Large Vessel Vasculitis [AGATA]

Vasculitis Clinical Research Consortium (VCRC)

www.RareDiseasesNetwork.Org/VCRC