Update on Treatment of Rheumatic Disease

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Faculty Disclosure

• Donald Miller reports he does not have actual or potential conflicts of interest associated with this presentation.

• Donald Miller has indicated that off-label use of medication will be discussed during this presentation.
Upon completion of this activity, pharmacists (or pharmacy technicians/student pharmacists) should be able to:

1. Explain how and why rheumatologists use aggressive treatment goals in managing rheumatic disease patients
2. Describe the pharmacology of JAK inhibitors, TNF-alpha inhibitors and newer biologic treatments
3. Choose a drug regimen appropriate for a rheumatic disease patient, based on safety and efficacy
4. Describe appropriate monitoring parameters for new drug and biological therapies
5. Evaluate the drug therapies as to their appropriateness for individual patients
A disease-modifying drug should be started immediately after a diagnosis of rheumatoid arthritis because such treatment will:
A. reduce symptoms within days
B. prevent long term joint damage
C. induce permanent remission in 80% of patients
D. eliminate a need for early corticosteroid therapy
A 30 year old female is newly diagnosed with mildly active rheumatoid arthritis. She is started on naproxen 250 mg twice daily and prednisone 5 mg daily. Her physician also wants to start her on a disease-modifying drug but the patient notes that she is leaving in less than one month for a 9 week dream trip across Europe with her husband. Since follow-up medical care could be problematic, which DMARD is the best choice for her at this time?

A. methotrexate
B. tofacitinib
C. infliximab
D. hydroxychloroquine
Rheumatoid Arthritis Epidemiology

- The most common inflammatory joint disease in the United States, rheumatoid arthritis (RA) affects an estimated 2.1 million Americans, or almost 1% of the population.
- This autoimmune disease, affecting women twice as often as men, is a chronic debilitating disease with the potential to cause substantial loss of function due to pain and joint destruction. It can affect people of any age, including children.
Pathogenesis of Rheumatoid Arthritis

NORMAL

Synovial membrane

RHEUMATOID ARTHRITIS

Synovial inflammation and angiogenesis

Erosion of bone and cartilage at the site of pannus

Pannus

Primary dysfunction of articular cartilage

Exudation of inflammatory cells

Synovial fluid

Capsule

Cartilage
Clinical Presentation of RA

Key Presenting Signs and Symptoms

- Joint pain
- Symmetric swelling of small peripheral joints
- Morning joint stiffness of prolonged duration
Rheumatoid Arthritis: Swollen Fingers

Photo: Copyright © American College of Rheumatology
Progression of RA

# Clinical Presentation of RA

**Signs & Symptoms**

<table>
<thead>
<tr>
<th>Articular</th>
<th>Systemic</th>
<th>Extra-Articular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain and Tenderness</td>
<td>Fever, Weight Loss, Fatigue</td>
<td>Rheumatoid Nodules</td>
</tr>
<tr>
<td>Morning Stiffness &gt; 30 Minutes</td>
<td>Depression</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Joint Swelling</td>
<td>Anemia</td>
<td>Pulmonary Fibrosis</td>
</tr>
<tr>
<td>Polyarticular, Symmetrical</td>
<td></td>
<td>Ocular Disease (Sicca, Episcleritis)</td>
</tr>
<tr>
<td>Limitation of Motion</td>
<td></td>
<td>Carditis, Pericarditis</td>
</tr>
<tr>
<td>Joint Deformity</td>
<td></td>
<td>Xerostomia</td>
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</tbody>
</table>
Joint Erosions Occur Early in RA

- Up to 93% of patients with <2 years of RA have radiographic abnormalities\(^1\)
- Erosions can be detected by MRI within 4 months of RA onset\(^2\)
- Rate of progression is significantly more rapid in the first year than in the second and third years\(^3\)

Mortality Rate Higher in RA Patients

RA Diagnosed in Rochester, Minn, 1955-1994

Expected

Observed

p < 0.001

Years After RA Diagnosis

Survival (%)

Why Are Early Diagnosis and Treatment of RA So Important?

- Irreversible joint damage occurs early in RA.
- Early diagnosis permits early referral to specialist care and early disease-modifying drug (DMARD) treatment.
- Early, aggressive DMARD treatment\(^1\)
  - Reduces symptoms and may induce remission
  - Reduces joint damage and later disability
  - Improves quality of life
  - May lower mortality risk\(^2\)

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New criteria published in 2010 rate patients on a scale of 0-10 points, with points assigned in four domains of signs and symptoms: joint involvement (number and type), serology (rheumatoid factor or anti-CCP antibodies), duration of symptoms, (> 6 weeks), and acute phase reactants (ESR or CRP elevation).

Patients who tally 6 or more points are considered to have RA. These criteria were set up to allow many patients to be classified with RA earlier in the disease process and consequently get treatment sooner (Arthritis Rheum 2010;62(9):2569-81).
Principles of RA Treatment

- American College of Rheumatology guidelines stress starting disease-modifying drugs in all patients with a diagnosis of RA [Arthritis Care and Research 2012;64(5):625-39] with remission as the target.
- Waiting for joint damage to occur before aggressive treatment has been likened to waiting for cancer to metastasize before treating it. Furthermore, the window of opportunity to reset the rate of disease progression may be quite short.
- RA is not a benign disease. Significant morbidity and mortality occur.
Early Treatment Reduces Disability 5 Years Later

Delay to Start of DMARD/Steroid Treatment

<table>
<thead>
<tr>
<th>Delay to Start</th>
<th>Degree of Disability* after 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>0.9 (n=60)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>2.4 (n=47)</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>2.3 (n=76)</td>
</tr>
</tbody>
</table>

* Odds ratio of HAQ ≥ 1

Principles of RA Treatment

• NSAIDs relieve symptoms but do not affect disease progress; in addition, they are dangerous drugs with significant adverse effects (GI, renal, cardiovascular).

• RA is most sensitive to DMARD treatment, and any DMARD is most likely to be effective, early in the disease.

• The most important principle for disease control is not which drugs are used but the intensity of treatment.
Obstacles to Treating RA

- Inability to make an early diagnosis
- Disease heterogeneity
- Limited ability to recognize those at highest risk
- Patients may fear aggressive therapy
- Lack of rheumatologists
Early DMARD Treatment Improves RA Outcome

• Reduces clinical signs and symptoms of RA
  o Fewer swollen, tender joints
  o Improved ESR, CRP, RF
  o Slowed radiographic progression

• Improves patient function
  o Early morning stiffness
  o Grip strength
  o Patient’s global assessment

• Reduces excess mortality

The number one goal in RA is rapid and sustained suppression of inflammation in order to prevent joint damage and induce remission (i.e. the absence of signs and symptoms) or at least very low disease activity. RA is not curable but is treatable, much like any other chronic disease.

There is substantial evidence that early start with DMARDs (and DMARD combinations) is beneficial in retarding clinical and radiographic progression compared to a delayed, watchful waiting approach. Consequently, early and consistent use of DMARDs in most patients is appropriate.

Quick referral by pharmacists of possible RA patients is essential, as a delay of even 3 months with DMARD treatment has been shown to affect outcomes.

Rapid referral to a rheumatologist advised with clinical suspicion of RA, which may be supported by the presence of the following:

- ≥3 swollen joints
- MTP/MCP involvement
- Morning stiffness ≥30 minutes

Early Treatment of RA

- There is considerable evidence that “tight control” of RA activity (and other inflammatory arthritis), much like tight control of blood sugar or lipids, is beneficial in preventing later disease complications and in achieving a durable remission.

- The BeSt study was a multicenter randomized comparison of 4 strategies for initial RA treatment. It found that initial combination therapy which included either prednisone or infliximab resulted in earlier functional improvement than starting with methotrexate monotherapy, and then adding or changing DMARDs as needed. However, at 2 years follow-up, aggressive control in each group allowed all groups to do equally well.

- The TEAR study in 2012 found that 28% of patients with early but aggressive RA responded well to methotrexate alone. Further, an initial combination of methotrexate/sulfasalazine/hydroxychloroquine was as good as methotrexate/etanercept. At 2 years, initial combination therapy did not produce better outcomes than initial monotherapy, although combinations produced a faster response.

ACR Guidelines for RA

- Recommend methotrexate or leflunomide as first choice DMARDs for all patients; hydroxychloroquine or minocycline are suitable for recent onset disease of mild severity, and sulfasalazine is also suitable for patients without a poor prognosis.

- Monotherapy with a DMARD is sufficient for most patients with early RA. Combination DMARD therapy or TNF inhibitors (with or without methotrexate) are recommended for new patients with high disease activity and poor prognostic features and in any patient with persistent disease despite sequential DMARD therapy.

- Three months is required to see benefit; after 3 months with little improvement therapy should be changed or drugs added.

Arthritis Care and Research 2012;64(5):625-39
General Strategies

- Step up (start with one DMARD, then switch and add as needed)
- Step down (combination treatment immediately, then taper as symptoms are controlled).
- Choice of strategy and drug(s) depend on disease activity, physician and patient preference, plus risk for adverse effects.
- In either case, must monitor every 3 months, using a disease-activity score, with aim of symptom remission.
- In the future, various biomarkers (e.g. c-reactive protein, interleukin-6, vascular cell adhesion molecule-1), in addition to early joint erosion, may help to guide aggressiveness and choice of drug.
• Relatively rapid onset of action (3 to 6 weeks)
• Flexible dose (7.5 to 25 mg/week po)
  o Current trend to start at higher doses, such as 15 mg/week
• Flexible dosage forms (oral tabs, s.c or IM injection)
  o New single-dose auto-injector available (Otrexup)
• Toxicity reduced with folate supplements (1 mg/day)
• Good efficacy. Current treatment standard and basis for most DMARD combinations
• Monitor CBC, liver transaminases, serum chemistries monthly for 2-3 months, then every 8-12 weeks.
Hydroxychloroquine (Plaquinil) may be the best tolerated DMARD
- Dose 200 mg bid, can be adjusted for weight (< 6.5 mg/kg/day)
- Efficacy less than most other DMARDs
- Good choice in mild, early disease or in combination with other drugs
- DMARD action takes several weeks
- Must monitor for retinal toxicity – risk increases only after 7 years
- No blood testing needed.
LEFLUNOMIDE

- Efficacy similar to methotrexate in short term studies, takes several weeks for effect
- Inhibits pyrimidine synthesis by inhibiting dihydroorotate synthetase
- 100 mg/day x 3 days loading dose (due to long half-life), then 20 mg/day
- ADRs: alopecia, diarrhea, nausea, rash, hepatotoxicity, teratogenic (cholestyramine washout needed)
- Monitor CBC and chemistry monthly at first, then every 2-3 months.
SULFASALAZINE

- Has a long history of use in Europe for RA and spondylarthropathies
- 500 mg qid; start at 500 mg bid
- Good efficacy – in short term comparable to methotrexate in some studies, but less effective over 5 year follow-up\(^1\).
- Again slow acting
- Numerous ADRS: nausea, headache, skin rashes, blood dyscrasias, male infertility
- Monitor CBC and chemistry monthly x 3 months, then every 3 months.

Tofacitinib

- An oral inhibitor of the Janus kinase (JAK) family of tyrosine kinases (JAK2, JAK3 and TYK2) found in lymphocytes and macrophages. JAK kinases are key intracellular mediators of cytokine signaling.
- Data suggest good responses to tofacitinib in RA patients through 24 weeks, though with a fairly high frequency of side effects, including infections, elevated LDL levels and neutropenia.
- Poised as an oral alternative to biologics, but its true place in therapy will take some time to establish.
Expected Effects of Targeting Cytokine Signaling Pathways with the Use of a JAK1 and JAK2 Inhibitor.

A

FERM domain

SH2

Pseudokinase domain

Kinase domain

Carboxyl terminus

JH7

JH6

JH5

JH4

JH3

V617F mutation

JH2

JH1

B

Receptors for:

Interleukins 3, 5, 12, and 23

G-CSF

OSM

LIF

Receptors for:

Erythropoietin

Thrombopoietin

G-CSF

Growth hormone

Prolactin

Receptors for:

Interferon

Interleukins 10, 19, 20, 22, 24, 28, and 29

γc subunit

Receptors for:

Interleukins 2, 4, 7, 9, 15, and 21

Phosphorylated STAT

Immune response

Proliferation

Apoptosis

Angiogenesis

Inflammation

JAK2

JAK2

JAK2

JAK2

JAK1

JAK2

JAK1

JAK2

JAK1

JAK1

JAK3

Phosphate

STAT

Tofacitinib

- Dosage is 5 mg oral twice daily, without regard to food. May be used with other DMARDS but not biologics, azathioprine, tacrolimus or cyclosporine.
- It also provides a response (with/without methotrexate) in 40 to 50% of patients who have failed a TNF inhibitor.
- Moderate to severe renal or hepatic impairment – reduce to 5 mg/day.
- Monitor CBC (hemoglobin, lymphocytes, neutrophils, platelets), lipids, liver transaminases monthly at first.
- Obtain pretreatment TB test.
- Potential to increase malignancies.
# Biologics - TNF Antagonists

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Administration</th>
<th>Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade®</td>
<td>Antibody to TNF-alpha</td>
<td>IV, every few weeks</td>
<td>RA, Crohn’s, AS, psoriatic</td>
</tr>
<tr>
<td>(infliximab)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enbrel®</td>
<td>Protein that binds with TBF molecule</td>
<td>Subcutaneous, weekly</td>
<td>RA, children, psoriatic, AS</td>
</tr>
<tr>
<td>(etanercept)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humira®</td>
<td>Humanized antibody to TNF-alpha</td>
<td>Subcutaneous, every other week</td>
<td>RA, AS, children, psoriatic, UC, Crohn’s</td>
</tr>
<tr>
<td>(adalimumab)</td>
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<td></td>
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</tbody>
</table>

AS = Ankylosing spondylitis, RA = rheumatoid arthritis, Crohn’s = Crohn’s disease, Psoriatic = psoriasis and psoriatic arthritis, UC = ulcerative colitis
# TNF Antagonists (continued)

<table>
<thead>
<tr>
<th>Therapy</th>
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<th>Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cimzia®</strong></td>
<td>PEGylated Fab fragment of a humanized TNF-alpha antibody</td>
<td>Subcutaneous, every 2-4 weeks</td>
<td>RA, AS, psoriatic, Crohn’s</td>
</tr>
<tr>
<td>(certolizumab pegol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Simponi®</strong></td>
<td>Humanized anti-TNF antibody</td>
<td>Subcutaneous or IV, once monthly</td>
<td>RA, psoriatic, AS</td>
</tr>
<tr>
<td>(golimumumab)</td>
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AS = Ankylosing spondylitis, RA = rheumatoid arthritis, Crohn’s = Crohn’s disease, Psoriatic = psoriasis and psoriatic arthritis
TNF Antagonists

- Clinical response may begin within 2 weeks, but still can take 3 months for full trial.
- Approved for use in early as well as late RA
- All are very expensive, running about $25,000/year and up. In unselected patients their efficacy is no better than methotrexate alone, so MTX remains the best choice for initial monotherapy. Combinations of MTX and TNF inhibitors are superior to either alone.
- No direct comparisons exist, and the 5 TNF inhibitors seem to have roughly equal efficacy to each other. Infliximab and adalimumab permit dose escalation if poor initial response. Etanercept and Humira most commonly used.
There is quite a bit of observational evidence that patients who fail with, or who initially respond to one TNF inhibitor but relapse (or have ADRs) may respond to a second TNF inhibitor. The reason is not clear but could be related to pharmacokinetic profile, antibody formation to the original drug, or ancillary effects of the drugs.

Long term response is excellent - only about 30% of initial responders will discontinue over 5 years follow-up. Long term data are available for up to 10 years continuous use.

If the drugs are stopped in well controlled patients, some patients stay under control for 6 to 12 months (mostly patients with milder, early-treated disease), while others relapse fairly quickly, within a month or two. Thus, continued maintenance treatment is usually necessary.
# Other Biologicals for RA

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Administration</th>
<th>Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kineret</strong> ® (anakinra)</td>
<td>Blocks interleukin-1</td>
<td>Subcutaneous, daily</td>
<td>RA</td>
</tr>
<tr>
<td><strong>Orencia</strong> ® (abatacept)</td>
<td>Blocks T cell stimulation</td>
<td>IV, every 2-4 weeks or s.c weekly</td>
<td>RA, children</td>
</tr>
<tr>
<td><strong>Rituxan</strong> ® (rituximab)</td>
<td>Antibody to B cells</td>
<td>IV, 2 infusions every 6 months</td>
<td>RA, lymphoma, CLL</td>
</tr>
<tr>
<td><strong>Actemra</strong> ® (tocilizumab)</td>
<td>Antibody to interleukin-6 receptor</td>
<td>IV, every 4 weeks</td>
<td>RA, children</td>
</tr>
</tbody>
</table>
Treatment Resistant Patients

- It is unclear what approach is optimal in patients with mild to moderate disease activity despite methotrexate (or other DMARD) therapy, and physician judgment plus patient preference should be considered.

- Typically, if MTX or other DMARD is well tolerated despite less than optimal response, the DMARD is continued when a biological is added. There are very few trials that compare different options for active disease despite initial DMARD/biological therapy, but two studies have shown that a combination of methotrexate/sulfasalazine/hydroxychloroquine is almost equal to adding etanercept to methotrexate.¹,²

Treatment Resistant Patients

• If a patient initially fails a TNF inhibitor there is still a reasonable chance (~40%) of good response to a different TNF inhibitor. Some but not all comparative studies show a slightly better chance of response to a different class of drug, especially in sicker patients.

• Patients who have failed a second-line biologic (abatacept, tocilizumab, rituximab) could be switched to any biologic or DMARD (or DMARD combination) not previously tried. There is no specific algorithm.
Additional Issues in RA

- Studies have shown about half of patients become noncompliant with DMARD/biological therapy for various reasons by 2 years, so it is important not to take compliance for granted, and to ask patients about concerns or barriers to continued treatment.
- Attention should also be given to preventing or treating common medical complications including infection, osteoporosis, and cardiovascular disease.
- If complete remission occurs, maintenance DMARD therapy is usually continued (NSAIDS/steroids are not needed). Patients brought into complete remission after early treatment have a reasonable chance of going drug free after a year or two of remission, but most patients will need some kind of maintenance drug treatment.
Belimumumab (Benlysta) for SLE

- A human antibody that binds to soluble B-lymphocyte stimulator (BlyS), thus preventing B cells from maturing. Approved for active, adult SLE. However, not studied in patients with severe lupus nephritis or severe CNS involvement.
- Overall efficacy fairly modest and was not effective in African Americans (although only small number of black patients were included in trials).
- Not associated with increased risk of infection or malignancy to date. Depression and hypersensitivity reactions have been reported as adverse effects.
- Given IV over 1 hour at 10 mg/kg every 2 weeks for three doses, then every 4 weeks.
Ustekinumab (Stelara) for Psoriatic Arthritis

- An inhibitor of interleukin 12 and 23, previously approved for psoriasis.
- Approved for treatment of active psoriatic arthritis not responding to previous therapy.
- Administered by 45 mg s.c. injection at week 0 and 4, then every 12 weeks thereafter.
- Adverse effects include risk of infection, including upper respiratory infections, diarrhea, headache and fatigue.
- TNF inhibitors are better established for psoriatic arthritis.
Apremilast (Otezla) for Psoriatic Arthritis

- One of a new class of selective oral phosphodiesterase-4 inhibitors that increase cyclic adenosine monophosphate (cGMP) in monocytes and macrophages (similar to roflumilast for COPD) and reduce expression of TNF.
- Just approved by FDA on March 21 at a dosage of 30 mg bid.
- Efficacy appears less than TNF inhibitors so may be best for patients with milder psoriatic arthritis.
- Diarrhea, nausea, abdominal pain and headache are frequent side effects (gradually increase dose over 1 week). Depression and weight loss also potential concerns.
- Approval also being sought for psoriasis and for ankylosing spondylitis.
Axial Spondyloarthritis (axSpA)

- **Spectrum of inflammatory diseases of the spine**
  - Ranges from mild (only detectable on MRI), self-limited inflammation to bony destruction of the spine
  - Includes patients with *ankylosing spondylitis (AS)* but also milder axial inflammation.
  - Newer classification criteria: Assessment of *SpondyloArthritis international Society* (or ASAS) classification criteria
  - TNF-inhibitors are now recognized as the most effective treatments in reducing symptoms. Treatment may be started in active non-radiographic axial spondyloarthritis even though FDA has not approved this indication.
Many options for disease suppression now available in RA and other rheumatic diseases.

Older DMARDs have well known and predictable ADRs, clearly control early RA.

Biologics have ability to improve symptoms, quality of life and radiographic progression at least as well as, or better than, older therapies, but are much more costly.

Combinations offer additional improvement.

Aggressive treatment goals are paramount!
Toficitinib works for treating RA:

a. By blocking the interaction of major cytokines with their cell receptor
b. Within the cell, downstream of inflammatory cytokine signals
c. At the same intracellular biochemical step as tumor necrosis factor inhibitors
d. Directly at lymphocyte CD4 receptors, independent of cytokine signals altogether
Which of the following medications for RA would require a tuberculin skin test before beginning therapy?

a. Tofacitinib
b. Methotrexate
c. Leflunomide
d. Hydroxychloroquine
Mrs. Smith is a 28 year old, 70 kg female recently diagnosed with RA and who has taken hydroxychloroquine 400 mg/day for her mildly active disease for 3 months. However, she now presents with a severe flare of joint inflammation. Which of the following disease-modifying options would control her flare most quickly?

a. Tofacitinib 5 mg twice daily
b. Etanercept 50 mg s.c. weekly
c. Methotrexate 7.5 mg weekly
d. Increase hydroxychloroquine to 600 mg daily
After 4 months with the new treatment Mrs. Smith now has disease activity that is rated as mild, and no significant side effects have occurred. What is the best action at this point?

a. leave everything well enough alone
b. begin tapering all drug therapy
c. add a NSAID in order to reduce DMARD therapy
d. intensify DMARD therapy