Ensuring Early Diagnosis and Targeting Treatment to Remission in Patients with Rheumatoid Arthritis: Recommendations for Primary Care Clinicians

Diane Horowitz, MD

Disclosures: None
Ensuring Early Diagnosis and Targeting Treatment to Remission in Patients with Rheumatoid Arthritis: Recommendations for Primary Care Physicians

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Faculty Disclosures

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Learning Objectives

- Implement screening to improve early diagnosis of rheumatoid arthritis (RA)
- Apply a treat-to-target approach that is consistent with current guideline recommendations for RA management
- Describe the mechanisms of action of approved targeted therapies for the treatment of RA
- Utilize strategies for early identification of important comorbidities and their management in patients with RA

Disease Overview of RA

Limited Data for RA Prevalence in the US

- Recent CDC statistics estimate 54.4 million adults (22.7%) have been diagnosed with arthritis\(^1\)
  - "Arthritis" self-reported and includes several musculoskeletal disorders in addition to RA
- More accurate and specific to RA\(^2\)
  - Gradual increase in prevalence could mean RA will affect 1.39 million adults by 2020

\(^1\)Derived from observational, cross-section study using ICD-9 data from 2 large insurance claims databases including 166 million adults over a 10-year period from 2004–2014.

### Socioeconomic Burden of RA in US

- **RA an expensive disease**
  - Annual direct and indirect costs: $19.3 billion*  
    - Medications and physician consultations  
    - Work productivity loss and absenteeism  
    - Adaptations to home and work environments  
    - Hired care/household help  
    - Job turnover expenses  
  - Estimated annual intangible costs: $39.2 billion  
    - $10.3 billion QOL deterioration  
    - $9.6 billion premature mortality  

*In 2005 dollars. QOL, quality of life.


### Common Complications of Long-Term RA

- CRP, C-reactive protein; Dkk-1, Dickkopf-1 protein factor; HDL, high-density lipoprotein; HPA, hypothalamic-pituitary-adrenal; LDL, low-density lipoprotein; RANKL, receptor activator of nuclear factor kappa B ligand; SERT, serotonin transporter; TNF-α, tumor necrosis factor alpha.


### RA Mortality

- **RA associated with early mortality**  
  - Lifespan reduced by 7–10 years¹  
  - 50% increased risk for early mortality²

### Leading Causes of Mortality in the Nurses Health Study² in Women with and without RA*¹

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>With RA</th>
<th>No RA</th>
<th>Risk Level for RA Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (total)</td>
<td>307 (31.8%)</td>
<td>28,501 (24.1%)</td>
<td>↑ HR 1.40, 95% CI 1.25–1.57</td>
</tr>
<tr>
<td>Cancer</td>
<td>80 (26.1%)</td>
<td>11,570 (40.6%)</td>
<td>↑ HR 0.93, 95% CI 0.93–1.95</td>
</tr>
<tr>
<td>CVD</td>
<td>70 (22.2%)</td>
<td>7,983 (21.8%)</td>
<td>↑ HR 2.46, 95% CI 1.14–1.83</td>
</tr>
<tr>
<td>Respiratory</td>
<td>44 (14.3%)</td>
<td>2,050 (7.2%)</td>
<td>↑ HR 2.86, 95% CI 1.54–2.80²</td>
</tr>
</tbody>
</table>

*Nurses’ Health Study followed 119,209 women for 36 years; 964 were eventually diagnosed with RA.
†Cancer determined not to be strongly associated with RA. RA patients who were considered seropositive (ie, presence of both ACPA and RF) had a nearly 3-fold increased risk of death from respiratory disease (HR 2.67, 95% CI 1.89–3.77).

ACPA, anti-citrullinated protein antibody; CVD, cardiovascular disease; RF, rheumatoid factor.

RA Health Burden with Common Comorbidities

Multiple concomitant CVD conditions often coexist with RA1-3

*Included 3,620 RA patients throughout 17 countries. COMORA, COMorbidities in Rheumatoid Arthritis; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MI, myocardial infarction.


Most common comorbidities according to COMORA* study4

- Hypertension: 16.6%
- Hyperlipidemia: 9.9%
- Diabetes: 6%
- Obesity: 5%
- Depression: 4.5%
- 6%
- COPD: 3.5%
- Asthma: 3%
- CVD Events (ie, stroke, MI): 20%
- Solid Tumors: 12%
- Infections (ie, HBV or HCV): 18.6%

*Included 3,620 RA patients throughout 17 countries. COMORA, COMorbidities in Rheumatoid Arthritis; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MI, myocardial infarction.

Pathophysiology of RA

- RA an autoimmune disorder of unknown etiology
- Pathophysiologic features of dysregulation in innate and adaptive immune system include
  - Dysregulated T- and B-lymphocytes, macrophages, mast cells, and synovial fibroblasts
  - Results in pro-inflammatory cytokines (primarily IL-6 and TNF-α) and MMPs involved in
    - Chronic joint inflammation
    - Inflammation in extra-articular organs
    - Destruction of joint cartilage
    - Excessive subchondral bone resorption leading to bone erosion

RA Assessment and Diagnosis

Common Early RA Symptoms

**Articular Symptoms**
- Morning stiffness
- Joint tenderness/swelling
- Joint pain/stiffness
- Decreased grip strength
- Decreased range of motion

**Non-Articular Symptoms**
- Fatigue
- Generalized aching/stiffness
- Depression
- Weight loss
- Hand swelling, redness

Venables PJW. Clinical manifestations of rheumatoid arthritis. UpToDate. [https://www.uptodate.com](https://www.uptodate.com).

Commonly Affected Joints in Early Disease

- Early disease not always symmetrical
- Small joints of the hand
  - MCP and PIP joints in fingers
  - IP joints in thumbs
- Wrist
- MTP joints of the toes
- Large synovial joints
  - Elbows, shoulders, ankles, knees

IP, interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; MTP, metatarsophalangeal.
Role of Imaging in RA

- Imaging can assist in diagnosis; most useful for detecting change over time
- Radiographs (aka, “x-rays”)
  - Often normal in early disease
  - Detects joint space narrowing and bone erosion
- MRI
  - Identifies synovitis, which precedes cartilage destruction
  - Detects bone erosion earlier than radiographs
- Ultrasound
  - Assesses degree and volume of inflammation
  - Identifies synovitis, cartilage destruction, and bone erosion

MRI, magnetic resonance imaging.

Lab Tests for RA

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Values</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACPA</td>
<td>&lt;20 U/mL</td>
<td>Diagnostic &amp; Prognostic</td>
</tr>
<tr>
<td>CRP</td>
<td>&lt;3.0 mg/dL</td>
<td>Prognostic</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt;30 mm/hr for women &lt;50 yrs; &lt;25 mm/hr for women &gt;50 yrs</td>
<td>Prognostic</td>
</tr>
<tr>
<td>RF</td>
<td>&lt;20 IU/mL</td>
<td>Diagnostic &amp; Prognostic</td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate.

ACR/EULAR Diagnostic Criteria

<table>
<thead>
<tr>
<th>Domain A &amp; Points Assigned</th>
<th>Domains B, C, D and Points Assigned</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Joints Involved</td>
<td>B: Serology*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 large joint</td>
<td>Negative RF and negative ACPA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1-3 small joints*</td>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4-10 small joints*</td>
<td>Normal CRP and normal ESR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10 joints‡</td>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C: Acute-Phase Reactants*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D: Duration of Symptoms</td>
<td>&lt;6 weeks</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;6 weeks</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

A total score ≥6 indicates definite RA

*R with or without large joint involvement. Large joints include shoulders, elbows, hips, knees, and ankles. Small joints include MCPs, PIPs, IPs, 2nd-5th MTPs, and wrists. ≥1 test required for classification. *≥1 small joint involved.

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

Defining Treat-to-Target (T2T) in RA

- Goal: complete remission or LDA using
  - Aggressive treatment
  - Vigilant monitoring
  - Prompt treatment adaptations if target not reached
  - Intensified therapy for tight control
- T2T verified in multiple clinical trials and advocated by ACR and EULAR
- Multiple drugs as monotherapy or in combinations

The strategy is more important than the drugs used

T2T Is Important Because . . .

- Early Dx + T2T with the goal to potentially achieve remission or LDA
- Avoids permanent joint damage & functional disability
- Tx should yield ≥50% improvement ≤3 months
- If not, modify, escalate, or switch

What Defines Disease “Improvement”? ACR Response Criteria

- In 1995, ACR established criteria to show disease improvement after treatment
  - ACR20 stipulated a 20% improvement in ≥3 core variables
  - Response criteria needed to differentiate active treatment from placebo effect
- As more effective treatments emerged, accelerated criteria emerged in the ACR50 and ACR70
- Also called “ACR Responder Index,” ACR20, -50, and -70 are used in clinical trials to demonstrate drug efficacy

LDA, low disease activity.


SJC, swollen joint count; TJC, tender joint count.


ACR Response Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Mandatory % Reduction</th>
<th>% Improvement in ≥3 of 5 Core Variables</th>
<th>Improvement Corresponds To</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>20%</td>
<td>Swollen joints and tender joints</td>
<td>50% in CDAI or SDAI (minimal response; superior to PBO)</td>
</tr>
<tr>
<td>ACR50</td>
<td>50%</td>
<td>PGA (VAS), EGA (VAS), PPA (VAS), functional disability (HAQ), acute-phase reactant response (ESR or CRP)</td>
<td>70% in CDAI or SDAI (moderate improvement)</td>
</tr>
<tr>
<td>ACR70</td>
<td>70%</td>
<td></td>
<td>85% in CDAI or SDAI (major response equates to LDA)</td>
</tr>
</tbody>
</table>

CDAI, Clinical Disease Activity Index; EGA, evaluator global assessment; HAQ, Health Assessment Questionnaire; PGA, patient global assessment; PRA, patient pain assessment; SDAI, Simplified Disease Activity Index; VAS, visual analog scale.

Defining Disease Improvement

<table>
<thead>
<tr>
<th>Tool</th>
<th>Components and Formula</th>
<th>Est. Time*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>SJC28 + TJC28 + PGA + EGA</td>
<td>Patient: ~10 sec Clinician: &lt;2 min</td>
</tr>
<tr>
<td>DAS28</td>
<td>Complex formula includes TJC28, SJC28, (ESR or CRP) and PGA</td>
<td>Patient: ~10 sec Clinician: 3–5 min</td>
</tr>
<tr>
<td>SDAI</td>
<td>SJC28 + TJC28 + PGA + EGA + CRP</td>
<td>Patient: ~10 sec Clinician: &lt;2 min</td>
</tr>
</tbody>
</table>

*Both DAS28 and SDAI require use of acute-phase reactants, which may delay score calculation depending on laboratory turnaround times. CDAI is the most commonly used disease severity measure in the US because of its simplicity and immediate calculation.

SDAI, swollen joint count using 28 joints; TJC28, tender joint count using 28 joints.

Composite Disease Severity Scales

<table>
<thead>
<tr>
<th>Tool</th>
<th>Scale</th>
<th>Remission</th>
<th>Low/Minimal</th>
<th>Moderate</th>
<th>High/Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>0–76</td>
<td>≤2.8</td>
<td>&gt;2.8–10</td>
<td>&gt;10–22</td>
<td>&gt;22</td>
</tr>
<tr>
<td>DAS28</td>
<td>0–9.4</td>
<td>≤2.6</td>
<td>&gt;2.6–&lt;3.2</td>
<td>&gt;3.2–&lt;5.1</td>
<td>&gt;5.1</td>
</tr>
<tr>
<td>SDAI</td>
<td>0–86</td>
<td>≤3.3</td>
<td>&gt;3.3–&lt;11</td>
<td>&gt;11–&lt;26</td>
<td>&gt;26</td>
</tr>
</tbody>
</table>

DAS28, Disease Activity Score using 28 joints.

Several ACR-endorsed measures of health and QOL are designed for patients
- Most frequently used is RAPID3
  - Asks about physical function, pain, and global well-being
  - Assigns points on a 0–10 scale, totaled, and divided by 3

### RAPID3 Disease Severity and Point Totals

<table>
<thead>
<tr>
<th>Severity</th>
<th>Point Translations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near Remission</td>
<td>1=0.3, 2=0.7, 3=1.0</td>
</tr>
<tr>
<td>Low Severity</td>
<td>4=1.3, 5=1.7, 6=2.0</td>
</tr>
<tr>
<td>Moderate Severity</td>
<td>7=2.3, 8=2.7, 9=3.0, 10=3.3, 11=3.7, 12=4.0</td>
</tr>
</tbody>
</table>


### RAPID3 Patient Assessment of Abilities and QOL: Part 1

1. Please check the ONE best answer for your abilities at this time:

<table>
<thead>
<tr>
<th>1. a. in the last week, were you able to:</th>
<th>WITHOUT ANY DIFFICULTY</th>
<th>WITH SOME DIFFICULTY</th>
<th>WITH MUCH DIFFICULTY</th>
<th>UNABLE to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Dress yourself, including tying shoeaces and doing buttons?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>b. Get in and out of bed?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>c. Lift 10 lb or glass of your mouth?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>d. Walk outdoors on flat ground?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>e. Wash and dry your entire body?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>f. Bend down to pick up clothing from the floor?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>g. Use regular faucets on and off?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>h. Get in and out of a car, bus, train, or airplane?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>i. Walk 2 miles or 3 kilometers, if you wish?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>j. Do any good right's sleep?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>k. Deal with feelings of depression or feeling blue?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

RAPID3 available at: [https://www.rheumatology.org/Portals/0/RAPID3%20Form.pdf](https://www.rheumatology.org/Portals/0/RAPID3%20Form.pdf)

### RAPID3 Patient Assessment of Abilities and QOL: Parts 2 and 3

2. How much pain have you had because of your condition OVER THE PAST WEEK?

   Please indicate below how severe your pain has been:

<table>
<thead>
<tr>
<th>NO PAIN</th>
<th>MILD AS BAD AS IT COULD BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

3. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

<table>
<thead>
<tr>
<th>VERY WELL</th>
<th>VERY POORLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

RAPID3 available at: [https://www.rheumatology.org/Portals/0/RAPID3%20Form.pdf](https://www.rheumatology.org/Portals/0/RAPID3%20Form.pdf)
Case Study: Amy

- 39-year-old Caucasian woman
  - Restaurant supply sales rep
  - Outgoing and actively involved in community events
  - Never married, no children, has a long-term boyfriend
- Medical history
  - Height: 5'6"; Weight: 175 lbs; BMI 27 (overweight)
  - Never been pregnant
  - Stopped taking oral birth control 6 months ago because she's approaching 40 and doesn't want to be on hormones
  - Taking levothyroxine 137 mcg for hypothyroid
  - Has smoked half a pack a day for >10 years

BMI, body mass index.

Case Study: Presentation and Diagnosis

- Amy presents to rheumatologist complaining of
  - Sore hands, morning stiffness, difficulty opening jars, difficulty handling cell phone
  - Feet hurt too; has had to stop wearing heels, which she says is a problem in sales because clients expect heels
  - Symptoms have been ongoing for 6 weeks
- Rheumatologist determines RA based on
  - 8 points on ACR/EULAR diagnostic criteria
    - All MCP and MTP joints show swelling/tenderness
Case Study: Disease Activity and Initial Treatment

- Disease is active: 15 points on CDAI; 4.0 on RAPID3
- Rheumatologist started Amy on 10 mg/week oral MTX
  - Dose titrated upward every month by 5 mg
- Amy returns 3 months after diagnosis, 1 month after starting MTX 20 mg/week
  - CDAI now 11; RAPID3 now 3.0
    - Slight improvement but disease activity still too high
- Amy is also now complaining of
  - Nausea
  - Hair loss
  - Coughing

MTX, methotrexate.

Case Study: 2nd-Line Treatment

- Rheumatologist asks Amy to
  - Get flu vaccination and chest radiograph for cough
  - Take test to assess TB status
  - Return to PCP to discuss smoking cessation
- Because of inadequate response to MTX, choices now include
  - Increasing MTX dose
  - Adding a corticosteroid
  - Adding a different csDMARD
  - Prescribing a TNF-α inhibitor
  - Prescribing a non-TNF biologic (ie, IL-6 or B-cell inhibitor)
  - Switching to a tsDMARD (ie, JAK inhibitor)

cDMARD, conventional synthetic disease-modifying antirheumatic drug; JAK, Janus kinase; PCP, primary care provider; TB, tuberculosis; tsDMARD, targeted synthetic disease-modifying antirheumatic drug;
## First-Line Interventions: csDMARDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
<th>Route/Doses</th>
<th>MOA</th>
<th>AE(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCQ</td>
<td>1955</td>
<td>Oral: 400–600 mg QD or BID</td>
<td>Antimalarial, blocks toll-like receptors</td>
<td>Blood and lymphatic system disorders; cardiomyopathy; ocular toxicity</td>
</tr>
<tr>
<td>LEF</td>
<td>1998</td>
<td>Oral: 10–20 mg QD</td>
<td>Inhibits pyrimidine synthesis</td>
<td>Liver effects, GI effects; teratogenesis</td>
</tr>
<tr>
<td>MTX</td>
<td>2000 SC 1999 Oral</td>
<td>Oral/SC: 15–25 mg QW</td>
<td>Inhibits AICAR transformylase</td>
<td>Liver effects; teratogenesis; hair loss; oral ulcers</td>
</tr>
<tr>
<td>SSZ</td>
<td>1950</td>
<td>Oral: 500–1000 mg BID</td>
<td>Folate depletion, other MOAs unknown</td>
<td>Anemia in glucose-6-phosphate dehydrogenase deficiency; GI effects</td>
</tr>
</tbody>
</table>

MOAs, mechanisms of action; QD, once daily; QW, once weekly; SC, subcutaneous; SSZ, sulfasalazine.


## MTX: Cornerstone of RA Treatment

- First-line therapy recommended for most by ACR and EULAR
- Efficacy as monotherapy or combination therapy
- Superior to placebo
- Comparable to other drugs, including anti-TNF therapy
- One-third of patients have no radiographic progression after 1 year
- Greater efficacy when combined with targeted biologics
- Reduces immunogenicity of bDMARDs
- Patients for whom MTX would not be preferred
  - Patients who have: HBV/HCV; liver dysfunction
  - Patients who are: sexually active but not taking birth control; unwilling to reduce alcohol intake

bDMARDs, biologic disease-modifying antirheumatic drugs.

## Inadequate Response to MTX Common

- Multiple drug classes are needed because ≥40% show inadequate response to MTX
  - Patients who never showed adequate response are primary nonresponders
  - Patients whose response has diminished over time are secondary nonresponders
  - Likely due to development of antidrug antibodies
- ACR recommendation for insufficient response to MTX
  1. Add TNF inhibitor
  2. Switch to non-TNF biologic, or small-molecule JAK inhibitor

**bDMARDs: TNF Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
<th>Route/Doses</th>
<th>MOA</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>2002</td>
<td>SC: 40 mg Q2W</td>
<td>Anti-TNF-α</td>
<td>Opportunistic bacterial and fungal infections; TB</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>2008</td>
<td>SC: 400 mg Q2W</td>
<td>Anti-TNF-α, pegylated</td>
<td>Opportunistic bacterial and fungal infections; TB</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1998</td>
<td>SC: 50 mg QW</td>
<td>Anti-TNF-α fusion protein</td>
<td>Opportunistic bacterial and fungal infections; TB</td>
</tr>
<tr>
<td>Golimumab</td>
<td>2009</td>
<td>IV: 2 mg/kg, SC: 50 mg QMT</td>
<td>Anti-TNF-α</td>
<td>Opportunistic bacterial and fungal infections; TB</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1998</td>
<td>IV: 3–10 mg/kg QMW–Q4W</td>
<td>Anti-TNF-α</td>
<td>Opportunistic bacterial and fungal infections; TB; Infusion reactions</td>
</tr>
</tbody>
</table>

IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, once monthly.


**Inadequate Response to Anti-TNF Also Common**

- Approximately ≥50% of patients do not respond to TNF inhibitors
  - ARTIS analysis showed 3,782 patients (of 9,139) discontinued TNF inhibitor after a median of 1.7 years
    - 51% due to inefficacy
    - 36% due to adverse events
- After anti-TNF discontinuation, improved ACR20, ACR50, ACR70 responses can achieved with:
  - Non-TNF biologics with targeted MOAs
  - JAK inhibitors
  - IL-6 inhibitors

ARTIS, Anti-Rheumatic Therapy in Sweden (the Swedish Biologics Register).

**bDMARDs: Non-TNF Biologics (T-Cell, B-Cell, and IL-1 Inhibitors)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
<th>Route/Doses</th>
<th>MOA</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>2005</td>
<td>SC: 125 mg QW, IV: 500–1000 mg QW</td>
<td>Co-stimulator blocker; cytotoxic T-cell antigen 4</td>
<td>Opportunistic infections</td>
</tr>
<tr>
<td>Anakinra</td>
<td>2001</td>
<td>SC: 100 mg QD</td>
<td>Anti-IL-1 receptor blocker</td>
<td>Opportunistic infections; injection-site pain</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1997</td>
<td>IV: 1000 mg QIM</td>
<td>Anti-CD20 B-cell inhibitor</td>
<td>Infusion reactions; opportunistic infections; PML</td>
</tr>
</tbody>
</table>

PML, progressive multifocal leukoencephalopathy; QIM, once every 6 months/twice per year.

### bDMARDs: Non-TNF Biologics (IL-6 Inhibitors)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
<th>Route/Doses</th>
<th>MOA</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarilumab</td>
<td>2017</td>
<td>SC: 150–200 mg Q2W</td>
<td>IL-6 receptor blocker</td>
<td>Opportunistic bacterial, fungal, viral infections; elevated liver enzymes; lipid abnormalities</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>2010</td>
<td>IV: 4–8 mg/kg Q4W SC: 162 mg QW or Q2W</td>
<td>IL-6 receptor blocker</td>
<td>Opportunistic bacterial, fungal, viral infections; elevated liver enzymes; lipid abnormalities</td>
</tr>
</tbody>
</table>


---

### tsDMARDs: Non-Biologics (JAK Inhibitors)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
<th>Route/Doses</th>
<th>MOA</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baricitinib</td>
<td>2018</td>
<td>Oral: 2 mg QD</td>
<td>JAK 1/JAK 2 inhibitor</td>
<td>TB: opportunistic bacterial, fungal, viral infections</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>2012</td>
<td>Oral: 5 mg BID XR: 11 mg QD</td>
<td>JAK 1/JAK 2/JAK 3 inhibitor</td>
<td>TB: opportunistic bacterial, fungal, viral infections</td>
</tr>
</tbody>
</table>

XR, extended release.


---

### Non-TNF Biologics and JAK Inhibitors for Nonresponders to Anti-TNF and csDMARDs

Newer non-biologics (ie, JAK inhibitors) and non-TNF biologics (ie, abatacept and IL-6 inhibitors) are effective treatment options for high percentage of TNF inhibitor and csDMARD nonresponders. Both classes recommended by ACR after anti-TNF failure because of their ability to show efficacy as monotherapy in addition to being used in combination with csDMARDs.

**IL-6: Efficacy in Anti-TNF Nonresponders**

**ACR Response Criteria with Sarilumab**

Source: Phase 3 TARGET trial of patients with inadequate response to ≥1 TNF inhibitors

![Graph showing ACR response criteria with sarilumab](image)

- SAR 200 mg Q2W + csDMARD (n=184)
- SAR 150 mg Q2W + csDMARD (n=181)
- PBO Q2W + csDMARD (n=181)

*All patients treated with background standard doses of HCQ, LEF, MTX, or SSZ.*

SAR, sarilumab.

**IL-6: Efficacy in Anti-TNF Nonresponders (cont)**

**ACR Response Criteria with Tocilizumab**

Source: Phase 3 RADIATE trial of patients with inadequate response to ≥1 TNF inhibitors

![Graph showing ACR response criteria with tocilizumab](image)

- TCZ 8 mg/kg Q4W + MTX (n=170)
- TCZ 4 mg/kg Q4W + MTX (n=161)
- PBO Q4W + MTX (n=158)

RADIATE, Research on Actemra Determining efficacy after Anti-TNF Failure; TCZ, tocilizumab.


**JAK: Efficacy in Anti-TNF Nonresponders**

**ACR Response Criteria with Baricitinib**

Source: Phase 3 RA-BEACON trial of patients who discontinued TNF inhibitors because of inadequate response or unacceptable AEs

![Graph showing ACR response criteria with baricitinib](image)

- BAR 4 mg QD + csDMARD (n=177)
- BAR 2 mg QD + csDMARD (n=176)
- PBO QD + csDMARD (n=176)

BAR, baricitinib.

JAK: Efficacy in csDMARD Nonresponders

ACR Response Criteria with Tofacitinib as Monotherapy and in Combination with MTX vs ADA

<table>
<thead>
<tr>
<th>Efficacy Over 6 Months</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>65</td>
</tr>
<tr>
<td>ACR50</td>
<td>73</td>
</tr>
<tr>
<td>ACR70</td>
<td>71</td>
</tr>
</tbody>
</table>

Source: Phase 3b/4 ORAL Strategy trial of patients with inadequate response to MTX.

TOF 5 mg BID (n=384)
TOF 5 mg BID + MTX (n=376)
ADA 40 mg Q2W + MTX (n=386)

Emerging Pharmacologic Treatments

Emerging Agents: RA Drugs in Phase 3 Trials

<table>
<thead>
<tr>
<th>Study ID # (Acronym)</th>
<th>No. Pts</th>
<th>Study Population</th>
<th>Experimental vs Comparator Arm</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02760368 (CREDO 1)</td>
<td>428</td>
<td>Adults w/ mod-sev active RA + IR to MTX</td>
<td>Agents: OKZ (2 doses) + MTX vs PBO</td>
<td>Endpoint: ACR20 change by week 12 Completed; Expected to be presented Fall 2019</td>
</tr>
<tr>
<td>NCT02760407 (CREDO 2)</td>
<td>1,575</td>
<td>Adults w/ severely active RA + IR to MTX</td>
<td>Agents: OKZ (2 doses) + MTX vs ADA or PBO</td>
<td>Endpoint: ACR20 change by week 12 Ongoing; Estimated completion December 2019</td>
</tr>
<tr>
<td>NCT02760433 (CREDO 3)</td>
<td>350</td>
<td>Adults w/ severely active RA + IR to TNF-α</td>
<td>Agents: OKZ (2 doses) + MTX vs PBO</td>
<td>Endpoint: ACR20 change by week 12 Ongoing; Estimated completion September 2019</td>
</tr>
<tr>
<td>NCT03120949 (CREDO 4)</td>
<td>1,880</td>
<td>Adults w/ severely active RA + IR to MTX or TNF-α</td>
<td>Agents: OKZ (2 doses) FU to CREDO-2/9</td>
<td>Endpoint: AE, AESIs, &amp; SAEs by week 106 Ongoing; Estimated completion July 2021</td>
</tr>
</tbody>
</table>

AESIs, adverse events of special interest; CREDO, Clinical Rheumatoid Arthritis Development for Olokizumab; F/U, follow-up; IR, inadequate response; mod-sev, moderately to severely; OKZ, olokizumab; SAE, serious adverse events.
## Emerging Agents: RA Drugs in Phase 3 Trials (cont)

<table>
<thead>
<tr>
<th>Study ID # (Acronym)</th>
<th>No. Pts</th>
<th>Study Population</th>
<th>Agents Being Studied</th>
<th>Primary Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAK Inhibitor: Filgotinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03289796 (FINCH 1)</td>
<td>1,755</td>
<td>Adults w/ severely active RA + IR to MTX</td>
<td>Agents: FIL (2 doses) + MTX +/- PBO vs ADA</td>
<td>Endpoint: ACR20 by week 12</td>
<td>Completed; Results to be presented¹</td>
</tr>
<tr>
<td>NCT03287356 (FINCH 2)</td>
<td>448</td>
<td>Adults w/ severely active RA + IR to bDMARDs</td>
<td>Agents: FIL (2 doses) + csDMARD +/- PBO vs ADA</td>
<td>Endpoint: ACR20 by week 24</td>
<td>Completed; Results presented at 2018 ACR/ARHP²</td>
</tr>
<tr>
<td>NCT02886728 (FINCH 3)</td>
<td>1,252</td>
<td>Adults w/ severely active RA + naıve to MTX</td>
<td>Agents: FIL (2 doses) + PBO +/- MTX vs ADA</td>
<td>Endpoint: ACR20 by week 24</td>
<td>Completed; Results to be presented¹</td>
</tr>
</tbody>
</table>


## Emerging Agents: RA Drugs in Phase 3 Trials (cont)

<table>
<thead>
<tr>
<th>Study ID # (Acronym)</th>
<th>No. Pts</th>
<th>Study Population</th>
<th>Agents Being Studied</th>
<th>Primary Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JAK Inhibitor: Upadacitinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02706847 (SELECT-BEYOND)</td>
<td>453</td>
<td>Adults w/ severely active RA + IR to MTX</td>
<td>Agents: UPA (2 doses) vs PBO</td>
<td>Endpoint: ACR20 by week 12</td>
<td>Completed; Results published in Lancet¹</td>
</tr>
<tr>
<td>NCT0306543 (SELECT-CHOICE)</td>
<td>654</td>
<td>Adults w/ mod-sev active RA + IR to bDMARDs</td>
<td>Agents: UPA vs ABA or PBO</td>
<td>Endpoints: DAS28 change by week 12</td>
<td>Ongoing; Estimated completion February 2020</td>
</tr>
<tr>
<td>NCT02629159 (SELECT-COMPARE)</td>
<td>1,629</td>
<td>Adults w/ mod-sev active RA + IR to MTX</td>
<td>Agents: UPA vs PBO or UPA vs ADA</td>
<td>Endpoint: ACR20 &amp; DAS28 CR by week 12</td>
<td>Completed; Results presented at 2018 ACR/ARHP²</td>
</tr>
</tbody>
</table>


## Emerging Agents: RA Drugs in Phase 3 Trials (cont)

<table>
<thead>
<tr>
<th>Study ID # (Acronym)</th>
<th>No. Pts</th>
<th>Study Population</th>
<th>Agents Being Studied</th>
<th>Primary Endpoint</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>JAK Inhibitor: Upadacitinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02706873 (SELECT-EARLY)</td>
<td>947</td>
<td>Adults w/ mod-sev active RA + IR to MTX naïve</td>
<td>Agents: UPA (2 doses) vs PBO or MTX + PBO</td>
<td>Endpoint: ACR20 &amp; DAS28 CR by week 24</td>
<td>Completed; Results presented at 2018 ACR/ARHP²</td>
</tr>
<tr>
<td>NCT02706951 (SELECT-MONOTHERAPY)</td>
<td>648</td>
<td>Adults w/ mod-sev active RA + IR to csDMARDs</td>
<td>Agents: UPA (2 doses) vs MTX + PBO</td>
<td>Endpoint: ACR20 by week 14</td>
<td>Completed; Results presented at 2018 ACR/ARHP²</td>
</tr>
<tr>
<td>NCT0270426 (SELECT-NEXT)</td>
<td>618</td>
<td>Adults w/ mod-sev active RA + IR to csDMARDs</td>
<td>Agents: UPA (2 doses) vs PBO</td>
<td>Endpoints: ACR20 &amp; LDA by week 12</td>
<td>Completed; Results presented at 2018 ACR/ARHP²</td>
</tr>
</tbody>
</table>

ACR Algorithm: Early Newly Diagnosed RA

DMARD-naïve Established RA

- Low Disease Activity
  - csDMARD monotherapy

- Moderate/High Disease Activity
  - csDMARD monotherapy

- Combination csDMARDs or
  - Anti-TNF +/- MTX or
  - Non-TNF biologic +/- MTX

ACR Algorithm: Established Newly Diagnosed RA

DMARD-naïve Established RA

- Low Disease Activity
  - csDMARD monotherapy

- Moderate/High Disease Activity
  - csDMARD monotherapy

- Combination csDMARDs or
  - Anti-TNF +/- MTX or
  - Non-TNF biologic +/- MTX or
  - tsDMARD (JAK inhibitor) +/- MTX
Monitoring/Management Strategies for Comorbidities

- Routinely monitor BP, BG, LFTs, SCr, and kidney function
- Screen for TC, LDL-C, HDL-C, and TGs
- Screening and/or counseling for poor diet, physical inactivity, overweight, obesity
- Screening and/or management of depression and anxiety
- Smoking cessation
- Vaccinations, including for influenza, pneumonia, TB, HZ
- Dental hygiene and treatment
- Vitamin D deficiency treatment
- Folic acid supplementation during MTX treatment

BG, blood glucose; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HZ, herpes zoster; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; TC, total cholesterol; TGs, triglycerides; SCr, serum creatinine.


Management of Patients with High-Risk Comorbidities

- Collaborate with specialists
- Frequent monitoring
- Oversee polypharmacy
- Avoid anti-TNFs or other biologics, depending on clinical circumstance

CHF, congestive heart failure.

Overarching Treatment Principles & Goals

- Shared Decision Making
  Between patient and physicians
- Reduce Inflammation
- Maximize Long-Term QOL
  . . . By controlling symptoms, preventing joint damage, and normalizing function
- T2T
  Measure disease activity regularly and adjust therapy to achieve clinical remission or LDA
Summary

- RA affects all physiologic systems, not just joints
- Disease has an enormous health, QOL, and socioeconomic burden
- Early diagnosis and T2T strategies can reduce comorbidities and permanent joint destruction
- Now a wide variety of csDMARDs, biologicals, and non-biologicals available to reduce inflammation and disease burden
  - A large percentage of patients show inadequate or no response to MTX and TNF-α inhibitors
  - Non-TNF biologics and tsDMARDs show efficacy in those who don’t respond to first-line MTX and anti-TNF inhibition