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

CanVasc meeting
Montreal
Nov 22 2012
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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

Souza Freitas D. Rheumatol Int (2012) 32:703–709
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
Souza Freitas D. Rheumatol Int (2012) 32:703–709
Résonance magnétique et angio-IRM

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%

Souza Freitas D. Rheumatol Int (2012) 32:703–709
Medical therapy

- **Azathioprine:**
  - steroid sparing (no control group)

- **Mycophenolate mofetil:**
  - remission (although not achieved by others)

- **Cyclosporine:**
  - improvement, decrease in prednisone doses

- **Cyclophosphamide:**
  - mixed results, toxicity

- **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

<table>
<thead>
<tr>
<th>Number of evaluable patients</th>
<th>Baseline assessment (n = 15)</th>
<th>3-month evaluation (n = 15)</th>
<th>6-month evaluation (n = 13)</th>
<th>12-month evaluation (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab efficacy (by physician), n (%)</td>
<td>–</td>
<td>13 (87)</td>
<td>10 (77)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Disease clinical activity, n (%)</td>
<td>11 (73)</td>
<td>3 (20)**</td>
<td>4 (31)*</td>
<td>3 (27)*</td>
</tr>
<tr>
<td><strong>Infliximab-associated treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSs (prednisone), n (%)</td>
<td>14 (93)</td>
<td>12 (80)</td>
<td>11 (85)</td>
<td>10 (92)</td>
</tr>
<tr>
<td>CSs (prednisone, mg/day)</td>
<td>20 (5-35)</td>
<td>15 (5-20)**</td>
<td>7.5 (5-18)*</td>
<td>6 (2.5-30)*</td>
</tr>
<tr>
<td>Steroid dependence, n (%)</td>
<td>8 (53)</td>
<td>2 (13)*</td>
<td>0**</td>
<td>1 (9)*</td>
</tr>
<tr>
<td>MTX, n (%)</td>
<td>7 (46)</td>
<td>8 (53)</td>
<td>6 (46)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>MTX, mg/week</td>
<td>15 (7.5-25)</td>
<td>15 (7.5-20)</td>
<td>15 (5-15)</td>
<td>15 (5-20)</td>
</tr>
<tr>
<td>AZA, n (%)</td>
<td>4 (27)</td>
<td>4 (27)</td>
<td>4 (31)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>AZA, mg/day</td>
<td>125 (100-175)</td>
<td>125 (100-175)</td>
<td>100 (100-175)</td>
<td>100 (100-175)</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological activity, n (%)</td>
<td>11 (75)</td>
<td>4 (27)*</td>
<td>4 (31)**</td>
<td>4 (42)**</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>60 (12-100)</td>
<td>15 (6-32)*</td>
<td>10 (4-64)*</td>
<td>8 (2-60)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>30 (4-70)</td>
<td>5 (0-57)*</td>
<td>6 (0-50)*</td>
<td>9 (0-100)</td>
</tr>
<tr>
<td>Fibrinogen, g/l</td>
<td>5.5 (3-7.5)</td>
<td>3 (1-6.5)*</td>
<td>2.5 (2-6)*</td>
<td>2 (2-4)</td>
</tr>
<tr>
<td>Leucocyte count, 10³/mm³</td>
<td>11 (2.4-20)</td>
<td>6 (3.6-15)*</td>
<td>6 (4.2-15)***</td>
<td>6 (3.8-16)</td>
</tr>
</tbody>
</table>

Values are medians with ranges or frequencies with percentages. Steroid dependence: prednisone ≥ 20 mg/day. Associated treatments were all initiated before infliximab. *P < 0.05 vs baseline, **P < 0.005 vs baseline, ***P = 0.06.
Biologics in Takayasu arteritis: TNF inhibitors

<table>
<thead>
<tr>
<th>Author, year (ref.)</th>
<th>No. of patients</th>
<th>Type of TNF inhibitor: no.</th>
<th>Remission</th>
<th>Sustained remission</th>
<th>Relapse</th>
<th>New arterial lesion during TNF inhibitor use</th>
<th>CS cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>20</td>
<td>Inflix: 17, Etan: 1, Ada: 2</td>
<td>18/20 (90)</td>
<td>10/20 (50)</td>
<td>6/18 (33)</td>
<td>0</td>
<td>7/12 (58)</td>
</tr>
</tbody>
</table>

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

Carlo Salvarani¹, Luca Magnani¹, Mariagrazia Catanoso¹, Nicolò Pipitone¹, Annibale Versari², Lucia Dardani¹, Lia Pulsatelli³, Riccardo Meliconi⁴ and Luigi Boiardi¹

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

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.

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

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

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
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

Arthritis Care Research 2012; 64: 1720-1729
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