

CLINICAL ISSUES IN RHEUMATOID ARTHRITIS

Debates & Discussions on the Evolving Role of JAK Inhibitors



Joel Kremer, MD, FACP, MACR

Moderator

*Pfaff Family Professor of Medicine
Albany Medical College
Director of Research, The Center for Rheumatology
Founder, Corrona, LLC
Albany, New York*



Maria Greenwald, MD, FACP

*Rheumatologist
Co-Director, Desert Medical Advances
Palm Desert, California*

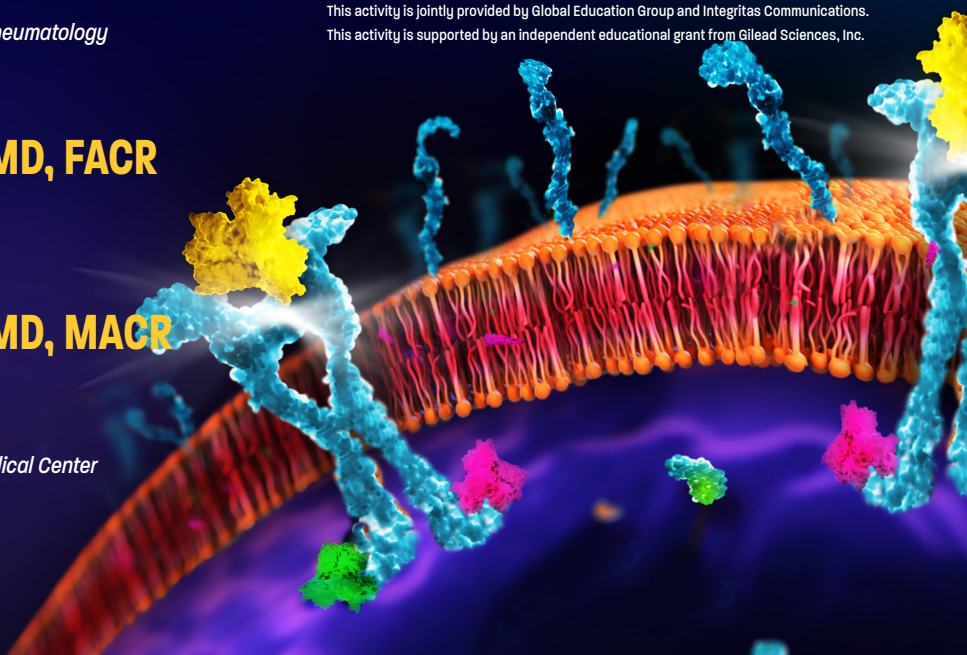


Roy Fleischmann, MD, MACR

*Co-Medical Director
Metroplex Clinical Research Center
Clinical Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, Texas*



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CME/MEDICAL COMMUNICATIONS INQUIRIES

info@integritasgrp.com

integritasgrp.com



FACULTY

Joel Kremer, MD, FACP, MACR

Moderator

*Pfaff Family Professor of Medicine, Albany Medical College
Director of Research, The Center for Rheumatology
Founder, Corrona, LLC
Albany, New York*

Maria Greenwald, MD, FACP

*Rheumatologist
Co-Director
Desert Medical Advances
Palm Desert, California*

Roy Fleischmann, MD, MACR

*Co-Medical Director, Metroplex Clinical Research Center
Clinical Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, Texas*

TARGET AUDIENCE

The educational design of this activity addresses the needs of clinical rheumatologists and specialist nurse practitioners (NPs), physician assistants (PAs), and nurses who manage patients with rheumatoid arthritis (RA).

PROGRAM OVERVIEW

This digital CME program, titled "Clinical Issues in Rheumatoid Arthritis: Debates and Discussions on the Evolving Role of JAK Inhibitors," has been created from the proceedings of a live symposium held during the American College of Rheumatology's (ACR) 2019 State-of-the-Art (SOTA) Clinical Symposium. In this activity, an expert panel of rheumatologists discuss and debate the latest insights regarding Janus kinase (JAK) activation in RA immunopathology, recent clinical trial data on the efficacy and safety of current and emerging JAK inhibitors, and the evolving roles of this disease-modifying antirheumatic drug (DMARD) class in day-to-day clinical practice.

STATEMENT OF NEED

Advances in our understanding of the immunopathologic mechanisms underlying RA have led to the development of DMARDs that effectively target relevant pathways. For instance, members of the JAK family play a pivotal role in transducing extracellular cytokine signaling, thereby contributing to such processes as cellular proliferation, homeostasis, and host defense against infections.¹ In RA, certain JAK-mediated signaling pathways are dysfunctionally active, leading to enhanced transcription of various

proinflammatory genes and aberrant immune responses.² The goal of this *Clinical Issues™* activity is to support participants in translating the latest evidence regarding the use of JAK inhibitors to clinical practice; thereby, providing improved care for their patients with RA.

REFERENCES

1. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol*. 2017;13(4):234-243.
2. Malemud C. The role of the JAK/STAT signal pathway in rheumatoid arthritis. *Ther Adv Musculoskelet Dis*. 2018;10(5-6):117-127.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Describe the roles of JAK/signal transducer and activator of transcription (STAT) signaling in immune responses and homeostasis, including contributions to the immunopathogenesis of RA
- Discuss the clinical profiles of current and emerging JAK inhibitors, including implications of enzyme specificity and evidence for efficacy and safety in RA
- Integrate JAK inhibitors into RA-treatment algorithms based on guideline recommendations, current clinical trial data, and patient preferences

PHYSICIAN ACCREDITATION STATEMENT

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Maria Greenwald, MD, FACP

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Roy Fleischmann, MD, MACR

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Ashley Cann Nothing to disclose

Celeste Collazo, MD Nothing to disclose

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1. Read the educational objectives, accreditation information, and faculty disclosures at the beginning of this activity.
2. Complete the Preactivity Questions.
3. Read or review the activity content.
4. Complete the Postactivity Test Questions and Evaluation.
5. Physicians must achieve a grade of 70% on the Postactivity Test Questions and complete the Evaluation to receive a CME Certificate.
6. All other participants who achieve a grade of 70% on the Postactivity Test Questions and who complete the Evaluation will receive a Certificate of Participation.

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There is no fee for this educational activity.

GLOBAL CONTACT INFORMATION

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Thank you for joining us. My name is Dr. Joel Kremer, I have had the pleasure of working in clinical research for the past 38 years and the privilege of spending a day with Dr. John O'Shea; who described the JAK system over 20 years ago. It is complex and in this first section, I will present a series of slides that provides a conceptual framework for how JAK inhibitor drugs work.



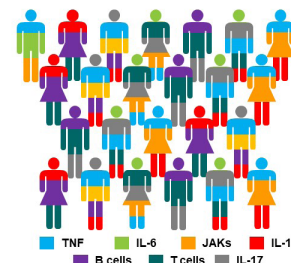
There is a pathophysiologic diversity in RA, which is an avenue to understand differential treatment outcomes. What affects this heterogeneity? Of course, genetics and epigenetics, which is the modification of gene expression. We know that there is only about 20% concordance in identical twins. Some of that is epigenetics and some is simply the vagaries of environmental factors and other extrinsic etiologies—for example, smoking.

The different colors in this slide are meant to conceptually—not accurately but conceptually—represent the contributions of the mediators below them to RA in each patient. Various cell populations, cytokines, and signaling pathways drive the autoimmune and inflammatory processes. This leads to the hallmark systemic and clinical manifestations.

Various conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) have been shown to be effective for RA, but treatment responses are variable. This is not terribly surprising if you look at various factors that can drive disease development, as represented by these different colors. No two patients are the same.

Pathophysiologic Diversity in RA An Avenue to Differential Treatment Outcomes

- Genetic, epigenetic, and environmental etiologies
- Various cell populations, cytokines, and signaling pathways drive the autoimmune and inflammatory processes
 - Lead to articular and systemic clinical manifestations
- Various csDMARDs, bDMARDs, and tsDMARDs are effective but treatment responses are variable

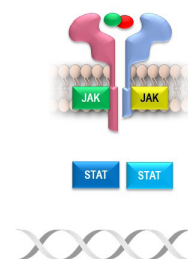


DMARD, disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; tsDMARD, targeted synthetic DMARD; bDMARD, biological DMARD; IL, interleukin; TNF, tumor necrosis factor.
Gottlieb L, et al. *Curr Med Res Opin*. 2011;27(4):697-711; Klearnsing L, et al. *Nat Clin Pract Rheumatol*. 2006;2(8):425-433; Singh JA, et al. *Arthritis Care Res (Hoboken)*. 2016;58(1):1-25; Smolen JS, et al. *Ann Rheum Dis*. 2014;76(8):960-977.

Let's shift our focus now to tsDMARDs and their role in RA; particularly beginning with the physiologic signaling of the JAK/signal transducer and activator of transcription (STAT) pathway. JAK molecules are located within the cell. JAK pairs are associated with a transmembrane receptor that binds to extracellular cytokines, causing a conformational change in the JAK molecules and phosphorylation. That phosphorylation leads to subsequent downstream intracytoplasmic activation of STAT proteins, which then are also phosphorylated in response to the docking cytokines. Following phosphorylation and activation, STAT proteins travel into the nucleus, culminating in the expression of

Physiologic Activities of JAK Molecules JAK/STAT Signaling

- JAKs are nonreceptor protein tyrosine kinases, activated after binding of various cytokines to their receptors
 - JAK1, JAK2, JAK3, and TYK2
- Unphosphorylated STAT proteins are latent cytoplasmic transcription factors
 - Phosphorylation at active type I or type II cytokine–receptor complexes activates specific STAT subsets
 - Family includes 7 STATs (1, 2, 3, 4, 5a, 5b, 6)
- Cytokine-specific control of gene expression



Malemod CJ. *Int J Mol Sci*. 2017;18(3):484.

Hello. I'm a rheumatologist in California and I've been honored to be working with JAK inhibitors for the past 30 years. My clinic manages over 1000 patients with RA and the JAK inhibitors that I will soon present to you are those that I have worked with in my own clinic.



Maria Greenwald, MD, FACR



This slide is a very simplistic representation of all the intricate cytokines and variations. This is my Yahtzee drawing of four JAKs, each one with six STATs. In reality, we now have eight STATs, but I can't find eight-sided Yahtzee dice. In any case, this slide portrays the 1296 possible responses that can occur depending on which cells are affected as well as the epigenetics of the individual person. So, you're not going to be able to substitute JAK inhibitor number 1 for JAK inhibitor number 2, JAK inhibitor number 3, or JAK inhibitor number 4. As we collect more information, we will learn more about the differences among them.

NOT A "ME-TOO" DRUG?



4 types of JAKs and 6 STATs=1296 possible reactions

What we're going to do is evaluate different JAK inhibitors that are currently on the market or very soon to be in your cabinet. The first one approved for RA was tofacitinib, which is considered a pan-JAK inhibitor. It does affect JAK1, JAK2, and JAK3. The other approved drug, baricitinib, tends to be much more JAK1 focused.

Upadacitinib, which was recently FDA approved, is mostly directed towards JAK1, even more strongly than baricitinib. Thus, there is a lot of focus on JAK1. This is because we're trying to get away from some of the side effects. Filgotinib is also directed towards JAK1. Of note, these results reflect in vitro experiments, and we are still in a phase where we are gaining knowledge as physicians.

JAK Inhibitors

Target and Stage of Development for RA

Compound	Primary Target(s)	Stage of Development
Tofacitinib	JAK3/JAK1>>JAK2	Approved by FDA and others at 5 mg BID and XR at 11 mg QD
Baricitinib	JAK1>JAK2	Approved by FDA at 2 mg QD Approved by EMA and others at 2 mg and 4 mg QD
Upadacitinib	JAK1>>JAK3	Approved by FDA at 15 mg QD
Filgotinib	JAK1>>JAK2	Phase 3

FDA, US Food and Drug Administration; EMA, European Medicines Agency; MMA, marketing authorization application; NDA, new drug application; QD, once per day; XR, extended release.
Winthrop, KL. *Nat Rev Rheumatol*. 2017;13(4):234-243; Genovese M, et al. *Arthritis Rheumatol*. 2016;58(12):2857-2866; Westhovens R. *Rheumatology (Oxford)*. 2019;58(suppl 1):i27-i33.

I'm going to summarize these trials, which show clinical research that's been done over the past 10 years with thousands and thousands of patients with RA. We have investigated tofacitinib monotherapy in patients who were resistant or inadequately responsive to csDMARDs or bDMARDs. Other tofacitinib trials include head-to-head comparisons with a tumor necrosis factor inhibitor (TNFi) in methotrexate inadequate responders, therapy in patients who were treatment-naïve, and treatment of inadequate responders who already tried multiple csDMARDs or bDMARDs.

Overall, as we review these different JAK inhibitors, you're going to see they have been investigated in patients who are naïve to treatment as well as those who have been treated previously with a TNFi, methotrexate, or csDMARDs.

Phase 3 Trials of Tofacitinib

Trial	Patient Populations	Treatment Arms
ORAL Solo	csDMARD-IR or bDMARD-IR (≥1 RA drug)	Tofacitinib monotherapy vs placebo
ORAL Standard	MTX-IR	Tofacitinib vs placebo compared to adalimumab (each with background MTX)
ORAL Start	MTX naïve	Tofacitinib vs MTX monotherapy
ORAL Sync	csDMARD-IR or bDMARD-IR (≥1 RA drug)	Tofacitinib vs placebo (each with stable background DMARD therapy)
ORAL Scan	MTX-IR and ≥3 joint erosions	Tofacitinib vs placebo (each with MTX) with radiographic outcomes
ORAL Step	TNFi-IR	Tofacitinib vs placebo (each with MTX)
ORAL Strategy	MTX-IR	Tofacitinib + MTX vs adalimumab + MTX vs tofacitinib

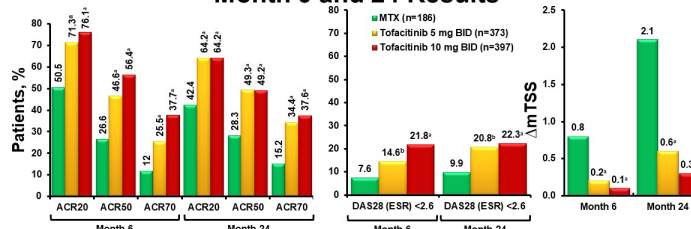
bDMARD-IR, inadequate response to ≥1 bDMARD; csDMARD-IR, inadequate response to ≥1 csDMARD; TNFi-IR, inadequate response to ≥1 TNFi; MTX-IR, inadequate response to MTX. Fleischmann R, et al. *N Engl J Med*. 2012;367(6):495-507; van Vollenhoven RF, et al. *N Engl J Med*. 2012;367(6):508-519; Lee EB, et al. *N Engl J Med*. 2014;370(25):2377-2386; Kremer J, et al. *Annals Intern Med*. 2013;159(4):253-261; van der Heijde D, et al. *Arthritis Rheum*. 2013;55(3):559-570; Burmester GR, et al. *Lancet*. 2013;381(9868):451-460.

This ORAL START trial investigated the efficacy of tofacitinib treatment in methotrexate-naïve RA; these were early patients who had not been treated previously for RA. In these data, the methotrexate arm is represented by the green bar. The first bar graph is ACR 20% improvement criteria (ACR20), ACR50, and ACR70 at 6 and 24 months showing that response continued. The second bar graph is DAS28 at 6 and 24 months, again showing an ongoing response. The green bars represent methotrexate monotherapy, the yellow bars represent the lowest effective dose, 5 mg, of the JAK inhibitor tofacitinib, and the red bars show the 10 mg dose. The 5 mg dose is the approved dose for RA in the US.

ORAL START in MTX-Naïve RA

Tofacitinib vs MTX

Month 6 and 24 Results



*P<0.001 versus MTX; ^aP≤0.05. N=956 patients with active RA and ≥3 radiographic erosions received tofacitinib 5 mg BID, tofacitinib 10 mg BID, or MTX. Primary endpoints: ACR70 at month 6 and ΔmTSS at month 6. ACR, American College of Rheumatology; ACR20, American College of Rheumatology 20% improvement criteria; ACR50, American College of Rheumatology 50% improvement criteria; ACR70, American College of Rheumatology 70% improvement criteria; DAS28, disease activity score-28 joints; ESR, erythrocyte sedimentation rate; mTSS, modified Total Sharp Score. Lee EB, et al. *N Engl J Med*. 2014;370(25):2377-2386.

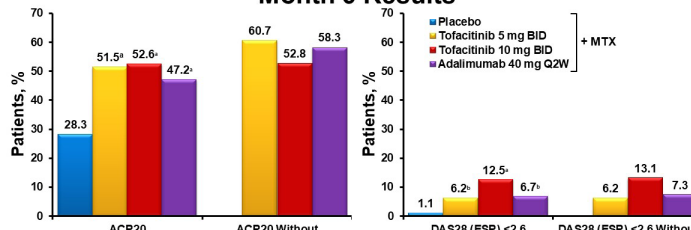
The last bar chart on this slide is the one I like best. You can see with methotrexate monotherapy there were quite a few—more than two—new erosions. However, when the patients were treated with a JAK inhibitor, the van der Heijde modified total Sharp score (mTSS), was significantly smaller. That's going to make a huge difference to patients' lifestyle, work, and play.

Now this ORAL STANDARD slide shows methotrexate inadequate responders and a comparison of treatment with tofacitinib vs the TNFi adalimumab. The yellow bars are the lowest effective dose of the JAK inhibitor, and the purple bars are the TNFi. You can see the effect in terms of ACR20 or the DAS28 are both similar.

ORAL STANDARD in MTX-IR RA

Tofacitinib vs Placebo Compared to Adalimumab

Month 6 Results



*P≤0.001 vs placebo; ^aP≤0.05 vs placebo. N=717 adults with RA and MTX-IR receiving stable MTX dose randomly assigned to tofacitinib 5 mg BID, tofacitinib 10 mg BID, adalimumab 40 mg Q2W, or placebo. Primary endpoints: ACR20 at month 6, HAQ-DI at month 3, and DAS28-4 (ESR) at month 6. HAQ-DI, Health Assessment Questionnaire-Disability Index; Q2W, every 2 weeks. van Vollenhoven RF, et al. *N Engl J Med*. 2012;367(6):508-519.

This slide shows the long-term effects of tofacitinib. Tofacitinib has been approved for more than 7 years. If you look overall from month 1 until about month 96, the response is very good. With respect to approximately 40% of the patients achieving ACR70 at month 96, they were pretty much in remission and maintained for years. We're talking 8+ years. The DAS28, the Health Assessment Questionnaire (HAQ), and the Clinical Disease Activity Index (CDAI) scores show similar benefits. Patients have really excellent responses to tofacitinib.

Long-Term Tofacitinib Efficacy in RA Up to Month 96 in Extension Studies

Tofacitinib (5 and 10 mg BID) ± Background csDMARDs

	Baseline	Month 1	Month 96
ACR Response Rates, %		n=4907	n=163
• ACR20	NA	73.7	77.9
• ACR50	NA	49.9	59.5
• ACR70	NA	29.2	41.7
DAS28 (ESR), Mean	6.32	3.75	3.34
HAQ-DI, Mean	1.42	0.82	0.77
CDAI, Mean vs Baseline	NA	-24.5	-30.7

N=4957 patients treated in the LTE studies (1757 with tofacitinib monotherapy and 3210 with background csDMARDs). NA, not applicable; LTE, long-term extension; CDAI, clinical disease activity index. Wollenhaupt J, et al. *Ann Rheum Dis*. 2018; 77(suppl 2):978.

The trials of baricitinib looked at similar groups of patients—ie, inadequate responders to bDMARDs, inadequate responders to methotrexate only, or those who have been on other csDMARDs without achieving disease control. The BEGIN study investigated early-onset disease. These were patients who hadn't been treated yet. The BEYOND study is a long-term extension of all the other studies. It included the lucky patients who have been on this agent for 10 years and keeps getting extended because we want to see how long patients can go with good results.

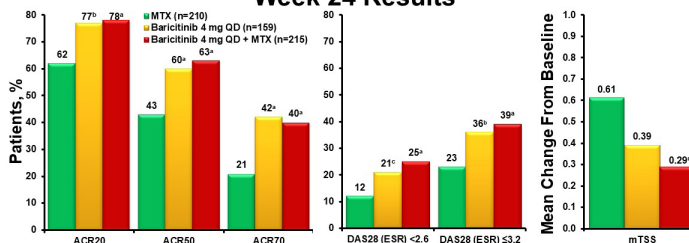
Phase 3 Trials of Baricitinib

Trial	Patient Populations	Treatment Arms
RA-BEACON	bDMARD-IR	Baricitinib vs placebo (each with background csDMARD)
RA-BEAM	MTX-IR	Baricitinib vs placebo or adalimumab (each with background MTX)
RA-BUILD	csDMARD-IR	Baricitinib vs placebo (each with background csDMARD)
RA-BEGIN	bDMARD and csDMARD naïve	Baricitinib vs MTX vs baricitinib+MTX
RA-BEYOND	Completers of previous studies	Baricitinib LTE

Genovese MC, et al. *N Engl J Med*. 2016;374(13):1243-1252; Taylor PC, et al. *N Engl J Med*. 2017;376(7):655-662; Dougados M, et al. *Ann Rheum Dis*. 2017;76(1):88-95; Fleischmann R, et al. *Arthritis Rheumatol*. 2017;59(3):506-517; ClinicalTrials.gov. Identifier NCT01885078. <https://clinicaltrials.gov/ct2/show/NCT01885078>.

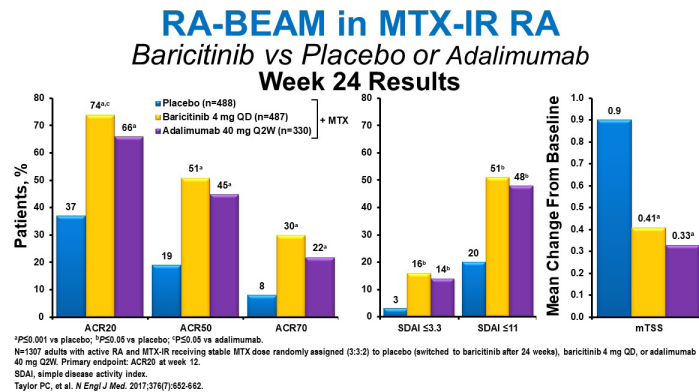
In the BEGIN study of treatment-naïve RA, the green bars are methotrexate monotherapy and the yellow bars are the JAK inhibitor baricitinib at a 4 mg dose. You can see that all the study arms do significantly better than methotrexate alone for ACR20, ACR50, ACR70, and DAS28. For a treatment-naïve patient, baricitinib is really preferred to methotrexate since it seems to double the chances of achieving remission (DAS28-ESR<2.6). With respect to bone damage, far less damage is seen in patients who received the JAK inhibitor compared with those who received methotrexate monotherapy.

RA-BEGIN in DMARD-Naïve RA Baricitinib vs MTX vs Baricitinib+MTX Week 24 Results



*P<0.001 vs MTX; †P<0.01 vs MTX; ‡P<0.05 vs MTX. N=588 patients with RA and no prior csDMARD (≤3 MTX QW doses permitted) and bDMARD randomly assigned to MTX, baricitinib 4 mg QD, or baricitinib 4 mg QD+MTX for 52 weeks. Primary endpoint: ACR20 at week 24. CRP, C-reactive protein; QW, every week. Fleischmann R, et al. *Arthritis Rheumatol*. 2017;59(3):506-517.

If we look at methotrexate inadequate responders in the RA-BEAM study, the blue bar shows that almost 40% of patients showed an ACR20 response to methotrexate. I think patients tend to do better in studies with methotrexate because we're checking them all the time and they get phone calls to make sure they are taking the study drugs; the results are often a little better in studies than in real life. Still, you can see that baricitinib performs better than both methotrexate monotherapy and adalimumab plus methotrexate. The data also show the Simplified Disease Activity Index (SDAI) scores as well, with methotrexate vs baricitinib and adalimumab.



The last graph is again bone loss. Patients on methotrexate monotherapy obviously had more erosions and damage to their cartilage and bone than those who were on either baricitinib or adalimumab.

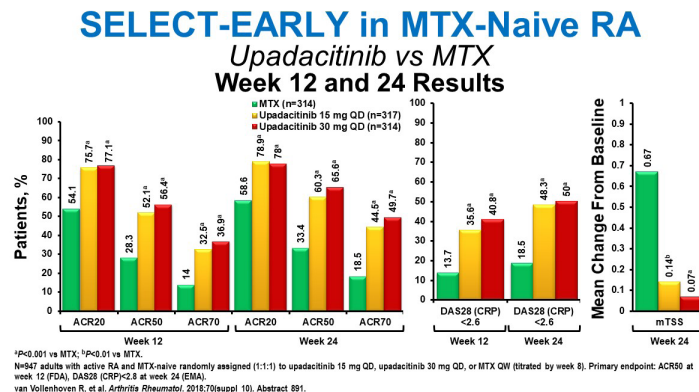
These are trials of upadacitinib, the latest FDA approved JAK inhibitor, which has been studied in the same patient populations: methotrexate inadequate responders, csDMARD nonresponders, new onset disease that hasn't been treated, and bDMARD inadequate responders. One particular trial is called SELECT-CHOICE. It is ongoing and directly compares upadacitinib to abatacept; which is a move away from just looking at comparisons with a TNFi.

Phase 3 Trials of Upadacitinib

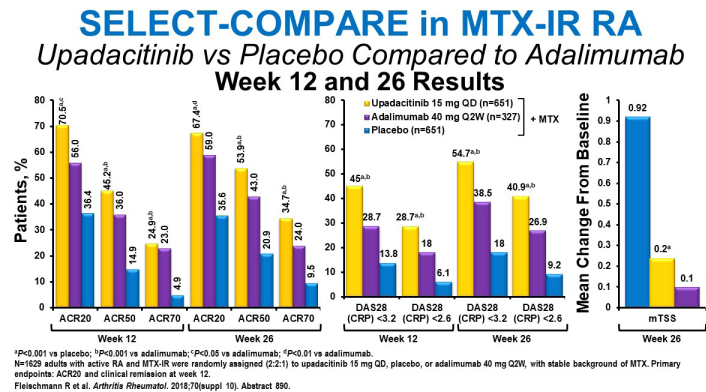
Trial	Patient Populations	Treatment Arms
SELECT-COMPARE	MTX-IR	Upadacitinib vs placebo compared to adalimumab (each with stable background MTX therapy)
SELECT-NEXT	csDMARD-IR	Upadacitinib vs placebo (each with stable background csDMARD therapy)
SELECT-EARLY	MTX-Naive	Upadacitinib vs MTX
SELECT-BEYOND	bDMARD Intolerant/IR	Upadacitinib vs placebo (each with stable background csDMARD therapy)
SELECT-MONOTHERAPY	MTX-IR	Upadacitinib vs MTX
SELECT-CHOICE	bDMARD Intolerant/IR	Upadacitinib vs abatacept (each with stable background csDMARD therapy)

Fleischmann R, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 890; Bermejo GR, et al. *Lancet*. 2018;391(10139):2503-2512; van Vollenhoven R, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 891; Genovese MC, et al. *Lancet*. 2018;391(10139):2513-2524; Smolen JS, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 889; ClinicalTrials.gov. Identifier NCT03086343. <https://clinicaltrials.gov/ct2/show/NCT03086343?term=ABT-494&phase=2>.

Here are the data for SELECT-EARLY in patients with treatment-naïve RA. The green bars are methotrexate only. The yellow bars are the lowest effective dose for the JAK inhibitor upadacitinib. Looking at these data, you will see a series of nice response rates, including 40% to 50% achieving ACR70 at week 24, good DAS28 scores, and preserved bone.



Here we see upadacitinib compared with adalimumab. In this study, all arms included a stable background of methotrexate, so the blue placebo bars are methotrexate monotherapy. You can see methotrexate produce the smallest efficacy responses. Upadacitinib outperformed the TNFi for the ACR20, ACR50, ACR70, and DAS28 data. If you look at bone erosions, there was really no difference between the TNFi group and the JAK inhibitor group.



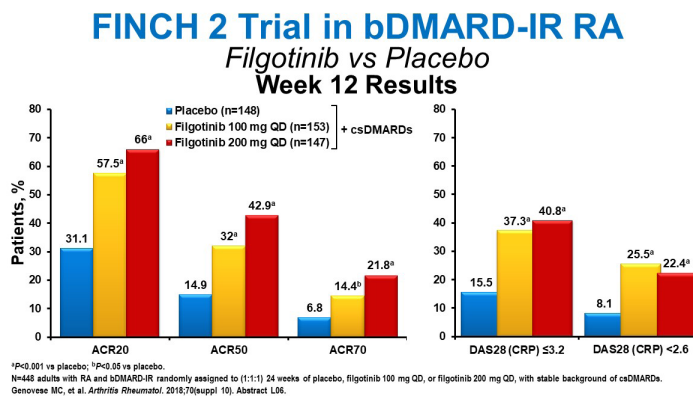
Now, let's look at filgotinib. Its phase 3 trials are fully enrolled, but because filgotinib hasn't been around as long, there aren't as many completed trials. We do have data in methotrexate inadequate responders, bDMARD inadequate responders, and methotrexate-naïve patients.

Phase 3 Trials of Filgotinib

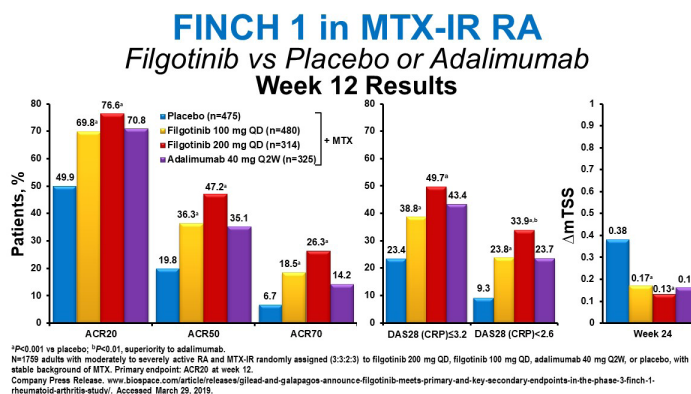
Trial	Patient Populations	Treatment Arms
FINCH 1	MTX-IR	Filgotinib vs adalimumab or placebo (each with background of MTX)
FINCH 2	bDMARD-IR	Filgotinib vs placebo (each with background csDMARD)
FINCH 3	MTX-Naïve	Filgotinib vs filgotinib+MTX vs MTX

Company Press Release. www.biopace.com/article/releases/gilead-and-galapagos-announce-filgotinib-meets-primary-and-key-secondary-endpoints-in-the-phase-3-finch-1-rheumatoid-arthritis-study. Accessed March 29, 2019. Genovese MC, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract L06. Company Press Release. www.nadacq.com/press-releases/gilead-and-galapagos-announce-filgotinib-meets-primary-endpoint-in-the-phase-3-finch-3-study-in-20190328-01138. Accessed March 29, 2019.

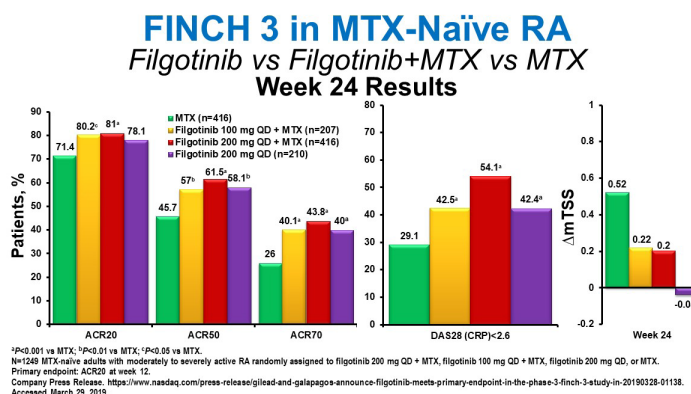
This slide is looking at 12-week data from the FINCH 2 trial in bDMARD inadequate responders. The trial compared any csDMARD, including methotrexate monotherapy to filgotinib with a background of csDMARDs. The yellow bars are the lowest effective dose, 100 mg once daily. The trial showed good responses in ACR20, ACR50, ACR70, and DAS28.



FINCH 1 is a head-to-head trial with adalimumab. You can see methotrexate monotherapy, represented by blue bars, produced an ACR20 in almost 50% of patients; that's a little unusual for real life, but we do see it in studies. Patients on filgotinib are represented by yellow or red bars and the adalimumab arm is purple bars. The takeaway is that JAK inhibitors in several trials are better than or at least not inferior to a TNFi or abatacept. If you look at the bone loss graph on the right, the data are similar to those for the other JAK inhibitors in preventing bone loss.



In methotrexate-naïve patients in the FINCH 3 trial, we see good response rates in terms of ACR20, ACR50, ACR70, and DAS28. In the last graph, we see a fairly high amount of bone loss with methotrexate because these patients have new-onset RA. However, if they were treated with filgotinib, they did very well, meaning it helped maintain both bone and cartilage.



This slide contains some information related to biomarkers and filgotinib treatment. There were many more factors, but I randomly chose a subset to show the effects of this JAK inhibitor. This medication is mostly specific for JAK1, so we're looking at JAK1 inhibition here. Looking at how filgotinib is affecting all these different biomarkers, these data show approximately 20% to 35% inhibition, instead of a complete blockade. If we looked at an anti-IL-6 receptor drug, you will see a >90% blockade of IL-6 signaling. If we use a JAK1 inhibitor, we blunt the IL-6 effect, but we're not cutting it off, which may have implications for safety.

Biomarker Changes With Filgotinib

	CRP	IFN γ	IL-1 β	TNF	MIP-1 β	VCAM-1	Leptin
Placebo	-8	-2	-2	1	0	0	6
Filgotinib	-78 ^a	-21 ^a	-26 ^a	-15 ^a	-7 ^a	-16 ^a	23 ^c
	IL-17A	GM-CSF	SAA	MMP1	MMP3	ICAM-1	VEGF
Placebo	2	0	7	7	-6	0	-2
Filgotinib	-18 ^a	-26 ^a	-67 ^a	-26 ^a	-43 ^a	-14 ^a	-26 ^a
	IL-23	IL-7	IL-12	IL-21	IL-2	YKL-40	IL-6
Placebo	-6	1	0	0	-7	-7	-20
Filgotinib	-25 ^a	-17 ^a	-24 ^a	-28 ^b	-20 ^b	-33 ^a	-63 ^a

Filgotinib reduces the levels of multiple markers of inflammation.

^aP<0.001; ^bP<0.01; ^cP<0.05.
ICAM-1, intercellular adhesion molecule 1; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; YKL-40, chitinase-3-like protein 1; SAA, serum amyloid A. Serum samples from RA patients who received either placebo, filgotinib 100 mg QD, or filgotinib 200 mg QD, and stable background of MTX, were collected at baseline. The median change of 50 soluble serum biomarkers was analyzed at week 12 for placebo (n=71) and filgotinib 200 mg QD (n=75).
Taylor P, et al. *Annals Rheum Dis*. 2017;76:281-282.

The next section covers safety and monitoring of JAK inhibitors in RA.



With respect to long-term safety, I was personally very concerned back in 2004-2005 during tofacitinib phase 1 studies. We put 20 patients on a JAK inhibitor and within 3 months, 4 of these patients had shingles. I had never seen an incidence rate like that in clinic before. We did not have vaccines. I called US Food and Drug Administration (FDA), the Institutional Review Board, and the study sponsor and I told them I was concerned. Now, however, it makes a certain amount of sense considering how JAK1 and JAK3 inhibition affects IFN signaling. Since we are directly interfering with the IFN-mediated protective mechanism against shingles in our body, we release the virus. However, if we vaccinate these patients, the risk of herpes zoster decreases drastically. In our experience, events of herpes zoster after vaccination are extremely rare: 2 cases in 1000.

In these tofacitinib data, we see an incidence rate of herpes zoster of about 3.5 to 4.0 per 100 patient-years. While everybody is always concerned about tuberculosis, I want you to check for herpes zoster. Tuberculosis (TB) is very rare in the US. So, although it's in every black box warning and every insurance form says to check for TB, I want you to also check for vaccines: flu, pneumonia, and herpes zoster. You will save a lot more lives. Mortality risks are very low with these drugs, and malignancy risks are low.

The long-term baricitinib studies include 6 years of safety data. The instance of herpes zoster is 3.3 per 100 patient-years.

Long-Term Tofacitinib Safety Incident Rates Using 8.5 Years of Clinical Trial Data

	All Tofacitinib Doses	Average Tofacitinib 5 mg BID ^a	Constant Tofacitinib 5 mg BID ^b
Total patient-years of exposure	19,406	6870	3623
• Serious (n=527) ^c	2.7	3.1	2.3
• HZ (n=703)	3.9	3.8	3.5
• Opportunistic, not TB (n=61)	0.3	0.4	0.2
• TB (n=36)	0.2	0.1	0.08
• Mortality (n=23)	0.1	0.2	0.2
• Malignancy, not NMSC (n=173)	0.9	1.0	0.8
• NMSC (n=118)	0.6	0.5	0.4

^aAverage dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the 5 mg twice daily group, patients receiving ≥15 mg/day were assigned to the 10 mg BID group. ^bConstant dosing without prior exposure to another tofacitinib dose or adalimumab during study, patients who switched doses not included. ^cRequired hospitalization or parenteral antimicrobial therapy, otherwise meeting SAE criteria. N=6194 patients received tofacitinib 1, 3, 5, 10, 15, or 30 mg BID or 20 mg QD, as monotherapy or with background DMARDs, data pooled from patients with RA treated with tofacitinib in phases 1 to 3 and LTE studies. NMSC, non-melanoma skin cancer; SAE, serious adverse event; TB, tuberculosis. Cohen SB, et al. *Ann Rheum Dis*. 2017;76(7):1253-1262.

Long-Term Baricitinib Safety Up to 6 Years of Safety Data

Baricitinib (2 mg or 4 mg QD) ± csDMARD

Safety	All-bari-RA (N=3492)
Total patient-years of exposure	7860
Serious TEAEs	231 (3.0)
Infections, n (IR)	
• HZ	258 (3.3)
• TB	11 (0.14)
Malignancy—excluding NMSC, n (IR)	63 (0.8)
Deaths, n (IR)	28 (0.35)

N=3492; "all-bari-RA" dataset included all patients with active RA exposed to any baricitinib dose from 8 randomized trials (four Phase 3, three Phase 2, one Phase 1b) and 1 LTE study (data up to April 1, 2017). IR, incidence rate per 100 patient-years; bari, baricitinib; TEAE, treatment-emergent adverse event. Genovese MC, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 962.

In filgotinib studies, herpes zoster looks particularly low. It may have to do with community vaccination. We now vaccinate everybody. So, if you're going to put your patients on a JAK inhibitor, I want you to think about vaccines. Additionally, if you treat a patient with corticosteroids, your responsibility as the physician is to think about their bones. Do they have calcium? Do they need vitamin D? Do they need alendronate?

The other issue I want to bring up is serious infections. Serious infection rates are always in the 1% to 2% range with almost all biologics as well as JAK inhibitors. Pneumonia, in particular, predominates. It's the one adverse event that really sends people to the hospital. So, think about the pneumococcal vaccine; it won't solve everything, but it will help!

Filgotinib Safety FINCH 1, 2, and 3

	Placebo/ csDMARD n=1039 No. (%)	Adalimumab 40 mg Q2W + MTX n=325 No. (%)	Filgotinib 100 mg + MTX/csDMARD n=840 No. (%)	Filgotinib 200 mg + MTX/csDMARD n=1038 No. (%)	Filgotinib 200 mg n=210 No. (%)	Filgotinib Total n=2088 No. (%)
Serious infections ^a	10 (1.0)	8 (2.5)	13 (1.5)	13 (1.3)	3 (1.4)	29 (1.4)
Herpes zoster ^a	4 (0.4)	2 (0.6)	5 (0.6)	6 (0.6)	1 (0.5)	12 (0.6)
DVT/PE ^a	3 (0.3)	0 (0)	0 (0)	1 (0.1) ^c	0 (0)	1 (<0.1)
Death ^b	2 (0.2)	0 (0)	1 (0.1)	3 (0.3)	0 (0)	4 (0.2)
Malignancy excluding NMSC ^a	4 (0.4)	1 (0.3)	1 (0.1)	0 (0)	0 (0)	1 (<0.1)
MACE ^a	5 (0.5)	1 (0.3)	2 (0.2)	2 (0.2)	1 (0.5)	5 (0.2)

^aTreatment-emergent events. ^bAll events. ^cExcludes one retinal vein occlusion. DVT, deep vein thrombosis; MACE, major adverse cardiac event; PE, pulmonary embolism. Company Press Release. <https://www.gilead.com/newsroom/news-releases/2019/03/28/1788015/0/en/gilead-and-galapagos-report-updated-safety-information-for-filgotinib-in-rheumatoid-arthritis-ra.html>. Accessed March 29, 2019.

If we look at laboratory changes, I think I can tell these 4 JAK inhibitors apart. It's always blinded to me, but we can get a sense from looking at the labs. If you see both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) elevated—which you will—they usually elevate in different fashions. For example, the HDL levels are often over 100 mg/dL with upadacitinib. If I'm looking at the labs and I see that a patient has an HDL of 126 mg/dL, I can guess which JAK inhibitor they're on. You will see variations.

Also, hemoglobin levels with filgotinib can go up markedly. You'll have a patient that begins at a 10 or 11 g/dL hemoglobin level, you start them on filgotinib, and 6 weeks later their hemoglobin is 12.5 g/dL. They look pretty normal and it seems a bit confusing when you realize JAK2 inhibitors would wipe that out. Filgotinib, however, is a JAK1 inhibitor, and that doesn't happen.

Laboratory Changes With JAK Inhibitors Mean Changes in Lab Parameters

	Tofacitinib	Baricitinib	Upadacitinib	Filgotinib
Targets	JAK1/JAK3 >> JAK2	JAK1>JAK2	JAK1>>JAK3	JAK1>>JAK2
Lymphocyte number	↓	No change	↓	No change
NK cell number	↓	↓	↓	No change
Neutrophil number	↓	↓	↓	↓
Hemoglobin level	↓	↓	↓	↑
Platelet count	↓	±	±	↑
Liver transaminase level	↑	↑	↑	No change
Creatine phosphokinase level	↑	↑	↑	NA
HDL level	↑	↑	↑	↑
LDL level	↑	↑	↑	↑
Creatinine level	↑	↑	↑	↑

NA, not available; NK, natural killer. Winthrop KL, et al. *Arthritis Rheumatol*. 2017;69(10):1969-1977. Kavanaugh A, et al. *Annals Rheum Dis*. 2017;76(6):1009-1019.

In terms of HDL and LDL, this slide is extremely simplistic. Peficitinib, a pan-JAK inhibitor, produces changes in HDL and LDL that are small and fairly similar. However, with upadacitinib, as I told you, you tend to see much larger effects on HDL and the LDL goes up as well. We do know that the efficiency of the way HDL works has a huge impact on circulation, heart disease, and stroke. So, looking at this slide may be helpful in that respect.

Lipid Abnormalities With JAK Inhibitors^a Are These Differences Relevant?

Inhibitor	Target	Serum HDL (mg/dL)		Serum LDL (mg/dL)	
		Change	% Change	Change	% Change
Peficitinib ^b	JAK1/JAK2/ JAK3/TYK2	+4.3	4.9	+2.0	9.7
Tofacitinib ^c	JAK1/3>>2	+7.7	10	+18.0	15
Baricitinib ^d	JAK1>2	+8.8	8	+20	24
Filgotinib ^e	JAK1>>JAK2	+7.3	11.5	+14.7	13.5
Upadacitinib ^f	JAK1>>JAK3	+11.7	19	+19.5	17
Tocilizumab ^g	IL-6 receptor blocker	+4		+25	

^aThese are separate reports with no direct comparison and no statistical analysis. ^b150 mg/d; ^c10 mg/d; ^d4 mg/d; ^e200 mg/d; ^f15 mg/d; ^g18 mg/d. Genovese MC, et al. *Arthritis Rheumatol*. 2017;69(5):933-942. Xeljanz [prescribing information]. New York, NY: Pfizer Labs.; 2016. Genovese MC, et al. *N Engl J Med*. 2016;374(13):1243-1252. Kavanaugh A, et al. *Ann Rheum Dis*. 2017;76(6):1009-1019; Kremer JM, et al. *Arthritis Rheumatol*. 2016;68(12): 2867-2877; Actemra [prescribing information]. San Francisco, CA: Genentech, Inc.; 2016.

The big concern during the last couple of months has been deep vein thromboses (DVT) and pulmonary embolism (PE). All studies using tofacitinib 10 mg BID have been stopped. I was given 24 hours to contact every patient to make sure that we got them off the higher dose. Not because it suddenly became dangerous after 8 years, but because the FDA was concerned. PE has been reported in 45 unique patients on tofacitinib, and some cases have been fatal. One of the fatalities was a 36-year-old woman. Pulmonary thrombosis has also been reported in 19 unique patients on tofacitinib. These are all unique cases; they are not the same patient experiencing another venous thromboembolism (VTE). Similarly, PE and thrombosis have been reported in postmarketing cases with ruxolitinib, the first JAK inhibitor approved in 2009 for myelofibrosis or polycythemia vera. With respect to ruxolitinib, 55 cases of PE and 9 cases of pulmonary thrombosis have been reported, including some leading to death.

The increased risks have now been reported in ruxolitinib, baricitinib, and tofacitinib with mechanisms unknown.

The tofacitinib 10 mg BID dose has been dropped for all diseases outside of ulcerative colitis. In general, the advice we've been given is to use the lowest effective dose. I believe there is going to be a black box warning for VTE and PE. This VTE issue is even more important than TB because TB is something for which you can screen. VTE is harder to anticipate.

DVT and Pulmonary Embolism

February 2019 Federal Reporting^a

- Pulmonary embolism
 - Reported in 45 unique patients on tofacitinib, some fatal
- Pulmonary thrombosis
 - Reported in 19 unique patients on tofacitinib
- Similar PE and thrombosis with ruxolitinib (55 and 9 cases)
- Increases in thromboembolism and PE
 - Reported for ruxolitinib, baricitinib, and tofacitinib
 - Mechanism unknown
- Tofacitinib 10-mg BID dose dropped from phase 4 studies
 - IR >0.4 for tofacitinib and <0.1 for TNF inhibitor

Black box: Thrombosis, including DVT, PE, and arterial thrombosis, have occurred during baricitinib treatment, sometimes fatal; promptly evaluate patients with thrombosis symptoms.

^aThe specific cases are reported by the FDA in the FDA Adverse Event Reporting System. FDA. Safety Report. Published February 25, 2019. <https://www.fda.gov/Drugs/DrugSafety/ucm631871.htm>. Accessed February 2019.

Pregnancy outcomes should be discussed. For women between the ages of 20 and 35 years, the rheumatologist should ask about reproductive plans. "Do you want to get pregnant this year?" Certain csDMARDs and bDMARDs have been shown to be safe during pregnancy, so it's a very reasonable question.

Tofacitinib data show that it clearly crosses the placenta. It also crosses into breast milk. In animal studies, tofacitinib has been shown to be teratogenic and to decrease fertility. Forty-seven cases of patients with either RA or psoriasis who were not planning pregnancy but became pregnant were followed. During the exposure, 25 healthy newborns, 7 spontaneous abortions, and 1 congenital malformation—a pulmonary valve stenosis—were reported. We do not have information on the other 14 cases; either lost to follow-up or otherwise. I cannot say that tofacitinib is safe and I would not recommend it to someone planning pregnancy. In Europe and Australia, it's classified as category D; you should stay away from this agent in someone who is planning to get pregnant.

Pregnancy Outcomes

Insights from Tofacitinib

- Potential to cross the placenta
- Reduced number of viable animal fetuses and fetal body weight with tofacitinib 146 × and 13 × greater than 5-mg BID
- 47 cases of RA and psoriasis (N=9815) with maternal exposure in clinical development program were followed
 - Healthy newborns: 25
 - Fetal death: 0
 - Spontaneous abortions: 7
 - Medical terminations: 8
 - Congenital malformations: 1 (pulmonary valve stenosis)
 - Pending/Lost to follow-up: 6
- Class D

Ciowase ME, et al. Drug Saf. 2016;39(8):755-762. Xeljanz [prescribing information]. New York, NY: Pfizer Labs.; 2018.

In summary, we do see neutropenia with all the JAK inhibitors. With most of them, we see lymphopenia and hemoglobin changes. One JAK inhibitor causes hemoglobin to go up and in others it goes down. Lipid changes do occur with all JAK inhibitors but vary according to the agent. Liver function tests change minimally. I've never had to take a patient off a JAK inhibitor for liver function abnormalities. With respect to increases in creatinine, I've also never had to change treatment. Data show an approximate 0.1 mg/dL change in creatinine, so if your patient begins at 0.8 mg/dL, you might end up at 0.9 mg/dL over the course of 8 years. It's not like you're dealing with nonsteroidal anti-inflammatory drugs (NSAIDs).

I also want to mention that creatine phosphokinase levels can rise but no reports have been symptomatic. Patients have an incredibly fast response to these JAK inhibitors. I have just shown you 12 weeks, 6 months, and 2 years of data. In the first week, patients feel remarkably better—very similar to your giving the patient a dose of prednisone.

We should also think about decreased male and female fertility. The FDA has mandated a study, counting sperm and looking at motility for some of the patients on JAK inhibitors because it may interfere with male spermatogenesis. There's also evidence of teratogenicity in animals.

Summary of Safety Findings Potential Adverse Events Associated With JAK Inhibitors

- Neutropenia (class effect)
- Lymphopenia
- Hemoglobin changes
- Lipid changes (class effect)
- LFT changes
- Increased creatinine (class effect)
- Decreased male/female fertility
- Teratogenicity
- DVT and PE
- HZ

Winthrop KL. *Nat Rev Rheumatol*. 2017;13(4):234-243.

These safety concerns are what we see with almost any of our disease-modifying agents. We need to be vigilant about vaccinating our patients and watching out for serious infection. We also need to protect our patients from the potential consequences of anemia, elevated liver enzymes, and possibly now VTE. These events are fairly rare. Frequently, it's the same as what you would expect with bDMARDs or what you see in RA in general. We closely monitor patients for signs or symptoms. There is a 2- to 3-fold greater risk of herpes zoster in patients treated with either tofacitinib or baricitinib. With vaccination, those numbers are coming down drastically.

Herpes zoster vaccination is recommended for all patients over 50. Ideally, vaccinate 4 weeks before you start the JAK inhibitor. That can be difficult if your patient is in pain or if they cannot perform activities of daily living. Use your best judgment. If you can, it's good to wait. We have a live vaccine as well as an inactivated recombinant, adjuvanted vaccine available.

The last thing I want to say about safety and efficacy is that I think these data are marvelous. If you look at how many patients with RA were on steroids in the year 2000, it's about 66%. Now, when you look at these long-term studies, how many of these patients are still on steroids today? In the patients on JAK inhibitors, it's less than 22%. We've taken away the need for prednisone. I haven't seen numbers for prescription opioids, but none of my patients require these drugs and we're not using much NSAIDs. When I see patients for the first time, they all walk in on high-dose NSAIDs and you're trying to make them wait 30 days for the vaccine to kick in. I don't need NSAIDs now. We've eliminated a lot of the major risks we were exposing patients to and now are looking for very rare events. I am now going to turn it over to my colleague Dr. Roy Fleishmann.

JAK Inhibitor Monitoring

- Safety concerns include serious infection, neutropenia, anemia, elevated liver enzymes and possibly VTE
 - Similar in nature and frequency to those associated with bDMARDs, especially IL-6R inhibitors
 - Closely monitor patients for signs/symptoms of infection during and after treatment
- 1.5- to 2-fold greater risk of HZ in patients treated with either tofacitinib or baricitinib compared with other patients with RA
 - HZ vaccination is recommended for patients 50 years and older, 2 to 4 weeks prior to starting treatment with tofacitinib 5 mg or 10 mg BID
 - Two types of vaccines available: live and recombinant (avoiding use of live is recommended)

Monitoring Recommendations	Lipids	Liver Enzymes	CBC with Differential	TB
Tofacitinib	4-8 weeks following initiation	Routine monitoring	Evaluate at baseline, 4-8 weeks after initiation, and every 3 months thereafter	Prior to administration
Baricitinib	12 weeks following initiation	Evaluate at baseline and thereafter according to routine patient management	Evaluate at baseline and thereafter according to routine patient management	Prior to administration
Upadacitinib	Evaluate at baseline and thereafter as clinically indicated	Evaluate at baseline and thereafter as clinically indicated	Evaluate at baseline, 4-8 weeks after initiation, and every 3 months thereafter	Prior to administration

Winthrop KL. *Nat Rev Rheumatol*. 2017;13(4):234-243; Scott IC, et al. *Drug Saf*. 2018;41(7):645-653; Winthrop KL, et al. *Arthritis Rheumatol*. 2017;69(15):1969-1977; Xeljanz [prescribing information]. New York, NY: Pfizer Labs.; 2018; Olumiant [prescribing information]. Indianapolis, IN: Lilly USA, 2018; Rinvoq [prescribing information]. Chicago, IL: AbbVie Inc., 2019.

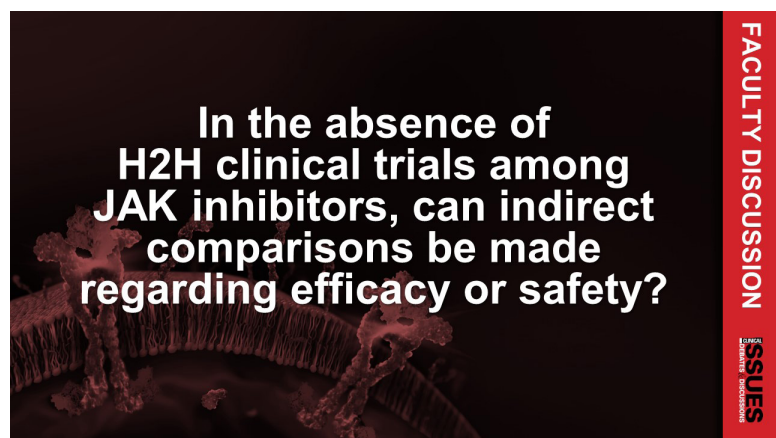
I'm going to talk about guidelines and then we'll take a look at how we can use them.



First, is there a difference between the JAK inhibitor drugs clinically?

Well, the data will actually speak to the differences. These JAK inhibitor drugs can work within a week, which is important. When you look at the trials that Dr. Greenwald discussed, we know that upadacitinib 15 mg once daily (QD) plus methotrexate is superior to adalimumab plus methotrexate clinically and functionally and is equivalent radiographically.

We know that baricitinib 4 mg QD plus methotrexate is superior to adalimumab, clinically, functionally, and radiographically. We don't know about the 2 mg dose because that wasn't tested in that study. I will shortly show the trial in which tofacitinib was equivalent to adalimumab plus methotrexate. In topline results from FINCH 1, the 100 mg QD dose of filgotinib, looks like it was noninferior to adalimumab.



So, Dr. Kremer, can we conclude that one JAK inhibitor is more effective than another?



**Joel Kremer,
MD, FACP**

We don't have enough data to answer that definitively. First of all, we all know that it's inappropriate to compare data from different randomized controlled trials. So, as an investigator who has studied all these drugs, I don't have enough overall data on any drug to make an informed, defensible decision on which one is better, worse, or equivalent.



**Roy Fleischmann,
MD, MACR**

Right. I think that is the key point. The key point is that no matter what we say about each one of the JAK inhibitors, because there are no head-to-head trials comparing them directly, we can't say one is better than the other. We can say that they're probably at least equal to a TNFi, but we cannot say one is better than the other.

Now let's talk about the practicalities of how we treat, how we should treat, or how we could treat and the guidelines that are intended to inform these practices.

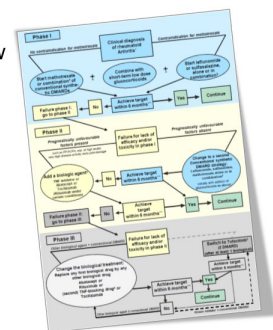


We know that 30% of patients are treated with methotrexate monotherapy and they really achieve very good levels of disease activity. Methotrexate is cheap and it should be used first. There's no question about that.

After methotrexate failure, we really don't have enough information to decide which option is best. Is it triple therapy? Or is it use of a biologic or is it use of a tsDMARD? Those decisions are based on comorbidities, contraindications, patient preference, physician preference, and patient access. We don't have predictive markers. Dr. Kremer expects that we'll have them within the next 10 years. I hope he's right because we do need predictive markers. We do have recommendations. We have recommendations from Europe, and we have guidelines from the US.

Sequencing DMARDs

- Approximately 30% of patients achieve low disease activity with MTX monotherapy
- No established sequence for selecting therapies after MTX failure
 - Therapeutic decisions are often based on comorbidities and contraindications
 - Predictive response markers are not available
- ACR/EULAR recommendations suggest bDMARDs or tsDMARDs as possible second-line options



EULAR, European League Against Rheumatism. van Vollenhoven RF, et al. *Lancet*. 2009;374(9688):459–466; Singh JA, et al. *Arthritis Care Res (Hoboken)*. 2016;58(1):1–25; Smolen JS, et al. *Ann Rheum Dis*. 2017;76(6):960–977.

Let's take a look at those from the US.



The ACR decided to use the GRADE process. It's a process that includes: 1) a core leadership team that decides what questions they want to ask, 2) a literature review team—not rheumatologists—who review the literature to back up the questions, 3) a content panel that may include rheumatologists who do not see patients, and 4) a voting panel of practicing rheumatologists who do see patients.

The GRADE Process

- ACR used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology
- Core leadership team supervised project and was responsible for defining scope, drafting clinical questions, coordinating literature review, and drafting manuscript
 - Composed of methodologists and experts in guideline development
- Literature review team conducted literature review, graded evidence, developed summary of findings tables, and produced evidence report
 - Composed of 3 MDs (nonpracticing), 3 BAs and 1 MLS
- Content panel reviewed and provided feedback on clinical questions and evidence report
 - Composed of 4 MDs (2 practice)
- Voting panel voted on final recommendations
 - Composed of rheumatologists and 2 patients

BA, Bachelor of the Arts; MLS, Master of Library and Information Science.
Guyatt GH, et al. *BMJ*. 2008;336(7660):924-925; Andreu JC, et al. *J Clin Epidemiol*. 2013;66(7):719-735.

They come up with a strong recommendation or conditional recommendation. This slide shows the definitions of what is strong and what is conditional.

Strength of Recommendations

	Strong Recommendation ^a	Conditional Recommendation ^b
Patients	Most people in your situation would want the recommended course of action, and only a small proportion would not	The majority people in your situation would want the recommended course of action, but many would not
Clinicians	Most patients should receive the recommended course of action	Be prepared to help patients make a decision that is consistent with their own values
Policy Makers	The recommendations can be adopted as a policy in most situations	There is a need for substantial debate and involvement of stakeholders

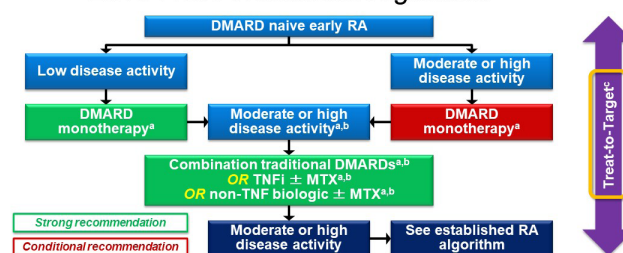
^aPanel is very confident that benefits of intervention for outweigh the harms (or vice versa); ^bDenotes uncertainty over the balance of benefits and harms, such as when the evidence quality is low or very low, or when patient preferences or costs are expected to impact the decision.
Singh JA, et al. *Arth Rheumatol*. 2016;68(1):1-26.

This is the 2015 ACR treatment sequence for early RA, which the ACR defines as less than 6 months of disease. The literature team provided evidence at that time, and strong evidence suggested that the first drug you should use for DMARD-naïve patients is tofacitinib; not methotrexate. Tofacitinib beat methotrexate head-to-head. If you show that it beats a drug head-to-head, that's the best evidence you have.

When this evidence went to the voting panel, the panel stated that tofacitinib was more expensive. We have so much experience with methotrexate and it works 30% of the time. Thus, methotrexate was selected and that's what we use today. We use csDMARD monotherapy, usually methotrexate. If that doesn't work, the panel decided a TNFi plus or minus methotrexate should be next, even though most TNFi drugs don't work really well without methotrexate. You can use a non-TNF biologic plus or minus methotrexate, although we know that all biologics work much better with methotrexate. What you don't see here is JAK inhibitors. In 2015, there were only 3 years of knowledge for tofacitinib. It had only been approved for 3 years. It had only been in development for about 6 years. We didn't know enough about it, so it wasn't included.

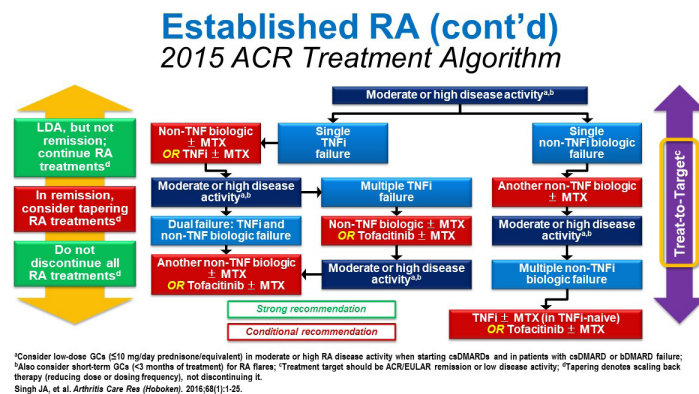
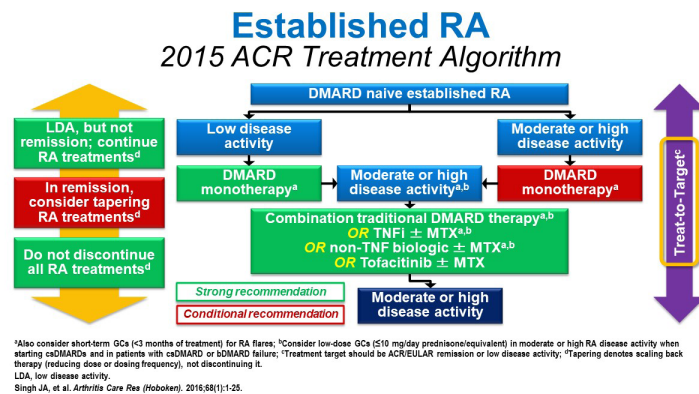
You can see the green boxes are strong recommendations; the red box is a conditional recommendation. If a patient still doesn't respond, they've failed methotrexate and will be considered as having established RA. What do you do?

Early RA 2015 ACR Treatment Algorithm



^aAlso consider short-term GCs (<3 months of treatment) for RA flares; ^bConsider low-dose GCs (≤10 mg/day prednisone/equivalent) in moderate or high RA disease activity when starting csDMARDs and in patients with csDMARD or bDMARD failure; ^cTreatment target should be ACR/EULAR remission or low disease activity.
GC, glucocorticoid.
Singh JA, et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-26.

Here, you can use TNFi, or you can use a non-TNF, or now you can use tofacitinib plus or minus methotrexate. Still treat-to-target and if you get into low disease activity (LDA), but not remission, don't stop treatment. LDA is still active disease. If you're in remission, consider tapering, but don't stop treatment. Do not discontinue all treatments. If the patient doesn't respond to the first biologic or tsDMARD, what do you do next? You just keep switching until you find the one to which the patient responds.



Here's a summary of the ACR guidelines. For moderate or high disease activity, there's no recommended preference for the DMARD. Use TNFi monotherapy before tofacitinib monotherapy—which I do not support—or use a TNFi plus methotrexate over tofacitinib plus methotrexate—which I also do not support. The reason behind these recommendations was a lack of experience with tofacitinib at that time.

If a patient still has moderate or high disease activity despite csDMARD monotherapy, then you can use another csDMARD or a TNFi or another biologic or tofacitinib. If there is still moderate-to-high disease despite a prior TNFi, then use a non-TNF. They are suggesting if patients fail a TNFi then you should try an agent with a different mechanism of action or tofacitinib, with no recommended preference.

ACR recommends a treat-to-target approach, regardless of the RA activity level.

Summary 2015 ACR RA Guidelines^a

1. Moderate-to-high disease activity despite DMARD monotherapy
 - a. No recommended order of preference for next DMARD
 - b. Use TNFi monotherapy before tofacitinib monotherapy **OR** use TNFi + MTX over tofacitinib+MTX (**because of lack of experience with tofacitinib in 2015**)
2. Moderate-to-high disease activity despite prior TNFi
 - a. Use non-TNF bDMARD before another TNFi or tofacitinib (± MTX) [≈ reason]
 - b. No recommended order of preference for next bDMARD

Use treat-to-target approach regardless of RA activity level.

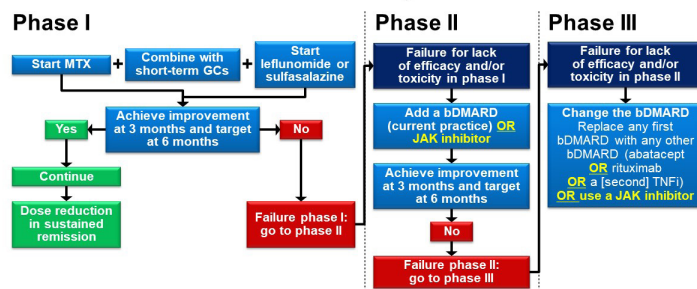
^aPublication of updated guidelines anticipated in late 2019/early 2020. Singh JA, et al. Arthritis Rheumatol. 2016;68(1):1-25.

What does EULAR say? EULAR is easier.



EULAR says you start methotrexate, unless you are in Romania, then you have to start leflunomide or sulfasalazine. If you reach your target, then you're good. If you don't, you move on to phase 2. Phase 2 adds a biologic or a JAK inhibitor; you can choose one or the other. If you achieve your target, then you're good. If not, phase 3 changes the treatment until you get to your target.

2016 EULAR RA Guidelines Summary



Smolen JS, et al. *Ann Rheum Dis*. 2017;76(6):960-977.



Participant

Dr. Kremer published a paper years ago combining methotrexate and leflunomide. Is that still an option?



Joel Kremer,
MD, FACP

Yes, I use it, but I think you have to be very careful. There have been deaths reported with that combination, so when you combine, you really need to look at LFTs weekly. We look at LFTs weekly with that combination for the first 6 to 8 weeks, and if you're in the normal range, you're in good shape. I personally use it, but

I think it's understandably fallen into some disfavor because you really can get significant hepatotoxicity unless you're monitoring carefully. You wouldn't put patients on those 2 drugs and say I'll see you in 3 months.

You can also see cytopenia as well. You need to monitor the drugs carefully and frequently in the beginning and select a patient who will tolerate the drugs and do well.



Roy Fleischmann,
MD, MACR

Your patients are in remission with that combination?



Joel Kremer,
MD, FACP

I get patients in Boolean remission with that combination.



Participant

Not everybody's insurance will approve expensive medications for RA.



Roy Fleischmann,
MD, MACR

That's the key. If you have a patient who has access issues, then you can use those kinds of combinations. Let's move forward to a summary of the recommendations.

The methotrexate dose should be optimized. ACR also suggests that you use steroids, particularly in the beginning and for flares. Treatment modification should be done every 3 months until you reach your target, not in 6 months, not in 12 months. The goal is remission.

Summary of Recommendations 2015 ACR and 2016 EULAR

- MTX dose should be rapidly optimized for maximum benefit
- Recommend low-dose GCs at inception of DMARD therapy and for flares
- Early treatment modification should be made early during course, 3 to 6 months, if disease control not achieved
 - Modifications include increase of csDMARDs, addition of bDMARD, or addition of JAK inhibitor
 - Following MTX-IR or failure, addition of bDMARD or JAK inhibitor is superior to adding another csDMARDs
 - Early response to bDMARD or JAK inhibitor predict higher remission/LDA rates and long-term benefits

Singh JA, et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25; Smolen JS, et al. *Ann Rheum Dis*. 2017;76(6):960-977.



Participant



Roy Fleischmann,
MD, MACR

How do you define remission?

I use CDAI remission, SDAI remission, or Boolean remission. That's the goal. It's not low disease activity.

Make early medication modifications, including increased doses of csDMARDs or the addition of a biologic or a JAK inhibitor. The BEST study showed that the combination of methotrexate and leflunomide doesn't really add that much to methotrexate. It does to some extent, but more patients will go into remission with a bDMARD or tsDMARD.

Following methotrexate failure, the addition of a biologic or JAK inhibitor is superior to adding another csDMARD in patients who can afford it. An earlier response to a biologic or JAK inhibitor predicts higher remission and LDA rates, less patient problems, and long-term benefits.

If patients cannot tolerate csDMARDs, such as methotrexate, and they have to be treated with monotherapy, the best drugs are an anti-IL-6 receptor biologic or a JAK inhibitor.

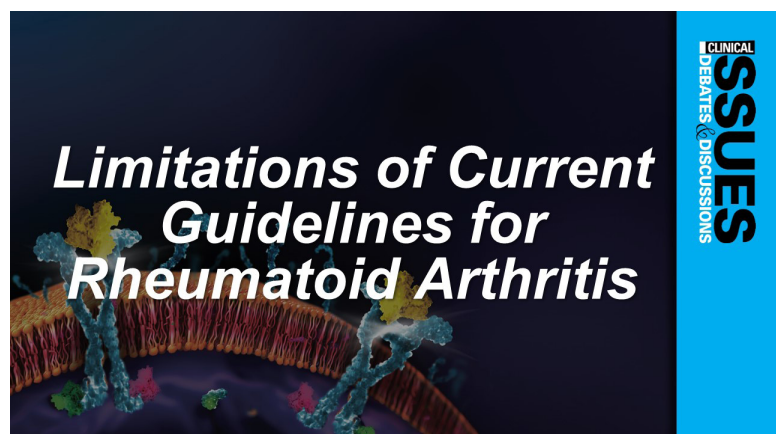
Virtually every JAK inhibitor has been shown to be superior to methotrexate as monotherapy.

Summary of Recommendations 2015 ACR and 2016 EULAR (cont'd)

- If patients cannot tolerate csDMARD, ie, MTX, and they will be treated with monotherapy, use of IL6 inhibitor or JAK inhibitor over other bDMARDs
 - ~1/3 of US patients are on monotherapy with bDMARD or tofacitinib

Singh JA, et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25; Smolen JS, et al. *Ann Rheum Dis*. 2017;76(6):960-977; Detert J, et al. *Biologics*. 2015;9:35-43.

Let's discuss the limitations of current guidelines.



What are the limitations of the ACR publication? A guideline is a rule or instruction, developed by the GRADE method. The strong ACR recommendations, however, may have a low level of evidence. Cost is also considered, which does not necessarily agree with the best risk:benefit profile for the patient. There's lack of face validity—the degree to which guidelines are effective in terms of their stated aims—in certain situations. Most experienced rheumatologists use what they've learned in practice, what they've heard, what they've read, and what they've seen in patients to make their decisions. They don't necessarily follow the ACR guideline all of the time.

Limitations of 2015 ACR RA Guidelines

- **Guideline: A rule/instruction that shows or tells how something should be done**
- **Recommendation:** The act of saying that someone or something is good and deserves to be chosen; a suggestion about what should be done
- **ACR guidelines:**
 - Developed with the GRADE methodology, based on peer-reviewed evidence published ≤2 years before the publication
 - There are strong recommendations with low-level of evidence and conditional recommendations with high-level evidence
 - Cost is considered (not necessarily the medication with the best risk:benefit profile)
 - Lack of face validity in certain situations

Most experienced rheumatologists use clinical experience, the most current information available, patient preference, and access to medications in making treatment decisions.

Here's the grades of evidence and how they are used.

Grades of Evidence

Very Low	We are very uncertain about the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
High	Further research is very unlikely to change our confidence in the estimate of effect
When more than one treatment is included as an option, the order does not imply any hierarchy, ie, each of the treatment options (A or B or C) is recommended equally.	

GRADE website: <http://www.gradeworkinggroup.org/>. Accessed November 2015.

Here are the recommendations. You can see some of the strong recommendations have very low evidence, and a few of the moderate recommendations have very high evidence. A few of the conditional recommendations have very high evidence.

If a patient can't or won't take methotrexate, the evidence strongly supports an anti-IL-6 receptor biologic or a JAK inhibitor, not a TNFi or another biologic without methotrexate. The guideline, however, states that you should start with a non-TNF or TNFi. Why?

Recommendations Early RA

Recommendation	Level of Evidence
Use a T2T strategy—target should be LDA or remission. Another target may be chosen because of risk tolerance of patients or comorbidities.	Low
For DMARD-naïve patients with LDA, DMARD (MTX preferred) monotherapy over double or triple DMARD	Low
Patients with MDA or HDA who are DMARD naïve: • DMARD (MTX) monotherapy over double therapy • DMARD (MTX) monotherapy over triple therapy	Moderate High
Patients with MDA or HDA despite the above, with or without GC), combination DMARDs or TNF-i or non-TNF bDMARD (all choices with or without MTX)	Low
MDA or HDA despite DMARDs: • TNFi monotherapy over tofacitinib monotherapy • TNFi + MTX over tofacitinib + MTX	Low Low
MDA or HDA despite DMARD, add low-dose GC	Moderate
MDA or HDA despite bDMARD, add low-dose GC	Low
GC for short duration for flares	Very low

HDA, high disease activity; MDA, moderate disease activity; T2T, treat to target. Singh JA, et al. *Arth Rheumatol*. 2016;68(1):1-26.

The limitations of EULAR guidelines are that they are primarily opinion-based. They include literature searches and expert opinion. Expert opinion is not necessarily evidence based.

Limitations of 2016 EULAR Recommendations

- **Guideline:** A rule/instruction that shows or tells how something should be done
- **Recommendation:** The act of saying that someone or something is good and deserves to be chosen; a suggestion about what should be done
- **EULAR recommendations**
 - Developed after a literature search but decided by “experts” (some of whom see patients) by consensus and “expert opinion”
 - Different countries have different agendas and require their agenda to be included
 - Cost is a major component of the recommendations
 - There are recommendations with a low level of evidence

In many countries, although considered “recommendations,” the recommendations must be followed.

Let's shift topics for a minute to our window of opportunity in RA. We know that if you can treat RA early and get the patient under control, the patient will do better. Early TNFi therapy—if the patient doesn't respond to methotrexate—is effective. The patient feels better, and there is less fatigue, improved functional status, decreased job loss, and reduced loss of work time. As expensive as they are, if the patient is able to work and avoids hospitalization, these drugs can be cost-effective. Treatment benefits, not just health care costs, should be assessed. It really is never too early and never too late to treat. If a patient comes in with 5 years of disease, my goal is still the same. It's still remission, not LDA.

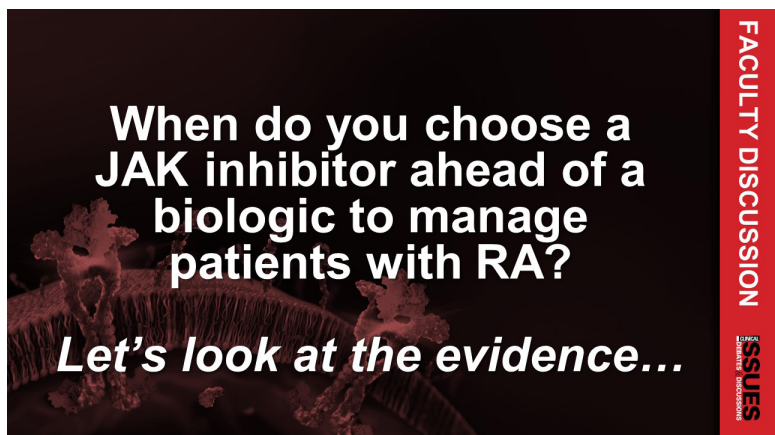
Window of Opportunity in RA

- csDMARDs in early RA improve outcomes compared with later treatment
- Early anti-TNF therapy improves clinical outcomes
 - Also induces remission, prevents radiographic progression, reduces fatigue, and improves patients' functional status, and HRQoL
- Early anti-TNF therapy has been shown to decrease job loss and reduce loss of work time
- Cost-effective? Drug costs of initial combination therapy are high, BUT may reduce lost productivity
- Treatment benefits, not just healthcare costs, must be assessed
- Physicians should advocate for access to effective therapies

Evidence reveals it is never too early—and never too late—to treat RA. Earlier is better!

HRQoL, health-related quality of life.
Breedveld F. Clin Rheumatol. 2011;30(suppl 1):S33-S39.

When would you pick a JAK inhibitor ahead of a bDMARD to manage patients with RA?



When do you choose a JAK inhibitor ahead of a biologic to manage patients with RA?

Let's look at the evidence...

FACULTY DISCUSSION

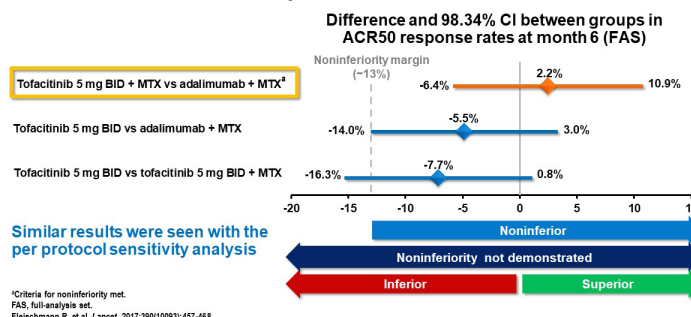
ISSUES

Here's the evidence. This is tofacitinib in ORAL STRATEGY, a true head-to-head study. In this powered, head-to-head trial, the data show that tofacitinib plus methotrexate was equivalent to methotrexate plus adalimumab. Pick one or the other, and you'll get the same result. Tofacitinib monotherapy is not quite as good as either combination. So, in my experience, if a patient is a methotrexate incomplete responder, I add tofacitinib. If the patient goes into remission, then I try to eliminate the methotrexate. I'm able to do that about 70% of the time.

The safety data in this study were also fairly similar.

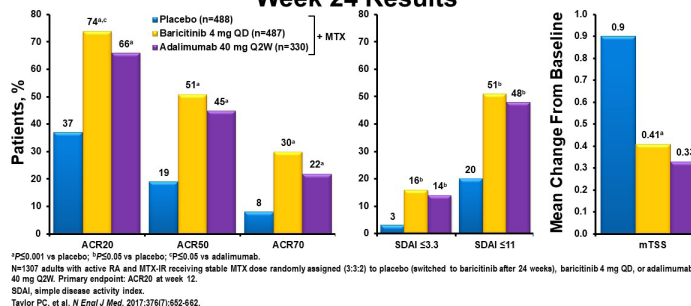
Dr. Greenwald pointed out there was a little more herpes zoster with tofacitinib vs adalimumab. Herpes zoster occurs with adalimumab as well. This trial was interesting because patients received the live zoster vaccine before we started. There was no effect. The live zoster vaccine has very little effect in patients with RA. There have been no studies to date, but we hope that the inactivated recombinant zoster vaccine will be more effective.

Tofacitinib Noninferiority of ACR50 at Month 6



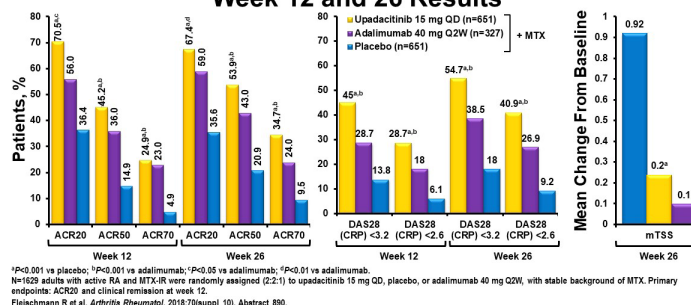
In the RA-BEAM study—where they also looked at herpes zoster and the live vaccine was again ineffective—the 4 mg dose of baricitinib plus methotrexate was superior to adalimumab plus methotrexate.

RA-BEAM in MTX-IR RA Baricitinib vs Placebo or Adalimumab Week 24 Results



If you look at the SELECT-COMPARE trial, the 15 mg QD dose of upadacitinib was superior to adalimumab.

SELECT-COMPARE in MTX-IR RA Upadacitinib vs Placebo Compared to Adalimumab Week 12 and 26 Results



Participant



Roy Fleischmann, MD, MACR

In this particular study, are the long-term safety data for adalimumab superior?

No. There were more thromboembolic events with adalimumab than there were with upadacitinib. Adalimumab was more likely to produce a problem.



Maria Greenwald, MD, FACR

I was going to refer to the new FDA doctor letter on the large tofacitinib trial. Most of these trials include 200 or 400 patients. The change in the FDA guidance is due to the fact that this study included 10,000 RA patients randomly assigned to a TNFi or tofacitinib. The events were related to the tofacitinib 10 mg BID dose which had more DVTs, PEs, and a death compared with the 5 mg BID dose. The actual incidence rate was 0.1 per 1000 patient-years for the patients on the TNFi. Most data support that. The incidence data for tofacitinib 10 mg were 0.4 per 1000 patient-years or 4 times as often. That is why there was concern about baricitinib. It started to pop up as a signal, but we're still talking about events that are extremely rare. We're talking about 0.4 per 1000 patient-years, and if you think of the side effects of prednisone or deaths related to opioid analgesics, these are very rare occurrences. The TNFi drugs clearly have less risk for thrombotic effects.



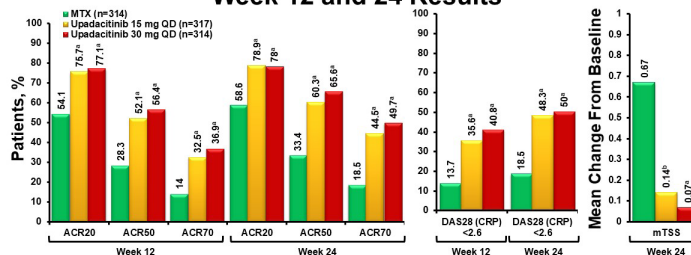
Roy Fleischmann, MD, MACR

Okay, but there is a large-scale study of tofacitinib safety, which the FDA mandated when it was approved. The data safety monitoring board reported to the FDA and the study sponsor that it had concerns with the 10 mg dose because of excess mortality and PE. The FDA has now requested the data. We haven't seen all the data. Dr. Greenwald's numbers may be accurate, but we don't know because we don't have access to all the data. We don't know how to put it together. I think it's not unreasonable to say that it's dose-related, but we don't know for sure yet. We need to see all the data.

These data are for early RA. In early RA, it's nice to see that these drugs are better than methotrexate; but right now, you wouldn't start a patient on a JAK inhibitor. Why? Cost and access.

SELECT-EARLY in MTX-Naive RA

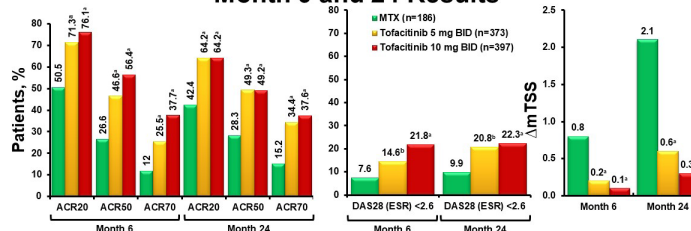
Upadacitinib vs MTX Week 12 and 24 Results



*P<0.001 vs MTX; **P<0.01 vs MTX. N=647 adults with active RA and MTX-naïve randomly assigned (1:1:1) to upadacitinib 15 mg QD, upadacitinib 30 mg QD, or MTX QW (titrated by week 8). Primary endpoint: ACR50 at week 12 (PDA). DAS28 (CRP) <2.6 at week 24 (ESRA). van Vollenhoven R, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 891.

ORAL START in MTX-Naive RA

Tofacitinib vs MTX Month 6 and 24 Results

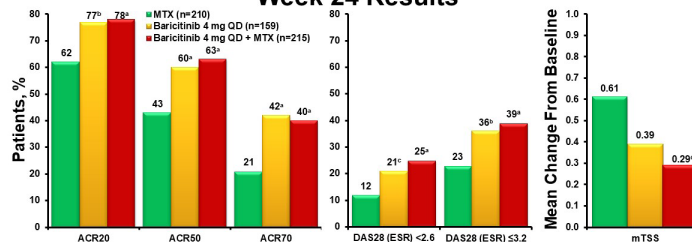


*P<0.001 versus MTX; **P<0.05. N=956 patients with active RA and 23 radiographic erosions received tofacitinib 5 mg BID, tofacitinib 10 mg BID, or MTX. Primary endpoints: ACR70 at month 6 and ΔmTSS at month 6. ACR, American College of Rheumatology; ACR20, American College of Rheumatology 20% improvement criteria; ACR50, American College of Rheumatology 50% improvement criteria; ACR70, American College of Rheumatology 70% improvement criteria; ACR-N, N% improvement based on ACR criteria; DAS28, disease activity score-28 joints; ESR, erythrocyte sedimentation rate; mTSS, modified Total Sharp Score. Lee EB, et al. *N Engl J Med*. 2014;370(25):2377-2386.

RA-BEGIN in DMARD-Naïve RA

Baricitinib vs MTX vs Baricitinib+MTX

Week 24 Results

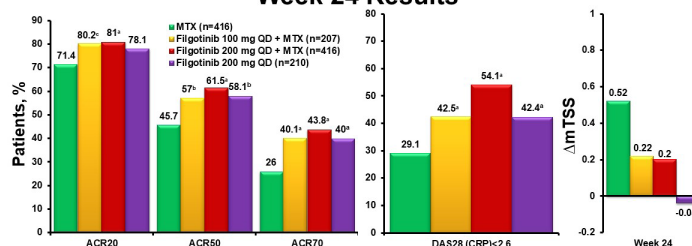


*P<0.001 vs MTX; †P<0.01 vs MTX; ‡P<0.05 vs MTX.
N=588 patients with RA and no prior csDMARD (≤5 MTX QW doses permitted) and bDMARD randomly assigned to MTX, baricitinib 4 mg QD, or baricitinib 4 mg QD+MTX for 52 weeks.
Primary endpoint: ACR20 at week 24.
CRP, C-reactive protein; QW, every week.
Fleischmann R, et al. *Arthritis Rheumatol* 2017;59(3):506-517.

FINCH 3 in MTX-Naïve RA

Filgotinib vs Filgotinib+MTX vs MTX

Week 24 Results



*P<0.001 vs MTX; †P<0.01 vs MTX; ‡P<0.05 vs MTX.
N=1249 MTX-naïve adults with moderately to severely active RA randomly assigned to filgotinib 200 mg QD + MTX, filgotinib 100 mg QD + MTX, filgotinib 200 mg QD, or MTX.
Primary endpoint: ACR20 at week 12.
Company Press Release. <https://www.nasdaq.com/press-release/gilead-and-galapagos-announce-filgotinib-meets-primary-endpoint-in-the-phase-3-finch-3-study-in-20190328-01138>.
Accessed March 29, 2019.

So, when would you select a JAK inhibitor ahead of a biologic? All JAK inhibitors have superior clinical function and radiographic improvements compared with methotrexate in methotrexate-naïve RA. So, if costs were equal, would you use a JAK inhibitor before methotrexate?

JAK inhibitor or bDMARD

When do you select JAK inhibitors ahead of bDMARDs?

- All JAK inhibitors have superior clinical, functional and radiographic improvements compared with MTX in MTX-naïve RA
 - IF cost were equal, JAK inhibitors would conceivably be first line to treat early RA
 - HOWEVER, cost is not equal AND MTX can be effective
 - MTX is currently the preferred first-line treatment for RA
- In csDMARD-IR, JAK inhibitors are at least, if not more, effective than adalimumab in head-to-head trials
 - IF patient access is equal, it is reasonable to use JAK inhibitors ahead of bDMARDs

EULAR recommendations suggest bDMARDs or JAK inhibitors following csDMARD failure; ACR guideline places JAK inhibitors after bDMARDs.



Joel Kremer,
MD, FACP

No, because I have 60 years of experience with methotrexate and 30% to 40% of patients—perhaps more if you know how to use it subcutaneously with folic acid—will respond well to methotrexate. JAK inhibitors are more expensive and I cannot, with absolute certainty, predict that I will do no harm when compared with methotrexate. I love these drugs. I've been involved in their studies. But I think stepping back is a good idea, particularly with the issues that have emerged, I'm not sure if there are class effects regarding DVT and PEs.



Roy Fleischmann,
MD, MACR

So, I asked Dr. Kremer because he has so much experience with JAK inhibitors and I agree with him. I want to know about the VTE. I think Dr. Greenwald is right that if the inactivated recombinant zoster vaccine has been shown to be safe and work, then I may not have a problem. I may go for a JAK inhibitor as first line.



Joel Kremer,
MD, FACP

My problem with the inactivated recombinant zoster vaccine is that it is highly adjuvanted. I'm giving a strong adjuvant to my patients with autoimmune disease. I've heard nice anecdotal stories that it's safe. I also heard an anecdotal story at the ACR in which a patient went from 4% to 40% psoriatic involvement after vaccination. I think a safety study is needed to go beyond the anecdotal stories to show that the highly adjuvanted vaccine is indeed safe for my patients with autoimmune disease and is not going to make their disease worse.

In summary, this has been a very interesting exchange. Hopefully, we have provided some good information on this critical topic. Activation of the JAK/STAT signal transduction pathways is a critical event in RA pathogenesis, no question. JAK inhibitors have demonstrated efficacy in terms of key clinical outcome measures. Tofacitinib and baricitinib have received FDA approval for the treatment of RA. The selective JAK1 inhibitor upadacitinib was recently approved, and filgotinib is in late-stage development. With respect to class differences and characteristics, safety profiles based on distinct potency against select JAK targets may emerge and may have clinical implications in future practice. I do not believe we're there yet. Mild-to-moderate inhibition of JAKs does not carry the same risk as loss of function.

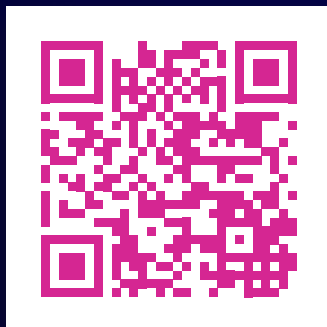
Mitigating potential safety risks by adopting recommended monitoring protocols for JAK inhibitors is warranted; let's be safe. I think JAK inhibitors are going to dominate the treatment of many autoimmune diseases, including beyond the rheumatology sphere. Examples of potential diseases that may benefit from the inhibition of various JAKs include ulcerative colitis, psoriasis, psoriatic arthritis, spinal arthropathies, and other areas. The first decade of the 21st century was all about TNFi drugs, the second was about other biologics, and I think the third decade will be about careful, informed use of JAK inhibitors across many different autoimmune diseases.

Summary

- Activation of the JAK/STAT signal transduction pathway is a critical event in RA pathogenesis
- JAK inhibitors have demonstrated efficacy in terms of key clinical outcome measures
 - To date, tofacitinib, upadacitinib, and baricitinib have received FDA approval for the treatment of RA
- Selective JAK1 inhibitor filgotinib is in late-stage development with registration soon expected
- Decreased use of steroids, narcotics, and NSAIDs have been observed
- In-class differences and characteristic safety profiles based on distinct potency against select molecular targets may emerge with potential clinical implications for future practice
- Mild-to-moderate inhibition of JAK/STAT does not carry the same risk as loss of function
- Mitigating potential safety risks by adopting recommended monitoring protocols for JAK inhibitors is warranted

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