Presentation and Treatment of Rheumatoid Arthritis

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Disclosures

- NONE

Learning Objectives

- By the end of the session you should be able to:
  - Understand how Rheumatoid arthritis is diagnosed
  - Appreciate the need for early initiation of treatment
  - Be aware of the extra-articular manifestations of Rheumatoid Arthritis
  - Recognize the types of treatment strategies that are used.
  - Name some common DMARD and Biologic drugs

There are many different types of arthritis

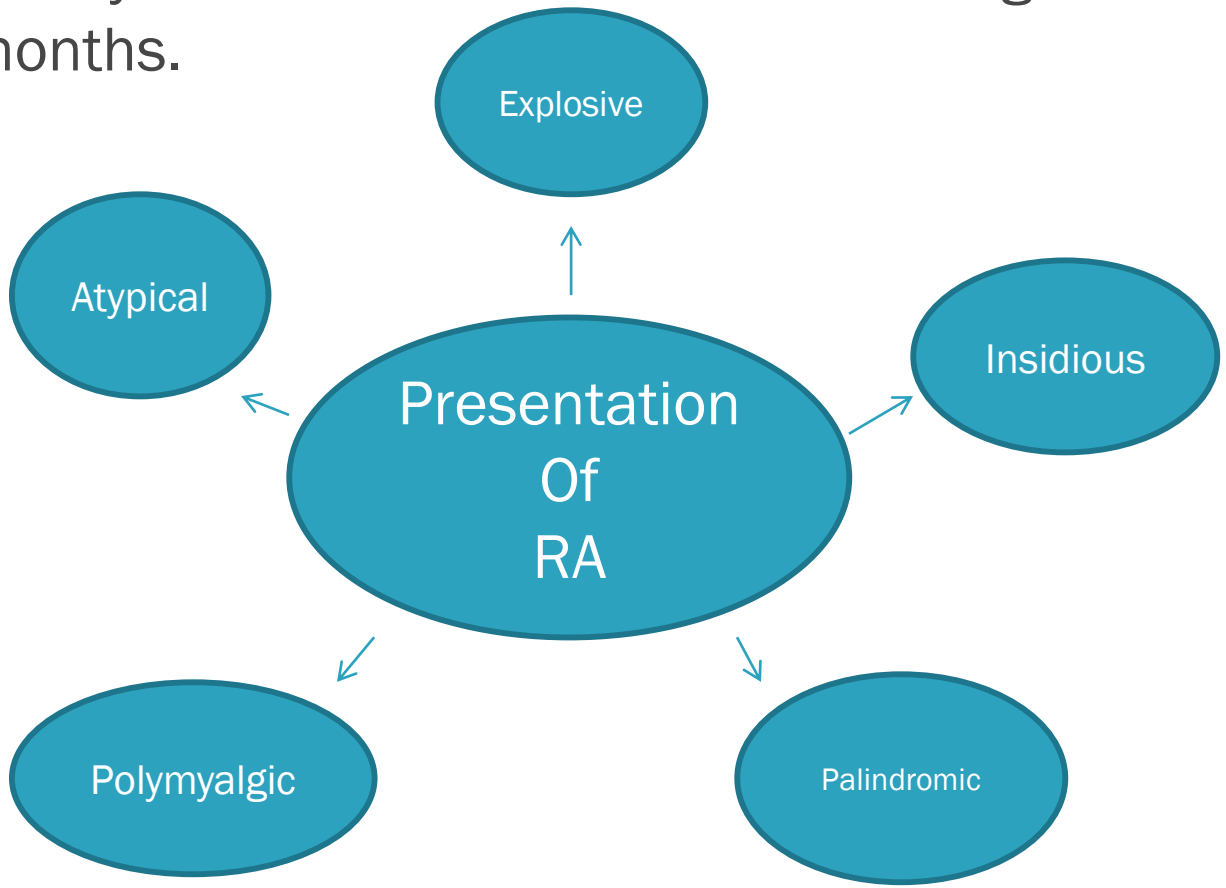
- Osteoarthritis
- Rheumatoid Arthrits
- Psoriatic arthritis
- Ankylosing spondylitis
- Reactive arthritis
- IBD- related arthritis
- Viral arthritis
- Juvenile idiopathic arthritis
- Lyme Arthritis
- Pigmented villonodular synovitis
- Gout
- Pseudogout
- Systemic Lupus Erythematosus
- Sjogren's Syndrome
- Sarcoidosis
- Ochronosis

Epidemiology

- Prevalence
  - Estimated to affect 0.5-1% of the general population
  - China and Japan: 0.2%-0.3%, Rural Africans: 0.1%
  - Native Americans: more than 5%
    - Columbian Exchange(?): While Native American remains as early as 6500 B.C.E. demonstrate skeletal changes consistent with modern RA, no convincing evidence of RA in Europe prior to the 17th century.
    - Rosenstein proposes the trade of sugar from the West Indies around 1755-1765 and resultant periodontal disease.
- Incidence
  - 40 per 100,000
- Mortality and Morbidity
  - 40% of all deaths in individuals with RA are attributable to CVD
  - 2009 there were 15,600 hospitalizations with RA as primary diagnosis

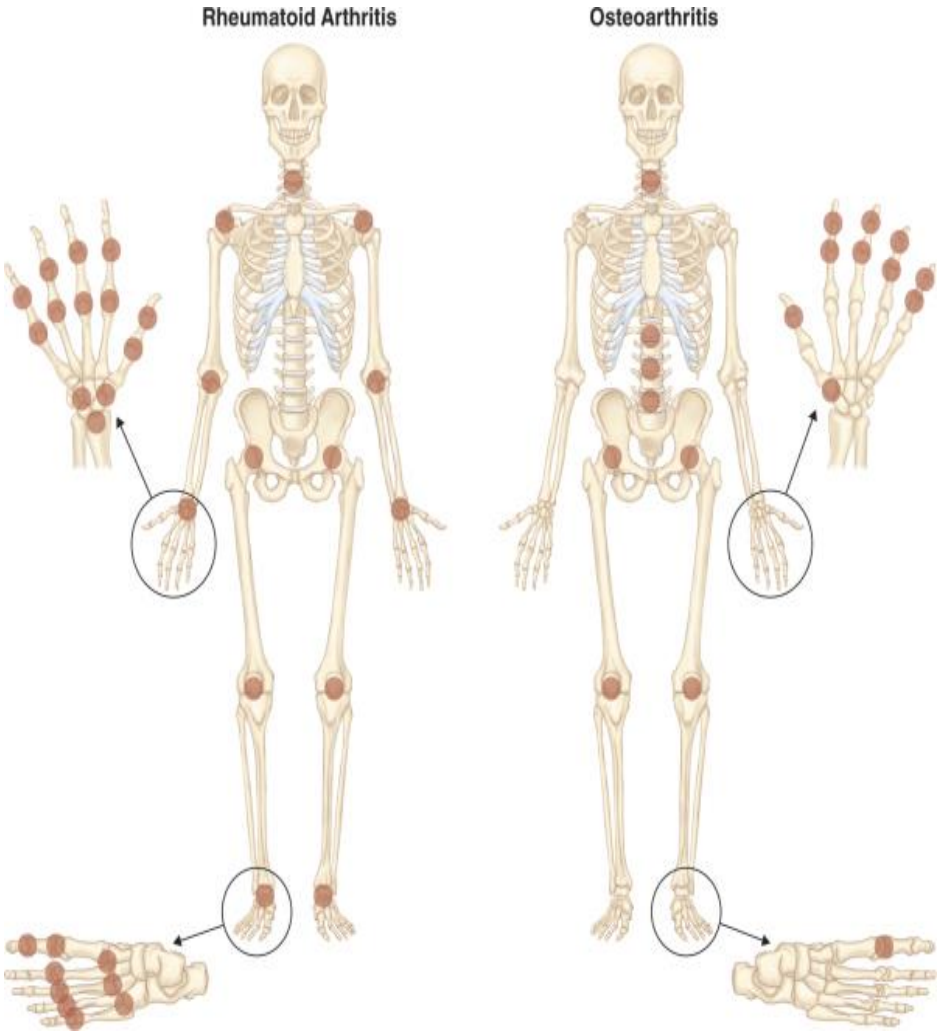
Onset

- Most commonly the onset is INSIDIOUS occurring over weeks to months.



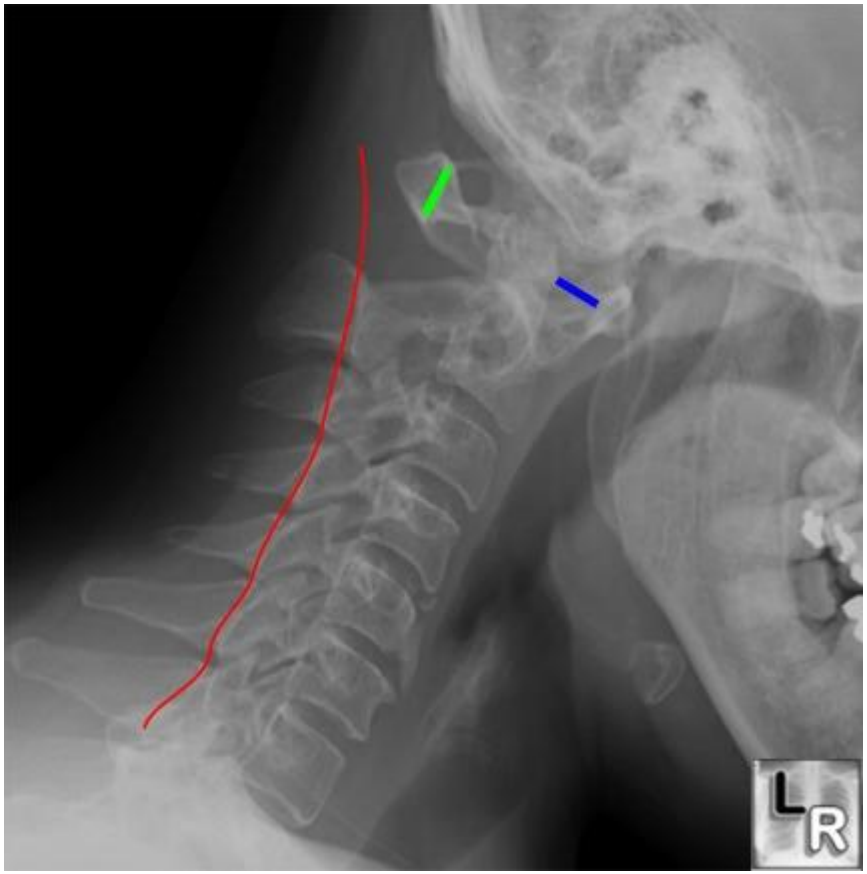
Affected Joints

- Affects diarthrodial joints- synovial lined joints
- Early disease this is typically small joints of the hands, wrist and feet.
  - Pattern is characteristic: symmetric, MCP and PIP predominant, with IP joints of thumbs, wrists, and MTP joints of the feet.
- As the disease progresses larger joints are affected.
- Hip occurs in 20% of RA patients.



Affected Joints

- Axial skeleton
  - CERVICAL spine at C1-2:
    - Major complication in advanced RA is atlantoaxial subluxation from tenosynovitis of the transverse ligament of C1 which stabilizes odontoid process.
  - Spares thoracic, lumbar and SI joints



Patient Presentation

- RA is an inflammatory arthritis
  - Joint swelling: fusiform swelling can be apparent at the PIP joints
  - Morning stiffness
  - Better with increased use or warming up
  - Gel Phenomena: stiffness recurs after prolonged inactivity
  - Metatarsalgia: Pain in ball of feet particularly upon waking
  - Widening of the forefoot (patient may complain of shoe size increase).
- Constitutional symptoms:
  - Fever
  - Malaise
  - Myalgias
  - Decreased appetite/weight loss

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Diagnositc Criteria

- 1987 ACR Criteria
- 4 or more of:
  - Morning stiffness at least 1 hour
  - Soft tissue swelling of at least 3 or more joint areas
  - Swelling of the PIP, MCP or wrist.
  - Symmetrical Arthrits
  - Subcutaneous Nodules
  - +RF
  - Radiographic evidence of erosions oer periarticular osteopenia of hand or wris

  Above 4 must be present:
  - 6 weeks

Problems with this Criteria:

Although specific, lacked sensitivity in early disease

Radiographic signs may occur late

RF can be negative

Presentation can vary

The net results was many late diagnosis and delayed treatment.

2010 ACR/EULAR Classification Criteria for RA

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
SEROLOGY (0-3)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
SYMPTOM DURATION (0-1)	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

Serologies

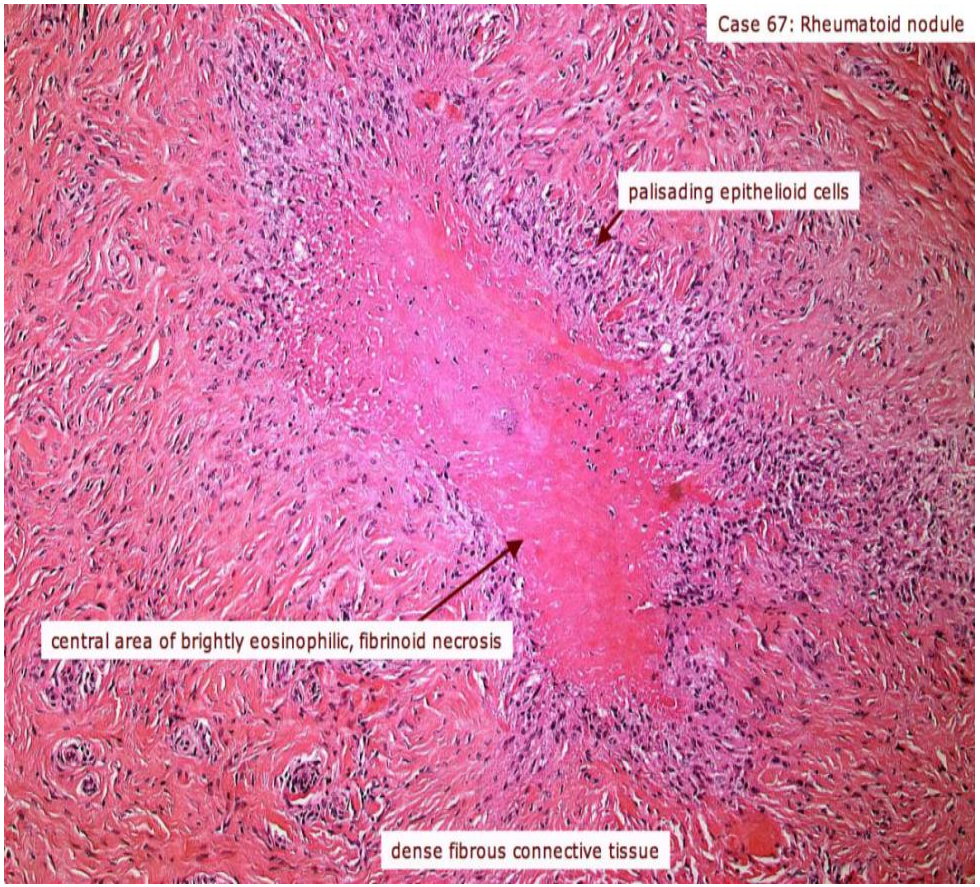
- Rheumatoid Factor: IgM antibody that recognized the Fc portion of an IgG molecule.
  - 70% are RF+ at disease onset, with 10-15% become RF + within the first 2 years after onset
  - +RF without clinical evidence does NOT suggest RA: hepatitis C, SLE, Sjogren's, bacterial endocarditis (recall DUKE minor criteria)
- Anti-citrillunated peptide antibody (CCP or ACPA):
  - **Highly specific 98%**
  - Seen in 70% of RF+ patients, and 33% or RF- (seronegative) RA patients.
- ANA: 30% RA patients can have.

Extra-Articular Manifestations

- Present in nearly 50% of patients during the course of disease.
  - Skin
  - Hematologic
  - Felty's Syndrome
  - Hepatic
  - Pulmonary
  - Cardiac
  - Ophthalmologic
  - Neurologic
  - Muscular
  - Renal
  - Vacular
- The most common is Sjogren's syndrome (secondary Sjogrens) occurring in 35% of patients.

Skin

- Rheumatoid Nodules: 25%
  - Firm, nontender, adherent to underlying periosteum.
  - Common over pressure areas: Achilles tendons, fingers, scalp, elbows, ischial tuberosity
  - Associated with seropositivity
  - Worsened with MTX use
  - Classic Pathology: 3 layers
    - outer CT and fibroblasts
    - palisading monocytes and macrophages
    - necrotic center.



Skin

- Pyoderma Gangrenosum
  - Deep ulceration with necrosis with typic undermining at the border
  - Can be seen in other diseases UC/CD, myeloma
  - Treated with corticosteroids and immunosuppresants.

Cardiac

- Pericarditis is the most common manifestation and typically asymptomatic found on autopsy
  - Bread and butter
- Accelerated atherosclerosis and CAD
  - Considered Coronary artery disease equivalent
  - Rheumatoid Arthritis patients (particularly WOMEN) have 2-3 x increased risk of MI when age adjusted.

Pulmonary

- Pleurisy: Up to 50% of patients have pleural thickening at autopsy

- Pleural effusions 2-3% patients
  - Typic Rheumatoid Pleural Fluid:
    - **EXQUISITELY low GLUCOSE!**
    - Low to modest WBC
    - High LDH
    - Exudative
    - Low pH

- 30% of patient will have parenchymal lung disease:
  - Pulmonary nodule (Necrobiotic nodules)-can cavitate and rupture causing empyema
    - Do not occur w/o +RF
    - Can also increase with MTX.
  - IPF
  - Bronchiectasis
  - BOOP (now COP: cryptogenic Organizing Pneumonia)

Felty's Syndrome

- The Super Rheumatoid:
  - Seropositive RA (RF +)
  - Splenomegaly (typic for triad
  - Neutropenia (not just Leukopenia)
  - HLA-DR4 in virtually all.

- Treatment remains the same
  - Splenectomy out of favor
  - Caution with Granulocyte colony stimulating factors as this can cause increased arthritis and vasculitis.

Others

- Hematologic: Typically will see NCNC anemia of chronic inflammation
  - Do not forget to r/o IDA from GIB given steroids and NSAIDS with most RA patients
- Hepatic: Nonspecific transaminitis.
  - Can see elevation in Alkaline phosphatase with active disease
- Neurologic: peripheral entrapment neuropathy (particularly CTS). Myelopathy due to subluxation of cervical spine
  - ***Patient with bilateral CTS: THINK***: amyloid, RA or other inflammatory arhthritis, Pregnancy, Thyroid, Acromegaly

Others

- Vacular: small vessel vasculitis and systemic vasculitis
- Muscular: Muscle atrophy, inflmmatory myositis
  - **MCTD: U1-RNP +** : SLE, SS, polymyositis. Can see erosive polyarthropathy with MCTD as well.
  - ASE of D-Penicillamine in past. (Myasthenia gravis)
- Renal: low grade membranous glomerular nephropathy, amyloidosis (late disease).

Early Treatment

- Radiographic progression of Rheumatoid Arthritis most aggressive and found to occur in the first 2 years.
- BeSt Study:
  - recent-onset RA prednisone or infliximab results in earlier clinical improvement and less joint damage progression than initial monotherapy.
  - **DAS-driven treatment adjustments** were effective to suppress disease activity and damage progression in all groups
- TICORA:
  - A strategy of intensive outpatient management of rheumatoid arthritis substantially improves disease activity, radiographic disease progression, physical function, and quality of life at no additional cost

Treatment

- Traditional DMARDs
  - Sulfasalazine:
    - Metabolized by intestinal bacteria to 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP)
  - Methotrexate:
    - Antimetabolite, inhibits **dihydrofolic acid reductase** which is an enzyme needed for synthesis of purine nucleotides
    - Comcomitant use with **Trimethoprim** can lead to **agranulocytosis**
    - Must supplement with 1mg daily folic acid
  - Arava (Leflunomide):
    - Interferes with **dihydroarotate dehydrogenase**, inhibiting pyrimidine synthesis, DNA synthesis
  - Azathioprine:
    - Is an Imidazoylyl derivative of 6-mercaptourine and will metabolize to 6-mercatopurine (6-MP)
  - Plaquenil:
    - Inhibits stimulation of the toll-like receptor (TLR) 9 family receptors
    - Inhibits IL-1
  - Cyclosporin A:
    - Inhibits production of IL-2 by helper T cells thereby blocking T cell activation and proliferation

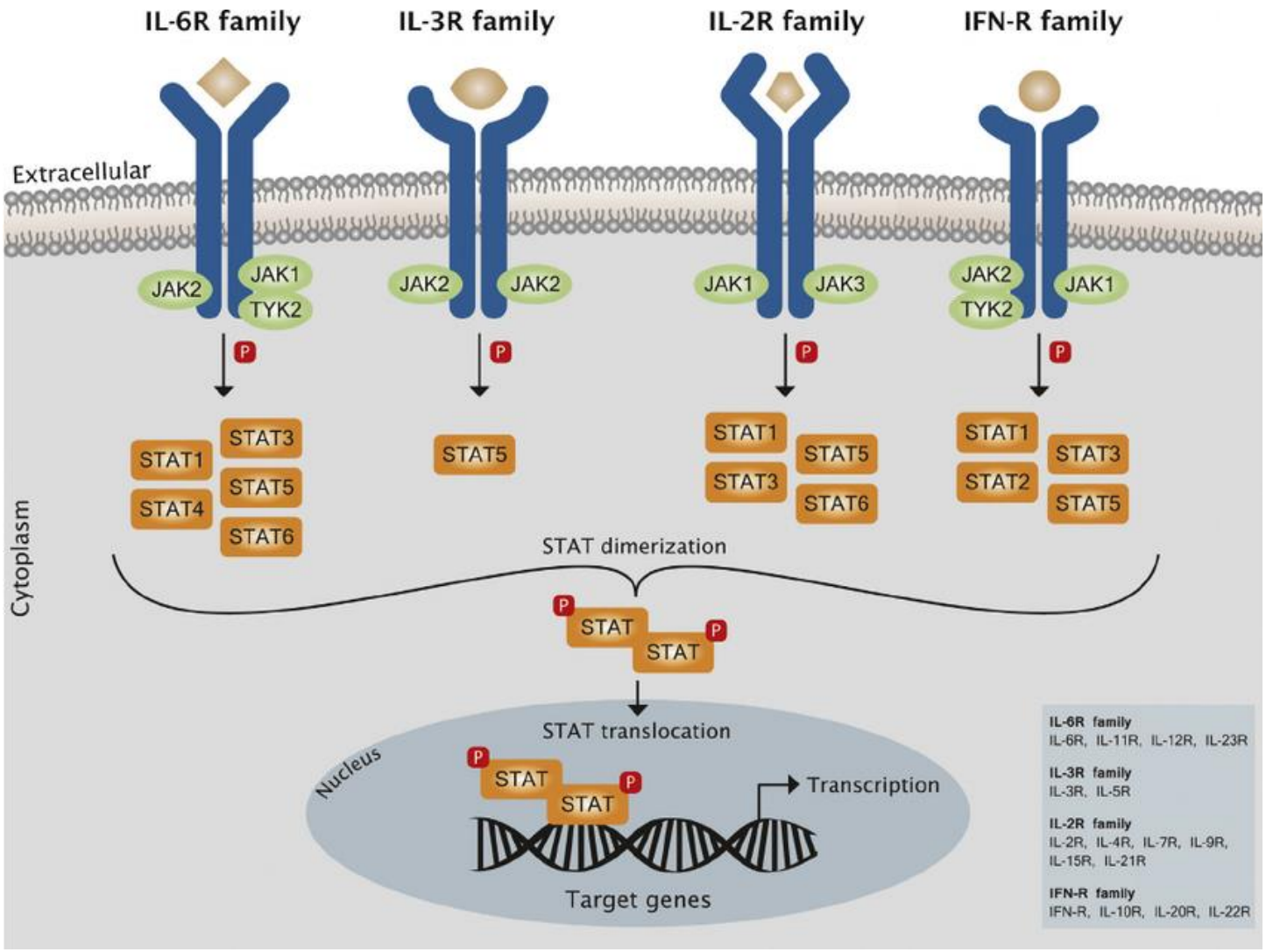
Biologics

- **Anti-TNF**
  - Enbrel- Etanercept (1997)
  - Remicade- Infliximab (1998)
  - Humira – Adalimumab (2002)
  - Symponi- Golimumab (2009)
  - Cimzia- Certolizomab (2009)
- **T-cell co-stimulatory specific**
  - Orencia -Abatacept (2005)
- **B-cell depletion:**
  - Rituxan –Rituximab (RA 2006)
- **IL-6 inhibition:**
  - Actemra - Tocilizumab (2010)
- **Small Molecules: Jak inhibitor**
  - Xeljanz (2012)- Tofacitanib First oral medication .
  - Baricitinib this year

Tofacitinib/Baricitinib

- MOA: tyrosine kinase (JAK) inhibitor
  - Tofacitinib inhibits JAK 1, 3 and less so 2. Baricitinib inhibits JAK 1, 2
  - JAK are intracellular proteins that form dimers with each other and transduce signals from cytokine and growth factor receptors
- Tofacitinib Dosage: 5mg PO BID and don't need to eat food with. Renal/hepatic dose: 5mg daily; Can also give w/ MTX
- Monitor: CBC, CMP, Lipid panel, hepatitis profile. CBC, CMP q4 weeks for 3 months, then q 3mo thereafter. Recheck lipid panel in 6-8 weeks (max effect by then)
- Side effects: infections, headache, leukopenia, anemia, slight increase in LDL and HDL, reports of GI perforation

Statue of Janus
Vatican Museum


IL-6R family
IL-3R family
IL-2R family
IFN-R family
Extracellular
JAK2
JAK1
TYK2
JAK2
JAK2
JAK1
JAK3
JAK2
TYK2
JAK1
P
STAT1
STAT3
STAT4
STAT5
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STAT2
STAT3
STAT5
Cytoplasm
STAT dimerization
STAT
STAT
STAT translocation
Nucleus
Transcription
Target genes
IL-6R family
IL-6R, IL-11R, IL-12R, IL-23R
IL-3R family
IL-3R, IL-5R
IL-2R family
IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, IL-21R
IFN-R family
IFN-R, IL-10R, IL-20R, IL-22R

Nebraska triple therapy

- Combination of MTX, SSZ, Hydroxychloroquine
- Popular combination therapy
- Can be very effective.
- Typically well tolerated.

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Thank You