The Need for Early Treatment of Rheumatoid Arthritis

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Learning Objectives

- Learn the need for early diagnosis and treatment of RA
- Understand the mechanism of action of biologic therapies
- Appreciate the issues regarding efficacy and safety of the newer biologic drugs
RA: Burden of Illness

- **Prevalence**
  - 2.1 million in the United States; 165 million worldwide

- **Estimated costs**
  - $8.74 billion in 1994
  - 0.3% of the gross domestic product

- **Direct medical costs are $5,919/case/year**

- **Indirect costs**
  - 3 to 4 times higher than direct cost

Direct Costs of RA

- Hospital admissions: 51.7%
- Drugs: 26.1%
- Physician visits: 8.6%
- AHP visits: 1.4%
- Testing: 4.7%
- Other expenses: 7.5%

AHP = allied health professional.
Assessment and Prediction of Functional Disability in RA

- Functional decline begins early
- 50% of patients will reach HAQ disability scores of:
  - 1 within 2 years (moderate loss of function)
  - 2 within 6 years (severe loss of function)
  - 2.5 within 10 years (very severe loss of function)
Modifiable Predictors of Mortality in RA

- Predictors of significant mortality in >67% of studies:
  - Patient questionnaire measures
  - Physician’s global assessment of disease status
  - Measures of physical functional status
  - Patient’s global assessment of disease status
  - Patient psychological distress

- Predictors of significant mortality in 50%-67% of studies:
  - TJC
  - ESR

- Predictors of significant mortality in <50% of studies:
  - Pain score
  - RF

Which Patients Have More Aggressive Disease?

Predictors of Disease Severity

- Disease duration
- Number of swollen joints
- Presence of joint erosions
- Rheumatoid factor titer
- Presence of anti-cyclic citrullinated peptides (anti-CCP)
- CRP or ESR levels
- Presence of rheumatoid nodules

Diagnostic Tests in RA:  
Anti-CCP Antibodies

- Diagnostic value of anti-CCP
  - Sensitivity
  - Specificity
  - Positive predictive value
    - With and without RF
  - Value in primary care and rheumatology practice settings

- Prognostic value
  - Disease activity
  - Radiographic progression
Anti-CCP Antibodies

Background

- Citrullinated proteins/peptides found in RA synovium

  Arginine deiminase

- Arginine $\rightarrow$ Citrulline + NH$_3$

- Antibodies against these proteins found in RA:
  - Anti-perinuclear factor (APF)
  - Anti-keratin antibodies (AKA)
  - Anti-filaggrin antibodies
  - Anti-cyclic citrullinated peptides (anti-CCP)
  - Anti deiminated fibrinogen (ADF)

- Previously reported to have high specificity for RA
- Association with erosive disease and predictive of joint damage

Diagnostic Tests in RA: Anti-CCP Antibodies

Clinical suspicion of early RA

Rheumatoid factor

Positive

High titer (>50 U/ml)
- Good tool for diagnosis
- Good predictor of erosiveness

Low titer (20–50 U/ml)

Negative (<20 U/ml)
- Anti-CCP
- Adds significant diagnostic and prognostic value

Anti-CCP in RA

- Anti-CCP is highly specific for RA
  - Positive anti-CCP antibodies were found significantly more frequently in RA patients (31 cases, 67.4%) compared with OA patients (1 case, 2.4%) ($P<0.001$)

- Sera and synovial fluids of 46 RA patients and of 41 knee OA patients were tested for anti-CCP antibodies

- Mean levels of anti-CCP antibodies in serum (22.7±27.9 units) and synovial fluid (23.5±32.0 units) have shown a good correlation ($r=0.87$, $P<0.01$) in RA

- No significant correlation of anti-CCP serum or synovial levels with clinical parameters, DAS28, HAQ, and disease duration

### Diagnostic tests in RA: Anti-CCP Antibodies

Predictive value of individual autoantibodies for erosive disease

<table>
<thead>
<tr>
<th></th>
<th>Erosive (n=36)</th>
<th>Non-erosive (n=29)</th>
<th>$P$-value</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up time</td>
<td>33 months</td>
<td>28.5 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF (20–50 U/ml)</td>
<td>24</td>
<td>9</td>
<td>$P=0.004$</td>
<td>73%</td>
</tr>
<tr>
<td>High-titre RF (&gt;50 U/ml)</td>
<td>21</td>
<td>6</td>
<td>$P=0.002$</td>
<td>78%</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>22</td>
<td>3</td>
<td>$P&lt;0.001$</td>
<td>88%</td>
</tr>
<tr>
<td>Anti-RA33</td>
<td>11</td>
<td>7</td>
<td>$P=0.565$</td>
<td>61%</td>
</tr>
<tr>
<td>All 3 positive</td>
<td>7</td>
<td>0</td>
<td>$P&lt;0.001$</td>
<td></td>
</tr>
</tbody>
</table>

Obstacles to Curing RA

- Lack of knowledge of etiology
- Incomplete understanding of pathogenesis
- Lack of means to intervene in most of the relevant disease processes
- Disease heterogeneity
- Inability to make an early diagnosis
- Limited ability to recognize those at risk

Stages of RA

Early RA

Intermediate RA

Late RA

RA Progression

Severity (arbitrary units)

Duration of Disease (years)

Graph: Adapted from Kirwan JR. J Rheumatol. 2001;28:881-886.
Photo: Copyright © American College of Rheumatology.
RA Pathology and Clinical Manifestations

Normal Synovium  RA Synovium

Joint Erosions Occur Early in RA

- 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

Ultrasonography Detects More Erosions in Early RA

Magnetic Resonance Imaging as Diagnostic Tool

Erosions Detected: X-rays vs MRI (%)

Long-term Outcomes in RA

- Joint destruction
- Work disability
- Psychosocial dysfunction

Reduced QOL & life expectancy

- Functional disability
- Treatment Side effects
- Comorbidity

DMARD Treatment: The Earlier the Better

- Delayed treatment (median treatment lag time, 123 days; n = 109)
- Early treatment (median treatment lag time, 15 days; n = 97)

DMARDs = chloroquine or salazopyrine

*p < 0.05 vs delayed-treatment group.
Early Referral Algorithm for Newly Diagnosed RA

Rapid referral to a rheumatologist advised with clinical suspicion of RA, which may be supported by the presence of any of the following:

- ≥3 swollen joints
- MTP/MCP involvement
  - Positive squeeze test
- Morning stiffness ≥30 minutes

Historical Approach to Treatment of RA

Efficacy of Traditional DMARD Therapy

- Signs and Symptoms
- Radiographic Progression
Efficacy of Triple Therapy in RA


- **P** = 0.05
- **P** = 0.002
- **P** = 0.005

<table>
<thead>
<tr>
<th></th>
<th>ACR-20</th>
<th>ACR-50</th>
<th>ACR-70</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX + HCQ</td>
<td>60</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>MTX + HCQ + SSZ</td>
<td>78</td>
<td>55</td>
<td>26</td>
</tr>
<tr>
<td>MTX + SSZ</td>
<td>49</td>
<td>29</td>
<td>18</td>
</tr>
</tbody>
</table>

Persistent Disease Activity With Traditional DMARDs in Many Patients

Remission
- SJC = 0
- TJC = 0
- CRP < 0.5 mg/dL

Partial Remission
- SJC ≤ 2
- TJC ≤ 2
- CRP ≤ 1.0 mg/dL

No Remission
- 21%
- 27%
- 51%

Smolen JS. Data presented at EULAR. Lisbon, Portugal, June 2003.
Cytokine Signaling Pathways Involved in RA

TNF: A Pivotal Cytokine in RA

- **Macrophages**: Increases proliferation and cytokine production

- **B cell**: Increases proliferation and differentiation

- **Synovial Lining Cell**: Enhances proliferation, increases IL-2 receptor
  - Induces synthesis of IL-1, GM-CSF, Stromelysin, collagenase prostaglandins

- **Activated T cell**: Enhances proliferation, increases IL-2 receptor

- **Endothelial Cells**: Expression of ICAM-1, VCAM-1, ELAM-1, IL-8

*From Harris Jr. ED: Rheumatoid Arthritis*
Etanercept

Fc Region of Human IgG1

Extracellular Domain of Human p75 TNF Receptor

$\text{CH}_3\quad\text{CH}_2$
Etanercept in Early RA: HAQ-DI Scores at 24 Months

- ≥ 0.5 Improvement:
  - MTX 20 mg: 37%
  - Etanercept 25 mg: 55%

- ≥ 1.0 Improvement:
  - MTX 20 mg: 25%
  - Etanercept 25 mg: 29%

*P < 0.001
Etanercept + MTX: ACR Response Rates at 24 Weeks

*P < 0.001; †P < 0.05
Chimeric Anti-TNF Monoclonal Antibody

Infliximab  

Mouse  
(binding site for TNF-α)

Human (IgG1)

- Chimeric (mouse/human) IgG₁ monoclonal antibody
- Binds to TNF with high affinity & specificity

Knight DM et al, Mol Immunol, 1993
Infliximab + MTX (ATTRACT): ACR Response Rates at 30 and 54 Weeks

*P ≤ 0.001 for each outcome compared with placebo, except †P = 0.027 and ‡P = 0.04

ATTRACT = Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group
Infliximab + MTX (ATTRACT)

Changes in Total Sharp Scores

Mean Change From Baseline

- 30 Weeks
- 54 Weeks
- 102 Weeks

MTX Alone

MTX + Infliximab

P values are vs MTX alone

Adalimumab Characteristics

- Fully Human Anti-TNF\(\alpha\) Antibody
- With T\(\frac{1}{2}\) ~ 2 weeks
- Binds only TNF\(\alpha\) and not other TNF family members
Adalimumab + MTX (ARMADA):
ACR Response Rates at 24 and 52 Weeks

*P ≤ 0.001

ARMADA = Anti-TNF Research Program of the Monoclonal Antibody D2E7 [adalimumab] in Rheumatoid Arthritis Study
Adalimumab + MTX: Sustained Inhibition of Radiographic Progression Over 2 Years

Total Sharp Scores

- 67% of patients receiving adalimumab throughout the study had no increase in total Sharp scores after 2 years of treatment

*Adalimumab 40 mg every other week + MTX.
Adalimumab in Early vs Established RA

ACR Response Rates at 24 Weeks

Early RA
(≤ 2 years; n = 46)

- Adalimumab 40 mg EOW plus MTX: 70% responders (ACR-20), 59% responders (ACR-50), 4% responders (ACR-70)
- Placebo plus MTX: 37% responders (ACR-20), 5% responders (ACR-50), 5% responders (ACR-70)

Established RA
(> 2 years; n = 361)

- Adalimumab 40 mg EOW plus MTX: 62% responders (ACR-20), 36% responders (ACR-50), 18% responders (ACR-70)
- Placebo plus MTX: 29% responders (ACR-20), 10% responders (ACR-50), 2% responders (ACR-70)

TNF Antagonists
- Safety Issues-

- Infection - common/opportunistic
- Pancytopenia/aplastic anemia
- Demyelinating disorders
- SLE-like symptoms
- Congestive heart failure
- Lymphoproliferative disorders
Infection Rates Among Patients With RA

- Patients with RA have 0.03-0.09 serious infections per pt-y
- These rates are higher than in patients without RA
- Increased risk of infection in patients with RA correlates with
  - Degree of disability
  - Concomitant disease
  - Concomitant corticosteroids and other immunosuppressive agents

Tuberculosis

• Animal models of TB\(^1\)
  – TNF necessary for granuloma homeostasis
  – Inhibition of TNF associated with shortened survival

• TB in patients with RA
  – Background rates vary with geography
  – Cases of TB have been associated with all TNF antagonists\(^2\)
    • Commonly extrapulmonary (~50%)
    • Most cases are likely due to reactivation
  – Corticosteroids and diabetes are additional risk factors
  – Patients should be routinely screened for TB prior to starting TNF-antagonist therapy\(^3\)

## Expected Tuberculosis Rates

<table>
<thead>
<tr>
<th>Region</th>
<th>Subject Population</th>
<th>Rate per 100 Pt-Y</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>Background¹</td>
<td>0.006</td>
<td>–</td>
</tr>
<tr>
<td>RA</td>
<td>0.006</td>
<td></td>
<td>1x</td>
</tr>
<tr>
<td>(vs background)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European Union</td>
<td>Background²</td>
<td>0.02</td>
<td>–</td>
</tr>
<tr>
<td>RA</td>
<td>0.10</td>
<td></td>
<td>5x</td>
</tr>
<tr>
<td>(vs background)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

TB Summary

• TB rates overall
  – Higher in European than US population
  – In European Union, rate among RA patients is 5x higher than in general population

• TB screening prior to initiation of anti-TNF therapy decreases rate of TB
TNF and Malignancy

- The role of TNF in carcinogenesis and tumor surveillance has not been fully established.
- In preclinical studies, TNF has been shown to both inhibit and promote tumor growth\(^1-4\).
- Mice deficient in TNF are more resistant to tumor formation than wild-type mice\(^5,6\).
- Overproduction of TNF in B-cell chronic lymphocytic leukemia and hairy cell leukemia is associated with more severe disease progression and decreased survival\(^7,8\).

Lymphoma and RA

• The risk of lymphoma in RA increases with the severity and duration of disease\textsuperscript{1,2}
• Reports of reversible lymphomas developing in RA patients receiving MTX suggest a causal relationship\textsuperscript{3,4}

## Lymphoma Incidence in RA: Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of RA Patients</th>
<th>Years of Follow-up</th>
<th>SIR for Cancer</th>
<th>SIR for Lymphomas (OR–Disease Activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gridley, 1993</td>
<td>Sweden</td>
<td>11,683</td>
<td>20</td>
<td>1.0</td>
<td>2.0</td>
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<tr>
<td>Mellemkjaer, 1996</td>
<td>Denmark</td>
<td>20,699</td>
<td>14</td>
<td>1.1</td>
<td>2.5</td>
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<tr>
<td>Isomaki, 1978</td>
<td>Finland</td>
<td>46,101</td>
<td>7</td>
<td>1.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Wolfe, 1994</td>
<td>US and Canada</td>
<td>3,501</td>
<td>35</td>
<td>0.3</td>
<td>8.0</td>
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<tr>
<td>Matteson, 1991</td>
<td>Canada</td>
<td>530</td>
<td>7</td>
<td>1.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Baecklund, 1998</td>
<td>Sweden</td>
<td>11,683</td>
<td>18</td>
<td>–</td>
<td>(1.0–Low)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(5.4Medium)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(25.8–High)</td>
</tr>
</tbody>
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SIR = standardized incidence ratio; OR = odds ratio.

ACR Treatment Algorithm

Establish diagnosis of RA early

Initiate therapy

Periodically assess disease activity

Adequate response
Inadequate response

Change/add DMARDs

MTX naïve
MTX Other Combination monotherapy

Suboptimal MTX response

Combination Other monotherapy

Biologics
Monotherapy Combination

Multiple DMARD failure
Symptomatic and/or structural joint damage

Newer Therapeutic Targets
CD20+ B-Cell
Rationale for Targeted B-cell Therapy

- CD20
- TNF
- IL-1
- IL-15
- C
- Ag
- T
- Rituximab
- Antibodies
- Follicular Signals
- Inflammation
- Antigen Presentation

(R.I.P.)
Rituximab: A B-Cell Chimeric mAb in the Treatment of Rheumatoid Arthritis

MTX (≥10mg/wk)

Rituximab, (1g x 2)

Cytoxan (750mg x 2)

Rituximab (1g x 2)

MTX (≥10mg/wk)

17 day Corticosteroid Regimen in all arms

Baseline 24 Weeks

MTX partial responders (≥10mg/wk for ≥16wks)

R = Randomization

Edwards et al, Arth Rheum 2002 (Abst # 446)
These are Exciting Times in Rheumatology