A patient with polyarthritis

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Presentation
- Previously fit 60 yo man complaining of a swollen left knee
- No other joints involved
- PH
  - Tonsils
  - Appendix
  - One episode iritis
- SH
  - Accountant
  - Smokes 10 cigs per day
- FH
  - Mother RA
  - Aunt with Hashimotos

Diagnosis
- Osteoarthritis
- Spondylo-arthritis
  - Reactive Arthritis
  - Psoriatic Arthritis
  - Ankylosing Spondylitis
  - Undifferentiated SpA
- Gout
- Pseudo-gout
- Infection
- Rheumatoid Arthritis
- Vasculitis

Clues
- OA
  - Gelling, worse after use, old injury etc
- SpA
  - Family history, previous episode, preceding GI infection, iritis, back pain with MS, heel pain (enthesitis), psoriasis, dactylitis, SI joint tenderness
- Gout
  - Previous acute attacks, family history, polynesian comorbidities
- Pseudo-gout
  - Atypical OA
- Infection
- RA
  - Systemic symptoms
- FH
  - Tender mtp
- Investigation?
Joint Aspirate

- Normal: <50/mm³
- Minimal inflammation: 200-2000
- Inflammation: 2000-75000
- Infection: >100,000

Synovial fluid microscopy

Imaging: X-RAY Early RA

- Early erosions at a typical site on the ulnar styloid in early rheumatoid arthritis

MRI in early RA
Blood Tests?
- HLA-B27
- Rheumatoid Factor
- Anti-CCP antibodies
- ANA
- ANCA
- Urinalysis
- Ca, PO4
- Ferritin

Anti-CCP antibodies

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Anti-CCP</td>
<td>0.68</td>
<td>0.96</td>
</tr>
<tr>
<td>Anti Keratin Ab</td>
<td>0.46</td>
<td>0.94</td>
</tr>
<tr>
<td>IgM RF</td>
<td>0.75</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Note: 37% RF neg samples CCP pos.

Union et al. Arthritis Rheum, 2002;46:1185-95
Bas et al. Rheumatology, 2002;41:809-814

Presentation of RA and CCP
- Peripheral Polyarthritis
- Palindromic Rheumatism
- Intermittent polyarthritis
- Mono-arthritis
- Polymyalgia Rheumatica
Presentation

- Previously fit 60 yo man complaining of a swollen left knee
- No other joints involved
- **PH**
  - Tonsils
  - Appendix
  - One episode iritis
- **SH**
  - Accountant
  - Smokes 10 cigs per day

**FH**
- Mother RA
- Aunt with Hashimoto

Heritability of RA

- Twin studies
  - MZ concordance 15%
  - DZ concordance 4%
- Families
  - 1st degree rel OR 1.5
  - Uncles/aunts 1.95
- Heritability estimate 50% – 65%

RA Genetics HLA-DR

- DR β1: 0401/0404/0405/0408
- DR β2: 0101/0102
- DR β3: 1001
- DR β3: 1402/1406
- **Shared Epitope**
  - Residues 70 – 74
  - QKRAA, QRRAA, RRRAA

RA: Genetics

1. T allele-Trp for Arg at codon 620
2. RA OR T allele (620W) 1.5 – 2.0
3. T allele-T allele 4
4. Diabetes Type I, SLE, Graves Disease, Hashimoto Thyroiditis
5. Not MS or Crohn’s Disease

RA: Genetics and Smoking

- Shared epitope DR4 2.8
- Smoker 2.4
- SE plus smoker 7.5
- SE homozygote plus smoker 15.7

Klareskog et al. Arthritis and Rheumatism 2004;50:3085-3092
RA: HLA-DR and smoking

38 y woman c/o 8 wk pain and stiffness hands
Examination shows mild swelling
Wrist
MCPs
PPPs
Feet tender to trans-metatarsal pressure
RF pos, CCP 155

What treatment will we give?

DMARD options
- Mild
  - Minocycline, Hydroxychloroquine
- Moderate
  - Sulphasalazine
- Strong
  - Methotrexate, Leflunomide
- Steroids
- Combination
  - MTX, SAS, HCQ; MTX, Lef; (MTX, CyA)
- Biologics

Early RA treatment
- Milier presentation
  - Prodromal
  - Intermittent arthritis
  - Mild Rx: minocycline, HCQ, SAS
- Moderate presentation
  - Active persistent arthritis
  - SAS if mild
  - Straight to MTX otherwise
- Severe presentation

Early RA Rx: Severe
- Indicators of severity
  - Persistent active arthritis affecting many joints
  - Persistent high CRP
  - Extra-articular and systemic features
  - High levels autoantibodies: RF, CCP
  - Early joint damage: MRI (X-ray)
- Treatment
  - MTX, start 10-15 mg/wk; escalate 5 mg/month
  - Steroids
  - Combination early: MTX, SAS, HCQ, MTX, Lef
- Biologic

Early RA Rx: Steroids: BeSt Trial
- BeSt trial: 508 patients, 4 groups
- Groups:
  - Monotherapy: MTX, then SAS, then Lef, then MTX, TNF
  - Combination: MTX, add SAS, add HCQ, add prednisone
  - Combination plus steroids: MTX, SAS, HCQ plus pred
  - MTX plus anti-TNF (Infliximab)
The role of corticosteroids in the treatment of Rheumatoid Arthritis

1. Diurnal variation in symptoms
2. Mechanisms of action
3. Do they have a disease modifying effect?

Conn DL, Lim SS. Current Opinion in Rheumatology, 2003;15:193-6
Moreland and O’Dell Arthritis and Rheumatism 2002;46:2533-2563

Glucocorticoid regulated genes

<table>
<thead>
<tr>
<th>Increased gene transcription</th>
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<tbody>
<tr>
<td>Lipocortin-1 (anaxin-1)</td>
</tr>
<tr>
<td>I$_{3}$-adrenoceptor</td>
</tr>
<tr>
<td>Secretory leucocyte inhibitory protein, CC-10</td>
</tr>
<tr>
<td>IL-RI, IL-1ra</td>
</tr>
<tr>
<td>I$<em>{E}$-B$</em>{x}$</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Decreased gene transcription</th>
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</thead>
<tbody>
<tr>
<td>Cytokines: IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-11, IL-13, TNF-α,</td>
</tr>
<tr>
<td>GM-CSF</td>
</tr>
<tr>
<td>Chemokines: RANTES, eotaxin, MIP1-α, MCP-1, MCP-3</td>
</tr>
<tr>
<td>Enzymes: ICAM-1, VCAM-1</td>
</tr>
</tbody>
</table>

Adcock et al, Immunology and Cell Biology, 2001;79:376-384

Circadian rhythms in RA

- Cortisol peak is blunted in active RA
- TNF peak is increased in active RA
- Aim: restore steroid peak and suppress TNF peak
- Give prednisone in rising phase of TNF production
- Prednisone dose at 2 am
- Controlled release prednisone


Sharp Score

- 81 patients with new onset RA
- 41 prednisone 10 mg mane
- 40 placebo
- could start sulphasalazine at 6 months as rescue therapy
- significantly less erosion (Sharp Score) at 12 months and 18 months (p=0.04) and at 24 months (p=0.02)

Steroids in RA

1. Bridging therapy — i/m use, eg, monthly x 3
2. Intra-articular
3. Disease modifying—probably-use in early disease confers benefit for up to 5 years

Zoledronate in RA: erosions

- Zoledronate 5 mg in addition to MTX at 6 months
- Arthritis and Rheumatism 2006;54:1410-1414
Treatment of RA with MTX plus etanercept

Intent to treat analysis

% Responders

- ACR 20%
- ACR 50%
- Remission

Months on continuation therapy (MTX + LEF)

ACR 20% ACR 50% Remission

60
50
40
30
20
10
0

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

% Responders

Anti-TNF Joint Protection

- Comparison of MTX plus placebo vs MTX plus anti-TNF
- Open = ACR 20 not achieved, closed ACR 20 achieved
- Treatment with anti-TNF protected joints even when inflammation not suppressed
- Arthritis and Rheumatism 2005;52: 1020-1030

ERA Extension

Adverse events at 2y

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>Etanercept t 25 mg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction</td>
<td>9</td>
<td>39</td>
<td>0.05</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>20</td>
<td>0.05</td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>17</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Infection/hospital treatment</td>
<td>9</td>
<td>7 pts</td>
<td></td>
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<tr>
<td>Malignancy</td>
<td>4</td>
<td>4 pts</td>
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</table>

Mortality in Rheumatoid Arthritis

- 1955 Cohort Mayo
- A+R 2003;49:54-58

Infection

<table>
<thead>
<tr>
<th>Infection site</th>
<th>RA</th>
<th>Matched</th>
<th>OR</th>
<th>95% limits</th>
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</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>294</td>
<td>142</td>
<td>2.11</td>
<td>1.72-2.58</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>101</td>
<td>53</td>
<td>1.92</td>
<td>1.37-2.67</td>
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<tr>
<td>Septicemia</td>
<td>61</td>
<td>28</td>
<td>2.19</td>
<td>1.40-3.42</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>41</td>
<td>13</td>
<td>3.16</td>
<td>1.69-5.91</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>19</td>
<td>1</td>
<td>19.04</td>
<td>2.55-142.23</td>
</tr>
</tbody>
</table>

Immuno-incompetence related to disease or Medication
RA Rx and Infection

- Increased with Prednisone, dose related
- Increased with Leflunomide
- A+R 2006;54:628-634, A+R 2007;56:1754-1764

Mortality in RA: Malignancy

- Standardised Incidence Ratios
  - Cancer Overall 1.07
  - Lymphoma 2.0
    - Non-Hodgkins Lymphoma 1.85
  - Edstrom et Al Arthritis Rheumatism 2003:48:963-970

RA, Lymphoma, Active Disease

- Increased lymphoma
- Mainly large B cell
- Related to cumulative disease activity
- Not related to medication
  - HCQ, Au, SAS, MTX: neutral
  - Azathioprine increase
  - Steroids protective
  - A+R 2006;54: 685-688, 692-701 and 3774-3781

RA morbidity: fractures

- Increased fracture risk in RA: pelvis and spine
  - OR RA greater than 10 y 3.4 (3.0-3.9)
  - OR low BMI 3.9 (3.4-4.9)
  - OR steroids 3.4 (3.0-4.0)
  - Arthritis and Rheumatism 2006:54:3104-3112

Coronary Artery Dis in RA

- CHF risk increased OR 1.87 pp 412-420
- Risk of CVS death 2.03 pp 722-732
- Sustained ESR >60 3.0

RA: increased risk MI

**Methotrexate and mortality in RA**

**Hazard Ratios**

- All cause mortality: 0.4 (0.2-0.8)
- Cardiovascular mortality: 0.3 (0.2-0.7)
- Non-cardiovascular mortality: 0.6 (0.2-1.2)


**Improved Treatment Outcomes**

- 125 pts 1985, 150 2000 cross-sectional study
- MTX 10% vs 76%
- No DMARD 66% vs 13%
- DAS>5.1 69% vs 30%
- mHAQ 1.0 vs 0.4
- Pincus et al Arthritis and Rheumatism 2005:52: 1009-1019

**Survival in RA: 1955 vs 1985**

- 1955 Cohort Mayo
- A+R 2003:48:54-58
- 1985 Cohort Dutch
- ARD 2000;59:954-958

**Summary**

Management of RA

- Treat early and hard for good outcome
- Gain control then maintain tight control
- Manage comorbidity
  - Atherosclerosis: statins, BP, weight etc
  - Infection: vaccination for flu, pneumovax
  - Malignancy: watch for lymphoma, BCC, SCC, cervical

**Pregnancy**

- 12 months later she has been doing well on salazopyrin and has been well. Now she has missed a period. Testing confirms pregnancy.
- Will the baby be alright?
- How will the pregnancy affect her treatment and her arthritis?
Postpartum

- During pregnancy she elects to stop salazopyrin but remains very well.
- 6 weeks after delivery she is very tired due to the demands of breastfeeding including at night. She has also become very stiff and sore again.
- Should she restart salazopyrin?
- What will you give her for her acute symptoms?

Sulphasalazine

- **GI upset**
- **Rash**
- **Neutropenia**
  - Abnormal LFTs
  - Decreased Hb, Hypogammaglobulinemia, pneumonitis etc

Monitoring

FBP, LFTs, CRP
Fortnightly for 2 months then monthly

MTX administration

- Weekly single oral dose 7.5-25 mg
- Injection subcut or im alternative
- Weekly folate 5 mg 24h after dose

MTX toxicity

- **Bone marrow: cytopenias**
  - Monitor blood count
  - Avoid trimethoprim, cotrimoxazole
  - Folate supplementation
- **Hepato toxicity including cirrhosis**
  - Avoid alcohol
  - Monitor LFTs
- **Teratogenic**
  - Effective contraception vital
  - 3-6 months off before conception
- **Pneumonitis**
  - Baseline CXR, RFTs
  - Beware cough, fever, SOB
MTX monitoring
- Fortnightly FBP, LFTs, CRP whilst increasing dose
- Monthly when stable
- Check creatinine from time to time
- Stop MTX for cytopenia.
  - Watch for downward trend, progressive macrocytosis
  - Check B12 and folate
  - Check other meds eg trimethoprim
  - Resume at lower dose when normalised
- With abnormal LFTs check NSAIDs, alcohol, herbal remedies
- Reduce dose if persistent elevation of AST
- Consider liver Bx for persistent abnormality

Leflunomide
- Efficacy equivalent to Methotrexate
- Monitor FBP and LFTs
- Watch for immunosuppression: infection, malignancy
- Watch BP, weight
- Watch for pneumonitis

Failure of MTX plus Leflunomide
- Despite MTX plus Leflunomide is worse
- Prolonged morning stiffness
- 10 tender joints
- 16 swollen joints
- Has had to stop work
- What are our options now?

Short-term management options
- Joint injection
- Steroids I M: kenacort 60 mg - depomedrol 120 mg
- Oral steroids?

X-rays at baseline and at 5 years