

RHEUMATOID ARTHRITIS

Howard L. Feinberg, D.O., M.A.C.O.I., F.A.C.R.
ACOI 2022

“Extreme remedies are very appropriate for extreme diseases.”



RHEUMATOID ARTHRITIS



EPIDEMIOLOGY

- **Approximately 1% of the total adult population is affected by RA**
- **Will die 10-15 years earlier than expected without aggressive treatment**
- **40%-60% with functional class IV will survive 5 years or less**

RHEUMATOID ARTHRITIS

- **Morning stiffness > 1 hour**
- **Symmetric joint swelling**
- **Onset may be abrupt or insidious**
- **Peak incidence – women in their 50's**
- **Joint pain less related to use**
- **Prolonged stiffness with inactivity**
- **Not limited to the musculoskeletal system**

ACR/EULAR CRITERIA

- **Must have at least one joint with synovityis not explained by another problem**
- **Must have 6 points**

ACR/EULAR CRITERIA

□ **Domain Joint Involvement**

- **1 medium-large joint 0 points**
- **2-10 medium – large joints 1 point**
- **1-3 small joints 2 points**
- **4-10 small joints 3 points**
- **> 10 small joints 5 points**

ACR/EULAR CRITERIA

□ **Domain - Serology**

- **Negative RF, Anti-CCP 0 points**
- **One test positive in low titer 2 points (Less than 3 times normal)**
- **One test at high titer 3 points**

ACR/EULAR CRITERIA

- **Domain - Duration**
 - **Less than 6 weeks 0 points**
 - **> 6 weeks 1 points**
- **Domain – Phase Reactant**
 - **Normal ESR, CRP 0 points**
 - **Abnormal ESR or CRP 1 point**

LABORATORY DATA

LABORATORY

DATA IS NOT

DIAGNOSTIC

HEMATOLOGIC

- **Anemia**
- **Leukopenia**
- **Thrombocytopenia**
- **Lymphadenopathy**
- **Lymphoma**

LABORATORY DATA

- **Rheumatoid factor**
- **Anti – CCP antibody (cyclic citrullinated peptide)**
- **ESR**
- **CBC**
- **C-reactive protein**
- **Phase reactants**

LABORATORY DATA

RHEUMATOID FACTOR

Patients with...	Prevalence %	Patients with...	Prevalence %
Rheumatoid arthritis	80	Pulmonary Disease	
		Chronic bronchitis	62
Juvenile RA	20	Pulmonary Fibrosis	32
		Asthma	17
Infections		Silicosis	15
Endocarditis	48		
Hepatitis	24	Sjogren's Syndrome	>90
Leprosy	24	Cirrhosis	36
Nonspecific viral	15	Sarcoidosis	17
Tuberculosis	11	Myocardial Infarction	12

ANTI CCP ANTIBODY

- **Sensitivity 50-70%**
- **Specificity 95%**
- **Psoriatic arthritis**
- **Vasculitis**
- **Interstitial Lung Disease**
- **COPD**
- **Idiopathic Pulmonary Fibrosis**

RADIOGRAPHIC DATA

- **Obtain baseline films**
- **Ask for evidence of specific parameters**
- **Not diagnostic by itself**

RHEUMATOID ARTHRITIS

THE FEINBERG DEFINITION:

A systemic disease whose major manifestation is in the joints.

Body Systems Involved In Rheumatoid Arthritis

- **HEENT**
- **Cardiovascular**
- **Pulmonary**
- **GI**
- **GU**
- **Neurologic**
- **Psychiatric**
- **Musculoskeletal**

SYNDROMES

□ **Sjogren's**

□ **Felty's**

□ **Caplan's**

□ **Amyloid A**

□ **Vasculitis**

□ **Immunodeficiency**

□ **Depression**





TREATMENT OF RA

- **Rational For Early Treatment**
 - **90% of radiographic erosions occur within 2 years of synovitis onset**
 - **Early intervention with DMARDs may prevent long term disability and premature mortality**

TREAT TO TARGET

- **Target is a level of disease control which prevents all progression of disease**
- **Clinical remission**

- **Disease Activity Scores**
 - **DAS**
 - **Rapid 3**
 - **CDAI**
 - **SDAI**
 - **PAS**
 - **PAS II**

TREATMENT

▣ OBJECTIVES

- **Preserve Function**
- **Diminish Symptoms**
- **Delay or Prevent Progression**

▣ Components

- **Education**
- **Balanced rest and exercise**
- **Physical Therapy**
- **Occupational Therapy**
- **Medication**

NSAID

□ Objectives

- Control of symptoms
- Decrease swelling
- Decrease stiffness

□ Efficacy

- Provide symptom control
- Do not alter the course of the disease

□ Side Effects

- GI
- Renal
- Hepatic
- Cardiac

STEROIDS

- **Intra-articular**
- **Systemic**
- **Pulse**

- **Objectives**
 - **Control of symptoms**
 - **Decrease swelling**
 - **Decrease stiffness**

- **Efficacy**
 - **Provide symptom control**

- **Side Effects**

DMARDs

- **Hydroxychloroquine**
- **Sulfasalazine**
- **Penicillamine**
- **Cyclosporine A**
- **Methotrexate**
- **Arava (Leflunamide)**
- **Azothiaprims**
- **Ridaura (Auranofin)**
- **Gold sodium thiomalate**
- **JAK**
 - **Xeljanz (tofacitinib citrate)**
 - **Olumiant (baricitinib)**
 - **Rinvoq (Upadacitinab)**
- **IL-1 Kineret (Anakinra)**
- **IL-6**
 - **Kevzara (sarilumab)**
 - **Actemera (tocilizumab)**
- **Anti TNF alpha**
 - **Enbrel (etanercept)**
 - **Humira (adalimumab)**
 - **Cimzia (certolizumab pegol)**
 - **Simponi (golimumab)**
 - **Remicade (adalimumab)**
- **CTLA-4 Orencia (Abatocept)**
- **CD 20+ B cells Rituxan (Rituximab)**

Major Issues

- **Infection**
 - TB
 - Hepatitis
 - HIV
- **Blunted response to immunizations**
- **Anemia/Bone marrow suppression**
- **Cancer**
- **Demyelinating disorders**
- **Pregnancy**

□ **Orencia**

- **COPD**

□ **Anti TNF**

- **Demyelinating**

□ **Rituxan**

- **Severe infusion reaction/death**
- **Severe mucocutaneous reaction**

□ **Actemera**

- **GI perforation**

□ **JAK**

- **Blood clots**
- **MACE (MI, Stroke, Cardiovascular)**

□ **Methotrexate/Arava**

- **Liver toxicity**

□ **Gold compounds/ Penicillamine**

- **Rash**

□ **Plaquenil**

- **Rash**
- **Eye toxicity**

Mediators and Modulators of Inflammation: Determining the Target

Proinflammatory

IFN- γ
GM-CSF
IL-8 and other
chemokines

IL-1 TGF- β
IL-15 IL-6
IL-16 IL-12
IL-17
IL-18

Anti-inflammatory

IL-4 IL-13 sIL-1R
IL-10 IL-18BP sTNFR
IL-11 IL-1Ra

TNF

SIMPONI (golimumab)

- **Once a month injection**
- **4% develop antibodies**
- **Human monoclonal antibody against TNF-alpha**
- **Steady state at 3 months**

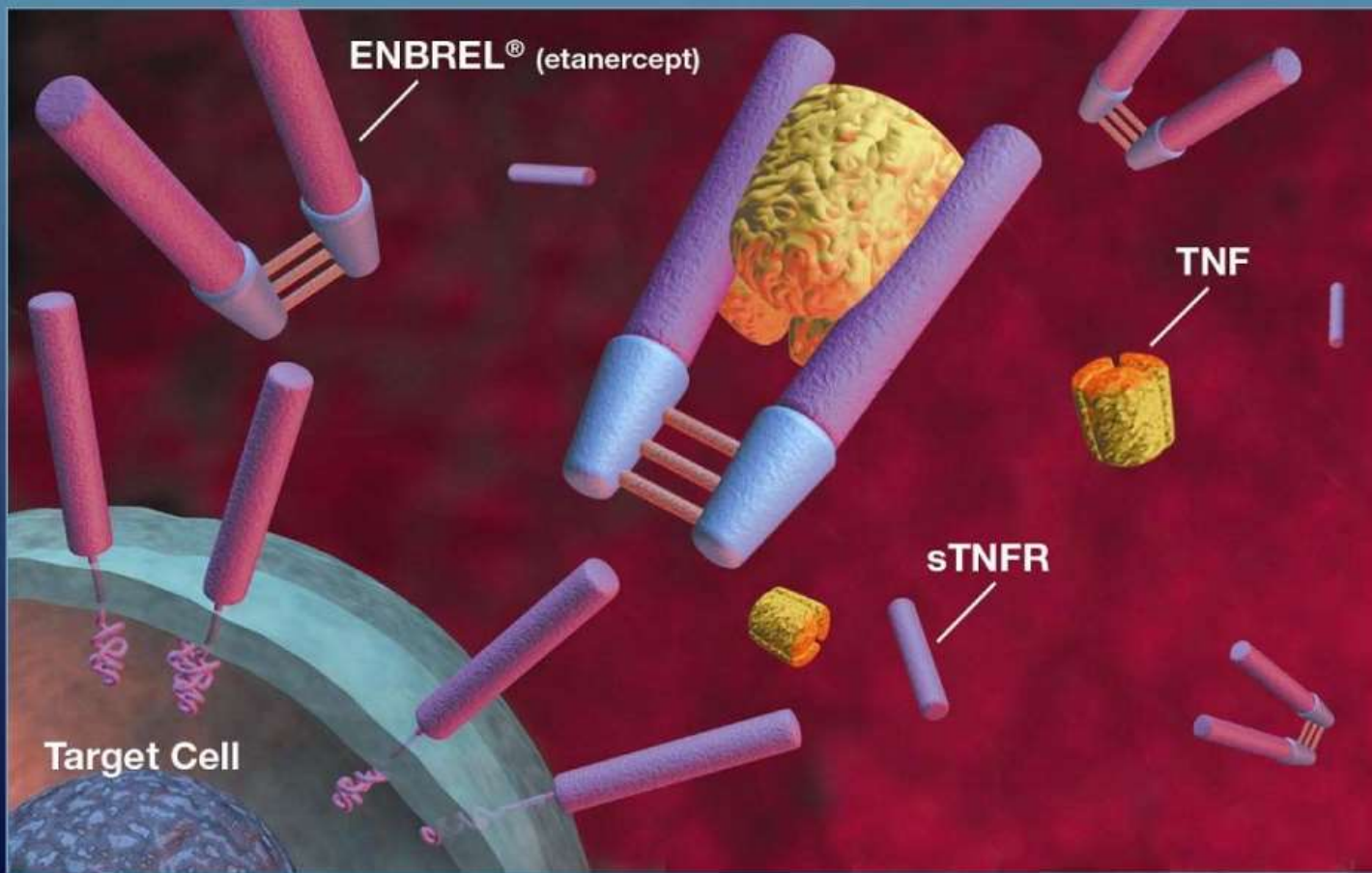
CIMZIA (certolizumab pegol)

- **SQ injection every 2-4 weeks**
- **Pegylated protein (polyethylene glycol used to stabilize the protein)**
- **Humanized anti TNF antibody**
- **Binds membrane bound and soluble TNF**

ENBREL (etanercept)

- **Blocks TNF – alpha**
- **Human fusion protein**
- **Produces non-neutralizing antibodies**

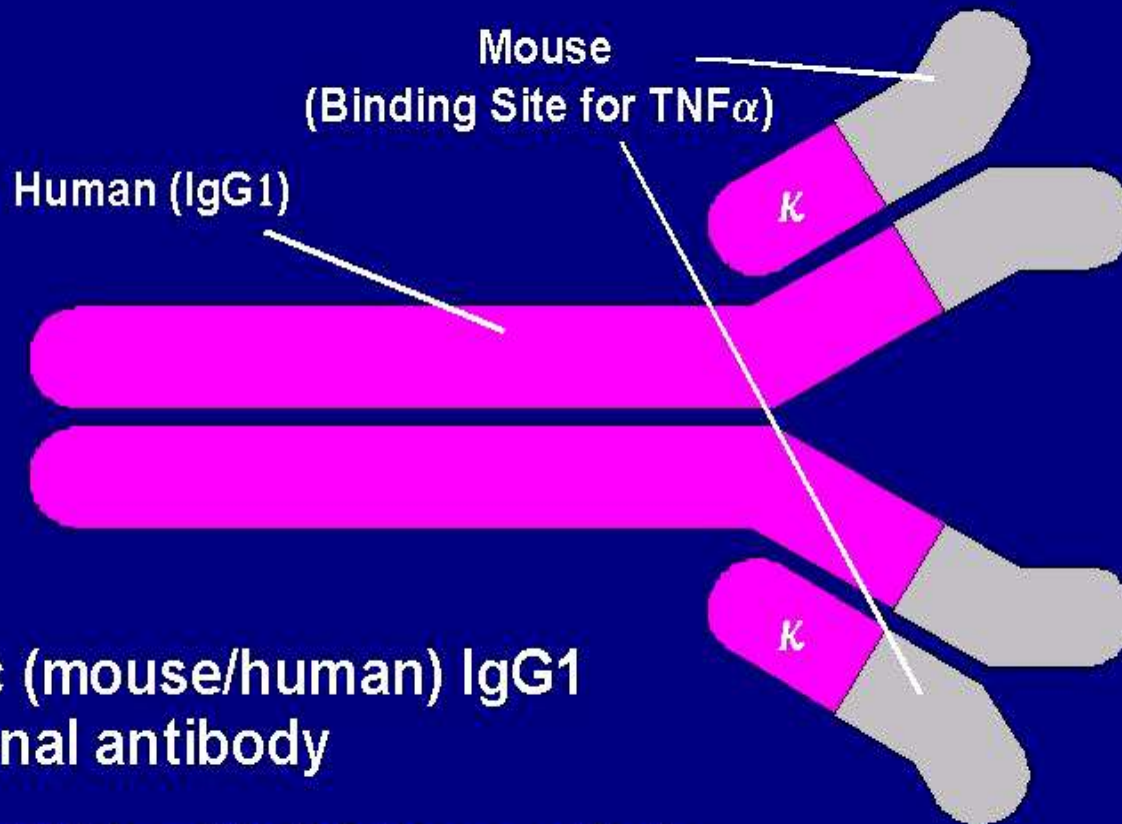
Etanercept Helps Restore a Natural TNF Balance



REMICADE (infliximab)

- **Given as I.V. Infusion**
- **Antibody directed against TNF – alpha**
- **Produces neutralizing antibodies**
- **Mouse/Human Chimeric molecule**

Structure of Infliximab



- Chimeric (mouse/human) IgG1 monoclonal antibody
- Binds to TNF α with high specificity, high affinity, and high avidity

HUMIRA (adalimumab)

- **Human Monoclonal Antibody**
- **No neutralizing antibodies**
- **Given SC every other week**

KINERET (anakinra)

- **Antibody to IL-1**
- **Given SC daily**
- **Lyophilized powder**
- **Less than 1% neutralizing antibody production**

ACTEMERA (tocilizumab)

- **Monoclonal antibody to IL-6**
- **Given I.V. monthly**
- **2% develop antibodies**
- **Increase in LFT**
- **Increase in Lipids**

KEVZARA (sarilumab)

- **Humanized monoclonal antibody that inhibits IL-6 signaling**
- **Given SQ every 2 weeks**
- **Neutropenia**
- **Elevated LFT, cholesterol, LDL, triglycerides, thrombocytopenia**

ORENCIA (abatacept)

- **Prevents activation of T cells by binding to CD 80 and CD 86**
- **Human cytotoxic T lymphocyte associated antigen**
- **Selective T cell costimulator modulator**

RITUXAN (rituximab)

- **Blocks CD 20 positive B cells by binding to CD 20 receptor and inducing cell lysis**

THE FUTURE ?

B-cell

- **Ocrelizumab (anti cd-20)**
- **Ofatumumab (anti cd-20)**

IL-12, IL-15, IL-17, IL-23, PDE-4

Gene Therapy

**Genetic testing for treatment
decisions**

Antiosteoclast



HowardFeinberg@mytumg.org

HOWARD FEINBERG, D.O., M.A.C.O.I., F.A.C.R.