Vasculitis: Pearls for early diagnosis and treatment of Giant Cell Arteritis

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Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Mary Beth Humphrey

I have no relevant financial relationships or affiliations with commercial interests to disclose.
Experimental or Off-Label Drug/Therapy/Device Disclosure

I will be discussing experimental or off-label drugs, therapies and/or devices that have not been approved by the FDA.
Objectives

• To recognize early signs of vasculitis.
• To discuss Tocilizumab (IL-6 inhibitor) as a new treatment option for temporal arteritis.
• To recognize complications of vasculitis and therapies.
Professional Practice Gap

**Gap 1**: Application of imaging recommendations in large vessel vasculitis

**Gap 2**: Application of tocilizumab in treatment of giant cell vasculitis
GCA

Cranial Symptoms

Aortic Aneurysm

Vision loss

Arm Claudication

PMR

FUO
Which is not a risk factor or temporal arteritis?

A. Smoking
B. Female sex
C. Diabetes
D. Northern European ancestry
E. Age
Which is **not** a risk factor or temporal arteritis?

A. Smoking  
B. Female sex  
C. Diabetes  
D. Northern European ancestry  
E. Age
Giant Cell Arteritis

• Most common form of systemic vasculitis in adults
  – Incidence: ~ 1/5,000 persons > 50 yrs/year
  – Lifetime risk: 1.0% (F) 0.5% (M)

• Cause: unknown

At risk:

Women (80%) > men (20%)
Northern European ancestry>>>AA>Hispanics
Age: average age at onset ~73 years
Smoking: 6x increased risk

Biomarkers predicting biopsy proven GCA

For predicting biopsy proven GCA

- ESR: 89% have ESR > 50
  - 11% have ESR < 50 mm/h
  - Sens 84%

- C-Reactive Protein
  - Sens 86%; Spec 30%; NPV 88%
  - 4% of biopsy proven GCA had normal ESR and CRP

- Both elevated: OR 3.06 (95% CI 2.03, 4.62)

2 Kermani TA et al. Semin Arthritis Rheum. 2011 Nov 23
What is not a symptom of GCA?

A. Visual loss
B. Arm claudication
C. Vertebral artery stroke
D. Hallucinations
E. Muscle weakness
What is not a symptom of GCA?

A. Visual loss
B. Arm claudication
C. Vertebral artery stroke
D. Hallucinations
E. Muscle weakness
## Giant cell arteritis: Clinical presentation & labs

<table>
<thead>
<tr>
<th>Clinical Manifestation</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional symptoms: (including fevers/FUO)</td>
<td>Almost all</td>
</tr>
<tr>
<td>New onset headache</td>
<td>76%</td>
</tr>
<tr>
<td>Jaw claudication: most specific</td>
<td>34%</td>
</tr>
<tr>
<td>Vision loss: complete or partial; unilateral or bilateral</td>
<td>15-20%</td>
</tr>
<tr>
<td>• Visual hallucinations</td>
<td>20%</td>
</tr>
<tr>
<td>• Diplopia: highly specific</td>
<td>5%</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>40-50%</td>
</tr>
<tr>
<td>Temporal artery abnormality</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>ESR ≥ 50 mm</td>
<td>90%</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>~25%</td>
</tr>
</tbody>
</table>
Two ends of the same disease spectrum?

Polymyalgia Rheumatica
15-20% have GCA

Giant Cell Arteritis
40-60% have PMR
Case #1

65 y/o white man with headache, visual changes and increased inflammatory markers

• 3 months of fatigue and decreased appetite without weight loss, attributed to stress
• 3 months of episodic blurry vision, affecting both eyes for the past 2 months. No visual field defect.
• New occipital and temporal headache for the past 2 weeks, with no previous history of headaches
• No fevers, scalp tenderness, shoulder/hip girdle symptoms, or jaw claudication
• Exam: Well appearing. Symmetric blood pressures in arms and legs, no carotid bruits. Temporal arteries non-tender with normal pulses
• ESR 12, CRP 72.8 (normal <8.0 mg/dL)
What should be the next step performed in his diagnostic evaluation?

A. Biopsy the temporal artery
B. Obtain color Doppler ultrasound of the temporal and/or axillary arteries
C. Obtain high resolution magnetic resonance angiogram of the cranial arteries
D. Obtain positron emission tomography with low-dose computed tomography imaging of the cranial arteries
Imaging in large vessel vasculitis: EULAR

• Recommendation 1: **early imaging test** is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.
  - In settings where imaging modalities are not readily available or expertise with imaging in GCA is questionable, a biopsy should still be favored in first place.
  - Imaging should be performed before or as early as possible after initiation of therapy, **best within 1 week**, because treatment with glucocorticoids rapidly reduces the sensitivity of imaging.
Additional EULAR recommendations

• Recommendation 3: Ultrasound of temporal + axillary arteries is recommended as the first imaging modality in patients with suspected predominantly cranial GCA. A non-compressible ‘halo’ sign is the ultrasound finding most suggestive of GCA.

• Recommendation 4: High resolution MRI of cranial arteries to investigate mural inflammation may be used as an alternative for GCA diagnosis if ultrasound is not available or inconclusive.
Imaging: Ultrasound

Color Doppler ultrasound (temporal +/- axillary arteries)

- Stenosis, occlusion, and/or concentric hypoechogenic mural thickening
  - Stenosis or occlusion: sensitivity 8%-80%, specificity 73%-100%
  - Halo sign: sensitivity 55%-100%, specificity 78%-100%

- Differences in performance characteristics:
  - Variability in operator experience, equipment, probe settings, clinical context

- Less experience with ultrasound in the United States:
  - Does not replace biopsy

Buttgereit F et al. JAMA 2016
Imaging: Temporal Artery MR

Contrast-enhanced high-resolution MRI of temporal and occipital arteries
- Arterial wall thickening with mural and periadventitial contrast enhancement
- Sensitivity 68-89%, specificity 73-97% (5 studies, n=341 total)

171 patients with suspected GCA: Postcontrast T1-weighted spin-echo MRI of scalp arteries (using 3T MRI) followed by temporal artery biopsy
- Positive temporal artery biopsy 18% (n=31); abnormal MRI 35% (n=60); clinical dx of GCA 48%
- Sensitivity 94%, specificity 78%
- Negative predictive value 98%, positive predictive value 48%

Buttgereit F et al. JAMA 2016; Rheaume M et al. Arthritis Rheumatol 2017
Imaging: MRA of cranial vessels

- Note:
  - Single radiologist at single institution
  - Experience and volume are critical
  - Rapid changes with prednisone—need to obtain within days of starting

Rheume M et al. Arthritis Rheumatol 2017
EULAR Imaging Recommendations

• Recommendation 5: CT and PET are not recommended for the assessment of inflammation of cranial arteries.

• Recommendation 6: Ultrasound, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of large vessel GCA.
GCA
Upper Extremity Arterial Involvement

- Frequency by imaging:
  - PET CT - 74%
  - CT angio - 42%
  - Ultrasound - 30%
- Symptoms < 10%
- Isolated PMR
  - PET - 31%

[\(^{18}\text{F}\)]FDG PET for GCA

- Not useful for the temporal arteries
- **Useful for select cases**
  - Negative TA biopsy
  - Atypical symptoms
  - FUO
- Exclude other conditions

**GCA**

**Lower Extremity Arterial Involvement**

- **Imaging**
  - PET: 37%
  - Ultrasound: 12-50%

- **Proximal arterial disease**

- **Clinical**
  - Leg Claudication 1-20%
  - Often presenting feature
  - 15-30% critical leg ischemia

GCA - Arterial Stenosis
Aortitis is common at onset of GCA

CT Angio (thickening)

- 65%
- Non-involved
- Aorta inflamed

GCA

Diagnostic algorithm

Age ≥50 yrs
Inflammatory process

Cranial Sx
Refractory PMR
Constitutional syndrome
Claudication

Temporal artery biopsy
Vascular Imaging (CTA, MRA, PET)
• Thoracic Aortic Aneurysms
  - 17.3x fold increased risk
  - 12% - 33% incidence (10 yr F/U)

• No consistent clinical predictors
  - Aortic Regurgitation

Robson JC. Ann Rheum Dis. 2013 Oct 4
Aortic aneurysm & dissection lead to increased mortality in GCA

Aneurysm screening in GCA

- Expert recommendations:
  - Yearly Chest X-ray
  - Echocardiogram
- Baseline CT scan or MRI (ACC/SVM)
- To detect one previously unknown thoracic aorta aneurysm or dissection
  - 5 to 10 patients with GCA would need aortic imaging

Bongartz, Matteson. Curr Opin Rheumatol 2006;18:10–17
Aortic Aneurysm - Mainly a late complication when the disease is clinically in remission

P = 0.009 for trend

GCA

Who should be referred for biopsy?

- **Positive predictors**
  - Jaw claudication (LR 4.2, 95% CI 2.8-6.2)
  - Diplopia (LR 3.4, 95% CI, 1.3-8.6)

- **Negative predictors of +biopsy**
  - Normal ESR
  - No Jaw claudication
  - No temporal artery tenderness
  - Synovitis

GCA Complications

- Blindness
- Tongue infarction
- Scalp infarction
Histologic appearance of Giant Cell Arteritis
Diagnosis of GCA

• Temporal artery biopsies always preferred.
  - Symptomatic side, PPV 90%
  - If negative, biopsy other side (1-5%)

• Biopsy length matters! Longer is better due to skip lesions (<6mm 19%+, 6-19mm 70%+, >20mm 89%+)

• Do not withhold steroids. Biopsies will still show active or healing vasculitis for 6 weeks of steroid therapy!

• Sensitivity ~70-90%

• ~20-30% of suspected GCA pts have positive bx
GCA Treatment

72 y/o woman presents with classic symptoms of giant cell arteritis including amaurosis fugax of the left eye. Temporal artery biopsy shows transmural mononuclear cell infiltrates with multinucleated giant cells. Your initial treatment of choice is:

A. High dose oral prednisone (e.g., 1-2 mg/kg/day)
B. Pulse steroids (500 mg-1 g/day x 3 days) followed by oral prednisone 1-2 mg/kg/day
C. Glucocorticoids + methotrexate
D. Glucocorticoids + tocilizumab
E. Glucocorticoids + TNFα inhibitor
GCA: Treatment Options

- **Glucocorticoids (GC):** mainstay of therapy; started early to prevent ischemic complications (start 40-60mg daily)
  - Reconsider diagnosis if no response after 1 week or biopsy negative
  - Conflicting limited data regarding use of pulse GC
  - Taper over months (not years) to minimize complications osteoporosis, infection, DM, cataracts, etc.
- **Tocilizumab:** FDA approved for GCA, steroid sparing
- **Methotrexate:** Modest benefit in meta-analysis, steroid sparing
- **Aspirin:** prevent ischemic complications (with previous cardiac history?)
- Not efficacious in clinical trials: anti-TNF therapy (adalimumab, infliximab, etanercept)
**GCA: Treatment course**

- **Population-based Cohort:**
  - Median duration: 2.1 years
  - 75% off CS after 5 years

- **Referral Cohort:**
  - Discontinuation of GC
    - 24% by 2 years
    - 54% by 5 years

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GiACTA: Tocilizumab (TCZ; anti-IL-6)

Screen (42 days) → Baseline (BS) randomization

<table>
<thead>
<tr>
<th>52-week double blind (part 1)</th>
<th>104-week open-label extension (part 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ 162 weekly</td>
<td>Patients in remission at 52 weeks</td>
</tr>
<tr>
<td>Prednisone, n = 100</td>
<td>Long-term followup off the study drug</td>
</tr>
<tr>
<td>TCZ 162 mg every 2 weeks</td>
<td>Patients with disease activity or flare</td>
</tr>
<tr>
<td>Prednisone, n = 50</td>
<td>Open-label TCZ 162 mg weekly</td>
</tr>
<tr>
<td>Prednisone, n = 50</td>
<td></td>
</tr>
</tbody>
</table>

Primary efficacy endpoint: sustained remission at 52 weeks

Stone JH et al. NEJM 2017
Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.

## GiACTA: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TCZ weekly + prednisone (6 months) (n=100)</th>
<th>TCZ qo wk + prednisone (6 months) (n=49)</th>
<th>Placebo + prednisone (6 months) (n=50)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained remission at 52 weeks, n (%)</td>
<td>56 (56)</td>
<td>26 (53)</td>
<td>7 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative prednisone dose, median (range)</td>
<td>1862 (630-6602)</td>
<td>1862 (295-9912)</td>
<td>3296 (932-9778)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Safety:
- Similar incidence of infection, injection site reactions
- TCZ: 6 pts developed neutropenia; 1 with anterior ischemic optic neuropathy
- No GI perforations

Stone JH et al. NEJM 2017

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GiACTA: Long-term followup

Figure 1. Kaplan-Meier plot of time to first flare over 3 years (double-blind and part 2 periods; censored for open-label TCZ; ITT population).

Patients without GCA Flare, %

Study Week

No. of Patients

PBO+26 (n=50)
PBO+52 (n=51)
TCZ QW (n=100)
TCZ Q2W (n=49)

Patients never in remission were censored at day 1. Patients who withdrew were censored from the time of withdrawal. Dashed line indicates start of part 2.

GiACTA: long-term followup

<table>
<thead>
<tr>
<th></th>
<th>TCZ Qweek</th>
<th>TCZ Q2 week</th>
<th>Placebo/26 week</th>
<th>Placebo/52 week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintained CR</td>
<td>38/81 (47%)</td>
<td>13/36 (36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment free</td>
<td>33/51 (65%)</td>
<td></td>
<td>17/38 (45%)</td>
<td></td>
</tr>
<tr>
<td>Median time to 1st flare while not on TCZ (days)</td>
<td>575</td>
<td>428</td>
<td>162</td>
<td>295</td>
</tr>
<tr>
<td>Cumulative GC dose over 3 years (median)</td>
<td>2373</td>
<td>2863</td>
<td>5006</td>
<td>5322</td>
</tr>
</tbody>
</table>

- Retreatment with TCZ restore CR in pts who flared
- No additional safety signals observed

Tocilizumab, weekly or every other week, combined with a 26-week prednisone taper was superior to either 26-week or 52-week prednisone tapering plus placebo in achieving and maintaining GC-free remission

GCA - Methotrexate

- **Meta-analysis (3 randomized trials)**
  - 84 on MTX
  - 77 on placebo

- **MTX reduced:**
  - Risk of 1st relapse by **35%**
  - Risk of 2nd relapse by **51%**
  - Exposure to steroids

Conclusions

• **Tocilizumab**, weekly or every other week, combined with a 26-week prednisone taper was **superior** to either 26-week or 52-week prednisone tapering plus placebo

• Longer follow-up is necessary to determine the durability of remission and safety of tocilizumab.
Summary

- **GCA** is an inflammatory vascular syndrome with feature of cranial and/or large vessel vasculitis, systemic inflammation, and PMR
- **GCA** and PMR are among the most common rheumatic inflammatory diseases in the elderly; prevalence will increase with our aging population
- Multiple imaging modalities can assist in the diagnosis
- Chronic vessel wall injury and repair can lead to late aneurysm and dissection
- Tocilizimab is now FDA approved as first line therapy for GCA