Early Arthritis Workshop

The clock is ticking

Andrew Harrison
Assoc Prof in Medicine, University of Otago, Wellington
HoD, Wellington Regional Rheumatology Unit
The purpose of this workshop

By the end of this session you should be able to:

• understand the significance of early treatment of RA
• recognise the key diagnostic features of early RA
• recognise the risk factors for poor prognosis
• develop a structured approach to assessment of early arthritis
Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet
Case 1

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Undifferentiated polyarthritis
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Undifferentiated polyarthritis

Is that all we need to know?
Case 1

Amanda, 35 years. presents with 2 week history of pain, EMS, swelling hands and feet

Undifferentiated polyarthritis

Is that all we need to know?

Advantages of classification
• prognosis
• specific management
• urgency of management
• reference point
Undifferentiated peripheral inflammatory arthritis

- differential diagnosis
  - rheumatoid arthritis
  - reactive arthritis
  - osteoarthritis
  - psoriatic arthritis
  - viral arthritis
  - crystal arthritis
  - spondyloarthritis (undiff, AS)
  - connective tissue disease
  - sarcoidosis
  - polymyalgia rheumatica
  - Lyme disease
  - paraneoplastic
  - hepatitis
  - endocrine-related
  - fibromyalgia/pain syndrome
  - systemic autoimmune disease

Case 1

Amanda, 35 years, UPIA
- differential diagnosis
  - rheumatoid arthritis
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Case 1

Amanda, 35 years, UPIA

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  - hepatitis
  - endocrine-related
    - osteoarthritis
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Why is it important to diagnose and treat RA early?

• Early treatment is dependant on early diagnosis
• If there was no effective Rx, early diagnosis wouldn’t matter
• If there were effective Rx but no benefit in early Rx, early diagnosis wouldn’t matter
Why is it important to diagnose and treat RA early?

- Early treatment is dependant on early diagnosis
- If there was no effective Rx, early diagnosis wouldn’t matter
- If there were effective Rx but no benefit in early Rx, early diagnosis wouldn’t matter

- What is the evidence that delaying treatment is harmful?
Why is it important to diagnose and treat RA early?

Trials of treatment strategies
- Egmose 1995. Early RA - immediate HCQ v 8 month delay
- at 5 years, differences in outcome measures were sustained
- demonstrated a “therapeutic window”

Why is it important to diagnose and treat RA early?

Trials of treatment strategies
- van der Heide 1996. Recent onset RA, DMARD v placebo
- 12 month study
- The placebo group had higher disability, pain and ESR at 6 and 12 months

Why is it important to diagnose and treat RA early?

Trials of treatment strategies

• Tsakonas 2000. Early RA - immediate HCQ v 9 month delay
• at 3 years delayed group had worse pain and physical disability

Why is it important to diagnose and treat RA early?

Trials of treatment strategies
• Lard 2001. Recent onset RA, cohort study
• 1993-1995 analgesics then chloroquine / SSZ (mean 123 days)
• 1996-1998 immediate chloroquine / SSZ (mean 15 days)
• early Rx had less radiographic damage at 2 years
• AUC disease activity 64 U in early v 73 U in delayed

Why is it important to diagnose and treat RA early?
Why is it important to diagnose and treat RA early?
Predictors of adverse outcome

- female gender
- insidious onset
- high disease activity
- multiple joints
- baseline erosions
- genetic factors – shared epitope
- serology – RF, anti-CCP
Can we predict prognosis from baseline variables?

Predictors of adverse outcome

- female gender
- insidious onset
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Concept 1: Prognosis is determined by AUC disease activity v time
Influenced by innate (gender, SE) and acquired factors (serology)
Can we predict prognosis from baseline variables?

How low should you go? Towards personalized treatment targets for disease activity in RA. Y. M. R. De Punder 1, T. L. Jansen 1, A. E. van Ede 1, A. A. den Broeder 2, P. L. van Riel 1, J. Fransen 1. 1Rheumatology, Radboud University Nijmegen Medical Centre, 2Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands. EULAR, Madrid, 2013.
Case 1

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Diagnoses to consider

- rheumatoid arthritis
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Case 1

Amanda, 35 years. presents with 2 week history of pain, EMS, swelling hands and feet

No diagnosis as yet

How do the principles discussed above inform us?

• the window is wide open but there is some urgency to assess
• predictors of prognosis
  - female gender
  - multiple joints
  - disease activity?
  - serology?
  - erosive status?
  - genetics?
Case 1

Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

No diagnosis as yet

How do the principles discussed above inform us?

- the window is wide open but there is some urgency to assess
- predictors of prognosis
  - female gender
  - multiple joints
  - disease activity? (CRP, ESR)
  - serology? (RF, anti-CCP)
  - erosive status? (x-rays hands and feet)
  - genetics? (no need for shared epitope)
Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

Other diagnostic indicators
• connective tissue disease (ESR, ANA, ENA, ds-DNA)
• viral arthritis (?Parvovirus B19)
• reactive arthritis (chlamydia, HLA-B27)

Concept 2: The priority in early arthritis is not to make a diagnosis but to manage the risk of the possible diagnoses, especially the bad ones
Case 1

Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

a. Observe (masterly inactivity)
b. Investigate and monitor
c. Investigate and introduce mild treatment (NSAIDs, LD pred, HCQ)
d. Treat intensively
Case 1

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presents with 2 week history of pain, EMS, swelling hands and feet

a. Observe (masterly inactivity)
b. Investigate and monitor
c. Investigate and introduce mild treatment (NSAIDs, LD pred, HCQ)
d. Treat intensively

Urgency determined by the size of the window
COMET study: patients divided into

- VERA  <4 months of diagnosis
- ERA    4–24 months
- Primary goal of therapy was remission (DAS28 < 2.6)
- Were remission rates improved by very early treatment with either MTX or MTX and TNFi?
- Assessed at 52 weeks

Intensive treatment in early arthritis

% patients in remission

ETN + MTX

MTX

VERA

ERA

$\text{p}=0.0035$

$\text{p}=0.7037$

44/63

75/157

34.7

31.8

69.8

47.8

79/49

47/148
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A 4 month delay reduced chance of remission with TNFi
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Concept 3: RA may be more treatable (?curable) in the very early stages
Intensive treatment in early arthritis

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A 4 month delay reduced chance of remission with TNFi

Concept 3: RA may be more treatable (?curable) in the very early stages

Should Amanda start DMARDs?
Case 1

Amanda, 35 years.
presents with 2 week history of pain, EMS, swelling hands and feet

Results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>CRP</td>
<td>17</td>
</tr>
<tr>
<td>ESR</td>
<td>32</td>
</tr>
<tr>
<td>RF</td>
<td>26</td>
</tr>
<tr>
<td>ANA</td>
<td>1:40</td>
</tr>
<tr>
<td>ENA</td>
<td>-ve</td>
</tr>
<tr>
<td>ds-DNA</td>
<td>-ve</td>
</tr>
<tr>
<td>anti-CCP</td>
<td>&gt; 300</td>
</tr>
<tr>
<td>Parvo</td>
<td>-ve</td>
</tr>
<tr>
<td>x-rays</td>
<td>normal</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>studies -ve</td>
</tr>
</tbody>
</table>
**Antibodies to citrullinated peptide**  
**Link between genetic and environmental risk factors**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
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<tbody>
<tr>
<td>RF</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>68</td>
<td>96</td>
</tr>
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Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Rantapaa-Dahlqvist 2003
Stored sera from 83 RA patients who had been blood donors

<table>
<thead>
<tr>
<th></th>
<th>controls %</th>
<th>pre-RA %</th>
<th>early RA %</th>
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<tr>
<td>IgM RF</td>
<td>6.0</td>
<td>19.3</td>
<td>73.1</td>
</tr>
<tr>
<td>anti-CCP</td>
<td>1.8</td>
<td>33.7</td>
<td>70.1</td>
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Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Rakieh 2013.
• Screening of patients with non-specific MSk symptoms
• 122 anti-CCP +ve, 22 had clinical synovitis (CS)
• 100 patients followed up
• 44 had developed CS median 26 weeks
• EMS predicted CS (59 min v 19 min)
• Power doppler and MRI were predictive of CS

Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Concept 4: There is a preclinical phase to RA

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<tr>
<td>genetics</td>
<td>environmental</td>
<td>morning stiffness</td>
<td>immune-mediated</td>
<td>chronic inflammation</td>
</tr>
<tr>
<td></td>
<td>citrullination</td>
<td>no clinical inflammation</td>
<td></td>
<td>erosions</td>
</tr>
<tr>
<td></td>
<td>anti-CCP</td>
<td>US/MR synovitis</td>
<td></td>
<td>deformity</td>
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Antibodies to citrullinated peptide  
Link between genetic and environmental risk factors  

Concept 4: There is a preclinical phase to RA

Where should we intervene?
Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Concept 4: There is a preclinical phase to RA

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Where should we intervene?
Antibodies to citrullinated peptide
Link between genetic and environmental risk factors

Concept 4: There is a preclinical phase to RA

Where should we intervene?
Walter, 42 years, smoker
6 week history of morning stiffness fingers and pain in MTPJs in a.m.
• examination - SJC = 0, +ve MTP squeeze test
• CRP <3, ESR 9, RF –ve, ANA 1:160, urate 0.53
Walter, 42 years, smoker
6 week history of morning stiffness fingers and pain in MTPJs in a.m.
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Other investigations?
Case 2

Walter, 42 years, smoker
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- examination - SJC = 0, +ve MTP squeeze test
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Other investigations?
- anti-CCP 162 IU/ml
- x-rays hands and feet normal
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Now what?
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Other investigations?
• anti-CCP 162 IU/ml
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Now what?
a. treat symptoms and wait until synovitis develops
b. start on HCQ
c. prednisone 40 mg / 20 mg / 10 mg over 3/52
d. prednisone plus MTX
What is the evidence for corticosteroids in early RA?

Landewe 2002 COBRA study

SSZ/MTX/Prednisone 60/40/25/20/15/10/7.5 mg v SSZ
By week 56 DMARD use was the same
After 5 years COBRA group had lower DAS28 and fewer erosions

Use of prednisone was considered main factor

What is the evidence for corticosteroids in early RA?

Goekoop-Ruiterman 2005 BEsT study

4 strategies in early RA
1. sequential monotherapy DMARDs
2. step-up combination DMARDs
3. initial combination DMARDs plus COBRA prednisone
4. initial MTX/etanercept

What is the evidence for corticosteroids in early RA?

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4 strategies in early RA
1. sequential monotherapy DMARDs
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At 1 year, groups 3 and 4 had less disability than 1 and 2
SvdH scores – 2.0, 2.5, 1.0, 0.5

Initial remission induction with corticosteroid or TNFi improved long term outcome

Breakfast Session
Professor Andrew Harrison
University of Otago
Wellington

Early onset inflammatory arthritis - the clock is ticking - AbbVie Breakfast Session
Sunday, 23 June 2013
Start 7:30am
Duration: 60mins
Baytrust
Undifferentiated peripheral inflammatory polyarthritis

- consider the differential diagnosis

  - rheumatoid arthritis
  - reactive arthritis
  - osteoarthritis
  - psoriatic arthritis
  - viral arthritis
  - crystal arthritis
  - spondyloarthropathy (undiff, AS)
  - connective tissue disease
  - sarcoidosis
  - polymyalgia rheumatica
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  - hepatitis
  - endocrine-related
  - fibromyalgia/pain syndrome
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Undifferentiated peripheral inflammatory polyarthritis

- consider the differential diagnosis
- rank in order of likelihood

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Undifferentiated peripheral inflammatory polyarthritis

- Consider the differential diagnosis
- Rank in order of likelihood
- Investigate as appropriate
  - Rheumatoid arthritis
  - CRP, RF, anti-CCP, x-rays,
  - Reactive arthritis
  - CRP, Chlamydia, HLA-B27
  - Psoriatic arthritis
  - CRP, HAL-B27, x-rays
  - Viral arthritis
  - CRP, Parvovirus B19
  - Connective tissue disease
  - ESR, CRP, ANA, ENA, dsDNA
  - Spondyloarthropathy (undiff, AS)
  - CRP, HLA-B27, x-rays
  - Sarcoidosis
  - CRP, CXR, Ca++, serum ACE
  - Fibromyalgia/pain syndrome
  - ESR, CRP, ANA, autoantibodies
  - Systemic autoimmune disease
  - CRP, Lyme serology
  - Lyme disease
  - Radiology, tumour markers etc.
  - Paraneoplastic
  - LFTs, hepatitis serology
  - Hepatitis
  - TFTs, ACTH, corticol etc.
  - Endocrine-related
  - Osteoarthritis
  - Crystal arthritis
  - Polymyalgia rheumatica
Undifferentiated peripheral inflammatory polyarthritis

If still undifferentiated
• determine risk of adverse prognosis

Clinical

Table 2. Summary of history and physical examination features found to have diagnostic and prognostic value in UPIA.

<table>
<thead>
<tr>
<th>Eventual RA Diagnosis</th>
<th>Persistent Disease</th>
<th>Remission</th>
<th>Erosive Disease</th>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age, yrs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Female</td>
<td>+</td>
<td>+ (male)</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Longer symptom duration</td>
<td>+</td>
<td>+ (shorter duration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer/more severe morning stiffness</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher disability at baseline</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Higher tender joint count</td>
<td>+</td>
<td></td>
<td>(fewer joints)</td>
<td></td>
</tr>
<tr>
<td>Higher swollen joint count</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint distribution (small/large, upper/lower)</td>
<td>+</td>
<td>+ (lack of hand involvement)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTP compression pain</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symmetrical joint involvement</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of extraarticular features</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If still undifferentiated
- determine risk of adverse prognosis

RF and anti-CCP status

Undifferentiated peripheral inflammatory polyarthritis

If still undifferentiated
• determine risk of adverse prognosis

Baseline erosions

Table 2. Likelihood ratios extracted from the different articles on undifferentiated arthritis (UA) and mixed populations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prognostic Factor</th>
<th>Outcome</th>
<th>LR+ (95% CI)</th>
<th>LR− (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Aken 2005</td>
<td>Erosive disease (SvdH) hands or feet CR</td>
<td>RA (ACR) at 1 year</td>
<td>3.5 (2.1–6.0)</td>
<td>0.8 (0.7–0.9)</td>
</tr>
<tr>
<td>Duer 2008</td>
<td>Larsen grade 1 hand or foot CR</td>
<td>RA (ACR) at 2 years</td>
<td>10.9 (1.4–87.3)</td>
<td>0.7 (0.4–1.0)</td>
</tr>
<tr>
<td>Mixed population</td>
<td></td>
<td>RA according to panel</td>
<td>4.1 (1.7–9.5)</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>Devauchelle 2001</td>
<td>Erosions hands CR</td>
<td>RA according to panel</td>
<td>8.6 (1.9–37.6)</td>
<td>0.8 (0.7–0.9)</td>
</tr>
<tr>
<td>Devauchelle 2004</td>
<td>Erosions feet CR</td>
<td></td>
<td>5.7 (1.6–19.8)</td>
<td>0.8 (0.7–1.0)</td>
</tr>
<tr>
<td>Devauchelle 2006</td>
<td>Erosions hands CR</td>
<td>RA according to panel</td>
<td>6.2 (2.4–15.6)</td>
<td>0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Devauchelle 2006</td>
<td>Erosions and/or decalcifications hands CR</td>
<td>RA according to panel</td>
<td>1.8 (1.0–3.1)</td>
<td>0.9 (0.8–1.0)</td>
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<tr>
<td>Saraux 2001</td>
<td>Erosions hands or feet CR</td>
<td>RA according to panel</td>
<td>9.7 (3.4–27.2)</td>
<td>0.8 (0.7–0.9)</td>
</tr>
<tr>
<td>Gough 1994</td>
<td></td>
<td>Persistent disease*</td>
<td>6.0 (1.9–18.7)</td>
<td>0.7 (0.7–0.9)</td>
</tr>
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If still undifferentiated
• determine risk of adverse prognosis
• manage to level of risk

How low should you go? Towards personalized treatment targets for disease activity in RA. Y. M. R. De Punder 1, T. L. Jansen 1, A. E. van Ede 1, A. A. den Broeder 2, P. L. van Riel 1, J. Fransen 1. 1Rheumatology, Radboud University Nijmegen Medical Centre, 2Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands. EULAR, Madrid, 2013.
Summary

Concept 1: Prognosis is predicted by AUC disease activity v time Influenced by innate (gender, SE) and acquired factors (serology)

Concept 2: The priority in early arthritis is not to make a diagnosis but to manage the risk of the possible diagnoses, especially the bad ones

Concept 3: RA may be more treatable (?curable) in the very early stages

Concept 4: There is a preclinical phase to RA
Summary

There is a therapeutic window, after which delaying treatment may worsen the long-term outcome.

Early remission induction, e.g. with corticosteroids, provides lasting benefit.

Even without a diagnosis, baseline variables can be used to determine the urgency and appropriate intensity of treatment.

Long-term outcome depends on maintaining remission, with the optimal target being determined by the level of risk.
Failure has consequences

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Success brings rewards

- outcome of RA is improving