Disease Modification in Individuals with

MODERATE-TO-SEVERE RHEUMATOID ARTHRITIS:

Optimizing Treatment Through the Finely Tuned Selectivity for JAKs

MEETING INFO

TeleECHO Presentation
Wednesday, February 16, 2022
6:00 – 7:00 PM ET
5:00 – 6:00 PM CT
4:00 – 5:00 PM MT
3:00 – 4:00 PM PT

FACULTY

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Disease Modification in Individuals with MODERATE-TO-SEVERE RHEUMATOID ARTHRITIS: Optimizing Treatment Through the Finely Tuned Selectivity for JAKs

Agenda

I. Managing Rheumatoid Arthritis (RA)

a. Features of rheumatoid arthritis
b. RA pathophysiology
c. Treatment options for RA
d. Guideline recommended care of RA
    i. Initial DMARD choice
    ii. Options after inadequate response to initial therapy
e. Treating to target

II. JAK Inhibitors for the Management of Moderate-to-Severe RA

a. JAK inhibitor mechanism of action and selectivity
b. Review of clinical trial data of the efficacy and safety of JAK inhibitors:
    i. Monotherapy
    ii. Combination therapy
    iii. Patients with inadequate response to methotrexate (MTX IR)
    iv. MTX naive populations
    v. Long-term safety data

III. Application of Societal Guidelines for Moderate-to-Severe Disease – ACR & EULAR

a. Focus on JAK inhibition and its place in management of patients
b. Comorbid conditions and RA treatment considerations

IV. Conclusions

V. Interactive Case Studies

VI. Q & A

Disease Modification in Individuals with Moderate-to-Severe Rheumatoid Arthritis: Optimizing Treatment Through the Finely Tuned Selectivity for JAKs

FACULTY

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Associate Professor of Medicine
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New York, NY

PROGRAM OVERVIEW

This TeleECHO series will explore the use of JAK inhibitors for the management of rheumatoid arthritis (RA) through interactive case studies. Faculty will review emerging efficacy and safety data, discuss guideline recommended care of RA, and help clinicians identify candidates for treatment with JAK inhibitors.

TARGET AUDIENCE

This CME initiative is designed to meet the educational needs of rheumatologists, nurses and allied healthcare professionals involved in the care of patients with rheumatoid arthritis.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Review the members of the JAK family, involvement in RA pathology, and selectivity of JAK targets and associated effects
- Discuss the clinical trials findings for Janus Kinase inhibitors in patients with moderate-to-severe RA
- Describe the application of ACR/EULAR management recommendations to clinical practice for patients with moderate-to-severe rheumatoid arthritis

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CNE Credits: 1.0 ANCC Contact Hour.

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The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

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Disease Modification in Individuals with Moderate-to-Severe Rheumatoid Arthritis: Optimizing Treatment Through the Finely Tuned Selectivity for JAKs

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- During the course of this lecture, Dr. Giles may mention the use of medications for both FDA-approved and non-approved indications.

This activity is supported by an educational grant from AbbVie Inc.

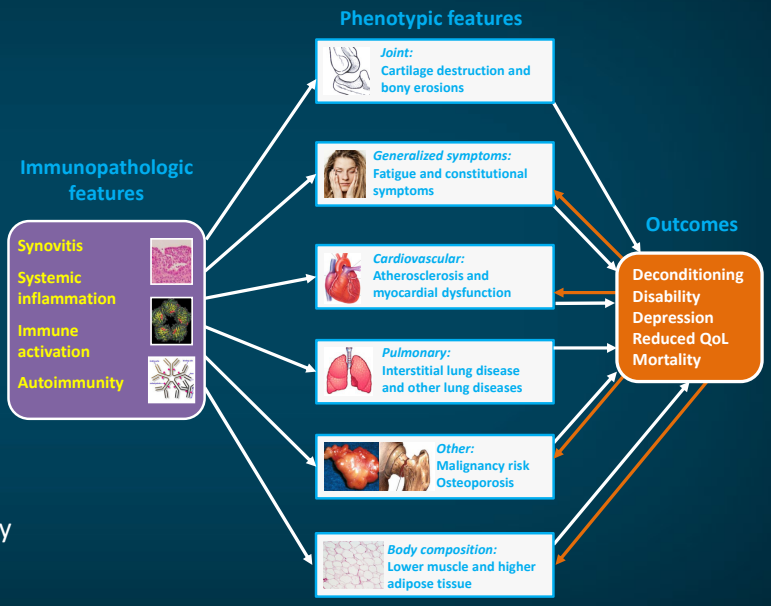
Learning Objectives

- Review the members of the JAK family, their involvement in RA pathology, and selectivity of JAK targets and associated effects
- Discuss the clinical trials findings for JAK inhibitors in patients with moderate-to-severe RA
- Describe the application of ACR/EULAR management recommendations to clinical practice for patients with moderate-to-severe rheumatoid arthritis

JAK = Janus kinase; RA = rheumatoid arthritis; ACR = American College of Rheumatology; EULAR = European League Against Rheumatism.

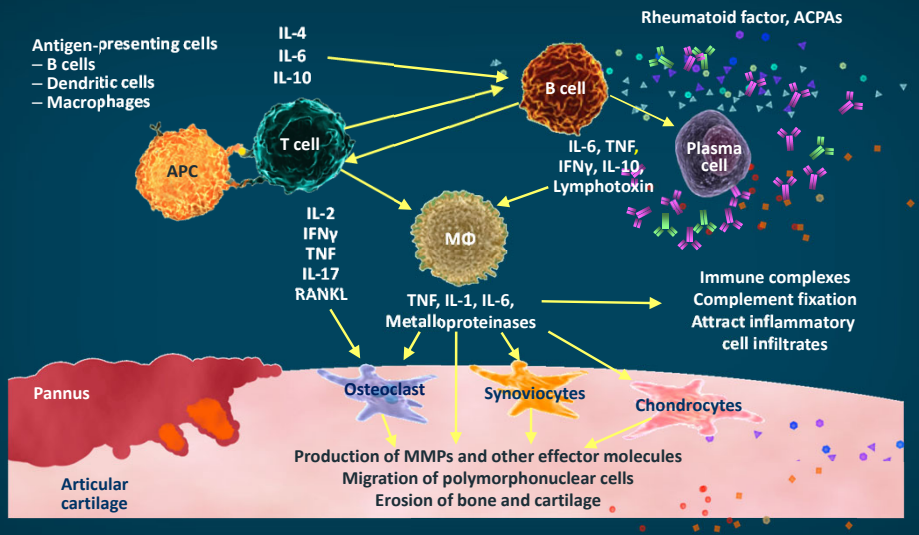
Features of Rheumatoid Arthritis

- RA is autoimmune disorder
  - Prevalence 1% worldwide
    - 3–4 million in U.S
  - Peak incidence in 4th to 6th decade of life
  - Female:male ratio of 3:1
- Characterized by:
  - Synovitis
  - Systemic inflammation
  - Extra-articular features
  - Increased morbidity/mortality



RA = rheumatoid arthritis; QoL = quality of life.

RA Pathobiology



ACPA = anti-citrullinated protein antibody; APC = antigen-presenting cell; IFN = interferon; IL = interleukin; MMP = metalloproteinase; RANKL = receptor activator of nuclear factor-κB ligand; TNF = tumor necrosis factor.

Adapted from Smolen JS, Steiner G. *Nat Rev Drug Discov.* 2003;2;473-488. Choy EH, Panayi GS. *N Engl J Med.* 2001;344:907-916. Silverman GJ, Carson DA. *Arthritis Res Ther.* 2003;5(suppl 4):S1-S6.

Disease-Modifying Pharmacotherapies for RA Available in US

Oral non-biologics
Methotrexate
Sulfasalazine
Hydroxychloroquine
Leflunomide
Azathioprine
Cyclosporine
Tacrolimus
Cyclophosphamide

Prednisone

Selective cytokine inhibitors

TNF inhibitors
Etanercept
Infliximab
Adalimumab
Certolizumab
Golimumab

IL-1 inhibitors
Anakinra

IL-6 inhibitors
Tocilizumab
Sarilumab

B-cell depletion
Rituximab

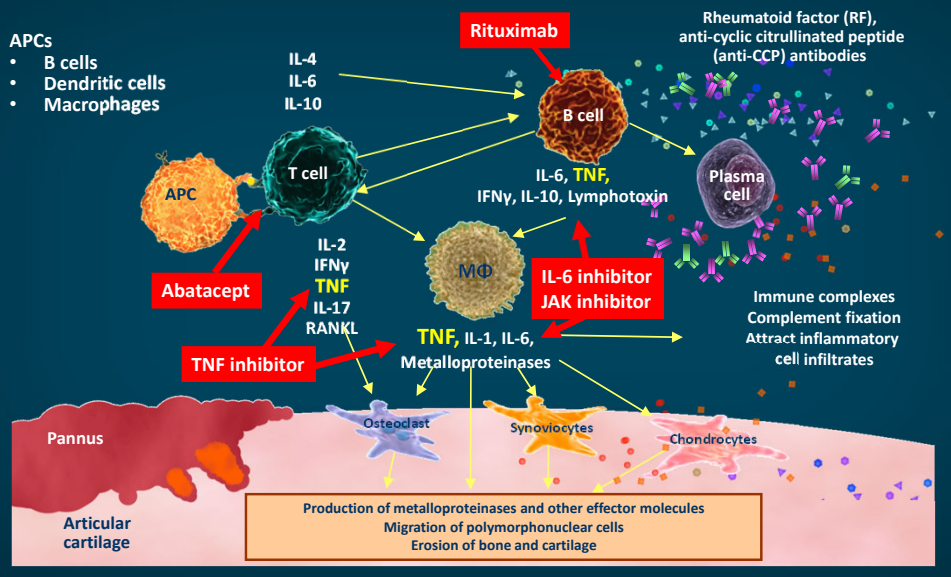
T cell co-stimulation blockade
Abatacept

JAK inhibition
Tofacitinib
Baricitinib
Upadacitinib

US = United States; JAK = Janus kinase.

Köhler BM, et al. *J Clin Med.* 2019;8:938.

Targets of Therapy in RA



Adapted from Smolen JS, Steiner G. *Nat Rev Drug Discov.* 2003;2;473-488. Choy EH, Panayi GS. *N Engl J Med.* 2001;344:907-916. Silverman GJ, Carson DA. *Arthritis Res Ther.* 2003;5(suppl 4):S1-S6.

Initial DMARD Choice

American College of Rheumatology (ACR) 2021 RA Treatment Guideline

Initiation of DMARD treatment of patients with RA	
ACR recommendations	**Certainty of evidence**
Initiation of treatment in DMARD-naïve patients with MODERATE-TO-HIGH disease activity	
Methotrexate (MTX) monotherapy is strongly recommended over:	
Hydroxychloroquine or sulfasalazine	Very low/low
bDMARD or tsDMARD monotherapy	Very low/moderate
Combination of MTX + non-TNFi bDMARD or tsDMARD	Low/very low
MTX monotherapy is conditionally recommended over:	
Leflunomide	Low
Dual or triple csDMARD therapy	Moderate
Combination of MTX + TNFi	Low
Initiation of csDMARD without short-term (<3 months) glucocorticoids is conditionally recommended over initiation of csDMARD with short-term glucocorticoids	Very low
Initiation of csDMARD without longer-term (≥3 months) glucocorticoids is strongly recommended over initiation of csDMARD with longer-term glucocorticoids	Moderate
Initiation of treatment in DMARD-naïve patients with LOW disease activity	
Hydroxychloroquine is conditionally recommended over other csDMARDs	Very low
Sulfasalazine is conditionally recommended over MTX	Very low
MTX is conditionally recommended over leflunomide	Very low
Initiation of treatment in csDMARD-treated, but MTX-naïve, patients with MODERATE-TO-HIGH disease activity	
MTX monotherapy is conditionally recommended over combination of MTX + bDMARD or tsDMARD	Moderate/very low

DMARD = disease-modifying antirheumatic drug; bDMARD = biologic DMARD; tsDMARD = targeted-synthetic DMARD; csDMARD = conventional synthetic DMARD; TNFi = TNF inhibitor.

Fraenkel L, et al. *Arthritis Care Res*. 2021;73:924-939.

Failure of Initial Treatment Choice

ACR 2021 RA Treatment Guideline

Treatment modification following inadequate response to initial treatment	
Recommendations	**Certainty of evidence**
T2T approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs	Low
T2T approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs	Very low
Minimal initial treatment goal of low disease activity is conditionally recommended over goal of remission	Low
Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target	Very low
Switching to bDMARD or tsDMARD of different class is conditionally recommended over switching to bDMARD or tsDMARD belonging to same class for patients taking bDMARD or tsDMARD who are not at target	Very low
Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target	Very low
Addition of/switching to DMARDs (± IA glucocorticoids) is conditionally recommended over use of IA glucocorticoids alone for patients taking DMARDs who are not at target	Very low

T2T = treat-to-target; IA = intraarticular.

Fraenkel L, et al. *Arthritis Care Res*. 2021;73:924-939.

The Principles of Treating to Target

- T2T by measuring disease activity and adjusting therapy accordingly will result in better patient outcomes
- The primary target for treatment should be clinical remission, defined as the absence of signs and symptoms of significant inflammatory disease activity
- In some cases, low disease activity (LDA) may be an acceptable treatment goal, particularly in patients with long-standing, established disease

Smolen JS, et al. *Ann Rheum Dis.* 2010;69:631-637.

So, Can T2T Be Implemented in the Real World? A First Look…

- RA BIODAM (**BIO**markers of joint **DAM**age): RA registry in 10 countries[1,2]
  - At 41% of visits, T2T protocol was not implemented[1]
  - Main reason: physician felt current treatment was adequate (69%)[2]
- CORRONA (**C**onsortium **o**f **R**heumatology **R**esearchers **o**f **N**orth **A**merica)[3,4]
  - Failure to escalate occurred at ~50% of visits
  - 2 main reasons: doctor said treatment needed more time to work (eg, 3 more months) or patient refused
- Implications for patients with persistently active disease
  - Patients and doctors feel that current treatment is "good enough"
  - Patients are risk averse to add/change therapy

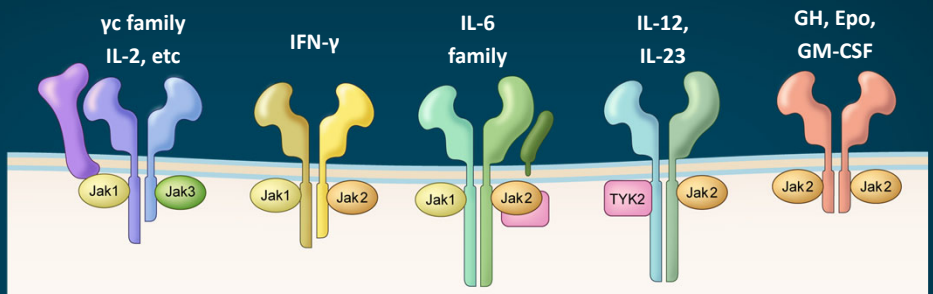
1. Ramiro S, et al. *Ann Rheum Dis.* 2020;79:453-459. 2. Maksymowych WP, et al. *Arthritis Rheumatol.* 2014;66(suppl 10): abstract 2912. 3. Harrold L, et al. *Arthritis Rheumatol.* 2015;67(suppl 10): abstract 3185. 4. Harrold LR, et al. *Arthritis Care Res (Hoboken).* 2018;70:379-387.

Unmet Need for RA Treatments

- Rates of "low disease activity" and "remission" have improved over time
  - 5 years after symptom onset in 2009, 45% reached sustained remission (SR) compared with only 16% in 1999
  - Largely due to the availability of new treatments and adoption of T2T
- However, SR is only observed in ~25%
  - Fluctuating disease activity/flares
  - Secondary loss of response
  - Treatment resistance in a subset
  - Intolerance/side effects
- Complete treatment refractoriness is rare

Einarsson JT, et al. *Rheumatology (Oxford)*. 2020;59:205-212. Mierau M, et al. *Rheumatology (Oxford)*. 2007;46:975-979. Prince FHM, et al. *Arthritis Res Ther.* 2012;14:R68.

Signaling by Type I/II Cytokine Receptors and JAK Inhibitors



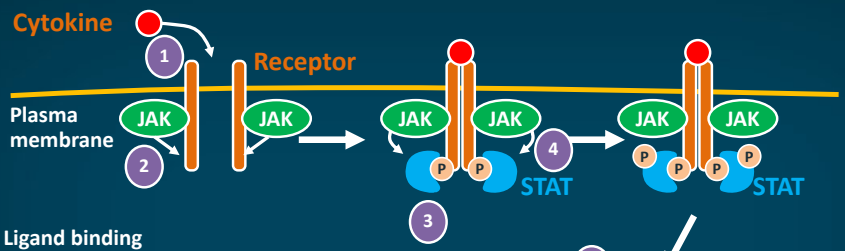
	γc family IL-2, etc	IFN-γ	IL-6 family	IL-12, IL-23	GH, Epo, GM-CSF
TOFA (JAK 1/3)	+	+	+	+	+
BARI (JAK 1/2)	+	+	+	+	+
UPA (JAK 1)	+	+	+		
FIL* (JAK 1)	+	+	+		
PEF* (JAK 1/3)	+	+	+	+	+

*Not FDA approved.

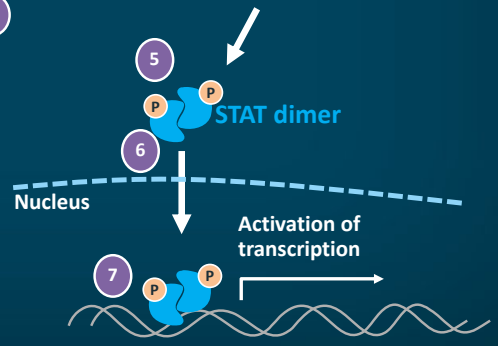
GH = growth hormone; Epo = erythropoietin; GM-CSF = granulocyte macrophage colony-stimulating factor; TYK = tyrosine kinase; TOFA = tofacitinib; BARI = baricitinib; UPA = upadacitinib; FIL = filgotinib; PEF = peficitinib.

Fragoulis GE, et al. *J Allergy Clin Immunol*. 2021;148:941-952.

JAK/STAT Signaling



1. Ligand binding
2. Receptor dimerization activates JAK phosphorylation of receptor
3. STAT binds phosphorylated receptor
4. JAK phosphorylates STAT
5. STAT dimer forms
6. STAT dimer travels to nucleus
7. STAT dimer binds DNA and changes gene expression



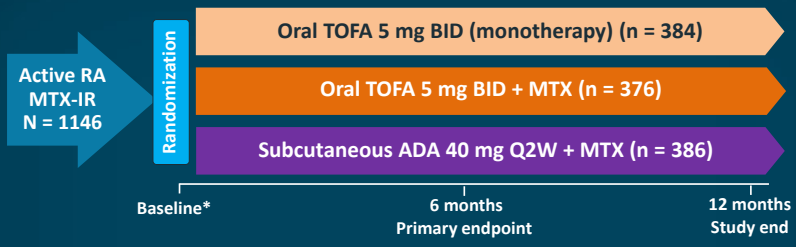
STAT = signal transducer and activator of transcription; P = phosphorylation; DNA = deoxyribonucleic acid.

Adapted from Ivashkiv LB, Hu X. *Arthritis Res Ther*. 2004;6:159-168.

ORAL Strategy

TOFA vs
TOFA + MTX vs
ADA + MTX
in MTX-IR

Double-blind, phase 3b/4, head-to-head, non-inferiority RCT in patients with active RA despite MTX therapy



- **Primary endpoint**: ACR50 response at 6 months in full analysis set
- **Secondary endpoints (all at 6 months):** ACR20 and ACR70; proportion of patients achieving LDA; proportion of patients achieving remission; proportion of patients achieving HAQ-DI response; and LSM change from baseline for SDAI, CDAI, DAS28-4 (ESR), DAS28-4 (CRP), and HAQ-DI

*All DMARDs other than MTX were washed out before baseline visit.

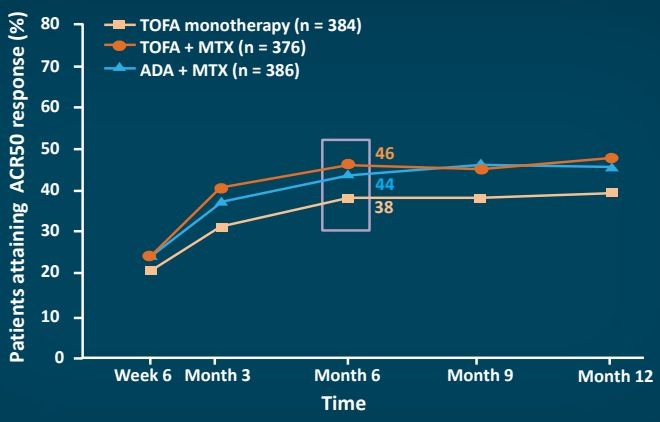
ADA = adalimumab; IR = inadequate response; RCT = randomized controlled trial; BID = twice daily; Q2W = every 2 weeks; ACR = American College of Rheumaology; ACR20/50/70 = ACR response of at least 20%, 50%, or 70%; HAQ-DI = Health Assssment Questionnaire-Disability Index; LSM = least squares mean; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; DAS28-4 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Fleischmann R, et al. *Lancet*. 2017;390:457-468.

TOFA vs
TOFA + MTX vs
ADA + MTX
in MTX-IR

ORAL Strategy: Efficacy

Primary Endpoint: ACR50 at 6 Months



- Tofacitinib + MTX non-inferior to adalimumab + MTX
- Tofacitinib monotherapy did not meet non-inferiority criteria compared with tofacitinib + MTX
- Tofacitinib monotherapy did not meet non-inferiority criteria compared with adalimumab + MTX

Fleischmann R, et al. *Lancet.* 2017;390:457-468.

ORAL Strategy

AEs, Serious AEs, and Discontinuations

	TOFA monotherapy (n = 384)	TOFA + MTX (n = 376)	ADA + MTX (n = 386)
Total number of AEs, n	598	652	620
Patients with AEs, n (%)	226 (59%)	231 (61%)	253 (66%)
Patients with treatment-related AEs, n (%)	101 (26%)	111 (30%)	133 (35%)
Patients with serious AEs, n (%)	35 (9%)	27 (7%)	24 (6%)
Patients discontinuing due to AEs, n (%)	23 (6%)	26 (7%)	37 (10%)
Patients with severe AEs, n (%) (defined by investigator)	24 (6%)	17 (5%)	23 (6%)
Deaths, n (%)	2 (1%)	0	0
AEs of special interest, n (%)			
Serious infections	6 (2%)	10 (3%)	6 (2%)
HZ (serious and non-serious)	4 (1%)	8 (2%)	6 (2%)
HZ (serious and non-serious) in vaccinated patients	1/69 (1%)	2/75 (3%)	0/72 (0%)
Opportunistic infections (not TB)	2 (1%)	1 (< 1%)	2 (1%)
TB	0	2 (1%)	0
MACE (non-fatal)	0	0	2 (1%)
Malignancy (not non-melanoma skin cancer)	1 (< 1%)	0	0
Non-melanoma skin cancer	2 (1%)	0	1 (< 1%)

AE = adverse event; HZ = herpes zoster; TB = tuberculosis; MACE = major adverse cardiovascular event.

Fleischmann R, et al. *Lancet.* 2017;390:457-468.

Venous Thromboembolism (VTE) With JAK Inhibitors

Primary analysis: VTE events identified from inpatient claims with as-treated follow-up approach

Data source and exposure group	VTE events, n	Total PYs of follow-up	Incidence rate per 100 PYs (95% CI)	Unadjusted HR (95% CI)	Propensity score-adjusted HR (95% CI)
Truven MarketScan					
TNFi initiators (n = 32,164)	98	28,951	0.34 (0.27–0.41)	Reference	Reference
TOFA initiators (n = 1910)	8	1326	0.60 (0.26–1.19)	1.70 (0.82–3.49)	1.55 (0.75–3.18)
Medicare claims					
TNFi initiators (n = 16,091)	117	12,660	0.92 (0.76–1.11)	Reference	Reference
TOFA initiators (n = 995)	<11*	625	1.12 (0.45–2.31)	1.16 (0.54–2.49)	1.12 (0.52–2.40)
Pooled					
TNFi initiators (n = 48,255)	215	41,611	0.52 (0.45–0.59)	Reference	Reference
TOFA initiators (n = 2905)	15	1951	0.77 (0.43–1.27)	1.42 (0.84–2.40)	1.33 (0.78–2.24)

- Higher rates of VTE noted in interim analysis of large safety study for tofacitinib 10 mg BID
- EMA recommended caution for use of JAK inhibitors for people at risk for VTE
- Rates of VTE across phase 3 trials of all studied JAK inhibitors ≈ 0.5/1000 PYs

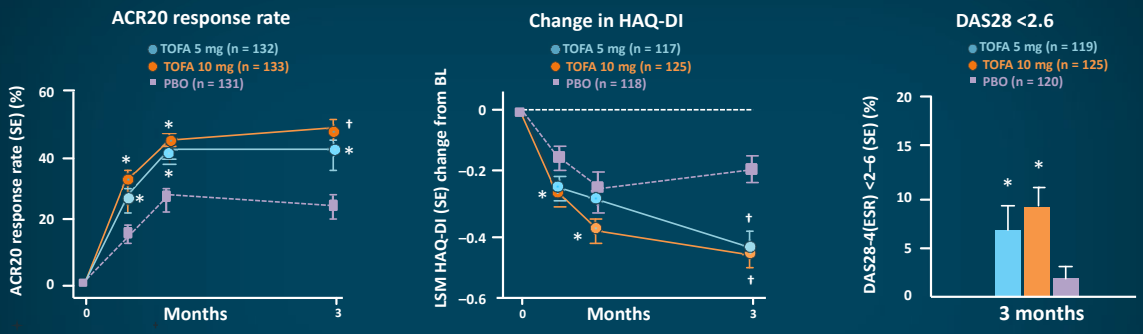
*Actual number suppressed; required by data use agreement with Medicare and Medicaid Services for counts <11.

HR = hazard ratio; CI = confidence interval; PY = person-year; EMA = European Medicines Agency.

Desai RJ, et al. *Arthritis Rheumatol.* 2019;71:892-900. Sandborn WJ, et al. *Aliment Pharmacol Ther.* 2019;50:1068-1076. EMA (www.ema.europa.eu/en/medicines/human/referrals/xeljanz). Accessed 12/21/2021.

Efficacy and Safety of Tofacitinib (JAK 1/3) + MTX in TNFi-IR Patients

Phase 3 trial outcomes for treatments at 3 months[1]



- Tofacitinib has consistent, manageable safety profile across studies; no new safety signals[1]
- Consistent safety through 114 months; sustained clinical efficacy through 96 months[2]
- 5-year analysis of AEs with tofacitinib vs bDMARDs reported in CORRONA RA registry shows higher incidence of HZ but not MACE or other serious infections[3]

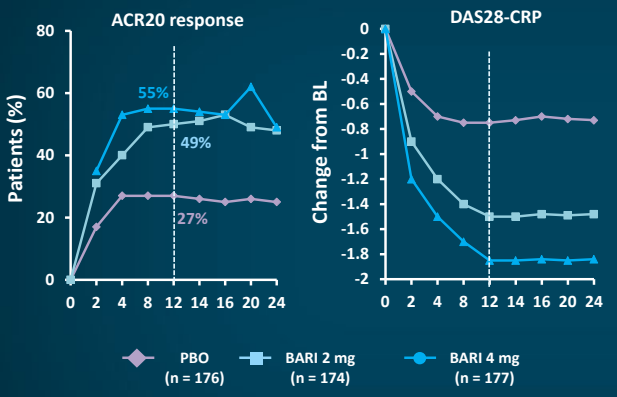
*$P \leq .05$, †$P < .0001$ vs PBO.

PBO = placebo; SE = standard error; BL = baseline.

1. Burmester GR, et al. *Lancet.* 2013;381:451-460. 2. Wollenhaupt J, et al. ACR/ARHP 2017: abstract 522. 3. Kremer J, et al. EULAR 2019: abstract OP0028.

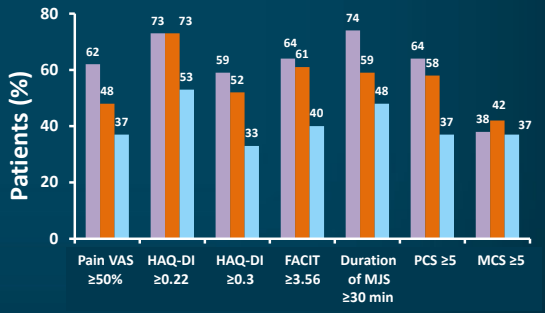
Efficacy and Safety of Baricitinib (JAK 1/2) in bDMARD-IR Patients

RA-BEACON phase 3 trial[1,2]



RA-BEAM phase 3 trial[3]

Patients meeting/exceeding clinically relevant improvement thresholds at week 12 after rescue



VAS = visual analog scale; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; MJS = morning joint stiffness; PCS = physical component score; MCS = mental component score; min = minute(s).

1. Genovese MC, et al. *N Engl J Med.* 2016;374:1243-1252 and supplement. 2. Genovese MC, et al. *Rheumatology (Oxford).* 2018;57:900-908. 3. Fautrel B, et al. ACR/ARHP 2017: abstract 508.

Baricitinib

- Baricitinib led to more AEs (including infections) than placebo[1]

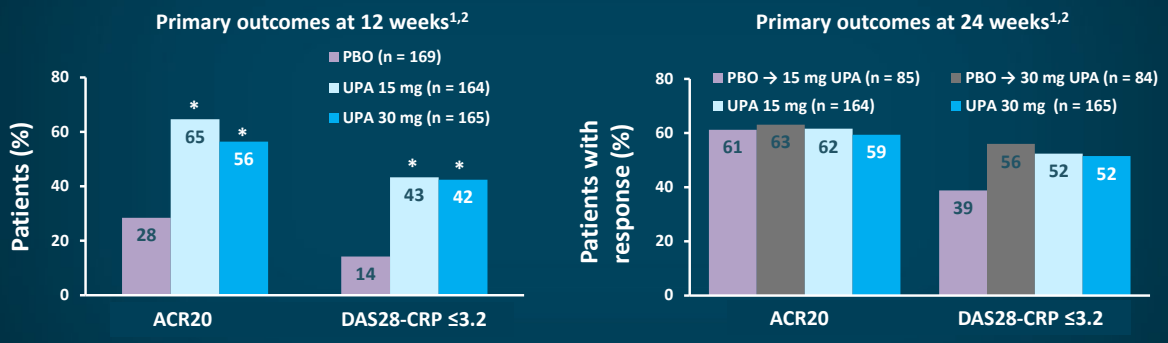
  Most common infections were respiratory tract, urinary tract, bronchitis[1]
- Rates of serious AEs through week 24 were similar among patient groups[1]
- Post-hoc analysis of RA-BEACON: ORs favored use of baricitinib over placebo regardless of bDMARD history (number or type)[2]
- 7-year integrated safety analysis from phase 3 trials show increased risk for HZ and deep vein thrombosis/pulmonary embolism but not for malignancy[3]

OR = odds ratio.

1. Genovese MC, et al. *N Engl J Med.* 2016;374:1243-1252. 2. Genovese MC, et al. *Rheumatology (Oxford).* 2018;57:900-908. 3. Genovese MC, et al. EULAR 2019: abstract THU0078.

Efficacy and Safety of Upadacitinib (JAK 1) in bDMARD-IR Patients

Phase 3 trial SELECT-BEYOND



*P <.0001 relative to PBO.

1. Genovese MC, et al. *Lancet*. 2018;391:2513-2524. 2. Genovese MC, et al. ACR/ARHP 2017: abstract 10L.

Upadacitinib

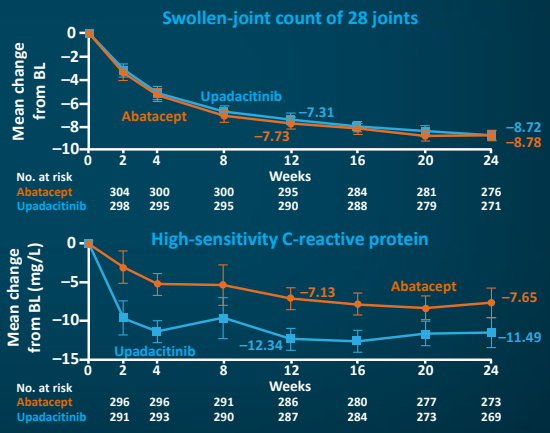
- In a post-hoc analysis, upadacitinib showed comparable efficacy whether administered with methotrexate or with other non-methotrexate csDMARDs[1]
- UPA treatment also resulted in significant, clinically meaningful improvements in PROs among patients[2]
- Pooled safety analysis across phase 3 trials showed higher risk for serious infections and HZ but not for VTE, MACE, or malignancy (vs comparators)[3]
- Safety and efficacy remained consistent after 60 weeks of treatment[4]

PRO = patient-reported outcome.

1. Kremer J, et al. *Ann Rheum Dis.* 2019;78(suppl 2): A749 (abstract FRI0155). 2. Strand V, et al. *Ann Rheum Dis.* 2018;77(suppl 2):990 (abstract SAT0255). 3. Cohen SB, et al. *Ann Rheum Dis.* 2019;78(suppl 2):357 (abstract THU0167). 4. Genovese MC, et al. *Ann Rheum Dis.* 2019;78(suppl 2):360 (abstract THU0172).

Efficacy and Safety of Upadacitinib vs Abatacept in bDMARD-IR Patients

- Phase 3 trial SELECT-CHOICE
- Assessed non-inferiority (primary outcome) and superiority (secondary outcome) of oral upadacitinib 15 mg daily vs IV abatacept monthly for change in DAS28-CRP
  - Stable background non-biologic DMARDs continued
  - Primary endpoint measured at week 12
- Upadacitinib was non-inferior and superior to abatacept at week 12
  - Primary driver was change in CRP
- Remission at week 12 higher for upadacitinib vs abatacept
  - 30.0% vs 13.3% (*P* <.001)
- Adverse events higher for upadacitinib
  - Serious infection, MACE, VTE
  - HZ not higher, but low frequency at week 12

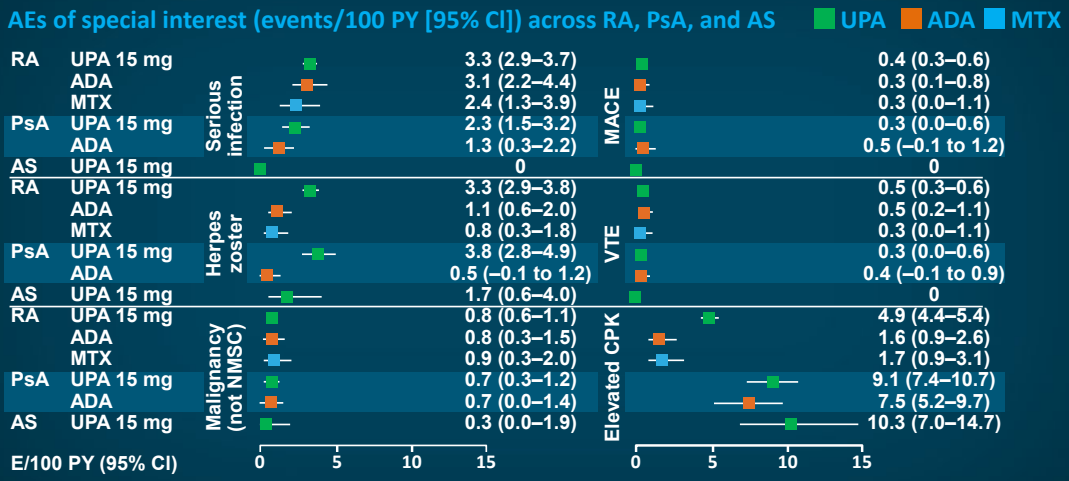


IV = intravenous.

Rubbert-Roth A, et al. *N Engl J Med.* 2020;383:1511-1521.

Longer Term Safety of Upadacitinib from Open-Label Trial Extensions

Across Indications and Compared with Adalimumab and MTX



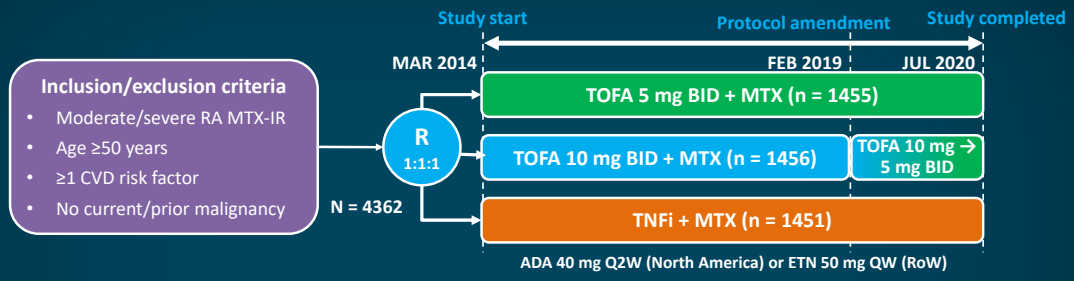
4298 patients received ≥1 dose UPA 15 mg (n = 3209 RA; n = 907 PsA; n = 182 AS)

PsA = psoriatic arthritis; AS = ankylosing spondylitis; NMSC = non-melanoma skin cancer; CPK = creatine phosphokinase.

Burmester G, et al. ACR 2021, abstract 1691.

ORAL Surveillance Safety Trial: Tofacitinib vs TNF Inhibitors

Randomized, Open-Label Phase 4 Non-inferiority Trial



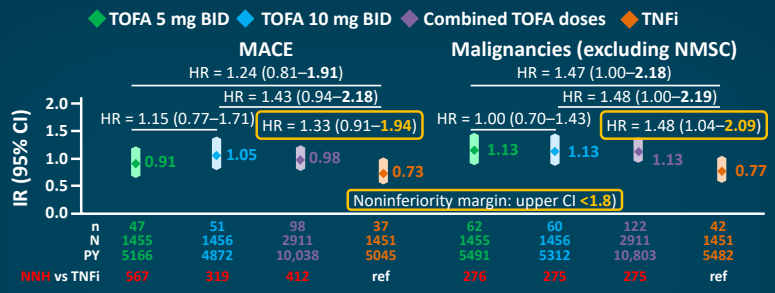
- Co-primary outcomes: MACE and malignancy (combined TOFA doses vs TNFi)
  - Non-inferiority margin set at 1.8
- After a signal for VTE was detected for TOFA 10 mg BID in Feb 2019, patients on this dose were changed to 5 mg BID
- The study was completed once ≥1500 patients were followed for ≥3 years, ≥103 MACE were reported, and ≥138 malignancies excluding NMSC were reported

CVD = cardiovascular disease; ETN = etanercept; QW = each week; RoW = rest of world.

Ytterberg SR, et al. ACR 2021, abstract 831

ORAL Surveillance Safety Trial: Tofacitinib vs TNF Inhibitors

HRs (95% CI) and IRs (95% CI) for adjudicated MACE and malignancies

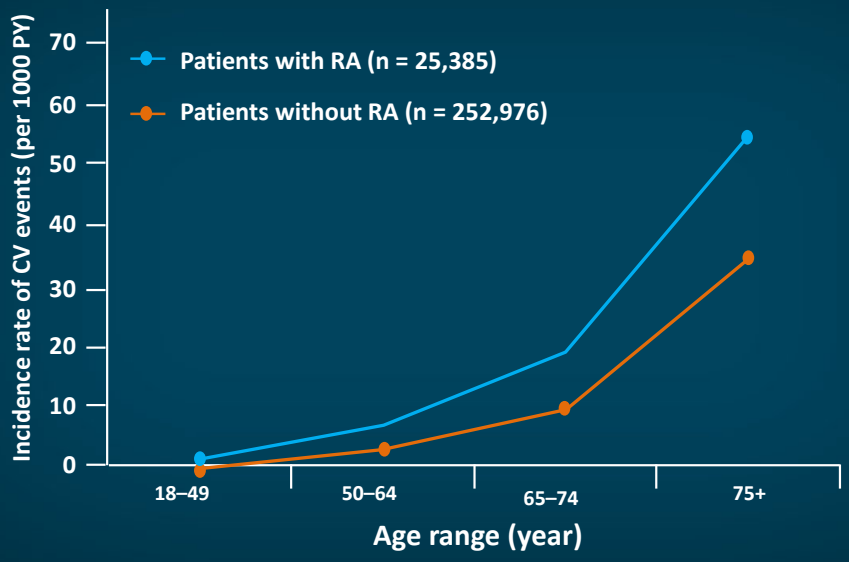


- Combined tofacitinib doses were not non-inferior to TNFi for either MACE or malignancy
- No difference between tofacitinib doses
- Most MACE and malignancies occurred in patients >65 years and/or ever smokers
- MACE difference for tofacitinib vs TNFi primarily for MI
- Malignancy difference for tofacitinib vs TNFi primarily for lung cancer, lymphoma, and NMSC

IR = incidence rate; NNH = number needed to harm; MI = myocardial infarction.

Ytterberg SR, et al. ACR 2021, abstract 831. Charles-Schoeman C, et al. ACR 2021, abstract 958. Curtis J, et al. ACR 2021, abstract 1940.

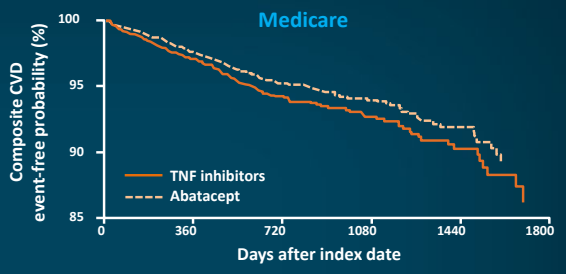
RA Is an Independent Risk Factor for Cardiovascular Events*

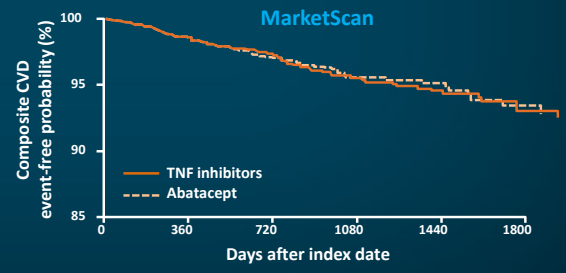


*MI and stroke.
CV = cardiovascular.
Solomon DH, et al. *Ann Rheum Dis*. 2006;65:1608-1612.

DMARDs and CVD Events in RA

- Methotrexate and TNF inhibitors are most studied
- Observational data only
- Comparison group problematic
- MTX use associated with 28% reduction in all CVD events across 8 cohort studies (HR = 0.72 [95% CI, 0.57–0.91], *P*= .007)[1]
- TNFi use associated with 30% reduction in CVD events across 16 cohort studies (HR = 0.70 [95% CI, 0.54–0.90], *P*= .005)[1]
- Abatacept similar to etanercept from claims data[2]
- Tocilizumab similar to etanercept in head-to-head randomized clinical trial[3]





1. Roubille C, et al. *Ann Rheum Dis.* 2015;74:480-489. 2. Kang EH, et al. *J Am Heart Assoc.* 2018;7:e007393. 3. Giles JT, et al. *Arthritis Rheumatol.* 2020;72:31-40.

RA Treatments and Comorbid Disease Considerations from the ACR Treatment Guideline

RA treatments and comorbid disease considerations	
Recommendations	**Certainty of evidence**
Previous serious infection	
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy	Very low
Addition of/switching to DMARDs is **conditionally** recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within previous 12 months who have moderate-to-high disease activity	Very low
Pulmonary disease	
Methotrexate is **conditionally** recommended over alternative DMARDs for 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
Heart failure	
Addition of a non-TNFi DMARD or tsDMARD is **conditionally** recommended over addition of a TNFi for patients with New York Heart Association (NYHA) class III or IV heart failure and an inadequate response to csDMARDs	Very low
Switching to a non-TNFi bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNFi for patients taking a TNFi who develop heart failure	Very low

Fraenkel L, et al. *Arthritis Care Res*. 2021;73:924-939.

RA Treatments and Comorbid Disease Considerations from the ACR Treatment Guideline (continued)

RA treatments and comorbid disease considerations	
Recommendations	**Certainty of evidence**
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
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
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
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

Fraenkel L, et al. *Arthritis Care Res*. 2021;73:924-939.

Conclusions

- RA is a chronic inflammatory disease with significant morbidity and disability if left untreated
- Advances in our understanding of RA pathogenesis have led to the development of new and more effective therapies; most recently, these have included newly developed agents that block JAK signaling
- Optimal approach to therapy needs to consider comorbidities, quality of life, T2T, tailoring regimens when needed, and promoting strategies that improve adherence

Case Study: New Mother

Case Study: Patient History

- Tracey is a 35-year-old woman who gave birth to her second child 4 months ago.
- Not long after the delivery, she began noticing morning stiffness in her hands and wrists, and she felt like she was walking “on rocks” when she took her first steps out of bed in the morning.
- She attributed the symptoms to the fatigue and lack of sleep that accompany caring for an infant, but the symptoms worsened over time.
- Her primary care doctor evaluated her and ordered some lab tests after observing some joint swelling in her fingers and wrists.
- She is seropositive for anti-CCP and RF, and her inflammatory markers are moderately elevated.
- She is referred to a rheumatologist for her first evaluation.

Case Study: Question #1

What are some of the challenges for treating Tracey?

Case Study: Considerations

- Patients like Tracey are not uncommon since RA often presents in women of childbearing age. The immediate post-partum period is a common time at which RA initially presents.
- In initiating therapy, the physician needs to consider treatments that are compatible with breastfeeding.
- Additional consideration should be made for whether Tracey is thinking of having more children and her timeframe for having them.

Case Study: Question #2

- Tracey is ready to stop breastfeeding now but wants to have another child in the next 6 to 12 months.
- What initial RA treatment options are appropriate for Tracey today?
  A. Start methotrexate, as recommended as first-line therapy in the ACR guidelines
  B. Hold off on any treatment until Tracey has her next child
  C. Treat with prednisone only during this time
  D. Start a TNF inhibitor
  E. Start a JAK inhibitor

Case Study: Treatment Considerations

- Although methotrexate is typically used first-line in RA, it is class X for conception, pregnancy, and breastfeeding. It must be discontinued at least 3 months before attempting conception, which does not fit well into Tracey's timeline.
- Not treating Tracey's RA until after she delivers her next child is not ideal, since you do not know how long it will take for her to conceive. If there is a long period before conception, she would have joint symptoms and potentially experience joint damage.
- The same is true for prednisone use, which is associated with multiple side effects with prolonged use.
- TNF inhibitor therapy is an option, since it can be used through conception. Most rheumatologists will stop therapy when pregnancy is confirmed since RA tends to abate during pregnancy.
- Little to no data are available about the effect of JAK inhibitors on pregnancy outcomes or their safety during breastfeeding.

Case Study: Tom

Case Study: Tom

- Tom is 68-year-old man diagnosed with RA 3 years ago.
- He is seropositive for both RF and anti-CCP.
- He was initially treated with MTX but had an inadequate response to monotherapy. He was later treated with a TNF inhibitor and abatacept in combination with MTX, neither of which were effective.
- He has received two treatment courses of rituximab in the last 6 months. While he has had a partial response, he still reports 90 minutes of morning stiffness and has more than 6 swollen and tender joints on exam. He states that he feels that rituximab has made his RA "40% better."
- His current CRP is 9.0 mg/L, and his ESR is 45 mm/hour.
- He is currently also taking prednisone 7.5 mg per day and sometimes needs more for flaring symptoms.

Case Study: Considerations

- Tom has several non-RA comorbidities:
  - Diabetes, with a current HbA1c of 9%
  - Current BMI of 32 kg/m^2
  - Hypertension that is treated with two antihypertensives
- After having smoked an average of a half pack of cigarettes per day for the last 40 years, Tom recently has been trying to cut down.

Case Study: Question #1

What treatment options are available for Tom?

A. Continue with another treatment course of rituximab
B. Try a different TNF inhibitor than the one he used in the past
C. Increase the corticosteroid dose until he has symptom control
D. Start an IL-6 inhibitor
E. Start a JAK inhibitor

Case Study: Treatment Considerations

- Tom has had two treatment courses of rituximab and has not responded adequately. He is unlikely at this point to respond to another course of rituximab.
- It is possible that he might respond to another TNF inhibitor. However, if he had no initial response to the first TNF inhibitor (ie, primary non-response), he has a higher chance of not responding to a second TNF inhibitor.
- His RA is not well controlled, even on a dose of corticosteroids that is already higher than appropriate for his various comorbidities.
- Starting an IL-6 inhibitor would be an option for him since he has not been tried on this class of medication before.
- Starting a JAK inhibitor would also be an option.

Case Study: Additional Treatment Considerations

- You would want to have a discussion with Tom about the higher rates of MI that were observed in older RA patients with CV risk factors using JAK inhibitors compared with etanercept in the ORAL Surveillance Trial. Higher rates of lung cancer were also observed in older RA patients and those with a history of smoking.
- However, absolute risks were still quite low.
- His current level of overall systemic inflammatory burden increases his risk for CVD and cancer, particularly lymphoma; not treating these adequately may place him at risk.
- In addition, chronic used of corticosteroids also increases his risk for CV events, worsening of hypertension and diabetes outcomes, infection, and a host of other side effects.
- Any intervention that is effective at reducing his disease activity and tapering/discontinuing corticosteroids for him is preferred to continued high disease activity requiring corticosteroids.

Case Study: JAK Inhibitors and Lipids

- After discussing treatment options with you, Tom decides to start a JAK inhibitor because he wants to take a pill rather than have an injection or infusion.
- After starting the JAK inhibitor, his swelling and stiffness improve. His inflammatory markers normalize, and he is able to taper off of corticosteroids.
- About a month after starting the JAK inhibitor, he has changes in his lipid profile.
  - Total cholesterol increases from 200 mg/dL to 260 mg/dL.
  - LDL-C increases from 135 mg/dL to 160 mg/dL.
  - HDL-C increases from 40 mg/dl to 65 mg/dL.

LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol.

Case Study: Question #2

What do you tell Tom about the changes in his lipid profile?

A. Don't worry about it, elevated LDL-C is an expected antiinflammatory effect of JAK inhibition
B. Studies have not shown that increasing LDL-C after starting a JAK inhibitor is associated with an increase in cardiovascular events
C. You discuss diet and exercise with him
D. You initiate statin therapy

Case Study: Treatment Considerations Due To Lipid Changes

- Part of the mechanism of JAK inhibition is the decrease in numbers of LDL receptors on cells that scavenge LDL-C. The effect can be a relatively rapid increase in circulating LDL-C.
- However, long-term effect on CV events has not been established.
- Diet and exercise alone are unlikely to modify this level of dyslipidemia.
- Tom already has an indication for being on a statin (ie, diabetes), and he has other CV risk factors in addition to his RA.
- Studies have shown that statins are effective in lowering LDL-C increase associated with IL-6 inhibitors and JAK inhibitors and may have additional beneficial effects on systemic inflammation and disease activity.

McInnes IB, et al. *Ann Rheum Dis*. 2014;73:124-131.

Thank You!

Q&A

Disease Modification in Individuals with Moderate-to-Severe Rheumatoid Arthritis: Optimizing Treatment Through the Finely Tuned Selectivity for JAKs

Resource	Address
Burmester G, Cohen S, Winthrop K, et al. **Long-term safety profile of upadacitinib in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis.** Presented at: ACR Convergence; November 9, 2021; Abstract 1691.	https://acrabstracts.org/abstract/long-term-safety-profile-of-upadacitinib-in-patients-with-rheumatoid-arthritis-psoriatic-arthritis-or-ankylosing-spondylitis/
Burmester GR, Blanco R, Charles-Schoeman C, et al. **Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: A randomised phase 3 trial.** *Lancet*. 2013;381:451-460.	https://pubmed.ncbi.nlm.nih.gov/23294500/
Desai RJ, Pawar A, Weinblatt ME, Kim SC. **Comparative risk of venous thromboembolism in rheumatoid arthritis patients receiving tofacitinib versus those receiving tumor necrosis factor inhibitors: An observational cohort study.** *Arthritis Rheumatol*. 2019;71:892-900.	https://pubmed.ncbi.nlm.nih.gov/30552833/
Fleischmann R, Mysler E, Hall S, et al. **Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): A phase 3b/4, double-blind, head-to-head, randomised controlled trial.** *Lancet.* 2017;390:457-468.	https://pubmed.ncbi.nlm.nih.gov/28629665/
Fraenkel L, Bathon JM, England BR, et al. **2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis.** *Arthritis Care Res (Hoboken)*. 2021;73:924-939.	https://pubmed.ncbi.nlm.nih.gov/34101387/
Fragoulis GE, Brock J, Basu N, McInnes IB, Siebert. **The role for JAK inhibitors in the treatment of immune-mediated rheumatic and related conditions.** *J Allergy Clin Immunol*. 2021;148:941-952.	https://pubmed.ncbi.nlm.nih.gov/34450118/
Genovese MC, Fleischmann R, Combe B, et al. **Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): A double-blind, randomised controlled phase 3 trial.** *Lancet*. 2018;391:2513-2524.	https://pubmed.ncbi.nlm.nih.gov/29908670/
Genovese MC, Kremer J, Zamani O, et al. **Baricitinib in patients with refractory rheumatoid arthritis.** *N Engl J Med.* 2016;374:1243-1252.	https://pubmed.ncbi.nlm.nih.gov/27028914/

Köhler BM, Günther J, Kaudewitz D, Lorenz HM. **Current Therapeutic Options in the Treatment of Rheumatoid Arthritis.** *J Clin Med*. 2019;8:938.	https://pubmed.ncbi.nlm.nih.gov/31261785/
Rubbert-Roth A, Enejosa J, Pangan AL, et al. **Trial of upadacitinib or abatacept in rheumatoid arthritis.** *N Engl J Med.* 2020;383:1511-1521.	https://pubmed.ncbi.nlm.nih.gov/33053283/
Smolen JS, Aletaha D, Bijlsma JW, et al. **Treating rheumatoid arthritis to target: Recommendations of an international task force.** *Ann Rheum Dis*. 2010;69:631-637.	https://pubmed.ncbi.nlm.nih.gov/20215140/
Ytterberg SR, Bhatt DL, Mikuls T, et al. **Safety and efficacy of tofacitinib vs TNF inhibitors in RA patients aged 50 years or older with one or more cardiovascular risks: Results from a phase 3b/4 randomized safety trial.** Presented at: ACR Convergence; November 7, 2021; Abstract 831.	https://acrabstracts.org/abstract/safety-and-efficacy-of-tofacitinib-vs-tnf-inhibitors-in-ra-patients-aged-50-years-or-older-with-one-or-more-cardiovascular-risks-results-from-a-phase-3b-4-randomized-safety-trial/