Objectives

• Identify the major chemicals and cells involved in the pathophysiology of Rheumatoid Arthritis (RA)
• Describe the clinical presentation and diagnostic criteria
• Discuss the difference between non-disease modifying drugs and disease modifying anti-rheumatic drugs (DMARDs)
• Explain 2015 ACR recommendations for the treatment of RA
• Outline typical use, adverse effects, contraindications and monitoring parameters for non-biologic DMARDs, biologic DMARDs and Janus kinase (JAK) inhibitors
• Identify methods used to measure efficacy and list the parameters typically evaluated
• Recall patient education considerations
Epidemiology

• Affects 1-2% of the population worldwide

• Annual incidence ~ 40 per 100,000

• Affects 3x as many women as men

• Prevalence increases with advancing age
  – Peak onset between the ages of 50 and 75

• One of the most common causes of disability

• Associated with decreased life expectancy

Risk Factors/Possible Causes

• Smoking

• Genetic susceptibility, “shared epitope”

• Gender specific factors- possible hormonal influences

• Occupational exposures (silica, electrical work, asbestos)

• Infectious triggers (hypothesized but not proven)

• Presence of autoantibodies-Rheumatoid Factor (RF), anti-cyclic citrullinated peptide (anti-CCP)
**Pathophysiology**

- Autoimmune disease, etiology of inflammation unknown
- Effects of pro-inflammatory cytokines (e.g. tumor necrosis factor (TNF), IL-1, IL-6) outweigh those of anti-inflammatory cytokines
- Association with macrophages, T cells, B cells, and eventually osteoclasts
- Chronic inflammation and proliferation of synovial tissue which invades the cartilage and eventually the bone surface causing erosions

**Clinical Presentation**

- **Symmetrical** joint swelling (*synovitis*)
- **Morning stiffness** lasting for ≥ 1 hour
- Joint pain and tenderness, muscle aches
- **Sx in small joints**, e.g. hands and feet
- Low-grade fever, weight loss, fatigue, weakness, loss of appetite
Clinical Presentation

- Distal interphalangeal joint (DIP)
  - Uncommon in RA
  - Common in OA
- Proximal interphalangeal joint (PIP)
  - Common in RA
  - Common in OA
- Metacarpophalangeal joint (MCP)
  - Almost always in RA
  - Uncommon in OA
- Neck/back/hips/knees
  - Uncommon in RA
  - Common in OA

Clinical Presentation: Synovitis

Diagnosis: ACR Diagnostic Criteria

- At least 4 of 7:
  1. Morning stiffness
  2. Arthritis of ≥ 3 joint areas
  3. Arthritis of hand joints
  4. Symmetric arthritis
  5. Rheumatoid nodules
  6. Serum rheumatoid factor (RF)
  7. Radiographic changes

Diagnosis: ACR/EULAR Criteria

- Released 2010

- Effort to diagnose earlier disease (mainly for epidemiologic studies and clinical trials), not necessarily for clinical diagnosis

- ≥ 6 points = definite RA
  - 4 domains; only the highest point level that patients fulfill within each domain is counted


Diagnosis: ACR/EULAR Criteria

- Joint involvement (swollen or tender joint on exam)
  - 1 (0 points) or 2-10 (1 point) large joints (shoulder, elbow, hip, knee, ankle)
  - 1-3 (2 points) or 4-10 (3 points) small joints (MCP, PIP, 2nd-5th MTP, thumb interphalangeal joint, wrist)
  - > 10 joints (≥ 1 small joint) (5 points)

- Serology
  - (-) RF and anti-cyclic citrullinated peptide (anti-CCP) antibody (0 points)
  - (+) RF and/or anti-CCP at low titer (≤ 3 x ULN) (2 points)
  - (+) RF and/or anti-CCP at high titer (> 3 x ULN) (3 points)

- Acute phase reactants
  - (-) C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (0 points)
  - (+) CRP and/or ESR (1 point)

- Duration of symptoms
  - < 6 weeks (0 points)
  - ≥ 6 weeks (1 point)


Disease Course

- Gradual onset (most common) or abrupt onset

- Waxing and waning inflammation, but progressively worse structural changes

- Eventual joint destruction and deformity

- Extra-articular manifestations include: vasculitis, interstitial lung disease, myositis, pericarditis, anemia, neutropenia, rheumatoid nodules, pleuritis, scleritis and episcleritis

- RA is a systemic disease!!
Late Complications

Bony Erosions

Ulnar Deviation and Muscle Atrophy

Prognosis

• Poor prognosis is suggested by:
  – Functional limitation (HAQ Disability Index)
  – Positive RF or anti-CCP (esp high titer)
  – Extra-articular manifestations
  – Bony erosions by radiography

• New ACR recommendations not based on prognosis but focused on disease activity

TREATMENT

Treatment Goals

• Control disease activity (prevent joint destruction)

• Alleviate pain

• Maintain function for activities of daily living (ADLs) and ability to work (maintain joint function and mobility)

• Maximize quality of life

• Ultimate: induce complete remission
Evaluating Disease Activity

<table>
<thead>
<tr>
<th>Instrument (reference)</th>
<th>Thresholds of disease activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Activity Scale (PAS) or PASII (range 0–10) (149)</td>
<td></td>
</tr>
<tr>
<td>Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10) (155)</td>
<td></td>
</tr>
<tr>
<td>Clinical Disease Activity Index (CDAI) (range 0–76.0) (156)</td>
<td></td>
</tr>
<tr>
<td>Disease Activity Score (DAS) 28 erythrocyte sedimentation rate (ESR) (range 0–9.4) (157)</td>
<td></td>
</tr>
<tr>
<td>Simplified Disease Activity Index (SDAI) (range 0–86.0) (156)</td>
<td></td>
</tr>
</tbody>
</table>

Remission: 0–0.25
Low activity: >0.25–3.7
Moderate activity: >3.7 to <8.0
High activity: ≥8.0

Remission: 0–1.0
Low activity: >1.0–2.0
Moderate activity: >2.0–4.0
High activity: >4.0–10

Remission: ≥2.0
Low activity: >2.0–10.0
Moderate activity: >10.0–22.0
High activity: >22

Remission: <2.6
Low activity: ≥2.6 to <3.2
Moderate activity: ≥3.2 to ≤5.1
High activity: >5.1
Remission: ≥3.3
Low activity: >3.3 to ≤11.0
Moderate activity: >11.0 to ≤26
High activity: >26

* These 6 measures were endorsed by the American College of Rheumatology in 2012 (16). Other measures are now available to clinicians, but they were not included in this guideline because it was beyond the scope of this review. Adapted from ref. 16.


Non-Pharmacologic Therapy

- Rest
  - Systemic: naps, 8h of sleep nightly
  - Joint

- Physical therapy (PT)
  - Passive range of motion: maintains joint function, prevents contractures, minimizes muscle atrophy
  - Exercise: maintains good muscle tone/joint alignment; avoid active exercise during periods of active inflammation

- Occupational therapy (OT)

- Achievement of ideal body weight

- Stop smoking!
Non-Disease-Modifying Therapy

• Corticosteroids
  – Control symptoms quickly, often within days
  – Added to other therapy (or dose increased) in acute flares, or used chronically at low doses
  – Per ACR:
    • Low dose: ≤ 10 mg/day prednisone or equivalent
    • High dose: > 10mg/day prednisone or equivalent
    • Short-term (acute): <3 months
    • Long-term (chronic): ≥ 3 months
  – Usually used systemically but may be used intra-articularly
  – Use limited by many long-term adverse effects → add disease-modifying (steroid-sparing) agent

• NSAIDs
  – Used primarily for anti-inflammatory (vs. analgesic) effects, which can take up to 2-3 weeks
**Disease-Modifying Therapy**

- Disease-modifying anti-rheumatic drugs (DMARDs)
- **Start DMARD as soon as possible** in most patients
- Continue corticosteroid (or NSAID) until effect seen
- Grouped into the following categories:
  - conventional synthetic agents (csDMARD)
  - biologic original agents (boDMARD)
  - biologic biosimilar agents (bsDMARD)
  - targeted synthetic agents (tsDMARD)


**2015 ACR Recommendation Caveats**

- Focus on common cases
- No specific cost analyses performed
- Use a ACR-recommended disease activity measure **regularly**
- Perform assessment of the functional status **at least yearly**
  - Health Assessment Questionnaire/PROMIS physical function
- Switching between therapies in patients with low disease activity or remission should be the MDs/patients decision
- Preferred treatment recommendations do not imply non-preferred options are contraindicated
Strong vs. Conditional Recommendations

<table>
<thead>
<tr>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not*</td>
</tr>
<tr>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not</td>
<td></td>
</tr>
<tr>
<td>Clinicians</td>
<td>Be prepared to help patients to make a decision that is consistent with their own values</td>
</tr>
<tr>
<td>Most patients should receive the recommended course of action</td>
<td></td>
</tr>
<tr>
<td>Policy makers</td>
<td>There is a need for substantial debate and involvement of stakeholders</td>
</tr>
<tr>
<td>The recommendation can be adapted as a policy in most situations</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Implications of strong and conditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology recommendations [154]. * = majority means >50% of the people.


2015 ACR Recommendations for DMARD-Naïve or Early RA

Figure 2. 2015 American College of Rheumatology recommendations for the treatment of early rheumatoid arthritis (RA) in DMARD-naïve or early RA patients. Adapted from Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25.
Considerations Prior to DMARD Start

- Patient specific factors or history effecting drug selection
  - MTX and alcohol intake
  - Abatacept and COPD
  - CHF and anti-TNF agents

- Screening advised? Treatment needed?
  - TB, hepatitis B and/or C

- Diagnostic testing recommended?
  - ECHO
  - Chest X-ray

- Vaccinations needed?
  - Killed vaccines can be given while on non-biologic DMARDs, biologic DMARDs or JAK inhibitors (pneumococcal, influenza, Hep B, HPV)
  - Live attenuated vaccines---avoid while on biologic DMARDs or JAK inhibitors (herpes zoster)
    - Wait at least 2 wks after administration before starting a biologic or JAK inhibitor
### 2015 ACR Recommendations for Treatment of RA in High-Risk Conditions

#### Non-Biologic DMARDs

- **Commonly used**
  - Methotrexate (Rheumatrex®)
  - Leflunomide (Arava®)
  - Sulfasalazine (Azulfidine®)
  - Hydroxychloroquine (Plaquenil®)

- **Less common**** (not in ACR guidelines)
  - Azathioprine (Imuran®)
  - D-penicillamine (Cuprimine®, Depen®)
  - Gold salts
  - Minocycline (Minocin®)
  - Cyclosporine A (Neoral®, Gengraf®, Sandimmune®)

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<table>
<thead>
<tr>
<th>High-Risk Condition</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Use combination DMARDs or non-TNF biologic or biologic over TNF inhibitors (≥ C-D)</td>
<td>Moderate to Very low (III-IV)</td>
</tr>
</tbody>
</table>

**Nonbiologic DMARDs**

- Commonly used
  - Methotrexate (Rheumatrex®)
  - Leflunomide (Arava®)
  - Sulfasalazine (Azulfidine®)
  - Hydroxychloroquine (Plaquenil®)

- Less common**** (not in ACR guidelines)
  - Azathioprine (Imuran®)
  - D-penicillamine (Cuprimine®, Depen®)
  - Gold salts
  - Minocycline (Minocin®)
  - Cyclosporine A (Neoral®, Gengraf®, Sandimmune®)
Methotrexate (MTX)

- **Cornerstone** of therapy

- Initial DMARD in many cases, esp. in more active disease or worse prognosis

- Onset 1-2 months

- **Dihydrofolate reductase inhibitor** → inhibits purine synthesis → reduced cell turnover of dividing cells (e.g. lymphocytes)
  - Also inhibits production of IL-1

Methotrexate

- Folic acid 1-3 mg/day used to decrease stomatitis, nausea, diarrhea, and possibly alopecia without significant loss in efficacy

- Adverse effects: **hepatotoxicity**, lung disease, myelosuppression, pregnancy category X

- Relatively contraindicated in renal impairment, liver impairment, alcohol abuse (**avoid/minimize alcohol**), or significant lung disease

- Dose: 10-25 mg po weekly (as 2.5 mg tablets)
  - SC injection available if unable to tolerate PO
Leflunomide (LEF)

- Alternative to MTX or can be used in combination with MTX (usually ↓ 10mg daily)
- Similar onset, efficacy and toxicities as MTX
- Inhibits dihydroorotate dehydrogenase → inhibits pyrimidine synthesis → inhibits lymphocyte production
- Long half-life (may take up to 2 years to reach low levels) due to enterohpatic recirculation
  - Prodrug → Teriflunomide (active metabolite)
- Dose: 100mg x 3 days, then 20 mg po daily

Sulfasalazine (SSZ)

- Often used in combination with HCQ and/or MTX or LEF
- Onset 1-3 months; ?MOA in RA
- Adverse effects
  - GI adverse effects (N/V/D, anorexia) common
    - Tend to wane after the first few months
    - Lessened by starting low and going slow with dose
    - Take with food
  - Rash, urticaria, leukopenia, alopecia, stomatitis, transaminitis, yellow-orange skin or urine
- Avoid in sulfa allergy
- Dose: 500-1500 mg po bid
**Hydroxychloroquine (HCQ)**

- Proposed MOA: interferes with “antigen processing” in macrophages and other antigen-presenting cells → down regulation of the immune response

- Generally mild effects and slow onset (2-6 mo), so usually used in combination with SSZ and/or MTX or LEF

- Dose: 200mg- 400mg po daily

- Usually well-tolerated, occasional rash or GI c/o

- Potential for serious adverse effects on the eye

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**Hydroxychloroquine-Adverse Effects**

- Ocular toxicity
  - Cornea
    - Deposits of salts in the corneal epithelium
    - Mostly asymptomatic
    - Reversible with cessation of med
    - No correlation with retinal toxicity

  - Retinopathy
    - Asymptomatic → bull’s eye maculopathy → retinal atrophy → loss of central, peripheral, and night vision
Hydroxychloroquine-Retinopathy

• Irreversible
• Continued deterioration in vision after d/c drug
• Risk Factors
  – Daily Dose >6.5mg/Kg (IBW)
  – Cumulative dose >1000g** (>5 yrs of use)
  – Renal or hepatic impairment
  – Age >60yrs
  – Previous retinal and macular disease

• Recommend yearly eye exams, esp >5yrs use
  – Visual acuity, slit-lamp, fundoscopic and visual field exam

Advancing DMARD Therapy

• DMARD therapy should be modified in:
  – Repetitive flares
  – Unacceptable disease activity
  – Progressive joint damage

• Many different combinations possible
  – Multiple non-biologic DMARDs
  – Non-biologic DMARDs + biologic DMARD
  – Non-biologic DMARDs + JAK inhibitor
Biologics

• Biologic—FDA definition
  – a biological product (as a globulin, serum, vaccine, antitoxin, or antigen) used in the prevention or treatment of disease

• Biologic products
  – Biological products, or biologics, are medical products. Many biologics are made from a variety of natural sources (human, animal or microorganism). Like drugs, some biologics are intended to treat diseases and medical conditions. Other biologics are used to prevent or diagnose diseases.

Biosimilars

FDA definition:
A biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity, and potency of the product.

The FDA definition of an interchangeable biological product:
“it must be shown that the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”

Per FDA mandate:
Biosimilar product names will be followed by a 4 digit suffix to differentiate between the available products
### Biologic DMARDs

- **Anti-TNF agents**
  - Etanercept (Enbrel®) (1998)
    - Etanercept-szzs (Erelzi®) (2016)
  - Infliximab (Remicade®) (1998)
    - Infliximab-dyyb (Inflectra®) (2016)
  - Adalimumab (Humira®) (2002)
    - Adalimumab-atto (Amjevita®) (2016)
  - Certolizumab (Cimzia®) (2009)
  - Golimumab (Simponi®) (2009)
  - Golimumab (Simponi Aria®) (2013)

### Biologic DMARDs

- **Anakinra (Kineret®) (2001)**
  - Recombinant interleukin-1 receptor antagonist

- **Abatacept (Orencia®) (2005)**
  - Works on the T-cell receptor resulting in down regulation of T cells

- **Rituximab (Rituxan®) (2006)**
  - Works on CD20 on B cells resulting in B cell depletion

- **Tocilizumab (Actemra®) (2010)**
  - Interleukin-6 receptor inhibitor
Biologic DMARDs: Basics

• Administered parenterally

• Improve radiographic progression, QOL, symptoms

• Generally work quickly (days or weeks, compared to months for the non-biologic DMARDs) with significant improvement within 12-16 weeks, although not all patients respond or response wanes over time

• Often effective in partial responders to non-biologic DMARDs

Biologic DMARDs: Basics

• Approved and/or used for other immune-related disorders, e.g. ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis

• Potential for serious side effects

• High cost (tens of thousands/yr, compared to hundreds for non-biologic DMARDs)

• Often require prior authorization from insurance
Biologic DMARDs: Use

• Used for moderate to severe RA

• Used alone or in combination with another non-biologic DMARD
  – Combination therapy is better
  – Generally current non-biologic DMARD therapy is continued when the biologic DMARD is started

• Can be added as a steroid sparing agent

• Special storage, administration and disposal instructions

Biologic DMARDs: Adverse Effects

• Many are overlapping
  – Do NOT combine ≥ 1 biologic DMARD!!

• Infection
  – Update vaccinations, avoid live vaccinations
  – Consider discontinuing in acute infections
  – Consider holding before procedures

• Malignancy
  • Above baseline elevated risk in RA patients
  • Absolute risk is still very low

• Cytopenias—neutropenia, thrombocytopenia, leukopenia

• Injection site/infusion reactions
Opportunistic Infections

- Bacterial (legionellosis, listeriosis)
- Fungal (histoplasmosis, aspergillosis, coccidioidomycosis)
- Viral (hepatitis B reactivation)
  - check Hep B surface Ag before start of a biologic (or JAK inhibitor)
  - reactivation of the varicella-zoster virus (shingles)

- Mycobacterial
  - ↑ susceptibility to tuberculosis (TB) or reactivation of latent TB (LTB)
  - Check TB test before treatment (blood test preferred)
    - Will remain + after treatment; no need to recheck this again
  - Treat LTB and active TB
  - If the pt has been previously treated for TB or LTB
    - ask about symptoms of TB at follow-up visits (cough, night sweats, wt loss)
    - consider repeating chest X-ray periodically

2015 ACR Recommendations for TB Screening for Biologics and Tofacitinib

Malignancies

- “Blood” cancers
  - Lymphomas
  - Leukemias

- Skin cancer
  - Non-melanoma > melanoma

- Others reported:
  - Breast
  - Colon
  - Prostate
  - Lung

Anti-TNF Agents: Use

- Generally first-line biologic DMARD due to efficacy, relatively fast onset of effect, clinical experience, and option for SC dosing

- Can choose any agent to start
  - Patient preference, indication, adherence concerns, insurance mandates...
  - Wait 3 months to see full effect

- Reasonable to try 2nd anti-TNF agent after failure of 1st
  - Antibody formation
Anti-TNF Agents: Dosing

- Etanercept 50 mg SC weekly
  - PFS or Sureclick autoinjector
- Infliximab 3 mg/kg IV over 2 hours at 0, 2, and 6 wks, then q8wks
  - Can ↑ dose up to 10 mg/kg or ↓ interval to q4wks
- Adalimumab 40 mg SC q2wks
  - PFS or PEN device
- Certolizumab 400 mg SC q2wks x 3 doses, then 200 mg SC q2wks or 400mg SC q4wks
  - PFS only
- Golimumab 50 mg SC monthly
  - PFS or Smartject autoinjector
- Golimumab 2mg/kg IV over 30 min at 0, 4, and then q8 wks

Anti-TNF Agents: Adverse Effects

- Common: HA, URI, nausea, injection site reactions
- Serious:
  - Infection
  - Malignancy
  - Psoriasis (new or exacerbation)
  - Lupus-like syndrome
  - Heart failure (HF) (new or exacerbation)
    - Esp. in severe HF (NYHA Class III or IV)
  - CNS or peripheral-demyelinating disorders (new or exacerbation)
    - Optic neuritis, multiple sclerosis, Guillain-Barre
  - Blood dyscrasias (thrombocytopenia, leukopenia)
  - Hepatotoxicity
  - Hypersensitivity
  - Infusion reactions
**Anakinra**

- IL-1 inhibitor

- Less effective than other biologics
  - Not used very often
  - Not included in 2015 ACR Recommendations

- Adverse effects:
  - Common: HA, URI, nausea, injection site reactions
  - Serious: infection, neutropenia

- 100 mg SC daily or 100mg qod if CrCl<30

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**Abatacept**

- Soluble fusion protein containing the extracellular domain of human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)

- Longer time to effect than anti-TNF agents

- Adverse effects:
  - Common: HA, URI/nasopharyngitis
  - Serious: infection, malignancy, infusion-related reactions (dizziness, HTN)

- ADEs more common in pt with COPD
  - exacerbations, cough, rhonchi, dyspnea

- IV dose: 500 mg (< 60 kg), 750 mg (60-100 kg), 1000 mg (> 100 kg) IV over 30 minutes at 0, 2, and 4wks, then q4wks

- SC dose: 125mg qweek (PFS or Clickject autoinjector)
Rituximab

- Depletes B cells by binding to CD20

- Does not require continuous therapy to maintain a response (effect lasts 4 mo to > 1 year)

- Use in combination with methotrexate

- No evidence of ↑ incidence of TB in patients using rituximab for lymphoma
  - No need to screen for TB

- No evidence of ↑ incidence of malignancy in patients with RA
  - Recommended biologic in pts with treated CA such as lymphoma, abatacept and tocilizumab are also conditionally recommended over anti-TNF

Rituximab

- Dose: 1000 mg IV infusion; one course of two infusions 2 wk apart, then repeat at least 16-24 wks later

- Adverse effects:
  - Common: fever, chills, weakness, cough, HA, pharyngitis, rhinitis
  - Serious:
    - Infection
      - Hepatitis B reactivation—check before administration
      - Progressive multifocal leukoencephalopathy (PML), caused by JC virus (rare)
    - Infusion reactions (38-45%), esp. with 1st dose
    - Cardiac arrhythmias
    - Mucocutaneous reactions, e.g. Stevens-Johnson
    - Cytopenias
    - Nephrotoxicity
Tocilizumab

• Decreases IL-6 mediated signaling which effects the inflammatory process

• **DO NOT** start med if any of the following:
  – ANC <2000
  – PLT <100,000
  – ALT or AST > 1.5x ULN

• Adverse effects:
  – Common: URI, nasopharyngitis, HA, HTN, ↑ ALT
  – Serious: infection, neutropenia, thrombocytopenia, GI perforation, malignancy, demyelinating disorders, serious infections, hepatotoxicity
  – Other: dyslipidemia

Tocilizumab

• IV dose: 4 mg/kg IV over 60 minutes q4wks, may increase to 8 mg/kg IV q4wks (maximum 800 mg/dose)

• SC dose: as a PFS
  – <100Kg: 162mg SC every other week then ↑ to weekly based on response
  – >100Kg: 162mg SC weekly
Newest Class: Janus Kinase Inhibitors (JAK)

- JAKs: intracellular enzymes which transmit signals, arising from cytokine or growth factor-receptor interactions on the cellular membrane, to influence cellular processes of hematopoiesis and immune cell function

- Tofacitinib (Xeljanz®) – specificity for JAK 1 and 3

- Use alone or in combo with MTX (or other non-biologic DMARD)

- DO NOT combine with a biologic DMARD

- DO NOT start if:
  - ANC <1000
  - Lymphocytes <500
  - Hb < 9

Tofacitinib

- Good oral bioavailability: 74%

- Elimination:
  - 70% liver metabolism
    - CYP 3A4 primarily but also CYP 2C19
  - 30% renal excretion of parent drug

- Loss of effectiveness with CYP3A4 inducers
  - Phenytoin, carbamazepine, St. John’s wort, rifampin

- ↑ risk for toxicities with inhibitors of CYP 3A4 or 2C19
Tofacitinib

- **Dose:**
  - IR: 5mg PO bid
  - ER: 11mg PO daily

- **Reduce to 5mg daily in pts with:**
  - Moderate to severe renal insufficiency (limited data with CrCl <40mL/min)
  - Moderate hepatic impairment
  - Potent inhibitors of CYP 3A4 (ketoconazole)
  - Moderate inhibitors of CYP 3A4 + potent inhibitors of CYP 2C19 (fluconazole)

Janus Kinase Inhibitor

- **Cautions similar as biologics; screen the same**
  - TB, serious infections, malignancy

- **Adverse effects:**
  - Common: URI, nasopharyngitis, HA, HTN
  - Serious: infection, malignancy, lymphopenia, neutropenia, anemia, hepatotoxicity, GI perforation
  - Other: dyslipidemia

- **Avoid in patients taking other potent immunosuppressive drugs such as azathioprine, tacrolimus, cyclosporine**
MONITORING

Efficacy Monitoring

• Presence of actively inflamed joints on exam
• Progression on X-ray
• Degree of joint pain
• Duration of morning stiffness
• Duration of fatigue
• Reduction in ESR or CRP (inflammatory markers)
• Limitation of function/Disease activity
  – Rheumatoid Arthritis Disease Activity Scales
  – Health Assessment Questionnaire

Toxicity Monitoring

- **NSAIDs:** BP, CBC, Scr, and LFTs at baseline, then at 3 months, then q 6-12 months

- **Corticosteroids:** BP, CMP, glucose, DEXA scan, weight (osteoporosis, HTN, weight gain, fluid retention, hyperglycemia, cataracts, skin fragility, premature atherosclerosis)

- **Methotrexate, sulfasalazine, leflunomide:**
  - CBC, Scr, and LFTs at baseline then...
  - every 2-4wks for the first 3 months
  - every 8-12wks for the next 3 months
  - every 12wks after 6 months of treatment

- For methotrexate check CXR at baseline and q6-12 months for pulmonary changes (fibrosis, pneumonitis)

- **Hydroxychloroquine:** ocular exam yearly

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Toxicity Monitoring

- **Anti-TNF agents:**
  - Infection (TB yearly, hepatitis B)
  - CBC and LFTs at baseline then q3-6 months

- **Anakinra:**
  - Infection, CBC at baseline then q3months

- **Abatacept:**
  - Infection (TB yearly, hepatitis B), CBC periodically

- **Rituximab:**
  - Infection (hepatitis B), CBC, Chem 7, and LFTs at baseline and 2 wks, then q2-3 months
Toxicity Monitoring

• Tocilizumab:
  – Infection (TB yearly, hepatitis B)
  – CBC at baseline and q4-8wk
  – LFTs at baseline and q4-8wk
  – Lipids panel 4-8wk after start of therapy, then q6 months

• JAK inhibitor:
  – Infection (TB yearly, hepatitis B)
  – CBC at baseline, then at 4-8 wks, then q3 months
  – LFTs at baseline then q3 months
  – Lipid panel 4-8 weeks after start of therapy, then q6 months

Conclusions

• RA is a progressive autoimmune disease that can cause severe disability
• Non-pharmacologic therapy, corticosteroids, and NSAIDs are used for symptomatic relief
• DMARDs, including biologics and JAK inhibitors, are the mainstay of therapy
• Methotrexate is the most commonly used DMARD, as monotherapy or in combination
• Biologic DMARDs can be effective additions, but may also cause serious adverse effects
• Tofacitinib (Xeljanz®) is the first of a new class used to treat RA, but is also linked to serious adverse effects
References

- www.micromedex.com
- www.FDA.gov