Case presentation

- 49-year old female without previous medical history
- Joint pain since 6 months: hands, feet, knees
- Morning stiffness: 1h
- 10 painful and swollen joints

What is your differential diagnosis?
What tests should you prescribe?

Results

- ESR: 30 mm/h, CRP 21 mg/L
- RF IgM: negative; RF IgA: negative
- Anti-CCP: 200 (N<50)
- ANA: 160 (N<80), anti-dsDNA: negative
- Hb 11g/L
- X-rays: normal

S'agit-il d’une PR?

- Critères cliniques
- Quels tests et quelle sensibilité/specificité
- Algorythme diagnostic
Rheumatoid Arthritis

Frequency: 1%
Female:male 3:1
Higher incidence 40-60 yr

ACR 1987 Classification Criteria

1. Morning stifness \(\geq 1\) h
2. Arthritis \(\geq 3\) joints
3. Arthritis wrists, hands
4. Symetrical arthritis
5. Rheumatoid nodules
6. Rheumatoid factors
7. Erosions (X-rays)

Sensibilité 91%, spécificité 89%
High Predictive Value of anti-CCP
Similar results in non-Caucasian subjects


<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>RA</th>
<th>RBD (n = 54)</th>
<th>RA (n = 51)</th>
<th>Sensitivity (n = 50)</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUROC (ROC) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF IgM (%)</td>
<td>42</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td>27</td>
<td>77</td>
<td>95</td>
<td>90</td>
<td>88 (0.719 to 0.901)</td>
</tr>
<tr>
<td>RF IgG (%)</td>
<td>47</td>
<td>8 (16)</td>
<td>0 (0)</td>
<td>94</td>
<td>92</td>
<td>85</td>
<td>91</td>
<td>0.88 (0.83 to 0.94)</td>
</tr>
<tr>
<td>Anti-CCP (%)</td>
<td>46</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>92</td>
<td>96</td>
<td>96</td>
<td>91</td>
<td>0.90 (0.85 to 0.95)</td>
</tr>
<tr>
<td>Anti-CCP (%)</td>
<td>49</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>77</td>
<td>94</td>
<td>90</td>
<td>98</td>
<td>0.94 (0.91 to 0.97)</td>
</tr>
<tr>
<td>SE 1 or 2 copies (%)</td>
<td>17</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td>30</td>
<td>88</td>
<td>90</td>
<td>92</td>
<td>0.94 (0.91 to 0.97)</td>
</tr>
<tr>
<td>SE 1 copy (%)</td>
<td>15</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td>27</td>
<td>88</td>
<td>90</td>
<td>92</td>
<td>0.94 (0.91 to 0.97)</td>
</tr>
<tr>
<td>SE 2 copies (%)</td>
<td>2</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>0.52 (0.42 to 0.62)</td>
</tr>
</tbody>
</table>

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

OVERARCHING PRINCIPLES
1. Rheumatologists are the specialists who should primarily care for patients with rheumatoid arthritis (RA)
2. Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
3. RA is expensive in regards to medical costs and productivity costs, both of which should be considered by the treating rheumatologist

Principles of RA Management
• Control pain and avoid subsequent damage and disability
• Take into account patient’s expectations and risk factors of adverse events
• Take into account the presence of signs of aggressive disease
  – Serological markers (Anti-CCP, Rheumatoid factors)
  – Early structural damage
  – Clinical presentation (number of inflamed joints)
  – High inflammatory response (high C-reactive protein / ESR levels)

Principes généraux de prise en charge
• Prise en charge précoce utile?
• Quelle cible de traitement ?
• Prise en charge physique?
• Prise en charge médicamenteuse?
**Recommendations for the management of RA**

Treatment with synthetic disease modifying anti-rheumatic drugs (DMARDs) should be started as soon as the diagnosis of RA is made.

Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible; treatment should be adjusted by frequent (1-3 months) and strict monitoring.

Methotrexate (MTX) should be part of the first treatment strategy.

DAS28 = 0.56 * \(\sqrt{TJC} \) + 0.28 * \(\sqrt{SJC} \) + 0.70 * ln (ESR) + 0.014 * GH

\[ \text{where TJC} = \text{tender joint count}; \text{ SJC} = \text{swollen joint count}; \text{ ESR} = \text{erythrocyte sedimentation rate}; \text{ GH} = \text{general health assessment} \]

DAS28 provides a number on a scale from 0 to 10 which indicates the current activity of the disease.

**How to achieve these objectives?**

1. **To measure** – Disease Activity Score (tender and swollen joints + ESR/CRP)

2. **Non-pharmacological means**
   - Education
   - Occupational therapy
   - Physical therapy (balneotherapy, thermotherapy, exercise)

3. **Pharmacological therapies**
   - Disease Modifying Antirheumatic drugs (DMARDs)
   - Glucocorticoids (systemic or local injections)
   - Non-steroidal antiinflammatory drugs (NSAIDs)

**Non-pharmacological interventions**

- **Balneotherapy:** 6 RCT, 355 patients, Positive findings but studies were methodologically flawed

- **Aerobic exercise:** 14 RCT, 1040 patients
  Improved QoL, function (HAQ), pain (VAS)
  Baillet et al Arthritis Res Ther 2010

- **Thermotherapy:** 3 RCT, 79 patients
  No effect on objective measures but high level of patient preference
  Welch et al. Cochrane Database Syst Rev 2001

- **Occupational therapy:** 15 studies (6 controlled studies)
  Positive effect on functional ability
  Steultjens et al. Cochrane Database Syst Rev 2004

- **Tai chi:** 4 RCT (206 patients)
  No significant on most outcomes of disease activity
  Significant improvement of ankle plantar flexion
  Han et al. Cochrane Database Syst Rev 2004
Quels médicaments?

- Que doit savoir l'interniste non rhumatologue?
- Principes généraux du traitement
- Suivi des effets secondaires
- Complications/ précautions

Methotrexate

First trial in RA in 1951

- Greatest experience - open- RCT- comparative trials
- Long term treatment, functional and X-Ray evolution
- High retention rate (50% after 5 yrs)
- Easy to dose - 10 mg/wk to 25 mg/wk
- Oral or parenteral (sc/im)
- Toxicity well described
- Monitoring guidelines
- Folic and folinic acid to reduce toxicity
- Decreases the mortality of RA
- Low cost

Evolution of DMARDs Use From 1970 to 2000

Leflunomide

Biologics

Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study)

- 110 RA patients randomized to
  - Routine care
  - Intensive care (monthly DAS assessment followed by change of therapy (DMARDs and CS) to achieve DAS < 2.4)

<table>
<thead>
<tr>
<th>Women</th>
<th>Intensive group (n=55)</th>
<th>Routine group (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 (55)</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>55 (15)</td>
<td>51 (13)</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>45 (75%)</td>
<td>40 (75%)</td>
</tr>
<tr>
<td>Disease activity score</td>
<td>4.5 (10)</td>
<td>4.5 (10)</td>
</tr>
<tr>
<td>Swollen joint score (0-6)</td>
<td>12 (10)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>RHI joint index</td>
<td>23 (10)</td>
<td>23 (12)</td>
</tr>
<tr>
<td>Pain score (0-100)</td>
<td>62 (20)</td>
<td>52 (20)</td>
</tr>
<tr>
<td>Patient global assessment (0-100)</td>
<td>60 (21)</td>
<td>63 (23)</td>
</tr>
<tr>
<td>Physician global assessment (0-100)</td>
<td>70 (18)</td>
<td>65 (18)</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>44 (52)</td>
<td>48 (29)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>45 (15)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>Health assessment questionnaire score (0-3)</td>
<td>2.0 (1.8)</td>
<td>1.9 (1.7)</td>
</tr>
<tr>
<td>Short form-12 physical summary</td>
<td>28 (7)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>Short form-12 mental health summary</td>
<td>30 (12)</td>
<td>28 (12)</td>
</tr>
<tr>
<td>Median total Sharp score (0-90)</td>
<td>21.5 (10-35-5)</td>
<td>24.5 (13-35-47)</td>
</tr>
<tr>
<td>Total Sharp score</td>
<td>28 (23)</td>
<td>33 (27)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number of patients (%), unless otherwise indicated. "0"-no disability, "10"-max disability. *P*<0.05 vs Intensive group.

Table 1: Baseline characteristics

C. Grigor et al., Lancet 2004; 364: 263-69

Alateha & Smolen, Rheumatology 2002
The TICORA study
At 18 months

- Intensive group had a significantly better outcome regarding:
  - Function
  - Erosion score
  - Pain score
  - Global assessment
  - ESR and CRP

Biological Agents Licensed for the Management of Rheumatoid Arthritis

- Tumor Necrosis factor (TNF)-alpha antagonists
  - Infliximab, Adalimumab, Golimumab
  - Certolizumab pegol
  - Etanercept

- Interleukin-6 receptor antagonist
  - Tocilizumab

- B Lymphocyte depleting agent
  - Rituximab

- Co-Stimulation Inhibitor (inhibition of T cell activation)
  - Abatacept

Clinical and Radiographic Responses

Improvement in Signs and Symptoms: ACR 70

Inhibition of Radiographic Progression:

Risk of RRP (%)

3 patients with these characteristics need to be treated with IFX + MTX in order to avoid that one patient treated with only MTX will progress rapidly.

SJC: Swollen joint count; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; RRP: Rapid radiographic progression; NNT: Number needed to treat.
If treatment target is not achieved by the first DMARDs, biological therapy should be started; current practice would be to start a TNF inhibitor, which should be combined with MTX.

Patients for whom the first anti-TNF has failed should receive another TNF inhibitor or another biological agent.

Intensive medication should be considered in every patient.

If a patient is in persistent remission, one can consider tapering biological treatment especially if this therapy is combined with a synthetic DMARD.

Glucocorticoids

Systemic glucocorticoids (GC) added at low to moderate doses to synthetic DMARDs provide benefit as initial short-term treatment, but should be tapered rapidly as clinically feasible.

Low dose GC < 10 mg/day (best dosage: 5 to 7.5 mg/day).

Intra-articular GC administration should be considered if a few joints remain active despite appropriate DMARD therapy (no more than 4x/year). Do not forget the systemic effects of intra-articular glucocorticoids.

Long-term follow-up

- Treatment maintenance
- Disease-related (or treatment-related) complications
  - Infections
  - Cancer
  - Cardiovascular events
  - Osteoporosis
  - Vasculitis
  - Lung disease
  - Eye disease
  - Felty’s syndrome

Maintenance of Therapy with TNF Antagonists in RA Patients

- Median duration on anti-TNF 31 months (IQR 12-68)
- Age does not influence the time to discontinuation
- Ineffectiveness is the leading cause of treatment discontinuation
- Highest discontinuation rates in infliximab-treated patients, mainly because of allergic reactions

Genevay et al. Arthritis Care Res 2006
Martin du Pan et al. Arthritis Care Res 2009
Case presentation

Following the diagnosis of rheumatoid arthritis, MTX was started at a dosage of 15 mg weekly sc

After 3 months the disease was still active (DAS28: 4.9) Etanercept was started in combination with MTX
After 3 months: there was a very good clinical response (DAS28: 2.5)

After 10 months, the patient complained of severe acute left knee pain. On physical examination, the joint was swollen

A quoi le médecin traitant doit-il/elle être attentif?
Complications/ précautions

• Complications/ risques infectieux
• Complications oncologiques
• Complications cardiovasculaires
• Autres

Incidence of Infections in Subjects With/Without RA

![Incidence graph]


Treatment for Rheumatoid Arthritis and the Risk of Hospitalization for Pneumonia

16'788 patients followed for 3.5 yrs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone ≤ 5 mg/day</td>
<td>1.7 (1.5-2.0)</td>
</tr>
<tr>
<td>Prednisone 5-10 mg/day</td>
<td>1.4</td>
</tr>
<tr>
<td>Prednisone &gt; 10 mg/day</td>
<td>2.1</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.1 (0.6-1.9)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.1 (0.9-1.4)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.1 (0.6-1.9)</td>
</tr>
</tbody>
</table>

Serious Infections in Rheumatoid Arthritis Patients on Anti-TNF Therapy

<table>
<thead>
<tr>
<th></th>
<th>DMARD</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons-years</td>
<td>1'352</td>
<td>9'868</td>
</tr>
<tr>
<td>Incidence rate ratio [95% CI]</td>
<td>1.28 [0.94-1.76]</td>
<td></td>
</tr>
<tr>
<td>Adjusted for prednisone use</td>
<td>1.03 [0.68-1.57]</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>4.28 [1.06-17.17]</td>
<td></td>
</tr>
<tr>
<td>Skin infections</td>
<td>0.77 [0.46-1.31]</td>
<td></td>
</tr>
</tbody>
</table>

No difference between the three anti-TNF agents

19 cases bacterial intracellular infection only in anti-TNF treated patients

10 M. Tb, 2 Legionella, 3 Listeria, 1 M. fortuitum, 3 Salmonella

W.G. Dixon et al Arthritis Rheum 2006

Vaccination

Patients with RA should be vaccinated against seasonal influenza

Patients with RA treated with biological agents should receive pneumococcal vaccine

Patients with RA treated with MTX, leflunomide, immunosuppressants, or biological agents should not receive live vaccines

Vaccination against H1N1 adjuvanted vaccines was safe

Immune response after one dose was lower than controls but patients achieved similar responses after 2 doses of vaccine

Rheumatoid Arthritis and Malignancy

Symmons and Silman Arthritis Rheum 2004

Results from Other Registries

Three US and Canada registries

1152 RA patients treated with biologic agents

OR= 1.37 [95% CI 0.71-2.60] for hematological cancer

OR= 0.91 [95% CI 0.65-1.26] for solid tumors

National Data Bank for Rheumatic Diseases (USA)

13000 patients (49'000 patients-yrs)

Anti-TNF treated patients had increased skin cancer melanoma OR= 2.3, non melanoma OR=1.5
### Lymphoma and Leukemia in RA Patients

**Three RA cohorts (Sweden)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR (95%CI)</td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>481</td>
<td>1.7 (1.5-1.8)</td>
<td>15</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>319</td>
<td>1.9 (1.7-2.1)</td>
<td>11</td>
</tr>
<tr>
<td>Myeloma</td>
<td>45</td>
<td>0.8 (0.6-1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Leukemia</td>
<td>107</td>
<td>2.1 (1.7-2.5)</td>
<td>4</td>
</tr>
<tr>
<td>(all but CLL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No difference after adjustment for age, sex, disease duration

Askling et al. *Ann Rheum Dis* 2005

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### Cardiovascular Morbidity and Mortality in Women Diagnosed with Rheumatoid Arthritis

**Nurses’Health Study:**

- 114'342 women free of CV disease at baseline in 1976
- 527 cases of incident RA
- 3622 cases of MI and stroke

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### Meta-analysis on CV Related Standardized Mortality Ratio in RA Patients

C. Meune et al. *Rheumatology* 2009

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### CV Risk and Rheumatoid arthritis cohort CARRE

- Population-based study in the Netherlands
  - Cohort CARRE: 335 RA with a CV follow-up of 3 yrs
  - Comparison with 1,852 matched controls of the cohort HOORN (metabolic risk factors)
- Evaluation of CV event risk factors (Myocardial infarction, stroke, CV-related death)

**CV Risk and Rheumatoid arthritis**

- HR adjusted
  - General population
  - All RA
  - Diabetic controls
  - Type 2 diabetes
  - RA without diabetes

<table>
<thead>
<tr>
<th></th>
<th>HR adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1.0</td>
</tr>
<tr>
<td>All RA</td>
<td>2.0 (1.2-3.4)</td>
</tr>
<tr>
<td>Diabetic controls</td>
<td>1.0</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.4 (0.8-2.6)</td>
</tr>
<tr>
<td>RA without diabetes</td>
<td>1.9 (1.1-3.5)</td>
</tr>
</tbody>
</table>

* Ajusted for age, sex, blood pressure, cholesterol, smoking, statin use, aspirin use

CV risk in RA similar to type 2 diabetes

RA is an independent CV risk factor as diabetes


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CV risk in RA similar to type 2 diabetes
RA is an independent CV risk factor as diabetes

Paters et al. ACR 2008
Take home messages

• La polyarthrite rhumatoïde est une maladie grave et il est par conséquent important de faire un diagnostic précoce
• Le traitement de fond doit être commencé dès que le diagnostic est posé
• L'objectif du traitement est la rémission et tout doit être mis en œuvre pour arriver à ce but
• Il faut connaître les complications associées à la maladie et aux traitements