Diagnose en therapie van artritis

Patrick Verschueren MD, PhD
What’s in a name?
The diagnostic process

• Anamnesis is key!
  – presenting symptom: pain, swelling, stiffness...
  – symptom character: inflammatory/mechanical
  – time course: (sub)acute or chronic, circadian
  – joint type: small, medium or large
  – distribution: number of joints, symmetry
  – other articular problems: enthesitis, dactylitis
  – axial complaints: buttock, neck or back pain
  – extra-articular manifestations: gut, skin, mouth, eye...
  – global setting: context, history, organ function...
Joint pain:
Mechanical versus Inflammatory
Acute versus chronic arthritis

Disease Activity

- Gout arthritis
- Viral or reactive arthritis
- Chronic Arthritis
- Rheumatoid Arthritis
- Spondyloarthropathy

Time

1w 6w
Chronic

- Psoriatic Arthritis
- Reactive Arthritis
- Ankylosing Spondylitis

Acute

- Septic Arthritis
- Gout/Crystal Arthritis
- Systemic vasculitis
- Systemic diseases

Rheumatoid Arthritis
Mono-arthritis (1)

- Septic Arthritis
- Gout/Crystal Arthritis
- Systemic vasculitis
- Rheumatoid Arthritis

Oligo-arthritis (<5)

- Ankylosing Spondylitis
- Reactive Arthritis
- Psoriatic Arthritis
- Systemic diseases

Poly-arthritis (>5)

Early Chronic Arthritis
The diagnostic process

• Clinical examination: be systematic!
  – make sure the patient is comfortable
  – look your patient in the eyes
  – start carefully with the culprit joint
  – go step by step: inspection > palpation > function
  – examine all joints, one by one, including the back
  – look for skin/nails, vascular/neurologic signs
  – do a general physical examination
The diagnostic process

• **Technical examinations: be selective!**
  – blood: CRP/BSE, biomarkers, function tests
  – ultrasound: confirmation of synovitis, tendinosis
  – X-ray: culprit joint + both sides + hands/feet
  – CT: differential diagnosis bone problems
  – MRI: clinical uncertainty and suspicion of SpA
  – scintigraphy: suspicion of cancer, widespread pain
Meta-analysis of 86 studies: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP</td>
<td>67% (CI, 62% to 72%)</td>
<td>95% (CI, 94% to 97%)</td>
<td>12.46 (CI, 9.72 to 15.98)</td>
<td>0.36 (CI, 0.31 to 0.42)</td>
</tr>
<tr>
<td>RF</td>
<td>69% (CI, 65% to 73%)</td>
<td>85% (CI, 82% to 88%)</td>
<td>4.86 (CI, 3.95 to 5.97)</td>
<td>0.38 (CI, 0.33 to 0.44)</td>
</tr>
</tbody>
</table>

Nishimura K et al. Ann Intern Med 2007; 146(11):797-808

Diagram showing the correlation between phenotype and disease activity over time:

**Phenotype**
- ACPA-positive
- ACPA-negative

**Onset of disease**
- IRF5, C-type lectins
- Infections?

**Same clinical presentation**
- Higher disease activity
- Lower disease activity

**Time**
- Higher all-case death rate
- Lower all-case death rate
- More destruction
- Less destruction

**More cardiovascular complications**
- Higher all-case death rate
- Fewer cardiovascular complications
Ultrasound examination of soft tissue: (teno)synovitis
X-ray examination of hard tissue: cartilage loss and bone erosions

- **Early RA**
  - Soft tissue swelling

- **Progressive RA**
  - Juxta-articular osteoporosis
  - Jointspace narrowing and erosion

- **Established RA**
  - Progressive erosion, functional ankylosis
  - Axis deviation, subluxation, deformities

MRI examination: axial inflammation
Bone scintigraphy: atypical presentation

Pierre-Marie Bamberger
hypertrophic osteoarthropathy

Diffuse skeletal metastasis
Acute monoarthritis

Differential diagnosis:
• First rule out septic arthritis
• Think about crystal arthritis

Diagnostic procedure number one: arthrocentesis
- Gram staining and culture
- WBC count and microscopic examination for crystals
Acute monoarthritis

Circumstantial evidence
- Calor-rubor-dolor-tumor
- Fever, illness
- Skin lesions
- Tophi

Diagnostic procedure: bloodsample
- Bloodculture
- CRP +++
- Serum uric acid (lowered in acute phase)
Acute monoarthritis: septic arthritis

• Treatment
  ➢ ubi pus ibi evacua
  ➢ antibiotics (6w) according to culture/abiogram

• Prognosis
  ➢ destructive arthropathy
  ➢ cave contractures
  ➢ cave osteomyelitis
Acute monoarthritis: crystal arthropathy

• Treatment (acute phase)
  ➢ Colchicine 1mg followed by 0.5mg/12 hours
  ➢ Strong NSAID at anti-inflammatory dosages
  ➢ In case of kidney problems: moderate dose GC

• Prognosis
  ➢ Spontaneous resolution acute phase 4-7 days
  ➢ Repeated arthritis attacks are destructive
  ➢ Longstanding gout can become chronic/polyarticular
Acute monoarthritis: crystal arthropathy


- Aspirine (large dose)
- Diuretica
- Furosemide
- Cyclosporine and cytostatics
- Ethambutol / pyrazinamide
- Levodopa
- Nicotine acid

Urine acid > 6mg/dl
Acute monoarthritis: crystal arthropathy

Initieer een acute behandeling (NSAID's, colchicine, of corticosteroiden)

1-2 jicht-aanvallen

Overweeg het starten van een UVT en profylaxe (colchicine of NSAID's), met als streefwaarde sUA 5 of 6 mg/dl

(2 weken)

Stop de profylactische behandeling en hou de patiënt op een UVT.

(6 maanden)

asymptomatische hyperurikemie

controleer sUA

(6 maanden)

controleer sUA

controleer sUA

* Net zoals het cholesterolgehalte regelmatig opgevolgd dient te worden, moet ook de sUA regelmatig gemeten worden om een sUA onder de 5 of 6 mg/dl te bekomen.
Subacute mono- oligoarthritis

Keratoderma Blenorhagicum

Conjunctivitis

Enthesitis

Gastroenteritis

Sarcoidosis arthritis
Subacute polyarthritis

- SLE
- Parvovirus B19
- RS3PE, McCarthy Syndrome
- Tophous Gout
Chronic mono-oligoarthritis

Lyme arthritis

Psoriatic arthritis

IBD related arthritis

Ankylosing Spondylitis
Chronic polyarthritis

RA

PsA

OA

SLE
### 2010 ACR/EULAR classification criteria for RA

- Patients with at least one joint with definite clinical synovitis (swelling).
- The synovitis cannot be better explained by another disease.
- A score of $\geq 6/10$ is needed for classification as definite RA.

#### A Joint involvement

<table>
<thead>
<tr>
<th>Joint involvement</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (with or without large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without large joints)</td>
<td>3</td>
</tr>
<tr>
<td>$&gt;10$ joints (at least 1 small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

#### B Serology

<table>
<thead>
<tr>
<th>Serology</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF or low positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF or high positive ACPA</td>
<td>3</td>
</tr>
</tbody>
</table>

#### C Acute phase reactants

<table>
<thead>
<tr>
<th>Acute phase reactants</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

#### D Duration of symptoms

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;6$ weeks</td>
<td>0</td>
</tr>
<tr>
<td>$\geq6$ weeks</td>
<td>1</td>
</tr>
</tbody>
</table>
RA: an inflammatory disease of the synovium

Early RA

Progressive RA

Established RA

Images show different stages of RA with associated histological images.
The synovium as a lymphoid organ

Immune response develops

Joint inflammation

Joint destruction

Synovial macrophage

Pannus

Synovial fibroblast
**Inflammation / Loss of function**

- Inflammation
- Disability
- Radiography Scores

Preclinical phase

Duration of Disease (Years)

Inflammation                                          Function loss                                                  Damage

“No time to waste”

“The window of opportunity

• Rheumatic diseases are chronic and progressive:
  – Reumatoid arthritis
  – SLE
  – Ankylosing Spondylitis
  – …

• Time window in which the effectiveness of any intervention is bigger

Reversible → Definitive

Inflammation → Function loss → Damage
The arsenal: disease modifying antirheumatic treatment

Current treatment paradigm for RA based on Belgian reimbursement criteria
Traditional DMARDs versus Biologics

**Traditional DMARDS**
- Chemical compounds
- Use based on experience
- Mode of action largely unknown
- Improve symptoms slowly
- Control inflammation slowly
- Improve function slowly
- Slow down radiographic damage
- Specific toxicity profile
- Mostly cheap
- Available for everyone

**Biologics**
- Biosynthesized Proteins
- Use based on insight in pathology
- Sophisticated targeted therapy
- Improve symptoms rapidly
- Control inflammation rapidly
- Improve function rapidly
- Stop radiographic damage
- Specific toxicity profile
- Expensive (production cost...)
- Only for the happy few...
Reimbursement criteria for biologicals in RA

First request for reimbursement:
- Severe rheumatoid arthritis
- Having failed 2 DMARDs (MTX + other)
  - Insufficient response at optimal dosage for at least 3 months
  - Intolerance
- DAS28 score $\geq 3.7$
- Absence of active tuberculosis

Prolongation of reimbursement:
- After six months and yearly afterwards
- First treatment was efficacious: moderate to good EULAR response

Additional criteria for rituximab:
- Insufficient response/toxicity on anti-TNF therapy for rituximab
The arsenal: glucocorticoids

Handle with care!
- just as much as needed
- for as long as needed
Status praesens

✧ Future for newly onset RA patients looks bright
...at least through the **window of opportunity**
for therapeutic intervention

✧ Two basic strategic principles
  ➢ rapid remission induction
  ➢ treat to target

Boers (1997) Randomised comparison of combined step-down prednisolone, MTX and sulphasalazine with sulphasalazine alone in early RA (Cobra Trial)
Goekoop-Ruiterman (2007) Comparison of treatment strategies in early rheumatoid arthritis (BeST trial)
Remission induction with Cobra

- **Cobra-like** induction therapies
  - efficacious (=biologics)
  - cost-effective (>biologics)
  - feasible in daily practice

- However **not widely used** in clinical practice
  - Doubts about the ideal DMARD combination
  - Doubts about initial high prednisone dosage
  - Many other barriers for implementation...

Not for everybody ?!

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Choy (2008) Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis (Cardera trial)
Treat to target: Disease Activity Score (DAS)

DAS (ESR) = 0.54*sqrt(TJC RAI) + 0.065*(SJC 44) + 0.33*Ln(ESR) + 0.0072*GH

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Low DAS

Moderate DAS

High DAS

Remission

Which intervention?

- Dose increase DMARD
- Start corticosteroids
- Social assistant
- Change DMARD
- Start physiotherapy
- Start NSAID
- Plan operation
- Local injection

= Flexible tight control
Can we do better than this? Yes we can!

Traditional Pyramid Approach to RA Treatment

1995 Diagnosis

2005 Diagnosis

Can we do better than this? Yes we can!
CareRA trial

✧ 2 year multicenter investigator-initiated pragmatic RCT
  ✓ Implementing Rapid Remission Induction + Treat to Target
  ✓ Global Early RA Management = the CareRA “package”

✧ Inclusion criteria:
  • **All** patients with early RA (<1 year, ACR 1987 criteria +)
  • Previously untreated with DMARDS
  • No contraindications for corticosteroids or DMARDS
  • Willing to give written informed consent

✧ 13 actively recruiting centers in Flanders
CareRA trial

Trial design

Stratification procedure

Randomization procedure
CareRA trial: high risk group

✧ High-Risk early RA patients were randomized to 3 treatment arms:

1. COBRA Classic
   ✧ Methotrexate 15mg weekly
   ✧ Sulphasalazine 2g daily
   ✧ Prednisone step down, from initially 60mg tapered to 7.5mg from W7

2. COBRA Slim
   ✧ Methotrexate 15mg weekly
   ✧ Prednisone step down, from initially 30mg tapered to 5mg from W6

3. COBRA Avant-Garde
   ✧ Methotrexate 15mg weekly
   ✧ Leflunomide 10mg daily
   ✧ Prednisone step down, from initially 30mg tapered to 5mg from W6

✧ Treatment was adjusted to a target DAS28(CRP) ≤ 3.2 from W8
✧ Prednisone was further tapered from W28 and stopped at W34
✧ DMARD monotherapy was aimed for in all schedules from W40
# Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>COBRA CLASSIC</th>
<th>COBRA SLIM</th>
<th>COBRA AVANT-GARDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>98</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.2 ± 11.9</td>
<td>51.8 ± 13.1</td>
<td>51.1 ± 12.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 4.3</td>
<td>26.8 ± 4.2</td>
<td>26.5 ± 4.2</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>65.3%</td>
<td>64.3%</td>
<td>68.8%</td>
</tr>
<tr>
<td>Smoking Status (ever)</td>
<td>57.1%</td>
<td>59.2%</td>
<td>60.2%</td>
</tr>
<tr>
<td>Symptom Duration (weeks)</td>
<td>33.8 ± 35.5</td>
<td>33.2 ± 38.2</td>
<td>44.3 ± 65.9</td>
</tr>
<tr>
<td>RF (yes)</td>
<td>79.6%</td>
<td>83.7%</td>
<td>75.3%</td>
</tr>
<tr>
<td>ACPA (yes)</td>
<td>77.6%</td>
<td>79.6%</td>
<td>77.4%</td>
</tr>
<tr>
<td>Erosions (yes)</td>
<td>32.7%</td>
<td>32.7%</td>
<td>34.4%</td>
</tr>
<tr>
<td>Total TJC</td>
<td>14.7 ± 9.5</td>
<td>13.7 ± 8.2</td>
<td>14.1 ± 9.0</td>
</tr>
<tr>
<td>Total SJC</td>
<td>11.9 ± 8.9</td>
<td>10.8 ± 6.5</td>
<td>10.6 ± 6.7</td>
</tr>
<tr>
<td>PGA (0-100)</td>
<td>59.5 ± 21.7</td>
<td>56.2 ± 21.7</td>
<td>54.8 ± 24.2</td>
</tr>
<tr>
<td>Pain (0-100)</td>
<td>59.5 ± 23.6</td>
<td>56.5 ± 21.9</td>
<td>57.5 ± 23.8</td>
</tr>
<tr>
<td>Fatigue (0-100)</td>
<td>50.6 ± 26.0</td>
<td>49.0 ± 21.3</td>
<td>48.9 ± 23.7</td>
</tr>
<tr>
<td>PhGA (0-100)</td>
<td>54.7 ± 18.5</td>
<td>53.1 ± 18.1</td>
<td>51.7 ± 17.9</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>33.5 ± 25.2</td>
<td>32.1 ± 23.4</td>
<td>25.0 ± 17.6</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>19.7 ± 28.9</td>
<td>21.5 ± 33.2</td>
<td>14.5 ± 19.2</td>
</tr>
<tr>
<td>DAS28(ESR)</td>
<td>5.4 ± 1.3</td>
<td>5.2 ± 1.2</td>
<td>5.0 ± 1.3</td>
</tr>
<tr>
<td>DAS28(CRP)</td>
<td>5.0 ± 1.2</td>
<td>4.8 ± 1.1</td>
<td>4.7 ± 1.2</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>1.2 ± 0.7</td>
<td>1.0 ± 0.7</td>
<td>1.0 ± 0.6</td>
</tr>
</tbody>
</table>
Results high risk group

DAS28 (CRP) remission from baseline to W52

- Cobra Classic
- Cobra Slim
- Cobra Avant-Garde

Time (Weeks)
Results: Radiographic Progression BL-W52

Change in Sharp-van der Heijde Score vs. Cumulative Probability

- Cobra Classic
- Cobra Slim
- Cobra Avant-Garde
Results: Safety

Number of Adverse Events per Patient (median - IQR)

<table>
<thead>
<tr>
<th></th>
<th>Cobra Classic</th>
<th>Cobra Slim</th>
<th>Cobra Avant-Garde</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 0.038</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients with ≥ 1 AE (%)</th>
<th>Discomfort Medication</th>
<th>Toxicity</th>
<th>Infection</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cobra Classic</strong></td>
<td>66/98 (67.3%)</td>
<td>143</td>
<td>24</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cobra Slim</strong></td>
<td>65/98 (66.3%)</td>
<td>100</td>
<td>20</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cobra Avant-Garde</strong></td>
<td>71/93 (76.3%)</td>
<td>137</td>
<td>26</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
Low-Risk early RA patients were randomized to 2 treatment arms:

1. **Tight Step Up**
   - Methotrexate 15mg weekly
   - Prednisone was not allowed in this treatment arm

2. **COBRA Slim**
   - Methotrexate 15mg weekly
   - Prednisone step down, from initially 30mg tapered to 5mg from W6
   - Prednisone was further tapered from W28 and stopped at W34

Treatment was adjusted to a target DAS28(CRP) ≤ 3.2 from W8
   - First adjustment was a dose increase of MTX to 20 mg
   - Second adjustment was the addition of leflunomide 10 mg daily
   - Together with these adjustments one IM injection of depomedrol was allowed
### Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MTX TSU</th>
<th>Cobra Slim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=47</td>
<td>n=43</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.02 ± 14.00</td>
<td>51.42 ± 14.42</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.98 ± 4.22</td>
<td>25.40 ± 4.27</td>
</tr>
<tr>
<td>Women</td>
<td>80.9%</td>
<td>76.7%</td>
</tr>
<tr>
<td>Smokers (ever)</td>
<td>38.3%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Alcohol users</td>
<td>61.7%</td>
<td>55.8%</td>
</tr>
<tr>
<td>Symptom duration (weeks)</td>
<td>33.11 ± 62.21</td>
<td>34.42 ± 68.16</td>
</tr>
<tr>
<td>RF positive</td>
<td>23.4%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Anti-CCP positive</td>
<td>23.4%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Erosions</td>
<td>0.0%</td>
<td>2.3%</td>
</tr>
<tr>
<td>TJC28</td>
<td>9.49 ± 7.46</td>
<td>8.51 ± 7.80</td>
</tr>
<tr>
<td>SJC28</td>
<td>6.89 ± 6.11</td>
<td>7.79 ± 6.03</td>
</tr>
<tr>
<td>PGA (0-100)</td>
<td>49.89 ± 22.99</td>
<td>48.60 ± 30.68</td>
</tr>
<tr>
<td>Pain (0-100)</td>
<td>52.09 ± 23.23</td>
<td>48.23 ± 31.19</td>
</tr>
<tr>
<td>Fatigue (0-100)</td>
<td>45.91 ± 22.07</td>
<td>39.40 ± 27.66</td>
</tr>
<tr>
<td>PhGA (0-100)</td>
<td>48.34 ± 23.37</td>
<td>48.63 ± 20.80</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>23.04 ± 16.90</td>
<td>30.00 ± 29.40</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>13.53 ± 18.62</td>
<td>20.14 ± 39.25</td>
</tr>
<tr>
<td>DAS28(CRP)</td>
<td>4.55 ± 1.63</td>
<td>4.50 ± 1.63</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>0.99 ± 0.67</td>
<td>0.92 ± 0.85</td>
</tr>
</tbody>
</table>
Results low risk group

- **DAS28 (CRP)**
- **MTX-TSU**
- **Slim**

- **HAQ**

- **PGA**
Results: Radiographic Progression BL-W52

ΔSvdH score vs Cumulative Probability

- Blue dots represent MTX-TSU
- Orange dots represent Cobra Slim
Results: Safety

- MTX-TSU: 30/47 (63.8%)
- Cobra Slim: 22/43 (51.2%)

<table>
<thead>
<tr>
<th>AE Category</th>
<th>MTX-TSU</th>
<th>Cobra Slim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort medication (e.g. diarrhoea, general malaise)</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>Toxicity (e.g. abnormal liver function values)</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Infection (e.g. pulmonary infections)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

p = 0.737
### Treatment at W52

**Single DMARD (observed):**
263/346 = 76%

**Glucocorticoids (observed):**
18/346 = 5%

**Biologicals (observed):**
26/346 = 7.5%

---

<table>
<thead>
<tr>
<th>Treatment at W52</th>
<th>COBRA CLASSIC</th>
<th>COBRA (High-Risk)</th>
<th>COBRA AVANT-GARDE</th>
<th>MTX-TSU</th>
<th>COBRA SLIM (Low-Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients in trial</td>
<td>N=98</td>
<td>N=98</td>
<td>N=93</td>
<td>N=47</td>
<td>N=43</td>
</tr>
<tr>
<td>Number of Treatment Adaptations</td>
<td>1</td>
<td>21 (21.4%)</td>
<td>38 (38.8%)</td>
<td>22 (23.7%)</td>
<td>17 (36.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (3.1%)</td>
<td>16 (16.3%)</td>
<td>5 (5.4%)</td>
<td>9 (19.1%)</td>
</tr>
<tr>
<td>cumulative prednisone dose (mg)</td>
<td>2597.2 ±666.8</td>
<td>1526.9 ±378.7</td>
<td>1585.6 ±422.9</td>
<td>36.3 ±49.6</td>
<td>1554.0 ±307.6</td>
</tr>
<tr>
<td>daily prednisone dose (mg)</td>
<td>6.5 ±2.7</td>
<td>3.8 ±1.6</td>
<td>4.0 ±1.6</td>
<td>0.1 ±0.1</td>
<td>3.8 ±1.6</td>
</tr>
<tr>
<td>Patients with GC injections</td>
<td>15 (15.3%)</td>
<td>31 (31.6%)</td>
<td>15 (16.1%)</td>
<td>17 (36.2%)</td>
<td>6 (13.9%)</td>
</tr>
<tr>
<td>Patients followed per protocol until W52</td>
<td>N=62 (63.2%)</td>
<td>N=75 (76.5%)</td>
<td>N=60 (64.5%)</td>
<td>N=36 (76.6%)</td>
<td>N=30 (69.9%)</td>
</tr>
<tr>
<td>Therapy at W52:</td>
<td>On MTX only</td>
<td>58 (93.5%)</td>
<td>68 (90.7%)</td>
<td>36 (60.0%)</td>
<td>31 (86.1%)</td>
</tr>
<tr>
<td></td>
<td>On LEF only</td>
<td>4 (6.5%)</td>
<td>7 (9.3%)</td>
<td>4 (6.7%)</td>
<td>5 (13.9%)</td>
</tr>
<tr>
<td>On MTX+SSZ</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>On MTX+LEF</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MTX+GC</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>LEF+GC</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MTX only</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>LEF only</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSZ only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Patients in remission at W52</td>
<td>49 (79.0%)</td>
<td>52 (69.3%)</td>
<td>45 (72.5%)</td>
<td>24 (66.7%)</td>
<td>25 (83.3%)</td>
</tr>
<tr>
<td>Patients in low disease activity at W52</td>
<td>55 (88.7%)</td>
<td>65 (86.7%)</td>
<td>53 (85.5%)</td>
<td>32 (88.9%)</td>
<td>29 (96.7%)</td>
</tr>
<tr>
<td>Patients not followed per protocol until W52</td>
<td>N=28 (28.6%)</td>
<td>N=14 (14.3%)</td>
<td>N=25 (26.9%)</td>
<td>N=8 (17.0%)</td>
<td>N=8 (18.6%)</td>
</tr>
<tr>
<td>Therapy at W52: Biological therapy</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
Take home messages

✧ Very high remission rates can be achieved in eRA patients with combinations of DMARDs and a step down regimen of glucocorticoids

✧ After Cobra induction therapy a large majority of patients achieves sustained remission, decreasing the need for sophisticated targeted biological therapies

✧ Cobra-like treatment strategies are feasible in daily practice
  - in high- as well as low-risk eRA patients
  - in different health care settings

✧ Cobra Slim could be considered a one-size-fits-all for initial eRA treatment
  - just as intensive as needed
  - less “collateral damage” as with combination therapies and with a better retention rate

✧ A flexible treat to target approach should be followed after remission induction

✧ There is an urgent need for biomarkers allowing better treatment allocation
Future = Personalized medicine?

Initial therapeutic regimen à la carte for each individual RA patient

Based on biomarkers predicting disease severity and therapeutic response

But there are no reliable biomarkers yet!

- therapy choice based on personal experience and patient preference
- trial and error: best predictor of long term response is short term response
Is that all?
Unraveling Preferred Outcomes of Disease and Treatment in Patients with Early Rheumatoid Arthritis: a Longitudinal Qualitative Interview Study

Kristien Van der Elst, S Meyfroidt, A De Groef, E Binnard, D De Cock, P Moons, P Verschueren, R Westhovens

Return to being normal

Physical aspects
- Relief of pain and other physical symptoms
- Joint function and mobility
- Limited side effects
- Improved sleep

Aspects of disease control
- Less medication
- Proof of disease control
- Prevention or stabilization of joint damage

Aspects of participation
- Performing activities of daily living, autonomously
- Engagement in work and/or leisure time
- Performing family, social and/or societal roles
- Vitality

Mental aspects
- Fear, hope and emotional well-being
- Self-esteem and identity
- Life enjoyment
- Not feeling ill
The psychosocial window of opportunity
“It’s good to feel better but it is better to feel good”
Psoriasis Artritis

- Prognose afhankelijk van het subtype: heterogeen!
  - Oligoarticulair (5%) >> fluctuerend verloop
  - Polyarticulair symmetrisch (50%) >> gelijkend op RA, minder destructief (?)
  - Psoriatische artritis van de DIPs vd handen en voeten (5%) >> gelokaliseerd
  - Spondylitis (5%) >> gelijkend op ankyloserende spondylitis
  - Arthritis mutilans (5%) >> aggressief destructief verloop (telescoping fingers)

- Specifieke problemen als enthesitis en dactylitis
- Bijkomende moeilijkheden door cutane psoriasis

> In sommige gevallen zuiver symptomatisch beleid
> In andere gevallen intensief beleid met csDMARDs en/of bDMARDs
The EULAR 2015 algorithm for treatment of PsA with pharmacological non-topical treatments.

Available csDMARDs
- Methotrexate
- Leflunomide
- Sulphasalazine
- Cyclosporine A

Available bDMARDs
- TNF-alpha blockers
- IL-17 blocker: secukinumab
- IL-12/23 blocker: ustekinumab

Available tsDMARDs
- PDE4 blocker: apremilast

# Management of psoriatic arthritis in 2016: a comparison of EULAR and GRAPPA recommendations.

<table>
<thead>
<tr>
<th>Feature</th>
<th>EULAR⁵</th>
<th>GRAPPA⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>General principles</td>
<td>Treatment target defined as remission or, alternatively, low or minimal disease activity</td>
<td>Treating to target recommended, but no specific target defined</td>
</tr>
<tr>
<td></td>
<td>Overarching principle states that comorbidities should be considered</td>
<td>Specific literature review addressing prevalence of comorbidities, the need for screening, and potential effect on choice of therapy</td>
</tr>
<tr>
<td>Predominant axial or enthesal disease</td>
<td>bDMARDs without prior use of a csDMARD</td>
<td></td>
</tr>
</tbody>
</table>

**Drugs**

**Methotrexate**

- Recommended as the csDMARD of choice

**TNF inhibitors**

- Recommended for use after failure of csDMARDs for predominant peripheral disease or earlier in predominant axial or enthesal disease
- • Recommended for use after failure of csDMARDs
- • Clear preference for TNF inhibitors as the first-line bDMARD
- • Potential to use as a first-line therapy, before csDMARDs, in patients with severe active disease
- • No clear preference given to TNF inhibitors as the first-line bDMARD

**Secukinumab and ustekinumab**

- Recommended for use after failure of methotrexate, but TNF inhibitors are preferred as the first-line bDMARD

**Apremilast**

- Recommended for use after methotrexate if bDMARDs are contraindicated
- • Recommended for use after failure of csDMARDs or if csDMARDs are contraindicated
- • Conditionally recommended before csDMARDs in certain cases

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Ankyloserende Spondylitis

- Meestal fluctuerend verloop, met goede en minder goede periodes
- Grote meerderheid heeft een zeer gunstige prognose
- Kleine minderheid ontwikkelt ankylose wervelkolom

- Sommigen ontwikkelen ook perifere artritis
- Sommigen ontwikkelen ook extra-articulaire problemen: oogontsteking, darmontsteking

Meestal goede symptoomcontrole en behoud van functionaliteit mits oefening en NSAID

In bepaalde gevallen nood aan bDMARD: anti-TNF en anti-IL17
Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis.

Available csDMARDs
  ➢ Sulphasalazine

Available bDMARDs
  ➢ TNF-alpha blockers
  ➢ IL-17 blocker(s)

Désirée van der Heijde et al. Ann Rheum Dis 2017;76:978-991
ASAS-EULAR recommendations for the treatment of patients with “axial spondyloarthritis” with bDMARDs.

Rheumatologist’s diagnosis of axial SpA
and
Elevated CRP and/or positive MRI and/or Radiographic sacroiliitis*
and
Failure of standard treatment:
all patients
• at least 2 NSAIDs over 4 weeks (in total)
patients with predominant peripheral manifestations
• one local steroid injection if appropriate
• normally a therapeutic trial of sulfasalazine
and
High disease activity: ASDAS ≥ 2.1 or BASDAI ≥ 4
and
Positive rheumatologist’s opinion

* Radiographic sacroiliitis is mandatory for infliximab and IL17i

Désirée van der Heijde et al. Ann Rheum Dis 2017;76:978-991

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Everything an internist needs to know about arthritis in daily practice anno 2018

- Acute monoarthritis > punction: cell count, crystals, culture
- Early polyarthritis: there is no time to waste!
  - Good response to NSAID is no reason to postpone referral
  - Refer to rheumatologist before starting glucocorticoids
- Established polyarthritis: stay alert and systematic!
  - DMARDs can be toxic products but are essential to treat RA
    • Discuss potential toxicity with rheumatologist as soon as possible
    • Beware of secondary toxicity in case of problems with renal or liver function
  - Patients on biologics are immune compromised
    • Increased risk of atypical severe infections: need for invasive diagnostic procedures
    • Increased risk of paradoxical autoimmune reactions: sometimes phenotype switch
  - A flare is not always simply a flare: beware of pitfalls
  - Like all systemic diseases RA can affect other organs than the joints
Rheumatology: for the happy few ?!

- Preventie, diagnostiek en behandeling van niet traumatische musculoskeletale aandoeningen en systeemziekten.
- Diepgaande kennis van de kliniek en de pathofysiologie van aandoeningen zoals reumatoïde artritis, systeemlupus, systeemsclerose en vasculitiden, spondyloartritis, infectieuze artritis, kristalartropathieën, (osteo)artrose, osteoporose.

- Typisch competenties in de differentiaaldiagnostiek van musculoskeletale aandoeningen en het uitzetten van geïntegreerde therapiestrategieën bij diverse chronische reumatische aandoeningen.
- Coördineert hierbij veelal een multidisciplinaire benadering.
- Exclusiviteit in de indicatiestelling en het voorschrijven van gerichte biologische behandelingen voor chronische artritis.

- Centrale rol in de evaluatie van de chronische inflammatoire gewrichtsaandoeningen.
- Specifieke honorering voor evidence-based evaluatie van outcome, kostenefficaciteit en zorgkwaliteit
- Deelname aan klinisch wetenschappelijk onderzoek en registratie van de uitkomst van de nieuwe behandelingen is ook voor niet universitair werkende reumatologen een belangrijke taak.

- De reumatoloog heeft hoofdzakelijk ambulante activiteiten, meer en meer in associatie met meerdere collegae reumatologen. De nadruk ligt hierbij op consultaties maar ook op daghospitaal activiteiten voor toediening van gerichte biologische therapieën. Verder is er in grotere ziekenhuizen vaak een dienst reumatologie met ook opname faciliteiten.
- Binnen ziekenhuizen kunnen reumatologen deel uitmaken van de pool interne geneeskunde of samenwerken met specialisten in de fysische geneeskunde en revalidatie.