

Rheumatoid Arthritis

Diagnosis and Management

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 - Clinical focus: General Rheumatology, Rheumatology-Oncology

Disclosures

- Nothing to disclose

Discussion topics

- Definition of rheumatoid arthritis (RA)
- Diagnosing RA
 - Use of history, exam, serologies, imaging
- Treatments for RA
 - What to do before starting therapy
 - Major treatment categories and their benefits/risks
- Questions and answers

What is RA?



ACR Criteria for Diagnosis –pre 2010

- Four or more of the following criteria must be present:
 - Morning stiffness > 1 hour
 - Arthritis of ≥ 3 joint areas
 - Arthritis of hand joints (MCPs, PIPs, wrists)
 - Symmetric swelling
 - Serum rheumatoid factor
 - Radiographic changes

First 4 must be present for > 6 weeks

Re-defining RA: 2010 Classification Criteria from ACR/EULAR

- Who should be tested?
 - Patients with synovitis of at least one joint which has no other explanation
- Point system
 - $\geq 6/10$ points required to make the diagnosis of RA
- Points given based on
 - Number of joints involved
 - Serology (Rheumatoid factor and anti-CCP/ACPA)
 - Acute phase reactants
 - Duration of symptoms

Characteristic exam

- Symmetric synovitis
 - Small joint involvement is most common
 - Joints generally spared
 - Distal interphalangeal joints (DIPs)
 - Lumbosacral spine

Extraarticular involvement

- Lung
 - Interstitial lung disease
- Cardiovascular
 - Vasculitis
 - Pericarditis
 - Coronary artery disease
- Skin
 - Rheumatoid nodules

Characteristic lab findings

- Elevated inflammatory markers (ESR, CRP)
- Positive serologies
 - Rheumatoid factor
 - Positive in 70-80% of RA patients
 - Anti-CCP
 - High specificity for RA
- CBC
 - Anemia
 - Felty's syndrome
 - Neutropenia, splenomegaly, seropositive RA
- Inflammatory fluid on joint aspirate
 - Typically WBC >2,000 cells/uL

Characteristic imaging

- X-ray
 - Erosions, peri-articular osteopenia
 - Changes not generally seen for at least 3 months
 - Useful for diagnosis and staging
- MRI and ultrasound
 - Synovitis and tenosynovitis
 - Useful for confirmation of synovitis if not evident on exam

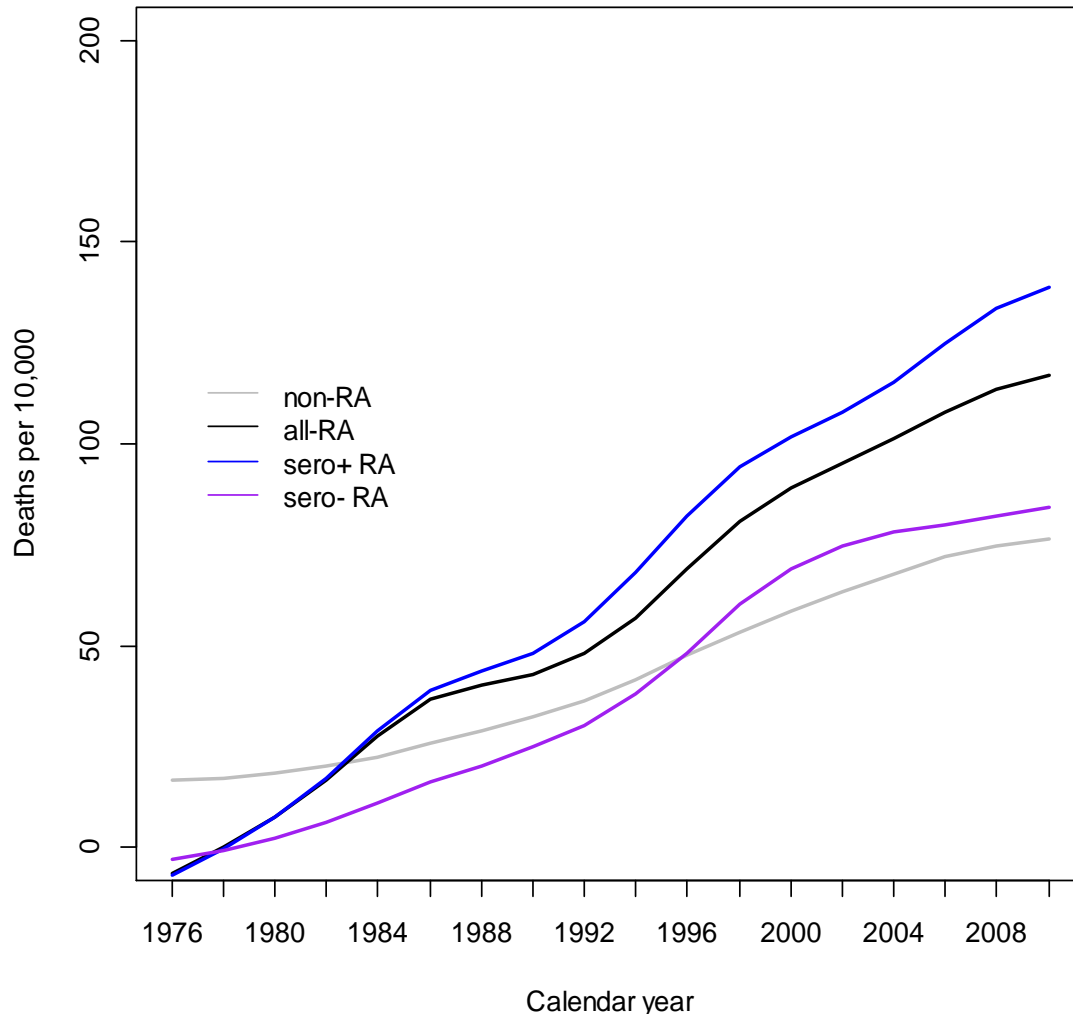


When to initiate treatment?

- As soon as you make the diagnosis
 - Early treatment has been linked to better outcomes for patients
 - Reduced surgeries
 - Reduced evidence of joint damage on imaging
 - Better chance of remission
 - Treatment of RA may improve life expectancy as well

Decreased life expectancy in RA

Age-Standardized Mortality 1976-2012 in NHS

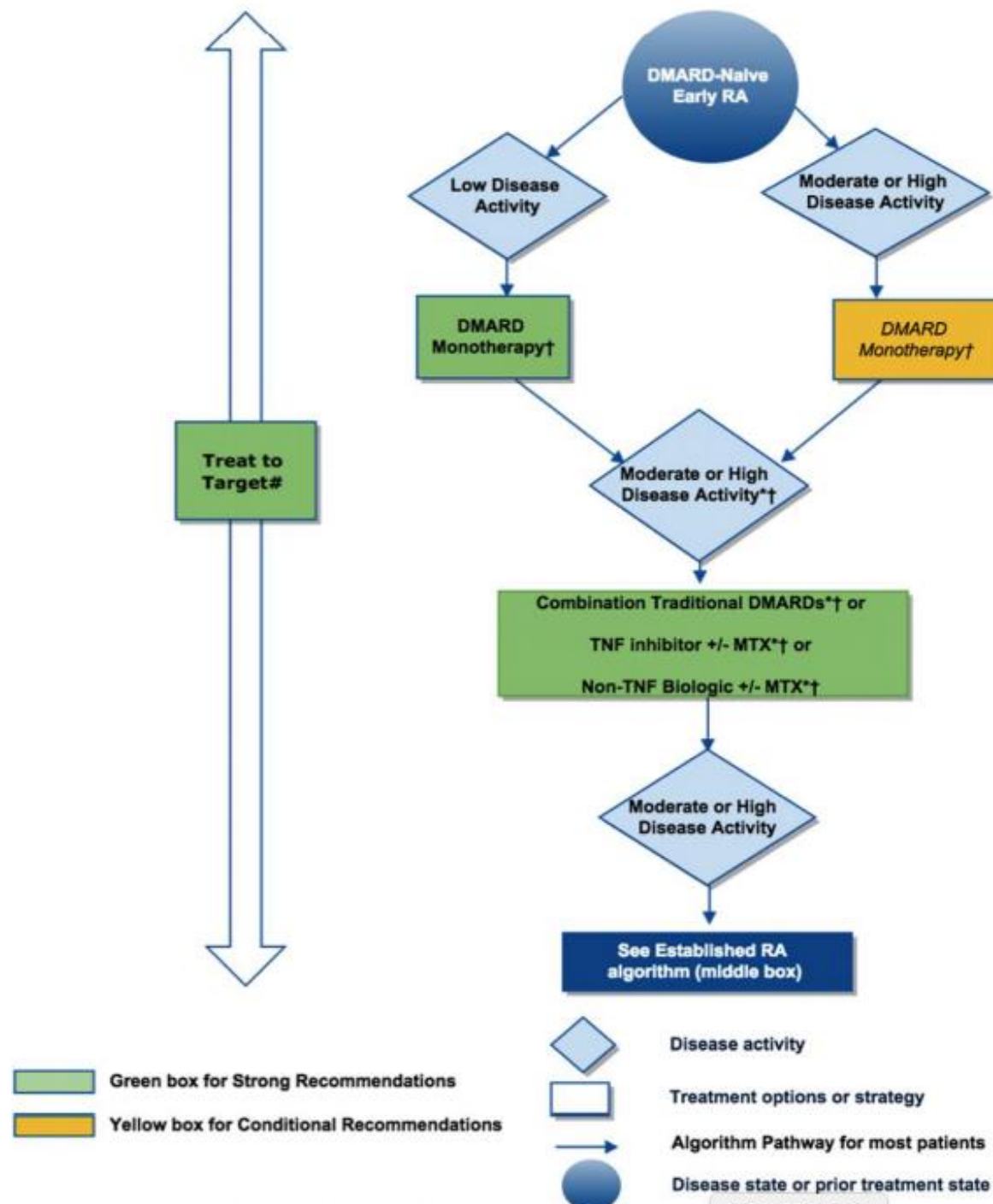


- Possibly due to increased risk of cardiovascular disease
- Treatment may substantially improve life expectancy

Sparks et al, presented at ACR 2014
Sparks et al, Arthritis Care Res, 2016
Avina-Zubieta et al, Arth Care Res, 2008
Wasko et al, Arth Rheum, 2014
Westlake et al, Rheumatology, 2010
Chiu et al, Arth Rheum 2021

What to ensure your patient has before starting immunosuppressive therapy

- Lab baseline
 - CBC, creatinine, liver function tests
- CXR
 - Optional but would consider in older patient or smoker
- Screening for underlying infections
 - T spot/quantiferon gold, hepatitis panel
- Vaccines
 - Influenza, Pneumonia (PCV20/21), COVID-19 vaccines, and non-live recombinant shingles (Shingrix)
 - Most live vaccines are CONTRAINDICATED on immunosuppressive therapy



2015 Guideline for
Treatment of RA
Singh et al, Arth
Care Res 2015

Steroids as disease modifying therapy?

- Helps to quickly decrease inflammation and may even halt progression of disease (ie a DMARD)
- Risks of long-term side effects of steroid-only therapy for RA likely outweigh benefit

Van Everdingen et al, Ann Intern Med, 2002
Boers, Ann Rheum Dis, 2022

Synthetic DMARDs

- Hydroxychloroquine
 - Overall very well-tolerated, but potential side effects
 - Common: Gastrointestinal discomfort, rash
 - Rare: Myopathies, cardiac conduction abnormalities, ocular toxicity (visual field testing recommended every 6-12 months)
- Sulfasalazine
 - Generally used as part of “triple therapy” regimen in RA
 - Potential side effects:
 - Gastrointestinal toxicity
 - Hematologic toxicity
 - Hypersensitivity reactions

What changed the face of RA treatment...



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

ARCHIVE

Efficacy of Low-Dose Methotrexate in Rheumatoid Arthritis

Michael E. Weinblatt, M.D., Jonathan S. Coblyn, M.D., David A. Fox, M.D., Patricia A. Fraser, M.D., Donald E. Holdsworth, M.D., David N. Glass, M.B., Ch.B., and David E. Trentham, M.D.

N Engl J Med 1985; 312:818-822 | [March 28, 1985](#) | DOI: 10.1056/NEJM198503283121303

Methotrexate

- Found to:
 - Change natural history of RA
 - Decrease extra-articular manifestations
 - Increase QOL and even potentially survival

Methotrexate

- Potential toxicities
 - Gastrointestinal discomfort (most common)
 - Liver and hematologic abnormalities
 - Opportunistic infections
 - Effect on reproduction
 - Rare complications:
 - Methotrexate lung injury/pneumonitis
 - Occurring within first year of therapy
 - This is separate from RA-ILD, for which methotrexate is NOT thought to be a culprit
 - Nephrotoxicity
 - ? Malignancy

Leflunomide

- Leflunomide – similar to methotrexate
 - Simple dosing schedule, quicker onset of action
 - Similar side effect profile as methotrexate
 - Teratogenic with long half-life
 - Avoid in women of child-bearing age

What if a DMARD is not enough?

- Options
 - Triple therapy (methotrexate, sulfasalazine, hydroxychloroquine)
 - Biologics
- How to make decision?
 - Both work well
 - Disease progression is similar
 - Possibly less radiographic progression with biologics
 - Possibly quicker time to effect with biologics
 - Consideration of side effects, patient adherence, and cost

Biologic Therapies as of 2025

- Anti-tumor necrosis factor (TNF) agents
 - etanercept, adalimumab, infliximab, golimumab and certolizumab pegol
- IL1-receptor antagonist
 - anakinra
- Co-stimulatory blocker
 - abatacept
- B cell depletion
 - rituximab
- IL6-receptor antagonist
 - tocilizumab, sarilumab
- JAK inhibition
 - tofacitinib, baricitinib, upadacitinib

Anti-TNF Therapy

- All have similar effects—with roughly a response rate of 60-70%
- Work in early disease and late disease
 - Clinical outcomes better in early disease
- Stabilize radiographic progression
- Decreased NSAIDs, steroids and methotrexate doses
- Remission in some studies upon withdrawal

Anti-TNF Therapy - adverse events

- Cutaneous
 - Injection site reactions
 - Diffuse rashes
- Infectious
 - Sepsis, septic joints, pneumococcal infections
 - Tuberculosis
- Cardiac
 - Increased risk class III-IV CHF
- Neurologic
 - Demyelination
- Oncologic
 - Initial concern for increased lymphoma risk
 - Possible increased risk of skin cancers

Brown et al, Arth Rheum, 2002

Solomon et al, Sem Arth Rheum 2014

Abatacept

- Blocks T-cell co-activation pathway
- Similar risks to anti-TNF but less TB risk
- May be used with or without methotrexate
- Usually after TNF “failure”—response rate 50%
- Onset 4-16 weeks

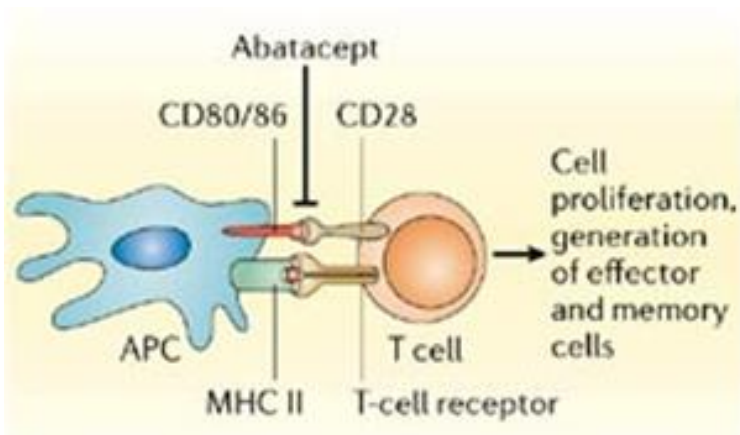


Image courtesy of 2006 Nature Publishing Group, Nature Reviews, Drug discovery

Rituximab

- B cell depletion (anti-CD20)
- For use mainly in seropositive patients
- Adverse side effects
 - Infections including PML, Hepatitis B
 - Ensure Hepatitis panel is checked prior to starting rituximab
 - Rashes including psoriasis
 - Low cell counts (WBC)
 - Low IgG for long durations

IL-6 Inhibition

- **Tocilizumab**
 - Monoclonal antibody that blocks IL-6R
 - Works quickly - onset 2-12 weeks
 - Impressive improvements in CRP, QOL, fatigue
 - Adverse events:
 - Infections
 - ? GI perforation - avoid in patients with history of diverticulitis
 - Lipid, leukocyte and liver test abnormalities
- **Sarilumab**
 - Monoclonal antibody that binds both soluble and membrane-bound IL-6 receptors

JAK inhibitor therapy

- Types
 - Tofacitinib
 - First “oral biologic”
 - Baricitinib
 - Upadacitinib
- Potential complications
 - Infections
 - Zoster- Important to consider vaccination before starting
 - Abnormal lab findings
 - Lipid and LFT abnormalities, neutropenia, anemia

JAK inhibitors may be associated with increased risk of thrombosis (2019)

FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR)

FDA Drug Safety Communication

US FDA communication, February and July 2019

JAK inhibitors may be associated with increased risk of cardiovascular events and lung cancer

Initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine Xeljanz, Xeljanz XR (tofacitinib)

FDA will evaluate the trial results

US FDA communication, February 2021

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H.,
Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D.,
Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D.,
Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D.,
Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D.,
for the ORAL Surveillance Investigators*

Patient with RA on therapy calls with a fever...

- Stop methotrexate/DMARD or biologic
- Have patient come into clinic to be assessed
- Consider further work-up and treatment (ie CXR, antibiotics) sooner than you would with an otherwise healthy patient

RA patients and vaccines

- Non-live vaccines are safe and strongly recommended!
 - Speak to rheumatologist before administering any live vaccines, which are often contraindicated
 - Immunosuppression can decrease efficacy of vaccines
 - If stable RA, consider holding immunosuppressives around the time of vaccines as this can increase efficacy

COVID vaccination and RA

Table 3: Guidance Related to the Use and Timing of Vaccine Dosing and Immunomodulatory Therapy in Relation to COVID-19 Vaccination in RMD Patients*

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination	Level of Task Force Consensus
	(applies to both primary vaccination and supplemental [booster] dosing)	
Abatacept IV	Time vaccination so that it occurs one week prior to the next dose of IV abatacept	Moderate
Abatacept SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
Acetaminophen, NSAIDs	Assuming that disease is stable, hold for 24 hours prior to vaccination. No restrictions on use post vaccination once symptoms develop.	Moderate
Belimumab SQ	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate
TNFi, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitors[†]	The Task Force failed to reach consensus on whether or not to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Hydroxychloroquine, IVIG	No modifications to either immunomodulatory therapy or vaccination timing	Strong (HCQ), Moderate (IVIG)
Rituximab or other anti-CD20 B-cell depleting agents	Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding [‡]	Moderate
All other conventional and targeted immunomodulatory or immunosuppressive medications (e.g., JAKi, MMF) except those listed above [§]	Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose	Moderate

COVID -19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases. Updated 2022, American College of Rheumatology

*Notes: individual medications that were specifically listed on by the task force are listed on separate rows and were not collapsed, even if the

Summary

- Rheumatoid arthritis is a treatable disease
- Early treatment is key
 - Less joint replacements and improved morbidity and mortality
- Ensure patient is up to date with monitoring and vaccines while on therapy
 - Do warn patients on certain immunosuppressives that the COVID vaccine and possibly other vaccines may not be as effective, and consider holding immunosuppressives around the time of vaccine
- There are a growing number of options of treatment

Question 1

- A 58-year-old male presents with polyarticular pain that has lasted for 6 weeks. He has had fevers and weight loss, and has a history of traveling to Cape Cod and Martha's Vineyard. He has morning stiffness, as well as shoulder, hip and MCP pain. Physical exam is normal except for MCP tenderness upon palpation and a small right knee effusion.

Question 1

- All should be a part of the initial diagnostic work-up *EXCEPT*:
 - A. CXR and hand and feet films
 - B. Lyme titer and ANA
 - C. Rheumatoid factor and anti-CCP
 - D. Aspiration of the knee
 - E. ESR and CRP

Question 1: Answer A

- **A: CXR and hand/foot films**
 - While it is not wrong to obtain a CXR (and in fact may be done when deciding drug therapy) it is not essential for diagnosis.
 - Hand and foot films are unlikely to reveal anything significant after only 6 weeks of symptoms.

Question 2

A 48-year-old man presents with rheumatoid arthritis. He is deciding what DMARDs to take. He has erosive disease, and has a history of travel to Russia and Peru, and has a vague sulfa allergy. His labs are unremarkable, except for a creatinine of 1.7 and an AST of 58.

Question 2

All tests should be done before deciding the next therapy
EXCEPT:

- a. CXR
- b. T-SPOT
- c. Pneumonia vaccination
- d. HCV and HBsAg and HBcAg
- e. ACE level and SPEP

Question 2: Answer E

- **ACE level and SPEP**
 - An ACE level would not be helpful in the diagnosis of rheumatoid arthritis and an SPEP, while always interesting, is not needed at this juncture.

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