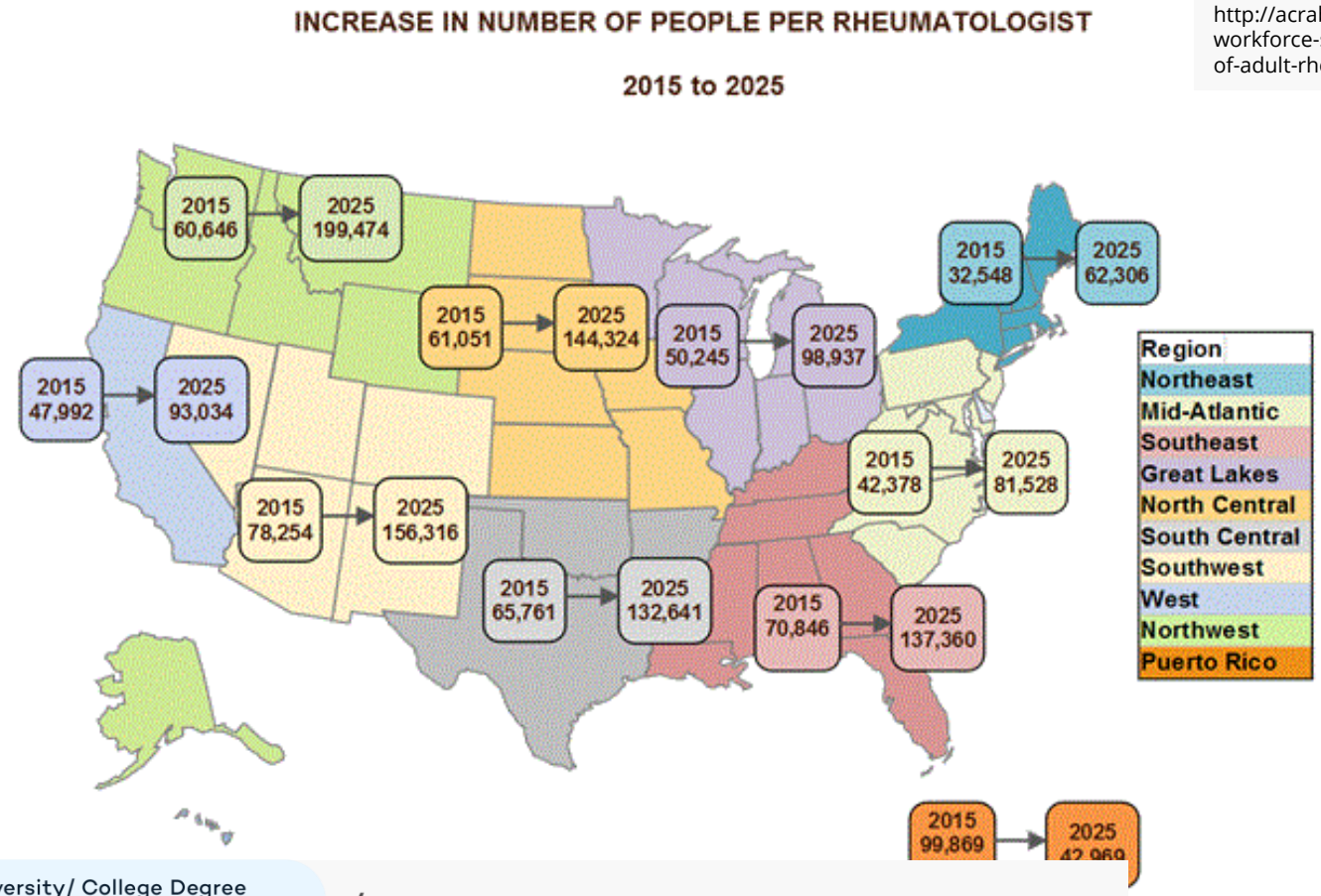
Virginia Mason™

Rheumatoid Arthritis

Erin M. Bauer MD
Rheumatology
December 2021

Figure 1. Adult Rheumatologists per Population, 2015 compared to 2025



Lawrence-Wolff K, Hildebrand B, Monrad S, Ditmyer M, Fitzgerald J, Erickson A, Bass AR, Battafarano D. 2015 ACR/ARHP Workforce Study in the United States: A Maldistribution of Adult Rheumatologists [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10). http://acrabstracts.org/abstract/2015-acrarhp-workforce-study-in-the-united-states-a-maldistribution-of-adult-rheumatologists/. Accessed January 17, 2017.

Adgenda

- Brief review of epidemiology
- 2010 classification criteria
- Initial treatment options and considerations/monitoring for biologics
- 2021 ACR updates
- JAKi drama

Rheumatoid Arthritis Epidemiology

Prevalence: 0.24 to 1 percent of the population and to be twice as common in women compared with men

Familial and genetic risk factors —estimated RA hereditability to be 40 percent. Familial risk was higher for seropositive and early-onset RA. Over 100 risk loci for RA have been identified, primarily in studies of Caucasian

Demographic risk factors

- **Age** – RA typically occurs in middle-aged and older individuals with peak incidence rates between the ages of 65 and 80 years.
- **Geographic regions and race/ethnicity** – Globally, RA is most common in Western Europe/North American. Highest rates in Native Americans

Lifes

- **Ciga**
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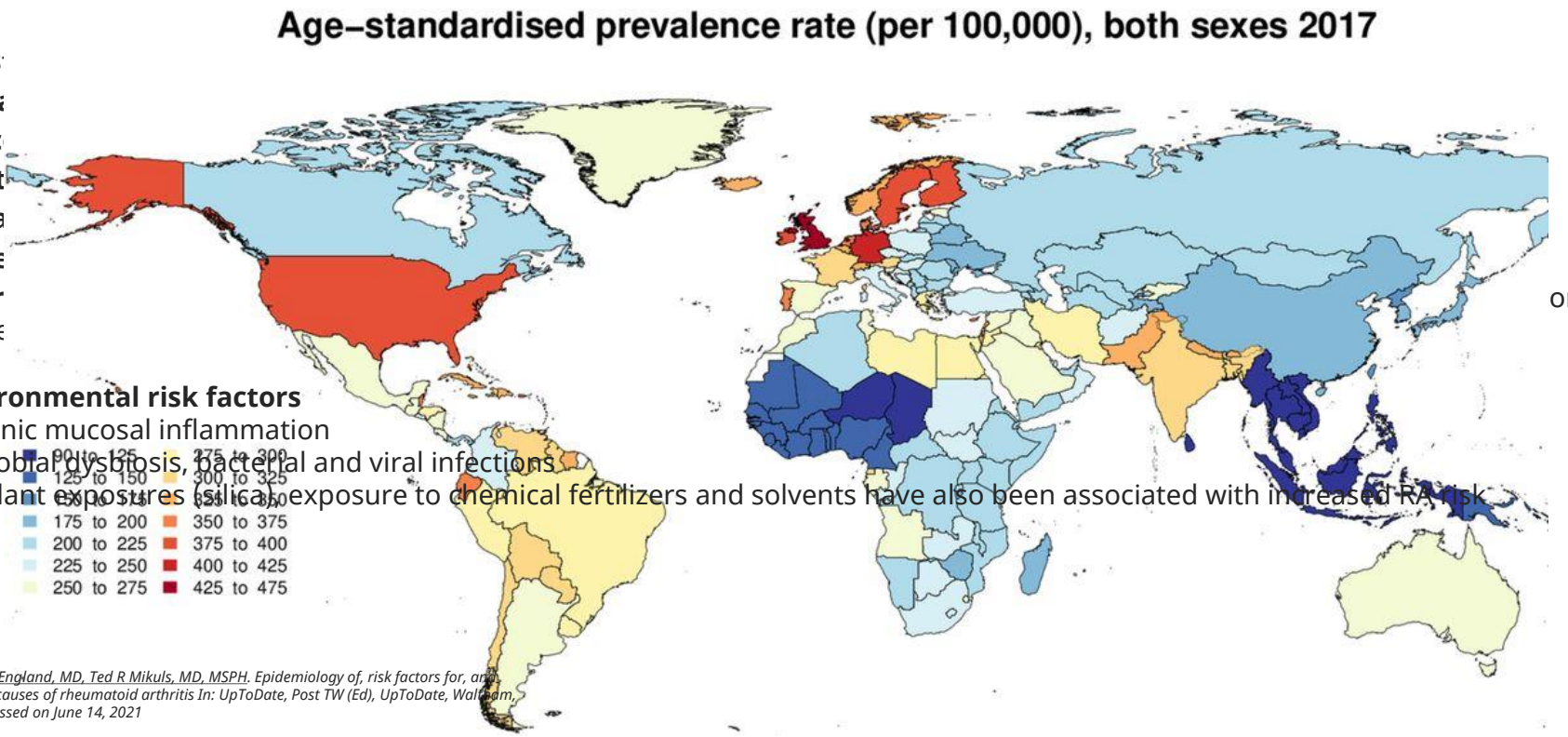


Environmental risk factors

Chronic mucosal inflammation

Microbial dysbiosis, bacterial and viral infections

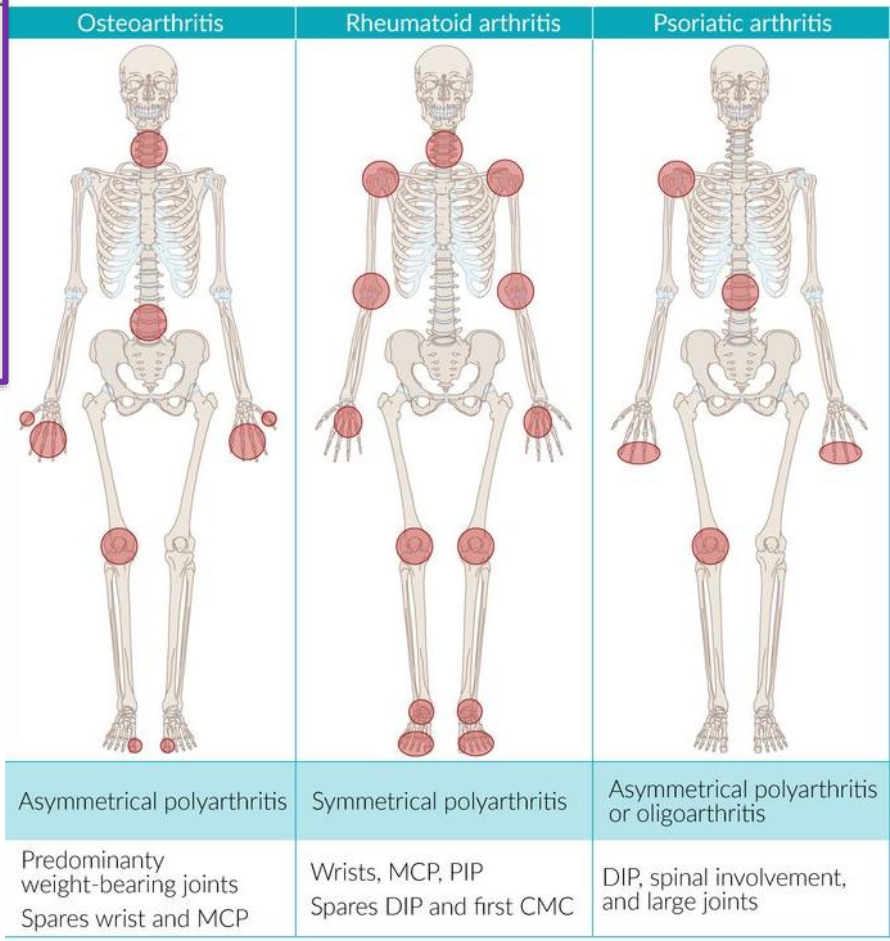
Inhalant exposures (silica exposure to chemical fertilizers and solvents have also been associated with increased RA risk

Bryant R England, MD, Ted R Mikuls, MD, MSPH. Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on June 14, 2021

Classification Criteria (ACR/EULAR 2010)

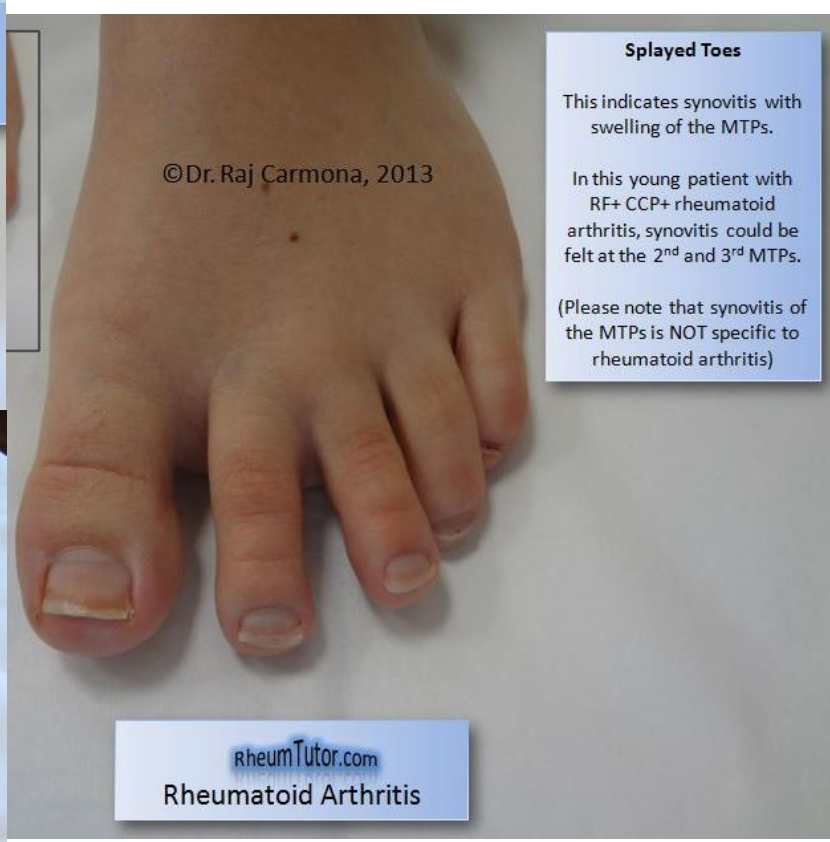
Criteria	Score
Joint distribution	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
Serology	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
Symptom duration	
<6 weeks	0
≥6 weeks	1
Acute phase reactants	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

A score of six or more equates to definite RA. This requires that the patient has at least one joint with definite synovitis and that the synovitis is not better explained by another disease. The score may be retrospective or prospective. ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.




Volar subluxation of MCPs
Metacarpal heads appear prominent because proximal phalanges have subluxed under them.
Swan Neck Deformity
Extension of PIP, flexion of DIP (4th finger)
Z-deformity of Thumb
Flexion of MCP, extension of IP
©Dr. Raj Carmona, 2013


Dorsal subluxation of Ulnar head (due to interruption of radioulnar ligament).
Radial deviation of hand at the wrist
Ulnar deviation of fingers at MCPs
©Dr. Raj Carmona, 2013


©Dr. Raj Carmona, 2013
Splayed Toes
This indicates synovitis with swelling of the MTPs.
In this young patient with RF+ CCP+ rheumatoid arthritis, synovitis could be felt at the 2nd and 3rd MTPs.
(Please note that synovitis of the MTPs is NOT specific to rheumatoid arthritis)
RheumTutor.com
Rheumatoid Arthritis

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The major nonrheumatic diseases associated with rheumatoid factor (RF)-positivity

Condition	Frequency of RF, percent
Aging (>age 60)	5 to 25
Infection	
Bacterial endocarditis*	25 to 50
Hepatitis B or hepatitis C*	20 to 75
Tuberculosis	8
Syphilis*	Up to 13
Parasitic diseases	20 to 90
Leprosy*	5 to 58
Other viral infection*	15 to 65
Pulmonary disease	
Sarcoidosis*	3 to 33
Interstitial pulmonary fibrosis	10 to 50
Silicosis	30 to 50
Asbestosis	30
Miscellaneous diseases	
Primary biliary cholangitis*	45 to 70
Malignancy*	5 to 25
After multiple immunizations	10 to 15

* Refers to disorders that may cause symptoms suggestive of rheumatoid arthritis. The best-documented examples of viral infection (in addition to hepatitis B and C) are rubella, mumps, influenza, and HIV. Chagas' disease, Leishmaniasis, onchocerciasis, and schistosomiasis are major parasitic diseases. B cell neoplasms are the most common malignancies.

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Although ACPA testing is more specific than RF for RA, positive results can occur in other diseases:

- Primary Sjogren's Syndrome, Psoriatic Arthritis
- Tuberculosis
- Chronic lung disease (alpha-1 antitrypsin deficiency, chronic obstructive pulmonary disease

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Viral Pathogen	Characteristic Clinical Features
Chikungunya	History of travel to endemic area + history of acute febrile illness with severe polyarthritis and or tenosynovitis
Rubella	Intensely erythematous maculopapular rash that migrates from head to toes/fingers
Parvovirus	Migratory, often additive, arthralgia and arthritis with flu-like illness and variable presence of transient erythematous rash on face or extremities
Hepatitis B	HBV transmission risk factors with polyarthritis and variable presence of pruritis, urticaria
Hepatitis C	HCV transmission risk factors with tenosynovitis, arthralgia, variable presence of purpura (usually affecting lower extremities)
HIV	HIV risk factors associated with features of psoriasis or reactive arthritis

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Erythrocyte sedimentation rate (ESR)
The rate (expressed in mm/hour) at which erythrocytes suspended in plasma fall when placed in a vertical tube
Indirect measure of acute phase response- fibrinogen

Influenced by:
immunoglobulins
changes in erythrocyte size, shape, and number
age, sex, adipose tissue

Increased ESR:
- Systemic and localized inflammatory and infectious diseases
- Malignant neoplasms
- Tissue injury/ischemia
- Trauma

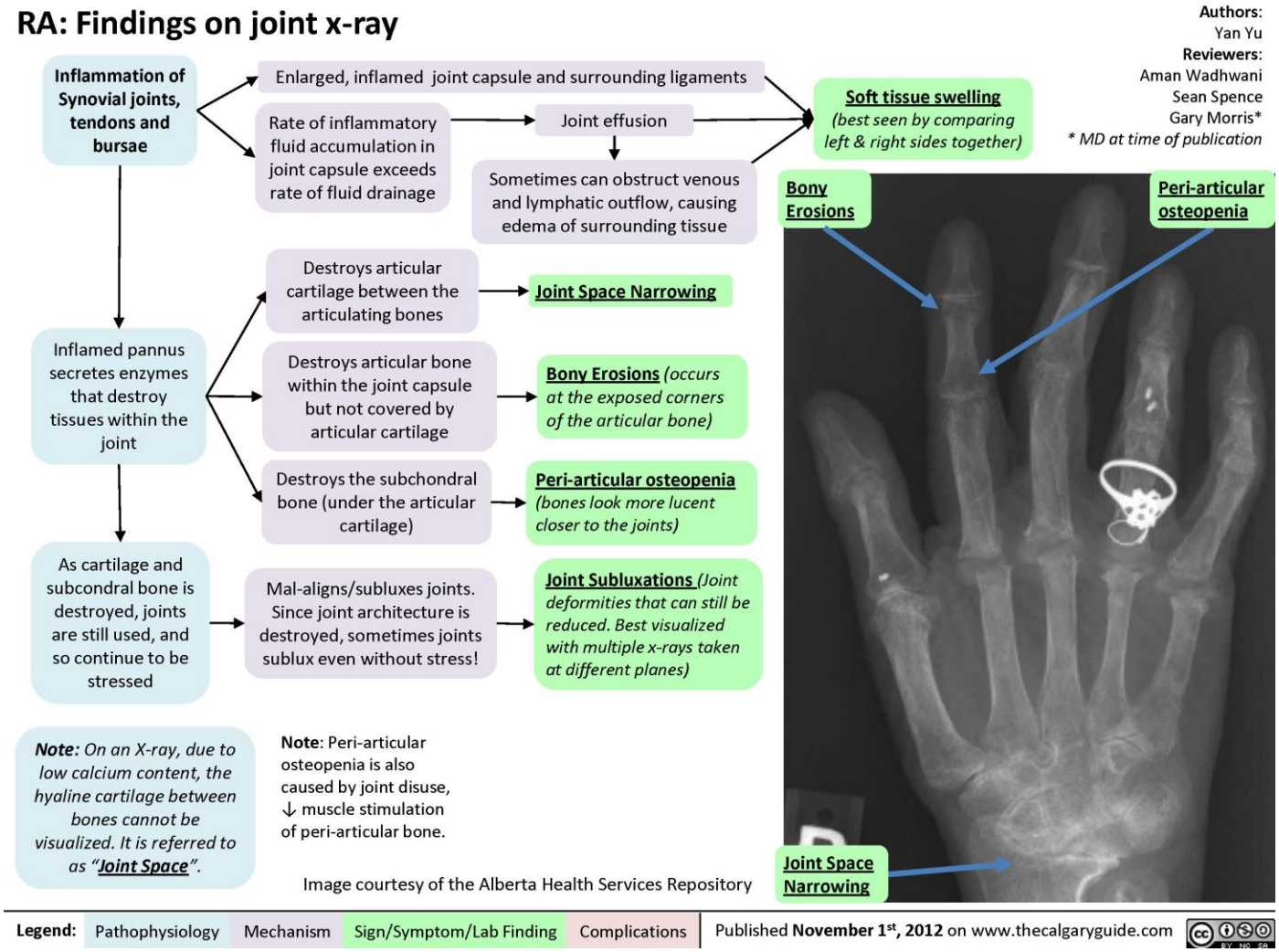
C-reactive protein
Influenced by age, sex, and ethnicity

Markedly elevated levels of CRP are strongly associated with infection

CRP both rises and falls more rapidly than the ESR

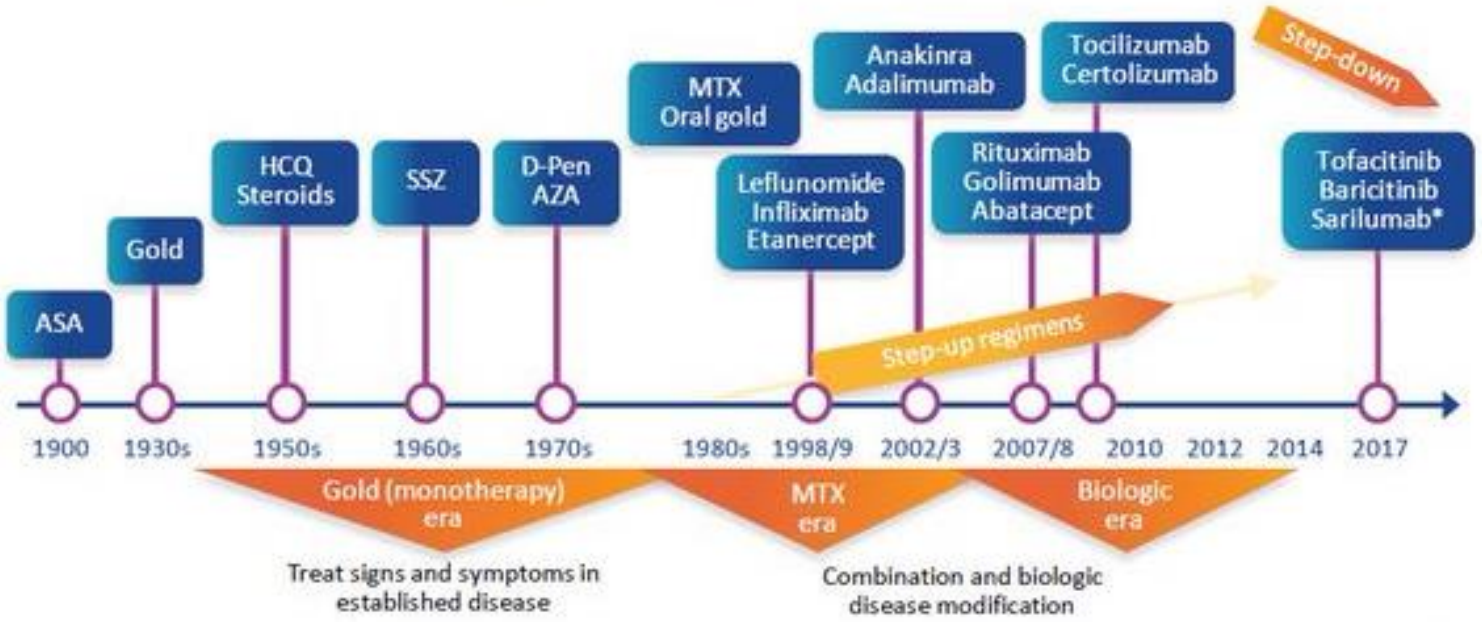
Treatment Options for RA

Persistent synovial inflammation, which is associated with a proliferative and destructive process in joint tissues, can lead to significant and irreversible joint injury as early as during the first two years of disease



https://calgaryguide.ucalgary.ca/rheumatoid-arthritis-ra-x-ray-features/

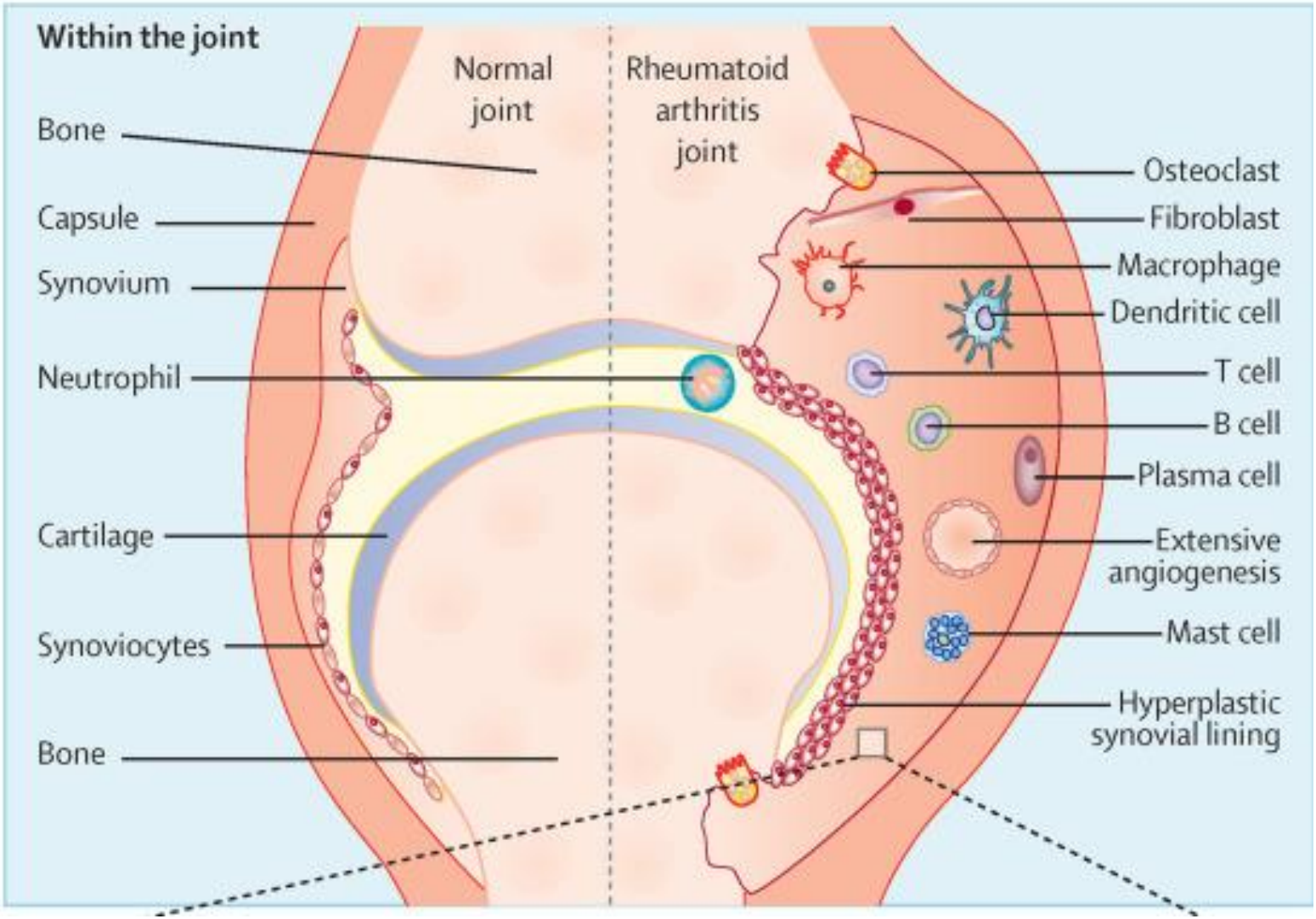
Treatment Options for RA



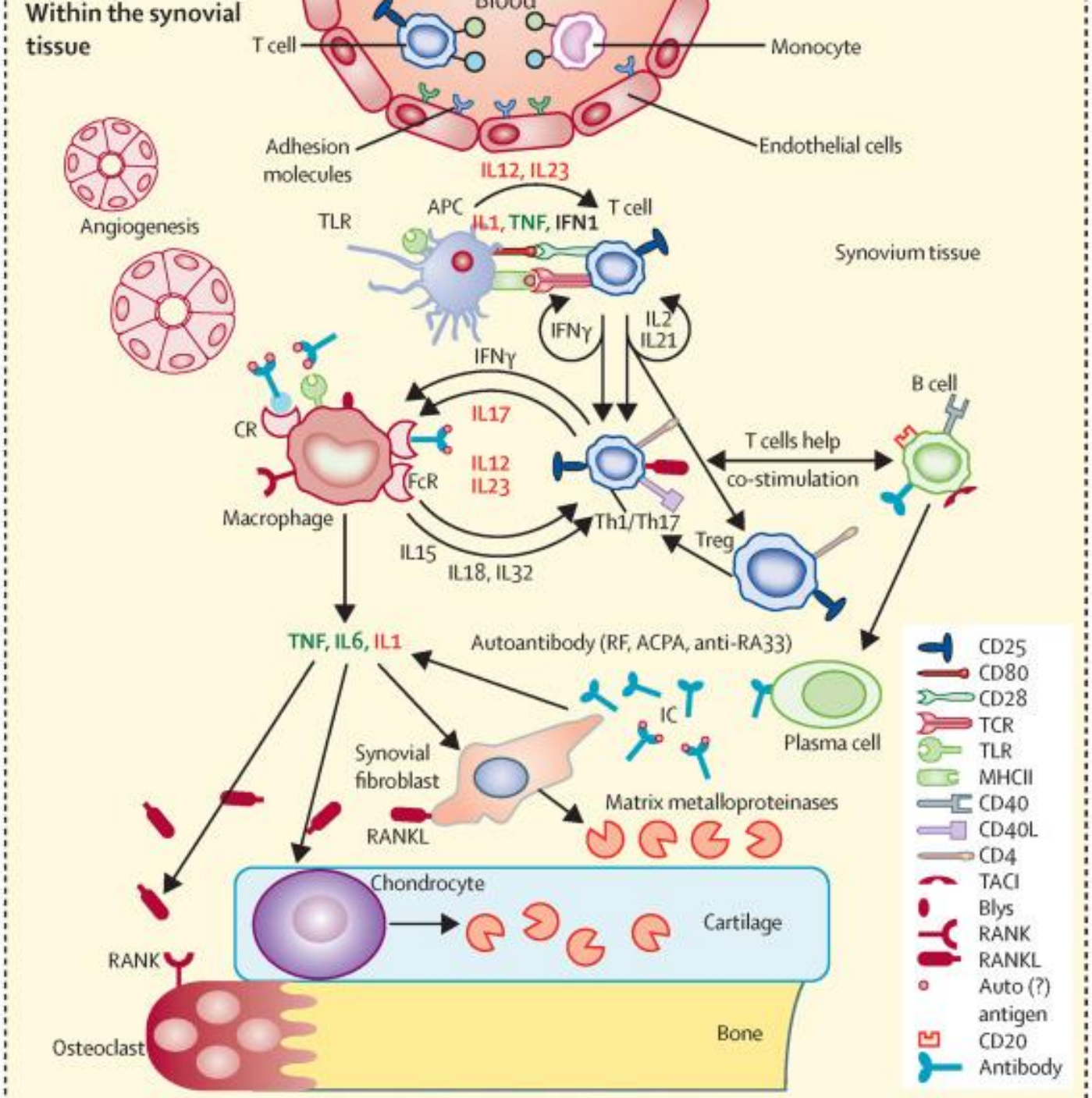
*Sarilumab is not approved for rheumatoid arthritis in Australia
ADA, adalimumab; ASA, aspirin; AZA, azathioprine; bDMARD, biologic disease-modifying antirheumatic drug;
D-Pen, D-penicillamine; HCQ, hydroxychloroquine; MTX, methotrexate; SSZ, sulfasalazine; TCZ, tocilizumab;
tsDMARD, targeted synthetic disease-modifying antirheumatic drug

1. Smolen JS, et al. Ann Rheum Dis 2010;69:631–7;
2. Smolen JS, et al. Ann Rheum Dis 2016;75:3–15;
3. Smolen JS, et al. Ann Rheum Dis 2017;0:1–18;
4. Singh JA, et al. Arthritis Care Res 2016;68:1–25;
5. Upchurch KS, Kay J. Rheumatology 2012;51(Suppl. 6):vi28–36;
6. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=761037 [last accessed May 30, 2017]

Pathobiology



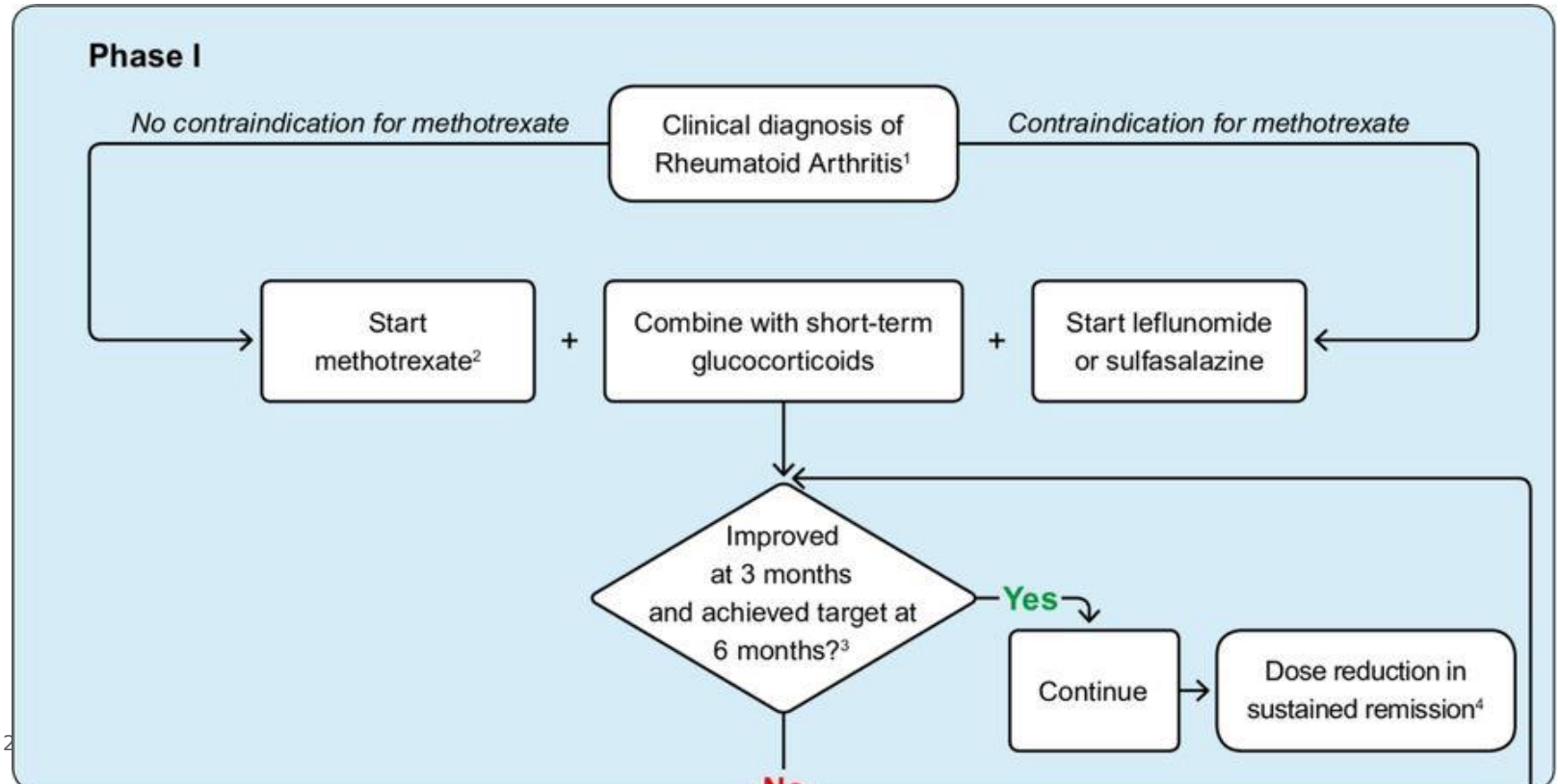
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30173-8/fulltext



Treatment Options for RA

First line nonbiologic DMARDs
- Methotrexate
- Sulfasalazine
- Leflunomide
- Hydroxychloroquine

Considerations for non biologic DMARDs
- Pregnancy planning
- EtOH use, liver function
- Renal function
- GI side effects
- ILD



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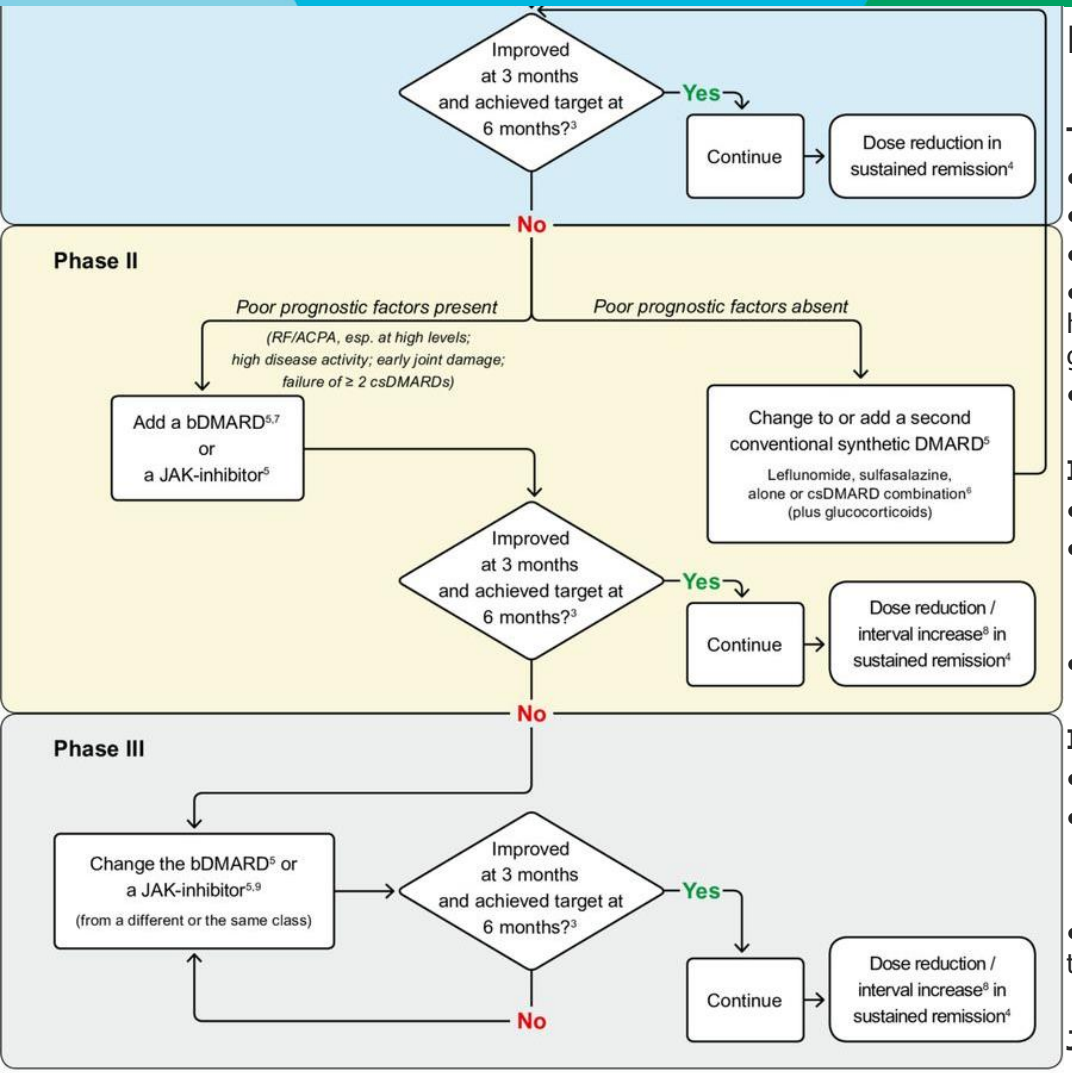

1. 2010 ACR-EULAR classification criteria can support early diagnosis.
2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids..
3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.
4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.
5. Consider contraindications and risks.
6. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.
7. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions): in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages.
8. Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD.
9. Efficacy and safety of bDMARDs after JAK-inhibitor failure is not fully known; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. Efficacy and safety of a JAK-inhibitor after insufficient response to a previous JAK-inhibitor is unknown.

Biologic DMARDs

TNF inhibitor

- Etanercept soluble p75 TNF-alpha receptor fusion protein
- Infliximab chimeric anti-TNF-alpha antibody
- Adalimumab fully human monoclonal anti-TNF-alpha ab
- Certolizumab pegol antigen-binding fragment (Fab') of a humanized monoclonal antibody coupled to polyethylene glycol
- Golimumab- human anti-TNF-alpha monoclonal antibody

IL-1 inhibitor

- Anakinra
- Canakinumab

Anti-CD20

- Rituximab

IL-6 inhibitor

- Tocilizumab
- Sarilumab

T-cell costimulation Blockade

- Abatacept soluble fusion protein comprising CTLA-4 and the Fc portion of immunoglobulin G1 (IgG1) (CTLA4-Ig)

JAK inhibitor

- Tofacitinib inhibits JAK-1 and JAK-3
- Baricitinib inhibits JAK-1 and JAK-2
- Upadacitinib inhibits JAK-1

Rheumatoid Arthritis Updates

Medication	Mechanism	Side Effects	Monitoring
***Abatacept (Orencia)**	Blocks T cell activation SQ / IV	Headache Nausea Abdominal pain	COPD?
***Tofacitinib (Xeljanz)**	JAK inhibitor PO BID/daily	URIs Zoster GI perforation Skin cancer PE/DVT?	CBC q 3 mo LFTs q 3 mo Annual Derm
Baricitinib (Olumiant)	JAK inhibitor PO daily	URIs Zoster GI perforation Skin cancer	CBC q 3 mo LFTs q 3 mo Annual Derm
Tocilizumab (Actemra)	IL-6 inhibition SQ q 2 wks / IV monthly	GI perforation	CBC q 3 mo LFTs q 3 mo **Lipids q 6 mo**
Sarilumab (Kevzara)	IL-6 inhibition SQ q 2 wks	GI perforation	CBC q 3 mo LFTs q 3 mo **Lipids q 6 mo**
* Also approved for PsA			

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American College of Rheumatology
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2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Liana Fraenkel,[1] Joan M. Bathon,[2] Bryant R. England,[3] E. William St.Clair,[4] Thurayya Arayssi,[5] Kristine Carandang,[6] Kevin D. Deane,[7] Mark Genovese,[8] Kent Kwas Huston,[9] Gail Kerr,[10] Joel Kremer,[11] Mary C. Nakamura,[12] Linda A. Russell,[13] Jasvinder A. Singh,[14] Benjamin J. Smith,[15] Jeffrey A. Sparks,[16] Shilpa Venkatachalam,[17] Michael E. Weinblatt,[16] Mounir Al-Gibbawi,[18] Joshua F. Baker,[19] Kamil E. Barbour,[20] Jennifer L. Barton,[21] Laura Cappelli,[22] Fatimah Chamseddine,[18] Michael George,[23] Sindhu R. Johnson,[24] Lara Kahale,[18] Basil S. Karam,[18] Assem M. Khamis,[18] Iris Navarro-Millán,[25] Reza Mirza,[26] Pascale Schwab,[21] Namrata Singh,[27] Marat Turgunbaev,[28] Amy S. Turner,[28] Sally Yaacoub,[18] and Elie A. Akl[18]

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The most recent update reported in 2015

The current recommendations address the following:

1) conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs)

2) glucocorticoids

3) use of these medications in certain high-risk populations.

Not addressed:

- the use of vaccines and nonpharmacologic treatment approaches (although initially part of this project)
- pretreatment screening and routine laboratory monitoring (refer readers to the 2008, 2012, and 2015 guidelines
- recommendations for the perioperative management of patients undergoing elective orthopedic surgery (addressed in 2017)
- regarding reproductive health- refer readers to the 2020 ACR Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases

Table 1. Guiding principles*

RA requires early evaluation, diagnosis, and management.
Treatment decisions should follow a shared decision-making process.
Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the DMARD(s) chosen.
Disease activity levels refer to those calculated using RA disease activity measures endorsed by the ACR (10).
Recommendations are intended for the general RA patient population and assume that patients do not have contraindications to the options under consideration.
Recommendations are limited to DMARDs approved by the US FDA for treatment of RA. csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate, leflunomide bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)† tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide.
Serious infection refers to an infection requiring intravenous antibiotics or hospitalization.
Biosimilars are considered equivalent to FDA-approved originator bDMARDs.
Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy.
Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission).
Target refers to low disease activity or remission.
Recommendations specify that patients be at target (low disease activity or remission) for at least 6 months prior to tapering.
Dose reduction refers to lowering the dose or increasing the dosing interval of a DMARD. Gradual discontinuation of a DMARD is defined as gradually lowering the dose of a DMARD and subsequently stopping it.

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Table 2. Disease-modifying antirheumatic drugs (DMARDs) initiation*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)†	Evidence table(s), in Supp. App. 2
Initiation of treatment in DMARD-naive patients with moderate-to-high disease activity			
Methotrexate monotherapy is **strongly** recommended over:			
Hydroxychloroquine or sulfasalazine	Very low/low‡	PICO 2a.C1/C2	p. 14–5
bDMARD or tsDMARD monotherapy	Very low/moderate	PICO 5a.C1–4/C5§	p. 61–78
Combination of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD¶	Low/very low	PICO 6a.C2–4/C5§	p. 109, 117–28
Methotrexate monotherapy is **conditionally** recommended over:			
Leflunomide	Low	PICO 2a.C3	p. 18
Dual or triple csDMARD therapy¶	Moderate	PICO 4a.C1–C2	p. 46–9
Combination of methotrexate plus a TNF inhibitor¶	Low	PICO 6a.C1	p. 110
Initiation of a csDMARD without short-term (<3 months) glucocorticoids is **conditionally** recommended over initiation of a csDMARD with short-term glucocorticoids.	Very low	PICO 7a	p. 167
Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is **strongly** recommended over initiation of a csDMARD with longer-term glucocorticoids.	Moderate	PICO 8a	p. 170
Initiation of treatment in DMARD-naive patients with low disease activity			
Hydroxychloroquine is **conditionally** recommended over other csDMARDs.	Very low	PICO 1a.C1–4	p. 1–6
Sulfasalazine is **conditionally** recommended over methotrexate.	Very low	PICO 1a.C2	p. 2
Methotrexate is **conditionally** recommended over leflunomide.	Very low	PICO 1a.C3	p. 5
Initiation of treatment in csDMARD-treated, but methotrexate-naive, patients with moderate-to-high disease activity#			
Methotrexate monotherapy is **conditionally** recommended over the combination of methotrexate plus a bDMARD or tsDMARD.**	Moderate/very low	PICO 6b.C1–4/C5§	p. 136–56

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; TNF = tumor necrosis factor; csDMARD = conventional synthetic DMARD.
† The closest matching PICO questions to each recommendation are provided.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second listed option.
§ The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.
¶ The direction of the beneficial effect is in favor of the nonpreferred option.
# Other recommendations for this patient population are the same as those for DMARD-naive patients.
** The direction of the beneficial effect is in favor of the nonpreferred option. The certainty of evidence is high for the combination of methotrexate plus a TNF inhibitor and moderate for other bDMARDs.

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Table 3. Methotrexate administration*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Oral methotrexate is **conditionally** recommended over subcutaneous methotrexate for patients initiating methotrexate.	Moderate	PICO 9	p. 181
Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is **conditionally** recommended over initiation/titration to a weekly dose of <15 mg.†	Moderate/ very low‡	PICO 10.C1–C3	p. 184–5
A split dose of oral methotrexate over 24 hours or subcutaneous injections, and/or an increased dose of folic/folinic acid, is **conditionally** recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate.	Very low	PICO 16 and PICO 15	p. 206–10
Switching to subcutaneous methotrexate is **conditionally** recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.	Very low	PICO 18	p. 235

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; DMARD = disease-modifying antirheumatic drug.
† This recommendation refers only to the initial prescribing of methotrexate and is not meant to limit further dose escalation, which often provides additional efficacy.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second option.

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Table 4. Treatment modification*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
A TTT approach is **strongly** recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs.	Low	PICO 12.a	p. 191
A TTT approach is **conditionally** recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs.	Very low	PICO 12.b	p. 199
A minimal initial treatment goal of low disease activity is **conditionally** recommended over a goal of remission.	Low	PICO 13	p. 201
Addition of a bDMARD or tsDMARD is **conditionally** recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target.	Very low	PICO 19.C2–C6†	p. 240–1
Switching to a bDMARD or tsDMARD of a different class is **conditionally** recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.	Very low	PICO 24–27†	p. 293–338
Addition of/switching to DMARDs is **conditionally** recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target.	Very low	PICO 23	p. 292
Addition of/switching to DMARDs (with or without IA glucocorticoids) is **conditionally** recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target.	Very low	PICO 28.C1–C2	p. 339–40

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; TTT = treat-to-target; bDMARDs = biologic disease-modifying antirheumatic drugs; tsDMARDs = targeted synthetic DMARDs; IA = intraarticular.
† The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.

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Table 5. Tapering disease-modifying antirheumatic drugs (DMARDs)*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Continuation of all DMARDs at their current dose is **conditionally** recommended over a dose reduction of a DMARD.	Low	PICO 54.a	p. 381
Dose reduction is **conditionally** recommended over gradual discontinuation of a DMARD.	Low	PICO 52.C2 and PICO 53. C2	p. 351–5, p. 372–6
Gradual discontinuation is **conditionally** recommended over abrupt discontinuation of a DMARD.	Low	PICO 52.C1 and PICO 53.C1	p. 351, 372
Gradual discontinuation of sulfasalazine is **conditionally** recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD.	Very low	PICO 58	p. 400
Gradual discontinuation of methotrexate is **conditionally** recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD.	Very low	PICO 59.C1	p. 401

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD.

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Table 6. Specific patient populations*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Subcutaneous nodules			
Methotrexate is **conditionally** recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity.	Very low	PICO 64	p. 427
Switching to a non-methotrexate DMARD is **conditionally** recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules.	Very low	PICO 65	p. 428
Pulmonary disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity.	Very low	PICO 67	p. 430
Heart failure			
Addition of a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs.	Very low	PICO 70	p. 435
Switching to a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.	Very low	PICO 71	p. 436

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Lymphoproliferative disorder			
Rituximab is **conditionally** recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity.	Very low	PICO 75 and PICO 76	p. 446–7
Hepatitis B infection			
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).	Very low	PICO 82	p. 459
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.	Very low	PICO 83	p. 464
Frequent monitoring alone is **conditionally** recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.	Very low	PICO 84	p. 471
Nonalcoholic fatty liver disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to-high disease activity.	Very low	PICO 87	p. 489
Persistent hypogammaglobulinemia without infection			
In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is **conditionally** recommended over switching to a different bDMARD or tsDMARD.	Very low	PICO 66	p. 429

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Previous serious infection			
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 88	p. 490
Addition of/switching to DMARDs is **conditionally** recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity.	Very low	PICO 90 and PICO 91	p. 496–7
Nontuberculous mycobacterial lung disease			
Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is **conditionally** recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease.	Very low	No relevant PICO	
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 92	p. 498
Abatacept is **conditionally** recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs.	Very low	PICO 93	p. 499

The recommendation statements in this update are not directly comparable to the ACR 2015 guidelines because they do not retain the early versus established RA subgroups.

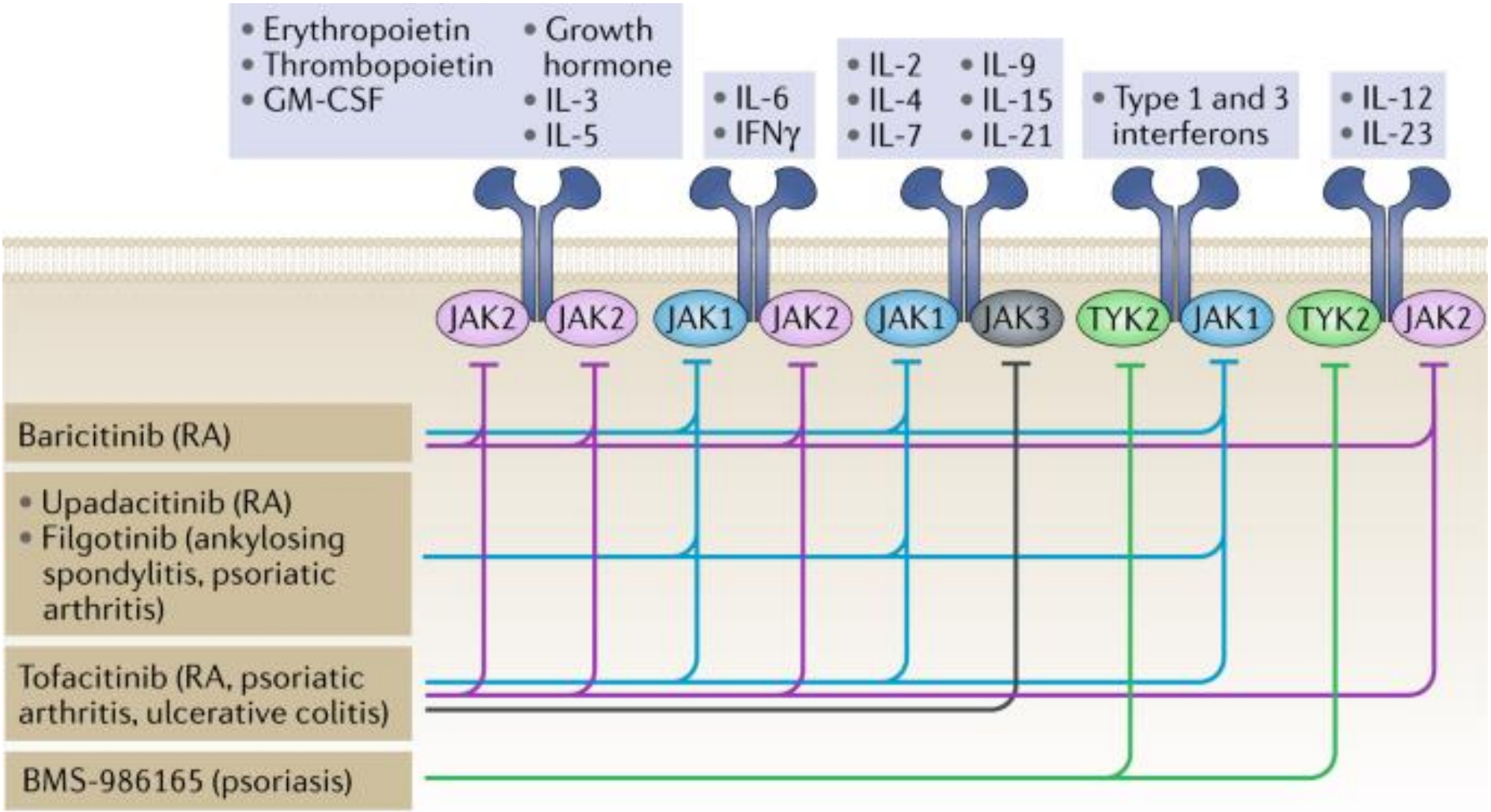
There are some notable differences:

1. The 2015 guidelines recommend csDMARD monotherapy, preferably with methotrexate, for patients with both low and moderate/high disease activity, whereas this update recommends an initial trial of hydroxychloroquine or sulfasalazine for those with **low disease activity**
2. The 2015 guidelines recommended DMARD tapering for patients who are in remission. In this update, **tapering recommendations** are made for patients who are in low disease activity or remission in the face of a paucity of data about when and how best to taper. The panel recommended that careful tapering might be considered if the patient wishes to cut back on their use of DMARDs
3. This update includes several recommendations **against the use of glucocorticoid therapy**. These recommendations were made in recognition of the frequent difficulty tapering glucocorticoids leading to undesirable prolonged use and the increasing evidence of the negative impact of glucocorticoids on long-term patient outcomes, including risk for infection, osteoporosis, and cardiovascular disease, in RA and other rheumatic diseases.

- On February 4, 2021, the FDA released a Drug Safety Alert noting a possible increased risk of major cardiovascular events and malignancies (excluding non-melanoma skin cancer) in patients with RA (over the age of 50 years with at least 1 risk factor for cardiovascular disease) participating in a randomized controlled trial designed to compare the safety of tofacitinib to adalimumab. **Recommendations will be reviewed once peer reviewed results are published**.

- Although previous recommendations cautioned against the use of TNF inhibitors in patients with skin cancer, the results of more recently published studies examining specific DMARD-related risks of nonmelanoma skin cancer and melanoma do not support making a definite recommendation for or against specific DMARDs.

JAK inhibition



O'Shea, J.J., Gadina, M. Selective Janus kinase inhibitors come of age. *Nat Rev Rheumatol* **15,** 74–75 (2019). https://doi.org/10.1038/s41584-018-0155-9

Xeljanz, Xeljanz XR (tofacitinib): Drug Safety Communication - Due to an Increased Risk of Blood Clots and Death with Higher Dose

Medical Product Safety Information

Drug Safety-related Labeling Changes

MedWatch Forms for FDA Safety Reporting

[Posted 07/26/2019]

AUDIENCE: Patient, Health Professional, Pharmacy, Gastroenterology, Rheumatology

ISSUE: FDA has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of Xeljanz, Xeljanz XR (tofacitinib), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. We approved these changes, including adding our most prominent Boxed Warning, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.

Table 2 Incidence rates for deep vein thrombosis and pulmonary embolism in tofacitinib clinical development studies

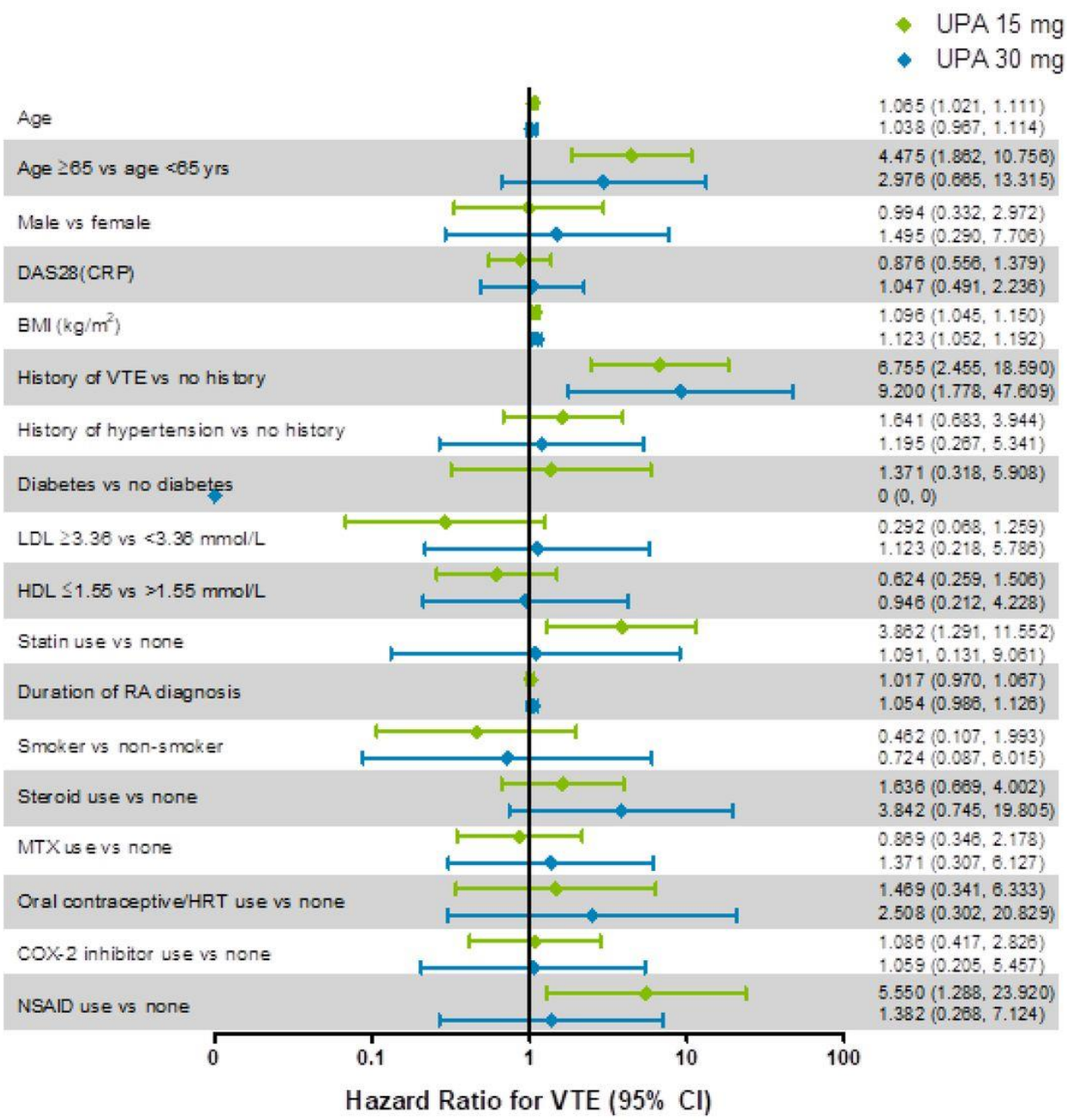
Adverse event	Placebo-controlled cohort			Dose-comparison cohort			
	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab 40 mg SC q2w	MTX 20 mg qw
DVT	0/1849 0 (0–0.9)	0/2024 0 (0–0.8)	1/1079 0.4 (0–2.4)	1/1849 0.1 (0–0.3)	1/2024 0.1 (0–0.3)	0/257 0 (0–0.9)	2/220.7 (0.1–2.5)
PE	0/1849 0 (0–0.9)	0/2024 0 (0–0.8)	1/1079 0.4 (0–2.4)	2/1849 0.1 (0–0.4)	3/2024 0.2 (0–0.4)	0/257 0 (0–1.9)	0/223 0 (0–1.3)

The data include 5368 patients with rheumatoid arthritis and 4440 person-years. Data are presented as n/N and incidence rate (95% confidence interval)

BID twice daily, *DVT* deep vein thrombosis, *IR* incidence rates, *MTX* methotrexate, *PE* pulmonary embolism, *q2w* every 2 weeks, *qw* every week, *SC* subcutaneous

Rajasimhan, S., Pamuk, O. & Katz, J.D. Safety of Janus Kinase Inhibitors in Older Patients: A Focus on the Thromboembolic Risk. *Drugs Aging* **37,** 551–558 (2020). https://doi.org/10.1007/s40266-020-00775-w

Figure: VTE Risk Factors in Patients Receiving UPA 15 or 30 mg QD Through Univariate Cox Regression



E. Choy et al. Ann Rheum Dis 2020;79:317-318

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MEETING ABSTRACTS

ABSTRACT NUMBER: 1939

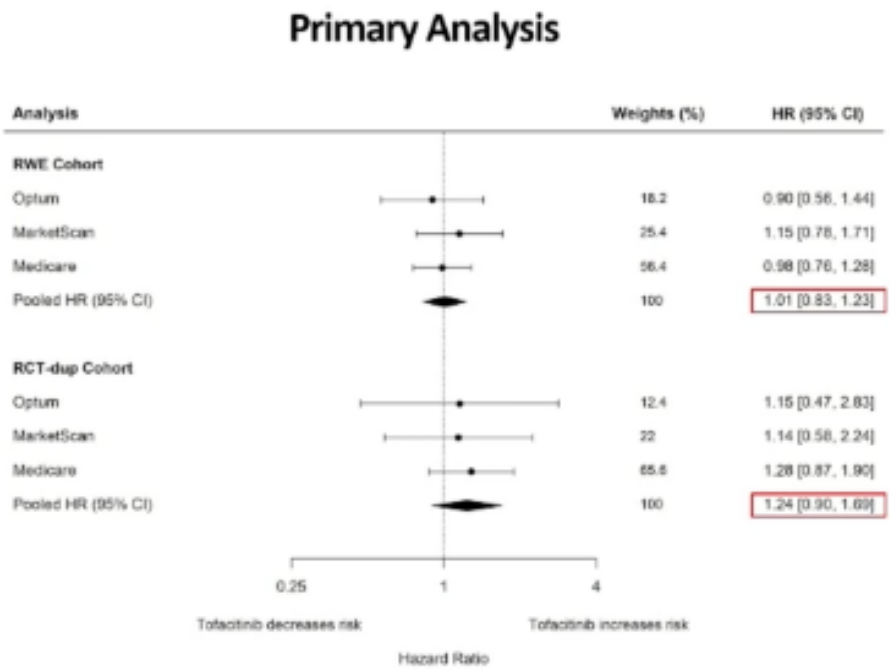
Risk of Cardiovascular Outcomes in Patients Treated with Tofacitinib: First Results from the Safety of TofAcitinib in Routine Care Patients with Rheumatoid Arthritis (STAR-RA) Study

Farzin Khosrow-Khavar, Seoyoung Kim, Hemin Lee, Su Been Lee and Rishi Desai, Brigham and Women's Hospital, Boston, MA

Meeting: ACR Convergence 2021

Keywords: Cardiovascular, **Disease-Modifying Antirheumatic Drugs (D**
Pharmacoepidemiology, **rheumatoid arthritis**

The STAR-RA study compared real world safety of TNFi vs. tofacitinib in several administrative databases with 102,263 patients of whom 9.5 to 13.2% were using tofacitinib and the rest TNFi (Khosrow-Khavar, F, ACR21 #1939). Overall there were no differences in CV outcomes and this was also found in the group enriched for CV events who mimicked the Oral Surveillance inclusion criteria. Drug use did not differentiate in an adjusted analysis.



AMERICAN COLLEGE of RHEUMATOLOGY
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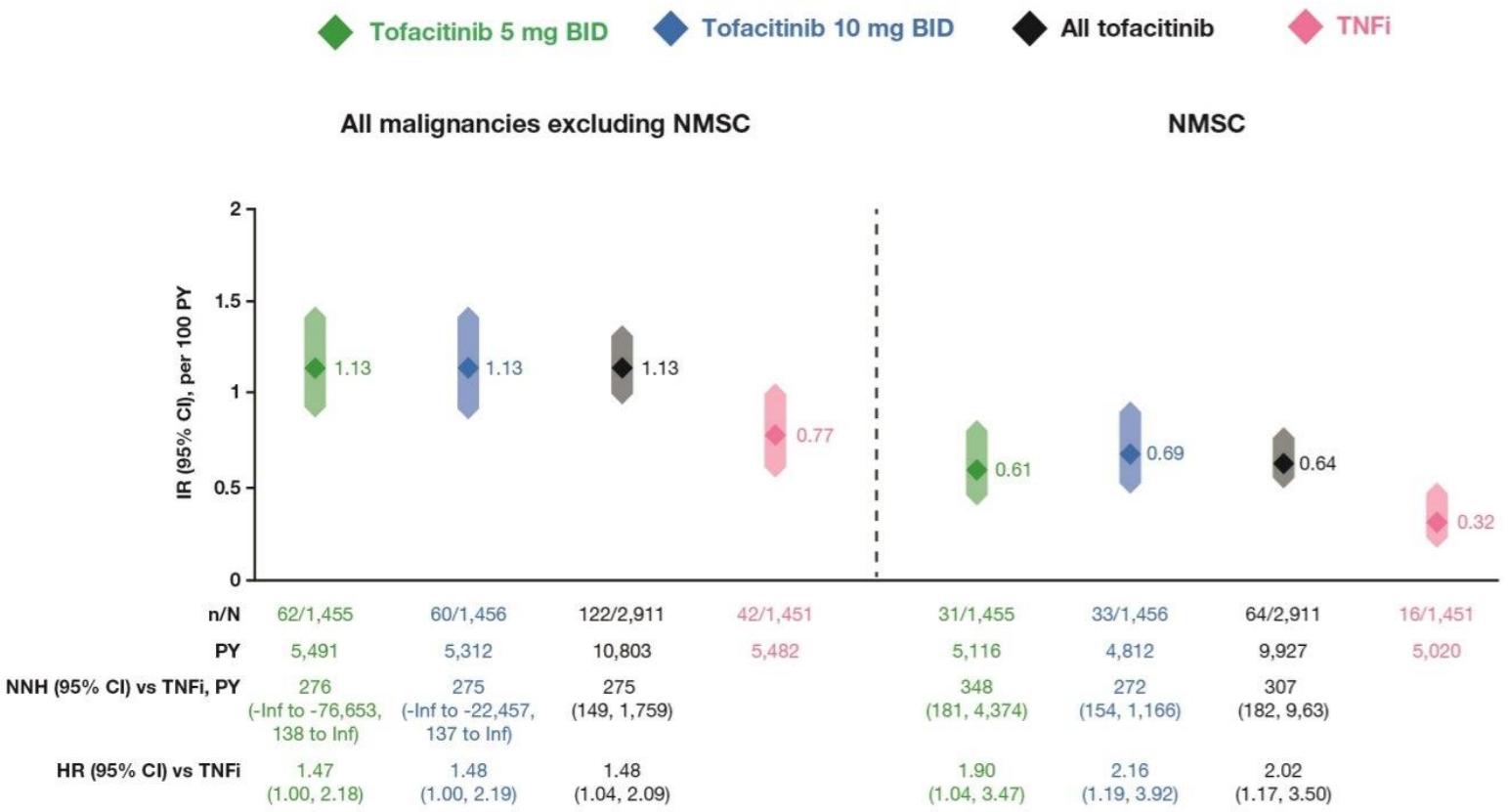
MEETING ABSTRACTS

ABSTRACT NUMBER: 1940

Malignancies in Patients Aged ≥ 50 Years with RA and ≥ 1 Additional Cardiovascular Risk Factor: Results from a Phase 3b/4 Randomized Safety Study of Tofacitinib vs TNF Inhibitors

Jeffrey Curtis[1], Kunihiro Yamaoka[2], Yi-Hsing Chen[3], Levent M Gunay[4], Naonobu Sugiyama[5], Carol A Connell[6], Vranic[7] and Juan J Gomez-Re
Department of Medicine, De
Birmingham, Birmingham, A
Infectious Diseases, Kitasatc
Hospital, Taichung, Taiwan (
Inc, Tokyo, Japan, [6]Pfizer Inc
[8]Hospital Clínico Universitar



Vaccine	Type	Frequency	On MTX/LEF	On Biologic
Routine Vaccines				
Influenza	Fluviral, Agriflu, Fluzone (trivalent, 0.5mL IM)	Annually	OK	
	Fluad (adjuvanted, trivalent, 0.5mL IM)	Age >65, annually		
	FluMist (LIVE) (0.1mL each nostril)		Contraindicated	
Pneumococcal[a]	Prevnar 13 (conjugated) (0.5mL IM), followed by: Pneumovax (PPV-23) (polysaccharide) 0.5mL SC/IM	• Once • Give ≥8 weeks later	OK	OK Ideal administration[1]
	Pneumovax only (PPV-23)	Booster ≥5 years later at age ≥65		
Tetanus	Tdap (Adacel, Boostrix) (0.5mL IM)	Once as adult (pertussis)	OK	OK Ideal administration[1]
	Td (0.5mL IM)	Every 10 years		
Herpes Zoster[b]	Zostavax II (LIVE)	Age >50 ±history of shingles ≥1 year prior	OK	Generally Contraindicated[2-4]
Childhood Vaccinations (must be up-to-date)				
MMR	MMR-II or Priorix (LIVE) 0.5mL SC	If born >1970, no dose recorded (2 doses)	OK	Generally Contraindicated[2-4]
HPV[5]	Gardasil 9 (9 valent)	Age 9-26y, if at risk >26y	OK	
Varicella	Varilrix or Varivax III (LIVE)	Check titre/history of chicken pox Age <50y: 2 doses 12 weeks apart	Use with caution	Generally Contraindicated[2-4]
Meningococcal	MEN-C-ACYW-135 (quadravalent conjugate) (0.5mL IM)	If <25y, no dose recorded	OK	OK Ideal administration[1]
Vaccines for High Risk Groups				
Hepatitis A / Hepatitis B[5]	Twinrix (HAV+HBV) (1mL IM) Recombivax, Engerix-B (HBV only) (1mL IM)	0, 6-36months 0, 1, 6months	OK	OK Ideal administration[1]
Meningococcal[5]	MEN-C-ACYW-135 (quadravalent conjugate) (0.5mL IM)	Travel or At Risk 0, 8wks; booster every 5 years	OK	OK Ideal administration[1]
Cholera	Dukoral (oral)	Travel	Unnecessary - give antibiotics for treatment PRN	
Typhoid	Typherix or Typhim Vi Vivotif (LIVE)	Travel	OK Generally Contraindicated[2-4]	
Japanese				

Most live vaccines OK for:

MTX<20 mg weekly

Prednisone<20 mg daily

Imuran <100 mg daily

[1] Ideally, provide ≥14 days before biologic initiation or wait ≥3 half-lives after stopping biologic therapy

[2] Administer ≥4 weeks before biologic initiation or wait ≥3 half-lives after stopping biologic therapy

[3] To ensure minimal immunosuppression (reduce risk of infection) and optimal vaccine response: recommend waiting ≥3 half-lives after stopping biologics to give live vaccines.

CLINICAL SCIENCE

Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study

Victoria Furer ,[1,2] Tali Eviatar,[1,2] Devy Zisman,[3,4] Hagit Peleg,[5] Daphna Paran,[1,2] David Levartovsky,[1] Michael Zisapel,[1] Ofir Elalouf,[1,2] Ilana Kaufman,[1,2] Roni Meidan,[2,6] Adi Broyde,[1,2] Ari Polachek,[1,2] Jonathan Wollman,[1,2] Ira Litinsky,[1,2] Katya Meridor,[1,2] Hila Nochomovitz,[1,2] Adi Silberman,[1,2] Dana Rosenberg,[1,2] Joy Feld,[3] Amir Haddad,[3] Tal Gazzit,[3] Muna Elias,[3] Nizar Higazi,[3] Fadi Kharouf,[5,7] Gabi Shefer,[8] Orly Sharon,[8] Sara Pel,[1] Sharon Nevo,[1] Ori Elkayam[1,2]

METHODS:

Prospective observational exploratory multicentre study was conducted at the Rheumatology Departments of Tel Aviv Sourasky, Carmel, and Hadassah Medical Center, Israel, between December 2020 and March 2021.

End points of the study

The primary end point was immunogenicity of the BNT162b2 mRNA vaccine in adult patients with AIIRD compared with controls measured 2–6 weeks after the second vaccine dose.

Secondary end points included

1. Effect of immunosuppressive treatments on vaccine's immunogenicity.
2. Efficacy of vaccination, defined as prevention of COVID-19 disease, confirmed by a PCR testing.
3. Safety of vaccination in patients with AIIRD compared with controls.
4. Effect of vaccination on clinical disease activity in patients with AIIRD.

Table 4 Immunogenicity of the BNT162b2 messenger RNA vaccine according to the use of immunosuppressive treatments in comparison with controls

Immunosuppressive treatments, n	Seropositivity rate, n (%)	P value
GC, n=130	86 (66)	**<0.0001**
GC monotherapy, n=13	10 (77)	**<0.0001**
MTX, n=176	148 (84)	**<0.0001**
MTX monotherapy, n=41	38 (92)	**0.02**
HCQ, n=133	120 (90)	**0.001**
HCQ monotherapy, n=50	49 (98)	0.65
LEF, n=28	25 (89)	**0.004**
LEF monotherapy, n=11	11 (100)	NA
TNFi, n=172	167 (97)	0.15
TNFi monotherapy, n=121	119 (98)	0.48
TNFi +MTX, n=29	27 (93)	**0.04**
IL6i, n=37	37 (100)	NA
IL6i monotherapy, n=19	19 (100)	NA
IL6i+MTX, n=7	7 (100)	NA
Anti-CD20, n=87	36 (41)	**<0.0001**
Anti-CD20 monotherapy, n=28	11 (39)	**<0.0001**
Rituximab+MTX, n=14	5 (36)	**<0.0001**
IL17i, n=48	47 (98)	0.63
IL17i monotherapy, n=37	37 (100)	NA
IL17i+MTX, n=7	6 (85)	0.05
Abatacept, n=16	10 (62)	**<0.0001**
Abatacept monotherapy, n=7	5 (71)	**<0.0001**
Abatacept+MTX, n=5	2 (40)	**<0.0001**
JAKi monotherapy, n=21	19 (90)	**0.02**
JAK+MTX, n=24	22 (92)	**0.03**
Belimumab, n=9	7 (77)	**0.0001**
MMF, n=28	18 (64)	**<0.0001**

anti-CD20, CD20 inhibitors; GC, glucocorticoids; HCQ, hydroxychloroquine; IL6i, interleukin 6 inhibitors; IL17i, interleukin 17 inhibitors; JAKi, Janus kinase inhibitors; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; TNFi, tumour necrosis factor inhibitors.

Immunogenicity of the BNT162b2 vaccine

The seropositivity rate was 86% (n=590) in patients with AIIRD compared with 100% in controls ($p<0.0001$).

The level of the S1/S2 antibodies was significantly reduced in patients with AIIRD compared with controls (mean±SD,
132.9±91.7 vs 218.6±82.06; $p<0.0001$).

In patients with PsA, axSpA, SLE and LVV, the seropositive rate was above 90%. In patients with RA, the seropositive rate was 82.1%, whereas the lowest seropositive rate (<40%) was observed in patients with AAV and IIM

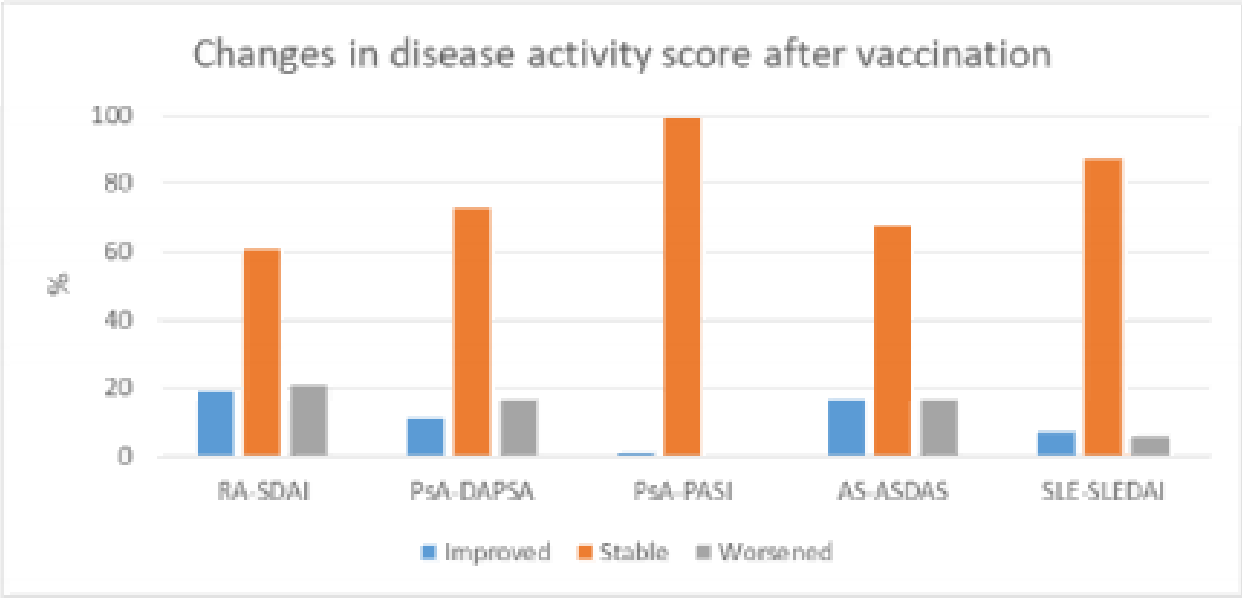


Figure 2 Disease activity scores before and after completing two doses of BNT162b2 vaccine. Data on prevaccination and postvaccination disease activity measures were available for 165 patients with RA-SDAI, 182 patients with RA-CDAI, 164 patients with RA-DAS-28-CRP, 121 patients with PsA-CDAI, 117 patients with PsA-DAPSA, 131 patients with PsA-PASI, 43 patients with AxSpA-ASDAS, 47 patients with AxSpA-BASDAI and 85 patients with SLE-SLEDAI. ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CDAI, Clinical Disease Activity Index; DAPSA, Disease Activity in Psoriatic Arthritis; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Disease Activity Index for SLE.

Prior to Rheumatology Referral

If you think the patient has an autoimmune/inflammatory arthritis:

- CBC with diff
- CMP
- ESR / CRP
- RF and CCP
- Uric acid
- XR of hands, feet and more painful joints
- HLA B27 (if you suspect spondyloarthropathy)
- Hepatitis B/C screening panel
- Quantiferon gold or PPD
- Relevant STI testing if indicated or concern for infectious etiology

When to order an **ANA**: if you think the patient has an ANA associated disease (lupus, scleroderma, autoimmune myositis, Sjogrens)

Questions?

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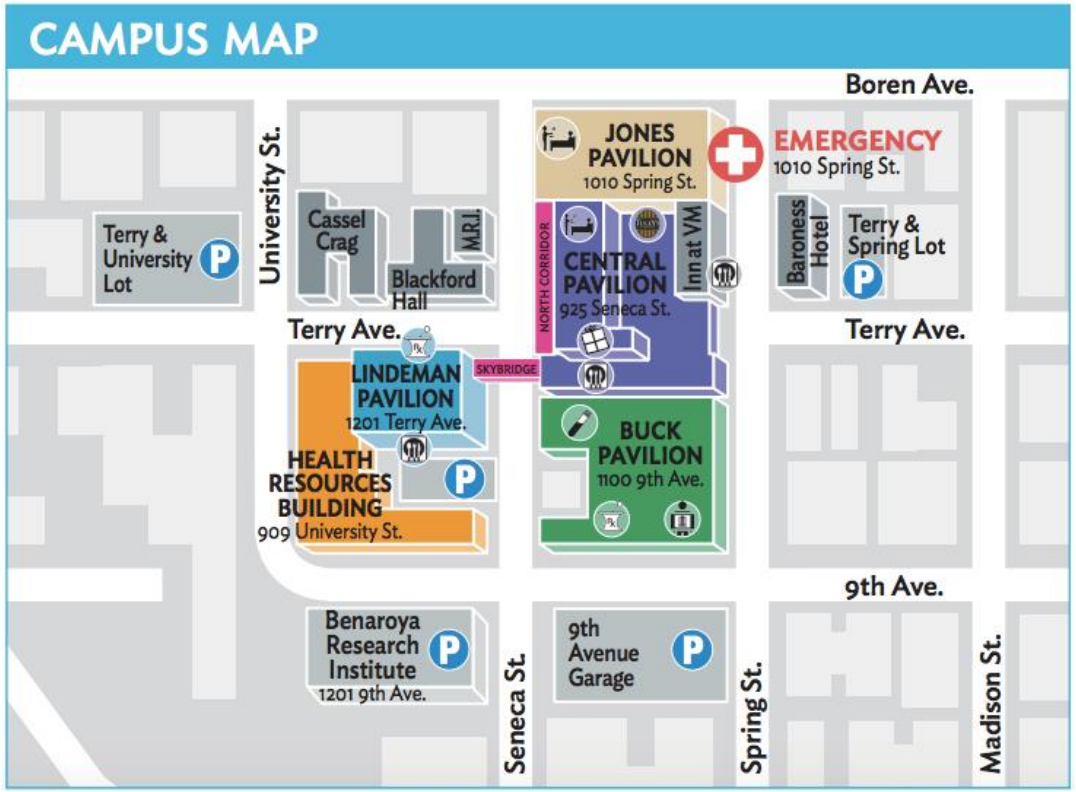

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