Large Vessel Vasculitis
*Takayasu Arteritis & Giant Cell Arteritis & IgG Related Disease*

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Immune Complex Small Vessel Vasculitis
- Cryoglobulinemic Vasculitis
- IgA Vasculitis (Henoch-Schönlein)
- Hypocomplementemic Urticarial Vasculitis
  (Anti-C1q Vasculitis)

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease

Anti-GBM Disease

ANCA-Associated Small Vessel Vasculitis
- Microscopic Polyangiitis
- Granulomatosis with Polyangiitis
  (Wegener’s)
- Eosinophilic Granulomatosis with Polyangiitis
  (Churg-Strauss)

Large Vessel Vasculitis
- Takayasu Arteritis
- Giant Cell Arteritis
Spectrum of Large Vessel Vasculitis

Takayasu Arteritis \[\implies\] Giant Cell Arteritis

Age 10 - 40 years \[\implies\] Age > 50 years

- Chronic idiopathic granulomatous vasculitides that affects large and medium sized arteries - Aorta & branch vessels
  - Stenosis
  - Occlusion
  - Aneurysm
  - Wall thickening, edema

- Pathogenesis and etiology are not known, but autoimmunity plays a central role
Epidemiology and Pathogenesis

- **Female predominance:**
  - Takayasu Arteritis: 5 : 1
  - Giant Cell Arteritis: 2 - 3 : 1

- **Prevalence:**
  - Takayasu: Asia and SE Asia descent
    - Japan, Turkey (3 per 100,000)
    - Nordics (1-1.7 per 100,000)
  - Giant Cell: White, Northern European descent
    - Nordics (> 17 per 100,000)
    - Southern Europe (12 per 100,000)
    - Rare in Blacks, Asians

T Cell Mediated

Seyahi E. Curr Opin Rheumatol 2017;29:51-56
32 Female presenting with an Acute Coronary Syndrome

- No history of smoking
- HDL 78, LDL 67
- No FH of premature atherosclerosis

What is/are the first step(s)?

A. LIMA to LAD, SVG to Cx
B. Pulse with high dose steroids
C. CT Angiogram of Chest/Abdomen/Pelvis
D. B & C
E. All of the above
32 Female presenting with a ACS

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- E. All of the above
Pitfall #1 -- Diagnosis Not Considered

• 32 year old woman presents with ACS
• Undergoes CABG with LIMA
• One year post-op, recurrent chest pain…

• WHAT IS THE MECHANISM OF HER RECURRENT CHEST PAIN?
Coronary Steal
Takayasu’s Arteritis
28 year old female with severe right arm claudication

Options:
• PTA
• Bypass Surgery
• Other

Takayasu’s Arteritis
Takayasu Arteritis Presentation

Three Phases of Disease

(1) “Pre-pulseless” Phase
- Constitutional signs and symptoms
- Many may be asymptomatic

(2) Inflammatory Phase
- Vascular inflammation
- Arterial tenderness

(3) Burnt Out (Inactive) Phase
- Arterial fibrosis, aneurysm formation
- Ischemic symptoms

- CNS
  - TIA, stroke, carotidynia

- Heart
  - Angina, MI, CHF, aortic insufficiency

- Lungs
  - Pulmonary HTN, dyspnea, hemoptysis

- GI
  - Mesenteric ischemia, pain

- Kidney
  - Renovascular HTN, renal failure

- Extremities
  - Claudication, asymmetric pulses and/or blood pressures
# TAKAYASU vs GIANT CELL

## 1990 ACR Criteria

<table>
<thead>
<tr>
<th>Takayasu Criteria</th>
<th>Giant Cell Criteria</th>
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<tbody>
<tr>
<td>1. Age Onset &lt; 40 years</td>
<td>1. Age ≥ 50 years</td>
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<tr>
<td>• 13-17.5% have onset &gt; 40 years</td>
<td>2. New onset localized HA</td>
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<tr>
<td>2. Claudication of the extremities</td>
<td>3. Temporal Artery tenderness or decreased pulse.</td>
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<td>3. Upper Extremity Blood Pressure discrepancy &gt; 10 mm Hg</td>
<td>4. Elevated ESR (≥ 50 mm/hour)</td>
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<td>4. Decreased brachial artery pulse</td>
<td>5. Temporal Artery biopsy with necrotizing arteritis (10-40% pathology negative)</td>
</tr>
<tr>
<td>5. Bruit over subclavian or aorta</td>
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<tr>
<td>6. Arteriographic abnormality</td>
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</table>

- Sensitivity 90.5%, Specificity 97.8% if ≥ 3 Features present.
- Decreases (60.4% and 77.4%) in India due to predominantly aortic involvement.

- Sensitivity 93.5%, Specificity 91.2% if ≥ 3 Features present.
- Temporal Arteritis is localized Giant Cell Arteritis.
- Patients may present with extremity claudication. 50% patients also experience PMR.

Cardiac Catheterization
Duplex of Left Subclavian Artery
Giant Cell Arteritis Presentation

**Headache**
**Vision change/complications**
**Jaw claudication/tongue pain**
**Temporal artery abnormality**

**Constitutional symptoms**

**Acute phase reactants**

**Aneurysm (aorta)**
**UE claudication, bruits**
**Raynaud’s phenomenon rarely**

**CRANIAL GCA**
**Temporal arteritis**

**LARGE VESSEL GCA**

**POLYMYALGIA RHEUMATICA**
**(1/3 subclinical LV vasculitis)**

**Bilateral shoulder/hip pain**
**Morning stiffness**
**Peripheral arthritis**

Large Vessel Arteritis Evaluation

- Serologies: C-reactive protein, Erythrocyte Sedimentation Rate, Interleukin-6
- Anemia, thrombocytopenia, leukocytosis, hypergammaglobulinemia
- Imaging: CT or MR angiography, duplex ultrasonography
  - Wall thickening and edema
  - Stenosis or Occlusion
  - Aneurysm

Ascending Aortic Aneurysm 4.2 cm
Pulmonary Artery Aneurysm 4.3 cm
The Incomplete Evaluation

- 39 F induced at 37w for presumed pre-eclampsia referred for HTN evaluation
- Blood pressure controlled” on nifedipine, labetalol, hydralazine:
  - Right Arm 117/75 mm Hg
  - Left Arm 145/76 mm Hg
- Bilateral carotid bruits
- Diminished right radial pulse
- Ankle blood pressures:
  - Right Ankle 189/90 mm Hg
  - Left Ankle 182/88 mm Hg
What Test Do You **Not** Need?

A. Carotid Duplex Ultrasound
B. Transthoracic Echo
C. Basic Labs – CMP, CBC, PT/PTT
D. Thrombophilia evaluation – FVL, PT gene and APLA labs
E. ESR, CRP, IL6
What Test Do You Not Need?

A. Carotid Duplex Ultrasound
B. Transthoracic Echo
C. Basic Labs – CMP, CBC, PT/PTT
D. Thrombophilia evaluation – FVL, PT gene and APLA labs
E. ESR, CRP, IL6
Findings on Carotid Duplex Ultrasound

- Smooth concentric wall thickening
- The “Halo” sign
Smooth Concentric Wall Thickening
Occluded Common Carotid Artery
Retrograde Flow in ECA, Antegrade in ICA
Giant Cell Arteritis
Takayasu Arteritis - MRI/MRA
Takayasu’s Arteritis
Abdominal Takayasu’s
### Imaging Evaluation

If large vessel vasculitis is suspected, *imaging of the entire aorta, its main branches and the iliac arteries* is recommended:

- Areas of wall thickening = suggest active disease
- Areas of stenosis or occlusion
- Aneurysms (location and size)

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<tr>
<td>• Stenoses may affect the entire aorta and main branches</td>
<td>• Stenoses mostly limited to the arch branch vessels</td>
</tr>
<tr>
<td>• Aneurysms (up to 32%) - aorta, carotid, innominate, subclavian, renal arteries</td>
<td>• Aneurysms - thoracic and abdominal aorta (up to 10%)</td>
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<tr>
<td></td>
<td>• Related dissection may also occur</td>
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Takayasu Arteritis vs Giant Cell Arteritis:

- Stenoses may affect the entire aorta and main branches in Takayasu Arteritis, whereas Giant Cell Arteritis mostly affects the arch branch vessels.
- Aneurysms are more common in Takayasu Arteritis, with a high prevalence in the aorta, carotid, innominate, subclavian, and renal arteries. In Giant Cell Arteritis, aneurysms are more localized to the thoracic and abdominal aorta, with a lower prevalence of related dissection.
Fluorodeoxyglucose (FDG) - PET

1. Hope to identify early disease activity and prevent complications
2. Monitoring disease activity is notoriously difficult
   - Biomarkers do not reliably correlate with disease activity\(^1\)
   - Arteriographic abnormalities on imaging may be stable over time

**BUT**

1. **Uptake is persistently seen in patients with clinically inactive disease; may be due to other conditions ie atherosclerosis (GCA patients)**
2. **Role in patients post-revascularization (ie bypass) is unclear**
3. **Not reimbursable for this indication**
The Difficulty of Determining Disease Activity in Large Artery Vasculitis*

Jeffrey W. Olin, DO, Nupoor Narula, MD

Large Vessel Vasculitis Treatment

- Glucocorticoids are first-line & early treatment is key:
  - Prednisone 1 mg/kg (max 60 mg/day) for 3 months
  - Slow taper over 6-12 mos once in remission -- up to 50% will relapse

- Steroid-sparing agents considered for recurrence:

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<th>Giant Cell Arteritis</th>
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<tr>
<td>Methotrexate</td>
<td>Yes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Rarely</td>
<td>No</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Rarely</td>
<td>No</td>
</tr>
<tr>
<td>Rituximab</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TNF-inhibitor</td>
<td>Yes</td>
<td>Not effective</td>
</tr>
<tr>
<td>Tocilizumab (Anti-IL6)</td>
<td>Yes - Increasing Evidence</td>
<td>Yes</td>
</tr>
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</table>
WHAT IS TOCILIZUMAB?

- Tocilizumab (Actemra) is a humanized monoclonal anti-human IL-6 receptor antibody that binds to soluble and membrane-bound IL-6 receptor.

- IL-6 is produced in large amounts by synovial cells and macrophages in rheumatoid arthritis. IL-6 overproduction results in polyclonal hypergammaglobulinemia, recruitment of inflammatory cells, angiogenesis, increase in metalloproteinases, osteoclast activation, increase in amyloid A (SAA) and AA amyloidosis, hypoalbuminemia, anemia, and increased platelet count.

- Also unique to IL-6, it inhibits differentiation of regulatory T cells, and increases the number of Th17 cells and thus promote development of arthritis.
### Tocilizumab in Giant Cell Arteritis

Humanized monoclonal IL6 receptor antibody administered as monthly IV infusions

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Tocilizumab plus prednisolone (N=20)</th>
<th>Placebo plus prednisolone (N=10)</th>
<th>Risk difference (95% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Complete remissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 12 weeks</td>
<td>17 (85%)</td>
<td>4 (40%)</td>
<td>45% (11 to 79)</td>
<td>0.0301</td>
</tr>
<tr>
<td>After 52 weeks</td>
<td>17 (85%)</td>
<td>2 (20%)</td>
<td>65% (36 to 94)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Patients whose prednisolone dose tapered to 0 mg per day</td>
<td>16 (80%)</td>
<td>2 (20%)</td>
<td>60% (30 to 90)</td>
<td>0.0041</td>
</tr>
</tbody>
</table>

Relapse: 1 patient (Tocilizumab) 5 patients (Placebo)

Tocilizumab in Takayasu Arteritis

Lorcera J¹, Blanco R¹, Hernández JL¹, Castañeda S², Humbría A², Ortego N³, Bravo B⁴, Freire M⁵, Melchor S⁶, Mínguez M⁷, Salvañera J³, González-Vela C¹, Calvo-Rio V¹, Santos-Gómez M¹, Pina T¹, González-Gay MA²

Abstract

OBJECTIVES: To assess the efficacy of tocilizumab (TCZ) in patients with Takayasu arteritis (TA).

METHODS: Multicentre open-label retrospective study.

RESULTS: Eight patients (all women) with a mean age of 34±18 years, median 36 years (range: 7-57) were assessed. The main clinical features at TCZ therapy onset were: constitutional symptoms (n=4), fever (n=3), headache (n=2), chest pain (n=1), abdominal pain (n=1), mesenteric ischaemia (n=1), myalgia involving the lower limbs (n=1), cerebral vascular insufficiency (n=1), malaise (n=1), upper limb claudication (n=1) and nodular scieritis (n=1). Besides corticosteroids and before TCZ treatment onset, 7 of 8 patients had also received several conventional immunosuppressive and/or biologic agents. Seven patients experienced marked clinical improvement in the first 3 months after the onset of TCZ therapy. After a median follow-up of 15.5 [interquartile range-IQR: 12-24] months, 7 patients were asymptomatic. The median C-reactive protein decreased from 3.09 [IQR: 0.5-12] to 0.15 [IQR: 0.1-0.5] mg/dL (p=0.018), and median erythrocyte sedimentation rate from 40 [IQR: 28-72] to 3 [IQR: 2-5] mm/1st hour (p=0.012). The median dose of prednisone was also tapered from 42.5 [IQR: 25-50] to 2.5 [IQR: 0-7.5] mg/day (p=0.011). However, TCZ had to be discontinued in 1 patient because she developed a systemic lupus erythematosus, and in another patient due to inefficiency. TCZ dose was reduced in a patient because of mild thrombocytopenia.

CONCLUSIONS: TCZ appears to be effective in the management of patients with TA, in particular in patients refractory to corticosteroids and/or conventional immunosuppressive drugs.
LARGE VESSEL ARTERITIS
TREATMENT POINTS

• Activity does not correlate with biomarkers. Need corollary imaging.

• All patients with suspected diagnosis should have a thorough assessment of the arterial tree.

• Early immunosuppression is key, although > 50% patients will relapse after remission.
  ▪ Prednisone 1mg/kg (up to maximum of 60 mg/day) for up to 3 months
  ▪ Slow taper over 6 – 12 months once in remission
  ▪ 2nd Agent if Relapse (ie MTX, Cyclophosphamide, Infliximab, Cellcept)
  ▪ Emerging data for IL-6 Antagonists (Tocilizumab) as rescue therapy

• Giant Cell life expectancy is unchanged. Vision loss in 15-20%.

• Takayasu Survival Rates:
  5 years  81 – 95%
  10 years  73 – 90%
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- Takayasu Survival Rates:
  - Vascular Claudication in 60%
  - Impaired ADLs in 74%
  - 5 years 81 – 95%
  - 10 years 73 – 90%
  - 23 – 47 % Fully Disabled
Surgery, angioplasty, and stent implantation have all been successful in the treatment of carotid, renal, coronary artery disease.

INTERVENTION SHOULD BE DELAYED (WHEN POSSIBLE) UNTIL THE ACUTE PHASE OF THE DISEASE IS ADEQUATELY TREATED. ANGIOPLASTY OR SURGICAL BYPASS INVOLVING AN ARTERY WITH MARKED INFLAMMATION OFTEN FAILS.
## Revascularization in LV Vasculitis

### Takayasu Arteritis
Endovascular and surgical revascularization have been successful therapeutic options. Revascularization should be delayed (when possible) until the acute phase of the disease is adequately treated. Revascularization of an actively inflamed artery often fails.

### Giant Cell Arteritis
Rarely indicated due to robust collateral network in the subclavian-axillary arteries that are normally affected. In cases refractory to medical management or with persistent symptoms, endovascular and surgical revascularization have been successful therapeutic options.
Conclusions

1. Takayasu and Giant Cell arteritis are inflammatory vasculitides affecting medium and large arteries across the age spectrum.

2. All patients with suspected disease should undergo imaging of the entire aorta and its branches to the common femoral arteries.
Conclusions

3. Glucocorticoids are first-line to achieve disease control and remission (1 mg/kg; max dose 60 mg/day)

4. Steroid-sparing agents have variable efficacy in patients with relapse, although there is emerging data to support the use of Tocilizumab (IL-6 receptor antibody) for severe/refractory disease

5. Revascularization should be delayed in patients with active disease (if at all possible). Endovascular and surgical options have been reported as successful therapeutic options.
IgG4 Related Disease (IgG4-RD)

- Retroperitoneal Fibrosis
  - Majority of cases formally called “idiopathic”
  - Infrarenal aorta and iliac arteries
IgG4 Related Disease (IgG4-RD)

- **Aortitis**
  - Can occur in thoracic aorta
  - Infrarenal and iliac arteries are more characteristic
  - May be associated with retroperitoneal fibrosis.
  - Can affect other organs
  - May have infiltration of IgG plasma cells and increased IgG serum levels
  - Patients may respond well to glucocorticoids
  - May degenerate into aneurysm
Ascending and Descending Aorta

Left subclavian, left CCA and innominate

Blue Arrow: Descending aorta

Right Common Iliac Wall Thickness
October 2017 --- RLQ Mass

March 28, 2018 - improved RLQ mass
March 28, 2018 - Improved
March 28- Improved: Compare to Slide 2 Blue Arrow.
Normal Common Iliac Arteries:
Compare to Slide 2 with Previous Wall Thickening of Right Common Iliac Artery