Large vessel vasculitis, diagnosis and treatment

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Disclosures

- Guest speaker at UCB-sponsored meetings: (Immunology Summits, Prague, 2012, 2013 & 2014, MACRO Meet the expert at the ACademy of RheumatOlogy, Bologna 13 - 14 April 2012, GRAPPA Workshop, Milan 29 January 2016) and Alfa-Wassermann sponsored meeting (Rhewind, Bologna, February 2016)

- PI for Italy for the gevokizumab in myositis Servier study (2014) and the sirukumab in GCA GSK study (2016)

- I have no conflicts of interest to declare

- Images shown may be copyrighted
Large-vessel vasculitis

vasculitis.org.uk
LVV in TAK and GCA at onset

• All patients with TAK have LVV

• 30 – 80% of patients with GCA have large-vessel involvement
% of patients with affected vessels

Grayson PC, Ann Rheum Dis 2012; 71:1329
GCA versus Takayasu

• Clinically similar: systemic symptoms, joint symptoms (GCA: PMR), carotidynia

• Age
  • <40 years → Takayasu
  • >50 years → GCA
GCA Classification criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset ≥50 years</td>
<td>Development of symptoms or findings beginning at age 50 or older</td>
</tr>
<tr>
<td>New headache</td>
<td>New onset of or new type of localized pain in the head</td>
</tr>
<tr>
<td>Temporal artery abnormality</td>
<td>Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries</td>
</tr>
<tr>
<td>Elevated erythrocyte sedimentation rate</td>
<td>Erythrocyte sedimentation rate ≥50 mm/1st hour by the Westergren method</td>
</tr>
<tr>
<td>Abnormal artery biopsy</td>
<td>Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
</tbody>
</table>

For purposes of classification, a patient with vasculitis is said to have giant cell arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 94% and a specificity of 91%

DCVAS: ACR criteria sensitivity 78%, specificity 64%

_Hunder GG, Arthritis Rheum 1990;33:1122; Seeliger B et al, 2015 (poster)_
Subsets of GCA

- Cranial GCA
- Large-vessel GCA
Takayasu arteritis criteria

• 1. Age at disease onset <40 years
• 2. Claudication of extremities
• 3. Decreased brachial artery pulse
• 4. BP difference >10 mm Hg
• 5. Bruit over subclavian arteries or aorta
• 6. Arteriogram abnormality

• For purposes of classification, a patient shall be said to have Takayasu arteritis if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.
Temporal artery biopsy (TAB)

- Gold standard for diagnosis of GCA
- A sample of at least 0.5 cm should be excised because inflammatory lesions occur with a patchy distribution
- Very low complications rates
- Negative in at least 10-20% of patients

Classical transmural inflammation

Transmural lymphomomononuclear infiltrate

Disrupted internal elastic lamina

Giant cells found in 50% of cases

Image by Dr. A. Cavazza, Pathology, Reggio Emilia; In: Pipitone N, Versari A, Salvarani A, Oxford Textbook of Rheumatology (submitted)
**Vasa vasorum vasculitis**

Note the preserved media and the lymphocytic infiltration around a small adventitial vessel

*Restuccia G et al, Arthritis Rheum 2012;64:549*
Small vessel vasculitis

Note the small lymphocytic cuffs around periadventitial vessels

Restuccia G et al, Arthritis Rheum 2012;64:549
Positive TAB: associations

Transmural GCA

VVV GCA
SVV GCA

GCA VVV
GCA SVV
Amyloidosis
SNV
PAN
Transmural GCA

Restuccia G et al, Arthritis Rheum 2012;64:549
Clinical relevance of TAB patterns

- Cranial symptoms more common in TMI
- Risk of visual loss and PMR similar in all histological groups

Can the yield of TAB be improved?

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

Germanò G et al, Rheumatology 2015; 54:400
CDS of the TA in GCA

- In 2002, Salvarani et al found that the halo sign of the temporal arteries had a **sensitivity of only 40%** with a specificity of 79% for biopsy-proven GCA.

- A meta-analysis from 2010 demonstrated that the halo sign in the temporal arteries had a **sensitivity of 75%** and a specificity of 83% for biopsy-proven GCA.

- The specificity of the halo sign for the diagnosis of GCA approaches 100% when the sign is bilateral.

CDS evolution over time

1997

2011

Schmidt WA et al, N Engl J Med 1997; 337:1336

Image courtesy of Dr. G. Germanò, Rheumatology, Reggio Emilia
Halo in classic versus non-classic GCA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, n/n (%) (95% CI)</th>
<th>Specificity, n/n (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVV and/or VVV Halo</td>
<td>6/30 (20.0) (8.4, 39.1)</td>
<td>54/67 (80.6) (68.7, 88.9)</td>
</tr>
<tr>
<td>Classic GCA Halo</td>
<td>52/63 (82.5) (70.5, 90.5)</td>
<td>54/67 (80.6) (68.7, 88.9)</td>
</tr>
</tbody>
</table>

Muratore F et al, Rheumatology 2013; 52:2268
The compression test
Images courtesy of Dr. Germanò, Reggio Emilia
CDS for large vessel screening

- Can show a halo and vessel wall thickening in involved large vessels
- CDS has a higher resolution power for superficial vessels compared to CT or MR → excellent tool to screen for vasculitis of the supra-aortic vessels

Pipitone N et al, Rheumatology 2008; 47:403
CDS in new-onset LVV GCA

- Ghinoi A, Rheumatology 2012;51:730: 29%
- Schmidt WA, Clin Exp Rheumatol 2002; 20:309; Rheumatology 2008;47:96: 30%
- Aschwanden M, Ann Rheum Dis 2010; 69:1356: 32%
- Czihal M, Scand J Rheumatol 2012; 41:231: 54%

Supra-aortic vasculitis (+halo) found in most GCA patients with LVV

Lower limb involvement is virtually always associated with supra-aortic vasculitis (Aschwanden M, 2010)

A minority of patients may have aortitis without supra-aortic vasculitis (Prieto-Gonzalez S, Ann Rheum Dis 2012; 71:1170; additional data kindly provided by Prof. Maria C. Cid)
CDS in TAK

- 95% of patients with TAK have signs of vasculitis in at least one epiaortic vessel

CDS in LVV: Limitations

- Cannot visualize the aorta
- Operator-dependent (but training ensures high inter-rater agreement ($\kappa = 0.85$) [Clin Exp Rheumatol 2009; 27(S52):S53])
- Need to differentiate vasculitis from atherosclerosis

Vasculitis
Longitudinal view showing hypoechoic wall swelling (Pipitone N, Best Pract Res Clin Rheumatol 2008)

Atherosclerosis
The wall change is localized only on one side of the artery. It is non-homogeneous and displays a calcification (Eur J Echocard 2010)
MR in large-vessel vasculitis

- Lower resolution than CDS but can visualize like CT deep, large arteries
- Enhancement and thickening of vessel walls sign of vasculitis
- T2 less sensitive than enhanced T1 sequences to detect inflammation

CT in large-vessel vasculitis

- Lower resolution than CDS but can visualize like MR deep, large arteries
- Thickening/enhancement of vessel walls signs of vasculitis

CT in early GCA

- Arterial thickening with or without enhancement

- In 40 untreated (or treated for <3 days) patients with new-onset GCA, CT demonstrated LVV in 68% of patients

FDG-PET for large-vessel vasculitis

Very sensitive - Shows increased FDG uptake by inflamed vessels.

Does not visualize the vessel wall or lumen, nor renal or temporal arteries.

Pipitone N et al, Rheumatology 2008; 47:403
FDG-PET

- A four-point (Meller) scale has been proposed to grade large-vessel FDG uptake

- **Grade 0** = no uptake
- **Grade 1** = minimal uptake (< liver)
- **Grade 2** = moderate uptake (= liver)
- **Grade 3** = marked uptake (> liver)

- **Grade 2 and 3** considered consistent with LVV
PET for large-vessel GCA

- PET showed abnormal vascular FDG uptake in at least one vascular region in 83% of 35 consecutive untreated GCA patients.
- A vascular score (0-3) was calculated for 7 vascular regions (range 0-21).

Blockmans D, Arthritis Care Res 2006; 55:131
Accuracy of PET in LVV

- In GCA
  - Sensitivity 90%
  - Specificity 98%

- In TAK
  - Sensitivity 87%
  - Specificity 73%
FDG-PET versus other imaging

• In a study, PET showed vasculitis in 76% of vascular regions (whole-body MRI 32%)

• In 25 patients with longstanding GCA, PET showed vasculitis in 80% and MRI in 88% of patients with GCA with suspected large-vessel involvement

• In 8 patients with large-vessel GCA, CDS showed vasculitis of upper limbs arteries in 7 patients and PET in 6 patients

• PET and CDS concordant in 11 patients with LV GCA

Limitations of imaging for diagnosis

• Atherosclerosis may cause false-positive results

• Glucocorticoid therapy may cause false-negative results

Intima
Media

B

Intima
Media

B

normal

arteritis

Images courtesy of Dr. G. Germanò, Rheumatology, Reggio Emilia
Patient with active vasculitis

31 consecutive patients with LVV (14 with Takayasu, 17 with GCA with large vessel involvement) underwent PET/CT and right carotid artery CEUS for a total of 35 assessments
CE US in LVV

- CEUS demonstrated severe vascularization within the R carotid artery in 12 examinations
- Patients with severe vascularization had more frequently an IMT >1 mm (100% versus 65%)
- When active vascular 18F-FDG uptake (>2) was considered the gold standard for defining vascular inflammation, carotid CEUS had a sensitivity of 100% and a specificity of 92%

Germano G, paper in press
Glucocorticoids (GC) in TAK

- Most patients initially respond to GC (60% in the NIH series)
- Relapses occur in about 2/3 of cases
- Side effects

Methotrexate (MTX) in TAK

• Used with GC at a mean dose of 17 mg/week in 16 patients with resistant TAK for 6/12 \( (R_x \) duration extended by 6/12 if patients responded by clinical, laboratory, and angiography criteria)

• 13/16 patients remitted (8 sustained remission)

• 7 relapsed on GC tapering to low doses, 3/7 responded again on retreatment

Hoffman GS, Arthritis Rheum 1994; 37:578
Azathioprine (AZA) in TAK

- 15 patients with new TAK treated with GC + AZA 2 mg/kg/day for 1 year

- All patients improved in clinical and laboratory outcomes within 3/12

- No new lesions developed on angiography (8/25 lesions worsened)

Valsakumar AK, J Rheumatol 2003; 30:1793
<table>
<thead>
<tr>
<th>Study</th>
<th>n° of pts</th>
<th>f’up</th>
<th>Previous IS</th>
<th>Clinical effect</th>
<th>Lab markers</th>
<th>Imaging</th>
<th>GC dose decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daina E, 1999</td>
<td>3</td>
<td>11/12</td>
<td>100%</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>23 → 15 mg/day</td>
</tr>
<tr>
<td>Shinjo SK, 2007</td>
<td>10</td>
<td>23/12</td>
<td>50%</td>
<td>✓</td>
<td>✓</td>
<td>Not done</td>
<td>25 → 6 mg/day</td>
</tr>
<tr>
<td>Goel R, 2010</td>
<td>21 (90% active)</td>
<td>3-10/12</td>
<td>48%</td>
<td>✓</td>
<td>✓</td>
<td>Not done</td>
<td>36 → 19 mg/day</td>
</tr>
<tr>
<td>Caltran E, 2014</td>
<td>2</td>
<td>24/12</td>
<td>CYC</td>
<td>✓</td>
<td>✓</td>
<td>1 PET+ 1 imag.+</td>
<td>8-500 → 4 mg/day</td>
</tr>
</tbody>
</table>

**MMF IN TAK**
ASA in TAK

• ASA at 20 mg/kg inhibits interferon-γ

• Low-dose ASA decreases cardiac and CV ischemic events (14% in patients treated with ASA, 82% in patients not receiving ASA, follow-up 6 years). Prevention most effective in patients with advanced vascular complications

Anti-TNF-α agents in TAK

- 120 patients with TAK reported to date
- Infliximab most commonly used, often in association with a synthetic DMARD, especially MTX
- Remission rates of 70-90%
- Improvement seen within 2 weeks to 2 months
- GC discontinued in 40%
- Still, relapses occur in nearly 40%
- Increased dosing, decreased treatment intervals, or switch to another anti-TNF-α required in ½ of patients

Clifford A, Hoffman GS, Curr Opin Rheumatol 2014; 26:7
## Rituximab (RTX) IN TAK

<table>
<thead>
<tr>
<th>Study</th>
<th>n° of pts</th>
<th>f’up</th>
<th>Previous IS</th>
<th>Clinical effect</th>
<th>Lab markers</th>
<th>Imaging</th>
<th>GC dose decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ernst D, 2012</td>
<td>1</td>
<td>14/12</td>
<td>YES; ongoing AZA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>30 → 5 mg/day</td>
</tr>
<tr>
<td>Hoyer BF, 2012</td>
<td>3</td>
<td>≥33/12</td>
<td>YES; ongoing IS</td>
<td>✓</td>
<td>✓</td>
<td>✓ (1/1)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Caltran E, 2014</td>
<td>2</td>
<td>24/12</td>
<td>YES; ongoing IS</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>500-8 → 4 mg/day</td>
</tr>
</tbody>
</table>
Tocilizumab (TCZ) IN TAK

- 44 cases
- TCZ mostly used at 8 mg/kg
- Median follow-up 15/12
- Clinical improvement at 6/12 in 78%
- Laboratory improvement at 6/12 in 89%
- PET imaging response in 57%
- Prednisone dose decrease from 15 to 10 mg/day

Abisror N, Autoimmunity Reviews 2013; 12:1143
TCZ versus anti-TNF in TAK

Circulation 2015; 132:1693
Other drugs

- Ciclosporin
- Cyclophosphamide
- Leflunomide
- Tacrolimus
Glucocorticoids in GCA

- GC still mainstay of treatment
- Prednisone should be used at 40-60 mg/day (1 mg/kg/day in patients at risk of ischemic events)
- Pulse GC not shown to be superior to high-dose oral GC in preventing ischemic events
- However, pulse GC at onset associated with a lower cumulative GC dose and sustained remission
- GC prevent, but usually do not revert, visual loss
- Alternate-day treatment imparts a high risk of flares
- Slow tapering reduces, but does not abolish, the risk of flares

Pipitone N, Salvarani C. Curr Opin Rheumatol 2008;20:17
DMARD in GCA

- Azathioprine (AZA) at a dose of 2 mg/kg/day has modest steroid-sparing properties in GCA which becomes apparent after 2 years.

- Methotrexate (MTX) at 11 mg per week reduces the risk of a first and a second relapse by 35% and 51%, respectively by ≥24 weeks.

- No evidence that AZA or MTX reduce the frequency/severity of GC-related adverse events.

Low-dose ASA in GCA

- Two retrospective studies have suggested that low-dose aspirin might prevent ischemic complications related to GCA (with 8% versus 29% and 16% versus 48% of those on ASA developing ischemic events compared to those not on ASA)
- Two other retrospective studies have not confirmed these findings
- A prospective trial is needed
- GC are very effective in preventing ischemic events

Salvarani C, Rheumatology 2009;48:250; Gonzalez-Gay MA, J Rheumatol 2000;27:2179
Biological agents in GCA

- TNF-alpha inhibitors
- Tocilizumab (IL-6R inhibitor)
Treatment of GCA – Anti-TNF

- RCT in recent-onset GCA: anti-TNF-α agents not effective


- Infliximab beneficial in 3 out of 4 patients with longstanding GCA

- Etanercept had steroid-sparing effects in relapsing GCA patients that had GC-related side effects

Relapse-free survival achieved in 17 (85%) patients in the TCZ group and two (20%) in the placebo group by week 52

Villiger P, Lancet 2016
Tocilizumab in GCA

- 33 patients treated so far (as reported in the literature) – 15 with cranial GCA, 18 with LVV

- TCZ used as monotherapy in 6 patients

- Two patients had failed major immunosuppressants
Tocilizumab in GCA

- Partial or complete response achieved in 94% of cases (one dubious response, one death – autopsy showed active vasculitis)

- Imaging improved in 100% when done
Other drugs used in GCA

• CYC
• Abatacept
• Leflunomide
Thank you for your attention