Takayasu Arteritis: How do I treat, how do I follow?

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Disclosures
• No FDA approved therapies for TAK
• All agents discussed constitute off-label use
• Research Grant
  – Roche
• Advisory Board/Speaker Fees
  – MSD, Pfizer

Evidence Based Medicine
• Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Arthritis Rheum 2007;56:1000-9
• Keser G, Direskeneli H, Aksu K. Rheumatology 2013 Oct 4 (epub)

Summary
• Primary Idiopathic large vessel vasculitis
• Typically a granulomatous arteritis
• Aorta and first order branches
• Age <50 years
• F>M (61-97%)
• Diverse racial profile
  – In US, Caucasian > Asian
• Incidence 2.6/million (USA), varies

Takayasu Arteritis

IF YOUR “GUT” ISN’T EXPERIENCED, GO WITH YOUR HEAD

KESER G, DIRESENEILI H, AKSU K. RHEUMATOLOGY 2013 OCT 4 (EPUB)
Objective 1

Describe the modalities available in assessing disease activity in Takayasu arteritis

Elements of Assessment

- History
- Physical
- Lab tests
- Imaging Studies

Symptoms

- SYSTEMIC
  - Fever
  - Weight loss
  - Fatigue/malaise
  - Myalgia/arthralgia

- ARTERIAL COMPROMISE
  - Limb claudication
  - Abdominal angina
  - Dissection/Aneurysm
  - Angina/Heart failure
  - Lightheadedness
  - TIA/CVA

- ARTERIAL INFLAMMATION
  - Headache
  - Thoracic pain
  - Carotidynia

- Asymptomatic disease progression can occur

How good is clinical exam?

- N= 100 patients (TAK = 68, GCA = 32)
- Standardized physical exam
  - 67% at least 1 or more abnormality (74% TAK, 53% GCA)
- Angiography carotid, subclavian, and axillary arteries
  - Arteriographic lesions in 76% (82% TAK, 63% GCA)

- Individual physical exam findings had poor sensitivity (range 14%-50%) and good-excellent specificity (range 71%-98%) to detect arteriographic lesions

- Considering physical exam findings in combination, at least 30% of arteriographic lesions were missed

Examination

- Peripheral pulses
- New onset hypertension
- BP symmetry —arms/legs
- Vascular bruits
- Tenderness e.g. carotid
- Cardiac auscultation
  — NB aortic regurgitation
- Fundoscopy
- Urinalysis

Correlation between Physical Exam and Imaging Findings

- Abnormal vascular system findings on physical examination are highly associated with the presence of arterial lesions
- Normal findings on physical examination do not exclude the possibility of arterial disease
- Serial angiographic assessment is advisable to monitor arterial disease in patients with established LVV

Grayson et al J Rheum 2012
Laboratory testing

- Regular Testing
  - ESR, CRP, CBC, Chem panel (incl Creat, AST/ALT)
- Assess disease activity
- Complications of therapy
- End organ damage
- Other co-morbidities
  - e.g. fasting lipids, glucose

How useful are ESR/CRP?

- 25% normal during active disease
- 46% have normal APRs with new MR changes or elevated APRs with unchanged MR
- If APRs normal – ongoing vigilance for activity
- If Elevated APRs
  - Rule out infection/other cause
  - Evaluate for active disease including imaging
  - Avoid treating purely based on elevated APRs

Is there a better biomarker?

- IL6
- SAA
- Fibrinogen
- Complement split fragments
- BAFF
- IL12
- MMP9
- PTX3

No proven biomarker for assessing disease activity

Imaging Modalities

- CT
- MR
- PET/PET-CT
- US
  - (Catheter-directed angiography)

- Best for Diagnosis?
- Best for follow-up?
- Influenced by therapy?
- Predict complications?
- How often?

At least as many questions as modalities......

Catheter-Directed Angiography

**PRO:**
- Historical gold standard for visualization of vascular lesions
- Can get accurate BP
- Permits vascular intervention

**CON:**
- Lumen only
- Radiation, IV contrast
- Invasive - infection, hemorrhage, vascular injury

MR Angiography

**PRO:**
- Lumen + vessel wall
  - Stenoses/aneurysms
  - Thickening/enhancement
- Non-invasive, no radiation

**CON:**
- Interpretation of increased signal, thickening uncertain
- Cost, availability
- Gadolinium
- Claustrophobia
- Pacemaker/implantable devices
CT Angiography

PRO:
- Availability
- Well tolerated
- Structural abnormalities
- Thickening/enhancement
- Calcification (atheroma)

CON:
- Radiation
- Contrast toxicity
- Relevance of persistent thickening

Ultrasound

PRO:
- Well tolerated
- No radiation/contrast
- Structural abnormalities
- Wall oedema

CON:
- Operator dependent
- Availability
- Unable to visualize thoracic aorta

PET

PRO:
- Vascular FDG uptake
- Non-invasive
- Whole body assessment

CON:
- CT needed to study lumen
- Interpretation of low grade uptake uncertain
- Isotope/radiation
- Cost, availability

Potential Pitfalls

- Worsening claudication with progression of pre-existing stenosis, may occur due to secondary atherosclerosis, fibrosis
  - Esp if cofactors smoking, HTN, HPL, DM
- Aneurysmal enlargement – may occur due to mechanical factors, esp with HTN
- Variable change in wall thickening/enhancement despite treatment – uncertain significance
- Only a new lesion in a previously unaffected vascular territory should be regarded as active disease

Imaging for monitoring disease activity

- In patients with established LVV – serial screening advised
- Evidence of 1 new vascular lesion should prompt a thorough evaluation for others (may be asymptomatic)
- Imaging aorta and all first order branches – neck – pelvis
- Other dedicated imaging of e.g. cerebral/coronary vessels based on symptoms/signs, past involvement

Imaging: Summary

- Optimal modality?
  - No published comparative studies
  - No gold standard – tissue correlate rarely available
  - Cost/accessibility vs radiation/toxicity
- VCRC study (USA): MR vs PET/CT
Imaging – How often?

- Modality/patient factors/cost/availability
- If relapse suspected based on clinical findings/acute phase response
- At least annually – even when clinical and lab parameters suggest inactive disease
  - Rule out asymptomatic disease progression
  - Evaluate for worsening due to mechanical factors
- Individual patients – more frequent – e.g. 6 monthly
- MR preferable on this basis

Disease Activity Assessment

- Kerr Criteria (NIH criteria)
  - New/worsening of at least 2 of the following:
    - Systemic symptoms/signs
    - Elevated ESR/CRP
    - Symptoms/signs of vascular insufficiency
    - New vascular lesions on serial imaging studies
- DEI-TAK
- Indian Takayasu Activity Score (ITAS)
- OMERACT

A validated disease activity score is a significant unmet need for TAK

Histology

- Rarely available
- Surgery generally undertaken in remission
- Bypass into ‘normal’ appearing vessel segment
- Approx half surgical specimens show active vasculitis
- 20% clinically active
- 93% active aortic infiltrates
  - Clifford et al (abst 1070 ACR 2013)

Elements of Assessment

- History
- Physical
- Lab tests
- Imaging Studies
- Histo-pathology

Careful consideration of all available information

Corticosteroids

- Prednisone 40-60 mg (1 mg/kg/day)
- Maintain dose for 1 month
- Taper by 5 mg/week until 20 mg/day
- Taper by 2.5 mg/week until 10 mg/day
- Taper by 1 mg/week until discontinuation

Objective 2

Describe the standard of care in the treatment of Takayasu arteritis
Corticosteroids: Outcomes

- Remission achieved in 60%
- Relapses occur in > 50% during taper

Disease control with prednisone alone?

- Infrequent (20%)
- 66-84% patients require other immunosuppressives
  - Maksimowicz-McKinnon K et al. Arthritis Rheum. 2007
  - Schmidt J et al. Mayo Clinic Proc 2013

Adverse Effects of Glucocorticoids

- Musculoskeletal:
  - Osteoporosis, fracture
  - Avascular necrosis
  - Myopathy
- Skin/soft tissues:
  - Striae
  - Thinning, purpura
  - Hirsutism, acne
  - Poor wound healing
  - Weight gain, body habitus changes
- Cardiovascular:
  - Hypertension
  - Dyslipidemia
  - Accelerated atherosclerosis
- Infectious:
  - Typical infections
  - Opportunistic agents
- Ocular:
  - Cataract
  - Glaucoma
- Neuropsychiatric:
  - Sleep disturbance
  - Akathisia
  - Anxiety
  - Depression/mania
  - Psychosis
- Endocrine:
  - Impaired glucose tolerance
  - Diabetes mellitus
  - HPA axis suppression
- Gastrointestinal:
  - Peptic ulcer disease, gastritis
  - Pancreatitis
  - Steatohepatitis
  - Visceral perforation

TAK: Initial Treatment

- Prednisolone
- Bisphosphonate
- Calcium/Vit D
- PPI
- Statin
- Anti-HTN
- Diabetic Rx

Other Agents

- Methotrexate
  - Hoffman et al Arthritis Rheum 1994 (n=16)
- Azathioprine
  - Valsakumar et al J Rheumatol 2003 (n=15)
- Mycophenolate mofetil
  - Shinjo et al Clin Rheumatol 2007 (n=10)
  - Goei et al Clin Rheumatol 2010 (n=20)
- Leflunomide
  - De Souza et al Scand J Rheumatol 2012 (n=15)
- Cyclophosphamide

None of these agents have been evaluated for TAK in a RCT

Relapsing disease

- Prednisone is increased by 10 mg over the last effective dose
- Methotrexate or Azathioprine is added
- Mycophenolate Mofetil 3rd line
- Cyclophosphamide for immediately life-threatening disease
  - Maksimowicz-McKinnon et al., Arthritis Rheum 2007
Second agent at first presentation?

- High likelihood of relapse
- All patients?
- If arterial damage? (stenosis/aneurysm)
- MTX/AZA

Aspirin?

- Lower frequency of ischemic events in TAK
  -- De Souza et al Circ J 2010

- Conflicting reports for GCA
  -- Decreased risk of cranial ischemic events
    - Lee MS et al Arthritis Rheum 2006
    - Nesher G et al Arthritis Rheum 2004
  -- No protective effect
    - Salvarani C et al Rheumatology 2009
    - Berger CT et al Rheumatology 2009

Low threshold for all, routinely for those with arterial stenosis/occlusion

Hypertension

- New onset HTN
- Renal artery stenosis (up to 80%)
- Aortic stiffness
- Headaches
- Congestive cardiac failure
- Hypertensive retinopathy
- Stroke incl. cerebral hemorrhage
- Renal insufficiency/proteinuria
- MAY GO UNRECOGNISED

Case

- 48-year-old female
- 28-year Hx of Takayasu arteritis (TA)
- Four right femoral bypass graft procedures
- Two aortoiliac bypass grafts
- The extent of her arterial disease:
  -- Stenoses of bilateral subclavian arteries, left renal artery, infra-renal aorta, superior and inferior mesenteric artery
  -- Stable pseudoaneurysm at the origin of right common iliac artery, which is occluded below this level

Treatment

- Medications:
  -- Methotrexate 15mg/weekly
  -- Infliximab 5mg/kg 6-weekly
  -- Aspirin
- TA stable since the introduction of infliximab
  -- No clinical or radiological progression
- Stable TA symptoms - bilateral leg claudication, left arm numbness on elevation
**Routine followup: right CRVO**
Mild headaches in weeks prior
Central aortic hypertension on angiography – gradient 30mmHg to right arm

**Objective 3**
Describe the emerging treatment options of Takayasu arteritis

**Anti-TNF therapy**
- Broadly compatible results in 3 other series
  - Schmidt et al 2012 (n=20)
  - Mekinian et al 2012 (n=15)
  - Quartuccio et al 2012 (n=15)

**Anti-TNF Therapy**
- N=25, refractory TAK
- Infliximab (21), etanercept (9)
  - Median 5mg/kg/6w
- 15 remission off prednisone (60%)
- 7 remission on prednisone <10mg/d (28%)
- Median 19mg (5-50mg) to 0mg (0-30mg)/day
- 9/18 (50%) able to taper/discontinue other therapy
- 8/9 that discontinued IFX relapsed (median 5mo)
- 4 relapses – 3 controlled with increased dose
- 4 AE withdrawals – 1 breast ca, 1 histo


**Potential New Directions**
- **Tocilizumab**
- **Abatacept**
  - RCT ongoing
- **Rituximab?**
  - Case reports
Refractory TAK?

Before escalating immunosuppressive Rx.....

- Exclude secondary vasculitis/mimics
  - Infection
    - E.g. TB, syphilis, HIV, mycotic aneurysms
  - Atherosclerosis/thromboembolic
  - Genetic disorders
    - E.g. Marfan, Ehlers-Danlos, Loeys-Dietz, others
  - Congenital
    - Coarctation, Turner, William syndromes
  - Others
    - E.g. Fibromuscular dysplasia

Non-pharmacologic Measures

Role of Diet?

Non-pharmacologic Measures
Vascular Intervention

Revascularization

- Plumbing approach ill-advised
- Affected vessels do not necessarily need to be ‘unblocked’
- Collateral flow
- High failure rates

Endovascular procedures

- Lesions often long, calcified, fibrotic
  - Careful selection of lesions essential
- Suboptimal outcomes
  - Initial patency
  - Restenosis
    - 53 vs 12 % (39mo followup) Kim et al J Vasc Surg 2012
    - 32 vs 11% (2yr followup) Lee et al Scan J Rheumatol 2013
- Newer approaches?
  - Drug eluting stents
  - Covered stents/stent grafts
    - Qureshi et al Semin Vasc Surg 2011

Surgical Intervention

- Aortic root reconstruction
- Vascular bypass graft
- Coronary artery bypass graft

- Bypass from aortic root
- Best performed during remission
  - Overall 5 year complication rate = 44%
    - 39/104 surgical proc. (37.5%) needed secondary intervention
    - 31/62 endovascular procedures, (50%) needed secondary intervention
  - 7x risk of failure if evidence of inflammation
    - Saddoun et al Circulation 2012

Conclusions

- Assessment of disease activity
  - Clinical assessment/labs/imaging
  - No single reliable modality

- Treatment
  - Corticosteroids
  - Conventional immunosuppressive agents
  - Biologic agents
  - No unequivocally proven therapy
TAK: Unmet Needs

- Targeted, effective therapy
  - Less toxicity
  - Control systemic AND vascular inflammation
  - Reduce/eliminate need for glucocorticoids

- Disease assessment
  - Disease activity score
  - Biomarkers
  - Imaging – optimal modality? Interval?

- Better understanding of disease pathogenesis
- Multi-center collaborative trials

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Thank you for your attention

Questions?