Pharmacotherapy Update in Rheumatoid Arthritis and Osteoarthritis

Rheumatoid Arthritis: The Good, The Bad, and The Ugly

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Objectives

- Summarize the role in therapy of disease-modifying antirheumatic drugs (DMARDs) including biologic agents, in the management of rheumatoid arthritis
- Identify similarities and differences among the available biologic disease-modifying antirheumatic drugs (DMARDs) used to treat patients with rheumatoid arthritis.

Rheumatoid Arthritis

- Distinctly different than osteoarthritis
- Affects 1% of the American population
  - 5.0% in women > 65 yrs
  - Female to male ratio is 3:1
  - Peak age of onset is between 20 and 50 years
- > 9 million medical visits annually:
  - National cost of RA > $8.5 billion
- 60% disability rate
- Increase risk of premature death primarily due to cardiovascular (CV) disease

Natural Course of Disease

Stage I: Presentation of unknown antigen to the T-cell; No symptoms

Stage II: Initiation and perpetuation of the inflammatory response; T- and B-cell proliferation, cytokine release; No symptoms

Stage III: Soluble mediators of inflammation and neutrophil infiltration into synovial fluid, synovial proliferation; Symptoms: joint pain/swelling, and morning stiffness

Stage IV: Radiographs show only juxta-articular osteoporosis; Symptoms - as in stage III

Stage V: Erosion of bone, distortion of the articular architecture; Radiographs reveal erosions and joint space narrowing; Symptoms – joint pain/swelling/instability

Clinical Presentation

- Insidious onset over several weeks to months
- Waxing and waning nature

Signs and Symptoms:
  - Systemic: fatigue, weakness, fever, ↓ appetite, myalgia
  - Syndromal: joint pain, stiffness, joint swelling, deformity

Joint involvement tends to be symmetrical
  - Most common: hands; wrists
  - Less common: elbows; knee; foot; ankle; spine
Diagnosis: ACR/EULAR Collaborative Initiative (2010)

- 'Definite RA' based on all of the following:
  - Synovitis in at least one joint with the absence of an alternative synovitis diagnosis
  - Total score of 6 or greater (of a possible 10) from the individual scores in four domains:
    • number and site of involved joints (range 0–5)
    • serological abnormality (range 0–3)
    • elevated acute-phase response (range 0–1)
    • symptom duration (two levels; range 0–1)

Goals of Therapy

- Ultimate goal is a complete remission
  - defined as the absence of:
    • (1) symptoms of active inflammatory joint pain,
    • (2) Morning stiffness,
    • (3) Fatigue,
    • (4) Synovitis on joint examination,
    • (5) Progressive radiographic damage,
    • (6) Elevated ESR or C-reactive protein
- Short of a complete remission:
  - control disease activity; pain relief; maintaining function essential for activities of daily living; maximizing QOL; and slowing the rate of joint destruction

Clinical Case

- Betty is 50-year-old woman who was just diagnosed with RA in 8 of her hand joints and in 8 feet joints. Her current pain is 4 out of 10 despite self-treatment with OTC naproxen 220 mg BID for the past 3 months, but her pain has not significantly improved.
- Her past medical history is significant for hypertension (treated with lisinopril 20 mg daily) and dyslipidemia (treated with dietary modifications).
- All of her recent laboratory tests are normal.

Pharmacotherapy for Rheumatoid Arthritis

- Disease modifying anti-rheumatic drugs (DMARDs)
  - Non-Biologic agents
  - Biologic agents
    - TNF-alpha blockers
    - Other biologic agents
- Corticosteroids
- Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Which of the following medications should be started to treat Betty's RA?

- Naproxen 500 mg BID
- Prednisone 10 mg daily
- Methotrexate 15 mg weekly
- Etanercept 50 mg once weekly
**Disease Modifying Anti-Rheumatic Drugs (DMARDs)**

- Essential treatment for patients with RA
- All patients are candidates for DMARD therapy
- Benefit:
  - Capable of reducing/preventing joint damage, preserve joint integrity/function
- Limitations:
  - may not prevent damage despite apparent control;
  - efficacy may not last long-term;
  - many agents have toxicities that require monitoring

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**Old Paradigm:**
Pyramid Approach to Rheumatoid Arthritis

- Radical Therapies
- 5th Level: Steroids
- 4th Level: Immunosuppressant’s
- 3rd Level: Penicillamine
- 2nd Level: Gold, Antimalarials, Methotrexate, Sulfasalazine
- 1st Level: Non-Steroidal Anti-inflammatory

Basic Therapy: Non-Pharmacological Modalities

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**Drug Therapy for RA:**
2002 ACR Guidelines

- DMARD within 3 months
- Consider NSAID
- Local or low-dose systemic steroids

If Inadequate Response

- Change or add DMARD

MTX Naive
- MTX Mono-therapy DMARD

Sub-optimal MTX
- MTX Combo DMARDs
- Other Monotherapy DMARD

Biologics
- Mono Therapy
- Combo Therapy

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**2008 ACR Guidelines**

Determination of non-Biologic and Biologic DMARD treatment

Three parameters are needed:
- Duration of Disease
- Assessment of Disease Activity
- Determination of Prognostic Factors

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**ACR Guidelines**

Determination of non-Biologic DMARD treatment :
- A: < 6 month duration

**ACR Guidelines**

Determination of non-Biologic DMARD treatment :
- B: 6-24 month duration

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ACR Guidelines

- Determination of non-Biologic DMARD treatment:
  - C: >24 month duration

Disease Activity

- Low or Moderate
- High

With Features of Poor Prognosis
- Without Features of Poor Prognosis

MTX+LEF
MTX+SSZ+HCQ
MTX
MTX+LEF
MTX+SSZ
MTX+HCQ
MTX+SSZ
MTX+HCQ

Methotrexate (MTX)

- Preferred first line DMARD, the “gold standard”:
  - ↓ signs/symptoms and structural damage; improves physical functioning
- CV disease mortality is lower in RA patients with methotrexate treatment
- GI intolerance is minimized by:
  - Splitting the weekly oral dose q 12 hours x 3
  - Supplemental folic acid 1 mg daily
  - Subcutaneous dosing instead of oral dosing
- Ethanol increases hepatotoxicity risk
- Routine laboratory monitoring is essential

Role of Cytokines in RA

Up-regulated cytokines in RA

Endogenous IL-1 receptor antagonist

Bone resorption

Biologic DMARDs in RA

- Significant innovations in therapy
  - ↓ signs/symptoms and ↓ bone erosion
- For moderate/severely active RA in those who have failed ≥1 DMARD(s)
- Generally in combination with another DMARDs, but never another biologic
- Typical annual cost is $10,000 to $30,000 (methotrexate is ~$1500)
- Approximate time to benefit is 1 to 3 weeks
### TNF-alpha Blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Role</th>
<th>Adult RA DOSAGE</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Soluble recombinant human TNF-α receptor protein that binds and neutralizes TNF-α</td>
<td>Moderate/severely active RA</td>
<td>50 mg SQ QW</td>
<td>Potential sepsis, injection site reaction, rash, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Monoclonal (murine) antibody to TNF-α</td>
<td>Moderate/severely active RA</td>
<td>3 mg/kg i.v. at 0, 2, 6 wks then q 8 wks</td>
<td>Potential sepsis, infusion reactions, antibody development, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Monoclonal (human) antibody to TNF-α</td>
<td>Moderate/severely active RA</td>
<td>40 mg SQ QOW</td>
<td>Potential sepsis, injection site reaction, rash, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Pegylated monoclonal antibody to TNF-α (does not have Fc region) to TNF-α</td>
<td>Moderate/severely active RA</td>
<td>400 mg SQ at 0, 2, 4 wks</td>
<td>Potential sepsis, injection site reaction, worsening or new onset heart failure</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Monoclonal (human) antibody to TNF-α</td>
<td>Moderate/severely active RA</td>
<td>50 mg SQ once monthly</td>
<td>Potential sepsis, injection site reaction, worsening or new onset heart failure</td>
</tr>
</tbody>
</table>

### Etanercept (Enbrel®)

**Soluble recombinant human TNF-α receptor protein that binds and neutralizes TNF**
- Approved for moderate/severely active RA:
  - Can be used with or without methotrexate
  - Also approved in juvenile RA, ankylosing spondylitis, psoriasis, psoriatic arthritis
- Dosing: 50 mg SQ QW
- Adverse effects: Potential sepsis, injection site reaction, rash, worsening or new onset heart failure

### Infliximab (Remicade®)

**Monoclonal (murine) antibody to TNF-α**
- Approved for active RA
  - Only for use in combination with methotrexate
  - Also approved in ankylosing spondylitis, Crohn disease, psoriasis, psoriatic arthritis, ulcerative colitis
- Dosing: 3 mg/kg i.v. at 0, 2, 6 wks then q 8 wks; 2-hr administration
- Adverse effects: Potential sepsis, infusion reactions, antibody development, worsening or new onset heart failure
- Contraindicated in moderate/severe heart failure, active infection, known murine allergy

### Adalimumab (Humira®)

**Monoclonal (human) antibody to TNF-α**
- Approved for moderate/severe active RA in patients with an inadequate response to one or more DMARDs
  - Can be used with or without another DMARD
  - Also approved in ankylosing spondylitis, Crohn disease, psoriasis, psoriatic arthritis
- Dosing: 40 mg SQ QOW (QW if monotherapy)
- Adverse effects: Potential sepsis, injection site reaction, antibody development, worsening or new onset heart failure

### Certolizumab pegol (Cimzia®)

**Pegylated monoclonal antibody (does not have Fc region) to TNF-α**
- Approved for moderate/severe active RA in patients with an inadequate response to one or more DMARDs
  - Can be used with or without another DMARD
  - Also approved in Crohn disease
- Dosing: 400 mg SQ at 0, 2, 4 wks, then 200 mg q 2 wks or 400 mg q 4 wks
- Adverse effects: Potential sepsis, injection site reaction, worsening or new onset heart failure

### Golimumab (Simponi)

**Monoclonal (human) antibody to TNF-α (both soluble and transmembrane active)**
- Approved for moderate/severe active RA in patients with an inadequate response to one or more DMARDs
  - Only for use in combination with methotrexate
  - Also approved in ankylosing spondylitis, psoriatic arthritis
- Dosing: 50 mg SQ once monthly
- Adverse effects: Potential sepsis, injection site reaction, worsening or new onset heart failure
### Pharmacotherapy Update in Rheumatoid Arthritis and Osteoarthritis

**Other Biologic DMARDs**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Role in RA Management</th>
<th>Adult RA Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anakinra (Kineret®)</strong></td>
<td>Recombinant human IL-1 receptor antagonist</td>
<td>Monoclonal receptor antagonist</td>
<td>100 mg SQ daily</td>
<td>Potential sepsis, injection site reaction, rash, leukoencephalopathy, hepatitis</td>
</tr>
<tr>
<td><strong>Abatacept (Orencia®)</strong></td>
<td>Decreases production of several cytokines (TNF-α, IL-2, interferon-γ) by inhibiting T-cell activation</td>
<td>Monoclonal receptor antagonist</td>
<td>4 mg/kg i.v. q 4 wk; may increase to 8 mg/kg if needed</td>
<td>Adverse effects: potential sepsis, infusion reactions</td>
</tr>
<tr>
<td><strong>Rituximab (Rituxan®)</strong></td>
<td>Monoclonal antibody that depletes CD20 B-cells</td>
<td>Monoclonal antibody that depletes CD20 B-cells</td>
<td>375 mg i.v. 2 doses separated by 2 wks, then q16-24 wks; may repeat course q16-24 wk; methylprednisolone 100 mg i.v. 30 min prior to reduce infusion reactions</td>
<td>Adverse effects: mucocutaneous reactions, hepatitis B reactivation, cardiac arrhythmias, progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td><strong>Tocilizumab (Actemra®)</strong></td>
<td>Anti-TNF and MTX receptor inhibitor</td>
<td>Active RA after an inadequate response to ≥1 TNF antagonants</td>
<td>125 mg SQ daily</td>
<td>Adverse effects: neutropenia, thrombocytopenia, dyslipidemia, hepatotoxicity</td>
</tr>
</tbody>
</table>

**Anakinra (Kineret®)**

- **Recombinant human IL-1 receptor antagonist**
  - Approved for moderate/severe active RA in patients who have failed one or more DMARDs
  - Can be used with or without another DMARD
  - Dosing: 100 mg SQ daily
  - Adverse effects: Potential sepsis, injection site reaction, rash
  - Contraindicated if known hypersensitivity to *e.coli* derived proteins

**Abatacept (Orencia®)**

- **Decreases production of several cytokines (TNF-α, IL-2, interferon-γ) by inhibiting T-cell activation**
  - Approved for moderate/severe active RA after an inadequate response to ≥1 DMARD(s), such as methotrexate or TNF antagonists
  - Also approved for certain lymphomas and leukemias
  - Dosing: 500–1000 mg i.v., then:
    - Second i.v. dose in 2-4 wks then q 4 wks, or
    - 125 mg SQ within 1 day then once weekly
  - Adverse effects: potential sepsis, infusion reactions

**Rituximab (Rituxan®)**

- **Monoclonal antibody that depletes CD20 B-cells**
  - Approved for moderate/severe active RA after an inadequate response to ≥1 TNF antagonists
  - Must be used in combination with methotrexate
  - Also approved for certain cancers (lymphoma, leukemia)
  - Dosing: 1000 mg i.v. 2 doses separated by 2 wks, may repeat course q16-24 wk; methylprednisolone 100 mg i.v. 30 min prior to reduce infusion reactions
  - Adverse effects: severe infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hepatitis B reactivation, cardiac arrhythmias, progressive multifocal leukoencephalopathy

**Tocilizumab (Actemra®)**

- **Monoclonal antibody that inhibits the interleukin-6 receptor**
  - Approved for moderate/severe active RA after an inadequate response to ≥1 TNF antagonists
  - Also approved for certain lymphomas and leukemias
  - Dosing: 4 mg/kg i.v. q 4 wk; may increase to 8 mg/kg if needed
  - Adverse effects: Neutropenia, thrombocytopenia, dyslipidemia, hepatotoxicity

**ACR Guidelines**

- **Determination of Biologic DMARD treatment:**
  - A: < 6 month duration
  - Low or Moderate Activity
  - High for < 3 months
  - High for ≥ 3 months
  - Disease Progression
  - Features of Poor Prognosis

See Figure 2A: Non-Biologic DMARDs

**Cost or Insurance Coverage Limitations**

- Anti-TNF and MTX
- Without
- See Figure 2A: Non-Biologic DMARDs

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ACR Guidelines

- Determination of Biologic DMARD treatment:
  - B: ≥ 6 month duration but failed MTX
  - C: ≥ 6 mo. duration but failed MTX or other non-biologics

ACR Position Statement:
New Agents for Arthritis, “Biologics”

- Very effective and offer the possibility of controlling rheumatic diseases to an extent not previously possible.
- Production is significantly more complicated than our previous treatments and their cost is significantly higher.
- Attempts to restrict use by guidelines/criteria that are outside the patient-physician relationship should be discouraged; cost based substitutions are inappropriate.
- Third party payers should not attempt to mandate the use of one agent over another based on population-based studies nor predetermined algorithms.

Clinical Case, cont...

- After 3 years of methotrexate therapy, Betty's pain is overall well controlled with 20 mg once weekly. Her other RA medications are folic acid, prednisone 10 mg daily, and ibuprofen 800 mg TID prn.
- All of her regularly monitored blood tests (CBC, LFTs, serum chemistries) are normal.
- She has routine X-rays of her hands. They show increased erosion of her affected joints compared to a year prior.

Which of the following is the most appropriate change to Betty's regimen?

1. Increase methotrexate to 30 mg weekly
2. Add adalimumab
3. Replace methotrexate with rituximab
4. No change; re-evaluate in 6 months

Post-Marketing Information Regarding Biologic Agents

- Infections and/or sepsis:
  - Temporarily stop if infection develops
  - Use with caution in immunosuppressed patients
- Can activate tuberculosis (TB):
  - PPD skin test prior to therapy
  - If positive, treat latent TB infection first
- Heart Failure with TNF-α blockers
FDA Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria

**Additional Information for Healthcare Professionals**

- Patients treated with TNFα blockers are at increased risk for developing serious infections involving multiple organ systems and sites that may lead to hospitalization or death due to bacterial, mycobacterial, fungal, viral, parasitic, and other opportunistic pathogens.
- The bacterial pathogens Legionella and Listeria have been added to the Boxed Warning for the entire class of TNFα blockers.
- The risks and the benefits of TNFα blockers should be considered prior to initiating therapy in patients with chronic or recurrent infection and patients with underlying conditions that may predispose them to infection.
- Patients greater than 65 years old and patients taking concomitant immunosuppressants may be at greater risk of infection.
- Prior to initiating TNFα blockers and periodically during treatment, patients should be evaluated for active tuberculosis and tested for latent infection.
- Patients should be monitored for signs and symptoms of serious infections while taking TNFα blockers.
- Empiric antifungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Healthcare professionals should encourage patients to read the Medication Guide that accompanies their prescription for a TNFα blocker.

**Other therapies for RA**

**NSAIDs**
- For symptomatic pain management of RA, but not the sole treatment
- Analgesic/anti-inflammatory effects only; will not prevent joint destruction
- Adverse effects are concerning
- High doses typically needed

**Corticosteroids**
- “Burst” therapy for acute exacerbations
- Maintenance therapy for active disease despite NSAIDs and after trial(s) of DMARDs; Joint damage may progress despite symptom control
- Bridging agent for symptom control after starting a new DMARD

**Clinical Case, cont…**

- Many years later, Betty’s RA is now treated with methotrexate 15 orally mg weekly, folic acid 5 mg once a week (separated from her methotrexate), adalimumab 40 mg SC every other week, prednisone 5 mg daily.
- Her past medical history still includes hypertension and dyslipidemia, but she had an MI last year.
- Her other medications are alendronate 70 mg weekly, calcium/vitamin D, lisinopril 40 mg daily, metoprolol 50 mg daily, aspirin 81 mg daily.

**Which of the following is the most appropriate recommendation to reduce Betty’s CV risk?**

1. Add simvastatin
2. Discontinue methotrexate
3. Increase the prednisone dose

**Cardiovascular Risk in RA**

**Expert Recommendations:**
- RA may be an independent CV risk factor, persistent inflammation is an additional risk factor;
- In patients requiring glucocorticoid therapy, use of the minimal effective dose to minimize CV risk;
- Methotrexate may protect against CV mortality;
- TNF-α antagonists are contraindicated in patients with RA and severe heart failure;
- Achieve recommended LDL-cholesterol goals;
- Consider statin therapy when needed;
- When aspirin is used, concomitant NSAID therapy may decrease antplatelet effects and increase GI side effects

**Conclusions**

- RA is a chronic, typically progressive, symptomatic inflammatory disease and diagnostic criteria have changed
- ACR guidelines recommend DMARDs for all patients with RA, particularly MTX as first-line
- Biologic agents are very effective agents in the treatment of RA, especially after MTX therapy, and TNF-blocking agents are the first biologic DMARDs of choice