An update on the management of Rheumatoid Arthritis

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Disclosure/Conflict of Interest

I, Kristen Helms, have no actual or potential conflict of interest in relation to this program.
OBJECTIVES:

- Describe the epidemiology, pathophysiology, and presentation of Rheumatoid Arthritis (RA)
- Provide an appropriate treatment approach for RA as defined by the American College of Rheumatology
- Recognize the major benefits and risks associated with acute therapies and disease modifying therapies for RA
- Describe safety monitoring plan, including appropriate counseling, for patients being treated for RA
**Impact:**
- Affects 1% of the population in the US
  - 5% of women >65 years of age
- Accounts for 9 million medical visits annually
- 60% disability rate
- National cost $8.5 billion annually

**Risk Factors:**
- Females 3X more likely to develop RA
- Onset bimodal
  - Early adulthood (20-30s)
  - Late adulthood (>65)
- Caucasians > other races
- Family history
PATHO PHYSIOLOGY

**Symptoms**

**Osteoarthritis**
- Localized pain
- Often unilateral
- Hands, *knees*, hips, spine, feet (“DIPS, PIPS, and hips”)
- Morning stiffness < 20-30 min
- Pain with activity

**Rheumatoid Arthritis**
- Systemic symptoms
- Bilateral/symmetrical multiple joints
- PIP, MCP, and wrists
- Morning stiffness > 60-90 min
- Myalgia/ joint and soft tissue swelling
- Pain at rest
What do we mean by systemic symptoms?

- Cardiovascular disease and peripheral artery disease
- Pulmonary fibrosis and pleurisy
- Major organ fibrosis and damage (liver, kidneys, etc.)
- Sjogren’s syndrome
- Psoriasis/skin manifestations
Rheumatoid arthritis usually affects joints symmetrically (on both sides equally), may initially begin in a couple of joints only, and most frequently attacks the wrists, hands, elbows, shoulders, knees and ankles.
CLINICAL COURSE

**Stage I:** Asymptomatic, no evidence of joint damage
  - T-cells stimulation

**Stage II:** Asymptomatic, early synovitis
  - Inflammatory response: B-cell and T-cell proliferation, cytokine release, production of immunoglobulins (including RF)

**Stage III:** Pain, erythema, edema, joint stiffness
  - Movement of inflammatory mediators into joint fluid, synovial damage and proliferation

**Stage IV:** Worsening pain, edema, joint stiffness
  - Hyperproliferation of synovium, degradation of cartilage

**Stage V:** Joint pain, swelling, deformities
  - Further degradation of cartilage with exposure of subchondral bone
AMERICAN COLLEGE OF RHEUMATOLOGY
GUIDELINES 2015
(CHANGES TO ACR 2012)
JC is a 32 year old female who was diagnosed with Rheumatoid Arthritis 2 months ago. She has been experiencing symptoms, including stiffness, swelling, and limitations in range of movement in multiple joints including her hands, wrists, shoulders, and hips for 4 months. She is ESR positive and has evidence of joint erosions on X-ray. The rheumatologist tells you that she has “high” disease activity based on both the Patient Activity Scale (PAS) test and Clinical Disease Activity Index. To date, JC’s symptoms have been managed with a combination of scheduled NSAIDs and oral prednisone.

How should JC be appropriately managed at this time?
2012

1. Disease duration
   - <6 months
   - >6 months = “established disease”

2. Disease activity
   - Low vs Moderate vs High
   - Presence/absence of features of poor prognosis

2015

1. Disease duration
   - <6 months = “early disease”
   - >6 months = “established disease”

2. Disease activity
   - Low vs Moderate/High

Singh et al. Arthritis Care & Research 2015.
MEDICATIONS

- **DMARD (Disease Modifying Anti-Rheumatic Drugs)**
  - Methotrexate
  - Hydroxychloroquine
  - Leflunomide
  - Sulfasalazine
- **Oral synthetic small molecule**
  - Tofacitinib
- **Biologic DMARDs**
  - **TNFi Biologics:**
    - Adalimumab
    - Certolizumab pegol
    - Etanercept
    - Golimumab
    - Infliximab
  - **Non-TNFi Biologics:**
    - Abatacept
    - Rituximab
    - Tocilizumab
DRUG THERAPIES
### DMARDs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>ADRs</th>
</tr>
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<tbody>
<tr>
<td>Methotrexate (Rheumatrex)</td>
<td>2.5mg-10mg PO weekly</td>
<td>Hepatic toxicity</td>
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<tr>
<td></td>
<td></td>
<td>Pulmonary fibrosis</td>
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<td></td>
<td></td>
<td>Blood dyscrasias</td>
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<tr>
<td>Hydroxychlorquine (Plaquenil)</td>
<td>300 mg PO daily maintenance dose</td>
<td>Ocular toxicity</td>
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<tr>
<td></td>
<td></td>
<td>Hepatic toxicity</td>
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<tr>
<td></td>
<td></td>
<td>Blood dyscrasias</td>
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<tr>
<td>Leflunomide (Arava)</td>
<td>100 mg X 3 days then 20 mg PO daily</td>
<td>Hepatic toxicity</td>
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<tr>
<td></td>
<td></td>
<td>Myelosuppression</td>
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<tr>
<td></td>
<td></td>
<td>Blood dyscrasias</td>
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<tr>
<td>Sulfasalazine (Asulfidine)</td>
<td>0.5 to 2 grams PO daily in divided doses</td>
<td>Hepatic toxicity</td>
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<tr>
<td></td>
<td></td>
<td>Blood dyscrasias</td>
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<tr>
<td></td>
<td></td>
<td>Nausea/vomiting</td>
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**BILOGIC AGENTS**

**TNFα Inhibitors**
1. Adalimumab (Humira)
2. Etanercept (Enbrel)
3. Infliximab (Remicade)
4. Certolizumab pegol (Cimzia)
5. Golimumab (Simponi)

**Non TNF Agents**
1. Abatacept (Orencia)
   - Inhibits CD80/86 on T cells
2. Rituximab (Rituxan)
   - Depletes B cells
3. Tocilizumab (Actemra)
   - Interleukin 6 receptor antagonist
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>40 mg SC Q14 days</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>50 mg SC weekly or 25 mg SC twice weekly</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>3 mg/kg IV at week 0, 2, and 6, then Q8 weeks</td>
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<tr>
<td>Certolizumab pegol (Cimzia)</td>
<td>400 mg SC at week 0, 2, and 4, then 200 mg Q 2 weeks</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>50 mg SC monthly</td>
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</table>
**TNF-Alpha Inhibitors**

- **Class ADRs/concerns:**
  - Increased risk of malignancy in children/adolescents
  - Reactivation of latent TB
  - Demyelinating disorders
  - Heart failure onset or exacerbation
  - Antibody formation
  - Allergic reaction (monoclonal antibody)
  - Increased risk of infection
  - Blood dyscrasias

- **Specific agents:**
  - Administer MTX to minimize antibody formation
  - Pre-medicate with diphenhydramine/acetaminophen before infusions
**NON-TNF AGENTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept (Orencia)</td>
<td>Inhibits CD80/86 on T cells</td>
<td>Weight-based IV infusion Q2 weeks X 2 doses, then Q 4 weeks:</td>
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<tr>
<td></td>
<td></td>
<td>• 500 mg if &lt;60 kg</td>
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<td></td>
<td>• 750 mg if 60-100 kg</td>
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<tr>
<td></td>
<td></td>
<td>• 1000 mg if &gt;100 kg</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Depletes B cells</td>
<td>1000 mg IV Q2 weeks</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>Interleukin 6 receptor antagonist</td>
<td>4 mg/kg IV infusion of 1 hour Q4 weeks</td>
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</tbody>
</table>
**Non-TNF Agents**

- **Abatacept (Orencia)**
  - No significant renal or hepatic considerations
  - ADRs: Nausea (10%), antibody formation, infusion reactions, infections (up to 40%), malignancy
  - Precautions: increased risk of COPD exacerbations

- **Rituximab (Rituxan)**
  - No significant renal or hepatic considerations
  - Severe infusion reaction (77% first infusion, 14-30% subsequent)
    - Requires DC and immediate treatment for anaphylaxis.
    - May rechallenge at $\frac{1}{2}$ dose
  - Rare ADRs: Cardiac arrhythmias, blood dyscrasias, progressive multifocal leukoencephalopathy (PML)
NON-TNF AGENTS

- Tocilizumab (Actemra)
  - No significant renal or hepatic considerations
  - ADRs: Hypertension (4-6%), blood dyscrasias, increase in lipids, increase in AST/ALT (up to 40%), GI perforations
  - CI: Use in patients with ANC <2000/mm$^3$ or platelets <100,000/mm$^3$
TOFACITINIB

Mechanism:
- Janus kinase (JAK) inhibitor
- JAK modulates specific cytokines (IL-7, IL-15, IL-21, IL-6, and IFN alpha and beta)
- Inhibition interferes with transmission of extracellular information into the cell nucleus.

Dosing: 5-10 mg PO BID as monotherapy or in combination with non-biologic DMARDs

PK: CYP3A4 substrate, renally (30%) and hepatically cleared

Concerns: Potential increased risks of malignant lymphomas
AMERICAN COLLEGE OF RHEUMATOLOGY 2015
**Recommendations for INITIATING therapy in EARLY disease (<6 months):**

1. Regardless of disease activity, use a “treat-to-target” strategy rather than “non-targeted” approach.

2. If disease activity is **low** and patient is DMARD naïve,
   - Use DMARD monotherapy (MTX preferred) over double therapy and triple therapy

*Singh et al. Arthritis Care & Research 2015.*
3. If disease activity remains moderate or high despite DMARD monotherapy, use combination DMARDs OR a TNFi OR a non-TNFi biologic.
   - Use TNFi monotherapy over tofacitinib monotherapy
   - Use TNFi + MTX over tofacitinib + MTX
   - Add low dose glucocorticoids

4. If disease flares occur, add short-term glucocorticoids at the lowest possible dose for shortest possible duration.
Potential DMARD combination therapies:

- 2 DMARDS:
  - MTX + HCQ
  - MTX + LEF
  - MTX + SSZ
  - SSZ + HCQ

- 3 DMARDS:
  - MTX + HCQ + SSZ
2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Management of Early Disease

Singh et al. Arthritis Care & Research 2015.
Recommendations for INITIATING therapy in ESTABLISHED disease:

1. Regardless of disease activity, use a “treat-to-target” strategy rather than “non-targeted” approach.
2. If disease activity is low and patient is DMARD naïve:
   - Use DMARD monotherapy (MTX preferred) over TNFi
3. If disease flares occur, add short-term glucocorticoids at the lowest possible dose for shortest possible duration.
Recommendations for ONGOING therapy in ESTABLISHED disease:

1. If disease activity remains moderate or high despite DMARD monotherapy, use combination DMARDs OR a TNFi OR a non-TNF biologic OR tofacitinib.

2. If disease activity is or remains low:
   - Continue DMARD therapy
   - Continue TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medications

3. If the patient’s disease is in REMISSION, do NOT discontinue all RA therapies [VERY LOW EVIDENCE]

Singh et al. Arthritis Care & Research 2015.
Management of treatment naïve patient with established disease

Singh et al. Arthritis Care & Research 2015.
MANAGEMENT OF PATIENT WITH ESTABLISHED DISEASE REMAINING IN HIGH ACTIVITY DESPITE INITIAL TREATMENT

Singh et al. Arthritis Care & Research 2015.
Switching among biologic agents due to lack/loss of effect:

1. Lack/loss of benefit of TNFi biologic, recommend:
   - Switch to another TNFi agent +/- MTX
   - Switch to a non-TNF biologic +/- MTX
   - Both recommendations above over tofacitinib +/- MTX

2. Lack/loss of benefit of non-TNF biologic, recommend:
   - Switch to another non-TNF biologic +/- MTX
   - Both recommendations above over tofacitinib +/- MTX

Singh et al. Arthritis Care & Research 2015.
4. Lack of benefit of several sequential TNFi biologics, recommend:
   - Switch to a non-TNF biologic +/- MTX over another TNFi or tofacitinib +/- MTX
   - Switch to tofacitinib +/- MTX over another non-TNF

5. If disease activity remains moderate/high despite use of at least one TNFi and one non-TNF biologic:
   - Utilize another non-TNF biologic +/- MTX over tofacitinib
   - If still remains high, use tofacitinib.

Singh et al. Arthritis Care & Research 2015.
**OTHER KEY RECOMMENDATIONS**

**HEPATITIS:**

1. Patients with active Hepatitis B or C receiving/received treatment may utilize same treatment approach as patients without hepatitis.

2. Patients with active Hepatitis C not receiving treatment should receive a DMARD over a TNFi.

**MALIGNANCY:**

1. Previously treated or untreated skin cancer should use DMARDs over biologics or tofacitinib.

Singh et al. Arthritis Care & Research 2015.
OTHER KEY RECOMMENDATIONS

HEART FAILURE:

1. Patients with CHF NYHA class III or IV with an EF $\leq$ 50% should use combination DMARD therapy, a non-TNF biologic, OR tofacitinib OVER a TNFi

2. Guidelines do concede that there may be times where use of a TNFi in STABLE heart failure may be warranted

INFECTIONS (NEW to guidelines):

1. In patient with previous severe infections, use combination DMARDs over biologic

2. If biologic is required, use abatacept over TNFi

Singh et al. Arthritis Care & Research 2015.
OTHER KEY RECOMMENDATIONS: TB SCREENING

1. Screen all patients considered for therapy with biologic agents for Latent TB Infection

2. Initial screening should include tuberculin skin test (TST) or interferon-γ-release assays (IGRAs)
   - Negative TST or IGRA should be evaluated for risk factors
   - Negative TST or IGRA on immunosuppressives should repeat in 1-3 weeks
   - Positive TST of IGRA should receive chest X-ray to rule out active TB

3. Patients positive for active or latent TB should initiate TB treatment, and biologics may be initiated
   - After 1 month of therapy for LATENT TB
   - After completion of therapy for ACTIVE TB

4. Patients likely to have TB exposure should maintain screenings annually

Singh et al. Arthritis Care & Research 2015.
VACCINATIONS

PRIOR TO THERAPY
- Pneumococcal
- Influenza
- Hepatitis
- Human papillomavirus
- Herpes zoster

AFTER THERAPY INITIATION
- Pneumococcal
- Influenza
- Hepatitis
- Human papillomavirus
- Herpes zoster (NOT in patients receiving biologics)

Singh et al. Arthritis Care & Research 2015.
Case Study

- JC is a 32 year old female who was diagnosed with Rheumatoid Arthritis 2 months ago.
- She has been experiencing symptoms, including stiffness, swelling, and limitations in range of movement in multiple joints including her hands, wrists, shoulders, and hips for 4 months.
- She is ESR positive and has evidence of joint erosions on X-ray.
- The rheumatologist tells you that she has “high” disease activity based on both the Patient Activity Scale (PAS) test and Clinical Disease Activity Index.
- To date, JC’s symptoms have been managed with a combination of scheduled NSAIDs and oral prednisone.

How should JC be appropriately managed at this time?
GUIDELINES: CLINICAL CONTROVERSIES
GLUCOCORTICOIDS IN DISEASE MODIFICATION?

- What we know:
  - Glucocorticoids have both anti-inflammatory and disease-modifying properties
  - DMARD monotherapy compared to DMARD combination therapy have shown to be equally efficacious
  - DMARD monotherapy compared to DMARD combination + glucocorticoids shows greater benefit in the combination group
  - No clear studies comparing physiologic dosing (7.5-10 mg daily) to high doses
  - Long term use of glucocorticoids have significant risks
    - Hyperglycemia, osteoporosis, thinning of hair/skin, etc.

CLINICAL CONTROVERSIES

- Management of patients achieving remission
- What we know:
  - 66% of patients who achieve remission flare when medications are discontinued (compared to 33% who maintain therapy)
  - Once out of remission, achieving remission again was more difficult
  - There is significant risk with maintaining therapies (ADRs, toxicities)

- EULAR Guidelines: Recommend tapering corticosteroids first, then slowly tapering off biologic agents. Non-biologic DMARDs should be tapered last.

An update on the management of Rheumatoid Arthritis

Kristen Helms, PharmD
Associate Clinical Professor
You are a pharmacist working in a rheumatology clinic as part of a multi-disciplinary team. You are presented with a patient who has recently been diagnosed with RA. This patient is a 33 year old female who has had symptoms for RA for less than 6 months, has low disease activity. The physician decides to initiate methotrexate. Do you agree with this decision?

A. Yes. This patient is a candidate for monotherapy, and methotrexate has been shown to be relatively safe and efficacious compared to other agents.
B. No. This patient is a candidate for monotherapy; however, leflunomide has been shown to be superior to methotrexate in decreasing joint damage and improving quality of life.
C. No. This patient should be started on a combination of two non-biologic DMARDs.
D. No. This patient should be started on a combination of a non-biologic DMARD and biologic agent.
E. No. This patient is not yet a candidate for DMARD therapy.
GR is a 42 year old male with long-standing RA. He has high disease activity, multiple indicators of poor prognosis, and has had no response to 3 months of therapy with methotrexate + sulfasalazine. What is the best option for this patient?

A. Stop sulfasalazine and add leflunomide.
B. Stop methotrexate and add hydroxychloroquine
C. Stop sulfasalazine and add infliximab (Remicade)
D. Stop methotrexate and sulfasalazine and add infliximab (Remicade) and abatacept (Orencia)
E. Continue methotrexate + sulfasalazine for another 3 months before determining treatment failure
You have been working with a 77 year old female with RA who just started infliximab (Remicade) in addition to methotrexate for her long-standing arthritis. Since her dose this morning, she is complaining of significant itching and myalgia. She wants to know if this is normal and if there is anything she can do to prevent this. Your respond:

A. This is a normal reaction and will resolve after several doses.
B. This is a normal reaction and can be prevented by pre-medication with acetaminophen and diphenhydramine.
C. This is likely an early indicator of anaphylaxis, and she should not receive another dose.
D. This reaction indicates that her methotrexate dose needs to be increased to help prevent formation of antibodies.
E. This is likely a result of her infusion rate being too high and should be verified at her next visit.
A physician approaches you with a patient who has been in remission for 12 months with a combination of prednisone, methotrexate, and etanercept. The physician would like your thoughts on discontinuation of drug therapy. Which of the following would be the most appropriate approach?

A. Discontinue all drugs at this time without taper
B. Begin taper of all three drugs at this time
C. Begin by tapering the etanercept and prednisone. Once taper, methotrexate can be stopped without taper.
D. Begin by tapering the prednisone. Once tapered, the patient can discontinue both the etanercept and methotrexate with tapering.
E. Begin by tapering the prednisone. Once complete, the patient should continue etanercept and methotrexate.
What is the mechanism of tofacitinib?

A. Interleukin 2 inhibitor
B. B cell depletor
C. T cell inhibitor
D. TNF alpha inhibitor
E. JAK inhibitor