Primary Care Diagnosis and Management of Rheumatoid Arthritis

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Denver Health
Objectives

• Understand the diagnosis and clinical signs of RA
• Develop an approach to selecting disease modifying antirheumatic drugs (DMARDs) prior to referral
• Describe the benefits of prompt treatment of RA
RA Pathophysiology

Normal Joint

- Capsule
- Synoviocytes
- Synovial membrane
- Cartilage

Early

- Synoviocyte accumulation
- Capillary formation
- Neutrophils
- T cells
- B cells
- Plasma cells
- Hyperplastic synovial membrane

Established

- Eroded bone
- Pannus
- Neutrophils

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RA Pathology and Clinical Manifestations

Normal Synovium

RA Synovium

ACR Criteria: Diagnosis of RA

- AM STIFFNESS (>1 h)
- INFLAMMATORY ARTHRITIS OF ≥ 3 JT AREAS
- INFLAMMATORY ARTHRITIS OF HAND JTS (wrist MCP PIP)
- SYMMETRIC ARTHRITIS
- RHEUMATOID NODULES
- SERUM RHEUMATOID FACTOR OR ANTI-CCP
- RADIOGRAPHIC CHANGES TYPICAL OF RA (erosions)
- FOR ≥ 6 WKS
- Any 4 = rheumatoid arthritis
- Sensitivity: 71-90% Specificity: 90-100%
Physical Examination

Rheumatoid Arthritis vs Osteoarthritis

[Image showing skeletal anatomy with highlighted joints for both conditions]
Physical Examination

• Joint count of actively inflamed joints
Physical exam
Laboratory and Radiology

- Rheumatoid factor: IgM against Fc of IgG
- Anti-cyclic citrullinated peptide (anti-CCP)
- HCV ab
- ESR or CRP
- CBC, electrolytes, creatinine
- LFTs
- Synovial fluid analysis
- Urinalysis
- Radiographs of hands and/or feet
# Serologic Factors in RA: Anti-CCP and RF

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>RA (n=102)</th>
<th>Non-RA (n=98)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF (&gt; 20 U/ml)</td>
<td>56</td>
<td>11</td>
<td>55</td>
<td>89</td>
<td>84</td>
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<tr>
<td>High titer RF (&gt;50 U/ml)</td>
<td>46</td>
<td>4</td>
<td>45</td>
<td>96</td>
<td>92</td>
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<tr>
<td>Anti-CCP</td>
<td>42</td>
<td>2</td>
<td>41</td>
<td>98</td>
<td>96</td>
</tr>
</tbody>
</table>

Nell VPK et al. Ann Rheum Dis 2005 64 1731-36
Patients presenting with early arthritis
RA 102 non RA 98

Rheumatoid factor

RF >50 U/ml
45% of RA
4% of non RA

High Risk of developing RA
High risk of developing erosive disease

RF < 50 U/ml

Anti-CCP

Positive
14% of RA
2% of non RA

Negative

Nell VPK et al. Ann Rheum Dis 2005 64 1731-36
Stages of RA

Early  Intermediate  Late
Poor Prognostic Indicators

- Earlier age at onset; female sex
- Polyarticular synovitis
- High titer rheumatoid factor and/or anti-CCP
- Elevated ESR or CRP level
- Erosions or cartilage loss on x-ray (in < 1 yr)
- HLA-DR4
- Poor functional status
- Extraarticular manifestations: rheumatoid nodules, scleritis, ILD, pericarditis, vasculitis

Rate of progression

- Up to 93% of patients with <2 years of RA may have radiographic abnormalities.
- Erosions can be detected by MRI within 4 months of RA onset.
- Rate of progression is significantly more rapid in the first year than in the second and third years.
DMARD Treatment: The Earlier the Better
Glucocorticoids

- Local injection: limited to a few joints
- Low-dose oral (<10 mg prednisone):
  - “Bridge-therapy” until DMARD response (polyarticular synovitis)
  - Control of disease despite NSAIDs and adequate trials of DMARDs
  - Loss of independence or employment; flares; special events
  - Toxicity (osteoporosis): dose and duration
- Triamcinolone acetonide (Kenalog): 60 mg IM prn flare
NSAIDS

- Reduce joint pain and swelling
- Improve function
# DMARD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of effect</th>
<th>Adverse effects</th>
<th>Monitoring Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidroxychloroquine</td>
<td>200-400 mg PO daily</td>
<td>2-6 months</td>
<td>GI upset, Retinal toxicity</td>
<td>Fundoscopy every 12 months</td>
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<tr>
<td>Sulfazalasine</td>
<td>2-3 grams daily</td>
<td>1-3 months</td>
<td>GI intolerance, Cytopenia, Rash, Oral ulcers, Red urine</td>
<td>CBC every 2-3 months</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5-25 mg PO,SC or IM Weekly + Folic acid 1 mg daily</td>
<td>1-2 months</td>
<td>GI intolerance, Rash, Cytopenias, Oral ulcer, Alopecia, Alopecia, Alopecia, Alopecia, Hepatitis, Pneumonitis, Teratogenic</td>
<td>LFT, CBC creatinine monthly x 6 m then every 2-3 months</td>
</tr>
</tbody>
</table>
Table 2. Recommendations for contraindications to starting or resuming therapy with nonbiologic and biologic disease-modifying antirheumatic drugs in RA patients*

<table>
<thead>
<tr>
<th>Organ system and contraindication</th>
<th>ABA</th>
<th>Anti-TNFα</th>
<th>DQO</th>
<th>LEF</th>
<th>MTX</th>
<th>MIN</th>
<th>RIT</th>
<th>SSZ</th>
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<tr>
<td>Infectious diseases and pneumonitis</td>
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<td>Acute serious bacterial infection or infection, currently receiving</td>
<td>X</td>
<td>X</td>
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<td>antibiotics</td>
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<td>Upper respiratory tract infection (presumed viral) with fever (&gt;101°F)</td>
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<td>Nonhealed infected skin ulcer</td>
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<td>Latent TB infection prior to initiation of latent TB initiation</td>
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<td>treatment, or active TB disease prior to completing a standard</td>
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<td>regimen of anti-TB therapy†</td>
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<td>Active life-threatening fungal infection</td>
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<td>Active herpes-zoster viral infection</td>
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<td>Interstitial pneumonitis (due to RA or unknown cause) or clinically</td>
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<td>significant pulmonary fibrosis</td>
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<td>Hematologic and oncologic</td>
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<td>White blood cell count &lt;3,000/mm³‡</td>
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<td>Platelet count &lt;50,000/mm³³</td>
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<td>Moderate to severe heart failure (NYHA III or IV) and left ventricular</td>
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<td>ejection fraction &lt;50%§</td>
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<td>Liver transaminase level 2 times the upper limit of normal</td>
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<td>Chronic hepatitis B viral infection, receiving therapy☆</td>
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<td>Chronic hepatitis B viral infection, not receiving therapy</td>
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<td>Chronic hepatitis C viral infection, receiving therapy</td>
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<td>Childc-Pugh class A</td>
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<td>Chronic hepatitis C viral infection, not receiving therapy</td>
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<td>Renal</td>
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<td>Creatinine clearance &lt;30 ml/minute</td>
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<td>Neurologic</td>
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<td>Multiple sclerosis or other demyelinating disorder</td>
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<td>Pregnancy and breastfeeding</td>
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<td>Planning for or current pregnancy</td>
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<td>Breastfeeding</td>
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</tbody>
</table>

*Please refer to the original source for complete details and context.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Organ system</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>Liver</td>
<td>Chronic Hepatitis B or C not receiving therapy Childs-Pugh class B or C</td>
</tr>
<tr>
<td>Sulfazalasine</td>
<td>Hematology, Liver</td>
<td>Plts &lt; 50,000&lt;br&gt;LFT elevation 2-folds the upper limit of normal&lt;br&gt;Acute hepatitis B or C&lt;br&gt;Chronic Hepatitis B or C Childs-Pugh class B or C</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>ID, Hematology, Liver, Pregnancy, Breastfeeding</td>
<td>Acute serious bacterial infection&lt;br&gt;Latent TB or active TB&lt;br&gt;Life threatening fungal infection&lt;br&gt;Active HSV infection&lt;br&gt;Interstitial Pneumonitis from RA or unknown cause&lt;br&gt;Clinical significant Pulmonary Fibrosis&lt;br&gt;WBC&lt;3,000&lt;br&gt;Plts &lt; 50,000&lt;br&gt;Myelodysplasia&lt;br&gt;Treated lymphoproliferative disease &lt; 5 years&lt;br&gt;LFT elevation 2-folds the upper limit of normal&lt;br&gt;Acute or Chronic hepatitis B or C regardless of Childs-Pugh class&lt;br&gt;Teratogenic&lt;br&gt;Contraindicated</td>
</tr>
</tbody>
</table>

Saag et al. Arth Care & Research. 2008;6; 762-784
Diagnosed rheumatoid arthritis

In anticipation of possible future biologic therapy:
- Check tuberculosis and candida control skin tests before placing on steroids or other DMARDS.
- Baseline chest radiograph

Erosions visible on radiograph?

No

Mild disease

Trial of hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), or minocycline (Minocin)

Adequate control of joint pain and swelling?

No

Trial of methotrexate,\(^*\) 10 to 15 mg once per week ± hydroxychloroquine ± sulfasalazine

Yes

Adequate control of joint pain and swelling?

Yes

Monitor disease activity every three to six months.
Annual radiographs

No

Increase dosage of methotrexate to 20 mg orally once per week; at 25 mg, switch to SC or IM.

Adequate control of joint pain and swelling?

Yes

No

Switch from methotrexate to leflunomide (Arava) or azathioprine (Imuran); or add leflunomide or azathioprine to methotrexate; or add a biologic agent to methotrexate.\(^\dagger\)
## Outcomes Measures

<table>
<thead>
<tr>
<th><strong>Instrument</strong></th>
<th><strong>Components</strong></th>
</tr>
</thead>
</table>
| DAS            | Ritchie index (assess tenderness)  
Comprehensive swollen joint count (44 joints)  
ESR  
Patient global assessment  
Remission: DAS < 1.6; low disease activity: ≤ 2.4; moderate RA: > 2.4 and ≤ 3.7; and severe RA: > 3.7 |
| DAS28 (http://www.das-score.nl/www.das-score.nl/index.html) | DAS with modifications to include 28-joint count of tender and swollen joints  
ESR or CRP  
Patient global assessment  
Remission: DAS28 < 2.6; low disease activity: ≤ 3.2; moderate RA: > 3.2 and ≤ 5.1; and severe RA: > 5.1 |

Brent LH. Post Med. 2009;121:2
Disease Activity Score (DAS 28)

Joint Status - 28 Joint Count

1. Joint Count TEN28
2. Joint Count SW28
3. ESR (after 1 hour in mm)

4. General Health or patient’s global assessment of disease activity
   How active has your rheumatoid arthritis been during the last 7 days?*

   no activity
   highest activity possible

   *Please let patient assess this by drawing a vertical line.

Patient’s assessment in mm

Formulas for DAS 28 calculation

\[ 0.56 \times \sqrt{\text{TEN28}} + 0.28 \times \sqrt{\text{SW28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{Patient’s assessment in mm}^2 \]

= DAS 28
<table>
<thead>
<tr>
<th>ACR Response Criteria</th>
<th>Improvement (20%, 50%, or 70%) in tender/swollen joint score AND 3 of 5 core set measures: Patient global assessment Physician global assessment Patient pain HAQ Acute-phase reactants (ESR, CRP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR Response Criteria</td>
<td>3 groups of patients based on DAS/DAS28 response criteria: Good responders Patients with &gt; 1.2 improvement from baseline DAS/DAS28 AND DAS endpoint ≤ 2.4 or DAS28 endpoint ≤ 3.2 Moderate responders Patients with &gt; 0.6 but ≤ 1.2 improvement from baseline DAS/DAS28 AND DAS endpoint &gt; 2.4 but ≤ 3.7 or DAS28 endpoint &gt; 3.2 but ≤ 5.1 Non responders Patients with ≤ 0.6 improvement from baseline DAS/DAS28 AND DAS endpoint &gt; 3.7 or DAS28 endpoint &gt; 5.1</td>
</tr>
</tbody>
</table>
ACR Criteria for Remission

• Five of the following must be present x 2 months:
  – AM stiffness < 15 min
  – No fatigue
  – No joint pain by hx
  – No joint pain or tenderness on motion
  – No synovitis in joints or tendon sheaths
  – ESR < 30 mm/hr in women; <20 mm/hr in men
MTX is our best anchor drug

<table>
<thead>
<tr>
<th></th>
<th>ACR20 12 m</th>
<th>ACR50</th>
<th>ACR70</th>
<th>HAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early RA¹ (ERA)</td>
<td>65%</td>
<td>43%</td>
<td>22%</td>
<td>-0.5</td>
</tr>
<tr>
<td>ASPIRE²</td>
<td>54%</td>
<td>32%</td>
<td>21%</td>
<td>-0.68</td>
</tr>
<tr>
<td>PREMIER³</td>
<td>63%</td>
<td>46%</td>
<td>28%</td>
<td>-0.80</td>
</tr>
</tbody>
</table>

MTX dose 15-20mg/ week

<table>
<thead>
<tr>
<th>Study (RA Duration)</th>
<th>Interventions</th>
<th>Remission/ Radiographic Outcomes</th>
</tr>
</thead>
</table>
| BeSt (≤ 2 y) 2005   | Sequential monotherapy (MTX)  
Step-up combination therapy (MTX)  
Combination therapy (MTX, SSZ) + high-dose prednisone  
Combination therapy (MTX) + infliximab | At 1 y, 32% of all patients had clinical remission (DAS44 < 1.6), with no differences between treatment groups.  
At 1 y, significantly more patients in the combination therapy groups (87% and 93%; both P ≤ 0.01) had no progression of radiographic joint damage than in the step-up (73%) or sequential therapy groups (67%). |
| COMET (≤ 2 y) 2008  | Monotherapy (MTX)  
Combination therapy (etanercept + MTX) | •At 1 y, significantly more combination therapy than monotherapy patients achieved remission (DAS28 < 2.6; 50% vs 28%; P < 0.001). |
SWEFOT: Triple DMARD vs MTX + anti-TNF

ERA
Symptoms <1 yr
No other DMARD
DAS28 >3.2
n=487

Screening
3 m
Randomization
if DAS28 >3.2
(n=258/487)

MTX monotherapy
(~20 mg/wk)
3–4 m

MTX + SSZ + HCQ (→ CsA); n=130

MTX + IFX (→ ETN); n=128

12 m
1º endpoint: % pts with EULAR Good response

Pt disposition

- 30% pts responded to the initial 3–4-month trial of MTX monotherapy (DAS28 <3.2)
- At 12 m, 75% maintained a low disease activity

van Vollenhoven, et al. EULAR Paris 2008, LB0001; ibid, OP0043
SWEFOT Trial: Early RA (ERA) Patient - Outcomes in Initial MTX Responders

- N=487 with ERA (symptom duration < 1 year) for SWEFOT trial
- All started MTX with rapid dose escalation to 20 mg/week
- After 3-4 months, 144 patients with DAS28<3.2 continued on MTX & did not enter controlled portion of SWEFOT trial

### Patient Outcomes for Initial MTX Responders (n=144)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time Points</th>
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<tr>
<td></td>
<td>6 months</td>
<td>9 months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>DAS28 values (mean ± SEM)</td>
<td>2.4 ±0.09*</td>
<td>2.43 ±0.12*</td>
<td>2.53 ±0.10*</td>
<td></td>
</tr>
<tr>
<td>% patients with DAS28 &lt; 3.2</td>
<td>87%*</td>
<td>79%*</td>
<td>75%*</td>
<td></td>
</tr>
<tr>
<td>% patients with DAS28 &lt; 2.6</td>
<td>61%*</td>
<td>59%*</td>
<td>60%*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001, compared with all other patients in SWEFOT trial analyzed as one group, including those intolerant to MTX

ERA initial MTX good responders (DAS28<3.2) continue to show very good clinical responses throughout the first year on MTX monotherapy.

SWEFOT Trial: Addition of DMARDs vs. anti-TNF Therapy in ERA Patients who Failed Initial MTX Therapy

- **Arm A:** Sulfasalazine 1000 mg BID + hydroxychloroquine 400 mg QD (n=130)
- **Arm B:** Infliximab 3 mg/kg/infusion given at 0, 2, 6 weeks, then q 8 wks (n=128)

**EULAR Good Response at 12 Months**

- * (p<0.01 vs. Arm A)

**ACR Responses at 12 Months**

- * (p<0.01 vs. Arm A)

*Subsequent addition of anti-TNF to reasonable trial of MTX is clinically superior than addition of conventional DMARDs.*

Studies on their way

<table>
<thead>
<tr>
<th>Study (RA Duration)</th>
<th>Interventions</th>
<th>Remission/ Radiographic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAR ( &lt;5 y) 2009</td>
<td>Init MTX/ETN</td>
<td>At 6 m, 28% of pt achieved remission on MTX alone. Also at 6m responses were better w/ initial aggressive therapy compared to step up (ACR 20 63 vs 45%). But similar outcomes at 2 years regardless of regimen (no difference in DAS scores)</td>
</tr>
<tr>
<td>Lasted 2 years</td>
<td>Init Triple DMARD</td>
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<tr>
<td></td>
<td>Step-up MTX/ETN</td>
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<tr>
<td></td>
<td>Step-up Triple DMARD</td>
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</tbody>
</table>
A Clinic Pharmacogenetic Model to Predict the Efficacy of Methotrexate Monotherapy in Recent Onset Rheumatoid Arthritis

• Non genetic model:
  – Smoking
  – Female
  – Positive RF
  – DAS at baseline

• Pharmacogenetics:
  – Observational variables +
  – Genes related to MTX mechanism of action, purine and pyrimidine synthesis:
    • AMPD1, ATIC, ITPA and MTHFD

Wessels AM et al Arthritis & Rheum 2007; 56:1765-1775
Pharmacogenetics
Summary

• Know the clinical and lab findings of RA
• RF is not equal to RA
• Methotrexate is our best anchor drug.
• You can start therapy before referral.
• Moderate to severe RA will likely require biologics.
• Pharmacogenetics could be the answer.
THANK YOU

ANY QUESTIONS?