Rheumatoid Arthritis: Challenges and Opportunities in the Evolving Treatment Landscape

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Therapy Selection for Patients with Rheumatoid Arthritis (RA)

- Disease duration*
  - Early RA: duration of disease/symptoms <6 mo
  - Established RA: duration of disease/symptoms of ≥6 mo
- Disease activity
  - Categorized as low, moderate, or high as per validated scales

*Denotes the length of time the patient has had symptoms/disease, not the length of time since RA diagnosis.

Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25.

Therapy Selection for Patients with RA

Patient-specific characteristics and history[1-4]

- Disease duration
- Disease activity
- Age
- Frailty
- Comorbidities
- Contraindications
- Treatment history

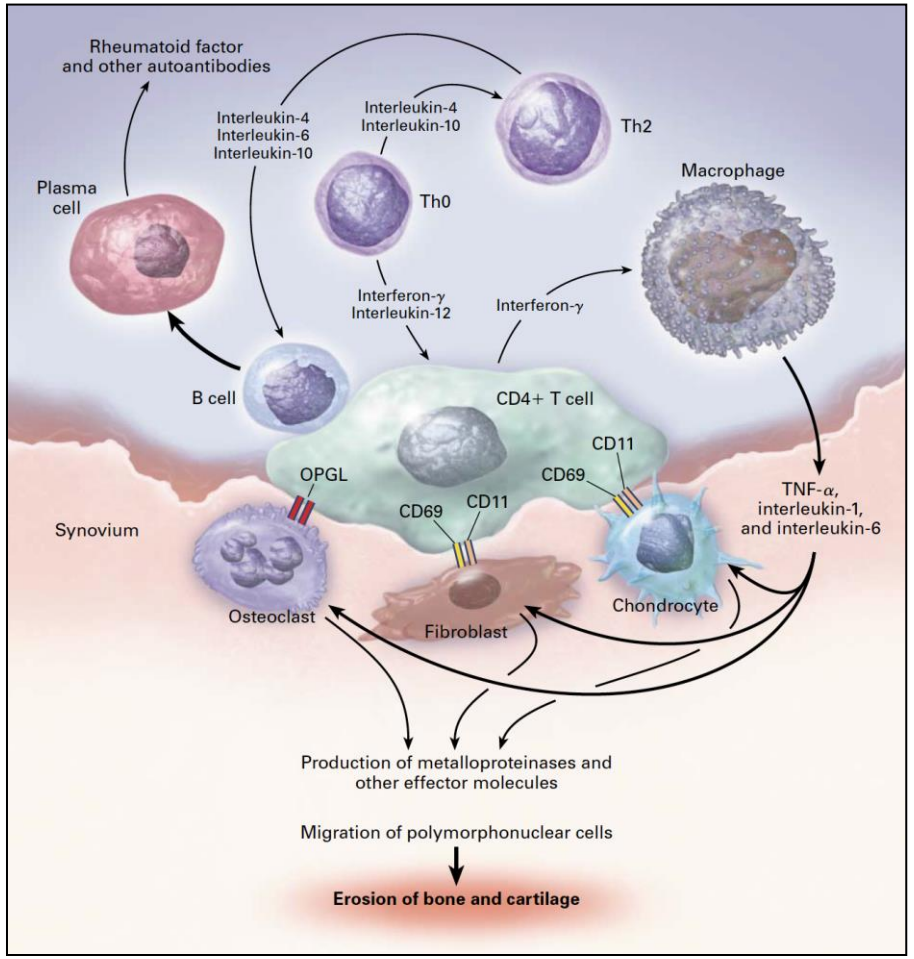
2015 ACR Recommendations for Early RA[4]

- Treat-to-Target
- Low disease activity
  - DMARD monotherapy
- Moderate to high disease activity
  - DMARD monotherapy
  - TNF inhibitor ± MTX
  - Non-TNF biologic ± MTX
  - Tofacitinib ± MTX

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drugs; MTX, methotrexate; TNF, tumor necrosis factor

1. Crane MM et al. *Arthritis Care Res (Hoboken)*. 2015;67(12):1646-1655. 2. Curtis JR et al. *Arthritis Care Res (Hoboken)*. 2013;65(2):235-243.
3. Kalkan A et al. *Implement Sci*. 2014;9:153. 4. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25.

Pathophysiology of RA and Targets for Biologics



OPGL, OPGL osteoprotegerin ligand; Th, T helper cell; TNF, tumor necrosis factor

Case Study: Janet

Personal and Family History

- Caucasian
- 42 years of age
- Family history of RA
- Diagnosed with RA at age 41
  - Moderate disease
- Initially started on MTX

Physical Exam and Lab Results

- BMI: 24 kg/m^2
- BP: 130/82 mm Hg
- Sodium: 135 mEq/L
- Potassium: 4.3 mEq/L
- Blood glucose: 100 mg/dL
- A1C: 5.2%
- Hemoglobin: 13.6 g/dL
- Hematocrit: 40%
- RBC count: 5.03 million cells/mcL
- WBC count: 10,000 cells/mcL
- Platelet count: 280,000/mcL

BMI, body mass index; BP, blood pressure; RBC, red blood cell; WBC, white blood cell

Case Study: Janet (cont'd)

- Janet has had good resolution of her Clinical Disease Activity Index (CDAI) on initial MTX
- However, she now complains of increased pain and swelling in her joints
- There has been a gradual increase in her CDAI back to baseline levels

Disease Activity Measures

Clinical Disease Activity Index (CDAI)

Range: 0–76.0

Thresholds of disease activity

- Remission: ≤2.8
- Low: >2.8–10.0
- Moderate: >10.0–22.0
- High: >22

- Disease Activity Score with 28-joint counts (DAS28) erythrocyte sedimentation rate (ESR)
- Routine Assessment of Patient Index Data with 3 measures (RAPID3)
- Simplified Disease Activity Index (SDAI)

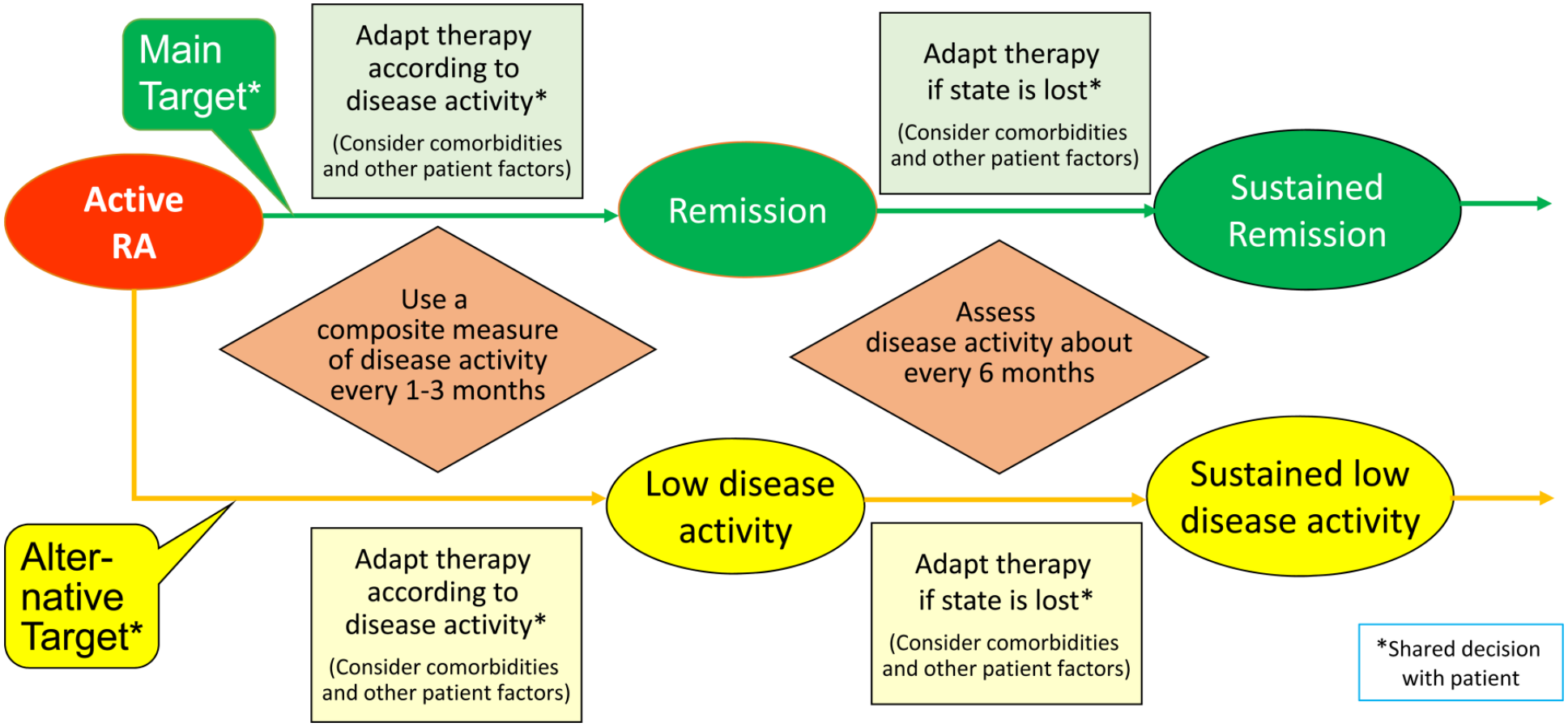
Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25.

2015 ACR Recommendations for Established RA

- Moderate to high disease activity
  - DMARD monotherapy
  - TNF inhibitor ± MTX
  - Non-TNF biologic ± MTX
  - Tofacitinib ± MTX
- Continued disease activity
  - Add DMARD to monotherapy
  - Switch within TNF inhibitor class
  - Switch to non-TNF biologic or JAK inhibitor
- Disease remission
  - May consider tapering therapy on an individual basis

Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25.

Monitoring and Follow-up



Smolen JS et al. *Ann Rheum Dis*. 2016;75(1):3-15. http://ard.bmj.com/content/annrheumdis/early/2015/05/12/annrheumdis-2015-207524.full.pdf.

Monitoring and Follow-up (cont'd)

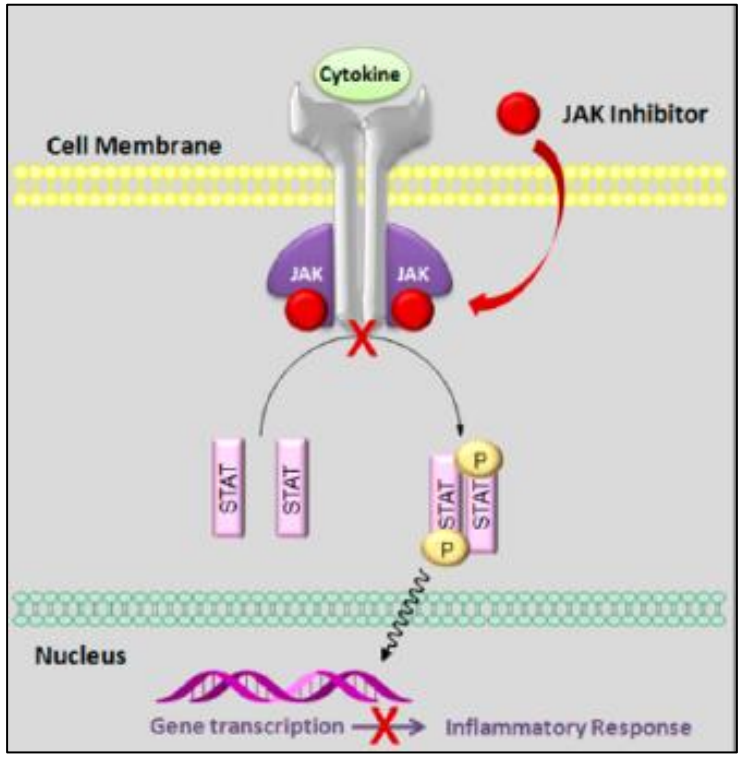
- Disease activity measures[1]
- Laboratory follow-up[1]
  - Complete blood count (CBC)
  - Liver transaminase
  - Serum creatinine
- Potential adverse events (AEs)[2]
  - Biologics increase risk for serious infection

1. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25. 2. Lampropoulos CE et al. *Clin Exp Rheumatol*. 2015;33(2):216-224.

New and Emerging Biologic Agents

- JAK inhibitors[1,2]
  - Tofacitinib JAK1/JAK3
  - Baricitinib JAK1/JAK2

JAK-STAT Signaling Pathway[2]



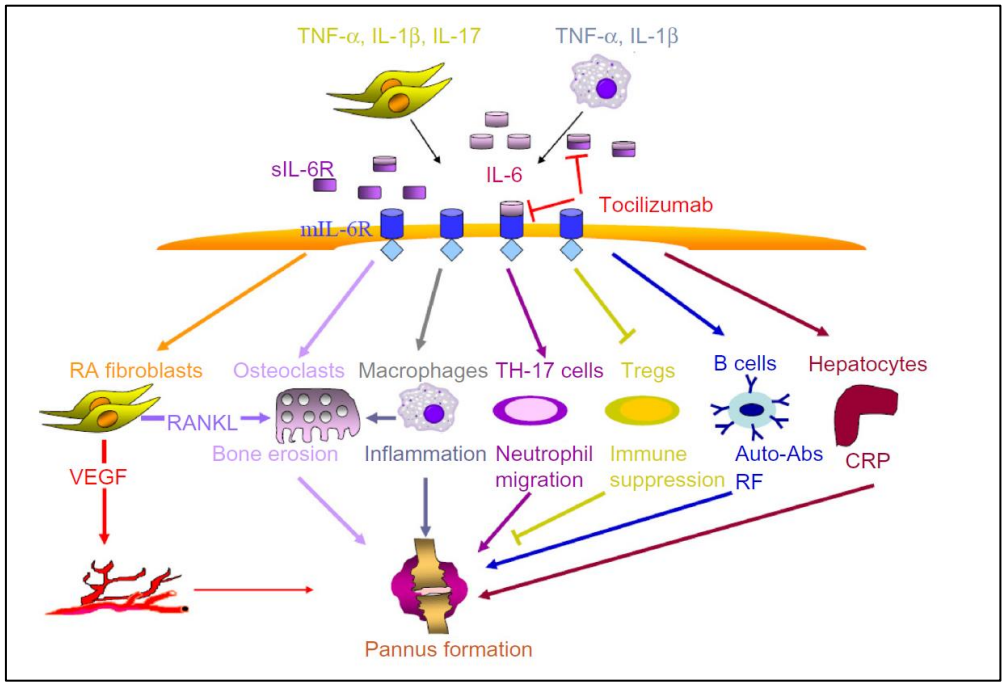
JAK, Janus kinase; STAT, signal transducer and activator of transcription

1. Kalden JR. *Rheumatol Ther*. 2016;3(1):31-42. 2. Clark JD et al. *J Med Chem.* 2014;57(12):5023-5038;3(11):900-911.

New and Emerging Biologic Agents (cont'd)

- IL-6/IL-6R inhibitors
  - Tocilizumab IL-6
  - Sarilumab IL-6R
  - Sirukumab IL-6

IL-6 Pathophysiology in RA



Shetty A et al. *Drug Des Devel Ther*. 201428;8:349-364. *Drug Design, Development and Therapy* by Dove Press Limited.
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Case Study: Janet (cont'd)

- Inadequate response to initial MTX
- Receives TNF inhibitor in addition to MTX
- A few months later, Janet has:
  - Severe disease
  - Inadequate response to TNF inhibitor therapy

Considering Comorbidities

- Common comorbidities include renal dysfunction, diabetes mellitus, pulmonary disorders, liver dysfunction, and CVD[1,2]
- Important not to exacerbate comorbidities with additional therapy and to ensure no new comorbidities have arisen[2]

CVD, cardiovascular disease

1. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25. 2. Inui K et al. *Ther Adv Musculoskelet Dis*. 2016;8(5):192-202.

Considering Comorbidities (cont'd)

The ACR recommends specific therapies for patients with certain high-risk comorbidities

- Non-TNF biologics or tofacitinib are preferred for patients with a history of or newly developed congestive heart failure (CHF)
- Abatacept or tofacitinib are preferred over TNF inhibitors for patients with a previously treated lymphoproliferative disorder
- Abatacept is recommended over TNF inhibitors for patients with a history of serious infection
- DMARDs/combination DMARDS are recommended over biologic agents for patients with CHF, hepatitis C, skin cancers, lymphoproliferative disorder, or a history of serious infection

Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25.

Drug Selection

- In patients with insufficient response to TNF-inhibitor therapy, biologics that interfere with different target mechanisms are generally expected to be effective[1,2]
  - However, all agents have lesser efficacy in TNF-experienced vs TNF-naïve patients
- Options include alternative TNF inhibitors[2]
  - However, these agents seem to be less efficacious in RA patients who previously had inadequate response to TNF-inhibitor therapy compared with TNF-naïve patients
- JAK inhibitor (tofacitinib) may also be appropriate per the 2015 ACR recommendations[3]

1. Smolen JS et al. *Lancet*. 2016;388(10055):2023-2038. 2. Moots RJ et al. *Rheumatology (Oxford).* 2012;51(12):2252-2261.
3. Singh JA et al. *Arthritis Care Res (Hoboken)*. 2015;68(1):1-25.

Monitoring and Follow-up (cont'd)

- Use of a validated composite measure of disease activity is needed in routine clinical practice to guide treatment decisions
- Measures of disease activity must be obtained and documented regularly, as frequently as:
  - Monthly for patients with moderate or high disease activity
  - About every 6 mo for patients in sustained low disease activity or remission
- Structural changes, functional impairment, and comorbidities should be considered when making additional clinical decisions
- Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 mo

Smolen JS et al. *Ann Rheum Dis*. 2016;75(1):3-15.

Key Takeaways

- The treatment of RA must be individualized
- The importance of disease activity measures (particularly the CDAI) in every RA patient at every visit cannot be understated
- Therapeutic decisions must be linked to disease activity scores

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