Rheumatoid Arthritis Update

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• I declare that neither I nor any member of my family have a financial arrangement or affiliation with any organization(s) that may have a direct interest in the subject matter of this continuing education presentation.
Learning Objectives

Pharmacists:
1. Discuss the pathophysiology and clinical presentation associated with rheumatoid arthritis and differentiate between osteoarthritis and rheumatoid arthritis based on a patient's clinical signs and symptoms.
2. Describe the therapeutic target and categorize the medications used in rheumatoid arthritis, including biologics and DMARDs (non-biologics).
3. Formulate an individualized treatment plan for rheumatoid arthritis, to include the appropriate medication(s), pertinent adverse reactions/toxicities, monitoring, and contraindications (taking into account special patient populations [pregnancy, elderly, etc] and co-morbidities), and develop a plan for patients who do not respond to initial therapy.
4. List recommended vaccinations for patients with rheumatoid arthritis as well as guidelines for tuberculosis screening.
5. Discuss the potential impact of biosimilars in the treatment of rheumatoid arthritis.
Learning Objectives

Technicians:

1. Describe the main differences between osteoarthritis and rheumatoid arthritis related to common patient symptoms and medicines used.

2. List the pharmacologic class for medications used in rheumatoid arthritis, including biologics and DMARDs (non-biologics).

3. Discuss important patient counseling points related to medications used in the treatment of rheumatoid arthritis, including storage and handling of medications.

4. List recommended vaccinations for patients with rheumatoid arthritis.
Rheumatoid Arthritis (RA)

Definition:

- Chronic, systemic, inflammatory **autoimmune** disease of unknown cause
- Progressive disease characterized by polyarticular, **symmetric** joint involvement
- Results in erosive synovitis, also erosions to cartilage and bone leading to joint deformity
Rheumatoid Arthritis (RA)

Extra-articular involvement:
- Rheumatoid nodules
- Vasculitis
- Eye inflammation
- Neurologic dysfunction
- Cardiopulmonary disease
- Lymphadenopathy, splenomegaly
Rheumatoid Arthritis (RA)

Epidemiology

• Affects 1% of population world-wide
• More prevalent in women
• 6:1 ratio women to men in ages 15 to 45
• RA is 6x more common in non-twin children of parents with rheumatoid factor-positive, erosive rheumatoid arthritis when compared with children whose parents do not have the disease.
Patient Case Study

32 year old female who has had a 3 week history of severe pain and stiffness in her hands and feet. The symptoms are worse in the morning and the stiffness gets better as the day progresses.

Despite self-treatment with ibuprofen and changing daily routine to rest joints, her pain is overall the same. PMH is non-contributory. Meds: pre-natal vitamins. FH: mother – RA, HF, HTN; father – CAD s/p CABG, asthma.
Pathophysiology

- Chronic inflammation of the synovial tissue lining the joint capsule results in the proliferation of this tissue → Pannus
- Pannus invades the cartilage and bone surface, producing erosions of bone and cartilage and leading to destruction of the joint.
- Most patients with RA form antibodies called rheumatoid factors.
- Seropositive patients tend to have a more aggressive course of their illness than do seronegative patients.
Pathophysiology

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Clinical Presentation

- Joint pain and stiffness of more than **6 weeks’ duration**
- Tenderness, warmth, swelling in affected joints (small joints of the **hands, wrists, feet**)
- **Symmetrical** pattern
- Fatigue, weakness, low-grade fever, loss of appetite (prodromal)
- Muscle pain and afternoon fatigue possible
- Joint deformity is seen late in the disease
- **Rheumatoid nodules** could be present
Classification Criteria

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Score</th>
<th>Target population (Who should be tested?): Patients who 1) have at least 1 joint with definite clinical synovitis (swelling)* 2) with the synovitis not better explained by another disease† Classification criteria for RA (score-based algorithm; add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>A. Joint involvement§</td>
</tr>
<tr>
<td></td>
<td>1 large joint¶</td>
</tr>
<tr>
<td>1</td>
<td>2–10 large joints</td>
</tr>
<tr>
<td>2</td>
<td>1–3 small joints (with or without involvement of large joints)#</td>
</tr>
<tr>
<td>3</td>
<td>4–10 small joints (with or without involvement of large joints)</td>
</tr>
<tr>
<td>5</td>
<td>&gt;10 joints (at least 1 small joint)**</td>
</tr>
<tr>
<td>0</td>
<td>B. Serology (at least 1 test result is needed for classification)††</td>
</tr>
<tr>
<td></td>
<td>Negative RF and negative ACPA</td>
</tr>
<tr>
<td>2</td>
<td>Low-positive RF or low-positive ACPA</td>
</tr>
<tr>
<td>3</td>
<td>High-positive RF or high-positive ACPA</td>
</tr>
<tr>
<td>0</td>
<td>C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡</td>
</tr>
<tr>
<td></td>
<td>Normal CRP and normal ESR</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal CRP or abnormal ESR</td>
</tr>
<tr>
<td>0</td>
<td>D. Duration of symptoms§§</td>
</tr>
<tr>
<td></td>
<td>&lt;6 weeks</td>
</tr>
<tr>
<td>1</td>
<td>≥6 weeks</td>
</tr>
</tbody>
</table>

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

**ARTHRITIS & RHEUMATISM. September 2010;62(9):2569–2581**
Diagnosis

- Labs/tests:
  - Rheumatoid Factor (RF) – detectable in 60-70% of patients
  - CRP, ESR (elevated)
  - Anticyclic citrullinated peptide (anti-CCP) antibodies: similar sensitivity to RF but more **SPECIFIC** (90%-95%); present earlier in the disease
  - CBC: **normocytic, normochromic** anemia
  - Joint radiographs, ultrasound (erosions, joint space narrowing)

- Features of poor prognosis:
  - Functional limitation (validated tools)
  - **Extra-articular** disease disease (see previous slide)
  - Positive Rheumatoid Factor (RF)
  - Positive anti-CCP antibodies
  - **Bony erosions** on radiograph
After experiencing symptoms for about 4 weeks, she decides to contact her PCP to ask about the pain and stiffness, especially considering her FH. A rheumatology panel is drawn and reveals a positive RF and slightly elevated CRP and ESR. She is referred to a rheumatologist and goes for her consultation about 8 weeks after her symptoms started. Upon PE, she reports discomfort in several small joints in her hands and feet. Repeat labs still show + RF, high positive anti-CCP antibodies, and mildly elevated CRP and ESR. X-rays as well as an ultrasound are taken of her hands and feet. The x-rays and US show inflammation and the US shows some small erosions in the hands and feet. A diagnosis of RA is confirmed.

• What clinical features did the patient possess?

• Does she have any markers of poor prognosis?
Comparison to Osteoarthritis (OA)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Rheumatoid Arthritis</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early onset (25-50 yoa)</td>
<td>Later onset</td>
</tr>
<tr>
<td>Common joints affected</td>
<td>Symmetric; hands, wrists, elbows, knees, shoulders, cervical spine</td>
<td>Asymmetric; hand, hip, cervical and lumbar spine</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Morning stiffness ≥1 hour, tender, red, swollen joints</td>
<td>Morning stiffness &lt; 30 mins, minimal warmth, redness or swelling</td>
</tr>
<tr>
<td>Labs</td>
<td>+RF, ↑ ESR, CRP; anemia</td>
<td>No pertinent labs</td>
</tr>
<tr>
<td>Radiographic features</td>
<td>Erosions</td>
<td>Joint space narrowing</td>
</tr>
</tbody>
</table>
Comparison to OA

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Treatment Guidelines

General Considerations

Early RA: < 6 months
Established RA: ≥ 6 months

** Target LOW DISEASE ACTIVITY/REMISSION as soon as possible (prevent joint damage)
- “Treat to Target”
- Also preserve joint ROM and QOL
- First RA guidelines to incorporate physician AND patient recommendations (strong vs. conditional)
- Guidelines did not address cost, though clinicians feel it should be strongly considered
Treatment of Early RA

Early RA: < 6 months

- DMARD-Naive Early RA
  - Low Disease Activity
    - DMARD Monotherapy
  - Moderate or High Disease Activity
    - DMARD Monotherapy

- DMARD-Naive Early RA
  - Moderate or High Disease Activity
    - Combination Traditional DMARDs or TNF inhibitor +/- MTX or Non-TNF Biologic +/- MTX

- See Established RA algorithm (middle box)
  - Disease activity
  - Treatment options or strategy
  - Algorithm Pathway for most patients
  - Disease state or prior treatment state

- Green box for Strong Recommendations
- Yellow box for Conditional Recommendations
Treatment of Established RA

Established RA: ≥ 6 months
Terminology

DMARD = Disease Modifying Anti-rheumatic Drug

- Oral, non-biologic drugs (Methotrexate, sulfasalazine, etc.)

Biologic: injectable, large molecule drugs (etanercept, rituximab, etc)

- Divided into TNF inhibitors and non-TNF inhibitors

**DMARDS (non-biologics) [should be started within 3 months of diagnosis]**
Pharmacotherapy

**NSAIDS/steroids:** can be used as bridge therapy or during acute flares

- The **LOWEST** dose of corticosteroid that controls symptoms should be used to reduce adverse effects (oral)
- High-dose bursts – help control disease flares (oral, IM, intra-articular)
- CS long-term complications: HPA axis suppression, Cushing's syndrome, osteoporosis, glaucoma, cataracts, gastritis, HTN, glucose intolerance, skin atrophy, and increased risk of infection
  - **Calcium/Vitamin D** supplementation
- Take both NSAIDs and steroids with food to reduce GI side effects.
Pharmacotherapy - DMARDs

*Methotrexate (MTX)*
- **Folic acid** analog
- **Backbone of therapy in RA**
- Slows progression of disease
- Can be given PO or IM/SubQ
  - Using injectable form can sometimes lessen GI side effects
- Dosing in RA:
  - 5-7.5 mg PO q week, increased by 5 mg every few weeks to a max weekly dose of ~20 mg
  - 10-25 mg IM/SubQ once weekly

- ADRs: N/V/D (common), hepatotoxicity, TCP, hair loss
- Supplement with **folic acid 1 mg daily** to reduce GI effects
- Monitoring: CBC, LFT’s, pregnancy test
- **DO NOT USE IN PREGNANCY**
Pharmacotherapy - DMARDs

Hydroxychloroquine (Plaquenil)
- Anti-malarial drug
- Delayed onset
- Lacks myelosuppressive, hepatic, and renal toxicities but less potent of drug in treating RA (usually not preferred for monotherapy)
- Maintenance dose: 200-400 mg daily
- ADRs: N/V/D – take with food; derm (rash, alopecia), ocular toxicity: accommodation defects, benign corneal deposits, blurred vision, scotomas, night blindness (eye exam required)

Sulfasalazine (Azulfidine)
- Lower priority in therapy; use limited by GI side effects (divide doses)
- Drug interactions with antibiotics, warfarin, iron supplements
- Can cause orange urine or stool
- Watch with sulfa allergy
- Monitoring: CBC
Pharmacotherapy - DMARDS

**Leflunomide (Arava)**
- Similar efficacy to MTX in RA; large doses given at initiation of therapy
- In combo with MTX \( \rightarrow \) more **hepatotoxicity**
- BBW for hepatotoxicity (Must monitor LFTs)
- **DO NOT USE IN PREGNANCY**

**Minocycline**
- **Tetracycline** antibiotic
- Inhibits proteins that are responsible for collagen breakdown
- Alternative for patients with low disease activity and without markers of poor prognosis
- Studies only showed mild improvement in joint pain/swelling
- TCN ADRs:
  - **DO NOT USE IN PREGNANCY**
Revisiting the Case...

The patient is started on MTX 7.5 mg once weekly with folic acid 1 mg daily; after 4 weeks, her MTX dose is titrated to 20 mg once weekly. Labs checked at baseline: CBC, CRP, CMP, TB test. After 3 months of MTX therapy, the patient’s symptoms are well-controlled (low disease activity) and she continues current therapy. Continued monitoring: CBC, CMP, CRP

- What other options are available to the patient at this point based on guidelines?

- What if our patient’s disease activity worsens after being on MTX monotherapy?
Pharmacotherapy: Biologics

**TNF inhibitors**

*TNF inhibitors*: biologics of choice; clinical response may be seen in days to weeks

**Etanercept (Enbrel)**
- Dose: 50 mg SubQ weekly or 25 mg SubQ twice weekly
  - Available as auto-injector or pre-filled syringe
- Few ADRs: injection site reactions, HA
- Store in refrigerator

**Infliximab (Remicade)**
- Dose: 3 mg/kg IV **infusion** at initiation; additional dose at 2 and 6 weeks, then infusion every 8 weeks
- Given with **MTX** (prevent antibody formation)
- ADRs: hepatotoxicity, infection risk, **infusion** reaction (pre-med)
Pharmacotherapy: Biologics

**TNF inhibitors**

**Adalimumab (Humira)**
- Less antigenic because **recombinant** mab
- Dose: 40 mg SubQ every other week (w/o MTX: 40 mg q week)
  - Available as pen or pre-filled syringe
- Store in refrigerator

**Golimumab (Simponi)**
- Dose: 50 mg SubQ q month
  - Available as auto-injector and prefilled syringe
- Can also give IV
- **Should be used with** MTX
- Store in refrigerator
- ADRs: URI, sore throat, nasal congestion
**Pharmacotherapy: Biologics**

**TNF Inhibitors**

*Certolizumab (Cimzia)*

- **Pegylated** inhibitor (delayed elimination) given subQ
- Dosing: 400 mg subQ every other week x 3 doses, then 200 mg every other week
  - Max dose 400 mg every other week
- Dosage forms: single-dose vial or prefilled syringe
- Pegylated formulation may accumulate in renal impairment (not studied)
- Store in refrigerator
- Intended for use in **moderate to severe RA**
- **Not** recommended for use with anakinra or other TNF inhibitors
Pharmacotherapy: Biologics

Non-TNF inhibitors

**Abatacept (Orencia)** – T cell co-stimulation blocker
- **Dosing:**
  - IV: weight based dose at 0, 2, and 4 weeks, then every 4 weeks
    - <60 kg: 500 mg
    - 60-100 kg: 750 mg
    - >100 kg: 1000 mg
  - SubQ: 125 mg weekly
    - If using IV loading dose, give regular subQ dose within 24 hours
- Should **not** be used with anakinra or TNF inhibitors
- **Do not give live vaccines**

**Rituximab (Rituxan)** – mab against CD20
- Useful if failed MTX or TNF inhibitors
- Dose: 1000 mg IV **infusion** on days 1 and 15, in combo with MTX; subsequent courses every 24 weeks
- ADRs: infusion reactions (pre-medicate); HTN, nausea, mucocutaneous reactions (SJS), bowel obstruction/perforation; Hep B reactivation
- **Do not give live vaccines**
Pharmacotherapy: Biologics

Non-TNF inhibitors

**Tocilizumab (Actemra) – IL-6 receptor antagonist**
- Dosing:
  - IV: 4 mg/kg IV Q4 weeks, may increase to 8 mg/kg
    - Max dose 800 mg
  - SubQ:
    - <100 kg: 162 mg every other week
    - >100 kg: 162 mg every week
- May cause alterations in cholesterol (monitor LDL)

**Anakinra (Kineret) – IL-1 receptor antagonist**
- May be less effective than others; not included in guidelines

**Tofacitinib (Xeljanz) – JAK enzyme inhibitor**
- Newest agent in therapy
- Dose: 5 mg PO BID (benefit over injections)
- ADRs similar to other drugs; hepatotoxicity, lipid abnormalities, GI perforation
- Do not give live vaccines

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- ADRs similar to other drugs; hepatotoxicity, lipid abnormalities, GI perforation
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General Warnings with TNF inhibitors

- Injection site reactions
- Can increase risk of TB (reactivation of latent) or other infections
- Increased risk of malignancies/lymphomas
- Possible Hepatitis B reactivation
- New or worsening heart failure (relative CI)
- Avoidance of live vaccines
Options for Non-response

After evaluating for at least 3 months

- Add another non-biologic DMARD or switch DMARDs
- Add or switch to biologic, usually anti-TNF first (non-TNF afterwards)

Tapering therapy

- If disease activity is in remission may consider tapering therapy, but do NOT discontinue all RA therapies
  - Reduce dose or frequency of one therapy at a time
Special Patient Populations

- HF: do NOT use TNF inhibitors
- Hepatitis C: use DMARDs if not on antiviral treatment
- Hepatitis B: start antiviral treatment before immunosuppressive therapy
- Skin cancer: use DMARDs
- Lymphoproliferative disease: use rituxan (preferred), do NOT use TNFi
- Solid organ malignancy: same as patients without disease
- Previous serious infections: combination DMARD or abatacept, do not use TNFi
Vaccines

- Whenever possible, all vaccines should be given before DMARDs or biologics
- Response to inactivated vaccines may be reduced during treatment with biologics
- Follow all CDC Advisory Committee on Immunization Practices (ACIP) recommendations

- **Pneumococcal:**
  - One dose of PCV13 for those patients who have not previously received the vaccine. A dose of PPSV23 should be given at least one year later.
  - For those who have already received one or more doses of PPSV23, the dose of PCV13 should be given at least one year after receiving the most recent dose of PPSV23.

- **Influenza:** do NOT give _________ vaccine
- **Hep B:** patients with RF for Hep B infection - ______________________
- **HPV:** ages 11-26 years
- **Zoster:** ≥ 50 YOA
  - Biologics: Give _______________________________ before starting therapy
Vaccines


<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Killed vaccines</th>
<th>Recombinant vaccine</th>
<th>Live attenuated vaccine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pneumococcal(^1)</td>
<td>Influenza (intramuscular)</td>
<td>Hepatitis B(^2)</td>
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<tr>
<td>DMARD monotherapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Combination DMARDs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TNFi biologics</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Non-TNF biologics</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Before initiating therapy**

**While already taking therapy**

(PICO J.4, J.5)\(^6\)

(PICO J.2, J.3)\(^7\)

Not recommended

(PICO J.2, J.3)\(^7\)

(PICO J.1)\(^5\)

(PICO J.1)\(^5\)
TB Screening with Biologics

- Recommended for all patients starting biologics or tofacitinib
- Repeat screening annually if risk factors for TB are present
  - Examples:

See flowchart next slide
**Biosimilars**

**Definition** -- a biopharmaceutical drug designed to have active properties *similar* to one that has previously been licensed

**US approved biosimilars**

<table>
<thead>
<tr>
<th>Date of Biosimilar FDA Approval</th>
<th>Biosimilar Product</th>
<th>Original Product</th>
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<tbody>
<tr>
<td>March 6, 2015</td>
<td>Filgrastim-sndz/Zarxio</td>
<td>filgrastim/Neupogen</td>
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<tr>
<td>April 5, 2016</td>
<td>infliximab-dyyb/Inflectra</td>
<td>infliximab/Remicade</td>
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<tr>
<td>August 30, 2016</td>
<td>etanercept-szzs/Erelzi</td>
<td>etanercept/Enbrel</td>
</tr>
<tr>
<td>September 23, 2016</td>
<td>adalimumab-atto/Amjevita</td>
<td>adalimumab/Humira</td>
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</table>
Biosimilars

Issues to consider with biosimilars:
• They are not the “same” as parent compound due to complex manufacturing processes
  – May not be able to substitute freely (without authorization)
• Experience in Europe tells us there may be safety issues
• Naming system
• Assumed cost reduction to patients
Biosimilars

Guidance documents available from FDA:


“The Purple Book”
Which of the following is/are usually associated with rheumatoid arthritis (versus osteoarthritis)? **Select all that apply**

A. Asymmetrical joint swelling  
B. Disease diagnosis later in life  
C. Swelling of small joints (hand, wrist)  
D. Abnormal ESR and CRP
TW is a previously healthy 25 year old female who presents with morning stiffness that persists for several hours, fatigue, and generalized muscle/joint pain for the past 4 months. Over the last month, her pain has limited her activity somewhat. PE reveals bilateral swelling, tenderness and warmth in the hands and feet. Home meds: none. Allergies: sulfa. Pertinent labs include: ESR 52 mm/hour (normal: 0-30 mm/hour), hemoglobin 10.6 g/dL, hematocrit 33%, positive anti-CCP, positive RF. An x-ray of the hands and feet shows soft tissue swelling and marginal erosions. Her disease activity is categorized as high.

Based on guidelines, which of following is the BEST initial treatment for this patient?

A. Methotrexate monotherapy  
B. Etanercept  
C. Methotrexate plus rituximab  
D. Hydroxychloroquine plus sulfasalazine
For the therapy initiated in the previous question, which of the following monitoring parameters are needed at baseline and periodically throughout therapy to assess for safety?

A. Pregnancy test, CBC, LFTs, eye exam
B. CBC, LFTs, renal function
C. Eye exam, pregnancy test, lipid panel
D. LFTs, lipid panel, CBC
Self-Assessment Questions
(3 of 4)

Which of the following should be taken with her RA treatment to help reduce side effects?

A. B12
B. Iron
C. Folic acid
D. Calcium
Which of the following vaccinations is **NOT** recommended, per guidelines, considering the patient’s new diagnosis (if vaccines are not up-to-date)?

A. Influenza  
B. Pneumococcal  
C. HPV  
D. Zoster
Self-assessment Question

Which of the following biologics does \textbf{NOT} have an approved biosimilar?

A. Etanercept  
B. Adalimumab  
C. Certolizumab  
D. Infliximab
Rheumatoid Arthritis Update

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