Inflammatory Arthritis Syndromes: What's New

HMS Internal Medicine
Comprehensive Review and Update 2022

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Disclosures

I have no financial support from industry

Learning Objectives

To review updates in the diagnosis, pathogenesis and management of chronic inflammatory arthritides

Chronic Inflammatory Arthritides

Rheumatoid Arthritis

Psoriatic Arthritis

Ankylosing Spondylitis

Juvenile Idiopathic Arthritis

Crystalline Arthritis

Other Spondyloarthropathies (SpA) (IBD-associated, Reactive Arthritis)

Case 1

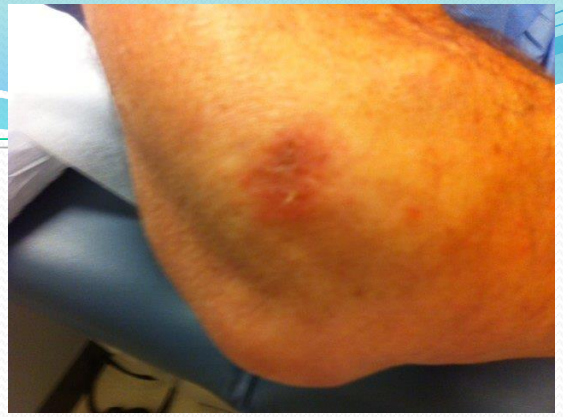
- *73 yo M with HTN, OSA, Lyme disease, now with hand pain. Three years ago, had a tick bite and bullseye rash, did not seek treatment initially. 2.5 months later developed fatigue, arthralgias, brain fog. +Lyme IgG antibodies. Treated with doxycycline and improved. However, developed worsening joint pain, additional doxycycline did not help.*
- *Currently complains of pain in all PIPs, stiffness lasts for several hours*
- *Sister has diagnosis of RA*
- *On exam has swelling and tenderness of PIPs especially R PIP3, LPIP4 and L PIP 5*

Studies: ANA, negative, negative RF, CCP, uric acid 5.0, CRP 25, ESR 29, Lyme IgG equivocal, 4 IgG bands

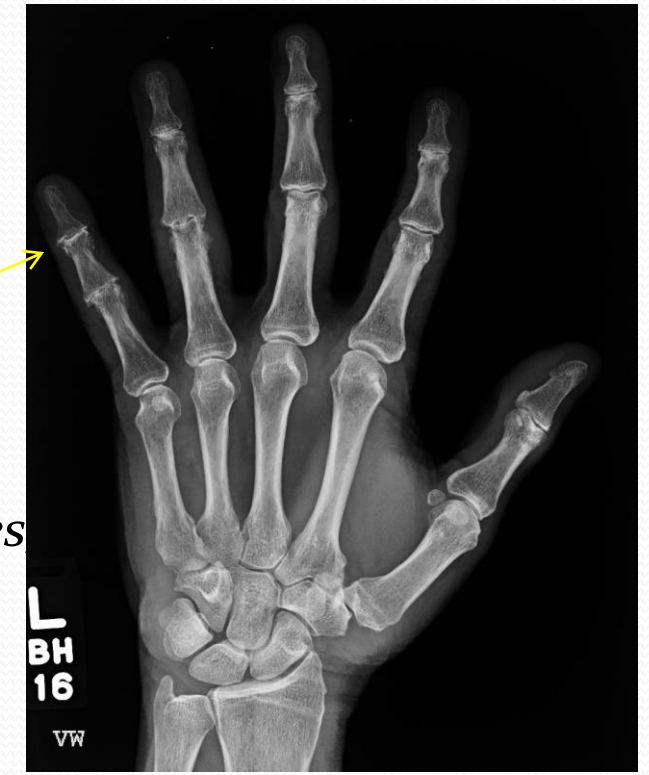
What diagnosis seems most likely?

- A. Lyme arthritis
- B. Post-treatment Lyme disease syndrome (PTLDS)
- C. Seronegative RA or spondyloarthropathy
- D. Osteoarthritis

Case 1-Answer



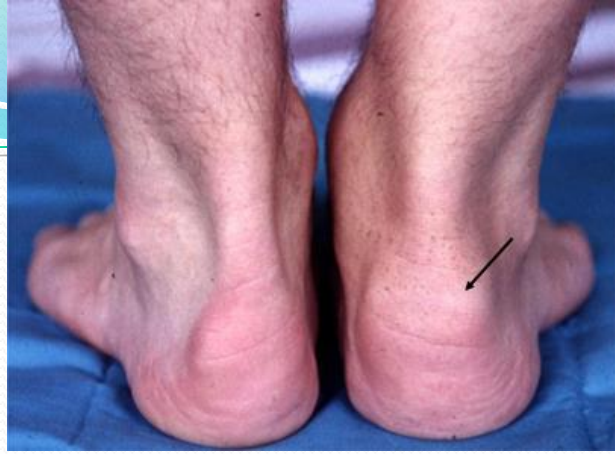
- **C. Seronegative RA or spondyloarthropathy**



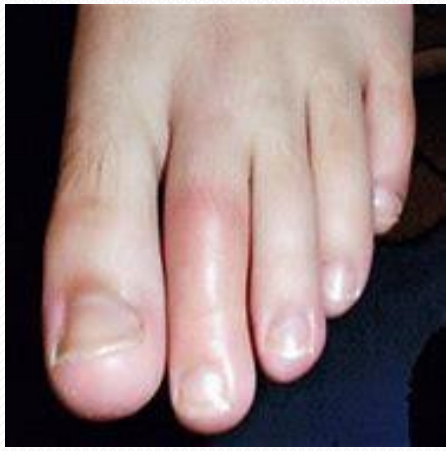
- *Patient was found to have erosions on X-rays of hands.*
- *He reported that 6 mos after the tick bite he developed scaly itchy lesions on scalp and extremities was treating with OTC steroid cream. No physician had noted this problem*

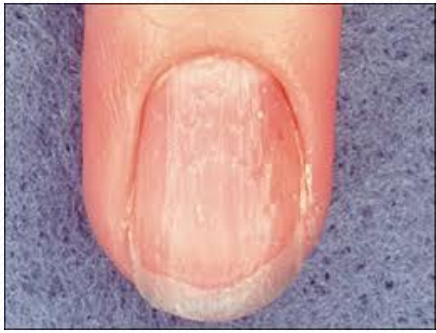
Psoriasis may be underreported/underrecognized. Inflammatory arthritis may follow infections.

Diagnosis-History



- Historical features remain important
  - Morning pain (also night pain in SpA)
  - Stiffness
  - Better with activity
- Family History (40% PsA)
- Extraarticular symptoms:
  - RA: fatigue, dry eyes/mouth (Sjogren's), uveitis
  - SpA: psoriasis (70%), uveitis, enthesitis, dactylitis, GI symptoms





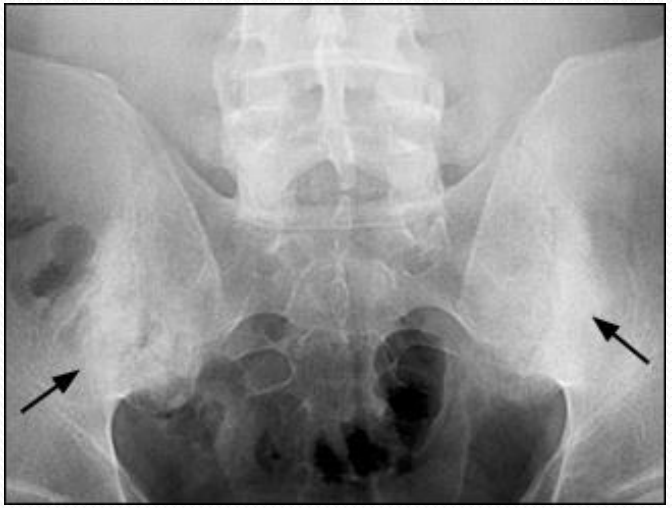
Psoriatic arthritis does not correlate with skin disease severity, skin disease may be subtle

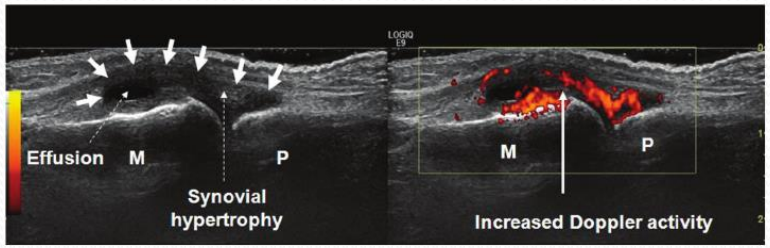
Diagnosis-Data

- Exam: swollen, tender joints
- Blood tests
  - RA: RF (less specific), CCP (95% specific)
    - 1/3 of patients lack RF/CCP
    - CCP monopositivity may be seen
  - ESR/CRP--may be normal
  - HLA-B27—variable depending on SpA type (ie 90% in AS vs 15% PsA) and ethnicity
- Joint fluid analysis
  - inflammatory but non-specific, helps rule out other etiologies

Diagnosis-Imaging

- Subtle physical exam findings in early inflammatory arthritis
- Obtain baseline X-rays
  - RA: hands and feet
  - SpA: SIJ
- X-rays normal in early disease
- MRI and ultrasound are more sensitive for earlier detection of inflammation/synovitis than physical exam and X-ray
- Axial disease such as sacroiliitis is particularly hard to diagnosis and MRI may be needed



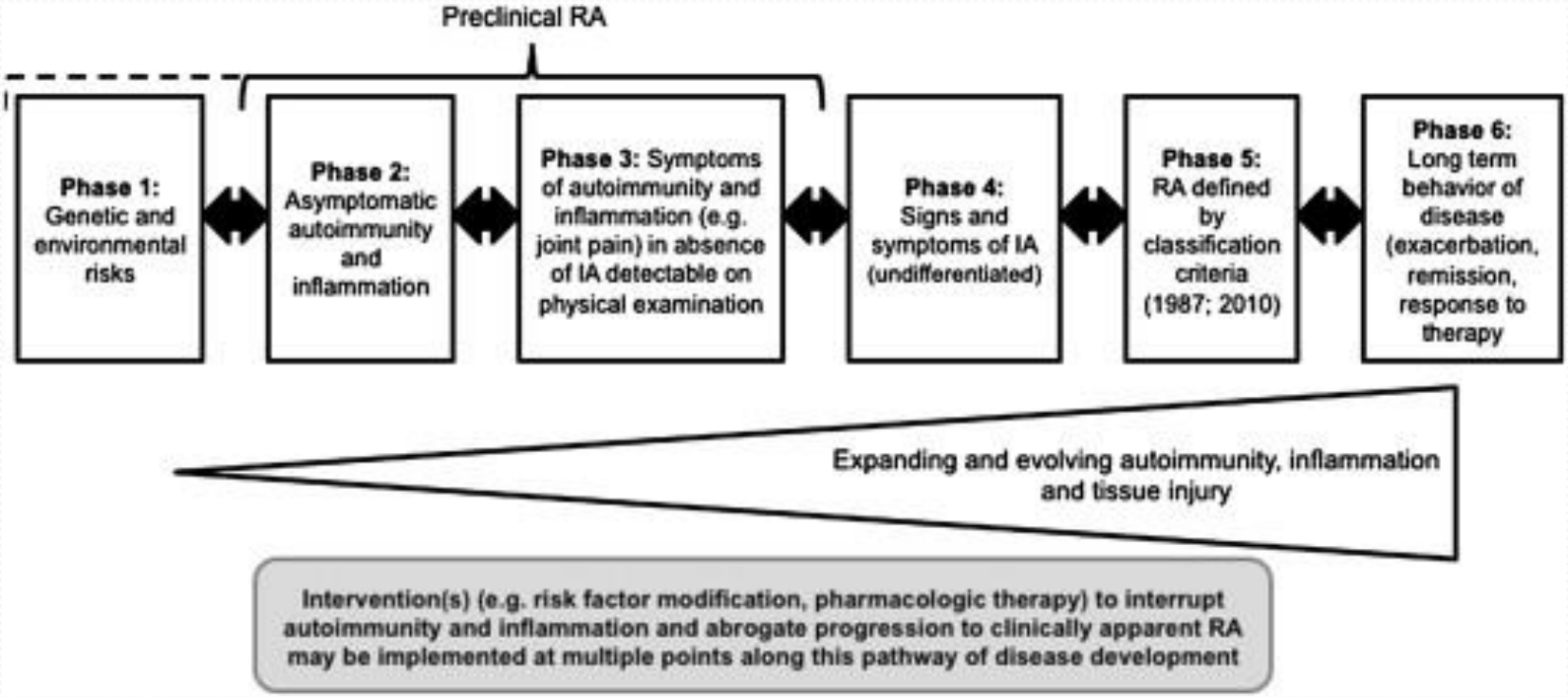


Consider advanced imaging when suspicion for inflammatory arthritis is high but labs/exam normal

A Current Paradigm

- 35 yo F, 1 year of hand pain, stiffness and swelling
- Seen in primary care several times, has MCP swelling on exam but RF negative, ESR/CRP normal
- Eventually referred to rheumatology but wait is 4-5 months for new patient appointment
- Eventually seen by rheumatology 15 months after symptom onset, early erosions seen on MSK ultrasound

Diagnosis—the Future



- Earlier diagnosis and treatment is better!
  - Less damage to joints
  - More potential for remission, cure in very early disease
- Prediction algorithms to identify pre-arthritis patients based on antibodies, inflammatory biomarkers, ultrasound findings

Emerging Paradigm

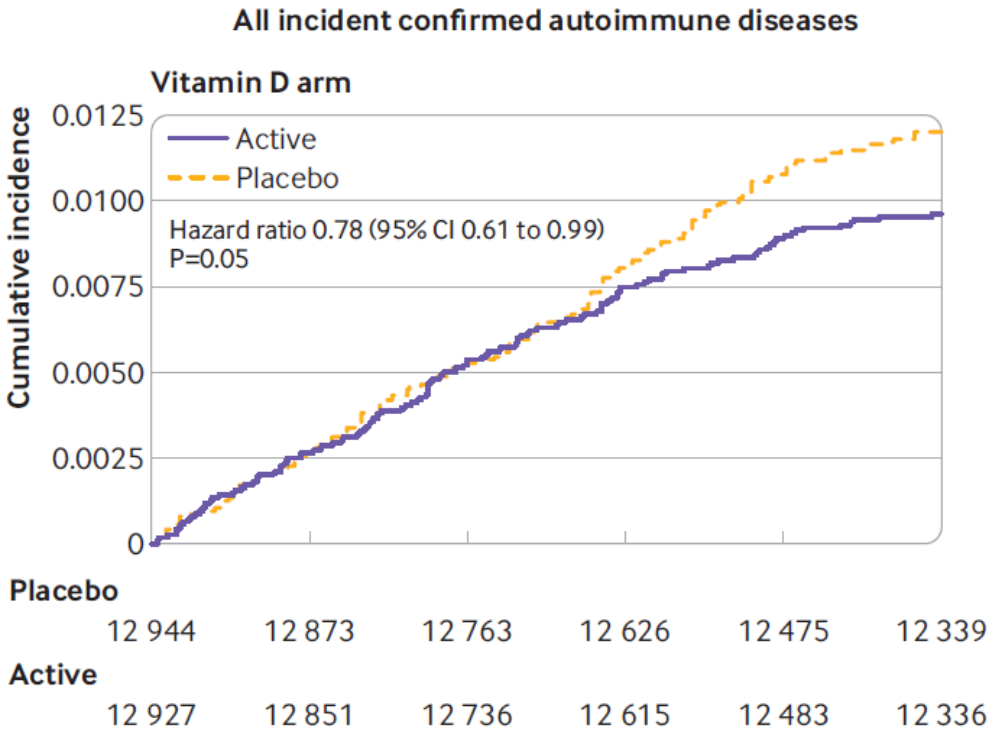
- *35 yo healthy F in your primary care clinic. She currently has no joint symptoms. However, her mother has RA. She wonders if she will also develop RA and if there is anyway to prevent it?*

  - **Exam:** no swollen or tender joints
  - **Studies:** RF44, CCP68, CRP 0.5, ESR 5,

How do we advise this patient?

Approach to Pre-RA

- Risk of RA with +CCP is ~20% in 3-5 years
- Smoking cessation
- Healthy diet and weight loss
  - ? Mediterranean diet
  - Vitamin D supplementation
- Promote Research
- Annual follow-up in rheumatology



VITAL randomized controlled trial: Hahn J, et al. BMJ 2022; 376 :e066452 doi:10.1136/bmj-2021-066452

Case 2

60 yo M, former smoker, with rheumatoid arthritis for 10 years controlled on methotrexate 15mg/week and adalimumab 40mg weekly, here for physical. On ROS endorses mild dry cough and DOE. A CXR is normal. What do you order next?

- A. T-spot
- B. Chest CT
- C. 6 min walk test
- D. NT-proBNP

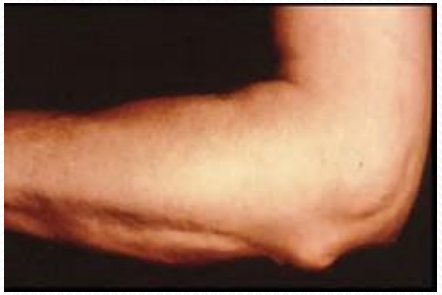
Case 2-Answer

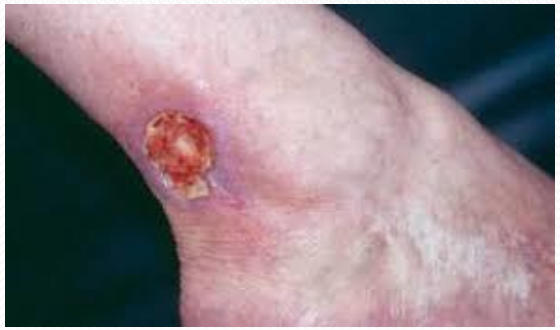
- B. Chest-CT

ILD in RA patients is insidious and CXR is insensitive

Extraarticular Manifestations

- Neuropathy and ulcers (vasculitis--RA)
- Hematologic (RA)
  - Felty's syndrome (splenomegaly, neutropenia)
  - Lymphoma
- Skin
  - Rheumatoid nodules
  - Psoriasis, nail changes
- Eye (conjunctivitis, uveitis)
- **Lung (interstitial lung disease--RA)**
- Cardiac
  - Pericarditis, aortic disease
  - **Cardiovascular disease/atherosclerosis**





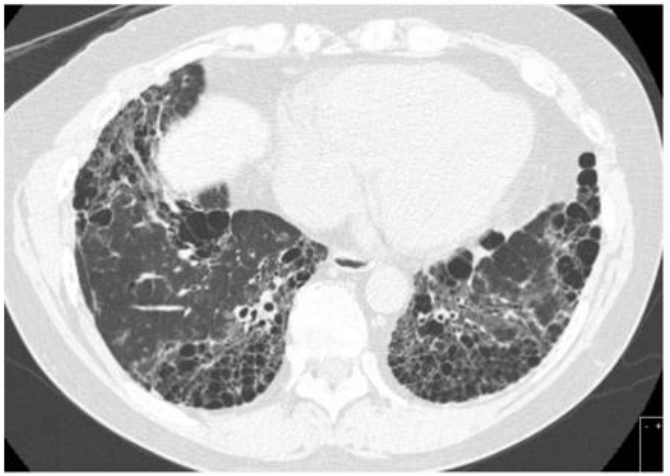
ILD

- Third most common cause of mortality in RA
- Prevalence in RA increasing
- May be subclinical
  - 30-60% on CT
- Occurs *later*
- Risk factors: age, gender, smoking, **MUC5B variant**
- NSIP and UIP (poor prognosis, similar to IPF)

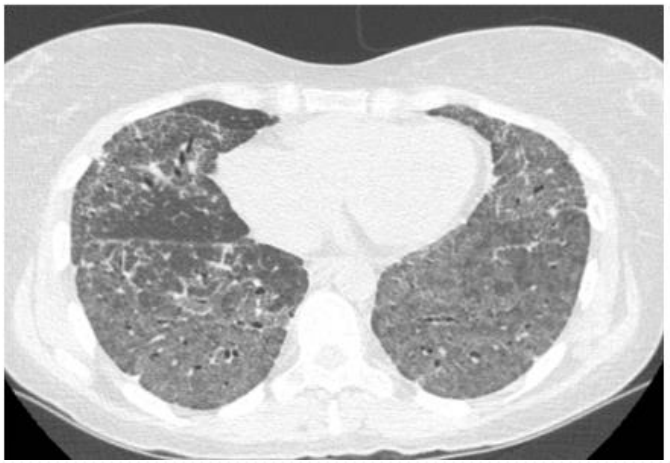
Juge PA et al, NEJM, 2018

HR CT types of RA- ILD

UIP: 44-66% Usual interstitial pneumonia



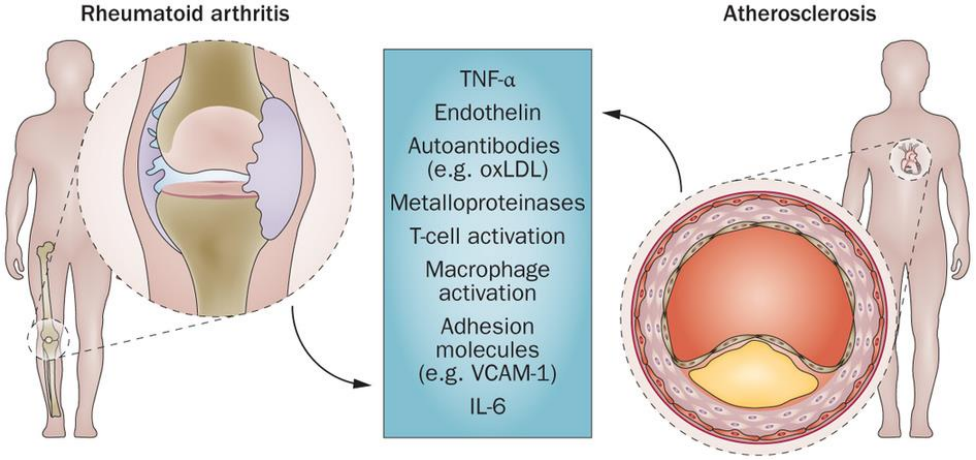
NSIP: 24-44% Non specific interstitial pneumonia



Inflammatory Arthritis Raises CVD Risk

- Inflammatory arthritis confers premature mortality
  - Mortality ratios: RA 1.3-2.3

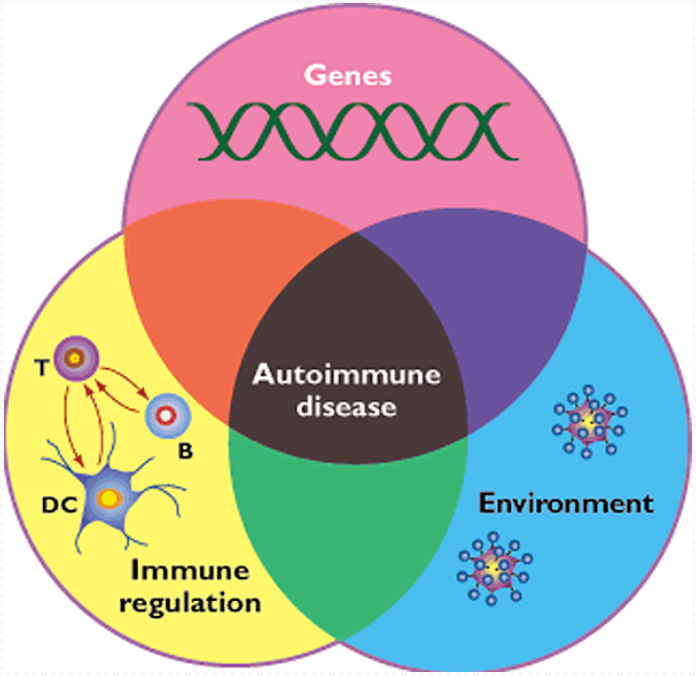
    AS 1.6-1.9 and PsA 0.8-1.6
  - Risk CAD ~DM-2 for RA
- Increased cardiac traditional risk factors
- Systemic inflammation increases plaques/rupture
- Lipid levels may be less reliable in RA patients (lipid paradox)
- Need to control inflammation, as well as modify cardiovascular risk factors , but usually lacking in routine care



Agca R et al, Atherosclerotic cardiovascular disease in patients with chronic inflammatory joint disorders. Heart, 2016 ; 102:7905

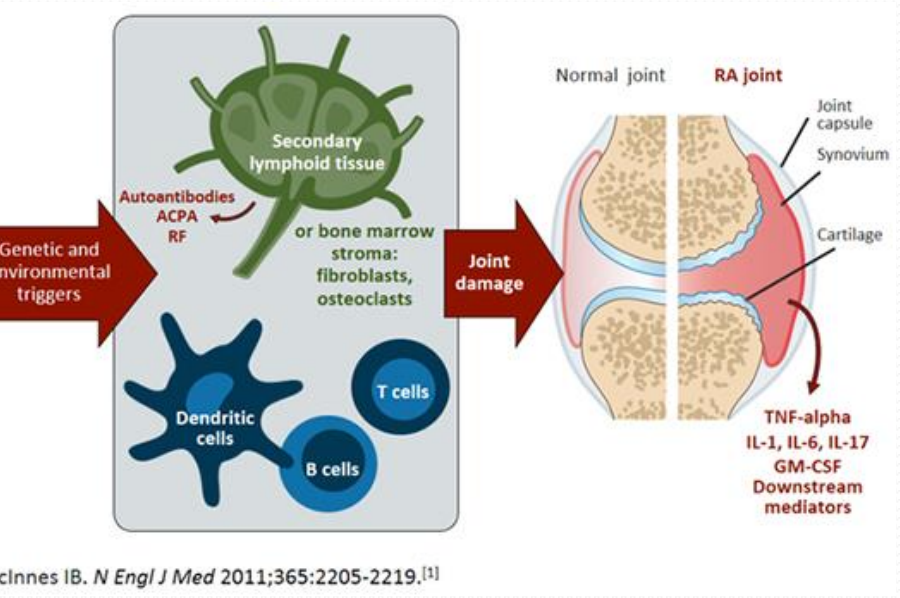
Triggers of Inflammatory Arthritis

- Genes: HLA (i.e. class II RA, class I (SpA), TNF, IL-23 explain only portion of risk
- Smoking
- Obesity
  - Live births, breastfeeding, alcohol: *protective* for *RA*
- Viral/bacterial infections?
- Microbiome
  - Oral/periodontitis
  - Lung
  - **Gut**
  - GU



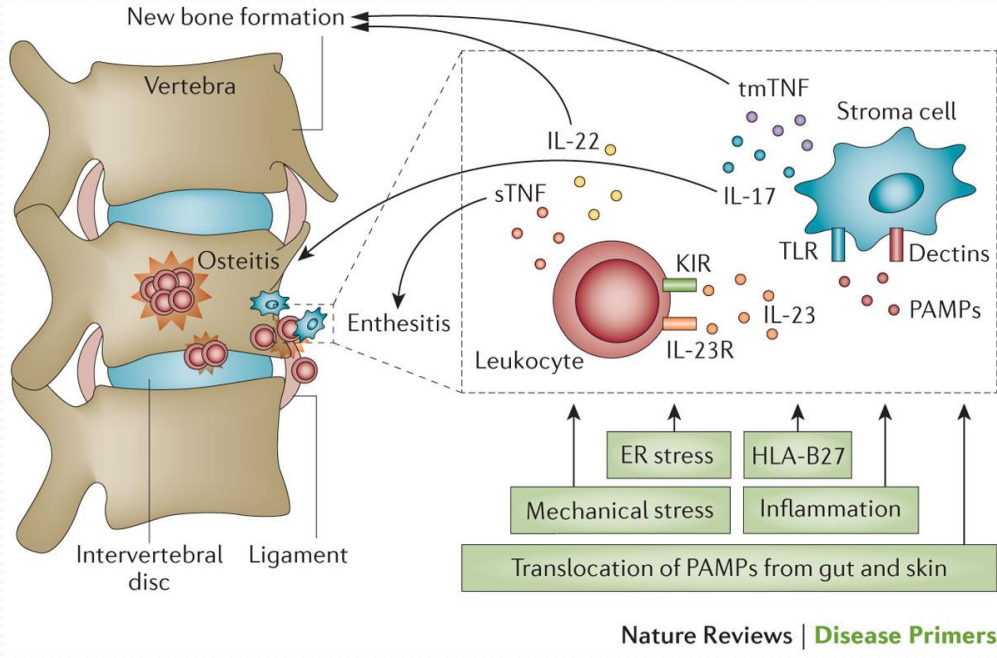
Pathogenesis RA vs SpA

RHEUMATOID ARTHRITIS



cInnes IB. *N Engl J Med* 2011;365:2205-2219.[1]

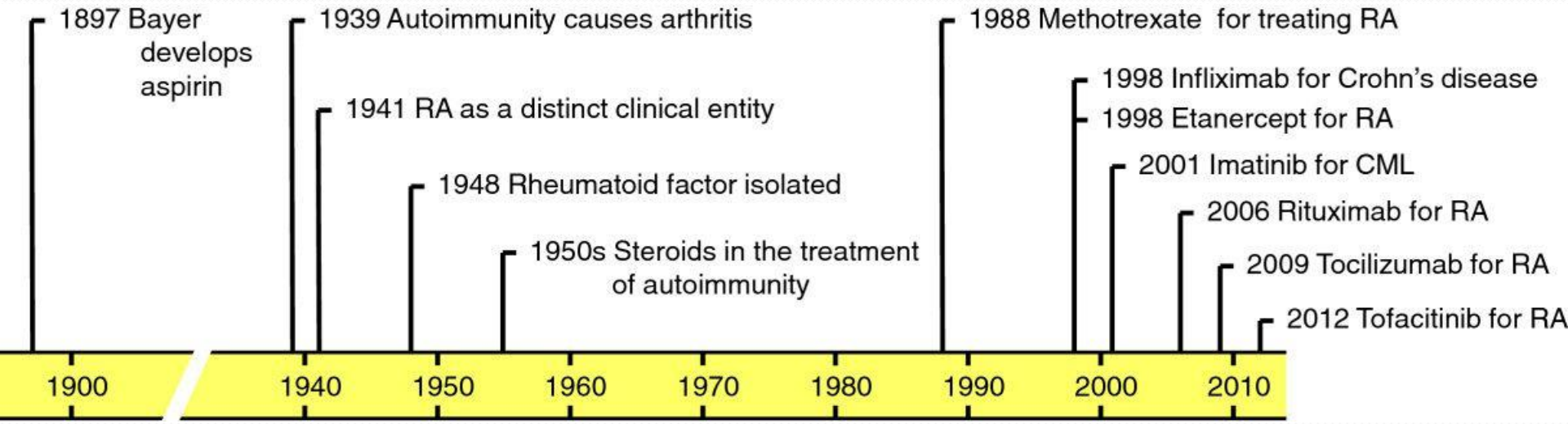
SPONDYLOARTHROPATHY



Autoantibodies
TNF, IL-6 dominant cytokines
Bone loss
Immune responses may develop in lung, gut, mouth)

No autoantibodies, more auto-inflammatory
IL-17/IL-23 axis important, as well as TNF
New bone formation
Enthesis a key site

Historical View of RA Treatment



Treatment of RA

- Conventional DMARDs*
  - **Methotrexate**
  - Sulfasalazine
  - Leflunomide
  - Hydroxychloroquine

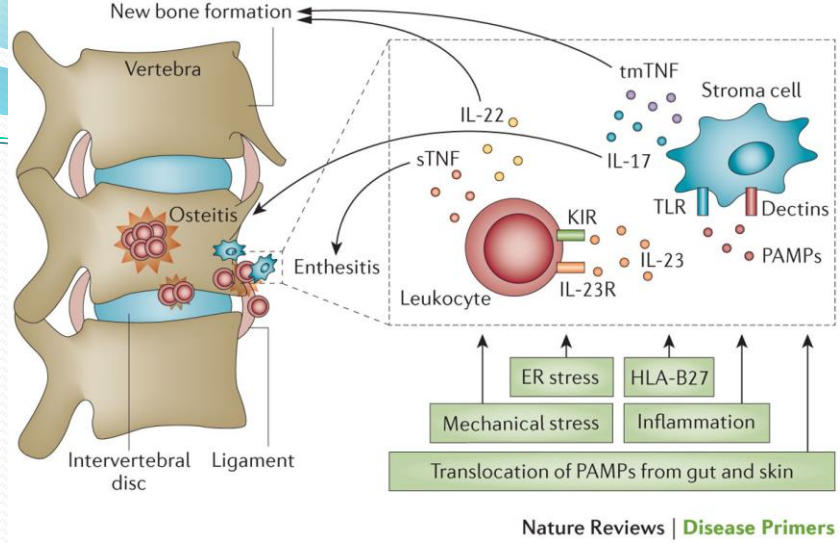
  Combination (dual, triple therapy) or monotherapy

- Biologic/targeted DMARDs
  - TNF inhibitors
    - Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab
  - IL-6 antagonist
    - Tocilizumab, Sarilimumab
  - Costimulation blocker (CTLA4Ig)
    - Abatacept
  - B-cell depletion
    - Rituximab
  - JAK-inhibitors
    - Tofacitinib, Baricitinib, Upadacitinb

*Disease-modifying anti-rheumatic drug

NSAIDs, steroids—not disease modifying, but adjunctive treatment, ***try to avoid steroids***

Spondyloarthropathy Treatment



Non-biologic

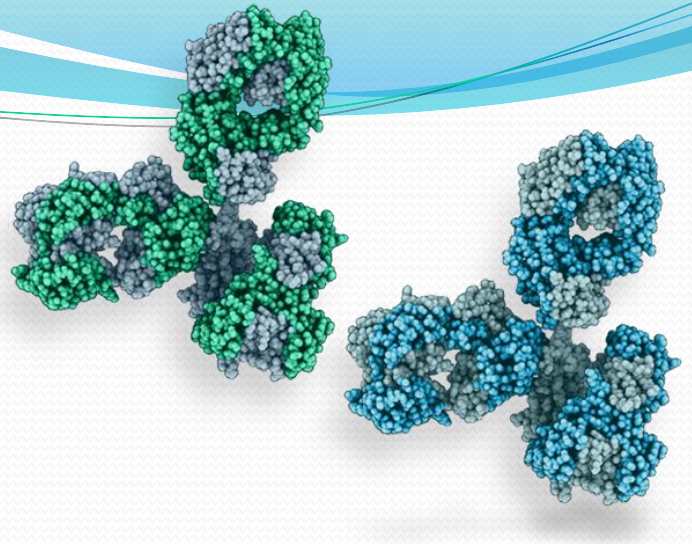
- NSAIDs
- Local steroid injections
- Conventional DMARDs (i.e. MTX, SSZ) for peripheral disease
- Apremilast (PDE4 inhibitor)

Biologics/Targeted DMARDs

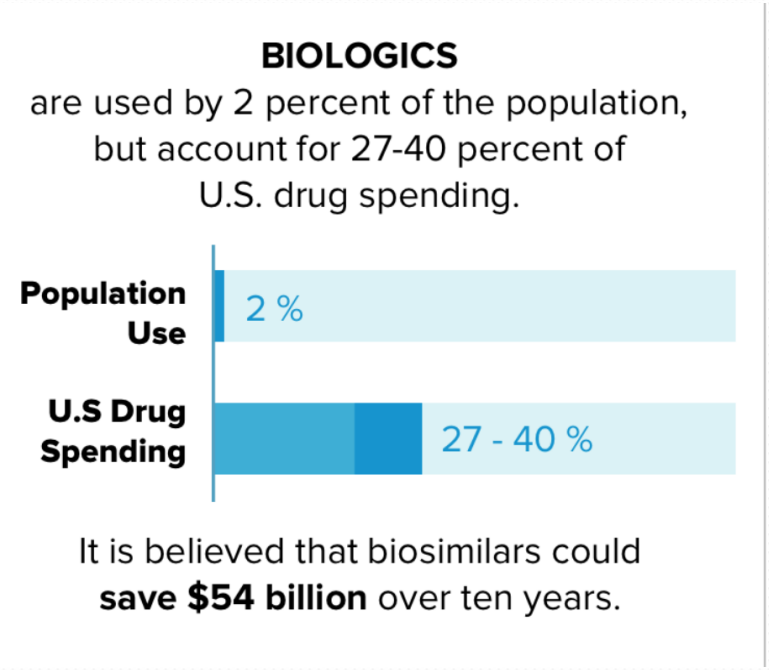
- TNF inhibitors
- **IL-17/IL-23 inhibitors**
  - Seckukinumab (PsA, AS)
  - Ustekinumab (anti-p40 IL-12/23) (PsA, IBD)
  - Ixekizumab (PsA)
  - Risankizumab (PsA)
- CTLA-4 Ig Abatacept (PsA)
- JAK inhibitors (PsA, IBD, AS)

For axial disease, if refractory to NSAIDS, move to biologics. NO role for conventional DMARDs

Biosimilars



- Few available in US currently
  - Inflectra (Infliximab-dyyb)
  - Renflexis (Infliximab-abda)
  - Avsola (Inflximab-axxq)
  - Truxima (Rituximab-abbs)
- Adalimumab and Etanercept biosimilars approved but not launched yet (planned 2023)
- Slow acceptance and still remain costly for many patients

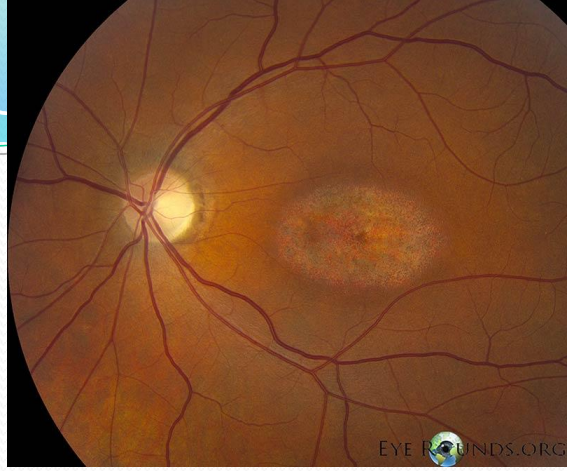


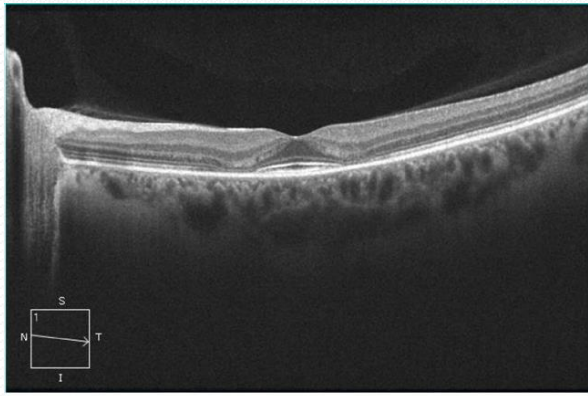
Principles of Treatment

- Earlier is better!
  - Thus need earlier diagnosis
- "Treat to target" aggressive strategy for RA
  - Defined clinical and disease activity endpoints
  - Frequent re-assessment
  - Less studied in SpA
- No biomarkers to guide treatment
  - Seropositive RA may respond better to RTX, Abatacept
  - Consider RTX for RA-ILD, nodules
  - IL-17/23 inhibition better for skin disease
  - TNF inhibition better for enthesitis
- No "cure" at present time
  - Medications usually needed long-term, although doses can be lowered and drug "holidays" achieved

Smolen J, et al. Annals of Rheumatic Disease 2010; 69:631-7

DMARD side effects





- **Infection is a side effect of nearly all DMARDs, biologics>conventional**
  - Exceptions: hydroxychloroquine, apremilast
  - Lower risk with IL-23 inhibition
- Biologics/MTX increase risk of non-melanoma skin CA
- Conventional DMARDs
  - MTX/Leflunomide require frequent (q 3 mos) lab monitoring due to risk of cytopenias and heptotoxicity
  - Hydroxychloroquine requires annual eye checks, dose <5mg/kg per ophthalmology (AAO)
  - QTc prolongation with HCQ does not seen to be significant in RA/SLE patients
- Secukinumab, Ixekizumab (anti-IL17)
  - May exacerbate underlying IBD
- Tocilizumab (anti-IL6) and JAK-inhibitors
  - cytopenias, hepatotoxcity, **hyperlipidemia, bowel/diverticular perforation**
  - High risk of Zoster with JAK-inhibitors

Case 3

66 yo F with history of DVT, DM2, HTN and rheumatoid arthritis currently not well controlled on methotrexate 25mg/week. Her treatment needs to be escalated and she is wary of self-injections. What medication addition should be avoided here?

- A. Sulfasalazine
- B. Tofacitinib (JAK-inhibitor)
- C. Hydroxychloroquine
- D. Infliximab (TNF-inhibitor)

Answer

- **B. Tofacitinib**

On September 1, 2021, based on review of a large, randomized safety clinical trial (ORAL surveillance study), FDA concluded that there is an increased risk of serious CV events such as heart attack or stroke, cancer, blood clots, and death with the arthritis and ulcerative colitis medicines Xeljanz and Xeljanz XR relative to TNF inhibitors

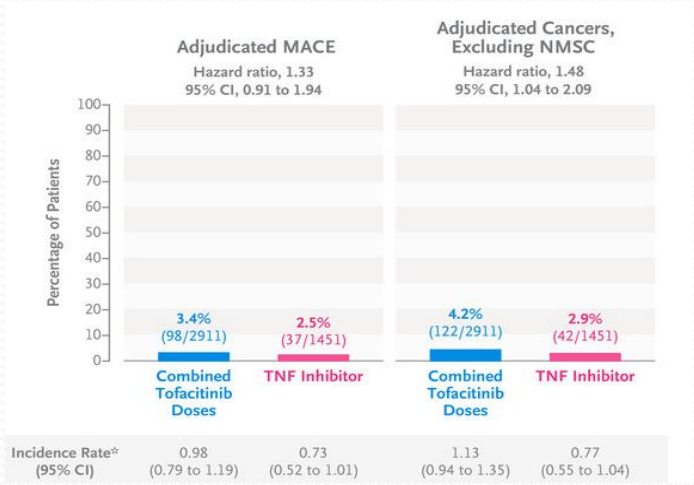
The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT



Avoid JAK-inhibition in patients over 65 and those with history/risk factors for DVT/CVD

Ytterberg, S. R. et al.. N. Engl. J. Med. ***386****, 316–326 (2022).*

Mitigating Infections-Vaccinations

- **COVID-19 primary vaccines and boosters for all patients**
  - **Risk of COVID-19 outweighs risk of disease flares**
- Influenza yearly
- Pneumonia vaccine for all
  - Prevnar 13 (PCV-13), followed by Pneumovax (PPSV-23) at 1 year
  - Ideally do prior to MTX or other DMARDs
- Shingles (consider age 50)
  - Ok to do Zostavax on MTX and prednisone <20mg/d
  - Shingrix more optimal as can be given to patients on biologics/JAKs and appears to be well tolerated
- Other age-appropriate vaccines (ie DT boosters)
- Avoid live vaccines on biologics
  - Varicella, Nasal influenza, Zostavax, Yellow Fever, MMR

Consider holding MTX for 2 weeks in patients with well-controlled RA receiving influenza vaccination to boost immune responses

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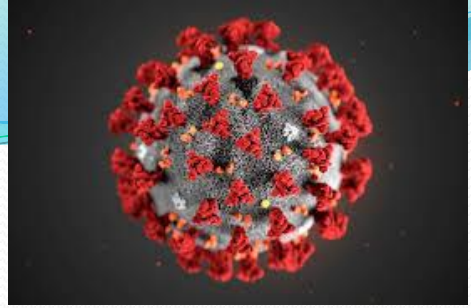
Table 3: Guidance Related to the Use and Timing of Vaccine Dosing and Immunomodulatory Therapy in Relation to COVID-19 Vaccination in RMD Patients*

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination (applies to both primary vaccination and supplemental [booster] dosing)	Level of Task Force Consensus
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

https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf

Inflammatory Arthritis and COVID-19



- Patients with RA and other rheumatic diseases may have small additional risk of SARS-COV2 infection
- Outcomes more influenced by comorbidities and particular treatments, disease activity
  - Steroids
  - Rituximab
- Mycophenolate and RTX may particularly affect vaccine responses

*Grainger, R., Kim, A.H.J., Conway, R. et al. COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. Nat Rev Rheumatol **18,** 191–204 (2022). https://doi.org/10.1038/s41584-022-00755-x*

Case 4

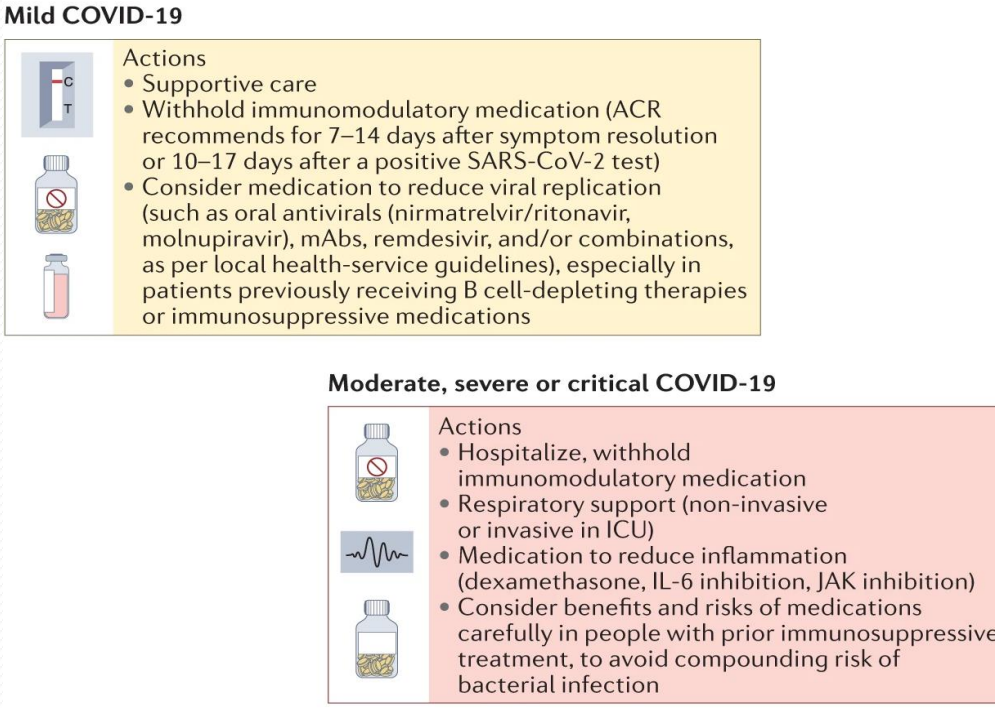
- *30 yo F with rheumatoid arthritis with mild residual disease activity on methotrexate 25mg/week has tested positive for COVID19 after having cough and fever for 2 days. She has been fully vaccinated and boosted. What do you recommend?*

- A. Recommend holding methotrexate and supportive care since patient has been fully vaccinated and age<55
- B. Recommend holding methotrexate and prescribing monoclonal antibody treatment
- C. Recommend holding methotrexate and prescribing tixagevimab/cilgavimab
- D. Recommend holding methotrexate and prescribing antiviral (nirmatrelvir and ritonavir)
- E. Recommend continuing methotrexate to avoid flare-up and prescribing antiviral therapy

Case 3-Answer

- **D. Recommend holding methotrexate and prescribing anti-viral (nirmatrelvir - ritonavir)**

SARS-CoV-2 post-infection considerations for people with rheumatic disease.



*Grainger, R. et al. Nat Rev Rheumatol **18,** 191–204 (2022).*

Take Home Points

- Recognition can still be challenging in early inflammatory arthritis
  - Advanced imaging studies can be helpful
- Understanding of pathogenesis has led to advances in treatment with development of numerous, highly effective biologic medications
  - DMARDs have unique side effect profiles
- Be aware of extra-articular manifestations and complications
  - ILD, cardiovascular disease