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Precision Medicine in Rheumatoid Arthritis: Examining the Evidence for Biomarkers in Diagnosis and Sustaining Remission During De-Escalation

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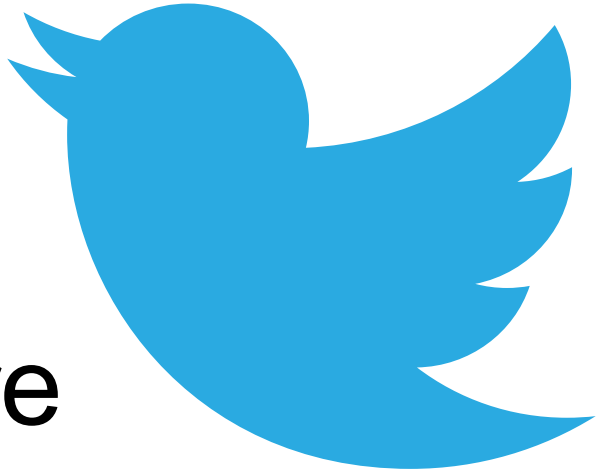

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Learning Objective 1

Assess the role of serologic biomarkers in accurate and timely diagnosis of RA.

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Learning Objective 2

Apply treatment strategies that consider disease activity and serologic biomarkers in patients with RA.

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Learning Objective 3

Evaluate methods of predicting sustained remission following de-escalation of therapy.

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Learning Objective 1

Assess the role of serologic biomarkers in accurate and timely diagnosis of RA.

Discussion Topics: Learning Objective 1

- Biomarkers in RA diagnosis
  - Biomarkers currently used in clinical practice
  - Proposed/emerging biomarkers

RA = Rheumatoid arthritis.

Audience Response

Which one of the following biomarkers is *NOT* among those commonly used in clinical practice?

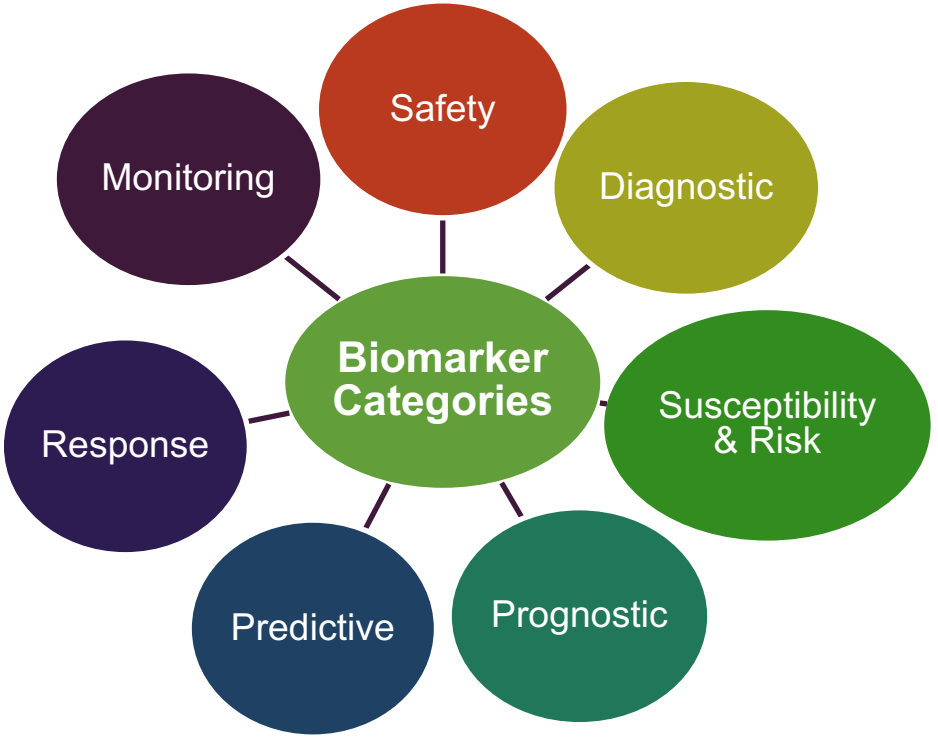
A. Antibodies to citrullinated peptides (ACPA)
B. Anti-mutated citrullinated vimentin (anti-MCV)
C. C-reactive protein (CRP)
D. Erythrocyte sedimentation rate (ESR)
E. I’m not sure

What is a Biomarker?

- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions
- Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers

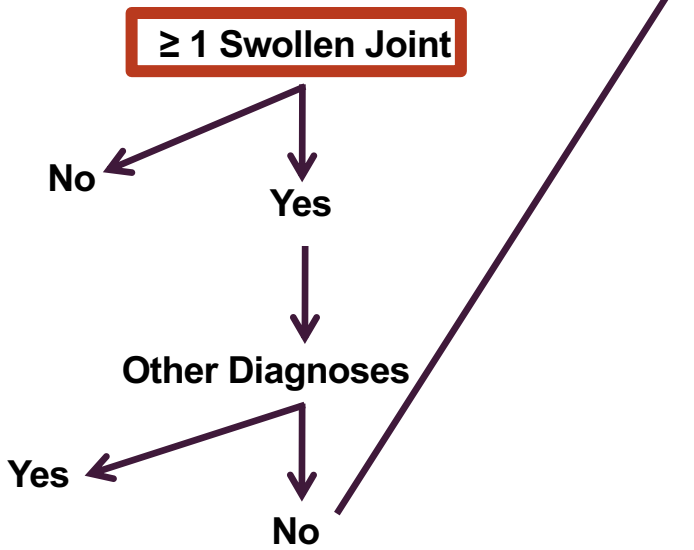
U.S. Food and Drug Administration (FDA). FDA Website. 2021. https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification#what-is. Accessed March 4, 2022.

Different Categories of Biomarkers



Adapted from Amur S. *Biomarker terminology: speaking the same language.* U.S. Food & Drug Administration Website. 2017. https://www.fda.gov/drugs/biomarker-qualification-program/transcript-biomarker-terminology-speaking-same-language. Accessed March 5, 2022.

2010 ACR/EULAR Classification Criteria



RA can be classifiable or diagnosed with a score ≥ 6

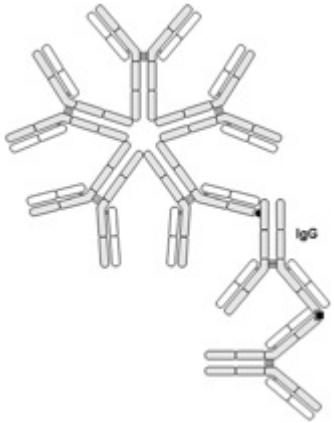
Joint distribution (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints excluded)	2
4-10 small joints (large joints excluded)	3
> 10 joints (at least 1 small joint)	5
Serology (0-3)	
Negative RF and negative ACPA	0
Low positive RF or ACPA (≤ 3x ULN)	2
High positive RF or ACPA (> 3x ULN)	3
Symptom duration (0-1)	
< 6 weeks	0
≥ 6 weeks	1
Acute phase reactants (0-1)	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

ACR = American College of Rheumatology. EULAR = European League Against Rheumatism. RF = Rheumatoid factor. ULN = Upper limit of normal.

Aletaha D, et al. *Arthritis Rheum.* 2010;62(9):2569-2581.

RF Seen in Rheumatic and Non-Rheumatic Diseases

- Rheumatic diseases
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren's syndrome
  - Systemic sclerosis
  - Dermatomyositis/ polymyositis
  - Vasculitis
  - Cryoglobulinemia
  - Juvenile rheumatoid arthritis



- Non-rheumatic diseases
  - Normal individuals (< 5%)
  - Elderly
  - Bacterial infections
    - Endocarditis, leprosy, syphilis, Lyme disease, periodontal disease
  - Viral infections
    - Hep A,B,C, parvovirus, rubella, CMV, HIV, EBV
  - Parasitic diseases
  - Lymphoproliferative disease
  - Interstitial lung disease
  - Chronic liver disease
  - Sarcoidosis
  - Post-vaccination
  - Malignancies

CMV = Coxsackie B virus. EBV = Epstein-Barr virus. Hep = Hepatitis. HIV = Human immunodeficiency virus.

Ingegnoli F, et al. *Dis Markers.* 2013;35(6):727-734. Tiwari V, et al. Congenital tibial pseudoarthrosis. *StatPearls [Internet]*. 2022. https://europepmc.org/article/NBK/NBK576443. Accessed March 7, 2022.

Biomarkers in RA - Diagnosis

- **Used in Practice**
  - Rheumatoid factors (RF)
  - Antibodies to citrullinated peptides (ACPA)
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- **Speculative; not endorsed by the ACR**
  - Anti-mutated citrullinated vimentin (anti-MCV)
  - Serum14-3-3eta (an intracellular chaperonin protein)
  - Antibodies to carbamylated proteins (anti-CarP)
  - Multi-biomarker disease activity (MBDA) test (Vectra™)
  - Molecular signature test (PrismRA™)

Shapiro SC. *Cureus.* 2021;13(5):e15063.

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Learning Objective 2

Apply treatment strategies that consider disease activity and serologic biomarkers in patients with RA.

Discussion Topics: Learning Objective 2

- Treat to target (ACR recommendations)
- Disease measures
- How biomarkers help
- Different drugs for RA – when to use

ACR-EULAR 2011 Definition of Remission

- ***For clinical trials***
- Boolean
  - SJC, TJC, PtGA, CRP all ≤ 1
- Index-based
  - SDAI ≤ 3.3
- *SDAI = SJC + TJC + PhGA + PtGA + CRP (mg/dL)*

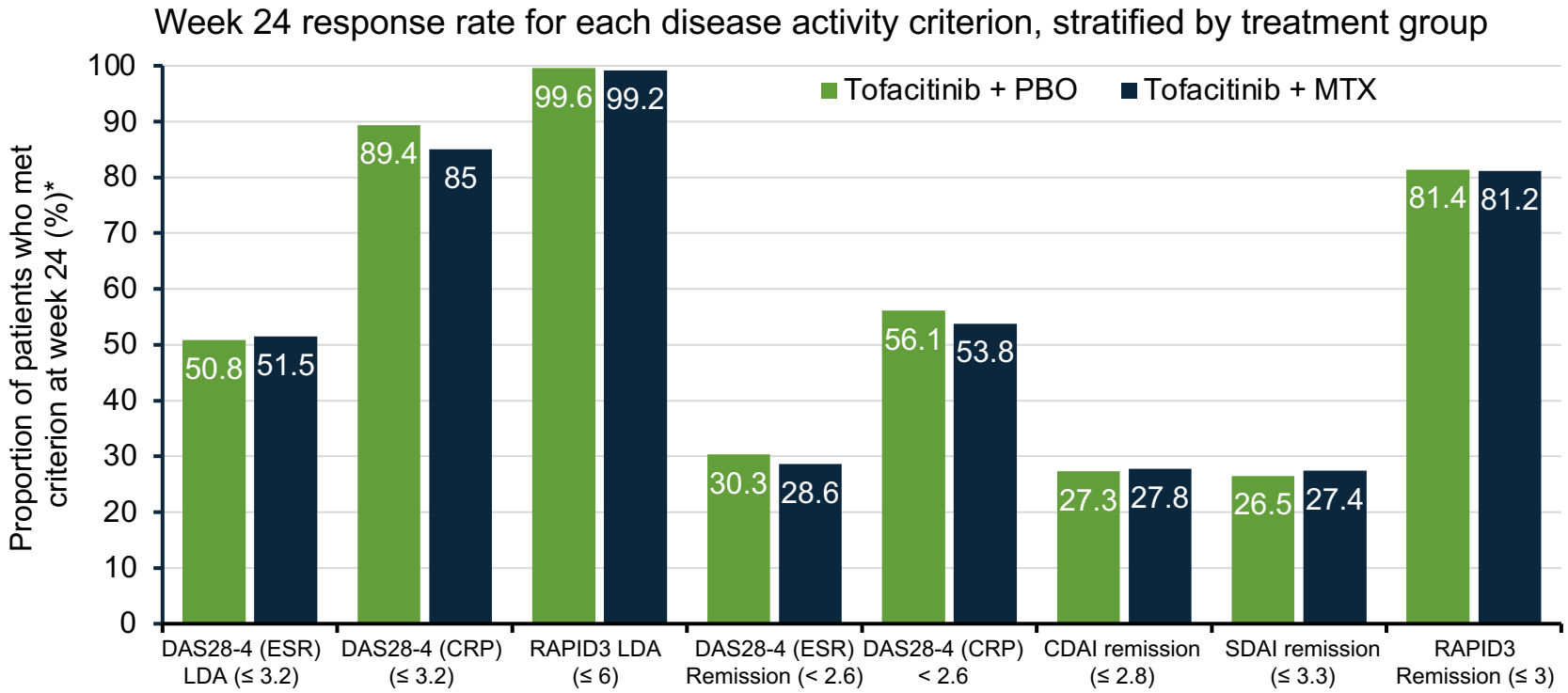
For clinical practice

- Boolean
  - SJC, TJC, PtGA all ≤ 1
- Index-based
  - CDAI ≤ 2.8
- *CDAI = SJC + TJC + PhGA + PtGA*

CDAI = Clinical activity disease index. Dl = Deciliter. Mg = Milligrams. PhGA = Physician's global assessment. PtGA = Patient global assessment of disease activity. SDAI = Simplified disease activity index. SJC = Swollen joint count. TJC = Tender joint count.

Bykerk VP, Massarotti EM. *Rheumatology (Oxford).* 2012;51 (Suppl 6):vi16-20.

Variability of Disease Metrics in RA



*Proportion calculated based on all patients who were randomized and received treatment in the double-blind phase of ORAL Shift. DAS28 = Disease activity score 28. LDA = Low disease activity. PBO = Placebo. RAPID3 = Routine Assessment of Patient Index Data 3.

Fleischmann R, et al. *Ann Rheum Dis.* 2021;80(Suppl 1);251.

AMPLE Trial: Impact of Baseline Anti-CCP on Efficacy Outcomes After Treatment With Abatacept or Adalimumab

Study Design

- 2-year, phase IIIb, randomized, investigator-blinded study
- Biologic-naïve patients with active RA and an inadequate response to MTX were randomized to 125 mg SC abatacept weekly or 40 mg adalimumab bi-weekly, both on background MTX

Inclusion Criteria

- ≥ 18 years of age with moderate to severe RA for ≤ 5 years
- Inadequate response to MTX and biologic naïve
- ≥ 3.2 DAS28-CRP and history of:
  - Seropositivity for anti-CCP or RF
  - Elevated ESR or CRP level

Methods

- Anti-CCP antibody concentration measured at baseline
- Antibody-positive patients divided into equal quartiles (Q1-Q4), representing increasing antibody concentrations
- Clinical outcomes analyzed by baseline anti-CCP status and quartile

AMPLE = Abatacept versus adalimumab comparison in biologic-naïve RA subjects with background methotrexate. Anti-CCP = Anti-cyclic citrullinated peptide. MTX = Methotrexate. Q = Quartile. SC = Subcutaneous.

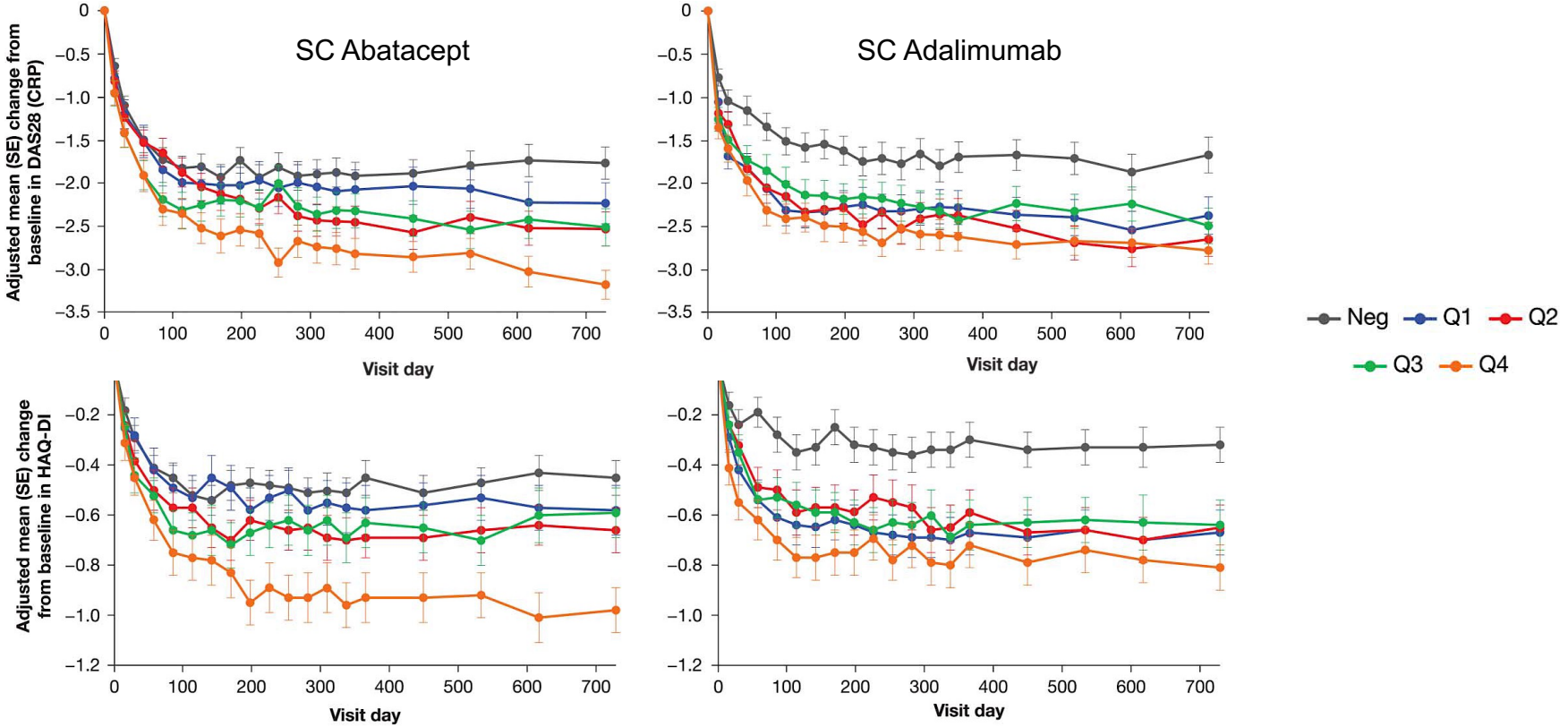
Sokolove J, et al. *Ann Rheum Dis*. 2016;75:709-714.

Audience Response

What was found at year 2 in the analysis of AMPLE-2, comparing baseline anti-CCP antibody status with clinical outcomes, in patients treated with abatacept or adalimumab on background MTX?

A. In both groups, anti-CCP antibody-negative patients responded better than antibody-positive patients
B. Improvements (in disease activity, disability and remission rates) were similar across all 4 quartiles in both treatment groups
C. Improvements were numerically higher in quartile 4 for abatacept only
D. Improvements were numerically higher in quartile 3 and 4 for both abatacept and adalimumab
E. I'm not sure

AMPLE Trial: Exploratory Analysis Results



DI = Disability index. HAQ = Health assessment questionnaire. SE = Standard error.
Schiff M, et al. *Ann Rheum Dis.* 2014;73:86-94.

Drugs for RA

- Nonbiologic DMARDs: Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, cyclosporine
- Anti-TNF-alpha agents: etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
- Non-TNF biologic DMARDs: IL-6 receptor antagonists (e.g., tocilizumab and sarilumab), T-cell blockers (e.g., abatacept), anti-CD20 B-cell depleting monoclonal antibody (e.g., rituximab)
- Targeted synthetic DMARDs: Janus kinases (JAK) inhibitors (e.g., tofacitinib, baricitinib, and upadacitinib)

When do we use them?

DMARD = Disease-modifying antirheumatic drugs.
Fraenkel L, et al. *Arthritis Care Res.* 2021;73(7):924-929.

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Learning Objective 3

Evaluate methods of predicting sustained remission following de-escalation of therapy.

Discussion Topics: Learning Objective 3

- Is de-escalation appropriate?
  - If yes, when?
- How do biomarkers help?

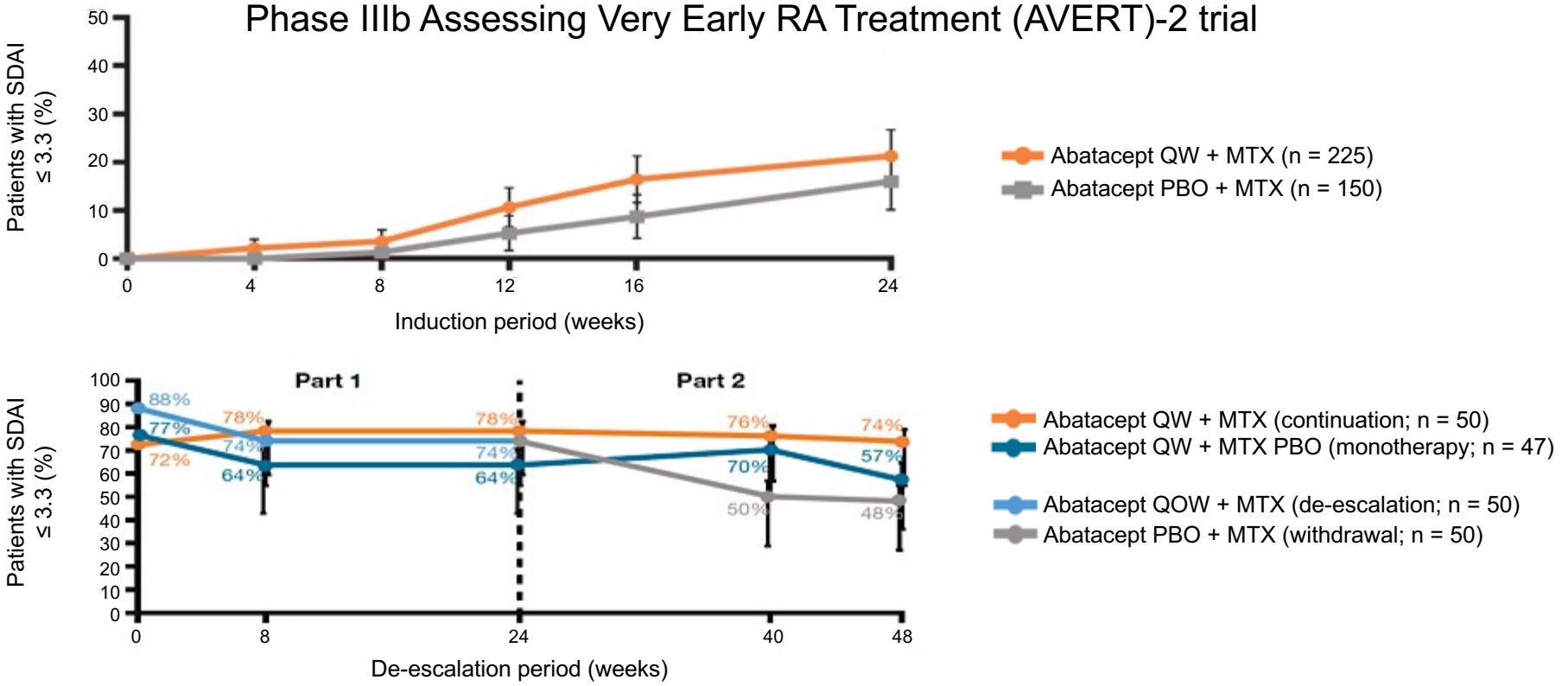
Audience Response

Which of the following is a predictor of sustained RA remission during therapy de-escalation?

A. Longer disease duration and treatment prior to de-escalation
B. Deep sustained remission with the appropriate metric
C. Moderate disease activity at the time of de-escalation
D. Stopping versus tapering bDMARDs
E. I'm not sure

bDMARDs = Biological DMARD.

Drug Maintenance, Tapering, and Discontinuation

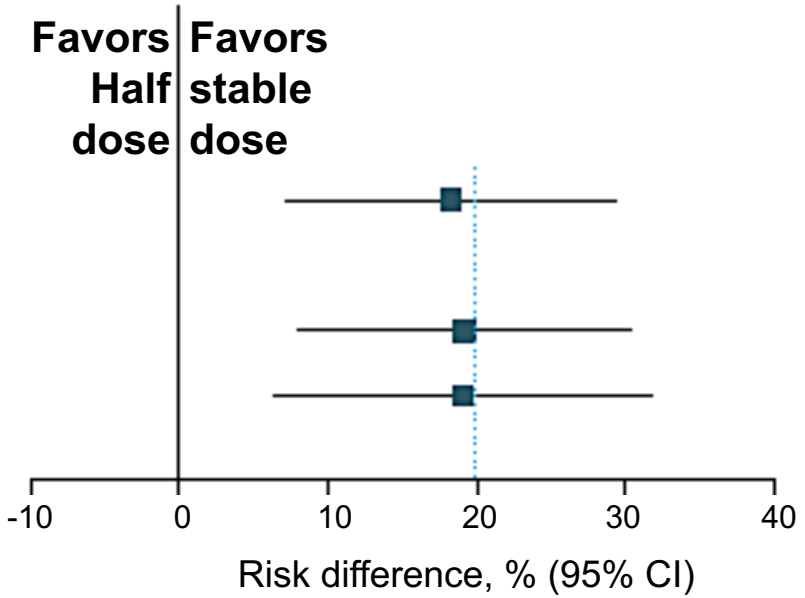


n = Number. QOW = Every other week. QW = Once weekly.

Emery P, et al. *Annals Rheum Dis*; 2020;79 (Suppl 1):985-986.

ARCTIC REWIND: Half Dose csDMARDs vs. Usual Dose

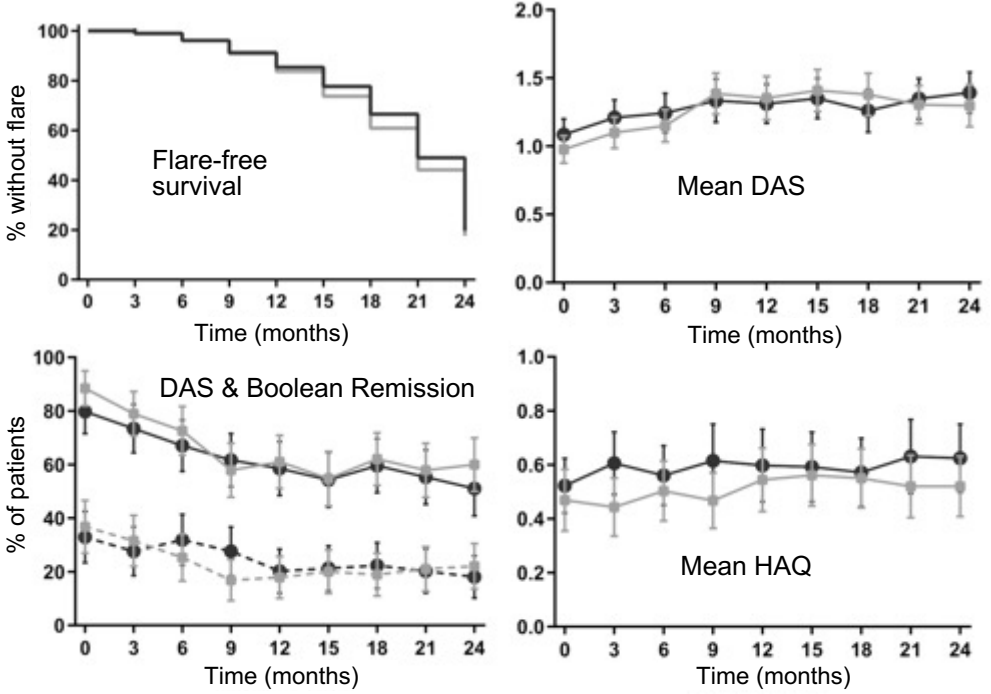
	csDMARD Group, n/N (%)		
	Half Dose	Stable Dose	Risk difference, % (95% CI)
Primary analysis	19/77 (25)	5/78 (6)	18 (7-29)
Additional analyses of primary outcome			
Randomized and initiated therapy	20/78 (26)	5/78 (6)	19 (8-30)
Methotrexate monotherapy	18/66 (27)	5/61 (8)	19 (6-32)



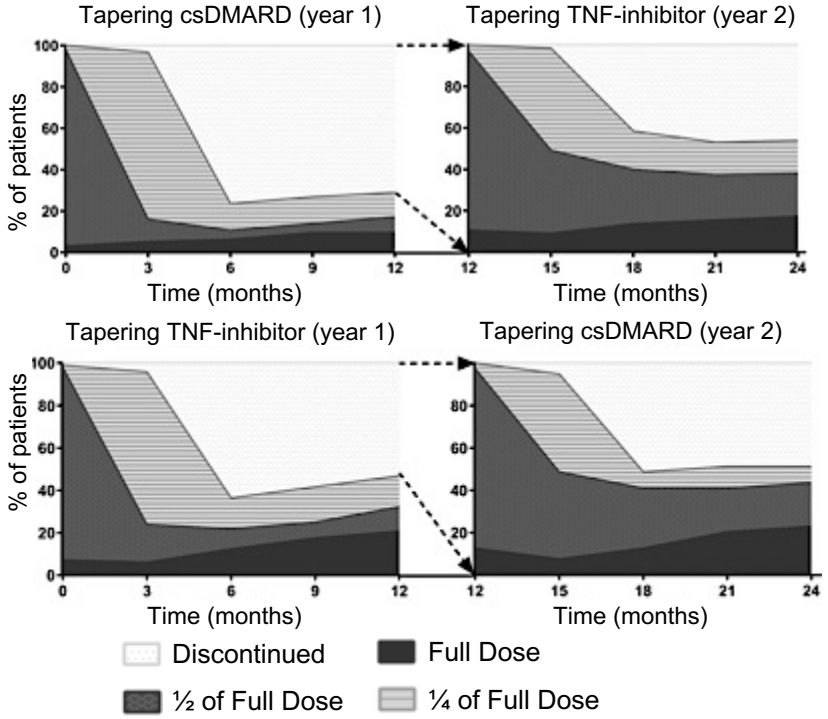
ARCTIC = Aiming for Remission in rheumatoid arthritis: a randomized trial examining the benefit of ultrasound in a Clinical TIght Control regimen. CI = Confidence interval. csDMARD = Traditional synthetic DMARD. N = Total number. REWIND = Remission in rheumatoid arthritis – assessing Withdrawal of disease-modifying antirheumatic drugs in a Non-inferiority Design.
Lillegraven S, et al. *J Am Coll Cardiol*. 2021;325(17):1755-1764.

TARA Trial: Tapering DMARD vs. TNFi in RA

Disease Activity Over Time



DMARD Usage Over Time



TARA = TApering strategies in Rheumatoid Arthritis. TNFi = Tumor necrosis factor inhibitor.

Van Mulligen E, et al. *Ann Rheum Dis*. 2020;79(9);1174-1181.

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Faculty Discussion

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- The presence of autoantibodies can support diagnosis and classification of RA
- Using biomarkers may help predict prognosis in patients not adequately treated
- Reasons for tapering therapy may include less toxicity and less cost -- but what is the result?
- Use caution when de-escalating therapy in RA as remission may be impacted and difficult to fully regain

To Ask a Question

Please select the *Ask Question* tab below the slide viewer.

Please include the faculty member's name if the question is specifically for them.

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AFTER THE SHOW

Questions & Answers

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