Giant cell arteritis: what is beyond steroid therapy

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Evidence Based Medicine

- The BSR/BHPR guidelines on Giant cell arteritis Rheumatology (Oxford) 2010; 2010; Aug 49(8):1594-7
- Fast-Track Pathway In Giant Cell Arteritis: A Cost-Effectiveness Analysis; ACR/AHP 2013 Tuesday, October 29, 2013,
- Design of the Tocilizumab in Giant Cell Arteritis Trial International Journal of Rheumatology Volume 2013, 912562, doi.org/10.1155/2013/912562 Epub April 7

Areas covered

- New clues on pathogenesis
- Diagnostic challenge, ultrasound, TABUL
- Sight loss & Fast track GCA pathway
- Promises and pitfalls of glucocorticoids
- Experience with disease modifying agents
- Biologics in GCA
- Raising awareness — role of patient groups
- What might the future look like for GCA patients?

Role of Annexin A1
Are neutrophils involved in GCA?

- Increase in circulating neutrophils and activation at 24 weeks
- 24 wk cells expressed a pro-adhesive phenotype
- Loss of suppressor neutrophils sub-population
- Evidence of a sub-clinical disease re-emergence?

Nadkarni et al Circ Res 2013

Disclosures

- Grants from EULAR, ACR
- Honoraria and consultancies
- Merck
- Amgen
- Mundipharma
- Astra Zeneca
- Roche

Evidence Based Medicine

- NKG2D stimulated T-cell autoreactivity in giant cell arteritis and polymyalgia rheumatica

- NKG2D – activating natural killer receptor expressed by senescent CD4+ T-cells
- NKG2D+CD4+ T-cells increased in GCA/PMR
- NKG2D positive T-cells mainly present in adventitia of GCA samples
- NKG2D ligand MICA strongly expressed in adventitia and media of GCA biopsies

Dejaco C, Duffner C et al, ARD 2013
Temporal artery biopsies

- Diagnostic gold standard
- Provide prognostic information
- Early TAB is desirable in all cases, preferably within a week of starting steroids.
- Biopsy specimens should be a minimum of 1 cm in length, ideally 2 cm or more
- Contra-lateral biopsies are not required
- All sites should link with a surgical unit

Dasgupta et al Rheumatology (Oxford) 2010; Aug 49(8):1594-7

Intimal hyperplasia is related to ischemic complications

<table>
<thead>
<tr>
<th>IH Score</th>
<th>n</th>
<th>NOC n (%)</th>
<th>Mean age</th>
<th>Male n</th>
<th>Median ESR</th>
<th>Median CRP</th>
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<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>0(0)</td>
<td>75.6</td>
<td>2</td>
<td>74</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>3(21)</td>
<td>76.5</td>
<td>2</td>
<td>84</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>6(75)</td>
<td>79.0</td>
<td>4</td>
<td>74</td>
<td>101</td>
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<tr>
<td>4</td>
<td>4</td>
<td>3(75)</td>
<td>78.8</td>
<td>2</td>
<td>82</td>
<td>105</td>
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</tbody>
</table>


Prognostic impact of Intimal hyperplasia on biopsy

- 30 consecutive cases with positive TA
- Degree of intimal hyperplasia graded
  - Grade 1 <50% luminal occlusion
  - Grade 2 50-75% occlusion
  - Grade 3 as >75% occlusion
  - Grade 4 complete occlusion

Rho positive staining in TAB

- Th17 cells and cytokines implicated in GCA
- ROCK activation associated with Th17 differentiation
- PERM staining, surrogate for ROCK activation
- GCA cases- both TAB positive and negative had more intense pERM staining in TAB specimens – compared to controls

Lally et al ACR 2013 Abstract no 896

Temporal artery ultrasound

- ‘Halo sign’ - Meta-analysis evaluating 23 studies – sensitivity 87%, specificity 96%
- Wall swelling, stenosis, occlusion
- Axillary artery can be included

Primary objectives:

- To evaluate the diagnostic accuracy (sensitivity and specificity) of Ultrasound (U/S) vs. TAB
- To evaluate the cost-effectiveness of Ultrasound vs. TAB

Study Design

- To recruit n=402 participants to give 90% power with 5% type I error
- To detect sensitivity change from 76% (TAB) → 87% (U/S)
- To detect specificity of U/S ≥ 0.83 (expected TAB = 0.96)

Chief Investigator: Raashid Luqmani, Oxford

Limitations of ultrasound

- Requires expertise and a learning curve
- At least 10 scans and several ‘hot cases’ before signing off beginners
- Highest positivity within 24-48 of steroids
- Variability in equipment and settings
- Standardisation of image acquisition
- Each examination can take 30-40 minutes
Large vessel GCA in PMR

How do we reduce sight loss?

Fast track pathway for GCA

Rationale for FTP in GCA

- Analogous to the ‘Time is Brain’ ACT-FAST campaign in stroke, ‘Time is Sight’ in GCA.
- Urgent recognition and prompt institution of GC therapy is key element in management of GCA.
- A retrospective audit in 2009 demonstrated delays from symptom onset to diagnosis, with a high incidence of visual loss.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes</th>
<th>No</th>
<th>%</th>
<th>Symptom onset to diagnosis Mean Time from:</th>
<th>Symptom onset to diagnosis Duration in days</th>
<th>Symptom onset to initial steroid mean time from</th>
<th>Diagnosis to initial steroid Mean Time from:</th>
<th>Diagnosis to biopsy Mean Time from:</th>
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</thead>
<tbody>
<tr>
<td>Headache</td>
<td>54</td>
<td>11</td>
<td>83</td>
<td></td>
<td>31 (4-112)</td>
<td>17 (3-56)</td>
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<td>6</td>
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<tr>
<td>Scalp tenderness</td>
<td>27</td>
<td>13</td>
<td>40</td>
<td></td>
<td>28 (2-84)</td>
<td>17 (3-56)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>31</td>
<td>30</td>
<td>47</td>
<td></td>
<td>32 (7-84)</td>
<td>36</td>
<td>2-337</td>
<td>0-23</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>23</td>
<td>32</td>
<td>40</td>
<td></td>
<td>35</td>
<td>2-337</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Vision loss</td>
<td>19</td>
<td>42</td>
<td>29</td>
<td></td>
<td>36</td>
<td>2-337</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>21</td>
<td>32</td>
<td>32</td>
<td></td>
<td>36 (14-112)</td>
<td>2-337</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>TIA</td>
<td>5</td>
<td>43</td>
<td>7.7</td>
<td></td>
<td>567</td>
<td>2-337</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Polymyalgia</td>
<td>18</td>
<td>39</td>
<td>29</td>
<td></td>
<td>567 (7-140)</td>
<td>2-337</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Mean Time from:
- Symptom onset to diagnosis: 35 days range 2-336
- Diagnosis to initial steroid: 0 days range 0-30
- Diagnosis to biopsy: 6 days range 0-23


Obstacles to early recognition

- Delayed presentation
- Delayed referral: failure to recognize symptoms/urgency
- Delayed therapy: Multiplicity of referral routes

INITIAL REFERRER
Suspicion of GCA

CONTACT RHEUMATOLOGY DEPARTMENT
Start high dose steroids without delay

1 working day

FTM GCA assessment

Within 24hrs

TEMPORAL ARTERY ULTRASOUND

Within 7 days

TEMPORAL ARTERY BIOPSY

2 weeks

GCA Clinic
2nd review

Agreed by Joint service development Board

ACR 2013 Poster no 1928, Patil et al. Outcomes of the Fast track pathway in GCA

SOUTHEND FAST TRACK GCA PATHWAY
Types of sight loss in conventional and fast track pathways

<table>
<thead>
<tr>
<th>Type of sight loss</th>
<th>GCA – conventional (n=17)</th>
<th>GCA – fast track (n=3)</th>
</tr>
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<tbody>
<tr>
<td>Partial, monocular</td>
<td>6 (35.3)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Complete, monocular</td>
<td>8 (47.1)</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Partial, bi-ocular</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Complete, bi-ocular</td>
<td>3 (17.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Results

- The percentage of GCA patients presenting with vision loss between 2003-2011 varied from 23 to 29%.
- In contrast, in 2012, 3/33 (9%) patients presented with vision loss.
- The ‘symptom to steroid time’ decreased from 46.5 days (range 7-224) in 2008 to 30.25 days (range 0-168) in 2012.

Cost effectiveness of FTP

Methodology

- Patient-level data of hospital and GP activity in relation to GCA management over first 6 months was collected with respect to:
  - GP appointments
  - A&E attendances
  - Out-patient appointments (Rheumatology, Neurology, Ophthalmology)
  - In-patient stays
  - Readmissions
  - Investigations
  - Medications

- Costs associated with treating a patient with suspected GCA before and after implementation of the FTP:

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Saving</th>
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<tbody>
<tr>
<td>Medication</td>
<td>£190</td>
<td>£190</td>
<td>£0</td>
</tr>
<tr>
<td>Investigations</td>
<td>£330</td>
<td>£290</td>
<td>£40</td>
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<tr>
<td>GP Attendances</td>
<td>£55</td>
<td>£50</td>
<td>£5</td>
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<tr>
<td>Outpatient Appointments</td>
<td>£665</td>
<td>£620</td>
<td>£45</td>
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<tr>
<td>Inpatient</td>
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<td></td>
<td></td>
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<tr>
<td>Inpatient stays</td>
<td>£1,100</td>
<td>£475</td>
<td>£625</td>
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<tr>
<td>Emergency presentations</td>
<td>£70</td>
<td>£50</td>
<td>£20</td>
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<tr>
<td>Readmissions</td>
<td>£190</td>
<td>£0</td>
<td>£190</td>
</tr>
<tr>
<td>Training of GP's</td>
<td></td>
<td>£525</td>
<td></td>
</tr>
<tr>
<td>Total Per Patient</td>
<td>£2,600</td>
<td>£2,200</td>
<td>£400</td>
</tr>
</tbody>
</table>

Average cost of diagnosing and treating a patient with suspected GCA

- Conventional pathway: £2,600
- Fast-Track pathway: £2,200

- A difference of £400 per patient treated for suspected GCA.
- A difference of 0.2 QALY’s between patients with and without sight loss due to GCA.
- Gain in QALY’s of 2.6 in those that didn’t lose sight.
- The ICER of implementing the FTP = -£840 per QALY.

Social costs of Blindness

- Low vision clinic assessment, provision of low vision aids, training in their use
- Low vision rehabilitation in activities for daily living
- Acute admission to geriatric ward for broken hip, total hip replacement, rehabilitation
- Registration as blind or partially sighted
- Community care— provision of a home care worker
- Social security benefits, in particular attendance allowance
- Blind person’s tax allowance
- Treatment and support of depression in the elderly

C Meads and C Hyde; Br J Ophthalmol 2003 87: 1201-1204
Why is better treatment needed?

Glucocorticoids & GCA

- Long term steroids are mainstay of treatment
- Prolonged therapy duration of at least 12-18 months, often long term
- Relapsing disease course (>50% relapse rate) resulting in high cumulative steroid dose
- Steroid resistant disease also seen
- Most cases (86%) have steroid-related side events
- 3 fold increased risk of diabetes (Proven 2003)
- Five fold increased risk of hip fracture

Steroid sparing therapies & GCA

- Methotrexate (Jover et al, 2001)
- Methotrexate (Spiera et al 2001)
- Methotrexate (Hoffman et al 2002)
- Meta-analysis of 3 studies (Mahr et al, 2007)
- Azathioprine (de Silva et al, 1986)
- Cyclophosphamide (de Vita et al, 1992)
- Ciclosporin (Schaufelberger et al, 1998)

Leflunomide in GCA

Adizei et al, 2012
- Case series Difficult to treat GCA (8)
- Partial/complete response achieved in 21/23
- Well tolerated, decrease in inflammatory markers, Decreased steroid doses

Diamantopoulos et al 2013
- Case series refractory GCA (11)
- 12.4 mg/dl (CI 95% 7.7-25.5, p=0.06) reduction in CRP
- 6.6 mg (CI 95% 2.8-10.3, p<0.01) reduction in prednisolone dose

Unmet need: Biologics

- Infliximab (Hoffman et al, 2007)
- Etanercept (Martinez-Taboada et al, 2008)
- Rituximab case reports (Bhatia A et al, 2005)
- Adalimumab (Mariette et al 2011)
- Trial of Abatacept is ongoing
Interleukin-6 in PMR/GCA

Rationale of IL-6 blockade

- Interleukin-6 (IL-6) is a key player in the pathogenesis of LVV.
- IL-6 is upregulated in inflamed arteries of patients with GCA and in the peripheral circulation.
- Serum levels mirror disease activity and decline with effective GCs therapy.

TCZ treatment of refractory FDG PET positive large vessel vasculitis

- 7 patients: 2 PMR, 4 GCA (1 initial PMR), 1 Patient with only constitutional symptoms
- All GCA patients were biopsy positive
- All had 18F-FDG PET- CT confirmed LVV
- All had prior steroid toxicity (Cushingoid, weight gain, hypertension, cataract) and poor response to IV/IM/oral steroids
- Refractory to steroids/DMARDs (MTX, Lef)
- Treated with TCZ 8mg/kg / 4week infusions
- Response assessed in terms of clinical and patient reported assessment, PMR/GCA symptoms and Inflammatory markers

Ultrasound right axillary artery

US right axillary artery pre-TCZ

US right axillary artery post 11 cycles TCZ

68 Years Old
6 Months Constitutional symptoms
Limb claudication
Polymyalgia Onset of LVV

Ultrasound right axillary artery

CT-A axillary artery occlusion
PET
Flare

63 Years Old
GCA
With severe constitutional symptoms
Bowel angina
CT-A: SMA stenosis
CRP average: 130

Steroid toxicity
Steroid dose was gradually reduced with return of headaches and rise in CRP. TCZ started with resolution of symptoms

Ultrasound right axillary artery

PET scan 4 months

TCZ

Flare

D 0  D 27  D 45  D 63  D 70  D 98  D 130  D 187  D 201  D 251  D 293  D 329  D 393  D 400

0  10  20  30  40  50  60  70

TCZ

Flare

D 0  D 14  D 28  D 44  D 76  D 89  D 123  D 167  D 180  D 227  D 257  D 337

0  10  20  30  40  50  60  70
• Known PMR
• GCA
• Severe constitutional symptoms
• CRP 244

63 year old

PET scan 3 months - partial metabolic response

Transient neutropenia - resolved on reducing dose to 4mg/kg

Flare

Outcome

• All patients achieved complete response on TCZ 6-12 infusions 8m/Kg monthly
• Relapses seen post stopping TCZ: 5
• Recurrent infections: 2 patients
• Hypercholesterolemia: 1 patient
• Transient neutropenia: 1 patient

Other therapy targets

• Modified release prednisone
• IL1 Blockade
• Other forms of IL-6 blockade
• Preventing vasculitic cell accumulation in vessel wall
• STAT pathway inhibition
• JAK Kinase inhibition

GIACTA: RCT of TCZ in new/refractory biopsy positive GCA or PMR with LVV

Standards of Care for GCA

what we need to do

• Address factors that prioritise NICE guidance:
• Burden of disease (population affected, morbidity, mortality)
• Factors stressing timeliness/urgency for guidance: preventable disability from GCA, sight loss, steroid AEs, large vessel involvement, aneurysms versus available effective and safe treatment
• Resource impact (i.e. the cost impact on the NHS or the public sector)
• Inappropriate variation in practice: emphasize that all patients need secondary care referral/investigations

A three day Symposium & Imaging Workshop on Polymyalgia Rheumatica (PMR), Giant Cell Arteritis (GCA) & Large Vessel Vasculitis (LVV)
22nd to 24th November 2013
Southend Airport Holiday Inn
77 Eastwood Crescent, Southend-on-Sea, Essex, SS2 6XG

The symposium will deliver an update on pathogenesis, clinical research and trials, guidelines, management, outcomes, patient experience and pathways for PMR, GCA & LVV.
A highlight of the meeting will be the imaging workshop with vascular radiologists, vascular surgeons and rheumatologists, to discuss different imaging modalities including vascular ultrasound for large vessel vasculitis and conditions seen mimicking diagnoses.

15th September 2013
Acknowledgment

• Department of Health
• Lord Frederick Howe
• Health Minister
• Lord Michael Wills
• NHS England
• NHS South Essex
• Castle Point & Rochford; Southend Clinical commissioning groups.
• Patients and their referring physicians
• PMRGCAUK, PMRGCA North East, PMRGCA Scotland, regional groups
• Fight for Sight
• Wolfgang Schmidt
• TABUL study team
• BSR guidelines group
• Members of the GCA work group
• Eric Matteson
• ACR & EULAR