Clinical Perspectives in RHEUMATOID ARTHRITIS:

Quality of Life, Comorbidities, and Evolving Targets

FACULTY

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This activity is provided by Med Learning Group.
This activity is co-provided by AMEDCO and Ultimate Medical Academy/Complete Conference Management (CCM).
This is supported by an educational grant from AbbVie Inc.

Agenda

I. RA: A chronic inflammatory disease
   - Disease mechanisms
   - Diagnosis: guideline-based diagnosis for timely treatment
   - Implications for development of targeted therapies

II. Treatment: A focus on the JAK/STAT pathway
   - What to do when a TNF inhibitor fails
   - IL-6 inhibitors – tocilizumab/sarilumab
   - The JAK/STAT pathway
     - What is the JAK/STAT pathway?
     - Systemic and articular effects of inflammatory cytokines with a focus on Janus kinase (JAK)/STAT pathway
     - Blockade of the JAK/STAT pathway as a therapeutic target
     - Current JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
     - Investigational agent(s) in late-stage trials
     - Clinical trials and safety

III. RA comorbidities
   - Cardiovascular (atherosclerosis, lipid changes, etc)
   - Thrombotic events, renal dysfunction, etc

IV. Strategies to optimize patient outcomes
   - Treating to target
   - Risks/benefits of steroids
   - Effect of management decisions on patient QOL
   - Optimal multidisciplinary team integration strategies

V. Case studies

VI. Questions and answers

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PROGRAM OVERVIEW
This case-based live activity will cover the treatment and management of patients with rheumatoid arthritis.

TARGET AUDIENCE
This activity is designed to meet the educational needs of rheumatologists, internists, and allied healthcare professionals involved in the care of patients with rheumatoid arthritis.

Learning Objectives
- Review clinical trials data for the efficacy and safety of JAK pathway inhibition in the treatment of moderate-to-severe rheumatoid arthritis
- Evaluate RA-related comorbidities and their management in patients with rheumatoid arthritis
- Assess ways in which to reduce the burden of RA while improving quality of life

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CNE ACCREDITATION STATEMENT
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CNE Content Review

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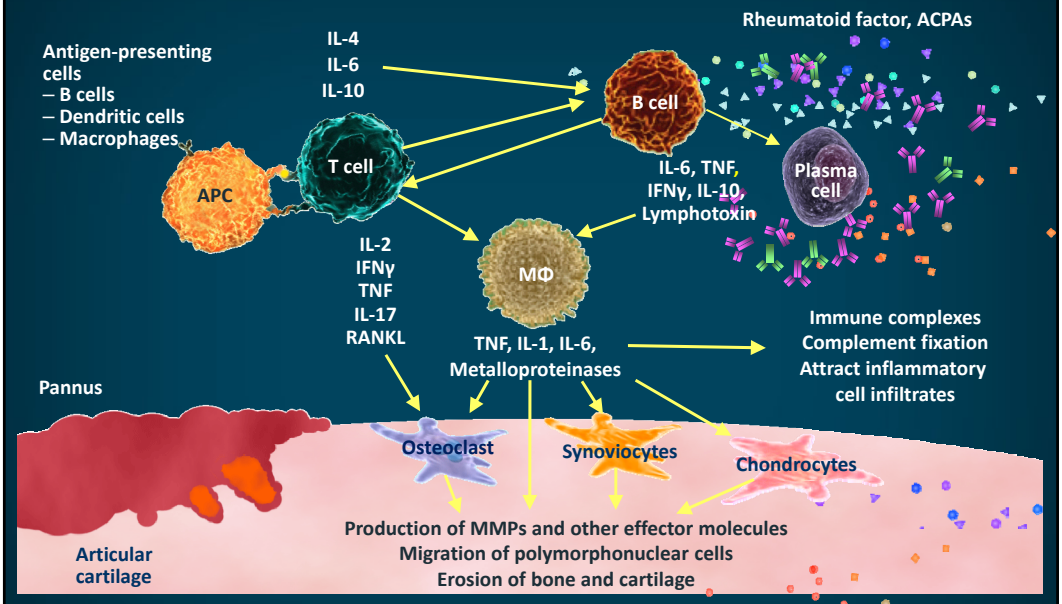
- Review clinical trial data for the efficacy and safety of JAK pathway inhibition in the treatment of moderate-to-severe RA
- Evaluate RA-related comorbidities and their management in patients with RA
- Assess ways in which to reduce the patient burden of RA while improving quality of life

JAK = Janus kinase; RA = rheumatoid arthritis.

Treatment Options in RA After MTX Failure: Can We Optimize Clinical Response?

RA Pathobiology

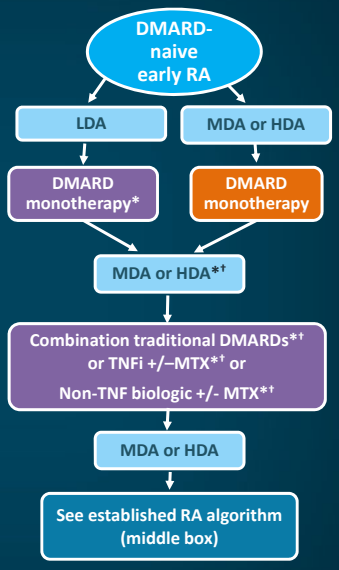


ACPA = anti-citrullinated protein antibody; APC = antigen-presenting cell; IFN = interferon; IL = interleukin; MMP = metalloproteinase; RANKL = receptor activator of nuclear factor-κB ligand; TNF = tumor necrosis factor.

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.

Guidelines for Initial Management of RA

- Initial choice is MTX, unless contraindicated
  - "Anchor drug" for RA
  - Relatively inexpensive, effective, safe, off-target beneficial effects; combined with all other DMARDs
  - Starting dose is 15 mg/wk, titrated, as needed, to 20 or 25 mg over 12–16 weeks
- 33–50% of patients will have acceptable response to monotherapy
- Additional agents added in IRs
  - Choices depend on patient/provider preference
  - TNFi is typically next choice for MTX IRs
  - Head-to-head studies of TNFi vs non-TNF biologic after MTX failure have mixed results
- T2T approach emphasized



*Also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares.
†Consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with MDA or HDA when starting DMARDs and in patients with DMARD failure or biologic failure.

DMARD = disease-modifying antirheumatic drug; LDA = low disease activity; HDA = high disease activity; IR = inadequate responder; MDA = moderate disease activity; MTX = methotrexate; T2T = treat to target; TNFi = TNF inhibitor.

Singh JA, et al. *Arthritis Rheumatol.* 2016;68:1-26. Schiff M, et al. *Ann Rheum Dis.* 2014;73:86-94.

2015 ACR/2016 EULAR Guidelines
Key Principles

- Perform disease activity measurements and functional assessments frequently
- Simplification of therapy in patients with LDA or remission at physician's discretion
- Arbitrary switching based on payer/insurance is not recommended
- Patients at risk of persistent arthritis should start DMARDs within 3 months, even if classification criteria are not fulfilled
- Oral CS can be added at the lowest effective dose and tapered
- Aim for remission within 3 months
- Maximize nonpharmacologic interventions (eg, PT/OT, smoking cessation, dental care, weight control, and vaccination updates) and patient education

ACR = American College of Rheumatology; CS = corticosteroid; EULAR = European League Against Rheumatism; LDA = low disease activity; OT = occupational therapy; PT = physical therapy.

Singh JA, et al. *Arthritis Rheumatol*. 2016;68:1-26. Combe B, et al. *Ann Rheum Dis*. 2017;76:948-959.

When a TNF Inhibitor Fails

Options After TNF Inhibitor Failure (Partial List)

- Triple therapy (TT)
  - RACAT[1]—etanercept (ETA) → TT[1]
- Second TNF-IR
  - EXXELLERATE[2]—adalimumab (ADA) ↔ certolizumab pegol (CZP) in nonresponders
  - GO-FORWARD[3]—TNF-IR → golimumab (GLM)
  - OPPOSITE[4]—TNF-IR → TNF
- Change mechanism of action
  - REFLEX[5]—TNF-IR → rituximab (RTX)
  - RADIATE[6]—TNF-IR → tocilizumab (TCZ)
  - ATTAIN[7]—TNF-IR → abatacept (ABA)
  - ORAL Step[8]—TNF-IR → tofacitinib (TOFA)
  - BEACON[9]—TNF-IR → baricitinib (BARI)
  - SELECT-BEYOND[10]—bDMARD → upadacitinib (UPA)
- Multiple options
  - French ROC trial[11]—rotation of TNFi or change of biologic

bDMARD = biologic DMARD.

1. O'Dell JR, et al. *N Engl J Med.* 2013;369:307-318. 2. NCT01500278 clinical study report. 3. Keystone EC, et al. *J Rheumatol.* 2016;43:298-306. 4. Furst DE, et al. *Ann Rheum Dis.* 2007;66:893-899. 5. Cohen SB, et al. *Arthritis Rheum.* 2006;54:2793-2806. 6. Emery P, et al. *Ann Rheum Dis.* 2008;67:1516-1523. 7. Genovese MC, et al. *N Engl J Med.* 2005;353:1114-1123. 8. Burmester GR, et al. *Lancet.* 2013;381:451-460. 9. Genovese MC, et al. *N Engl J Med.* 2016;374:1243-1252. 10. Genovese MC, et al. *Lancet.* 2018;391:2513-2524. 11. Rivière E, et al. *Arthritis Res Ther.* 2018;20:122.

When a TNF Antagonist Fails to Control RA

Efficacy Trials

	ACR50	
Trial	**MTX Alone (Placebo Group)**	**Drug + MTX**
ATTAIN (ABA)[1]	4%	20%
REFLEX (RTX + MTX)[2]	5%	27%
RADIATE (TCZ 8 mg/kg)[3]	4%	29%
TOFA (5 mg BID)[4]	11%	35%
BARI (4 mg QD)[5]*	13%	29%
UPA (15 mg QD)[6]	12%	34%

***At 24 weeks.**

ACR50 = ACR 50% improvement criteria; BID = twice daily; QD = once daily.

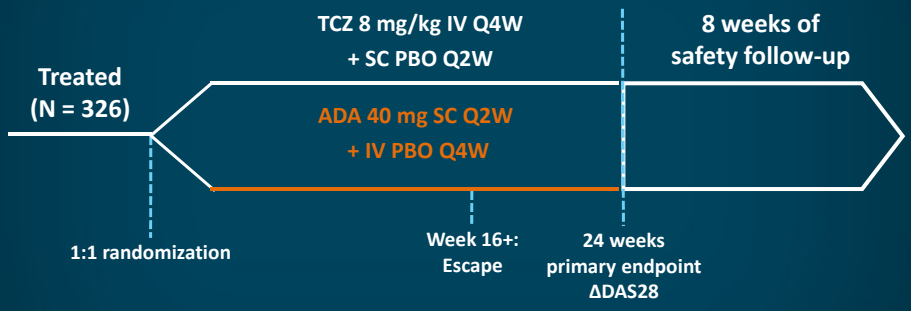
1. Genovese MC, et al. *N Engl J Med.* 2005;353:1114-1123. 2. Cohen SB, et al. *Arthritis Rheum.* 2006;54:2793-2806. 3. Emery P, et al. *Ann Rheum Dis.* 2008;67:1516-1523. 4. Burmester GR, et al. *Lancet.* 2013;381:451-460. 5. Genovese MC, et al. *N Engl J Med.* 2016;374:1243-1252 (supplement). 6. Genovese MC, et al. *Lancet.* 2018;391:2513-2524.

Head-to-head comparison

The ADACTA Study

Tocilizumab vs Adalimumab in RA

Phase 4, multicenter, randomized, double-blind study—superiority trial design



Criteria for escape: <20% improvement from baseline in SJC and TJC at week 16 or later

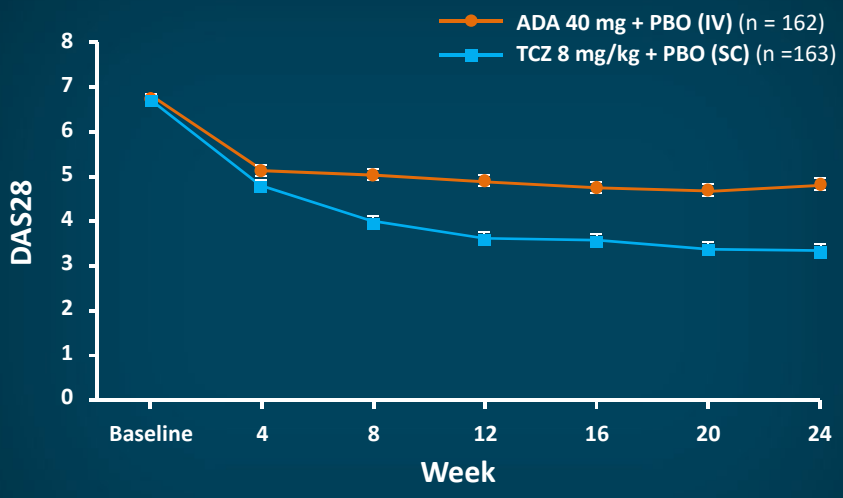
Escape therapy: weekly SC (ADA/PBO) injections; study medication remained blinded

IV = intravenous; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; DAS = Disease Activity Score calculator for RA; SJC = swollen joint count; TJC = tender joint count.

Gabay C, et al. *Lancet.* 2013;381:1541-1550.

Head-to-head comparison

ADACTA: Mean DAS28 Over Time



LOCF used for TJC and SJC. ESR and patient's global assessment of disease activity VAS, if ESR = 0, then ESR = 1 is substituted into DAS28 calculation to enable a non-missing DAS28

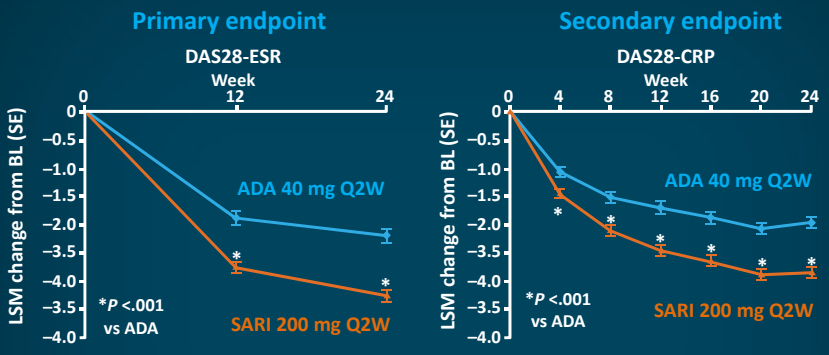
ESR = erythrocyte sedimentation rate; LOCF = last observation carried forward; VAS = visual analog scale.

Gabay C, et al. *Lancet.* 2013;381:1541-1550.

Head-to-head superiority trial

MONARCH Trial

SARI (SC) Monotherapy vs ADA (SC) Monotherapy: Phase 3

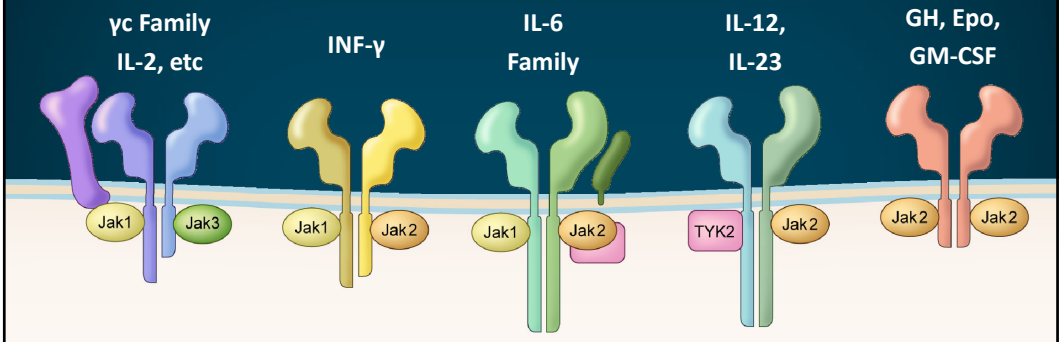


- Superiority also significant for ACR20/50/70 response rates, improvement in physical function (HAQ-DI), and proportion of patients reaching CDAI and LDA at 24 weeks
- AEs = 63.6% (ADA) vs 64.1% (SARI), most common being neutropenia and injection-site reactions (SARI) and headache and worsening RA (ADA); incidences of infection and serious infections were similar

SARI = sarilumab; SC = subcutaneous; ACR20 = ACR 20% improvement criteria; ACR70 = ACR 70% improvement criteria; AE = adverse event; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28-ESR = DAS28 using ESR; LSM = least squares mean; BL = baseline; HAQ-DI = Health Assessment Questionnaire Disability Index; SE = standard error.

Burmester GR, et al. *Ann Rheum Dis*. 2017;76:840-847.

Signaling by Type I/II Cytokine Receptors and JAK Inhibitors

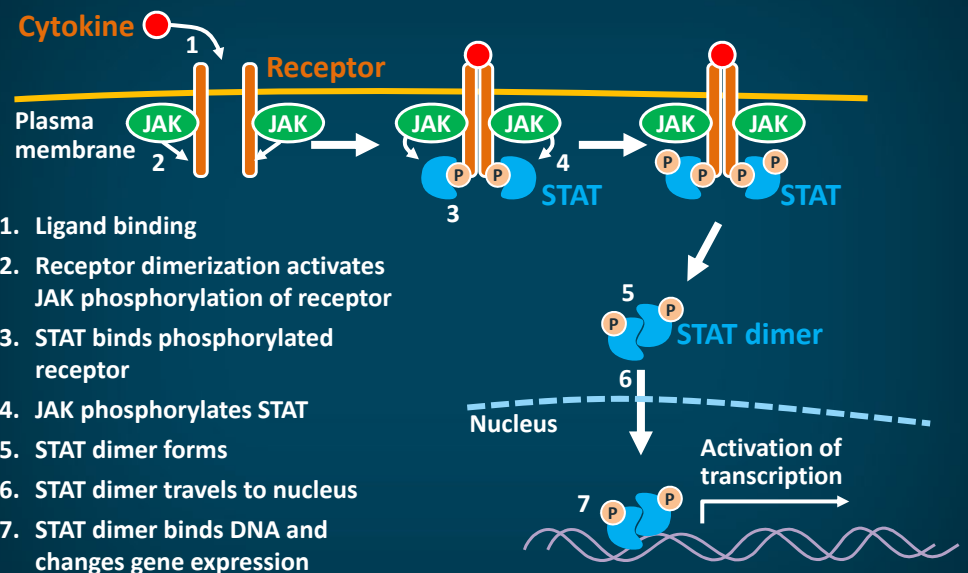


	γc Family IL-2, etc	INF-γ	IL-6 Family	IL-12, IL-23	GH, Epo, GM-CSF
TOFA	+	+	+		
BARI	+	+	+	+	+
UPA	+	+	+		
FIL*	+	+	+		
PEF*	+	+	+	+	+

*Not FDA approved.

FIL = filgotinib; GH = growth hormone; Epo = erythropoietin; GM-CSF = granulocyte macrophage colony-stimulating factor; PEF = peficitinib; UPA = upadacitinib.

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

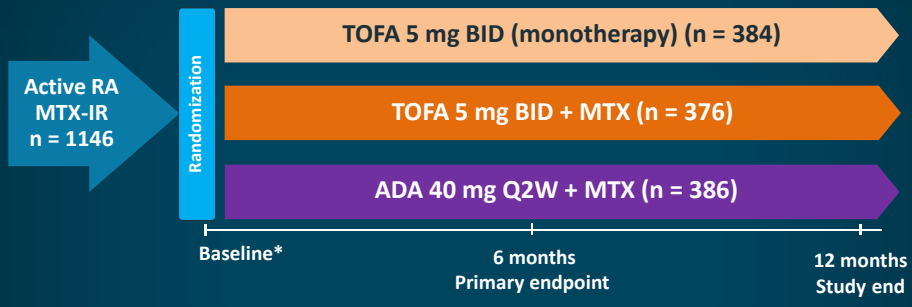
STAT = signal transducer and activator of transcription; DNA = deoxyribonucleic acid.

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

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

ORAL Strategy

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
- **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.

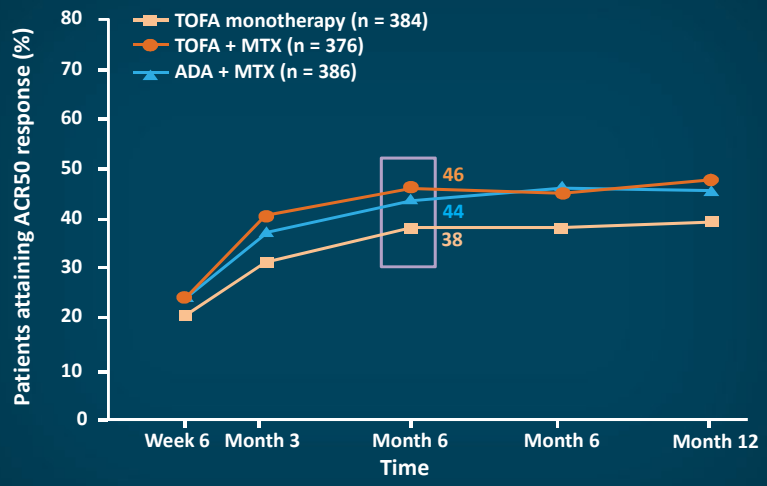
RCT = randomized controlled trial; SDAI = Simplified Disease Activity Index.

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.

AEs, Serious AEs, and Discontinuations

Safety Analysis Set

	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 patients who were vaccinated	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%)

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

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

Venous Thromboembolism (VTE) With JAK Inhibitors

Primary analysis: VTE events identified from inpatient claims with an 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.

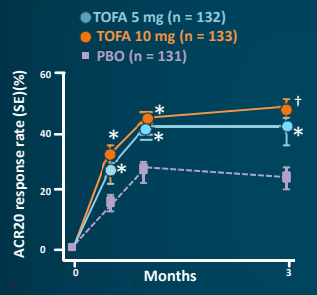
HR = hazard ratio; CI = confidence interval; PY = person-year; EMA = European Medicines Agency.

Desai RJ, et al. *Arthritis Rheumatol*. 2019;71:892-900. Sandborn WJ, et al. *Aliment Pharmacol Ther.* 2019;50:1068-1076. Brooks M. *Medscape.* (www.medscape.com/viewarticle/920647). Accessed 8/15/2020.

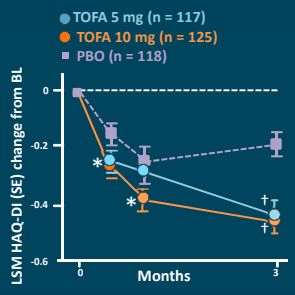
Efficacy and Safety of Tofacitinib (JAK 1/3) + MTX in TNFi-IR Patients

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

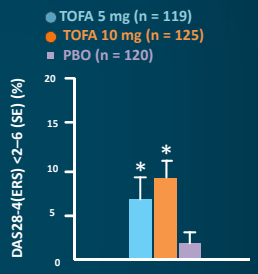
ACR20 response rate



Change in HAQ-DI



DAS28 <2.6



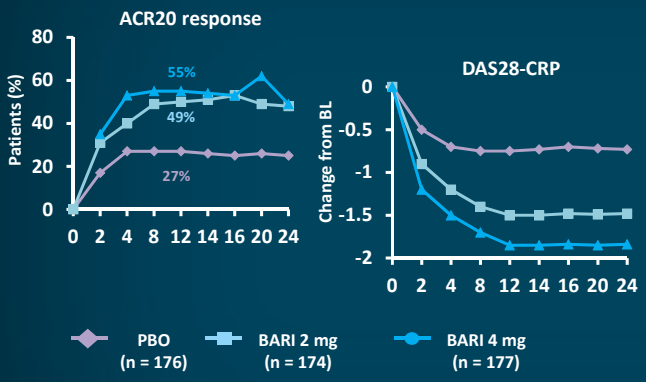
- Tofacitinib has consistent, manageable safety profile across studies; no new safety signals[1]
- Consistent safety through 114 months; sustained clinical efficacy through 96 months[2]
- 5-year analysis of AEs with tofacitinib vs bDMARDs reported in CORRONA RA Registry shows higher incidence of HZ but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

*$P \leq .05$, †$P < .0001$ vs PBO.

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.

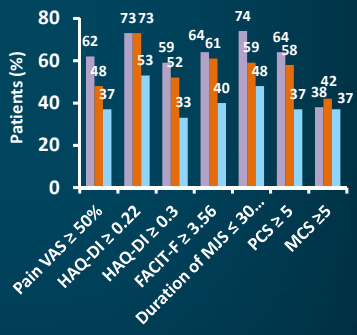
Efficacy and Safety of Baricitinib (JAK 1/2) in bDMARD-IR Patients

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



MCS = mental component score; MJS = morning joint stiffness; OR = odds ratio; PCS = physical component score.

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. Fautrel B, et al. ACR/ARHP 2017: abstract 508.

Baricitinib

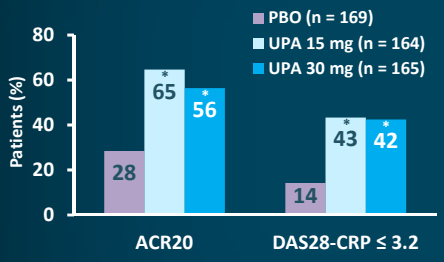
- Baricitinib led to more AEs (including infections) than placebo[1]
- Most common infections: respiratory tract, urinary tract, bronchitis[1]
- Rates of serious AEs through week 24 were similar among patient groups[1]
- Post-hoc analysis of RA-BEACON: ORs favored use of baricitinib over placebo regardless 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]

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.

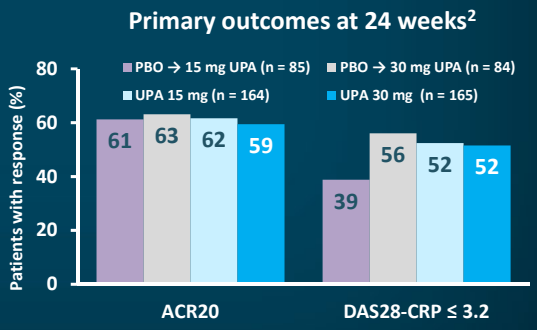
Efficacy and Safety of Upadacitinib (JAK 1) in bDMARD-IR Patients

Phase 3 trial SELECT-BEYOND

Primary outcomes at 12 weeks[1,2]



Primary outcomes at 24 weeks[2]



*P <.001 relative to PBO.

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

Upadacitinib

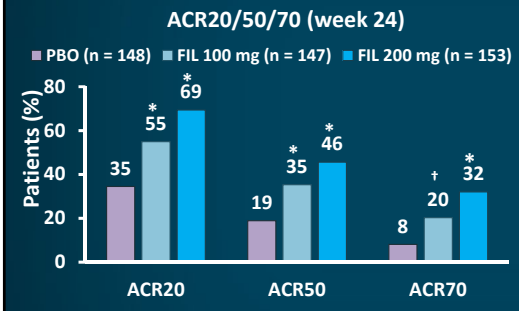
- In a post-hoc analysis, upadacitinib showed comparable efficacy whether administered with methotrexate vs other non-methotrexate csDMARDs[1]
- UPA treatment also resulted in significant, clinically meaningful improvements in PROs among patients[2]
- Pooled safety analysis across phase 3 trials showed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

PRO = patient-reported outcome.

1. Kremer J, et al. EULAR 2019: abstract FRI0155. 2. Strand V, et al. EULAR 2018: abstract SAT0256. 3. Cohen SB, et al. EULAR 2019: abstract THU0167. 4. Genovese MC, et al. EULAR 2019: abstract THU0172.

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

FINCH 2 phase 3 trial[1]



Other Efficacy Measures (Week 24)[2,3]

	PBO (n = 148)	FIL 200 mg (n = 147)	FIL 100 mg (n = 153)
Mean HAQ-DI (SD)	1.22 (0.68)	0.95 (0.71)	1.04 (0.71)
HAQ-DI, mean change from BL (SD)	–0.42 (0.60)	–0.75 (0.62)*	–0.60 (0.66)†
SF-36 PCS, mean change from BL (SD)	6.6 (7.95)	9.4 (8.23)*	9.0 (8.44)
FACIT-Fatigue, mean change from BL (SD)	7.0 (10.23)	11.6 (11.67)*	9.8 (10.39)†

*P <.001, †P <.01 compared with PBO.
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; SF-36 = Short Form-36 Health Survey; SD = standard deviation.

1. Genovese MC, et al. ACR/ARHP 2018: abstract L06. 2. Genovese MC, et al. EULAR 2019: abstract FRI0092. 3. Kalunian K, et al. EULAR 2019: abstract FRI0154.

Not FDA approved for RA at this time.

Filgotinib

- Treatment-emergent AE rates were similar between placebo and filgotinib groups
  - –4 HZ infections and 2 adjudicated MACE were reported
  - –No cases of opportunistic infection/active TB, malignancy, gastrointestinal perforation, or death[1]
- Efficacy and safety were comparable among patients who had <3 or ≥3 prior bDMARDs[2]
- Subanalysis among patients aged ≥65 vs <65 years show no association of age with incidence of safety effects and comparable efficacy among groups[3]

1. Genovese MC, et al. ACR/ARHP 2018: abstract L06. 2. Genovese MC, et al. EULAR 2019: abstract FRI0092. 3. Kalunian K, et al. EULAR 2019: abstract FRI0154.

*Not FDA approved for RA at this time.

JAK and IL-6 Inhibitors Have Shown Improvements in HRQoL

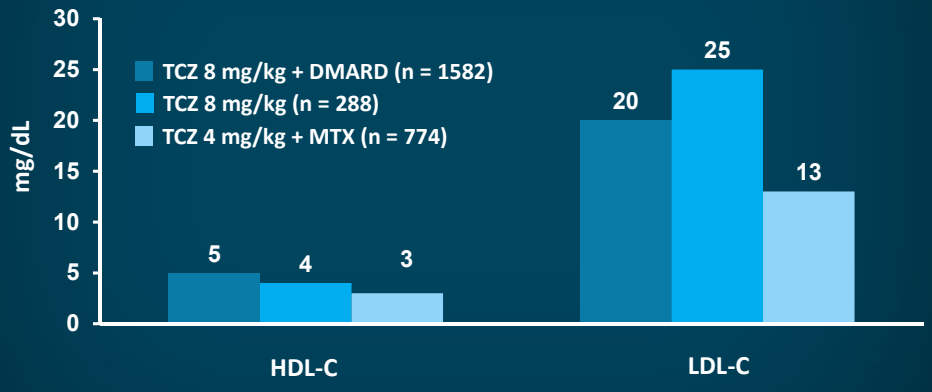
- QoL in RA is largely determined by an individual's disease activity and disability
  - Reducing these typically leads to QoL improvement
- JAK inhibitors and IL-6 inhibitors have shown a variety of improvements in PROs such as:[1-6]
  - HAQ-DI
  - Pain-VAS
  - Fatigue – FACIT
  - WPAI-RA
  - ISI
  - Overall, physical and/or mental components of SF-12/36

PRO – Patient-Reported Outcome. HAQ-DI – Health Assessment Questionnaire – Disability Index. VAS – Visual Analog Scale. FACIT – Functional Assessment of Chronic Illness Therapy. WPAI-RA – Work Productivity and Activity Impairment, Rheumatoid Arthritis. ISI – Insomnia Severity Index. SF-12/36: Short-Form Health Survey 12/36

1. Boyce E, et al. *Patient Relat Outcome Meas*. 2016;7:1-12. 2. Schiff M, et al. *Arthritis Res Ther*. 2017;19;208. 3. Strand V, et al. *Arthritis Res Ther*. 2019;21:263. 4. Orbai AM, et al. *Rheumatology*. 2020;59:1495-1504. 5. Strand V, et al. *Rheumatology (Oxford)*. 2012;51:1860-9. 6. Crotti C, et al. *Patient Relat Outcome Meas*. 2018;9:275-84.

Changes in Lipids Associated With Tocilizumab (IL-6 Receptor Antagonist)

Mean change from BL in 6-month controlled period



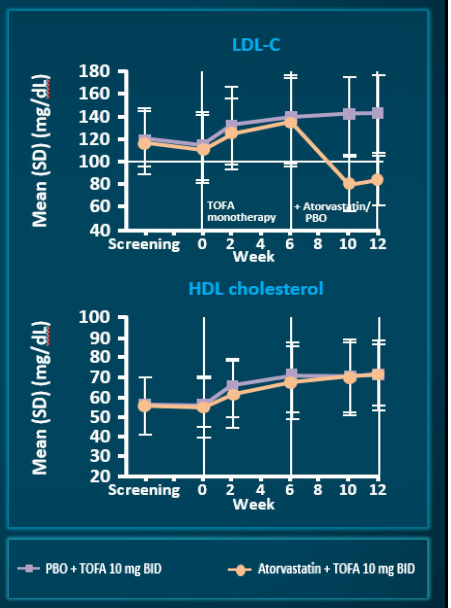
An identical pattern is observed with JAK inhibitors

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

Tocilizumab (Actemra®) PI 2020 (www.gene.com/download/pdf/actemra_prescribing.pdf). Accessed 8/15/2020.

Should I Monitor and Treat Lipid Changes Occurring After Starting Tocilizumab or Tofacitinib?

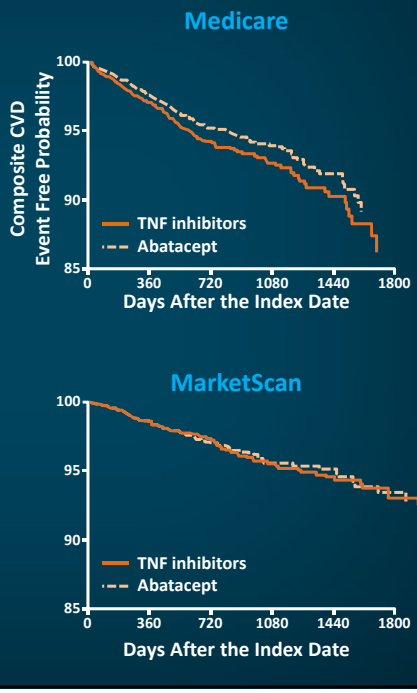
- 111 patients with RA started TOFA and were randomized to start atorvastatin 10 mg/d or PBO at 6 wks
- TC, LDL-C, and ApoB were reduced to below pretreatment levels
- DAS response and change in CRP at 12 wks was better with statin
- Effect on medium- and long-term outcomes is unclear
- Rise in LDL is usually lower in those already on a statin; some may require statin increase after starting IL-6 or JAK inhibitor



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

DMARDs and CVD Events in RA

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



1. Roubille et al. *Ann Rheum Dis* 2015 Mar;74(3):480-489.
2. Kang EH et al. J Am Heart Assoc. 2018 Jan 24;7(3). pii: e007393.
3. Giles JT et al. *Arthritis Rheum.* 2020;72:31-40.

Comorbidities

Comorbidities in Rheumatoid Arthritis

Variables	RA Cases % (95% CI)	Controls % (95% CI)
Cardiovascular		
Cardiac arrythmia	18.9 (18.7–19.2)	13.2 (13.1–13.3)
CHF	10.3 (10.1–10.4)	6.0 (6.0–6.1)
CHD	15.3 (15.1–15.5)	9.6 (9.5–9.6)
MI	1.4 (1.3–1.4)	0.8 (0.8–0.8)
Stroke	2.7 (2.6–2.8)	1.9 (1.9–2.0)
Valvular diseases	10.9 (10.7–11.1)	7.1 (7.0–7.2)
Vascular diseases	13.0 (12.8–13.2)	8.5 (8.5–8.6)
Thrombosis		
Arterial thrombosis/embolism	0.4 (0.4–0.5)	0.2 (0.2–0.3)
Venous thrombosis	2.9 (2.8–3.0)	1.5 (1.5–1.6)
Pulmonary embolism	1.1 (1.0–1.1)	0.5 (0.5–0.5)
CV risk factors		
HTN	62.5 (62.2–62.8)	47.9 (47.8–48.0)
Hyperlipidemia	39.9 (39.6–40.2)	32.3 (32.2–32.5)
Obesity	18.0 (17.8–18.2)	12.2 (12.1–12.3)

CHF = congestive heart failure; CHD = coronary heart disease; MI = myocardial infarction; CV = cardiovascular; HTN = hypertension.

Ramos AL, et al. *J Rheumatol*. 2019;46:L564-571.

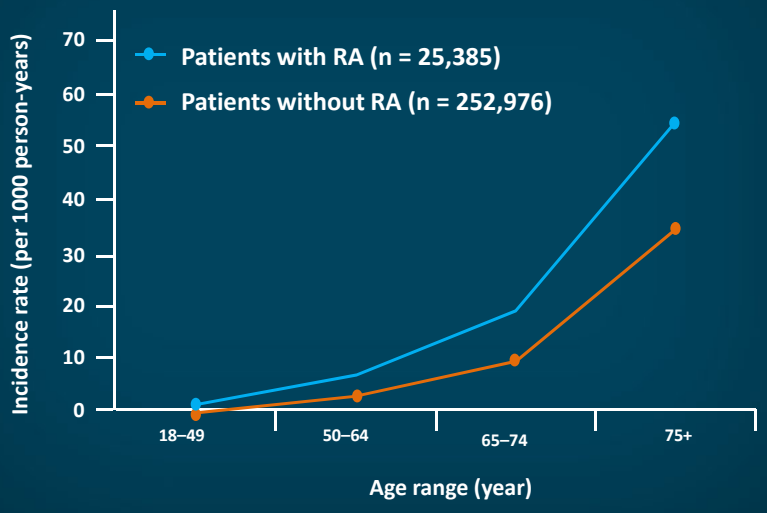
Comorbidities in Rheumatoid Arthritis (continued)

Variables	RA Cases % (95% CI)	Controls % (95% CI)
Musculoskeletal diseases		
Osteoarthritis	44.0 (43.7–44.3)	21.4 (21.2–21.5)
Osteoporosis	25.9 (25.6–26.2)	9.4 (9.3–9.5)
Neoplasms		
Lymphoma	1.0 (1.0–1.1)	0.6 (0.6–0.6)
Metastatic cancer	1.7 (1.7–1.8)	1.4 (1.4–1.5)
Solid tumor w/o mets	13.9 (13.6–14.1)	11.4 (11.4–11.5)
Pulmonary diseases		
Asthma	12.5 (12.2–12.7)	7.3 (7.2–7.3)
COPD	11.3 (11.1–11.5)	6.5 (6.4–6.5)
Other diseases		
Depression	31.8 (31.5–32.1)	20.1 (20.0–20.3)
Diabetes	21.7 (21.4–21.9)	15.2 (15.1–15.3)
Hypothyroidism	18.1 (17.9–18.4)	12.8 (12.7–12.9)
IBD	2.3 (2.2–2.4)	0.8 (0.8–0.9)
Liver disease	13.9 (13.7–14.2)	9.0 (8.9–9.0)
Renal failure	10.2 (10.0–10.4)	5.4 (5.4–5.5)

w/o = without; mets = metastases; COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease.

Ramos AL, et al. *J Rheumatol*. 2019;46:L564-571.

RA Is an Independent Risk Factor for Cardiovascular Events*



*Myocardial infarction and stroke.

Solomon DH, et al. *Ann Rheum Dis*. 2006;65:1608-1612.

Strategies to Optimize Patient Outcomes (by Participation in the RA Care Plan)

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, LDA may be an acceptable treatment goal, particularly in patients with long-standing, established disease

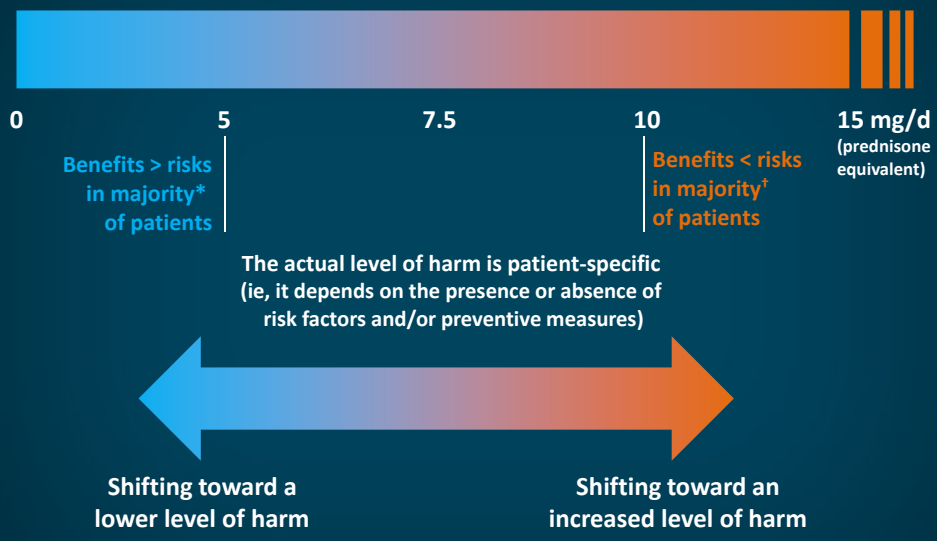
Smolen JS, et al. *Ann Rheum Dis*. 2010;69:631-637.

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

- RA BIODAM: RA registry in 10 countries
  - At 41% of visits, T2T protocol was not implemented
  - Main reason: physician felt current treatment was adequate (69%)
- CORRONA
  - 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

Ramiro S, et al. *Ann Rheum Dis.* 2020;79:453-459. Maksymowych WP, et al. *Arthritis Rheumatol.* 2014;66(suppl 10): abstract 2912. Harrold L, et al. *Arthritis Rheumatol.* 2015;67(suppl 10): abstract 3185.

Balancing Risks and Benefits: Glucocorticoids



*Not true for patients with high-risk CVD. †Not true for patients with (partial) glucocorticoid resistance.

Strehl C, et al. *Ann Rheum Dis*. 2016;75:952-957.

Conclusions

- RA is a chronic inflammatory disease with significant morbidity and disability if untreated
- Advances in our understanding of pathogenesis have led to the development of new and more effective therapies; most recently, these have included newly developed agents that block JAK signaling and IL-6-mediated effects
- Optimal approach to therapy needs to consider comorbidities, quality of life, T2T, tailoring regimens when needed, and promoting strategies that improve adherence

Case Studies

Case Study 1
Mr. T

Case Study 1

- Mr. T is a 62-year-old retired fireman with RA for 5 years
- Seropositive for anti-CCP and RF
- Complains of increasing joint symptoms over the past 6 months, and now has 2 hours of morning stiffness
- 6 swollen and 8 tender joints, DAS28 of 4.8, and CDAI of 21
- Continues to smoke half a pack/day with a 40-pack/year history
- Currently taking MTX 17.5 mg/wk and hydroxychloroquine daily, with prednisone 5 mg/d added without benefit. He is on metformin for AODM and atorvastatin for hypercholesterolemia
- Family history of AODM, HTN, and MI

AODM = adult-onset diabetes mellitus; CCP = cyclic citrullinated peptide; CDAI = Clinical Disease Activity Index; RF = rheumatoid factor.

Case Study 1: Considerations

- Mr. T is a challenging patient; like many patients with RA, he also has other illnesses/comorbidities
- It is possible that his flare is due to poor adherence, but he does come to monthly appointments, and blood is drawn before revisit
- Smoking not only is a risk factor for disease initiation but also can have adverse effects on therapeutic efficacy

Case Study 1: Treatment Considerations

- You could advance his methotrexate and prednisone dose, but this would be associated with an increased risk of toxicity in the long term
- Choice of a trial of a biologic agent or JAK inhibitor should be personalized to the needs and preferences of the patient, as well as considerations of relative risks

Case Study 2
Mrs. S

Case Study 2

- Mrs. S is a 66-year-old woman with RA for 7 years. She was initially treated with MTX and did well on it for several years. However, 2 years ago she began having more stiffness and swelling; a TNF inhibitor was added. It was moderately helpful, but she never achieved LDA or remission despite trying 2 different TNF inhibitors
- She is currently taking MTX 25 mg per week and is using daily NSAIDs to help with symptoms. She stopped her TNF inhibitor 3 months ago because she did not think it was helping, and her joint swelling and stiffness have gotten worse
- She has 8 swollen and 10 tender joints; her CRP is elevated at 10 mg/dL
- She has osteopenia based on her last DXA scan, with a FRAX score appropriate for a bisphosphonate, but she did not start it
- Her BMI is 32 (kg/m^2). Half of your time is spent discussing weight-loss strategies, but she never seems to lose any weight between visits

NSAID = nonsteroidal antiinflammatory drug; DXA = dual-energy x-ray absorptiometry (scan); FRAX = Fracture Risk Assessment Tool; BMI = body mass index.

Case Study 2: Follow-Up

- When you review her medical record, you see that she had a deep venous thrombosis 15 years ago.
- She was anticoagulated for 6 months and has not had a recurrence since then.

Case Study 2: VTE Risk

- Age, elevated BMI, and prior history of thromboembolic disease have been identified as risk factors for VTE in clinical trials of JAK inhibitors
- Although overall risk of VTE is low among patients treated with JAK inhibitors (about 1 in every 200 or less), the risk may be higher in those with risk factors
  - Especially those with prior VTE
- The European Medicines Agency recommends not using JAK inhibitors in patients with VTE risk factors

VTE = venous thromboembolism.

Case Study 3
Mrs. P

Case Study 3

- Mrs. P is a 34-year-old woman diagnosed with RA when she was 28 years old.
- She is seropositive for RF and anti-CCP antibodies.
- She had very active, difficult to treat disease when first diagnosed, and she developed fairly extensive erosive damage to her hands and wrists.
- She was treated with MTX and infliximab, titrated to maximum doses. She is now receiving infused infliximab 10 mg/kg every 4 weeks.
- This treatment has worked well for several years. However, over the past 6 months, the effect has started to wane. She gets more swelling and stiffness 7–10 days prior to infusion, and level of control after infusion is less than before.
- She is concerned that she will develop more damage to her joints if her RA is not brought back under control.

Case Study 3: Pregnancy

- She tells you that she is thinking about having another child.
- She wants to know what is the best treatment strategy that combines safety with the likelihood of regaining control of her RA

Case Study 3: Considerations

- MTX is teratogenic and must be stopped ≥3 months before conception
  - It cannot be used during pregnancy or lactation
- TNF inhibitors generally are considered safe during conception, pregnancy, and lactation
  - They are often held during pregnancy, since RA disease activity often improves spontaneously during pregnancy
- Remaining non-TNF inhibitor biologics do not have enough data available to make any recommendations
  - Generally avoided during conception, pregnancy, and lactation.
  - Usually held prior to conception, but for how long has not been firmly established
  - Current ACR guideline recommends discontinuation at conception
- There are limited data about safety of JAK inhibitors during conception, pregnancy, and lactation
  - Current recommendation is that they are incompatible with all stages of pregnancy and should be stopped prior to conception, although timing has not been firmly established.

Sammaritano LR, et al. *Arthritis Rheumatol.* 2020;72:529-556.

Case Study 4
Mr. M

Case Study 4

- Mr. M is a 58-year-old man diagnosed with RA 5 years ago
- He is seropositive for RF and anti-CCP, both at a high level
- Current treatment includes MTX 25 mg per week, etanercept weekly, and prednisone 5 mg per day, from which he is unable to wean without rebound joint symptoms and fatigue.
- He has smoked about a pack of cigarettes per day for the last 30 years.
- He is treated for HTN and he says his PCP told him he has prediabetes and borderline-high cholesterol. "She wants me to lose weight and exercise more."
- Today his BMI is 31 (kg/m^2), and his last HbA1c and LDL-C were 7% and 135 mg/dL, respectively
- Exam
  - Mild synovitis present in a few MCP and PIP joints, right wrist is swollen with dorsal tenosynovitis, and left knee is slightly warm with detectable synovitis and a small effusion
  - MTP rows have mild synovial thickening without pain

PCP = primary care provider; HbA1c = glycosylated hemoglobin; MCP = metacarpophalangeal; PIP = proximal interphalangeal; MTP = metatarsophalangeal.

Case Study 4: Considerations

- You discuss the options with him, and he tells you that even though he doesn't mind self-injecting, he would like to pursue an option without shots or infusions
- You decide to start a JAK inhibitor
  - He remembers a television commercial where shingles was mentioned as a possible side-effect
  - He reports that he had chicken pox as a child

Case Study 4: Shingles

- The risk of zoster is higher for IL-6 and JAK inhibitors than for MTX or etanercept.
  - Now is a good opportunity to vaccinate him with recombinant zoster vaccine (Shingrix®) and not live zoster vaccine (Zostavax®)
- Ideally, the entire vaccination course (2 doses) would happen several weeks prior to starting the JAK inhibitor to ensure maximal response.
- The minimum time between doses is 8 weeks.
- You opt to continue his current therapy until he can get both doses of recombinant zoster vaccine and wait an additional 2 weeks until starting the JAK inhibitor.

CDC. Shingles vaccine (www.cdc.gov/vaccines/vpd/shingles/public/shingrix/index.html). Accessed 8/15/2020.

Case Study 4: Follow-Up

- You start therapy with the JAK inhibitor and see him back 8 weeks later.
- At that visit, he reports:
  - Improvement in joint swelling and morning stiffness
  - More energy and less fatigue
  - His synovitis has almost completely resolved
- You check labs today, and his LDL-C has increased from 135 mg/dL to 160 mg/dl.

Case Study 4: CV Issues

- Part of the mechanism of JAK inhibition is 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
- He 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.

Clinical Perspectives in Rheumatoid Arthritis: Quality of Life, Comorbidities, and Evolving Targets

Resource	Address
Al-Salama Z, et al. Baricitinib: A review in rheumatoid arthritis. *Drugs*. 2018;78(7):761-772.	https://pubmed.ncbi.nlm.nih.gov/29687421/
Bansback N, et al. The economics of treatment in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol*. 2009;23:83-92.	https://pubmed.ncbi.nlm.nih.gov/19233048/
Dhillon S. Tofacitinib: A review in rheumatoid arthritis. *Drugs*. 2017;77(18):1987-2001.	https://pubmed.ncbi.nlm.nih.gov/29139090/
Dowty M, et al. Janus kinase inhibitors for the treatment of rheumatoid arthritis demonstrate similar profiles of in vitro cytokine receptor inhibition. *Pharmacol Res Perspect*. 2019;7(6):e00537.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6857076/
Fragoulis G, et al. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58(Suppl 1):i43-54.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6390879/
Jegatheeswaran J, et al. Comparison of janus kinase inhibitors in the treatment of rheumatoid arthritis: A systemic literature review. *Immunotherapy*. 2019;11(8):737-754.	https://pubmed.ncbi.nlm.nih.gov/30955397/
Kohler BM, et al. Current therapeutic options in the treatment of rheumatoid arthritis. *J Clin Med*. 2019 Jun 28;8(7):938.	https://pubmed.ncbi.nlm.nih.gov/31261785/
Kronzer V, et al. Comorbidities as risk factors for rheumatoid arthritis and their accrual after diagnosis. 2019;94(12):2488-2498.	https://pubmed.ncbi.nlm.nih.gov/31759675/
Ramos AL, et al. Comorbidities in patients with rheumatoid arthritis and their association with patient-reported outcomes: Results of claims data linked to questionnaire survey. *J Rheumatol*. 2019;46(6):564-571.	https://pubmed.ncbi.nlm.nih.gov/30647170/
Smolen J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying	https://pubmed.ncbi.nlm.nih.gov/28264816/

antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76(6):960-977.	
Smolen J, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomized, placebo-controlled, double-blind phase 3 study. *Lancet*. 2019;393(10188):2303-2311.	https://pubmed.ncbi.nlm.nih.gov/31130260/
Silvagni E, et al. One year in review 2020: Novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol*. 2020;38(2):181-194.	https://pubmed.ncbi.nlm.nih.gov/32213264/
Taylor P. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)*.2019;58(Suppl 1):i17-i26.	https://pubmed.ncbi.nlm.nih.gov/30806707/
Westhovens R, et al. Rheumatoid arthritis: Defining remission in patients with RA in clinical practice. *Nature Reviews Rheumatology.* 2012;8:445-447.	https://pubmed.ncbi.nlm.nih.gov/22751567/
Xie W, et al. Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: Systematic review and meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2019;78(8):1048-1054.	https://pubmed.ncbi.nlm.nih.gov/31088790/

Resources and Societies

Resource	Address
American College of Rheumatology	https://www.rheumatology.org/
Arthritis Foundation	https://www.arthritis.org/
National Rheumatoid Arthritis Society	https://www.nras.org.uk/
Rheumatology Research Foundation	https://www.rheumresearch.org/
World Health Organization	http://www.who.int/chp/topics/rheumatic/en/

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