Treating Rheumatologic Disease in Arizona: Good News, Bad News

Jeffrey R. Lisse, M.D.
Ethel P. McChesney Bilby Professor of Medicine
Chief, Section of Rheumatology
University of Arizona School of Medicine
Geographic distribution of Coccidioidomycosis
Longitudinal Course of RA

CCP, cyclic citrullinated peptide; CTLA4, cytotoxic T-lymphocyte antigen 4; GP39, cartilage glycoprotein 39; PADI4, peptidyl arginine deiminase, type IV; PTPN22, protein tyrosine phosphatase, non-receptor type 22.

RA Joints Commonly Involved
Early RA: Radiographic Findings

High-Detail X-Ray

Low-Field MRI

Courtesy of Charles Peterfy, MD.
Disease Progression

Early Rheumatoid Arthritis
- Neutrophils
- Hyperplastic Synovial Membrane
- Capillary Formation
- Hypertrophic Synoviocyte
- T Cells, B Cells

Established Rheumatoid Arthritis
- Neutrophils
- Plasma Cell
- Synovial Villi
- Extensive Angiogenesis
- Eroded Bone
- Pannus

Normal Joint
- Bone
- Cartilage
- Capsule
- Synovial Membrane
- Synoviocytes

Adapted with permission from: Choy EHS, Panayi GS. *N Engl J Med.* 2001;344:907-916. © 2001 Massachusetts Medical Society. All rights reserved.
RA—One of the Most Common Types of Inflammatory Arthritis

- Affects approximately 1% of the population\(^1\)
- One of the most common causes of disability in the Western world\(^2\)

Progression Over Time

Photos courtesy Lester Miller, MD, Santa Cruz, Calif.

Evolution of RA treatment

- **Injectable gold** (1930s)
- **HCQ, steroids** (1950s)
- **SSZ** (1960s)
- **D-Pen, AZA** (1970s)
- **MTX, oral gold** (1980s)
- **Anti-TNF-α, LEF, IL-1ra, cyclosporin** (1990s)
- **Inhibitors of co-stimulation, anti-B-cell** (2005)

- **Remission / cure**

Treat signs and symptoms in established disease
Aggressive MTX dosing
Early DMARD treatment
Combination therapy
Adverse Effects of Nonbiologic DMARD Therapy

- **Corticosteroids**
  - Osteoporosis
  - Cataracts
  - Diabetes
  - HTN

- **SSZ**
  - GI
  - Rash
  - Cytopenias (G6PD deficiency)

- **Hydroxychloroquine**
  - Retinopathy (extremely rare)
  - Rash
  - Cytopenias (G6PD deficiency)

- **Leflunomide**
  - Alopecia
  - Teratogen
  - Diarrhea
  - Liver
  - Infections

- **MTX**
  - Liver
  - Mucositis/ulcers
  - Headache
  - Alopecia
  - Nausea
  - Pulmonary
  - Infections

HTN = hypertension; GI = gastrointestinal.
Role of TNF-α in AS

TNF-α mRNA in Sacroiliac Biopsy

Molecular Structure of Biologic Agents

<table>
<thead>
<tr>
<th>Description</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chimeric anti-TNF mAb</td>
<td></td>
</tr>
<tr>
<td>TNF-receptor p75 IgG_{1} construct</td>
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</tr>
<tr>
<td>Fully human anti-TNF mAb</td>
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</tr>
<tr>
<td>PEGylated humanized</td>
<td></td>
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<tr>
<td>anti-TNF Fab-fragment</td>
<td></td>
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<tr>
<td>TNF-receptor p55 PEG</td>
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</tbody>
</table>

- **Human**
- **Mouse**
- **Synthetic element**
- **Polyethylene glycol**
Soluble Receptors Bind, Neutralize Soluble not Membrane-bound TNF-α, -β

Enbrel prescribing information.
Monoclonal Antibodies Bind and Neutralize Soluble and Membrane-Bound TNF-α
Joint Inflammation and Destruction in RA

MOA of Biologic DMARDs in RA

Adapted with permission from Klareskog L, Catrina AI, Paget S. Lancet. 2009;373(9664):659-672.
Binding of CTLA4 to CD80/86 prevents binding of CD28 to CD80/86

APC = Antigen-presenting cell

Rituximab in RA: Anti-CD20 mAb

- Genetically engineered chimeric mAb
- Variable light- and heavy-chain regions from murine anti-CD20 Ab
- Human IgGk constant regions
- B-cell lineage antigen; not expressed on stem cells, early pre-B cells, dendritic cells or plasma cells
- Rapid B-cell depletion without inducing hypogamma-globulinemia

Modified from Roche slide kit
Tocilizumab binds to both the mIL-6R and the sIL-6R, preventing binding of IL-6 and association with the gp130β chain and thus IL-6–mediated signaling.

**Signal Transduction Inhibited**

mIL-6R = membrane-bound IL-6 receptor; sIL-6R = soluble IL-6 receptor.

Mihara M, *Int Immunopharmacol*, 2005;5(12):1731-1740; Maini RN et
ACR Responses at Years 1 and 2
Prespecified Comparison HUMIRA + MTX vs MTX Alone

Patients who withdrew or had missing values were considered nonresponders

\( \xi P < 0.001 \) for HUMIRA + MTX vs HUMIRA alone and \( P = 0.022 \) vs MTX alone

\( * P < 0.001 \) vs HUMIRA alone and \( P = 0.002 \) vs MTX alone

\( \dagger P = 0.043 \) vs HUMIRA alone; \( # P < 0.001 \) vs HUMIRA alone and vs MTX alone


Please see full prescribing information.
No Radiographic Progression

Patients with $\Delta$ TSS $\leq 0.5$ at Weeks 52 and 104

Prespecified Comparison HUMIRA + MTX vs MTX Alone

- Approximately twice as many patients experienced no radiographic progression on HUMIRA + MTX vs MTX monotherapy at 2 years

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![Graph showing percentage of patients experiencing no radiographic progression at Weeks 52 and 104 for HUMIRA + MTX, HUMIRA, and MTX alone.]

- **HUMIRA + MTX** (n=268): 64% at Week 52, 61% at Week 104
- **HUMIRA** (n=274): 51% at Week 52, 45% at Week 104
- **MTX** (n=257): 37% at Week 52, 34% at Week 104

* $P<0.01$ for HUMIRA + MTX vs HUMIRA alone and MTX alone. † $P<0.01$ for HUMIRA alone vs MTX alone


Please see full prescribing information.
# Rates of Selected Serious Adverse Events (SAEs) in HUMIRA Long-Standing Moderate to Severe RA Clinical Trials

<table>
<thead>
<tr>
<th>Serious Adverse Events (SAEs)</th>
<th>Long-Standing RA Trials as of August 31, 2002 (N=2468, 4870 PY (E/100 PY))</th>
<th>Long-Standing RA Trials as of April 15, 2005 (N=10,050, 12,506 PY (E/100 PY))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td>4.90</td>
<td>5.10</td>
</tr>
<tr>
<td>Tuberculosis (TB)</td>
<td>0.27</td>
<td>0.27</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Demyelinating diseases</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.21</td>
<td>0.12</td>
</tr>
<tr>
<td>SLE/Lupus-like syndrome</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.29</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Data from long-standing trials with HUMIRA, including open-label extensions and ACT and ReACT early access programs.

Values are presented as events per 100 PY.


Please see full prescribing information.
Screening and TB Rates in HUMIRA RA Clinical Trials

Data from long-standing RA trials with HUMIRA, including open-label extensions and ACT and ReAct early access programs.

*DE018 + ReAct †DE019 + DE020 + ACT

Patients receiving HUMIRA should be monitored for signs and symptoms of active tuberculosis (TB), including patients who are TB skin test negative. Active TB has developed in patients receiving HUMIRA whose screening for latent TB infection was negative.


Please see full prescribing information.
Serious Infection Rates in adalimumab RA Clinical Trials

- The total infection rate (serious and nonserious) in placebo-controlled RA trials was 1 per patient year with HUMIRA vs 0.9 per patient year with placebo.
- RA population serious infection rates range from 3.1 to 9.6 per 100 PY.

Data from HUMIRA pivotal trials and open-label extension studies.

Range of serious infections in RA population based on rates reported in literature for RA population. One study investigating the relationship between serious infections and immunosuppressive use in RA patients reported an overall rate of 3.1 events per 100 patient years. Another population-based study reported a rate of infections requiring hospitalization of 9.57 events per 100 patient years.

*The incidence of serious infections was 0.04 per patient year in HUMIRA-treated patients and 0.02 per patient year in placebo-treated patients.


HUMIRA full prescribing information

Please see full prescribing information.
Thank you