Evidence-based Progress in the Management of Rheumatoid Arthritis

Cheng Yew Kuang
Rheumatologist
Singapore

24 July 2016
A 38 year-old Chinese lady, Ms RA, presented with inflammatory pain affecting both wrist for the past 6 weeks associated with early morning stiffness and swelling. Clinical examination reviewed bilateral bogginess of the wrist and metacarpal phalangeal joints. Her ESR and CRP was normal. Her RF and anti-CCP was positive. Which one of the following is the appropriate course of action?

a) To start on systemic steroids and to monitor for 3 months before starting a DMARDs (Disease Modifying Anti-Rheumatic Drugs) only if ESR and CRP are elevated

b) To start on NSAID and to monitor for 3 months before starting steroids only if ESR and CRP are elevated

c) To start DMARDs

d) To order an MRI wrists and start DMARDs if there are synovitis

e) To order an X ray of both wrist and start DMARDs if there are erosions
Lesson #1

Early diagnosis and early treatment is the key to good outcome in Rheumatoid Arthritis
Disease overview: rheumatoid arthritis

- Rheumatoid arthritis (RA) is a chronic, progressive and destructive autoimmune disease
  
- As the disease progresses, irreversible joint damage lead to loss of function and physical disability
  
- Associated with a reduction in life expectancy of 5 to 10 years

Lifelong condition

Characterised by painful inflammation of the joint lining

Suffer from pain, swelling, loss of movement

Eventually complete destruction of the joint

Greater risk for comorbid conditions including:

- Cardiovascular disease:
  - congestive heart failure
  - coronary heart disease
  - stroke

- Respiratory disease

- Depression and/or anxiety

Conventional Synthetic DMARD (csDMARD)

- Methotrexate
- Sulphasalazine
- Plaquenil
- leflunomide - LEF
- D Penicillamine
- Azathioprine
- Cyclosporine
- Gold
Biological DMARD (bDMARD)

- anti-TNFα mAb (e.g. Enbrel, Humira, Remicade)
- rIL-1 Ra (e.g. Anakiret)
- Anti-IL6 (e.g. Tociluzumab)
- B cell depletion therapy (e.g. Rituximab)
- Co-stimulation blockage (e.g. Abatacept)
Introduction

Biologics definition

**Biologics**

... defined as a medicinal product produced from or extracted from a biological (living) system. Biologics can be made up of living cells or tissues or complex protein structures and can be sourced from microorganisms (such as bacteria) and animal or human tissue.

... refers to medicines produced using recombinant DNA technology
Introduction

Timeline of development of biologics

(Adapted from Revers et al. 2010)
Current biologic therapies target specific cytokines

Production of metalloproteinases and other effector molecules
Migration of polymorphonuclear cells

Erosion of bone and cartilage

RF, rheumatoid factor
IL, interleukin
Th, T helper
Th2, T helper 2
IFN, interferon
CD, cluster of differentiation
OPGL, osteoprotegerin ligand

RF, rheumatoid factor
IL, interleukin
Th, T helper
Th2, T helper 2
IFN, interferon
CD, cluster of differentiation
OPGL, osteoprotegerin ligand

Cytokine binding of cytokine receptors activates JAK pathway signaling

1. Cytokines bind to cell surface receptors, which leads to receptor polymerization and activation of associated JAKs

2. Activated JAKs phosphorylate the receptors that dock STATs

3. Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus to activate new gene transcription

JAK, Janus kinase; P, phosphate; STAT, signal transducer and activator of transcription

Figure adapted from Shuai K, Liu B. Nat Rev Immunol 2003;3:900-911.
XELJANZ is a JAK inhibitor -targeted synthetic DMARD (tsDMARD)

1. Cytokine binding to its cell surface receptor leads to receptor polymerization

2. XELJANZ inhibits the autophosphorylation and activation of JAK

3. JAKs cannot phosphorylate the receptors. Therefore cannot dock STATs

4. Because the STATs cannot dock, they are not phosphorylated or activated. Gene transcription and cytokine production are thereby inhibited

JAK, Janus kinase; STAT, signal transducer and activator of transcription

Adapted from reference 1.

Need for early and effective treatment in RA

Long-term efficacy was evaluated in a subset of adult patients who received etanercept in initial studies and/or etanercept 25 mg BIW in the extension and had sufficient disease activity data available (n = 644).

As this extension is ongoing, this is an interim analysis whereby data are represented as “observed cases” at each time point. Results at successive time points are based on declining numbers of subjects reflecting withdrawals from the study OR subjects who had not achieved the particular time point at the time of this analysis.

Data on file, Amgen.
American College of Rheumatology (ACR) 20/50/70 Response

- 20/50/70% reduction in
  - Tender joint count
  - Swollen joint count
- 20/50/70% improvement in three of the following
  - Patient assessment of pain
  - Physician global assessment
  - Patient global assessment
  - Patient assessment of disability
  - ESR or CRP

Need for early and effective treatment in RA

ACR 20 Response Rates at 3 Years

71% etanercept (n = 223)
* \( P < 0.01 \) vs MTX and etanercept monotherapy

85% etanercept + MTX (n = 231)
† \( P < 0.05 \) vs etanercept
‡ \( P < 0.05 \) vs MTX
§ \( P < 0.01 \) vs MTX

At 3 years, the ITT population differs between LOCF and NRI analyses due to the exclusion of patients enrolled at sites that were closed prior to year 3. Patients remaining in the study at the time of site closure were excluded from the NRI analysis.

Data on file, Wyeth Pharmaceuticals Inc.
**Etanercept TEMPO Trial**

**ACR 50 Response Rates at 3 Years**

% of Patients Based on LOCF Analysis

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>1-Year NRI (%)</th>
<th>2-Year NRI (%)</th>
<th>3-Year NRI (%) #</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX + etanercept</td>
<td>63‡ (n = 231)</td>
<td>57* (n = 231)</td>
<td>47* (n = 212)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>43 (n = 223)</td>
<td>44† (n = 223)</td>
<td>32 (n = 210)</td>
</tr>
<tr>
<td>MTX</td>
<td>36 (n = 228)</td>
<td>30 (n = 228)</td>
<td>25 (n = 219)</td>
</tr>
</tbody>
</table>

*P < 0.01 vs MTX and etanercept monotherapy; †P < 0.01 vs MTX; ‡P < 0.05 vs MTX and etanercept monotherapy

#At 3 years, the ITT population differs between LOCF and NRI analyses due to the exclusion of patients enrolled at sites that were closed prior to year 3. Patients remaining in the study at the time of site closure were excluded from the NRI analysis.

Data on file, Wyeth Pharmaceuticals Inc.
ACR 70 Response Rates at 3 Years

| ACR 70 NRI       | 1-Year NRI (%) | 2-Year NRI (%) | 3-Year NRI (%)#
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX + etanercept</td>
<td>40†‡ (n = 231)</td>
<td>41* (n = 231)</td>
<td>34* (n = 212)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>22 (n = 223)</td>
<td>24† (n = 223)</td>
<td>20 (n = 210)</td>
</tr>
<tr>
<td>MTX</td>
<td>17 (n = 228)</td>
<td>16 (n = 228)</td>
<td>13 (n = 219)</td>
</tr>
</tbody>
</table>

*P < 0.01 vs MTX and etanercept monotherapy; †P < 0.05 vs MTX; ‡P < 0.05 vs etanercept

#At 3 years, the ITT population differs between LOCF and NRI analyses due to the exclusion of patients enrolled at sites that were closed prior to year 3. Patients remaining in the study at the time of site closure were excluded from the NRI analysis.

Data on file, Wyeth Pharmaceuticals Inc.
Need for early and effective treatment in RA

Remission Rates in Subjects With Active Early Rheumatoid Arthritis – 1 Year Results of COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis

P Emery,1 F Breedveld,2 S Hall,3 P Durez,4 R Pedersen,5 D Robertson,5 B Freundlich5

1 University of Leeds, Leeds, UK
2 Leiden University Medical Center, Leiden, Netherlands
3 Cabrini Health Hospital, Malvern, Victoria, Australia
4 Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
5 Wyeth Research, Collegeville, PA, USA

The Lancet Early Online Publication, 16 July 2008

Copyright Amgen Inc
Study Design

Double-Blind Randomized Clinical Trial

Randomize (N = 542)

etanercept + MTX (N = 274)

placebo etanercept + MTX (N = 268)

52 wks

etanercept + MTX (1a)
etanercept (1b)
etanercept + MTX (2a)
MTX (2b)

104 wks
ACR Responders at Week 52

- **MTX (N=243)**
  - ACR20: 67%
  - ACR50: 49%
  - ACR70: 28%

- **ETN + MTX (N=256)**
  - ACR20: 86%
  - ACR50: 71%
  - ACR70: 48%

*P < 0.001
Proportion of Subjects Achieving Normal Disability Levels (HAQ ≤ 0.5) at Week 52

- MTX (n=241): 39%
- ETN + MTX (n=256): 55%

*P < 0.001
Cumulative Work Days Missed

Subjects working at baseline MTX, n = 100; E + MTX, n = 101

*P < 0.05
DAS28 Remission and Low Disease Activity at Week 52

MTX (n = 263)
- DAS28 Remission: 28%
- DAS28 LDA: 64%

ETN + MTX (n = 265)
- DAS28 Remission: 50%*
- DAS28 LDA: 41%

*P < 0.001
Ms RA was started on DMARDs by her rheumatologist. In the initial phase while her disease is still active, which one of the following is the best course of action to ensure optimal outcome?

a) The frequency of follow up should be according to the clinical judgement of her rheumatologist; and therapy adjusted only after 3 months

b) The frequency of follow up should be monthly; and therapy adjusted according to disease activity score at each visit

c) The frequency of follow up should be monthly; and therapy adjusted according to ultrasound finding

d) The frequency of follow up should be monthly; and therapy adjusted based on ESR and CRP readings

e) The frequency of follow up should be followed monthly; and therapy adjusted according to patient’s symptoms.
Lesson # 2

Close monitoring and tight control is key to good outcome in RA
Intensive DMARD therapy improves disease activity in RA

**Intensive DMARD therapy**
(n=55)

- DMARD monotherapy (active synovitis/treatment failure)
  - Alternative monotherapy
  - + 2nd DMARD
  - + 3rd DMARD

- Intensive DMARD therapy
  (n=55)
  - Sulfasalazine (increasing dose)
  - Triplet therapy (sulfasalazine + methotrexate + folic acid + hydrochloroquine)
  - Triplet therapy (increasing methotrexate)
  - Triplet therapy (increasing sulfasalazine)
  - + prednisolone
  - Change triplet therapy (ciclosporin + methotrexate + folic acid)

**Routine DMARD therapy**
(n=55)

- Sulfasalazine (increasing dose)
- Triplet therapy (sulfasalazine + methotrexate + folic acid + hydrochloroquine)
- Triplet therapy (increasing methotrexate)
- Triplet therapy (increasing sulfasalazine)
- + prednisolone
- Change triplet therapy (ciclosporin + methotrexate + folic acid)

**ITT population**

- Disease activity score


*p<0.0001 vs routine therapy after month 3*
Tight monitoring of therapy improves outcomes in RA

**ITT population (LOCF)\(^1\)**

<table>
<thead>
<tr>
<th>Group</th>
<th>% Patients achieving DAS 28≤3.2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care group (n=179)</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Active treatment group (n=205)</td>
<td>31%</td>
<td>0.028</td>
</tr>
</tbody>
</table>

**ITT population (LOCF)\(^2\)**

<table>
<thead>
<tr>
<th>Group</th>
<th>% Patients achieving remission†</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care group (n=148)</td>
<td>37%</td>
<td>0.029</td>
</tr>
<tr>
<td>Intensive/tight control group (n=151)</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

**Assessment/measurement frequency**

- **Usual care group**: No systematic monitoring
- **Active treatment group**: Monitoring at 0, 4, 12 and 24 weeks
- **Intensive/tight control group**: Monitoring every 3 months

**Active treatment**

- Usual care group: Cox-2 inhibitors, DMARDs, oral steroids allowed
- Active treatment group: Methotrexate monotherapy followed by combination methotrexate/cyclosporin, oral steroids not allowed

**Target**

- DAS 28≤3.2
- Remission†

\(^*\) Remission defined as no swollen joints, and at least two of the following criteria: number of tender joints ≤3, erythrocyte sedimentation rate ≤20mm/hour and VAS general well-being ≤20mm for at least 3 months at any time during the 2 year trial.

Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,1,2 Daniel Aletaha,1 Johannes W J Bijlsma,3 Ferdinand C Breedveld,4 Dimitrios Boumpas,5 Gerd Burmester,6 Bernard Combe,7 Maurizio Cutolo,8 Maarten de Wit,9 Maxime Dougados,10 Paul Emery,11 Alan Gibofsky,12 Juan Jesus Gomez-Reino,13 Boulos Haraoui,14 Joachim Kalden,15 Edward C Keystone,16 Tore K Kvien,17 Iain McInnes,18 Emilio Martin-Mola,19 Carlomaizirio Montecucco,20 Monika Schoels,2 Desirée van der Heijde,4 for the T2T Expert Committee
Treat to Target (T2T) 
Overarching Principle

- Treatment of RA must be based on a shared decision between patient and rheumatologist
- The primary goal of treating the patient with RA is to maximize long-term HRQoL through control of symptoms, prevention of structural damage, normalisation of function and social participation
- Abrogation of inflammation is the most important way to achieve these goals
- Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in RA

# Instruments of Measurement of RA disease activity

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Thresholds of disease activity levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Activity Scale (PAS) or PAS-II</td>
<td>Remission: 0–0.25</td>
</tr>
<tr>
<td>(range 0–10) (31)</td>
<td>Low activity: 0.26–3.7</td>
</tr>
<tr>
<td>Routine Assessment of Patient Index</td>
<td>Moderate activity: 3.71 to &lt;8.0</td>
</tr>
<tr>
<td>Data 3 (range 0–10) (42)</td>
<td>High activity: ≥8.0</td>
</tr>
<tr>
<td>Clinical Disease Activity Index (range 0–76.0)</td>
<td>Remission: 0–1.0</td>
</tr>
<tr>
<td>(43)</td>
<td>Low activity: &gt;1.0 to 2.0</td>
</tr>
<tr>
<td>Disease Activity Score in 28 joints (range 0–9.4)</td>
<td>Moderate activity: &gt;2.0 to 4.0</td>
</tr>
<tr>
<td>(44)</td>
<td>High activity: &gt;4.0 to 10</td>
</tr>
<tr>
<td>Simplified Disease Activity Index (range 0–86.0)</td>
<td>Remission: ≤2.8</td>
</tr>
<tr>
<td>(45)</td>
<td>Low activity: &gt;2.8 to 10</td>
</tr>
<tr>
<td></td>
<td>Moderate activity: &gt;10.0 to 22.0</td>
</tr>
<tr>
<td></td>
<td>High activity: &gt;22</td>
</tr>
<tr>
<td>Index</td>
<td>Formula</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>DAS-28</td>
<td>$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \log(nat(ESR)) + 0.014 \times GH$</td>
</tr>
<tr>
<td>SDAI</td>
<td>$SJC28 + TJC28 + PGA + EGA + CRP$</td>
</tr>
<tr>
<td>CDAI</td>
<td>$SJC28 + TJC28 + PGA + EGA$</td>
</tr>
</tbody>
</table>

Abbreviations: DAS: Disease Activity Score; DAS-28: DAS based on a 28 joint count; CRP: C-reactive protein; EGA, evaluator global assessment of disease activity; ESR, erythrocyte sedimentation rate; GH, global health; PGA, patient global assessment of disease activity; SJC, swollen joint count; TJC, tender joint count.

* Remission vs. Low disease activity/low vs. moderate disease activity/moderate vs. high disease activity GH in mm VAS; SDAI: CRP in mg/dl; SDAI, CDAI: PGA, EGA in cm on a Visual Analogue Scale (VAS).
American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials

Table 6. American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials*

---

**Boolean-based definition:**
At any time point, patient must satisfy all of the following:
- Tender joint count \(\leq 1\)
- Swollen joint count \(\leq 1\)
- C-reactive protein \(\leq 1\) mg/dl
- Patient global assessment \(\leq 1\) (on a 0–10 scale)

**Index-based definition:**
At any time point, patient must have a
- Simplified Disease Activity Index score of \(\leq 3.3\)
Sustained Remission with Etanercept Tapering in Early Rheumatoid Arthritis

Paul Emery, F.R.C.P., Mohammed Hammoudeh, M.D., Oliver FitzGerald, M.D., Bernard Combe, M.D., Ph.D., Emilio Martin-Mola, M.D., Ph.D., Maya H. Buch, M.B., Ch.B., Ph.D., Marek Krogulec, M.D., Theresa Williams, P.A., M.S., Stefanie Gaylord, B.S.N., Ronald Pedersen, M.S., Jack Bukowski, M.D., Ph.D., and Bonnie Vlahos, M.B.A., R.N.
LDA, Remission, and Complete Response at Week 52

- **DAS28 LDA**: 95.9% (n=221)
- **DAS28 Remission**: 88.7% (n=221)
- **SDAI LDA**: 97.2% (n=215)
- **SDAI Remission**: 81.3% (n=215)
- **ACR/EULAR Boolean Remission**: 79.1% (n=215)
- **Complete Response**: 66.1% (n=221)
- **Complete Response**: 29.1% (N=306)

- **Observed Cases (Completers)**
- **LOCF**
- **Non-Responder Imputation**

*P<0.0001 vs baseline.

*Complete response is defined as a DAS28 <2.6, HAQ ≤0.5, and ΔmTSS ≤0 over 52 weeks. Non-responder imputation was used to handle missing data.

SDAI, Simplified Disease Activity Index; LOCF, last observation carried forward.
Is Clinical Remission in RA patient true remission?

• MRI and US detected synovitis in the majority of patients with clinical remission

  Brown et al A & R 2006

• In patients in clinical remission, MRI and US synovitis predict subsequent erosive progression on conventional radiography

  Brown et al A & R 2008
MCQ 3

• Ms RA was treated with DMARDs and she was in complete remission at the end of one year. Which of the following is the appropriate course of action?
  a. She should continue DMARDs, NSAID and steroids indefinitely
  b. She should taper her DMARDs but maintained on systemic steroids and NSAID
  c. She should taper her DMARDs once systemic steroids and NSAID are stop
  d. She should stop systemic steroids, NSAID and DMARDs together
  e. She should only stop steroids
Lesson # 3

Drug Free Remission is possible in RA!
BeSt

Comparing Four Treatment Strategies Using Tight Control Based on DA
Studying Treatment Strategy

Comparison of four treatment strategies using dynamic disease management

1. Sequential monotherapy (n=126)
2. Step-up combination therapy (n=121)
3. Initial combination therapy (COBRA) (n=133)
4. Initial combination with IFX (n=128)

Treatment Strategies in eRA

Maximal success through 2 to 3-monthly treatment-adjustments based on DAS44-scores:

- DAS44 > 2.4 → next step
- DAS44 ≤ 2.4 → continue therapy

Two consecutive assessments
- DAS44 ≤ 2.4 → step back/taper

Outcomes

• Primary endpoints
  – Functional outcomes (HAQ)
  – Radiographic joint damage (Sharp-Van der Heijde score / SHS)

• Secondary endpoints
  – Clinical remission (DAS44<1.6)
  – ACR 20, 50, 70

Sustained Drug-free Remission at 7 Years

Remission without any DMARDs for a median of 36 months

Adapted from Dirven et al. ACR 2010. Abstract 334.
5 Year Results: Remission**

**DAS<1.6

Includes remission and drug-free remission

With DAS-steered, tight-controlled treatment, 48% of all patients achieved remission and 14% drug-free remission.

Thank you