Brigham and Women's Hospital
Founding Member, Mass General Brigham

What's New in Rheumatology for the Generalist

Eli M. Miloslavsky, MD
Division of Rheumatology, Allergy and Immunology
Department of Medicine
Massachusetts General Hospital
Associate Professor of Medicine
Harvard Medical School

Eli Miloslavsky, MD

Icahn School of Medicine at Mount Sinai
Medicine Residency @ MGH
Rheumatology Fellowship @MGH
Associate Professor of Medicine@ HMS
Firm Chief, MGH Internal Medicine Program
Associate Program Director, MGH Rheumatology Fellowship

- Clinical focus: Vasculitis
- Research focus: Medical Education

DISCLOSURES

- Consulting – Otsuka pharmaceuticals

OBJECTIVES

- Review and apply recent advances in rheumatology to the evaluation and treatment of patients with
  - Rheumatoid Arthritis
  - Inflammatory back pain
  - Fibromyalgia
  - Anti-phospholipid antibody syndrome

Case 1

- 60 year old woman with a history of hypertension and RA on tofacitinib and methotrexate seen for annual visit
- Rheumatoid arthritis is well controlled with mild arthralgia not impairing daily function
- Exam with one swollen and two tender joints

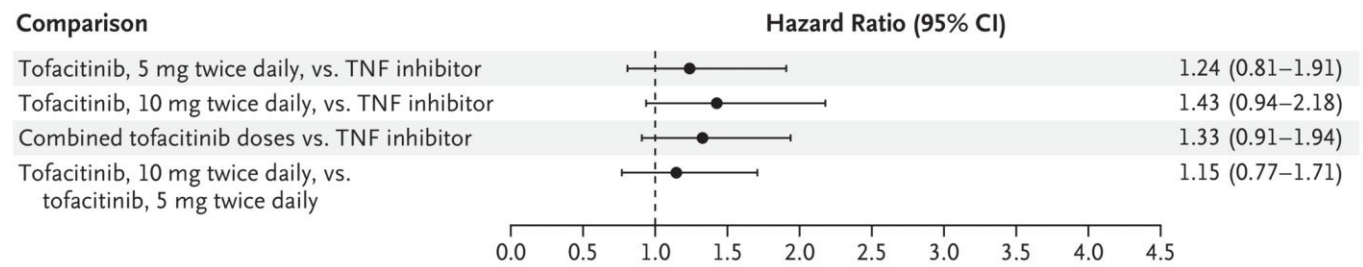
What would you recommend she discuss with her rheumatologist?

a. Continue tofacitinib
b. Recommend switch to another biologic
c. Discontinue tofacitinib and remain on methotrexate

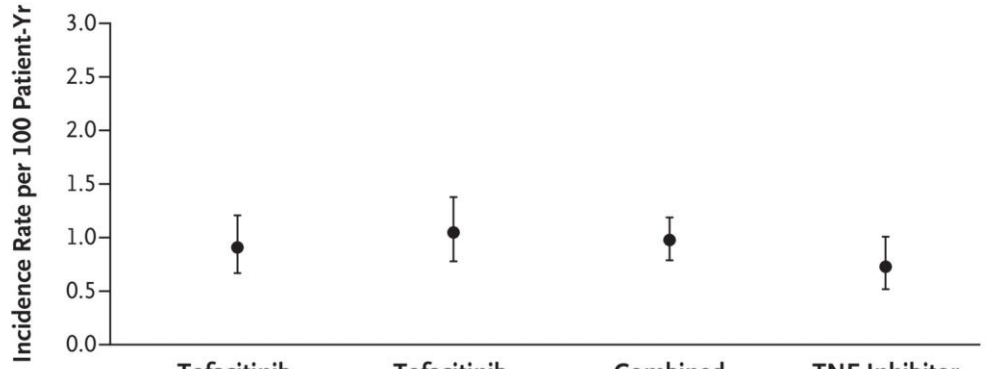
Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Ytterberg SR et al. DOI: 10.1056/NEJMoa2109927

A Hazard Ratio for MACE

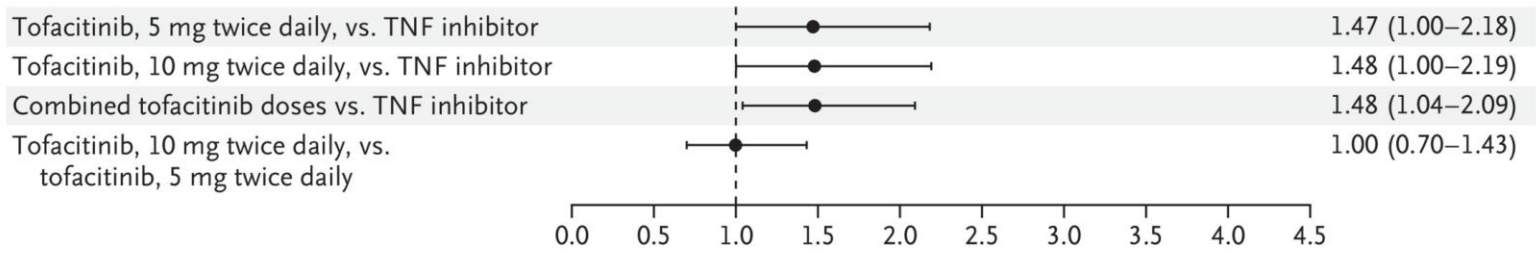


B Incidence Rate for MACE

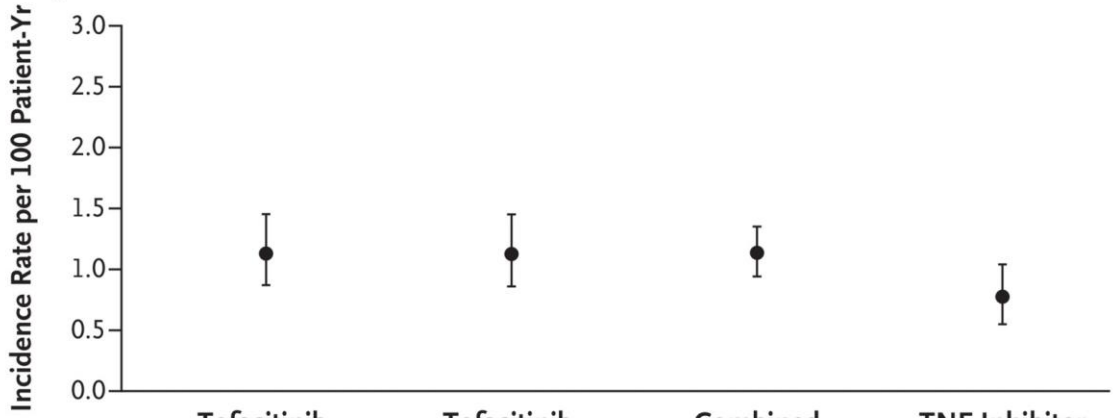


	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	47/1455 (3.2)	51/1456 (3.5)	98/2911 (3.4)	37/1451 (2.5)
No. of Patient-Yr	5166.32	4871.96	10,038.28	5045.27
Incidence Rate per 100 Patient-Yr (95% CI)	0.91 (0.67–1.21)	1.05 (0.78–1.38)	0.98 (0.79–1.19)	0.73 (0.52–1.01)
NNH (patient-yr) vs. TNF Inhibitor	567	319	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	113	64	—	—

A Hazard Ratio for Cancers, Excluding NMSC



B Incidence Rate for Cancers, Excluding NMSC

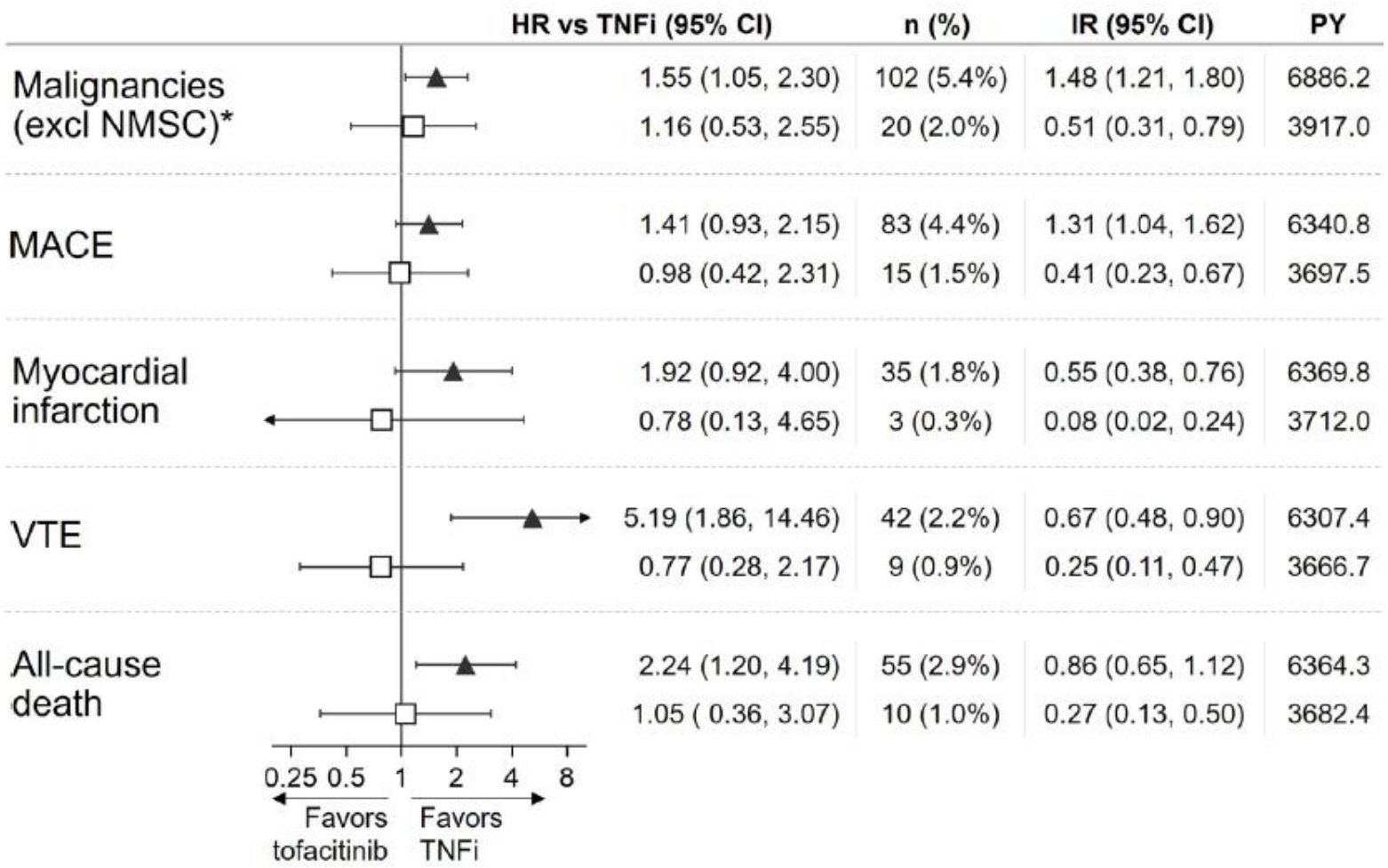


No. of Patients with First Event/Total No. (%)	62/1455 (4.3)	60/1456 (4.1)	122/2911 (4.2)	42/1451 (2.9)
No. of Patient-Yr	5491.48	5311.71	10,803.19	5482.30
Incidence Rate per 100 Patient-Yr (95% CI)	1.13 (0.87–1.45)	1.13 (0.86–1.45)	1.13 (0.94–1.35)	0.77 (0.55–1.04)
NNH (patient-yr) vs. TNF Inhibitor	276	275	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	55	55	—	—

Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance

▲ **Age ≥65 years or Ever smoked (High-risk)**
Tofacitinib (N=1895) vs TNFi (N=926)

□ **Age <65 years and Never smoked (Low-risk)**
Tofacitinib (N=1016) vs TNFi (N=525)



Ann Rheum Dis. 2023 Jul;82(7):901–910.

Case 2

- Lab testing reveals
  - LDL 120
  - HDL 40
  - TGs 280
- AHA risk score 5.8%

What would you recommend?

a. Start statin
b. Continue current management
c. Start fenofibrate

Rheumatic disease and CVD

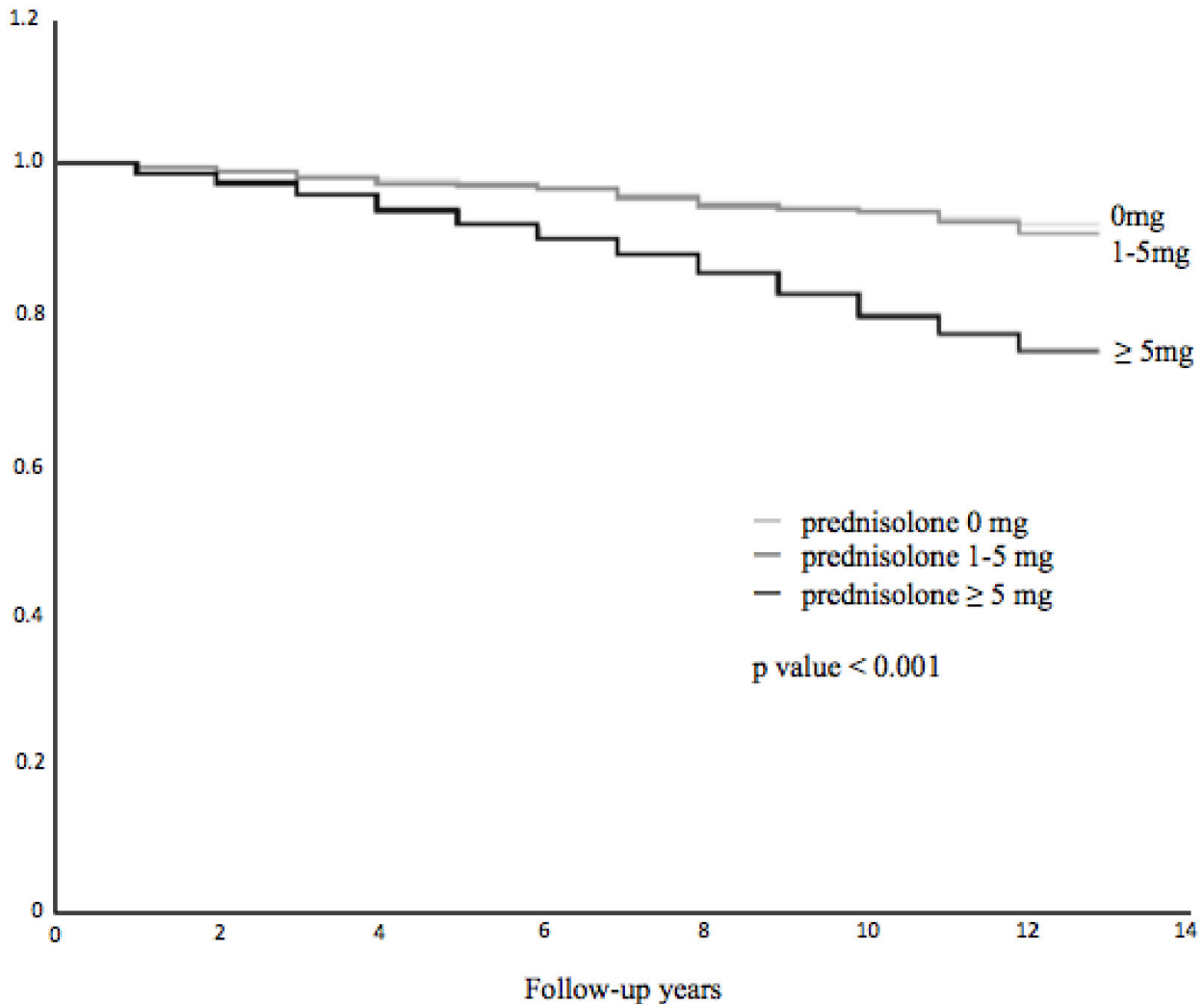
- CVD mortality 59% higher in RA
  - Inflammation
  - Exercise
  - Medications – prednisone, NSAIDs, JAK inhibitors
  - Other risk factors
- RA pts less likely to report chest pain
- SLE CAD risk 2x general population
- Perfusion abnormalities 81% of symptomatic and 43% of asymptomatic pts with SLE (age 22-45)

Avina-Zubieta et al Arthritis Rheum. 2008;59(12):1690
Low et al. Ann Rheum Dis. 2017;76(4):654.
Del Rincon et al. Arthritis Rheumatol. 2014;66(2):264
Douglas et al Ann Rheum Dis. 2006;65(3):348
Sun et al Rheumatology (Oxford). 2001;40(10):1106

Elevated triglyceride levels are associated with increased risk for major adverse cardiovascular events in statin-naïve rheumatoid arthritis patients: A nationwide cohort study

Baseline TG				
Q1	82	21,095	3.89	1 (reference)
Q2	119	18,835	6.32	1.18 (0.89–1.57)
Q3	147	17,380	8.46	1.35 (1.03–1.78)
Q4	184	15,822	11.63	1.74 (1.33–2.28)

Time and dose-dependent effect of systemic glucocorticoids on major adverse cardiovascular event in patients with rheumatoid arthritis: a population-based study



So H, et al. Ann Rheum Dis 2023;82:1387–1393.

Vaccination in the rheumatic diseases

MTX decreases vaccine response to pneumococcal and seasonal flu vaccines

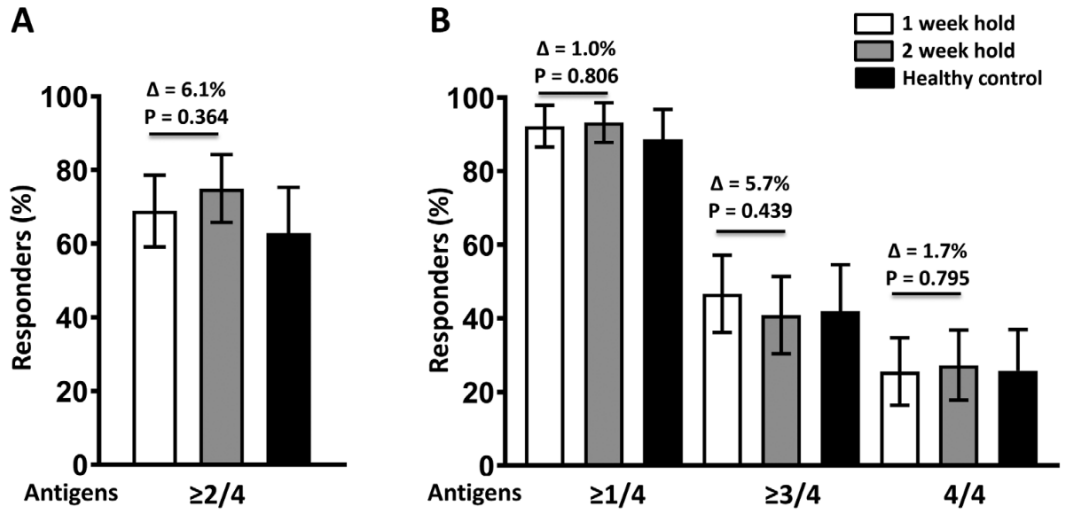
For those on a stable dose of MTX

- If held for 2 weeks, significantly increases immunogenicity to influenza vaccine without increasing disease activity
- If held for 4 weeks, resulted in a transient increase in disease activity (DAS28)

Could discontinuing MTX for 1 week be sufficient to improve immunogenicity?

Friedman MA. Ann Rheum Dis. 2021;80: 1255-1265
Park JK et al. Ann Rheum Dis. 2017; 76: 1559-1565
Park JK et al. Ann Rheum Dis. 2018; 77: 893-904

A Multicenter, Prospective, Randomized, Parallel-Group Trial on the Effects of Temporary Methotrexate Discontinuation for One Week Versus Two Weeks on Seasonal Influenza Vaccination in Patients With Rheumatoid Arthritis



2-week vs. 1 week hold groups

Change in DAS28-CRP score was 0.1 higher from baseline
RA flare 12.9% vs. 4.5% (p=0.05)
Rescue medications needed 8% vs. 3.4% (p=0.187)

Park JK, et al. Arthritis Rheum;2023:171-177

RA take-home points

- Risk of MACE, malignancy and VTE with tofacitinib remains an area of investigation. Risk in non-smokers under 65 may be low
- Risk of CV events is increased in RA requiring adjustment of risk in determining statin therapy. Triglycerides may play a greater role in patients with RA
- 1-week discontinuation of methotrexate is non-inferior to 2-week discontinuation and associated with fewer disease flares

Case 3

- 40 year old male presents for evaluation of low back pain
- Ongoing for 1 year, started insidiously
- 45 minutes of AM stiffness, improved with activity, worse with rest
- No improvement with NSAIDs, no nighttime awakening
- Exam without tenderness to palpation
- PT without improvement
- ESR, CRP normal
- SI joint and LS spine films normal

What is the best next step in management?

a. SI joint MRI
b. HLA-B27
c. No additional testing

Inflammatory back pain features

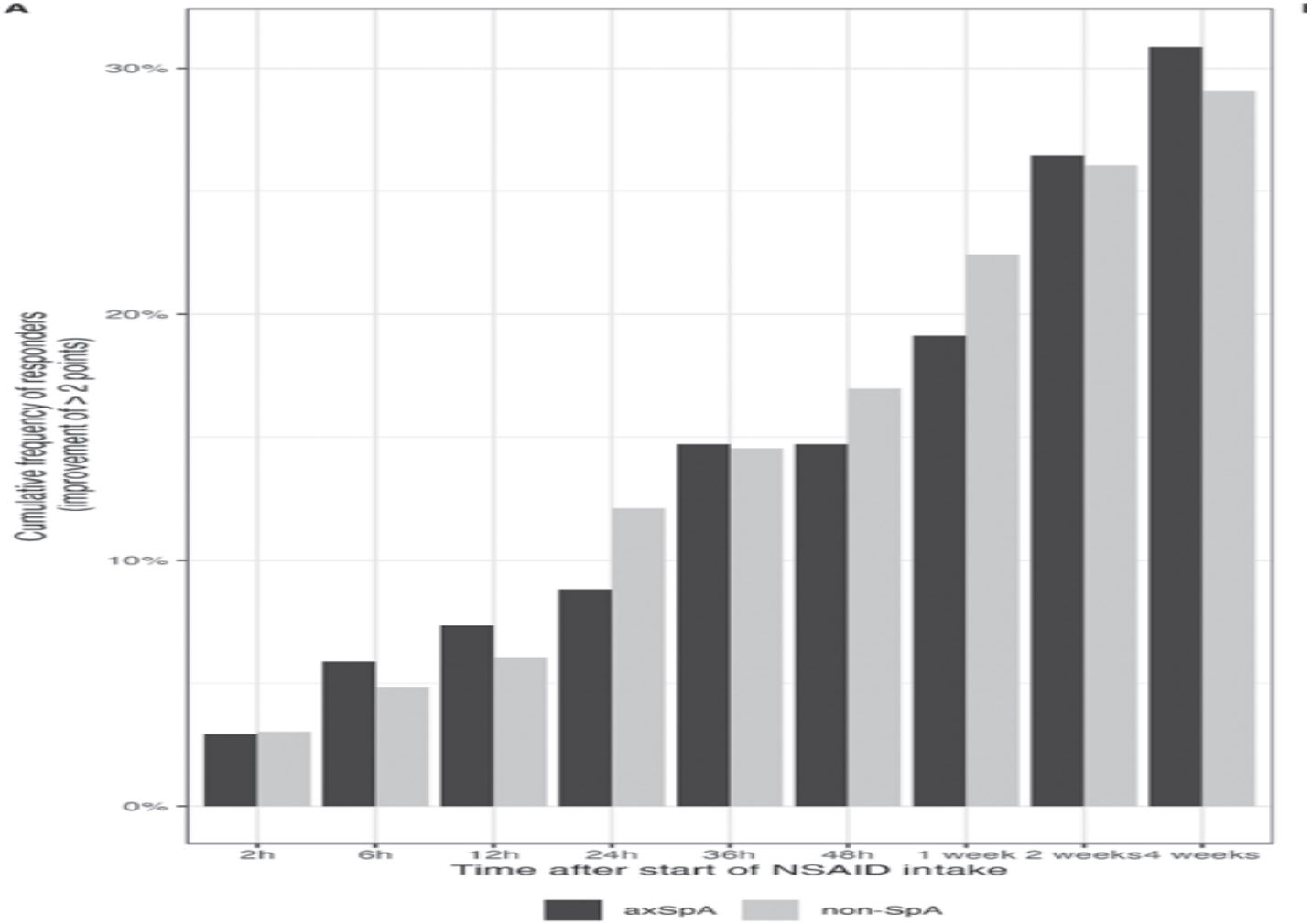
Table 2 Inflammatory back pain (IBP) parameters, according to experts

Parameter	Criteria
1	Age at onset <40 years
2	Insidious onset
3	Improvement with exercise
4	No improvement with rest
5	Pain at night (with improvement upon getting up)

Sensitivity 77.0% and specificity 91.7% if at least four out of five parameters are present. Note that sensitivity and specificity refer to the presence of IBP, not to diagnosis.

Annals of the Rheumatic Diseases 2009;**68:**784-788.

A Good Response to Nonsteroidal Antiinflammatory Drugs Does Not Discriminate Patients With Longstanding Axial Spondyloarthritis From Controls With Chronic Back Pain



ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

In patients with ≥ 3 months back pain and age of onset < 45 years

Sacroiliitis on imaging AND ≥ 1 SpA feature	OR	HLA-B27 positive AND ≥ 2 other SpA features

SpA features

- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's / colitis
- good response to NSAIDs
- family history of SpA
- HLA-B27
- elevated CRP

Sacroiliitis on imaging

- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to modified New York criteria

Sensitivity 82.9% Specificity 84.4%

Rudwaleit M et al. Ann Rheum Dis 2009;68:777-783

Case 4

- 45 year old female presents with multiple symptoms ongoing for 2 years
  - Daytime fatigue
  - Diffuse pain described as burning involving the face, arms, legs
  - Hands turn red at end of day and after hot showers
  - Orthostasis
  - Intermittent diarrhea – dx as IBS
- Exam with diffuse tenderness, no synovitis
- ESR/CRP, ANA, TSH, SPEP, A1c, B12/folate – wnl
- EMG without abnormalities

What is the next best step in management?

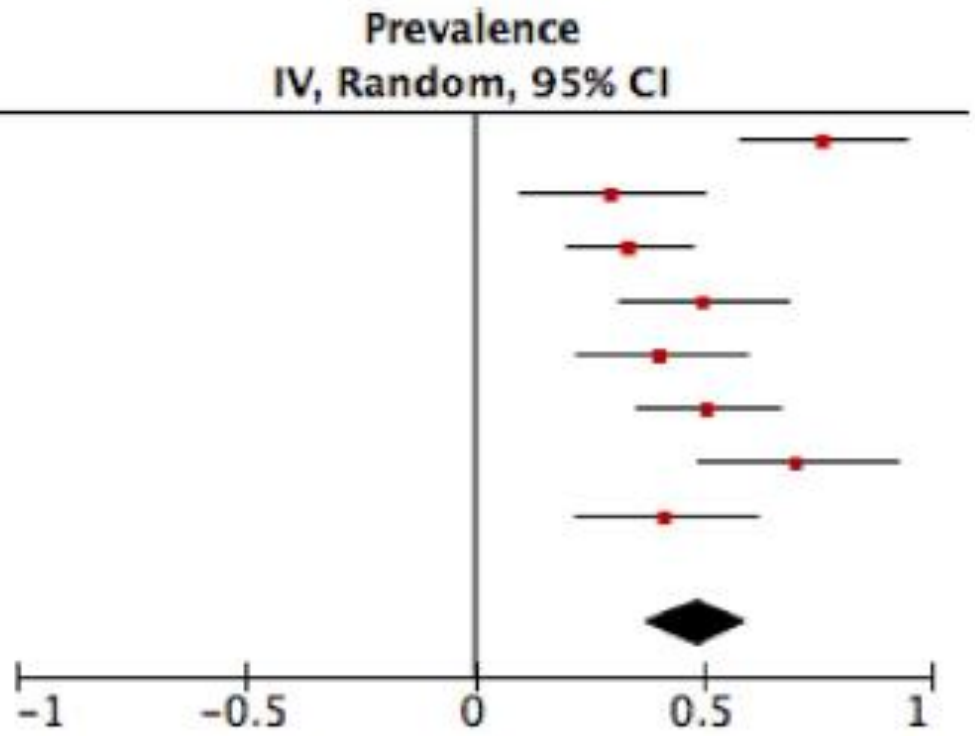
a. Start nortriptyline
b. Trial of prednisone
c. Refer to neurology for skin biopsy

A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis

Study or Subgroup	Prevalence	SE	Weight	Prevalence IV, Random, 95% CI
de Tommaso, 2014	0.762	0.093	12.5%	0.76 [0.58, 0.94]
Giannoccaro, 2014	0.3	0.102	11.7%	0.30 [0.10, 0.50]
Kosmidis, 2014	0.337	0.07	14.6%	0.34 [0.20, 0.47]
Leinders, 2016	0.5	0.094	12.4%	0.50 [0.32, 0.68]
Oaklander, 2013	0.407	0.095	12.3%	0.41 [0.22, 0.59]
Oudejans, 2015	0.51	0.08	13.7%	0.51 [0.35, 0.67]
Ramirez, 2015	0.705	0.111	11.0%	0.70 [0.49, 0.92]
Uceyler, 2013	0.417	0.101	11.8%	0.42 [0.22, 0.61]
Total (95% CI)			**100.0%**	**0.49 [0.38, 0.60]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 21.75$, $df = 7$ ($P = 0.003$); $I^2 = 68\%$

Test for overall effect: $Z = 8.53$ ($P < 0.00001$)



Grayston et al. Semin Arthritis Rheum. 2019 Apr;48(5):933-940.

Naltrexone 6 mg once daily versus placebo in women with fibromyalgia: a randomised, double-blind, placebo-controlled trial

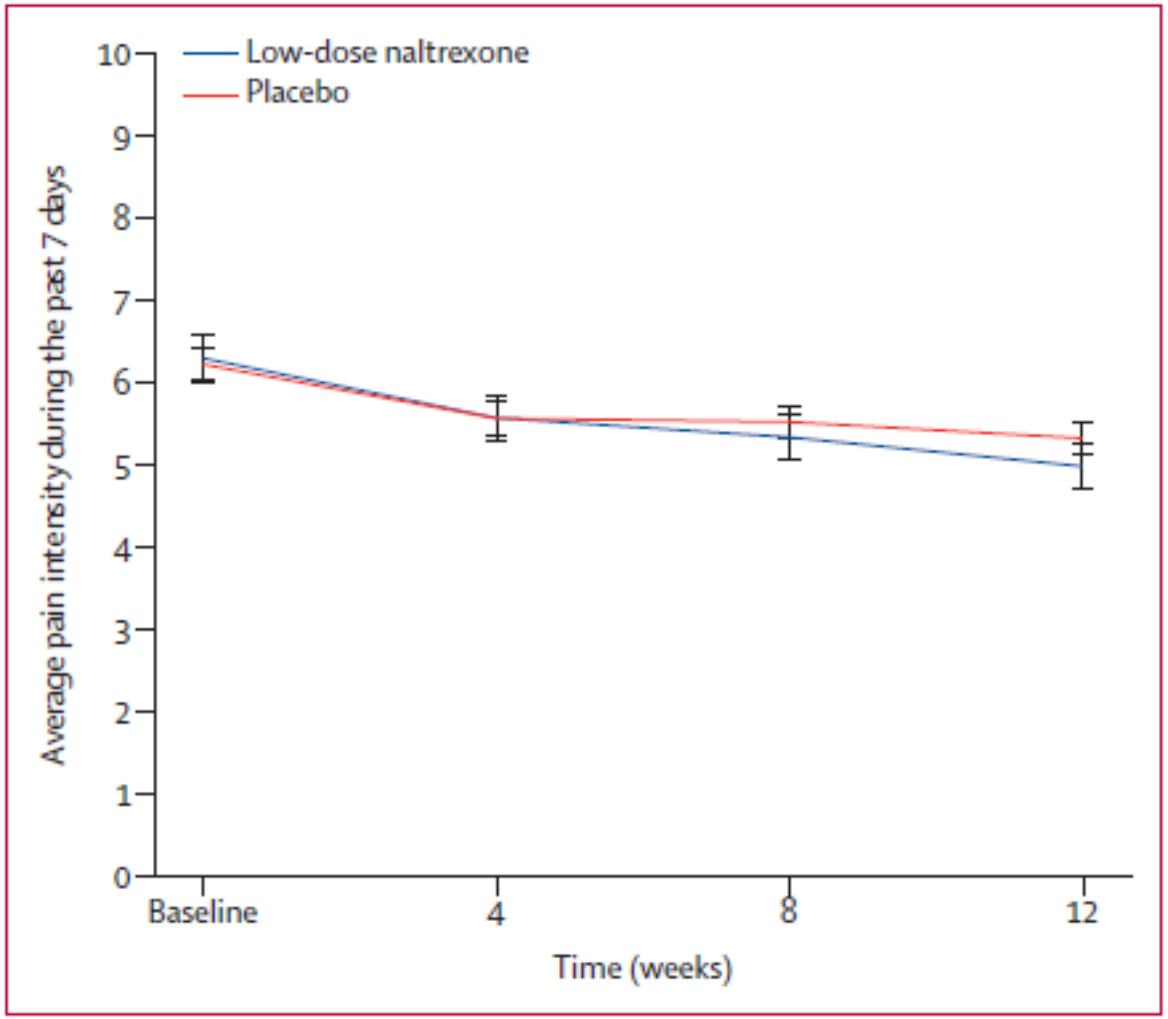


Figure 2: **Pain trajectory**

Lancet Rheumatol . 2024 Jan;6(1):e31-e39.

Case 5

- 35 year old female presents with unprovoked DVT
- Testing reveals ACL IgM 30 (ULN 20), ACL IgG 22, B2GP1 IgM/IgG negative, lupus anticoagulant negative

What is the next best step in management?

a. Start apixiban
b. Start enoxaparin to coumadin bridge
c. Start enoxaparin to coumadin bridge and recheck labs in 3 mos

The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

Laboratory

7. Antiphospholipid antibody (aPL) testing by coagulation-based functional assays: lupus anticoagulant test	A. Negative or not tested	0
	B. Positive (single—one time)	1
	C. Positive (persistent)	5
8. aPL testing by solid-phase assays: IgG/IgM anticardiolipin (aCL) and IgG/IgM anti–β_2-glycoprotein I (anti-β_2GPI) antibody enzyme-linked immunosorbent assay (persistent¶)	A. Negative or not tested	0
	B. Moderate or high positive (IgM alone) (aCL and/or anti-β_2GPI)§	1
	C. Moderate positive (IgG) (aCL and/or anti-ß$_2$GPI)	4
	D. High positive (IgG) (aCL or anti-β_2GPI)	5
	E. High positive (IgG) (aCL and anti-β_2GPI)	7

Clinical domains and criteria	Weight		Weight
D1. Macrovascular (Venous Thromboembolism [VTE])		**D2. Macrovascular (Arterial Thrombosis [AT])**	
VTE with a high-risk VTE profile[(c)]	1	AT with a high-risk CVD profile[(c)]	2
VTE without a high-risk VTE profile[(c)]	3	AT without a high-risk CVD profile[(c)]	4

- Microvascular manifestations (nephropathy, cardiomyopathy, alveolar hemorrhage)
- Cardiac valve thickening or vegetation
- Thrombocytopenia (< 130 x 10^9)

TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are at least 3 points from clinical domains AND at least 3 points from laboratory domains

Barbhaiya et al Arthritis Rheumatol. 2023 Oct;75(10):1687-1702

KEY TAKE HOME POINTS

- JAK inhibitors may be low risk in non-smokers under 65
- Take into account the presence of rheumatic disease when considering CV risk
- Holding methotrexate for 1 week after vaccination may be superior to 2 weeks
- Recognize inflammatory back pain
- Prevalence of small fiber neuropathy is high in patients with fibromyalgia. Understanding the impact of therapies on this population is an area of future investigation
- Recognize the multiple manifestations of APS and its laboratory diagnosis

REFERENCES

- Kristensen et al. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance. Ann Rheum Dis. 2023 Jul;82(7):901-910.
- Choi et al Elevated triglyceride levels are associated with increased risk for major adverse cardiovascular events in statin-naïve rheumatoid arthritis patients: A nationwide cohort studySemin Arthritis Rheum . 2023 Dec:63:152274
- So H, et al. Time and dose-dependent effect of systemic glucocorticoids on major adverse cardiovascular event in patients with rheumatoid arthritis: a population-based studyAnn Rheum Dis 2023;82:1387–1393.
- Park JK, et al. A Multicenter, Prospective, Randomized, Parallel-Group Trial on the Effects of Temporary Methotrexate Discontinuation for One Week Versus Two Weeks on Seasonal Influenza Vaccination in Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2023 Feb;75(2):171-177.
- Baraliokos et al. A Good Response to Nonsteroidal Antiinflammatory Drugs Does Not Discriminate Patients With Longstanding Axial Spondyloarthritis From Controls With Chronic Back PainJ Rheumatol. 2024;51(3):250.
- Due Bruun et al. Naltrexone 6 mg once daily versus placebo in women with fibromyalgia: a randomised, double-blind, placebo-controlled trialLancet Rheumatol . 2024 Jan;6(1):e31-e39.
- Barbhaiya et al. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification CriteriaArthritis Rheumatol. 2023 Oct;75(10):1687-1702