PRACTITIONER'S EDGE
Medical Education for Practical Application

Overcoming Barriers to the Early Recognition and Diagnosis of Rheumatoid Arthritis in Real-world Practice: Strategies to Expedite Treatment to Remission

INTEGRITY CONTINUING EDUCATION

Provided by Integrity Continuing Education, Inc.
Supported by an educational grant from Genzyme, a Sanofi Company, and Regeneron Pharmaceuticals.

Reminder…

- Complete Session Pre- and Post-Test
- Complete Online Session Evaluation at End of Session
  - https://www.surveymonkey.com/r/Nov_18_900_RA

****Links found in Event App**

Faculty Affiliation

Diane Horowitz, MD
Division of Rheumatology
Northwell Health
Assistant Professor of Medicine
Hofstra Northwell School of Medicine
Director, The Rheumatoid Arthritis Center
Director, Rheumatology Continuing Education

Faculty Disclosures

- Diane Horowitz, MD, has no real or apparent conflicts of interest to report.
- This CME-certified initiative, supported by an educational grant from Genzyme, a Sanofi company and Regeneron Pharmaceuticals.

4

Learning Objectives

- Implement routine screening to improve the early diagnosis of rheumatoid arthritis (RA)
- Apply guideline recommendations for treating to remission and preserving patient function in RA
- Review the underlying pathophysiology of RA and the role of emerging targeted therapies, including cytokine inhibition, for patients with RA
- Describe an integrated approach to RA patient care that includes a multidisciplinary healthcare team and patient education to improve shared decision-making

5

PRACTITIONER'S EDGE

RA Overview

RA Epidemiology and Burden

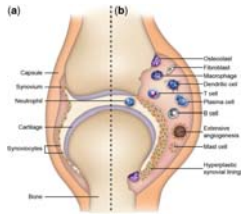
- Affects ~1.5 million US adults
- 2 to 3 times more prevalent in women vs men
- Prevalence increases with age (~ 1% in women >55 years of age)
- Presents at any age, but most common in the third to sixth decade of life
- Causes substantial disability and reduced QOL
- Is associated with multiple comorbid conditions, including CVD, which leads to shortened life expectancy

CVD, cardiovascular disease; QOL, quality of life.

Available at: http://www.cdc.gov/arthritis/basics/rheumatoid.htm
Myasoedova E, et al. *Arthritis Rheum.* 2010;62(6):1576-1582.

7

RA Pathobiology

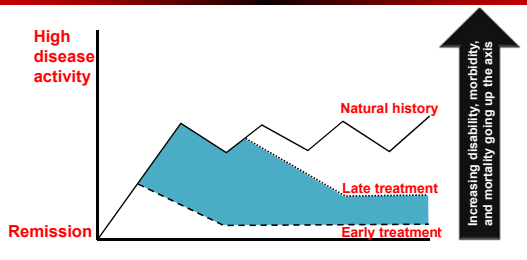


- Chronic autoimmune disease characterized by inflammation and synovial joint damage
- Inflammation of the synovial membrane
  - Leukocyte infiltration into normally sparsely populated synovial compartment

Smolen JS, et al. *Lancet.* 2016.
Choy E. *Rheumatology (Oxford).* 2012;51(suppl. 5):v3-11.

8

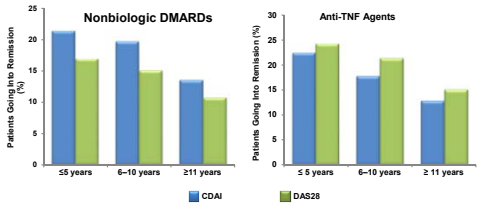
Altering Disease Progression



Adapted from: Roberts LJ, et al. *Med J Aust.* 2006;184(3):122-125.

9

Treatment Delays Reduce the Likelihood of Achieving and Sustaining Remission

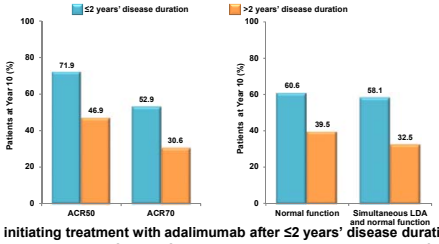


The likelihood of remission and sustained remission are reduced by 10% to 15% with every 5-year increase in disease duration prior to treatment initiation.

CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.
Furst DE, et al. *Arthritis Care Res*. 2011;63(6):856-864.

10

Beneficial Impact of Early RA Treatment on Patient Function

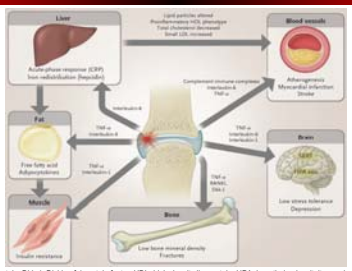


Patients initiating treatment with adalimumab after ≤2 years' disease duration were more likely to achieve ACR50, ACR70, low disease activity, and normal function.

ACR, American College of Rheumatology; ACR50, improvement of at least 50% in both tender and swollen joint counts; ACR70, improvement of at least 70% in both tender and swollen joint counts; LDA, low disease activity.
Furst DE, et al. *Rheumatology (Oxford)*. 2015;54(12):2188-2197.

11

Long-term Complications of 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.
McInnes IB, et al. *N Engl J Med*. 2011;365(23):2205-2219.

12

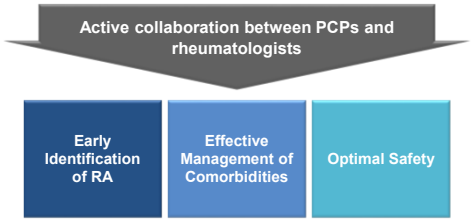
Current Focus in Clinical Practice

- Early identification and treatment to:
  - Alter disease course to prevent long-term joint damage
  - Control pain
  - Improve time to clinical remission
  - Restore/preserve function and regain/retain QOL
- Definition of:
  - Inadequate response
  - Remission
- Establishment of criteria for:
  - Monotherapy vs combination therapy
  - Switching treatment
  - Halting biologic treatment

Glauser TA, et al. *Rheumatol Ther*. 2014;1(1):31-44.

13

Collaborative Care of the Patient with RA



PCP, primary care provider.

14

PRACTITIONER'S EDGE

Screening and Diagnosis of RA

Case Study 1: Jane, a 45-Year-Old Woman with Early RA

- 3-month history of pain and inflammation in her fingers, wrist, knees, and feet
- Stiffness every morning accompanied by fatigue
- Loss of appetite in recent weeks
- Physical exam
  - Bilateral symmetrical swelling
  - Joint tenderness in hands, wrists, and feet

16

Screening and Diagnosis

- RA is a **clinical diagnosis**
- Lab tests may aid in monitoring and ruling out other types of arthritis:
  - C-reactive protein
  - Erythrocyte sedimentation rate (ESR)
  - Rheumatoid factor latex test
  - Antinuclear antibody (ANA)
  - X-rays
  - Joint aspiration, to look for crystalline arthritis or infectious arthritis

Available at: https://www.guideline.gov/summaries/summary/39244

17

ACR/EULAR Criteria for RA Classification

- Distinguishes **patients at high risk for persistent erosive and/or inflammatory disease** vs those with undifferentiated inflammatory arthritis
- Classification criteria:
  - Joint involvement
  - Serology
  - Acute-phase reactants
  - Duration of symptoms
- Total score >6 out of 10 indicates definite RA

EULAR, European League Against Rheumatism.
Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

18

Joint Involvement

Joints Involved	Score
1 large joint	0
2–10 large joints	1
1–3 small joints*	2
4–10 small joints*	3
>10 joints†	5

*With or without large joint involvement.
†At least 1 small joint.
Large joints refers to shoulders, elbows, hips, knees, and ankles whereas small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

Aletaha et al. *Ann Rheum Dis.* 2010;69(9):1580-8.

19

Serology, Lab Testing, and Symptom Duration

Serology*	Score
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-Phase Reactants*	**Score**
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of Symptoms	**Score**
<6 weeks	0
≥6 weeks	1

*At least one test required for classification.

Aletaha et al. *Ann Rheum Dis.* 2010;69(9):1580-8.

20

ACR-Endorsed Measures of Disease Activity

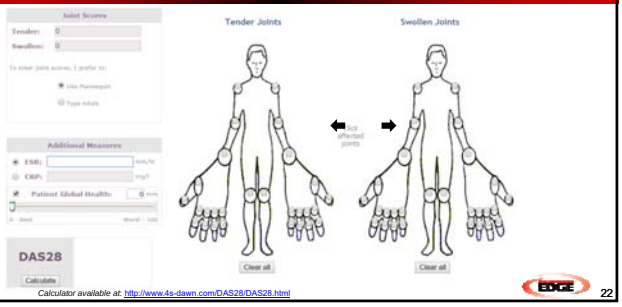
- DAS28 CRP/DAS28 ESR
- CDAI
- SDAI
- RAPID 3
- PAS
- PAS II

PAS, Patient Activity Scale; RAPID, Routine Assessment of Patient Index Data; SDAI, Simple Disease Activity Index.

Available at: http://www.rheumatology.org/Practice-Quality/Clinical-Support/Quality-Measurement/Disease-Activity-Functional-Status-Assessments

21

DAS28



Calculator available at: http://www.4s-dawn.com/DAS28/DAS28.html

CDAI Components

- Joint tenderness and swelling

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	

- Patient global assessment (scale: 0–10)
- Provider global assessment (scale: 0–10)

MCP = metacarpophalangeal; PIP = proximal interphalangeal.

Case Study 1: Jane's Lab Results

Test	Result
RF	50 IU/mL (normal: <20 IU/mL)
ACPA	80 U (normal: <20 U)
ESR	25 mm/hr (normal: <20 mm/hr for women <50 YOA)
CRP	3.2 mg/dL (normal: <3.0 mg/dL)
Serum creatinine	Normal range
BUN	Normal range
Liver enzymes	Normal range

BUN, blood urea nitrogen; YOA, years of age.

Case Study 1: Diagnosis

- Based upon her EULAR/ACR classification score, the patient is diagnosed with RA

Category	Score
Joint involvement	4
Serology	2
Acute-phase reactants	1
Duration of symptoms	1
Total score	8

- DAS28 score: 4.07 (moderate disease activity)
- Discussion: What are your primary treatment goals for Jane?

25

PRACTITIONER'S EDGE

Pharmacologic Management of RA

Treatment Options

Overarching Treatment Principles

Shared Decision-making
Between patient and physicians

Abrogation of Inflammation
(Not just control)

Maximization of Long-term QOL
Controlling symptoms, preventing joint damage, and normalizing function

Treat-to-Target
Measuring disease activity regularly and adjusting therapy to achieve clinical remission/LDA

Woodworth TG, et al. *Best Pract Res Clin Rheumatol*. 2015;29(4):543-549.

27

Synthetic DMARDs Approved for RA

- Methotrexate (MTX)
- Sulfasalazine (SSZ)
- Hydroxychloroquine (HCQ)
- Leflunomide
- Tofacitinib*

*The Janus kinase (JAK) inhibitor tofacitinib is a targeted synthetic DMARD.

Smolen JS, et al. *Lancet*. 2016. [Epub ahead of print]

28

Methotrexate: Cornerstone of RA Treatment

- First-line therapy
- Efficacy of MTX alone or as combination therapy:
  - Superior to placebo
  - Comparable to other drugs, including anti-TNF therapy
- At 1 year, one-third of patients on MTX have no radiographic progression
- Greater efficacy when combined with targeted biologics
- Reduces immunogenicity of biologic DMARDs
- GI toxicity is the most common (bone marrow, lung, and liver toxicity are rare)

GI, gastrointestinal.

Weinblatt ME. *Trans Am Clin Climatol Assoc*. 2013;124:16-25.

29

Biologic DMARDs Approved for RA

Class	Agent
TNF inhibitor	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab
Selective co-stimulation modulator	• Abatacept
B-cell inhibitor	• Rituximab
IL-6 Inhibitor	• Tocilizumab

IL-6, interleukin 6.

Smolen JS, et al. *Lancet*. 2016. [Epub ahead of print]

30

Efficacy of Combination Therapy vs MTX Monotherapy

Measure	MTX-Naive Patients	MTX-IR Patients
ACR50	Superior to MTX monotherapy: • Triple therapy (SSZ and HCQ) • MTX plus abatacept, adalimumab, etanercept, infliximab, rituximab, tocilizumab, or tofacitinib	Superior to MTX monotherapy: • Triple therapy • MTX plus HCQ, leflunomide, most biologics, or tofacitinib
Inhibition of radiographic progression	Superior to MTX monotherapy: • Combination with adalimumab, etanercept, certolizumab, or infliximab*	No treatments superior to MTX monotherapy

*Estimated mean change over 1 year with all treatments was less than the minimal clinically important difference of 5 units on the Sharp/van der Heijde scale.

MTX-IR, inadequate response to methotrexate.

Hazlewood GS, et al. *BMJ*. 2016;353:i1777.

31

Comparison of DMARDs

	Advantages	Disadvantages
sDMARDs	• Alleviate symptoms to some degree • Long track record of use	• Limited efficacy • Poor tolerability (majority of patients stop after 1–2 years) • Toxicity concerns
tsDMARDs	• Target specific molecular structures • Oral bioavailability	• Less evidence about impact on long-term disease progression • Potential for immunosuppression
bDMARDs	• Potential for inducing remission	• Shorter track record of use compared with traditional DMARDs • Potential for immunosuppression

bDMARDs, biologic DMARDs; sDMARDs, synthetic DMARDs; tsDMARDs, targeted synthetic DMARDs.

Smolen JS, et al. *Lancet*. 2016.

Ruderman EM. *Rheumatology (Oxford)*. 2012;51(suppl 6):vi37-43.

32

Emerging Agents for RA Treatment

Class	Agent	Mechanism of Action	Clinical Study Status
bDMARD	Sarilumab	Anti-IL-6	Phase 3
	Mavrilimumab	Anti-GM-CSF receptor	Phase 2
	Olokizumab	Anti-IL-6	Phase 2
	Sirukumab	Anti-IL-6	Phase 2
tsDMARD	Baricitinib	JAK inhibitor	Phase 3

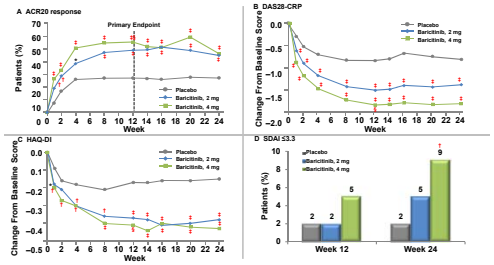
GM-CSF, granulocyte macrophage colony-stimulating factor.

Avci AB, et al. *Clin Exp Rheumatol*. 2016;34(4, suppl 98):39-44.

Smolen JS, et al. *Lancet*. 2016.

33

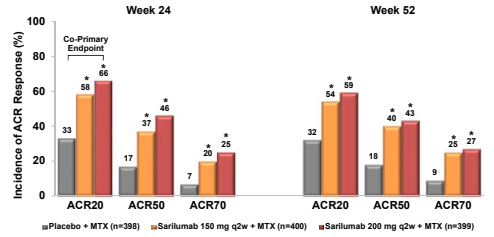
Targeting JAK1/2: Baricitinib for Mod-to-Severe RA with Inadequate Response to Anti-TNFs



*P≤.05; †P≤.01; ‡P≤.001; §P≤.001 for 4-mg dose baricitinib vs placebo.

Genovese MC, et al. *N Engl J Med*. 2016;374(13):1243-1252.

Targeting IL-6: Sarilumab for Mod-to-Severe RA with Inadequate Response to MTX

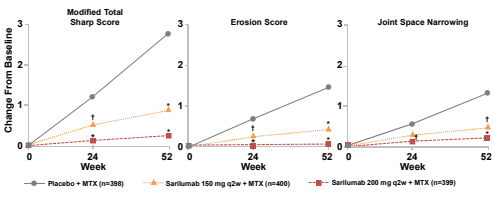


*P<.0001 vs placebo plus MTX (results based on nonresponder imputation).

q2w, every 2 weeks.

Genovese MC, et al. *Arthritis Rheum*. 2015;67(6):1424-1437.

Treatment with Sarilumab and MTX Reduces Signs of Radiographic Progression



*P<.001; †P<.01.

Genovese MC, et al. *Arthritis Rheum*. 2015;67(6):1424-1437.

PRACTITIONER'S EDGE

Pharmacologic Management

Safety Considerations

Overview of Safety with Biologic and Nonbiologic DMARDs

DMARD	Safety Concerns
MTX	• Hepatotoxicity • Cytopenias • Pneumonitis
Anti-TNFs	• Increased risk of infection (including serious infections) by bacterial pathogens, atypical fungi, and opportunistic pathogens • Reactivation of latent tuberculosis (screening is recommended) • Malignancy (evidence suggests no increased risk of solid tumors though nonmelanoma skin cancers are more common)
Tocilizumab	• GI perforation
Rituximab	• Progressive multifocal leukoencephalopathy
Abatacept	• Pulmonary infection

Note: Rare systemic adverse effects (AEs) include lupus, multiple sclerosis, congestive heart failure, and psoriasis.

Ruderman EM. *Rheumatology*. 2012;51(suppl 6):37-43; D'Haens G. *Gut*. 2007;56(5):725-732; Rubbert-Roth A. *Rheumatology*. 2012;51(suppl 5):v38-47.

38

Comparison of Biologic Therapy vs Placebo

- Biologic therapy* vs placebo in patients with any disease except HIV/AIDS
- 163 RCTs (N=50,010; mean duration = 6 months)
- 46 OLEs (N=11,954; mean duration = 13 months)

	OR	NNTH
Total AEs	1.19 (1.09–1.30)	30 (21–60)
Withdrawals due to AEs	1.32 (1.06–1.64)	37 (19–190)
TB reactivation†	4.68 (1.18–18.60)	681 (143–14706)

- **Serious AEs, serious infections, lymphoma,† and CHF† did not differ significantly between biologic vs control groups**

*Etanercept, adalimumab, infliximab, golimumab, certolizumab, anakinra, tocilizumab, abatacept, and rituximab.
†Limited data.
OLE, open-label extension; OR, odds ratio; NNTH, number needed to treat to harm; RCT, randomized controlled trial; TB, tuberculosis.
Singh JA, et al. *Cochrane Database Syst Rev*. 2011;(2):CD008794.

39

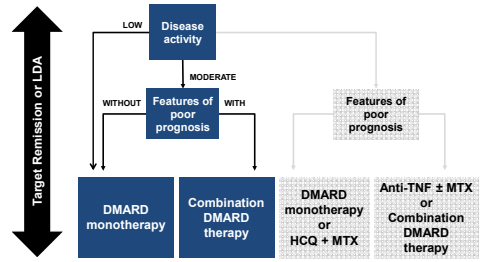
PRACTITIONER'S EDGE

Treatment of Early RA

Jane: Case Study Discussion

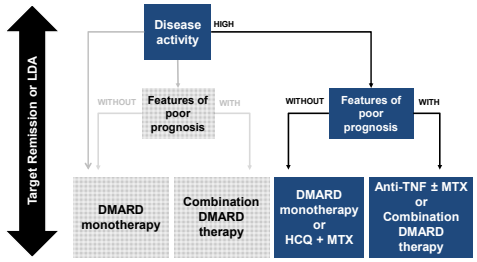
- Based upon Jane's clinical profile, what initial treatment would you prescribe for her?
- How do the relative safety concerns associated with the different treatment options impact your decision?
- How would your treatment decision differ if she demonstrated signs indicative of poor prognosis (eg, extra-articular symptoms) or a higher initial level of disease activity?

ACR Treatment Recommendations for Early RA



Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

ACR Treatment Recommendations for Early RA (cont'd)



Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

Jane: Case Study Discussion

- Jane is initiated on oral MTX (10–25 mg/week) plus a folic acid supplement
- What type of monitoring would you implement for Jane?
  - How frequently would you recommend that she be reevaluated?
  - At what point would you refer her to a specialist for follow-up?

Laboratory Monitoring During Treatment with DMARDs

Recommended Laboratory Monitoring Intervals for CBC, Liver Transaminase Levels, and SCr levels*

Therapeutic Agents	Monitoring Interval Based on Duration of Therapy† <3 Months	3–6 Months	>6 Months
Hydroxychloroquine	None after baseline	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

*More frequent monitoring recommended within first 3 months of therapy or after increasing dose, and the outer bound of monitoring interval is recommended beyond 6 months of therapy.
†Patients with comorbidities, abnormal laboratory results, and/or multiple therapies may require more frequent laboratory testing than generally for DMARDs in the table.
CBC, complete blood count; SCr, serum creatinine.

Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

Defining Treatment Failure

- Inadequate initial response (primary treatment failure)
- Attenuation of response over time (secondary treatment failure)
- Definition of "inadequate response"
  - Clinical outcomes or ACR or DAS criteria
  - Radiographic disease activity
  - Patient-reported outcomes
  - QOL

Emery P. *Rheumatology*. 2012;51(suppl 5):v22-v30.
Bergman MJ. *Clin Ther*. 2009;31(6):1219-1231.

46

PRACTITIONER'S EDGE

Treatment of Established RA

Case Study 2: John, a 50-Year-Old Male with Established RA

- Overweight (BMI 26 kg/m^2)
- Prediabetic (HbA1c: 5.8%)
- Previous diagnosis of RA
  - Persistent symmetric polyarthritis (synovitis) of hands
  - Progressive articular deterioration
  - Extra-articular involvement
  - Associated difficulty with ADLs
- Current medications
  - MTX
  - Sulfasalazine

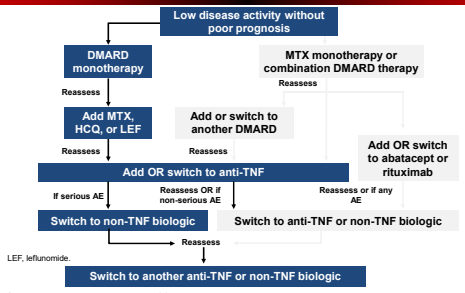
ADLs, activities of daily living; BMI, body mass index.

48

John: Case Study Discussion

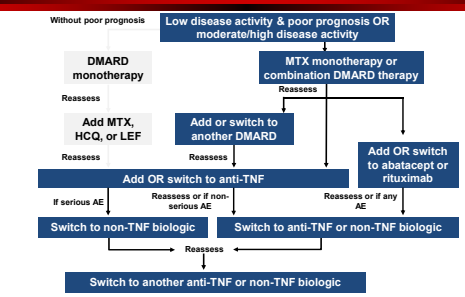
- How would you characterize John's level of disease activity?
- What alterations to his current treatment regimen would you recommend?

Treatment for Established RA: Low Disease Activity without Poor Prognosis



Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

Treatment of Established RA: Poor Prognosis or Moderate/High Disease Activity



Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

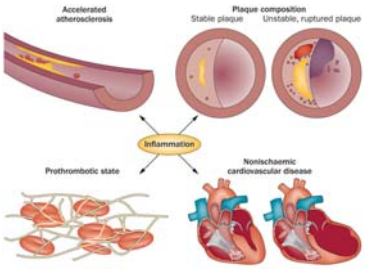
PRACTITIONER'S EDGE

Management of Comorbidities

Comorbidities of RA

- Cardiovascular disease
  - Hypertension
  - Hyperlipidemia
  - Congestive heart failure
- Metabolic disorders
  - Obesity
  - Diabetes
- Osteoporosis
- Fibromyalgia
- Malignancy
  - Lymphoma
- Infection
- Depression
  - Suicidal ideation

Role of Inflammation in CVD



Nurmohamed MT, et al. *Nat Rev Rheumatol*. 2015;11(12):693-704.

John: Case Study Discussion

- How is your treatment recommendation influenced by John's risk for CVD?
- Is his prediabetic status also an influencing factor?
- What type of monitoring would you recommend for him and how often would you reevaluate him?

55

CVD Prevention in Patients with RA: Screening and Monitoring

- Consider RA as an independent CV risk factor
- Routinely screen for symptomatic and silent CVD
- Monitor modifiable CV risk factors annually and during intensified antirheumatic therapy, at least from 40 to 50 years of age
- Adjust intensity of monitoring according to CV risk
- Maintain a low threshold for cardiologic investigation (CVD clinical profile in RA may be atypical)
- Consider causes other than atherosclerosis (eg, vasculitis)

CV, cardiovascular.

Hollan I, et al. *Autoimmun Rev*. 2015;14(10):952-969.

56

Additional Management Strategies for Reducing CVD Risk in Patients with RA

- Routine BP, PG, SCr, and urine monitoring
- TC, LDL, HDL, and triglyceride screening
- Screening and/or counseling for poor diet, physical inactivity, overweight, central obesity, and stress
- Screening and/or management of psychosocial factors
- Smoking cessation
- Routine vaccination
- Dental hygiene and treatment
- Vitamin D deficiency treatment
- Folic acid supplementation during MTX treatment
- Aspirin as recommended for general CVD prevention

BP, blood pressure; PG, plasma glucose; TC, total cholesterol.

Hollan I, et al. *Autoimmun Rev*. 2015;14(10):952-969.

57

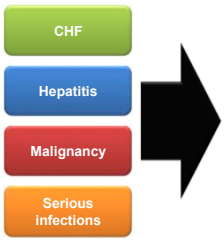
Case Study: John's Treatment Plan

- Based upon John's current level of disease activity despite combined therapy with MTX and SSZ, along with his risk for CVD, he is switched to adalimumab (40 mg SC q2w)
- What type of monitoring, if any, would be appropriate for John given the switch to a biologic treatment?

SC, subcutaneously.

Hollan I, et al. *Autoimmun Rev*. 2015;14(10):952-969.

Considerations for RA Patients with High-risk Comorbidities



- Specialist collaboration and monitoring
- Management of polypharmacy
- Avoidance of anti-TNFs or other biologics depending on clinical circumstance

CHF, congestive heart failure.

Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

PRACTITIONER'S EDGE

Patient Education and Shared Decision-making

Education for Patients with Inflammatory Arthritis

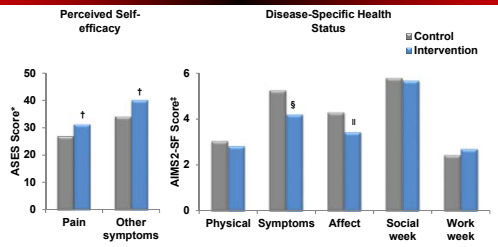
An education program should:

- Be an integral part of care to increase patient involvement in disease management
- Be offered throughout the disease course
- Include individual/group sessions via face-to-face or online interactions and supplemented by phone calls, written, or multimedia material
- Individually tailored and needs based
- Have a theoretical framework and be evidence based (eg, self-management, CBT, or stress management)
- Be evaluated for effectiveness using outcomes reflecting program objectives
- Be delivered by HCPs and/or by trained patients, if appropriate, in a multidisciplinary team

CBT, cognitive behavioral therapy; HCP, healthcare provider.
Zangi HA, et al. *Ann Rheum Dis*. 2015;74(6):954-962.

61

Needs-Based Patient Education: Impact on Self-efficacy and Health Outcomes in RA



*Higher score = greater self-efficacy. †Bonferroni-adjusted *P* value =.025 for significance at the α level; ‡Zero = good health status; §*P* = .013; ‖*P* = .006.
AIMS2-SF, short form of Arthritis Impact Measurement Scale 2; ASES, Arthritis Self Efficacy Scale.
Ndosi M, et al. *Ann Rheum Dis*. 2016;75(6):1126-1132.

62

Shared Decision-making Among Patients With RA

- SDM communication among patients with RA:

Patient Population	N	Percentage Reporting Suboptimal Communication in SDM (95% CI)
UCSF RA Cohort	234	30% (25%–37%)
RA Panel	275	32% (27%–38%)

- Factors associated with suboptimal SDM communication:
  - Low trust in physician (both cohorts)
  - Older age (UCSF RA Cohort)
  - Limited English proficiency (UCSF RA Cohort)
  - Limited health literacy (RA Panel)

SDM, shared decision-making; UCSF, University of California, San Francisco.
Smolen JS, et al. *Ann Rheum Dis*. 2010;69(4):631-637. Barton JL, et al. *J Rheumatology*. 2014;41(7):1290-1297.

63

Summary

- Early, accurate diagnosis is crucial to achieving remission, preserving function, and preventing long-term complications in patients with RA
- Many efficacious disease-modifying treatment options are currently available and continue to emerge
- Patients undergoing treatment should be monitored for clinical and radiographic indicators of disease activity, as well as the occurrence of adverse effects, as part of a treat-to-target algorithm
- Management strategies must take into consideration that patients with RA are at increased risk for comorbidities, especially CVD
- Optimal management of RA requires adequate communication and needs-based patient education to facilitate shared decision-making

64

Please Remember…

- Complete Session Pre- and Post-Test
- Complete Online Session Evaluation at End of Session
  - https://www.surveymonkey.com/r/Nov_18_900_RA

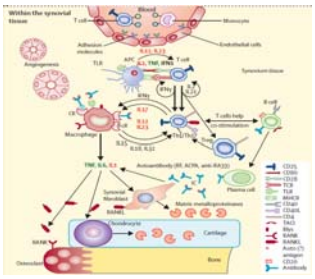
****Links found in Event App**

65

Thank You!

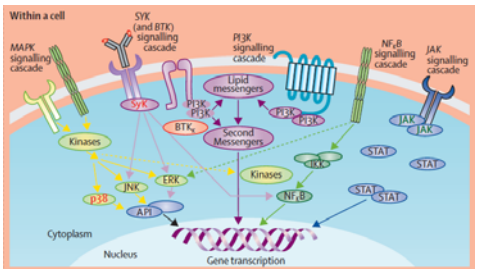
Back Up

Cell Biology



Smolen JS, et al. *Lancet*. 2016.

Molecular Biology



Smolen JS, et al. *Lancet*. 2016.

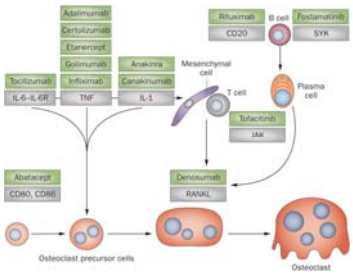
Treatment Target in RA

- The primary target of RA treatment should be a state of **clinical remission**, defined as the absence of signs and symptoms of significant inflammatory disease activity
- While remission should be a clear target**, low disease activity (LDA)** may be an acceptable alternative therapeutic goal (especially in established long-standing disease)

Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

70

Site of Action of Biologic DMARDs and Tofacitinib



Adapted from: Schett G, et al. *Nat Rev Rheumatol*. 2012;8(11):656-664.

71

ACR/EULAR Criteria for RA Classification

Joint Involvement	Joints Involved*	Score
	1 large joint	0
	2–10 large joints	1
	1–3 small joints†	2
	4–10 small joints†	3
	>10 joints‡	5
Serology	Test Results§	Score
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
Acute-Phase Reactants	Test Results§	Score
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of Symptoms	Time	Score
	<6 weeks	0
	>6 weeks	1
	Total Score	

*Large joints = shoulders, elbows, hips, knees, and ankles; small joints = metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

†With or without large joint involvement.

‡At least 1 small joint.

§At least one test required for classification.

Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.

72

Potential Adverse Effects of sDMARD Treatment

sDMARD	Potential AE
MTX	Marrow suppression Hepatitis Liver fibrosis Pneumonitis Lung fibrosis Teratogenicity
HCQ	Retinopathy
SSZ	Bone marrow suppression Skin rashes
Leflunomide	Bone marrow suppression Diarrhea Alopecia Rashes Headache Immunosuppression/Infections Teratogenicity

Ally M, et al. *SA Orthop J.* 2010;9:30-33.

73

Reported Rates of Serious Infection: bDMARDs and Tofacitinib

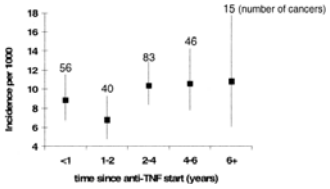
DMARD	SIEs Per 100 Patient-Years	
	Biologic	Comparator
Adalimumab	4.60	-
Certolizumab pegol	5.61	1.35 (placebo)
Abatacept	2.87	2.60 (placebo)
Rituximab	3.76	-
Tocilizumab	3.60	1.50 (MTX)
Tofacitinib	4.17*/2.32†	3.68 (placebo)

*5 mg bid; †10 mg bid.
bid, twice a day; SIE, serious infectious event.

Khraishi M, et al. *Clin Ther.* 2010;32(11):1855-1870; Weinblatt ME, et al. *J Rheumatol.* 2013;40(6):787-797; Boyce EG ,et al. *Patient Related Outcome Measures.* 2016;7:1-12; Genovese MC, et al. *Ann Rheum Dis.* 2009;68(12):1894-1897; van Vollenhoven RF, et al. *J Rheumatol.* 2015;42(10):1761-1766; Burmester GR, et al. *Ann Rheum Dis.* 2013;72(4):517-524.

74

Incidence of Malignancy With Anti-TNF Treatment



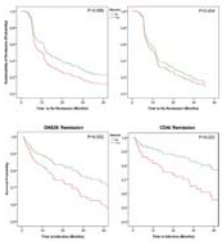
No change in the incidence of malignancy was observed with anti-TNF treatment over time (*P* = 0.36).*

*Adjusted for age and sex.

Gross RL, et al. *Arthritis Rheum.* 2014;66(6):1472-1481.

75

Impact of Concomitant Therapies: Combined Corticosteroid and Anti-TNF Treatment

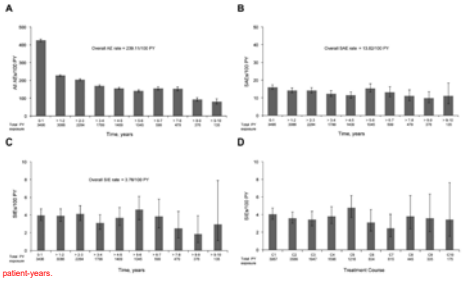


Oral corticosteroid treatment was associated with increased risk of development of infection without impacting sustainability of remission.

Haraoui B, et al. *Rheum Musculoskelet Open*. 2015;1(1):e000078.

76

Long-term Safety of Rituximab in RA

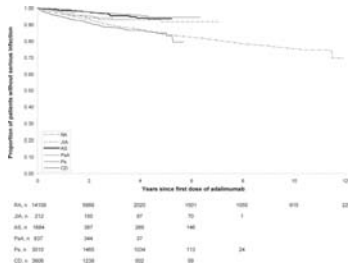


PY, patient-years.

van Vollenhoven RF, et al. *J Rheumatol*. 2015;42(10):1761-1766.

77

Long-term Safety of Adalimumab: Serious Infection Rates

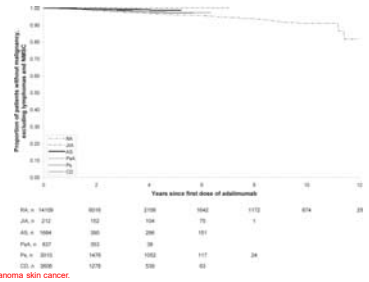


AS, ankylosing spondylitis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; Ps, psoriasis; PsA, psoriatic arthritis.

Burmester GR, et al. *Ann Rheum Dis*. 2013;72(4):517-524.

78

Long-term Safety of Adalimumab: Malignancy



NMSC, nonmelanoma skin cancer.

Burmester GR, et al. *Ann Rheum Dis*. 2013;72(4):517-524.

Use of Biologics in Patients With High-risk Comorbidities

Comorbidity/Clinical Circumstance	Recommended	Not Recommended
HEPATITIS • HCV • Untreated chronic HBV or with treated chronic HBV with Child-Pugh class B and higher*	Etanercept	Any biologic
MALIGNANCY • Treated solid malignancy or treated nonmelanoma skin cancer >5 years ago	Any biologic	
• Treated solid malignancy or treated nonmelanoma skin cancer in the last 5 years†	Rituximab	
• Treated skin melanoma†	Rituximab	
• Treated lymphoproliferative malignancy	Rituximab	
CHF • NYHA class III/IV and with an EF ≤50%‡		Anti-TNF biologic
SERIOUS INFECTION		Anti-TNF biologic

EF, ejection fraction; HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart Association.

Singh JA, et al. *Arthritis Rheum*. 2016;68(1):1-26.