Medscape EDUCATION

# Emerging Paradigms in Rheumatoid Arthritis: Focus on Janus Kinase Inhibition CME

Supported by an independent educational grant from AbbVie

https://www.medscape.org/viewarticle/899027

*This article is a CME activity.*
*To earn credit for this activity visit:*
***https://www.medscape.org/viewarticle/899027***

## Target Audience
This activity is intended for rheumatologists, primary care physicians, and obstetricians & gynecologists.

## Goal
The goal of this activity is to increase awareness of the role of the Janus-associated kinase/signal transducers and activators of transcription (JAK/STAT) pathway in the pathophysiology of rheumatoid arthritis (RA), as well as the most recent clinical data of JAK inhibitors in RA.

## Learning Objectives
Upon completion of this activity, participants will:

Have increased knowledge regarding the

- Role of JAK/STAT in the pathophysiology of RA
- Emerging evidence regarding JAK inhibitor therapy in the management of RA
- Place of JAK inhibitors in clinical practice

## Credits Available
**Physicians** - maximum of 1.5 *AMA PRA Category 1 Credit(s)*™

## Accreditation Statements
Medscape

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Medscape, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

**For Physicians**
Medscape, LLC designates this enduring material for a maximum of 1.5 ***AMA PRA Category 1 Credit(s)***™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## Instructions for Participation and Credit

There are no fees for participating in or receiving credit for this online educational activity. For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within the time designated on page 2; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity online during the valid credit period that is noted on page 2. To receive *AMA PRA Category 1 Credit*™, you must receive a minimum score of 75% on the post-test.

Follow these steps to earn CME/CE credit*:

1. Read the target audience, learning objectives, and author disclosures.
2. Study the educational content online or printed out.
3. Online, choose the best answer to each test question. To receive a certificate, you must receive a passing score as designated at the top of the test. We encourage you to complete the Activity Evaluation to provide feedback for future programming.

You may now view or print the certificate from your CME/CE Tracker. You may print the certificate but you cannot alter it. Credits will be tallied in your CME/CE Tracker and archived for 6 years; at any point within this time period you can print out the tally as well as the certificates from the CME/CE Tracker.

*The credit that you receive is based on your user profile.

## Hardware/Software Requirements

To access activities, users will need:

- A computer with an Internet connection.
- Internet Explorer 8.x or higher, the latest versions of Firefox or Safari, or any other W3C standards compliant browser.
- Adobe Flash Player and/or an HTML5 capable browser may be required for video or audio playback.
- Occasionally other additional software may be required such as PowerPoint or Adobe Acrobat Reader.

## Disclosures

### Faculty

**Charles J. Malemud, PhD**
Professor of Medicine and Anatomy
Case Western Reserve University
Cleveland, Ohio

Disclosure: Charles J. Malemud, PhD, has disclosed the following relevant financial relationships:

Other: Investigator for Pfizer Inc.;

Dr Malemud does not intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

Dr Malemud does not intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics not approved by the FDA for use in the United States.

**Roy M. Fleischmann, MD**
Clinical Professor of Medicine
University of Texas Southwestern Medical Center
Co-Medical Director
Metroplex Clinical Research Center
Dallas, Texas

Disclosure: Roy M. Fleischmann, MD, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: AbbVie Inc.; Lilly; Pfizer Inc.

Dr Fleischmann does not intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

Dr Fleischmann does intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics not approved by the FDA for use in the United States.

**Eric M. Ruderman, MD**
Professor of Medicine
Associate Chief for Clinical Affairs
Division of Rheumatology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Disclosure: Eric M. Ruderman, MD, has disclosed the following relevant financial relationships:

Served as an advisor or consultant for: AbbVie Inc.; Amgen Inc.; GlaxoSmithKline; Janssen Pharmaceuticals; Lilly; Novartis Pharmaceuticals Corporation; Pfizer Inc.;

Received grants for clinical research from: Coronna

Dr Ruderman does intend to discuss off-label uses of drugs, mechanical devices, biologics, or diagnostics approved by the FDA for use in the United States.

Dr Ruderman does intend to discuss investigational drugs, mechanical devices, biologics, or diagnostics not approved by the FDA for use in the United States.

**Editors**
**Karen Badal, MD, MPH**
Scientific Director, Medscape, LLC
Disclosure: Karen Badal, MD, MPH, has disclosed the following relevant financial relationships: Owns stock, stock options, or bonds from: Kallyope, Inc.

**Faith Reidenbach, CHCP**
Fellow of the American Medical Writers Association
Disclosure: Faith Reidenbach, CHCP, has disclosed no relevant financial relationships.

**CME Reviewer**
**Nafeez Zawahir, MD**
CME Clinical Director, Medscape, LLC
Disclosure: Nafeez Zawahir, MD, has disclosed no relevant financial relationships.

**Peer Reviewer**

This activity has been peer reviewed and the reviewer has disclosed no relevant financial relationships.

## Understanding the Pathophysiology of RA and the Value of Janus Kinase Inhibition

**Charles J. Malemud, PhD**

Adult rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology. At the cellular and molecular levels, RA is characterized by defects in innate and adaptive immunity that cause chronic inflammation of small and large synovial joints.[1] Some of the pathophysiological features of defective innate immunity in RA include abnormal complement signaling and hyperactivation of the transcription factor nuclear factor-κB. The innate and adaptive immune system defects in RA contribute to synovial tissue hyperplasia and maintain a continuous level of perpetually activated T lymphocytes, B lymphocytes, macrophages, mast cells, and synovial fibroblasts.[2] For the most part, these cells are responsible for the elevated levels of pro-inflammatory cytokines, chemokines, adhesion proteins, and matrix metalloproteinases (MMPs) that are characteristic of RA. All of these cell types are involved in:

- Maintaining chronic joint inflammation
- Inciting and maintaining inflammation in extra-articular organs
- Mediating the destruction of articular cartilage through degradation of extracellular matrix (ECM) proteins
- Contributing to a heightened resorption of subchondral bone that results in multiple sites of bone erosion and eventually the failure of the affected synovial joint

## The Role of Pro-Inflammatory Cytokines in RA

Pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-2, IL-3, IL-6, IL-7, IL-8, IL-12/IL-23, IL-17, IL-19/IL-20, IL-32, IL-35, tumor necrosis factor-α (TNF-α), interferon-α/ϒ (IFN-α/γ), and oncostatin M (OSM) are among the most prominently elevated cytokines in the sera and synovial fluid from patients with RA.[3-5] The primary role of pro-inflammatory cytokines is to activate signal transduction pathways. These signaling pathways regulate gene expressional events that modulate such diverse physiologic responses as cell fate determination, cell proliferation, and survival as well as programmed (ie, controlled) cell death, otherwise known as apoptosis.

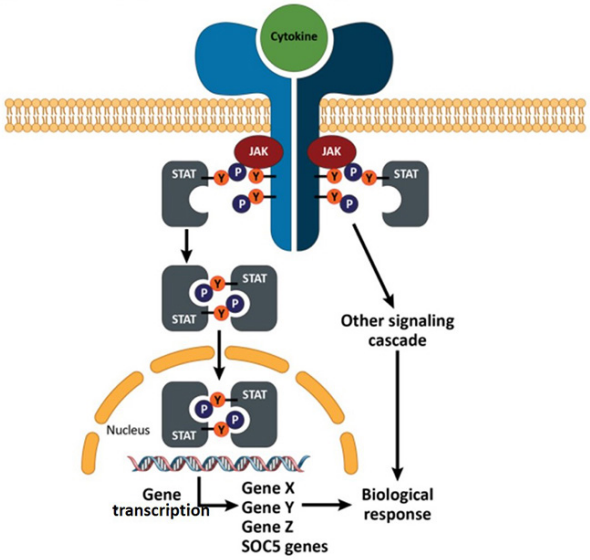
The cytokines IL-1β and TNF-α interact with their individual specific receptors on the surface of many cell types. In the case of IL-1β and TNF-α, specific ligand/receptor interactions activate the stress-activated/mitogen-activated protein kinase (SAPK/MAPK) pathway.[6-10] Activation of this signaling pathway causes the phosphorylation of extracellular-signal regulated kinase-1/2 (ERK1/2), p38 MAPK, and c-Jun-amino-terminal kinase-1/2 (JNK1/2), which upregulate the expression of MMP genes. MMPs are enzymes predominantly involved in the destruction of articular cartilage ECM proteins as well as other stromal tissue ECM proteins.

Other elevated pro-inflammatory cytokines, such as IL-6, IL-12/IL-23, IL-17, INF-γ, and OSM, have been shown to activate the Janus-associated kinase/signal transducers and activators of transcription (JAK/STAT) pathway. For example, IL-6 binds to its cognate receptor, IL-6 receptor-α (IL-6Rα), located on the cell membrane of many cell types. After the IL-6/IL-6Rα interaction occurs, a transducing protein known as gp130 facilitates the phosphorylation (ie, activation) of JAKs.[11] There are 3 main types of JAKs, namely, JAK1, JAK2, and JAK3, and a fourth member of this family, known as tyrosine kinase 2 (TYK2).[12]

## Overview of JAK/STAT Signaling

The activation of JAKs results in the phosphorylation of STAT proteins, most prominently STAT1, STAT3, STAT5, and STAT6 (Figure 1).[11] Phosphorylation of STAT proteins (p-STATs) facilitates the formation of STAT homo-dimers (eg, p-STAT1/p-STAT1) or STAT hetero-dimers (eg, p-STAT1/p-STAT3). The formation of p-STAT dimers facilitates their translocation from the cytoplasm to the nucleus, where activated p-STAT proteins act as transcription factors by binding to STAT-responsive elements in the promoter regions of certain genes.[13,14] Many of these STAT-responsive elements exist in genes that are responsible for the continual upregulation of pro-inflammatory cytokine genes, MMPs, and apoptosis/anti-apoptosis gene transcription. Thus, their eventual translation into proteins perpetuates the chronic state of inflammation that is characteristic of adult RA.

**Figure 1. JAK Signaling Pathway**[11]




Ordinarily, the regulation of JAK/STAT signaling by pro-inflammatory cytokines is stringently controlled by a few types of negative regulators, including suppressor of cytokine signaling (SOCS) proteins.[15-18] However, in the context of RA, SOCS proteins do not appear to be capable of adequately controlling JAK/STAT pathway activation. The level of SOCS proteins in RA is seriously deficient.[16] Additional negative regulators of cellular events mediated by JAK/STAT signaling, namely, cellular inhibitor of apoptosis protein/X-inhibitor of apoptosis protein (c-IAP/XIAP) and protein inhibitor of activated STAT (PIAS), are also affected in RA.[19,20]

Under normal conditions, the fundamental underpinning for the regulation of JAK/STAT signaling is rigorous control of cytokine and growth factor interactions with specific cell membrane receptors, thus limiting activation of JAKs. Once this was understood, it became clear that inhibiting the JAK pathways, thus inhibiting cytokine signaling, might interrupt the cycle of leukocyte recruitment and activation and pro-inflammatory cytokine expression at sites of inflammation.[21]

## Development of JAK-Selective Oral Medications for RA

JAK inhibitors, built on the heels of advances in computer technology and strategies involving advancements in medicinal chemistry, had already been designed for use in situations involving rejection of transplants.[22] Further research was conducted to examine the extent to which inhibition of JAK activation would dampen the aberrant gene expressional events that contribute to the progression of synovial joint destruction in RA.

In addition to the downstream dysregulation of genes associated with chronic inflammation, there was persuasive and compelling evidence that “cross-talk” could occur between activated JAK/STAT signaling and 2 additional signal transduction pathways, SAPK/MAPK and phosphoinositide-3-kinase/AKT/PTEN/mechanistic (mammalian) target of rapamycin (PI3K/AKT/PTEN/mTOR).[23,24] Both of these pathways were found to be intimately involved with upregulating the expression of MMP genes as well as skewing the balance between pro-apoptotic proteins and anti-apoptotic proteins toward the latter, resulting in abnormal cell survival. Thus, activation of PI3K/AKT signaling was found to cause the aberrant survival of immune and other accessory cells pertinent to the perpetuation of chronic inflammation in RA.

In view of all of these considerations, it was determined that molecules targeted against JAKs would represent a suitable intervention in RA. This viewpoint was further substantiated when it was discovered that limiting activation of STAT proteins via upstream inhibition of JAK phosphorylation suppressed the expression of many genes substantially linked to the inflammatory response.[25] Most notably, it was demonstrated that limiting STAT protein activation also resulted in significantly reducing the levels of IFN-γ, IL-6, IL-17, IL-19, IL-21, and IL-23 gene expression.

During the initial stages of developing JAK small molecule inhibitors (SMIs), it was crucial to consider what the effects would be of inhibiting each individual JAK. However, the benefits of inhibiting individual JAKs had to be weighed against the potentially negative effect of inhibiting the activation of all JAKs in the JAK/STAT signaling cascade. This issue became increasingly important when it was discovered using in vitro cell culture models that certain JAK SMIs were capable of inhibiting more than one JAK.[11] Cell-free protein kinase assays were designed to rigorously determine both the selectivity of JAK SMIs (as measured by comparing the half maximal inhibitory concentration of one JAK SMI against another) as well as the specificity of JAK SMIs for non-JAKs.

These analyses showed that certain JAK SMI formulations, such as baricitinib, inhibit both JAK1 and JAK2,[13] whereas tofacitinib, which was initially described as JAK3 selective, also inhibits JAK1, JAK2, and, to a lesser extent, TYK2.[26,27] Additional JAK SMIs with selective inhibitory activity for a specific JAK that are furthest along in investigation at this time include filgotinib and upadacitinib. The development of JAK inhibitors that selectively inhibit a specific JAK may have theoretical advantages over broader JAK inhibition in terms of limiting adverse effects (AEs); however, additional data will be needed to judge clinical safety relative to broader JAK inhibition. Filgotinib inhibits both JAK1 and JAK2 in kinase assays but displays a 30-fold selectivity towards JAK1 in whole blood assays.[28] Upadacitinib is 74-fold selective for JAK1 over JAK2, and with JAK2 and JAK3 signaling unaffected, this agent does not affect erythropoietin signaling or reduce peripheral NK cell counts at therapeutic doses.[28]

The net effect of the JAK inhibitors in RA is that they decrease synovial inflammation and structural joint damage by modulating multiple aspects of the overactive immune response.

## JAK Inhibitors for the Treatment of RA: Tofacitinib and Baricitinib

**Roy M. Fleischmann, MD**

When tofacitinib was approved by the US FDA in 2012, some news reports hailed it as “the first oral biologic” for RA. For proper interpretation of treatment guidelines, it is important to understand that JAK inhibitors are targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), not biologics. Biologics are large molecules, whereas JAK inhibitors are small molecules that interrupt the signaling pathway from inside the cell involved in the inflammatory pathway.
Key recommendations of the American College of Rheumatology (ACR) guidelines for treatment of RA are:[29]

a. Therapy should start with a conventional synthetic DMARD (csDMARD) such as MTX in a treat-to-target approach, with the target being remission or the lowest disease activity possible.
b. If the patient does not achieve the target and has established RA (at least 6 months), then a biologic DMARD (bDMARD) or a tsDMARD should be added, preferably with MTX. A TNF-α inhibitor is preferable to a non-TNF bDMARD, which is preferable to a tsDMARD.
c. If the target is still not reached at the appropriate time point, therapy should be switched to another bDMARD or tsDMARD until the target is reached.

Baricitinib, approved by the FDA in June 2018, was not mentioned in the 2015 ACR guidelines as it was not yet approved.[29] A revision is scheduled to be released in late 2019 or early 2020. Recommendation (b) may change now that there has been longer experience with non-TNF bDMARDs and tsDMARDs, and baricitinib should be addressed.

**Table 1 compares key information from the package inserts for tofacitinib and baricitinib.[30,31]**

| | Tofacitinib | Baricitinib |
|---|---|---|
| Indication | Treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX | Treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies |
| FDA limitations on use | Use in combination with other JAK inhibitors, bDMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended | |
| Dosing | • 5 mg twice daily*<br>• 11 mg once daily (ER formulation) | 2 mg once daily† |
| Administration instructions | • May be used as monotherapy or in combination with MTX or other non-bDMARDs<br>• Avoid initiation or interrupt in patients with hemoglobin <8 g/dL, absolute lymphocyte count <500 cells/mm3, or absolute neutrophil count <1000 cells/mm3 | |

*5 mg once daily in patients with moderate or severe renal impairment or moderate hepatic impairment.
†Not recommended for patients with moderate or severe renal impairment or severe hepatic impairment.

## Tofacitinib Pharmacology

Tofacitinib is a pan-JAK inhibitor. It was initially thought to be JAK3-selective, but later studies found that it has additional inhibitory action against JAK1 and, to a lesser extent, JAK2.[32]

Tofacitinib is rapidly absorbed and eliminated, with peak plasma concentration within about 1 hour and a half-life of approximately 3 hours. Clearance is by both hepatic metabolism (70%) and renal excretion (30%).[21] The effects of tofacitinib are rapidly reversible (1 day to 2 weeks for effects on biochemical targets and 2 to 6 weeks for effects on immune cells). When managing AEs such as infections and laboratory abnormalities, 14-day discontinuation of tofacitinib is reasonable.[21] Renal impairment may result in clinically significant increases in tofacitinib exposure; therefore, it is necessary to halve the recommended daily dose in patients with moderate or severe renal insufficiency.[30] No dose adjustments are required in patients with mild hepatic insufficiency.[30]

The pharmacodynamic effects of tofacitinib include declines in neutrophils, lymphocytes, and immune function that can persist for weeks after therapy is discontinued.[21] Tofacitinib-treated patients may have lower pneumococcal and influenza titers after vaccination.[33]

The metabolism of tofacitinib is principally mediated by cytochrome P450 3A4 (CYP3A4), with a minor contribution from CYP2C19. Exposure to tofacitinib is approximately doubled when it is co-administered with potent CYP3A4 inhibitors or with medications that moderately inhibit CYP3A4 and potently inhibit CYP2C19. Tofacitinib exposure is decreased when it is co-administered with potent CYP3A4 inducers.[21]

### Tofacitinib Efficacy

The FDA approval of tofacitinib was based on six phase 3 trials in patients with moderately to severely active RA, the "Oral" series. These studies demonstrated the efficacy of tofacitinib 5 mg twice daily, either as monotherapy or in combination with MTX or another csDMARD. The design of the trials is summarized in Table 2, and key efficacy results are given in Table 3.[34-39]

A seventh trial, Oral Strategy, was a head-to-head noninferiority study of tofacitinib and adalimumab.[40] (Oral Standard was designed to compare tofacitinib and adalimumab with placebo, not with each other.) As shown in Tables 2 and 3, the treatment arms were tofacitinib monotherapy, tofacitinib + MTX, and adalimumab + MTX. Tofacitinib monotherapy was effective, although not quite as effective as tofacitinib + MTX. The results on the primary endpoint, ACR50 response rate at month 6, and on key secondary endpoints showed similar results. There were no significant between-group differences in safety, other than fewer elevations in liver enzymes in the tofacitinib monotherapy group.

The results of Oral Strategy demonstrate that for a patient who has inadequate response to MTX, the addition of tofacitinib has equivalent clinical and functional efficacy as the addition of adalimumab. The data also suggest that in a patient who has inadequate response to MTX, response is more likely if tofacitinib is added to MTX than if the patient is switched to tofacitinib monotherapy.[41] Based on the results of Oral Strategy, monotherapy would probably be sufficient for two-thirds of patients.

**Table 2. Design of Phase 3 Studies of Tofacitinib in RA**

| Study | Patient population | Duration, mo | Relevant treatment arms* | Background therapy |
|---|---|---|---|---|
| Phase 3 Trials | | | | |
| Oral Start[34] | csDMARD-IR or bDMARD-IR | 6 | • T5 (n=243)<br>• PBO 3 mo → T5 (n=61) | • Allowed: NSAIDs, GCs |
| Oral Start[35] | MTX-naive | 24 | • T5 (n=373)<br>• MTX† (n=186) | • Allowed: NSAIDs, GCs |
| Oral Sync[36] | csDMARD-IR or bDMARD-IR | 12 | • T5 (n=315)<br>• PBO‡ → T5 (n=79) | • Allowed: MTX ≤25 mg/wk, low-dose GCs, NSAIDs |
| Oral Scan[37] | MTX-IR | 24 | • T5 (n=321)<br>• PBO‡ → T5 (n=81) | • Required: MTX<br>• Allowed: NSAIDs, low-dose GCs |
| Oral Standard[38] | MTX-IR | 12 | •T5 (n=204)<br>• ADA (n=204)<br>• PBO‡ → T5 (n=56) | • Required: MTX |
| Oral Step[39] | IR to TNF + MTX | 6 | Months 0-3<br>• T5 (n=133)<br>• T10 (n=134)<br>• PBO (n=132)<br><br>Months 3-6<br>• T5 (n=133)<br>• T10 (n=134)<br>• PBO→ T5 (n=66)<br>• PBO→ T10 (n=66) | • Required: MTX<br>• Allowed: Antimalarials |
| Phase 3b/4 Noninferiority Trial | | | | |
| Oral Step[40] | MTX-IR | 12 | • T5 (n=380)<br>• T5 + MTX (n=376)<br>• ADA + MTX (n=385) | • Required: MTX in the 2 combination arms<br>• Allowed: NSAIDs, GCs |

ADA = adalimumab; GC = glucocorticoid; IR = inadequate response; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; T5 = tofacitinib 5 mg twice daily.
*Arms that included tofacitinib 10 mg twice daily are not reported.
†Incrementally increased to 20 mg/week over 8 weeks.
‡PBO users could be rescued with T5 after 3 months; otherwise, duration of PBO was 6 months.

**Table 3. Efficacy Results from Phase 3 Studies of Tofacitinib in RA**

| Arm | ACR20, % | ACR50, % | ACR70, % | ΔHAQ-DI, mean |
|---|---|---|---|---|
| Phase 3 Trials | | | | |
| Oral Solo (csDMARD-IR or bDMARD-IR)[34] | | | | |
| T5 | 59.8* | 31.1* | 15.4* | −0.50* |
| PBO | 26.7 | 12.5 | 5.8 | −0.19 |
| Oral Solo (csDMARD-IR or bDMARD-IR)[34] | | | | |
| T5 | 71.3‡ | 46.6‡ | 25.5‡ | −0.8‡ |
| MTX | 50.5 | 26.6 | 12.0 | −0.6 |
| Oral Sync (csDMARD-IR or bDMARD-IR)[36] | | | | |
| T5 ± MTX | 52.7* | 34* | 13* | −0.46* |
| PBO ± MTX | 31.2 | 13 | 3.4 | −0.21 |
| Oral Scan (MTX-IR)[37] | | | | |
| T5 + MTX | 51.5* | 35* | 15.5* | −0.4† |
| T10 + MTX | 61.8* | 44.5* | 22.3* | -0.54* |
| PBO + MTX | 25.3 | 9.6* | 6 | −0.15 |
| Oral Standard (MTX-IR)[38] | | | | |
| T5 + MTX | 51.5* | 37* | 20* | −0.55† |
| T10 + MTX | 52.6* | 35* | 22* | -0.61† |
| ADA + MTX | 47.2* | 28* | 9* | −0.49† |
| PBO + MTX | 28.3 | 12 | 2 | −0.24 |
| Oral Step (IR to TNF + MTX)[39] | | | | |
| T5 + MTX | 41.7* | 26.5* | 13.6* | −0.43* |
| PBO + MTX | 24.4 | 8.4 | 1.5 | −0.18 |
| Phase 3b/4 Noninferiority Trial | | | | |
| Oral Strategy (MTX-IR)[40,41] | | | | |
| T5 | 64.8 | 38.3 | 18.2 | −0.54 |
| T5 + MTX | 73.1 | 46 | 25 | −0.59 |
| ADA + MTX | 71 | 43.8 | 20.7 | −0.54 |

*P <.001 vs placebo.
†P <.05 vs placebo.
‡P <.001 vs MTX.

In summary, the Oral trials established that in adults with active RA:

- Tofacitinib monotherapy is superior to placebo[34]
- Tofacitinib monotherapy is superior to MTX in MTX-naive patients[35]
- Tofacitinib with or without MTX is effective in patients with inadequate response to csDMARDs[36]
- Tofacitinib + MTX is effective in patients with inadequate response to MTX[37,38]
- Tofacitinib + MTX is effective in patients with inadequate response to a TNF inhibitor + MTX[39]
- Tofacitinib + MTX is noninferior to adalimumab + MTX in patients with inadequate response to MTX[40]

### Tofacitinib Safety

Patients taking tofacitinib should be carefully monitored for the development of serious infections, including tuberculosis (TB); elevated lipids, liver tests, and serum creatinine; and changes in neutrophils, lymphocytes, and hemoglobin.[30] A recent safety summary of tofacitinib presents pooled clinical trial data on 6194 patients with a median exposure of 3.4 patient-years, of whom 40% received tofacitinib for more than 4 years.[42] The most common AEs were nasopharyngitis, upper respiratory tract infection (URI), and urinary tract infection (UTI). Infection was the most common class of serious AEs (incident rate 9.4 cases per 100 patient-years of exposure), with pneumonia, herpes zoster (HZ), UTI, and cellulitis being most frequent. The most common causes of death with tofacitinib were infections, cardiovascular events, and malignancies. Tofacitinib carries boxed warnings that serious infections leading to hospitalization or death have occurred, and that lymphoma and other malignancies have been observed.[30,31]

A systematic review and meta-analysis of 98 tofacitinib studies concluded that the rates of serious infections in patients with moderate to severe active RA were within the ranges of those reported for bDMARDs.[43] A separate analysis found that TB was the most common opportunistic infection, although it was rare in regions of low or medium TB incidence.[44] According to the tofacitinib prescribing information, patients who plan to start the drug should be screened for latent TB, and if the screen is positive, treatment should be started prior to tofacitinib initiation.[30] In the phase 3 trials, 263 patients diagnosed with latent TB were treated with isoniazid and tofacitinib concurrently, and none developed TB.[44]

Studies have shown an approximately 1.5-to 2-fold greater risk of HZ infection in patients treated with tofacitinib compared to that usually observed in patients with RA.[45] In a population-based study from the post-marketing period, analysis showed that patients treated with tofacitinib appear to have a higher incidence of HZ infection than do those treated with biologic agents. The incidence of HZ associated with tofacitinib was approximately double that observed in patients using TNF inhibitors, abatacept, or rituximab.[46] Older age, female sex, and prednisone >7.5 mg/day were also associated with increased risk.

According to an integrated analysis of safety data across the tofacitinib RA development program, non-melanoma skin cancer occurred in 118/6194 tofacitinib-treated patients, and other malignancies occurred in 173/6194 patients (incident rate 0.6 and 0.9, respectively; overall median exposure was 3.38 patient-years).[42]The incidence of malignancy did not increase with longer exposure to tofacitinib, a finding confirmed in separate analyses.[47-49] Gastrointestinal perforation occurred in 22 patients, all of whom were using NSAIDs with or without GC.[42] Fifteen of the 22 patients had a history of diverticulitis, diverticulosis, or gastric ulcers.

In an analysis of hematological changes in phase 3 and LTE studies, mean neutrophil and lymphocyte counts decreased and mean hemoglobin levels increased in all tofacitinib treatment groups.[50] Hemoglobin levels and neutrophil counts stabilized in long-term extension studies. For lymphocyte counts, a further gradual decrease was observed up to month 48, which then stabilized. These findings should be interpreted cautiously, since patients who remain in extension studies are generally tolerating a drug well.[50]

Across phase 3 studies and their extensions, moderate increases in low-density and high-density lipoprotein cholesterol were generally observed within 1 to 3 months of tofacitinib initiation.[51] The levels stabilized thereafter. Incident rates of major cardiovascular events and heart failure were similar with tofacitinib and placebo, and they did not increase in extension studies. However, no definitive conclusion was reached. An ongoing post-marketing study is comparing the safety of tofacitinib and TNF inhibitors, particularly with regard to cardiovascular events and malignancies.[52]

According to the tofacitinib prescribing information, lipids should be measured about 4 to 8 weeks after initiation of tofacitinib.[30] Neutrophils and hemoglobin should be measured at initiation and about 4 to 8 weeks later. Lymphocyte counts should be measured at baseline and every 3 months thereafter, and liver function tests should be ordered routinely.[30]

### Baricitinib Pharmacology

Baricitinib inhibits JAK1 and JAK2 approximately 100 times more potently than JAK3.[53] Peak plasma concentrations are reached within approximately 1 hour.[31] Steady-state concentrations are achieved in 2 to 3 days, with minimal accumulation after once-daily administration. The elimination half-life in patients with RA is about 12 hours. Approximately 75% of the dose is eliminated in the urine and about 20% in the feces. The pharmacokinetics of baricitinib do not change over time. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Renal function was found to significantly affect baricitinib exposure; therefore, it is not recommended for use in patients with eGFR of < 60 mL/min/1.73 m2.[31]

Pharmacodynamic effects of baricitinib include decreases in immunoglobulins and C-reactive protein (CRP). In one study in RA, mean serum IgG, IgM, and IgA values decreased by 12 weeks after baricitinib initiation and remained stable through at least 52 weeks. In most patients, the values stayed within the normal reference range. Decreases in serum CRP were observed as soon as 1 week after baricitinib initiation and were maintained throughout dosing.[31]

CYP3A4 is the main metabolizing enzyme of baricitinib. Even so, laboratory studies showed no effect on the pharmacokinetics of baricitinib when it was co-administered with ketoconazole, fluconazole, or rifampicin. Neither did co-administration of baricitinib have any meaningful effects on the pharmacokinetics of MTX, diclofenac, ibuprofen, or cyclosporine. Baricitinib does inhibit organic anionic transporter 3 (OAT3), among other proteins that play roles in drug distribution, so baricitinib is not recommended for patients taking strong OAT3 inhibitors, such as probenecid.[31]

### Baricitinib Efficacy

The efficacy and safety of baricitinib 2 mg once daily were assessed in the RA-BUILD and RA-BEACON randomized, controlled, phase 3 trials. The design and results of these trials are summarized in Tables 4 and 5, respectively.[54-55] Two other phase 3 trials, RA-BEGIN and RA-BEAM, investigated 4 mg/day of baricitinib.[56-57] In June 2018, the FDA approved baricitinib 2 mg once daily for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies.[58] The Advisory Committee stated that the submitted data did not consistently show a benefit of 4 mg over the 2 mg dose. Given concerns about venous thromboembolism with the 4 mg dose, the benefit/risk assessment was more favorable for baricitinib 2 mg.[58]

**Table 4. Design of Phase 3 Studies of Baricitinib 2 mg/d in RA**

| Study | Patient population | Duration, wk | Treatment arms | Background therapy | Primary endpoint |
|---|---|---|---|---|---|
| RA-BUILD[54] | csDMARD-IR | 24 | B2 (n=229)<br>B4 (n=227)<br>PBO* (n=228) | Any stable therapies, including MTX | ACR20 at wk 12 |
| RA-BEACON[55] | TNF-IR | 24 | B2 (n=174)<br>B4 (n=177)<br>PBO* (n=176) | csDMARDs (including MTX), NSAIDs, analgesics, and/or GCs | ACR20 at wk 12 |

B2 = baricitinib 2 mg/day; B4 = baricitinib 4 mg/day.
*PBO users could be rescued with B4 at any time after 16 weeks.

**Table 5. Efficacy Results from Phase 3 Trials of Baricitinib 2 mg/d in RA**

| Arm | ACR20, % | ACR50, % | ACR70, % | HAQ-DI MCID ≥0.3, % | CDAI ≤2.8, % |
|---|---|---|---|---|---|
| RA-BUILD (csDMARD-IR, week 12)[54] | | | | | |
| B2 | 66* | 34* | 18* | 60* | 10* |
| PBO | 39 | 13 | 3 | 44 | 2 |
| RA-BEACON (TNF-IR, week 12)[55] | | | | | |
| B2 | 49* | 20† | 13* | 48† | 3 |
| PBO | 27 | 8 | 2 | 35 | 2 |

* P <.001 vs placebo.
†P <.01 vs placebo.

Assessments in RA-BUILD and RA-BEACON demonstrated that at the 2-mg/day dosage there were statistically significant early improvements in ACR responses, as early as week 1.[54,55] Recent data from RA-BUILD demonstrated that patients treated with baricitinib 2 mg/day also exhibited significant improvement in patient-reported outcomes across different domains, including pain, functional ability, and fatigue.[62] A long-term extension study, evaluating the safety of baricitinib 2 mg/day and 4 mg/day, is ongoing.[59]

Slowing of radiographic progression was also observed at week 24, with significant changes in the mean modified total Sharp score (mTSS) of 0.33 and 0.15 in the baricitinib 2 mg and 4 mg group respectively, compared with mTSS of 0.70 in the placebo group.[54] In the long-term extension study, RA-BEYOND, treatment with baricitinib 2 or 4 mg once daily was associated with reduced rates of structural progression, measured using mTSS, through 1 year in patients with RA who had an inadequate response to csDMARDs.[60] These data were analyzed using linear extrapolation. The beneficial effect was seen for both the erosion and the joint space narrowing score as well. The overall structural progression assessed by radiographic response showed consistent efficacy for baricitinib 4 mg dose, while the data for 2 mg was not as robust.

### Baricitinib Safety

In clinical trials of baricitinib, adverse reactions in ≥1% of patients included URI, nausea, herpes simplex, and HZ. According to the prescribing information, baseline and routine laboratory assessment is recommended due to the potential for changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids.[31]

Baricitinib carries boxed warnings that serious infections leading to hospitalization or death have occurred, and that lymphoma and other malignancies have been observed. The prescribing label recommends closely monitoring patients for infections during and after treatment with baricitinib. An integrated analysis presented as an abstract at the 2017 ACR meeting reviewed the safety of baricitinib (both dosages) across phase 1 to phase 3 trials (8 randomized trials) and one extension study (data up to September 2016).[65] Altogether, 3492 patients received baricitinib for 6637 patient-years of exposure. The median exposure was 2.1 years and the maximum was 5.5 years. The incidence rate for HZ was significantly higher for baricitinib 4 mg (n = 997) vs placebo (n = 1070), 4.3 and 1.0, respectively. The incident rate of serious infections for all patients exposed to any baricitinib dose was 2.9 cases per 100 patient-years of exposure (TB 0.15, all in endemic areas). Other incident rates reported were non-melanoma skin cancer, 0.4; other malignancies, 0.8 (lymphoma, 0.09); major cardiovascular events, 0.5; and gastrointestinal perforation, 0.05. In addition, as with any medication, it is important to consider the risks and benefits of the drug prior to initiating therapy in patients who may be at risk for any of these events.[31] Baricitinib also carries a boxed warning that thrombosis, including deep vein thrombosis (DVT), pulmonary embolism, and arterial thrombosis, may occur.[31]

## Investigational JAK Inhibitors for the Treatment of RA: Upadacitinib and Filgotinib

Eric M. Ruderman, MD

Besides tofacitinib and baricitinib, several other "Jakinibs," as JAK inhibitors are sometimes called, are being investigated for treatment of RA. In the United States, a new drug application for upadacitinib is expected to be submitted soon, and filgotinib has completed phase 2b trials.

### Upadacitinib Pharmacology

Upadacitinib is an orally administered JAK inhibitor that has greater selectivity for JAK1 than for JAK2 (~74-fold higher, with an IC50 of 8 nM compared with 600 nM, respectively, in cellular assays), and more selectivity for JAK1 compared to JAK3 (~58-fold higher, with an IC50 of 40 nM compared with 2.3 µM, respectively, in biochemical assays).[62,63] It has been proposed that selectivity for JAK1 could improve the safety of JAK inhibition,[64] although this has yet to be demonstrated in clinical trials.

In phase 1 research, the functional half-life of upadacitinib was approximately 4 hours, and the mean terminal elimination half-life ranged from 6 to 16 hours. Approximately 20% of an upadacitinib dose is eliminated unchanged in urine.[65] Upadacitinib is rapidly absorbed, with mean absorption time in healthy men of 0.08 hour.[66]

To further assess the effects of renal impairment on upadacitinib plasma exposure, a phase I study (presented in abstract form) compared subjects with normal renal function to those with mild, moderate, and severe renal impairment.[67] The data showed that upadacitinib mean plasma exposures (AUC) in subjects with severe renal impairment are within 44% of mean exposures in subjects with normal renal function. These results are consistent with the limited known role of urinary excretion in elimination of upadacitinib.

With regard to the effect of mild and moderate hepatic impairment on the pharmacokinetics of upadacitinib, a phase 1 study looked at the 15 mg dose of upadacitinib ER formulation.[68] Authors of the abstract found that there was no statistically significant difference in upadacitinib Cmax or AUC in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. With only <30% increase in upadacitinib AUC, it was concluded that dose adjustment is not needed in this patient population.

Upadacitinib is metabolized by CYP3A, potentially with minor metabolic contribution from CYP2D6.[66] In vitro, ketoconazole has been shown to increase upadacitinib exposures by approximately 75%.[69] In clinical use, pooled pharmacokinetic data showed no effect of concomitant use of CYP3A or CYP2D6 inhibitors, but the assessment was limited by small numbers of subjects and short duration of concomitant treatment.[66]

### Upadacitinib Efficacy

In phase 2 trials in RA, upadacitinib was typically administered as a twice-daily regimen of an immediate-release formulation.[70] Later, an extended-release formulation was developed to enable once-daily dosing.

The ER formulation was used in the phase 3 SELECT trials of upadacitinib at dosages of 15 and 30 mg once daily. The program has so far shown that upadacitinib administered with MTX[71] or as monotherapy[72] is efficacious in patients with RA who had an inadequate response to MTX or another csDMARD. Upadacitinib is also efficacious in patients who had inadequate response to bDMARDs or could not tolerate them.[73] Studies have also shown significantly lower radiographic progression with upadacitinib.[74,75] Table 6 summarizes the design of the trials and Table 7 gives the results.[71,72-75]

**Table 6. Design of Phase 3 Studies of Upadacitinib in RA**

| Study | Patient population | Treatment arms | Background therapy | Primary endpoints |
|---|---|---|---|---|
| SELECT-NEXT[71] | csDMARD-IR | • U15 (n=221)<br>• U30 (n=219)<br>• PBO (n=221) | • Required: 1 or 2 csDMARDs for 12 wk<br>• Allowed: NSAIDs, acetaminophen, oral or inhaled GC | At wk 12:<br>• ACR20, %<br>• DAS28-CRP ≤3.2, % |
| SELECT-BEYOND[73] (24-wk data) | bDMARD-IR | • U15 (n=164)<br>• U30 (n=165)<br>• PBO for 12 wk (n=169) → U15 or U30 | • Required: 1 or 2 csDMARDs for 24 wk<br>• Allowed: NSAIDs, acetaminophen, GC | At wk 12:<br>• ACR20, %<br>• DAS28-CRP ≤3.2, % |
| SELECT-MONOTHERAPY (interim data published in abstract form)[72] | MTX-IR | • U15 (n=217)<br>• U30 (n=215)<br>• MTX (n=216) | No MTX | At wk 14:<br>• ACR20, %<br>• DAS28-CRP ≤3.2, % |
| SELECT-EARLY (interim data published in abstract form) [74] | MTX naïve | • U15 (n=317)<br>• U30 (n=314)<br>• MTX (n=314) | No MTX | • At wk 12: ACR50<br>• At wk 24: DAS28-CRP ≤2.6, % |
| SELECT-COMPARE (interim data published in abstract form) [75] | MTX-IR | • U15 (n=651)<br>• ADA40 (n=327)<br>• PBO (n=651) | MTX | At wk 12:<br>• ACR20<br>• DAS28-CRP ≤2.6, % |

DAS28 = Disease Activity Score 28; U15 = upadacitinib 15 mg/day; U30 = upadacitinib 30 mg/day; ADA40 = adalimumab 40 mg.

**Table 7. Results of Phase 3 Studies of Upadacitinib in RA**

| Arm | ACR20, % | ACR50, % | ACR70, % | DAS28-CRP ≤3.2, % | ΔHAQ-DI, mean | CDAI ≤10 | SDAI ≤11 |
|---|---|---|---|---|---|---|---|
| SELECT-NEXT (csDMARD-IR , week 12)[71] | | | | | | | |
| PBO | 36 | 15 | 6 | 17 | −0.26 | 19 | 19 |
| U15 | 64* | 38* | 21* | 48* | −0.61* | 40* | 42* |
| U30 | 66* | 43* | 27* | 48* | −0.55* | 42* | 45* |
| SELECT-BEYOND (bDMARD-IR, week 12)[73] | | | | | | | |
| PBO | 28 | 12 | 7 | 14 | −0.16 | 14 | 14 |
| U15 | 65* | 34* | 12 | 43* | −0.41* | 32† | 34* |
| U30 | 56* | 36* | 23* | 42* | −0.44* | 34* | 35* |
| SELECT-MONOTHERAPY (MTX-IR, week 14)[72] | | | | | | | |
| MTX | 41 | 15 | 3 | 19 | −0.32 | 25 | NR |
| U15 | 68† | 42† | 23† | 45† | −0.65† | 35‡ | NR |
| U30 | 71† | 52† | 33† | 53† | −0.73† | 47† | NR |
| SELECT-EARLY (MTX-naive, week 24)[74] | | | | | | | |
| MTX | 54 (at wk 12) | 33 | 19 | 32 | -0.60 | 38 | NR |
| U15 | 76† (at wk 12) | 60† | 45† | 60† | -0.87† | 56† | NR |
| U30 | 77† (at wk 12) | 66† | 50† | 65† | -0.91† | 61† | NR |
| SELECT-COMPARE (MTX-IR, week 26)[75] | | | | | | | |
| PBO | 36 (at wk 12) | 21 | 10 | 18 | -0.33 | 22 | 22 |
| U15 | 71†‡ (at wk 12) | 54†§ | 35†§ | 55†§ | -0.69† | 53†§ | 54†§ |
| ADA40 | 63 (at wk 12) | 42 | 23 | 39 | -0.57 | 38 | 39 |

CDAI = Clinical Disease Activity Index; HAQ-DI = Health Assessment Questionnaire Disability Index; NR = not reported; SDAI = Simplified Disease Activity Index.
*P < .0001.
†P < .001.
‡P < .05.
§ P < .001 for UPA15 vs ADA40.

In SELECT-NEXT and SELECT-BEYOND, both doses of upadacitinib, when added to csDMARDs, led to significant improvements in RA signs and symptoms compared with placebo.[71,73] By week 12, significantly higher proportions of patients who received upadacitinib achieved not only ACR20 response, but also ACR50 and ACR70.

Upadacitinib therapy was also associated with clinically meaningful improvements in patient-reported outcomes, including physical function, pain, fatigue, and quality of life. For example, in SELECT-NEXT, better physical function as measured by HAQ-DI was seen in 72% of patients receiving U15 vs 49% of those receiving placebo (P <.05).[76] Similarly, in SELECT-BEYOND, improvements in HAQ-DI were observed in 63% in the U15 group vs 37% in the placebo group (P <.05).[77] SELECT-EARLY compared the clinical efficacy, including inhibition of structural damage, and safety of upadacitinib as monotherapy, vs MTX monotherapy, in MTX-naïve patients.[74] Following 24 weeks of treatment, both doses of upadacitinib (15 mg and 30 mg) significantly inhibited radiographic progression as measured by the change in modified total Sharp score (mTSS) from baseline, compared to MTX. Mean change in mTSS were 0.14 and 0.07 vs 0.67, respectively.[74]

SELECT-COMPARE evaluated the safety and efficacy of upadacitinib compared to placebo and adalimumab.[75] U15 showed superiority on improvement in RA signs and symptoms vs PBO and ADA40 in the MTX-IR population. At 26 weeks of treatment, U15 significantly inhibited radiographic progression as measured by the change in mTSS from baseline, compared to placebo (0.24 vs 0.92, P < .001).[75] In addition, significantly more patients had no radiographic progression (ΔmTSS ≤0) (83.5% vs 76.0%) in the upadacitinib group.

### Upadacitinib Safety

In SELECT-NEXT, 5 serious infections occurred: 1 with U15 (enterocolitis), 3 with U30 (varicella zoster virus, viral URI, staphylococcal wound infection), and 1 with placebo (pneumonia). There were 4 opportunistic infections (1 oral candidiasis with placebo, 3 oral candidiasis with U30) and 1 case of varicella zoster pneumonia in a patient who contracted a primary varicella zoster infection (U30 group). Three HZ infections occurred, 1 in each group; all involved a single dermatome.[71]

In SELECT-NEXT, 3 cardiovascular events occurred in the upadacitinib groups, all in patients with known cardiovascular risk factors. Two malignancies were noted, both in the U30 group (basal cell carcinoma, B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia). No gastrointestinal perforations, pulmonary embolisms, DVTs, or deaths were reported.[71] During the placebo-controlled portion of SELECT-BEYOND, serious AEs occurred in 7% of the U30 group, 5% of the U15 group, and 0% of the placebo group. During weeks 12 to 24, AEs and serious AEs occurred at similar frequencies in the groups that had received U15 or U30 from baseline. Serious AEs were more frequent in the groups that switched from placebo to upadacitinib than in those that received upadacitinib from baseline.[73]

During the first 12 weeks of SELECT-BEYOND, the number of serious infections was greater in the U30 group than in the other 2 treatment groups, but during weeks 12 to 24 the number was similar across groups. Four opportunistic infections were reported over 24 weeks. HZ occurred in 4 patients in the U30 group, 1 patient in the U15 group, and 1 patient in the placebo group during the first 12 weeks; during weeks 12 to 24, 2 cases of HZ were reported in each of the groups that had received upadacitinib from baseline. Two serious cases of HZ occurred in the U30 group; neither patient had been vaccinated.[73]

No cases of non-melanoma skin cancer or lymphoma were reported. One case of gastrointestinal perforation, with concurrent acute renal failure and sepsis, was reported during weeks 12 to 24 in a patient who received U30 from baseline. For this patient, the serious AEs resolved when upadacitinib was discontinued.[73]

Up to week 12, 1 case of pulmonary embolism (PE) was reported in the U15 group. Between weeks 12 and 24, 3 other adjudicated cases of PE were reported: 2 in patients receiving U15 (1 with concurrent DVT), and 1 in a patient receiving U30.[73]

In SELECT-MONOTHERAPY, the percentage of patients who experienced serious AEs was highest in the U15 group (5.1%). More infections were reported in the MTX and U30 groups than in the U15 group. HZ was more frequent with U30 vs U15 or MTX. Three malignancies (1 with MTX and 2 with U15) and 3 MACE (1 with U15 and 2 with U30) were reported. No TB, renal dysfunction, or gastrointestinal perforation was reported.

In SELECT-EARLY, the safety profile of upadacitinib was consistent with previously reported Phase 3 studies.[74] A higher number of patients on UPA30 reported serious infections (2.5%) vs MTX (1.3%) and UPA15 (1.6%). There were more cases of HZ in the UPA (14 cases) vs MTX (1 case) arms. Two VTEs were reported (1 PE on MTX, 1 DVT on UPA30, none on UPA15). In SELECT-COMPARE, serious infections occurred in 1.8% vs 1.5% vs 0.8% of patients in the U15, ADA40, and PBO groups, respectively.[75] There were no deaths in the U15 group, 2 deaths in the ADA40 group, and 2 deaths in the PBO group. No MACE were reported in the U15 group. There were 2 patients with MACE in the ADA40 group and 3 in the placebo group through week 26. In terms of VTEs through Week 26, one patient had a DVT and another had a PE in the U15 group, 3 patients had a PE in the ADA40 group, and 1 had a PE in the placebo group.

### Filgotinib Pharmacology

Another jakinib under investigation is filgotinib, a selective JAK1 inhibitor (half maximal inhibitory concentration (IC50): 629 nM or 267 ng/mL), displaying a 30-fold selectivity for JAK1- over JAK2-dependent signaling in human whole blood.[78] The average elimination half-life is 6 hours. Filgotinib is rapidly absorbed in healthy volunteers, although time to maximum concentration ranged from 0.5 to 5 hours in early studies, depending on dose.[79]

Filgotinib is metabolized to form a metabolite that in itself is a JAK1-selective inhibitor. The pharmacokinetic profile of this metabolite was also evaluated in phase I trials. After filgotinib dosing, metabolite concentrations reached a maximum within 3 to 5 hours, then slowly decreased, with an apparent elimination half-life of about 23 hours.[79]

Simulations of pharmacodynamic effects suggest that maximal JAK1 inhibition with filgotinib is determined by both the maximum concentration of parent drug and the sustained metabolite exposure.[79] Because of the relatively long duration of JAK1 inhibition, once-daily dosing was included in subsequent clinical trials of filgotinib.

Studies have demonstrated that the renal clearance for filgotinib and its metabolite decrease with the degree of renal impairment, leading to a maximum increase in AUC0-24h of 1.54-fold for filgotinib and 2.74-fold for the metabolite in subjects with severe renal impairment.[80] Mild to moderate impairment of renal function had limited impact on the PK of filgotinib. A study is currently underway to evaluate impact of hepatic impairment on the pharmacokinetics of filgotinib.[81]

### Filgotinib Efficacy

The latest published data on filgotinib come from the phase 2b DARWIN trials, in which patients who were MTX-IR added filgotinib to MTX[82] or used filgotinib monotherapy.[83] These trials were randomized, double-blind, and multicenter. Table 8 summarizes the design of the trials, and Table 9 gives the results.

By week 12 in DARWIN 1, significantly higher proportions of patients who received 100 mg once daily or 200 mg daily (regardless of the dosing scheduled) achieved ACR20 response, compared with placebo.[82] There was no significant difference in efficacy between the once daily and twice daily dosing regimens.

In DARWIN 2, filgotinib was as efficacious as monotherapy at all doses.[83] Higher doses of filgotinib were associated with greater reductions in disease activity and higher remission rates. Pooled assessment showed that improvements in nearly all patient-reported outcomes were significantly better with filgotinib than placebo, and some were noted as early as week 1 or week 4.[84]

| Study | Patient population | Duration, wk | Treatment arms | Background therapy | Primary endpoints |
|---|---|---|---|---|---|
| DARWIN 1[82] | MTX-IR | 24 | • F50 daily (n=82)<br>• F100 daily (n=85)<br>• F200 daily (n=86)<br>• F25 daily (n=86)<br>• F50 twice daily (n=85)<br>• F100 twice daily (n=84)<br>• PBO (n=86) | • Required: MTX<br>• Allowed: GC, NSAIDs | ACR20 at wk 12 |
| DARWIN 2[83] | MTX-IR | 24 | • F50 daily (n=72)*<br>• F100 daily (n=70)<br>• F200 daily (n=69)<br>• PBO for 12 wk (n=72) → F100 daily | • No MTX (≥4-week washout)<br>• Allowed: GC, NSAIDs | ACR20 at wk 12 |

F25 = filgotinib 25 mg; F50 = filgotinib 50 mg; F100 = filgotinib 100 mg; F200 = filgotinib 200 mg.
*Nonresponders were switched to F100 daily after week 12.

**Table 9. Results of Phase 2b Studies of Filgotinib in RA**

| Arm | ACR20, % | ACR50, % | ACR70, % | DAS28-CRP ≤3.2, % | ΔHAQ-DI, mean | CDAI ≤10 | SDAI ≤11 |
|---|---|---|---|---|---|---|---|
| DARWIN 1 (MTX-IR, week 12)[82] | | | | | | | |
| PBO | 44 | 15 | 8 | 7 | −0.38 | 15 | 9 |
| F50 daily | 56 | 33‡ | 16 | 12 | −0.58 | 24 | 23 |
| F100 daily | 64‡ | 38† | 21 | 12 | −0.65‡ | 24 | 26 |
| F200 daily | 69† | 43* | 24‡ | 15 | −0.75* | 27 | 27 |
| F25 twice daily | 57 | 28‡ | 14 | 13 | −0.59 | 19 | 22 |
| F50 twice daily | 60 | 34‡ | 19 | 11 | −0.58 | 22 | 21 |
| F100 twice daily | 79* | 55* | 31† | 14 | −0.84* | 32 | 32 |
| DARWIN 2 (MTX-IR, week 12)[83] | | | | | | | |
| PBO | 29 | 11* | 3 | 7 | −0.23 | 11 | 10 |
| F50 daily | 67* | 35* | 8 | 11 | −0.66* | 29 | 28 |
| F100 daily | 66* | 37* | 19† | 13 | −0.68* | 23 | 20 |
| F200 daily | 73* | 44* | 13‡ | 28 | −0.74* | 30 | 33 |

P <.001.
†P < .01.
‡P < .05.

### Filgotinib Safety

In DARWIN 1, 15 patients had ≥1 serious TEAE. The 1 death, in the filgotinib 100 mg twice-daily group, was due to pneumonia and septic shock and was considered possibly treatment related. Overall, treatment-related AEs were more frequent with filgotinib (21%) than placebo (11%), but few patients in any group discontinued due to AEs. Serious infections were observed in one patient in the placebo group and 5 patients in the filgotinib group. Herpes zoster infections were observed in 4 patients receiving filgotinib and one patient in the placebo group.[82]

In DARWIN 2, rates of treatment-emergent AEs were similar with filgotinib and placebo.[83] Nine serious TEAEs were reported (seven in the treatment group and two in the placebo group), four of which were serious infections (pneumonia, cellulitis, gastroenteritis and pyelonephritis). There was only one case of HZ infection in a patient receiving filgotinib 50 mg once daily.

No case of TB, opportunistic infection, lymphoma, or cancer was reported in either DARWIN trial. Changes in hematology, lipids, and liver enzymes were similar to those that have been reported for tofacitinib and baricitinib.[82,83]

Three phase 3 trials, the FINCH series, are evaluating the efficacy of filgotinib in RA.[85-87]

### Place of JAK Inhibitors in RA Therapy

There continue to be numerous challenges and unmet needs in the management of RA. Patients may not respond to certain therapies or are intolerant to a therapy; therefore, it is important for patients to have multiple treatment options available to best suit their disease-specific needs. JAK inhibition offers a new therapeutic strategy for rheumatologists. These agents have the advantages of being oral, which makes them much more convenient to patients, and having short half-lives, which means they can be eliminated in about a day if AEs occur.[41] Tofacitinib and baricitinib are recent additions to our therapeutic armamentarium for RA, and have demonstrated to be at least as effective as a TNF inhibitor in patients with incomplete response to MTX,[40,57] and as monotherapy these agents are superior to MTX in providing clinical, functional, and radiographic control of RA.[35,56] Further investigation is needed into the use of these drugs in patients who respond poorly to bDMARDs. In addition, extension trials now under way will provide further evidence about treatment-related infections, malignancies, and other long-term safety aspects of various JAK inhibitors.

**Abbreviations**

ACR = American College of Rheumatology
ACR20 = American College of Rheumatology 20
ADA = adalimumab
B2 = baricitinib 2 mg/day
B4 = baricitinib 4 mg/day
bDMARD = biologic disease-modifying antirheumatic drug
c-IAP/XIAP = cellular inhibitor of apoptosis protein/X-inhibitor of apoptosis protein
CDAI = Clinical Disease Activity Index
CRP = C-reactive protein
csDMARD = conventional synthetic disease-modifying antirheumatic drug
DAS28 = Disease Activity Score 28
DMARD = disease-modifying antirheumatic drug
DVT = deep vein thrombosis
ECM = extracellular matrix
ER = extended release
ERK1/2 = extracellular signal-regulated kinase-1/2
F25 = filgotinib 25 mg
F50 = filgotinib 50 mg
F100 = filgotinib 100 mg
F200 = filgotinib 200 mg
FDA = US Food and Drug Administration
GC = glucocorticoid
HAQ-DI = Health Assessment of Chronic Illness Therapy
HDL = high-density lipoprotein
HZ = herpes zoster
IFN-α/γ = interferon α/γ
Ig = immunoglobulin
IL = interleukin
IL-6Rα = interleukin-6 receptor-α
IR = inadequate response
JAK = Janus-associated kinase
JNK1/2 = c-Jun-amino-terminal kinase-1/2
LDA = low disease activity
LDL = low-density lipoprotein

MMP = matrix metalloproteinase
mTOR = mechanistic (mammalian) target of rapamycin
MTX = methotrexate
MTX-IR = methotrexate inadequate response
NR = not reported
NSAID = nonsteroidal anti-inflammatory drug
OAT3 = organic anionic transporter 3
OSM = oncostatin M
PBO = placebo
PI3K = phosphoinositide-3-kinase
PIAS = protein inhibitor of activated STAT
pSTAT = STAT protein
RA = rheumatoid arthritis
SAPK/MAPK = stress-activated/mitogen-activated protein kinase
SDAI = Simplified Disease Activity Index
SMI = small molecule inhibitor
SOCS = suppressor of cytokine signaling
STAT = signal transducers and activators of transcription
T5 = tofacitinib 5 mg twice daily
TB = tuberculosis
TNF = tumor necrosis factor
TNF-α = tumor necrosis factor-α
tsDMARD = targeted synthetic disease-modifying antirheumatic drug
TYR2 = tyrosine kinase 2
U15 = upadacitinib 15 mg/day
U30 = upadacitinib 30 mg/day
URI = upper respiratory infection
UTI = urinary tract infection

**Related Links**

Perspectives on the Impact of Inflammation in Osteoarthritis: Current Approaches and Future Options
https://www.medscape.org/viewarticle/901145

Systemic Lupus Erythematosus: Virtual Simulation Approach to Symptom Management
https://www.medscape.org/viewarticle/894273

Providing Hope and Opportunity: Advancing Clinical Trial Participation in Rheumatoid Arthritis
https://www.medscape.org/viewarticle/897247

**References**


1. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.
2. Karouzakis E, Neidhart M, Gay RE, Gay S. Molecular and cellular basis of rheumatoid joint destruction. Immunol Lett. 2006;106:8-13.
3. Fox DA, Gizinski A, Morgan R, Lundy SK. Cell-cell interactions in rheumatoid arthritis synovium. Rheum Dis Clin North Am. 2010;36:311-323.
4. Asquith DL, McInnes IB. Emerging cytokine targets in rheumatoid arthritis. Curr Opin Rheumatol. 2007;19:246-251.
5. Brennan F, Beech J. Update on cytokines in rheumatoid arthritis. Curr Opin Rheumatol. 2007;19:296-301.
6. Ohori M. ERK inhibitors as a potential new therapy for rheumatoid arthritis. Drug News Perspect. 2008;21:245-250.
7. Wylie MA, Meszaros EC, Malemud CJ. The effect of interleukin-6-type cytokines and adiponectin on MAPK activation in the immortalized human chondrocyte C28/I2 line and normal human chondrocytes. J Cell Biol Histol. 2015;1:110.
8. Malemud CJ. Small molecular weight inhibitors of stress-activated and mitogen-activated protein kinases. Mini Rev Med Chem. 2006;6:689-698.
9. Meyer LH, Pap T. MAPK signalling in rheumatoid joint destruction: can we unravel the puzzle? Arthritis Res Ther. 2005;7:177-178.
10. Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. Cell Death Differ. 2003;10:45-65.
11. Malemud CJ. The role of the JAK/STAT signal pathway in rheumatoid arthritis. Ther Adv Musculoskelet Dis. 2018;10:117-127.
12. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev. 2009;228:273-287.
13. Malemud CJ. Suppression of pro-inflammatory cytokines via targeting of STAT-responsive genes. In: El-Shemy H, ed. Drug Discovery. Rijeka, Croatia: InTech Publishing; 2013:373-411.
14. Darnell JE, Jr. STATs and gene regulation. Science. 1997;277:1630-1635.
15. Malemud CJ. Negative regulators of JAK/STAT signaling in rheumatoid arthritis and osteoarthritis. Int J Mol Sci. 2017;18.
16. Malemud CJ. Suppressor of cytokine signaling and rheumatoid arthritis. Integr Mol Med. 2016;18:484.
17. Greenhalgh CJ, Hilton DJ. Negative regulation of cytokine signaling. J Leukoc Biol. 2001;70:348-356.
18. Krebs DL, Hilton DJ. SOCS proteins: negative regulators of cytokine signaling. Stem Cells. 2001;19:378-387.
19. Lao M, Shi M, Zou Y, et al. Protein inhibitor of activated STAT3 regulates migration, invasion, and activation of fibroblast-like synoviocytes in rheumatoid arthritis. J Immunol. 2016;196:596-606.
20. Gadina M. Advances in kinase inhibition: treating rheumatic diseases and beyond. Curr Opin Rheumatol. 2014;26:237-243.
21. Hodge JA, Kawabata TT, Krishnaswami S, et al. The mechanism of action of tofacitinib: an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2016;34:318-328.
22. Borie DC, Si MS, Morris RE, Reitz BA, Changelian PS. JAK3 inhibition as a new concept for immune suppression. Curr Opin Investig Drugs. 2003;4:1297-1303.
23. Malemud CJ, Pearlman E. Targeting JAK/STAT signaling pathway in inflammatory diseases. Curr Signal Transduct Ther. 2009;4:201-221.
24. Banham-Hall E, Clatworthy MR, Okkenhaug K. The therapeutic potential for PI3K inhibitors in autoimmune rheumatic diseases. Open Rheumatol J. 2012;6:245-258.
25. Schwartz DM, Bonelli M, Gadina M, O'Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. Nat Rev Rheumatol. 2016;12:25-36.
26. Jiang JK, Ghoreschi K, Deflorian F, et al. Examining the chirality, conformation and selective kinase inhibition of 3-((3R,4R)-4-methyl-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-y l)-3-oxopropanenitrile (CP-690,550). J Med Chem. 2008;51:8012-8018.
27. Bodenmiller B, Zunder ER, Finck R, et al. Multiplexed mass cytometry profiling of cellular states perturbed by small-molecule regulators. Nat Biotechnol. 2012;30:858-867.
28. Norman P. Selective JAK inhibitors in development for rheumatoid arthritis. Expert Opin Investig Drugs. 2014;23:1067-1077.
29. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1-26.
30. Xeljanz® [package insert]. New York, NY: Pfizer Labs; 2018.
31. Olumiant® [package insert]. Indianapolis, IN: Lilly USA, LLC; 2018.
32. Yamaoka K. Janus kinase inhibitors for rheumatoid arthritis. Curr Opin Chem Biol. 2016;32:29-33.
33. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. Ann Rheum Dis. 2016;75:687-695.
34. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367:495-507.

35. Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370:2377-2386.
36. Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013;159:253-261.
37. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65:559-570.
38. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367:508-519.
39. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013;381:451-460.
40. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390:457-468.
41. Fleischmann R. Tofacitinib in the treatment of active rheumatoid arthritis in adults. Immunotherapy. 2018;10:39-56.
42. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis. 2017;76:1253-1262.
43. Strand V, Ahadieh S, French J, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther. 2015;17:362.
44. Winthrop KL, Park SH, Gul A, et al. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75:1133-1138.
45. Winthrop KL, Yamanaka H, Valdez H, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66:2675-2684.
46. Curtis JR, Xie F, Yun H, et al. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75:1843-1847.
47. Curtis JR, Lee EB, Martin G, et al. Analysis of non-melanoma skin cancer across the tofacitinib rheumatoid arthritis clinical programme. Clin Exp Rheumatol. 2017;35:614-622.
48. Curtis JR, Lee EB, Kaplan IV, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis. 2016;75:831-841.
49. Mariette X, Chen C, Biswas P, et al. Lymphoma in the tofacitinib rheumatoid arthritis clinical development program. Arthritis Care Res (Hoboken). 2018;70:685-694.
50. Schulze-Koops H, Strand V, Nduaka C, et al. Analysis of haematological changes in tofacitinib-treated patients with rheumatoid arthritis across phase 3 and long-term extension studies. Rheumatology (Oxford). 2017;56:46-57.
51. Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, et al. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. Semin Arthritis Rheum. 2016;46:261-271.
52. ClinicalTrials.gov. Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis. NCT02092467. https://clinicaltrials.gov/ct2/show/NCT02092467. Updated August 21, 2018. Accessed August 22, 2018.
53. Kuriya B, Cohen MD, Keystone E. Baricitinib in rheumatoid arthritis: evidence-to-date and clinical potential. Ther Adv Musculoskelet Dis. 2017;9:37-44.
54. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study [published correction appears in Ann Rheum Dis. 2017;76:1634]. Ann Rheum Dis. 2017;76:88-95.
55. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374:1243-1252.
56. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol. 2017;69:506-517.
57. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376:652-662.
58. FDA.gov. Summary of Resubmission and NDA 207924 DPARP/OND Recommendations. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000SumR.pdf. Accessed August 22, 2018.

59. Emery P, Blanco R, Maldonado Cocco J, et al. Patient-reported outcomes from a phase III study of baricitinib in patients with conventional synthetic DMARD-refractory rheumatoid arthritis. RMD Open. 2017;3:e000410.
60. van der Heijde D, Dougados M, Chen YC, et al. Effects of baricitinib on radiographic progression of structural joint damage at 1 year in patients with rheumatoid arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. RMD Open. 2018;4:e000662.
61. Genovese MC, Smolen JS, Takeuchi T, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 5.5 years: an updated integrated safety analysis [abstract 511]. Arthritis Rheumatol. 2017;69(suppl 10).
62. Graff C, Schwartz A, Voss JW, et al. Characterization of ABT- 494, a second generation Jak1 selective inhibitor [abstract]. Arthritis Rheum. 2014;66(suppl 10):S659-S660.
63. Voss J, Graff C, Schwartz A, et al. Pharmacodynamics of a novel Jak1 selective inhibitor in rat arthritis and anemia models and in healthy human subjects [abstract]. Ann Rheum Dis. 2014;73(suppl 2):222.
64. O'Shea JJ, Kontzias A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis. 2013;72(suppl 2):ii111-115.
65. Mohamed MF, Camp HS, Jiang P, et al. Pharmacokinetics, safety and tolerability of ABT-494, a novel selective JAK 1 inhibitor, in healthy volunteers and subjects with rheumatoid arthritis. Clin Pharmacokinet. 2016;55:1547-1558.
66. Klünder B, Mohamed MF, Othman AA. Population pharmacokinetics of upadacitinib in healthy subjects and subjects with rheumatoid arthritis: analyses of phase I and II clinical trials. Clin Pharmacokinet. 2018;57:977-988.
67. Mohamed M, Coppola S, Feng T, et al. AB0479 Characterisation of the effect of renal impairment on upadacitinib pharmacokinetics. Ann Rheum Dis. 2018;77:1400-1401
68. Mohamed M, Coppola S, Feng T, et al. AB0478 Mild and moderate hepatic impairment have no clinically relevant impact on upadacitinib pharmacokinetics: results from a dedicated phase 1 study. Ann Rheum Dis. 2018;77:1400.
69. Mohamed MF, Jungerwirth S, Asatryan A, et al. Assessment of effect of CYP3A inhibition, CYP induction, OATP1B inhibition, and high-fat meal on pharmacokinetics of the JAK1 inhibitor upadacitinib. Br J Clin Pharmacol. 2017;83:2242-2248.
70. Mohamed MF, Zeng J, Marroum PJ, et al. Pharmacokinetics of upadacitinib with the clinical regimens of the extended-release formulation utilized in rheumatoid arthritis phase 3 trials. Clin Pharmacol Drug Dev. 2018. doi: 10.1002/cpdd.462. [Epub ahead of print]
71. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391:2503-2512.
72. Smolen J, Cohen S, Emery P, et al. Upadacitinib as monotherapy: a phase 3 randomised controlled double-blind study in patients with active rheumatoid arthritis and inadequate response to methotrexate [abstract]. Ann Rheum Dis. 2018;77(suppl 2):67-68.
73. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet. 2018;391:2513-2524.
74. van Vollenhoven R, Takeuchi T, Pangan AL, et al. A phase 3, randomized, controlled trial comparing upadacitinib monotherapy to MTX monotherapy in MTX-naïve patients with active rheumatoid arthritis [abstract]. Arthritis Rheumatol. 2018;70(suppl 10).
75. Fleischmann R, Pangan AL, Mysler E, et al. A phase 3, randomized, double-blind study comparing upadacitinib to placebo and to adalimumab, in patients with active rheumatoid arthritis with inadequate response to methotrexate [abstract]. Arthritis Rheumatol. 2018;70(suppl 10).
76. Strand V, Pope J, Tundia N, et al. Upadacitinib improves patient-reported outcomes in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs: results from SELECT-NEXT [abstract]. Ann Rheum Dis. 2018;77(suppl 2):989-990.
77. Strand V, Schiff M, Tundia N, et al. Patient reported outcomes of upadacitinib: results from biologic inadequate responders (SELECT BEYOND PHASE III TRIAL) [abstract]. Ann Rheum Dis. 2018;77(suppl 2):990.
78. Van Rompaey L, Galien R, Van der Aar E, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1 for the treatment of inflammatory diseases. J Immunol. 2013;191:3568-3577.
79. Namour F, Diderichsen PM, Cox E, et al. Pharmacokinetics and pharmacokinetic/pharmacodynamic modeling of filgotinib (GLPG0634), a selective JAK1 inhibitor, in support of phase IIB dose selection. Clin Pharmacokinet. 2015;54:859-874.
80. Namour F, Fagard L, Van der Aa A, et al. Influence of age and renal impairment on the steady state pharmacokinetics of filgotinib, a selective JAK1 inhibitor. Br J Clin Pharmacol. 2018 Aug 8. [Epub ahead of print]
81. ClinicalTrials.gov. Study to evaluate the pharmacokinetics of filgotinib in participants with impaired hepatic function. NCT03417778. https://clinicaltrials.gov/ct2/show/NCT03417778. Accessed August 22, 2018.

82. Westhovens R, Taylor PC, Alten R, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis. 2017;76:998-1008.
83. Kavanaugh A, Kremer J, Ponce L, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). Ann Rheum Dis. 2017;76:1009-1019.
84. Genovese M, Westhovens R, Meuleners L, et al. Effect of filgotinib, a selective JAK 1 inhibitor, with and without methotrexate in patients with rheumatoid arthritis: patient-reported outcomes. Arthritis Res Ther. 2018;20:57.
85. ClinicalTrials.gov. Filgotinib in combination with methotrexate in adults with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate (FINCH 1). NCT02889796. https://clinicaltrials.gov/ct2/show/NCT02889796. Updated April 30, 2018. Accessed August 22, 2018.
86. ClinicalTrials.gov. Filgotinib versus placebo in adults with active rheumatoid arthritis (RA) who have an inadequate response to biologic disease-modifying anti-rheumatic drug(s) (DMARDs) treatment (FINCH 2). NCT02873936. https://clinicaltrials.gov/ct2/show/NCT02873936. Updated July 25, 2018. Accessed August 22, 2018.
87. ClinicalTrials.gov. Filgotinib alone and in combination with methotrexate (MTX) in adults with moderately to severely active rheumatoid arthritis who are naive to MTX therapy (FINCH 3). NCT02886728. https://clinicaltrials.gov/ct2/show/NCT02886728. Updated May 4, 2018. Accessed August 22, 2018.