Tocinib 5/10

Tofacitinib Tablets 5 / 10 mg

PRODUCT MONOGRAPH

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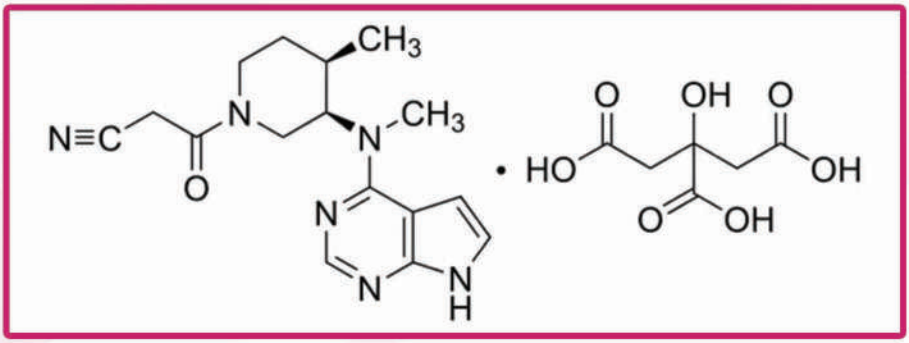
INTRODUCTION

HISTORY OF JANUS KINASE (JAK) INHIBITORS

Janus kinase (JAK) inhibitors, also known as JAK inhibitors or Jakinibs, are a class of small-molecule drugs that target the JAK-STAT (Signal Transducer and Activator of Transcription) pathway, which plays a critical role in immune signaling and inflammatory processes.



DISCOVERY AND EARLY RESEARCH (1990S-2000S)

- The JAK-STAT pathway was first described in the early 1990s as a key mechanism for cytokine signal transduction.
- Researchers identified four JAK family proteins: **JAK1, JAK2, JAK3, and TYK2.**
- Early studies suggested that inhibition of these kinases could suppress inflammation and autoimmune responses.
- Early development of **Tofacitinib** (**CP-690,550**), the first selective JAK inhibitor, in the late 1990s and early 2000s

PRODUCT INFORMATION

Brand Name	: Tocinib 5 & Tocinib 10
Generic Name	: Tofacitinib
Dosage Forms and Strengths	: Tablets: 5 mg, 10 mg
Route of Administration	: Oral
Pharmacologic Class	: Janus Kinase (JAK) Inhibitor

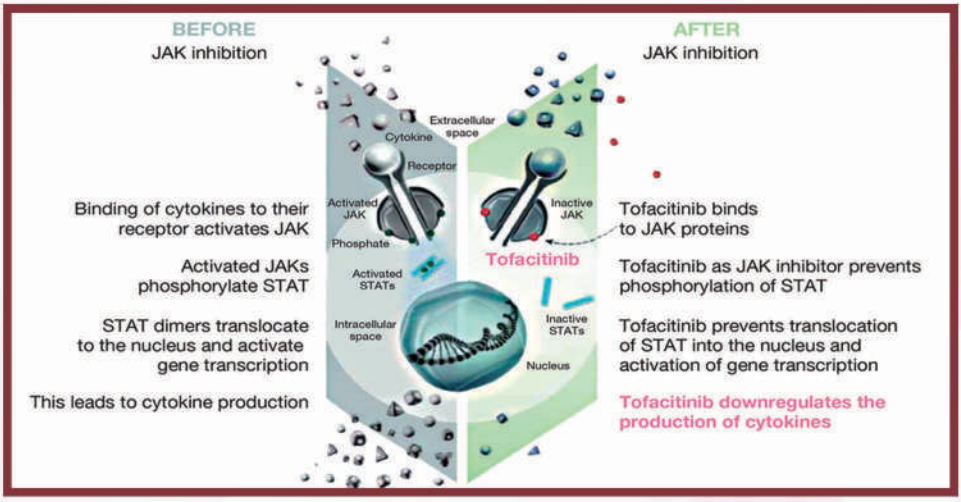
Description

Tofacitinib is an oral Janus kinase (JAK) inhibitor used for the treatment of autoimmune conditions. It selectively inhibits JAK1 and JAK3, modulating the immune response by affecting cytokine signaling pathways.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tofacitinib is a selective inhibitor of Janus kinases (JAKs), specifically JAK1 and JAK3, with moderate inhibition of JAK2 and tyrosine kinase 2 (TYK2). JAKs are involved in intracellular signaling pathways of various cytokines and growth factors that mediate immune and inflammatory responses. By inhibiting JAK1 and JAK3, tofacitinib disrupts the JAK-STAT (Signal Transducer and Activator of Transcription) pathway, reducing the production of pro-inflammatory cytokines such as interleukin (IL)-6, IL-2, and interferon-gamma, which are critical in the pathogenesis of autoimmune diseases.



Immune Cell Infiltration

↓

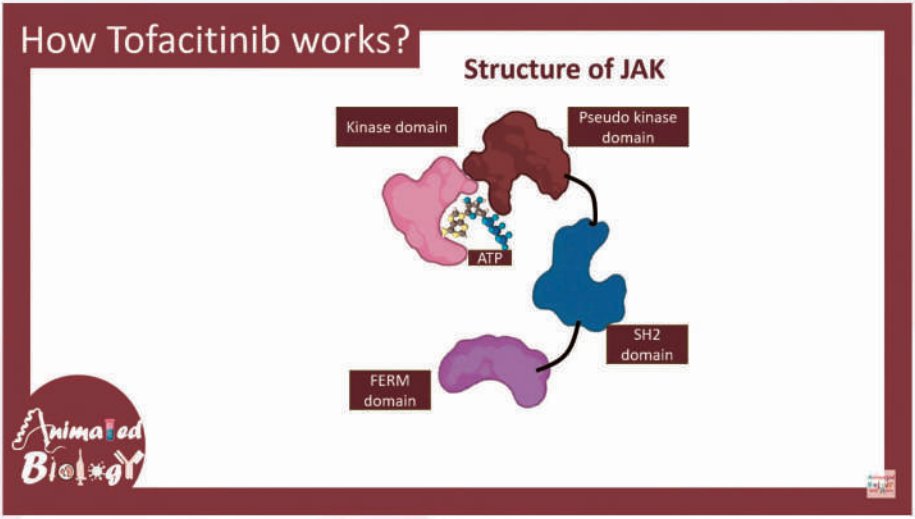
Cytokines Production

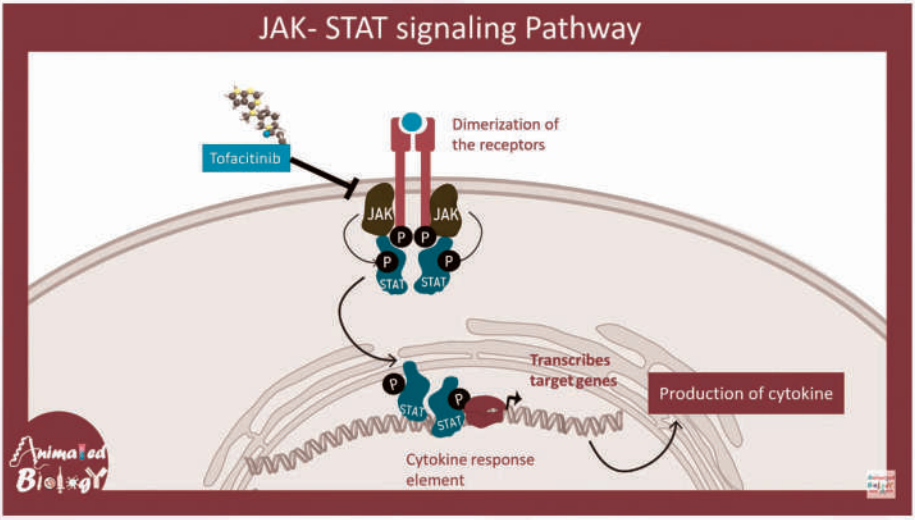
↓

Damage of the affected area

DETAILED MECHANISM OF ACTION

Tofacitinib **inhibit the ATP** on the Kinase domain of **JAK Protein and phosphorylated stat protein** which is responsible for **cytokine production via** the gene transcription in the nucleus.





PHARMACOKINETICS

- **Absorption:** Rapidly absorbed after oral administration, with peak plasma concentrations (Tmax) reached in 0.5 to 1 hour.
- **Bioavailability:** Approximately 74%.
- **Distribution:** Volume of distribution (Vd) is approximately 87 L, indicating moderate tissue penetration.
- **Protein Binding:** Approximately 40% bound to plasma proteins, primarily albumin.
- **Metabolism:** Extensively metabolized in the liver, primarily via CYP3A4 and to a lesser extent by CYP2C19.
- **Elimination:** Primarily excreted in urine (70%) and feces (30%), with 30% of the dose excreted unchanged.
- **Half-life:** 3-4 hours for immediate-release formulations and approximately 6 hours for extended-release formulations.

PHARMACODYNAMICS

- **Cytokine Inhibition:** Reduces levels of cytokines involved in autoimmune diseases, leading to decreased inflammation.
- **Dose-Dependent Effects:** Higher doses result in greater inhibition of JAK-mediated cytokine signaling.
- **Lipid Profile Changes:** Increases in total cholesterol, LDL, and HDL have been observed.
- **Immune Modulation:** Decreases levels of C-reactive protein (CRP), indicating reduced systemic inflammation.

INDICATIONS AND USAGE

Tofacitinib is indicated for the treatment of:

- **Rheumatoid Arthritis (RA):** In adult patients with moderate to severe RA who have had an inadequate response to methotrexate.

.• **Psoriatic Arthritis (PsA):** In combination with non-biologic disease-modifying antirheumatic drugs (DMARDs) for adult patients with active PsA.

• **Ulcerative Colitis (UC):** Indicated for adult patients with moderate to severe UC who have had an inadequate response to or intolerance to tumor necrosis factor (TNF) inhibitors.

• **Ankylosing Spondylitis**

• **Polyarticular course juvenile idiopathic arthritis (pcJIA)**

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis and Psoriatic Arthritis

• 5 mg twice daily

Ulcerative Colitis

• Induction: 10 mg twice daily for 8 weeks, followed by maintenance with 5 mg twice daily.

Psoriatic Arthritis

• 5 mg twice daily

Ankylosing Spondylitis

• 5 mg twice daily

Polyarticular course juvenile idiopathic arthritis (pcJIA)

• 5 mg twice daily

Dose Adjustments:

• Reduce dose in patients with moderate to severe renal or hepatic impairment.
• Avoid use in severe hepatic impairment.
• Reduce to 5 mg once daily in patients receiving CYP3A4 inhibitors.

CONTRAINDICATIONS

• Hypersensitivity to tofacitinib or any of its excipients.
• Severe hepatic impairment.
• Active serious infections, including tuberculosis.
• Patients at risk of venous thromboembolism (for higher doses).

WARNINGS AND PRECAUTIONS

- **Serious Infections:** Increased risk of infections, including tuberculosis, fungal, bacterial, and viral infections.
- **Malignancies:** Increased risk of lymphoma and other malignancies.
- **Thrombosis:** Risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), especially at higher doses.
- **Gastrointestinal Perforation:** Increased risk, particularly in patients using NSAIDs or corticosteroids.
- **Lipid Abnormalities:** Monitoring required as it may increase cholesterol levels.
- **Hematologic Abnormalities:** Cases of neutropenia, lymphopenia, and anemia have been reported.

ADVERSE REACTIONS

Common Adverse Reactions:

- Upper respiratory tract infections
- Headache
- Diarrhea
- Nausea
- Hypertension
- Rash

Serious Adverse Reactions:

- Tuberculosis and opportunistic infections
- Lymphoma and other malignancies
- Venous thromboembolism
- Severe hepatic dysfunction
- Gastrointestinal perforation

DRUG INTERACTIONS

- CYP3A4 inhibitors (e.g., ketoconazole, fluconazole): Increase tofacitinib levels; dose reduction required.
- CYP3A4 inducers (e.g., rifampin): Decrease tofacitinib effectiveness.
- Immunosuppressants (e.g., azathioprine, cyclosporine): Increased risk of immunosuppression and infections.

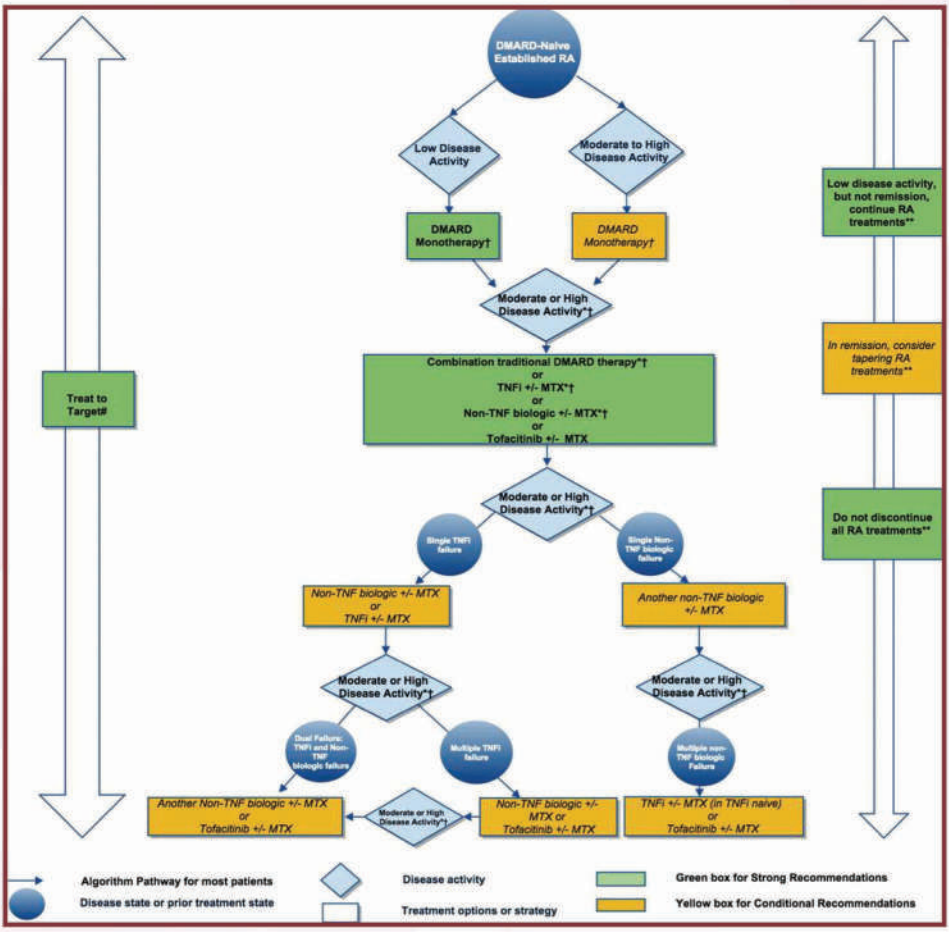
USE IN SPECIAL POPULATIONS

- **Pregnancy:** Use only if benefits outweigh potential risks. Not recommended due to potential fetal harm.
- **Lactation:** Not recommended; discontinue breastfeeding if treatment is necessary.
- **Pediatric Use:** Safety and efficacy not established in children under 18 years.
- **Geriatric Use:** Increased risk of infections and cardiovascular events; use with caution.
- **Renal/Hepatic Impairment:** Dose adjustments required.

CLINICAL GUIDELINES

ACR American College of Rheumatology

Usage of Tofacitinib in American College of Rheumatology Guideline for RA



TREATMENT OF ESTABLISHED RHEUMATOID ARTHRITIS (RA)

1.Initial Therapy (Methotrexate Naive)

For patients who are MTX-naïve and have moderate or high RA disease activity MTX with Tofacitinib is recommended

2.Following Failure of DMARDs

For patients who have moderate or high disease activity despite treatment with DMARD monotherapy or DMARD combination therapy, the recommendation is conditional for switching to MTX with Tofacitinib.

3.Following Failure of Non-Tumor Necrosis Factors Biologics

For patients who have moderate or high disease activity despite treatment with MTX + non-TNF biologic, the recommendation is conditional for switching to MTX-citinib.

Usage of Tofacitinib for Ulcerative Colitis in American College of Gastroenterology Guidelines

The American Journal of GASTROENTEROLOGY VOLUME 114 | MARCH 2019 www.amjgastro.com

Table 2. (*continued*)

25. In patients with moderately to severely active UC, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
26. In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
27. In patients with moderately to severely active UC, we recommend tofacitinib 10 mg orally b.i.d. for 8 wk to induce remission (strong recommendation, moderate quality of evidence).
28. In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend tofacitinib for induction of remission (strong recommendation, moderate quality of evidence).

ACG CLINICAL GUIDELINE UPDATE: ULCERATIVE COLITIS IN ADULTS

Induction of Remission in Moderately to Severely Active Ulcerative Colitis

- Tofacitinib is recommended

Maintenance of Remission in Previously Moderately to Severely Active Ulcerative Colitis

- To continue tofacitinib for maintenance of remission in patients after induction

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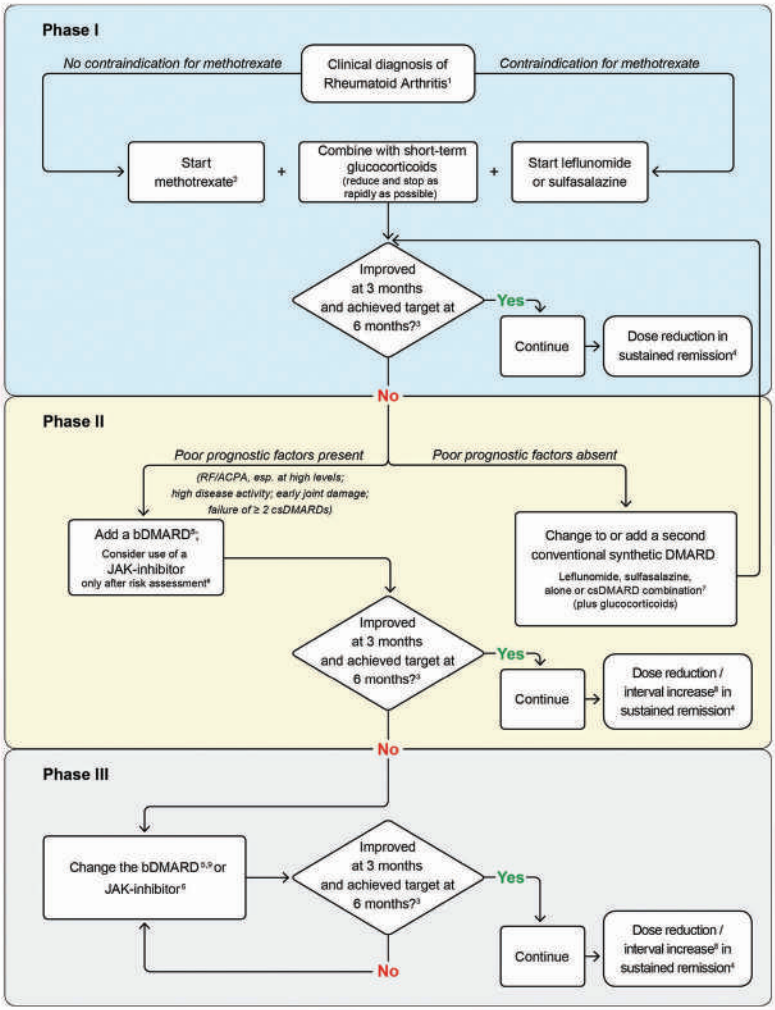
EUROPEAN CONGRESS OF RHEUMATOLOGY
2023 | 31 MAY - 03 JUNE

Usage of Tofacitinib in European Rheumatology Guideline for RA

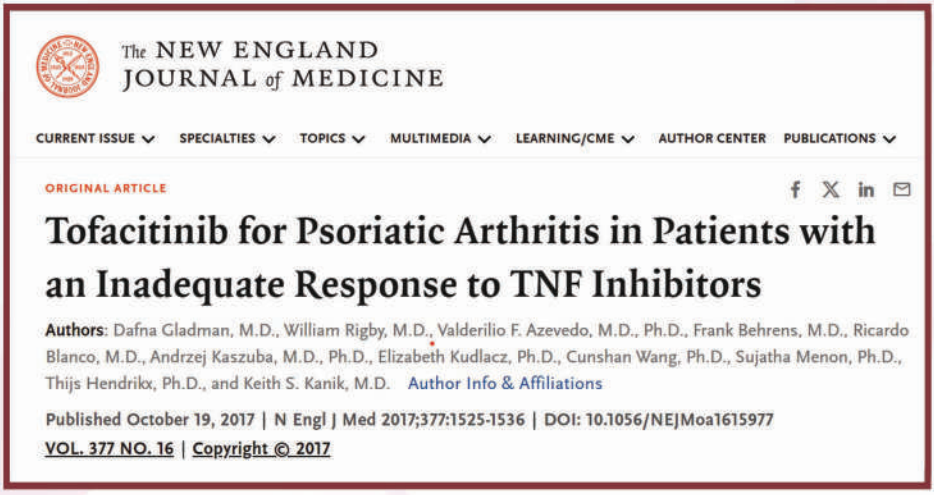


After using Cs DMARDs for 6 months (Phase I), and there is still poor prognosis

Consider JAK inhibitors or Biological DMARDs (Phase II) and there is still poor prognosis (But Risk assessment for JAK inhibitors has to be done)

CLINICAL TRIALS

Usage of Tofacitinib for Psoriasis Arthritis in New England Journal of Medicine and American College of Rheumatology Guideline



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS MULTIMEDIA LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors

Authors: Dafna Gladman, M.D., William Rigby, M.D., Valderilio F. Azevedo, M.D., Ph.D., Frank Behrens, M.D., Ricardo Blanco, M.D., Andrzej Kaszuba, M.D., Ph.D., Elizabeth Kudlacz, Ph.D., Cunshan Wang, Ph.D., Sujatha Menon, Ph.D., Thijs Hendrikx, Ph.D., and Keith S. Kanik, M.D. Author Info & Affiliations

Published October 19, 2017 | N Engl J Med 2017;377:1525-1536 | DOI: 10.1056/NEJMoa1615977
VOL. 377 NO. 16 | Copyright © 2017

BACKGROUND

Tofacitinib is an oral Janus kinase inhibitor that is under investigation for the treatment of psoriatic arthritis. We evaluated tofacitinib in patients with active psoriatic arthritis who had previously had an inadequate response to tumor necrosis factor (TNF) inhibitors.

METHODS

In this 6-month randomized, placebo-controlled, double-blind, phase 3 trial, we randomly assigned 395 patients, in a 2:2:1:1 ratio, to four regimens: 5 mg of tofacitinib administered orally twice daily (132 patients); 10 mg of tofacitinib twice daily (132 patients); placebo, with a switch to 5 mg of tofacitinib twice daily at 3 months (66 patients); or placebo, with a switch to 10 mg of tofacitinib twice daily at 3 months (65 patients). Data from the patients who received placebo during the first 3 months of the trial were pooled. The primary end points were the percentage of patients who had at least 20% improvement according to the criteria of the American College of Rheumatology (ACR20 response) and the change from baseline score on the Health Assessment Questionnaire–Disability Index (HAQ-DI; scores range from 0 to 3, with higher scores indicating greater disability) at the month 3 analysis.

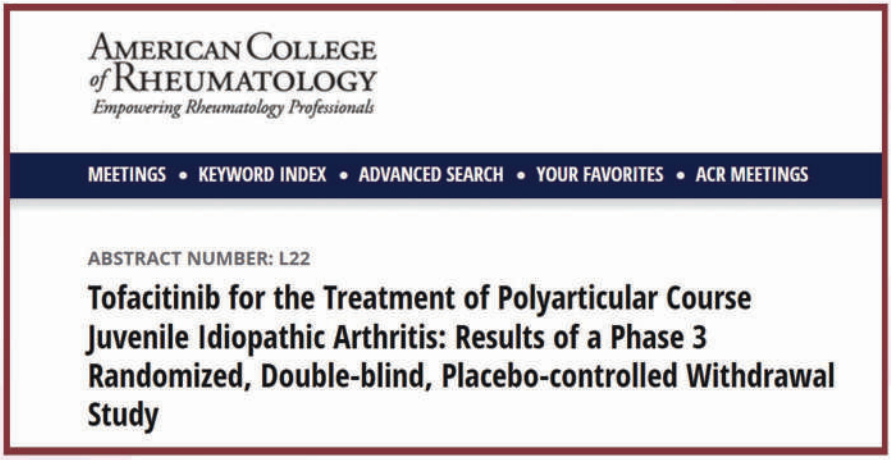
RESULTS

At 3 months, the rates of ACR20 response were 50% with the 5-mg dose of tofacitinib and 47% with the 10-mg dose, as compared with 24% with placebo.

CONCLUSIONS

In this trial involving patients with active psoriatic arthritis who had had an inadequate response to TNF inhibitors, tofacitinib was more effective than placebo over 3 months in reducing disease activity. Adverse events were more frequent with tofacitinib than with placebo.

Usage of Tofacitinib for Juvenile Idiopathic Arthritic in American College of Rheumatology



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MEETINGS • KEYWORD INDEX • ADVANCED SEARCH • YOUR FAVORITES • ACR MEETINGS

ABSTRACT NUMBER: L22

Tofacitinib for the Treatment of Polyarticular Course Juvenile Idiopathic Arthritis: Results of a Phase 3 Randomized, Double-blind, Placebo-controlled Withdrawal Study

BACKGROUND/PURPOSE

Tofacitinib is an oral JAK inhibitor that is being investigated for JIA. Here we assess the efficacy and safety of tofacitinib in patients (pts) with JIA.

METHODS

This was a Phase 3, randomized, double-blind (DB), placebo (PBO)-controlled withdrawal study in pts aged 2 to < 18 years with polyarticular course JIA (pcJIA), PsA or enthesitis-related arthritis (ERA) (NCT02592434). In the 18-week, open-label (OL), run in phase (Part 1), pts received tofacitinib. Pts achieving ≥ JIA ACR30 response1 at Week (W)18 were randomized 1:1 in the DB phase (W18–44; Part 2) to continue receiving tofacitinib or withdraw tofacitinib and newly receive PBO. Tofacitinib was administered according to body weight: 2–4 mg BID oral solution in pts < 40 kg; 5 mg BID tablet or oral solution in pts ≥ 40 kg. The primary endpoint was occurrence of disease flare2 by W44 (W26 of Part 2). Key secondary endpoints were JIA ACR50/30/70 response1 rates and change (Δ) from Part 2 baseline (BL) in Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) at W44.

RESULTS

225 pts with pcJIA (n=184), PsA (n=20) or ERA (n=21) were enrolled and received OL tofacitinib in Part 1 (Table 1). At W18, 173/225 (76.9%) pts entered Part 2 (pcJIA [n=142], PsA [n=15], ERA [n=16]). In pts with pcJIA, occurrence of disease flare in Part 2 was significantly lower with tofacitinib (29.2%) vs PBO (52.9%) by W44 (p=0.0041; primary endpoint; Figure 1a). JIA ACR50/30/70 response rates (Figure 1b) and improvement from Part 2 BL in CHAQ-DI (Figure 1c) at W44 were greater with tofacitinib vs PBO. Time to disease flare was greater with tofacitinib vs PBO in Part 2 (Figure 1d). Tofacitinib had a greater effect vs PBO in reducing signs and symptoms of pcJIA, in terms of Δ from Part 1 BL in JIA ACR core set variables at W44 (Figure 1e). From early time points in Part 2, disease activity (assessed by JADAS27-CRP) worsened with PBO but remained stable with tofacitinib (Figure 1f). Safety was generally similar in pts receiving tofacitinib or PBO (Table 2): 77.3% and 74.1% had adverse events (AEs); 1.1% and 2.4% had serious AEs. There were no cases of death, opportunistic infection or tuberculosis.

CONCLUSION

In pts with pcJIA, treatment with tofacitinib vs PBO resulted in significantly fewer disease flares, improved time to flare, improvements in disease signs and symptoms and physical functioning, and a sustained clinically meaningful improvement in disease activity. The safety profile of tofacitinib was consistent with that in adults with RA.

In Active Ankylosing Spondylitis, Tofacitinib has significant Efficacy

CLINICAL SCIENCE

Tofacitinib for the treatment of ankylosing spondylitis: a phase III, randomised, double-blind, placebo-controlled study

Atul Deodhar ,[1] Paula Sliwinska-Stanczyk,[2] Huji Xu ,[3] Xenofon Baraliakos ,[4] Lianne S Gensler,[5] Dona Fleishaker,[6] Lisy Wang,[6] Joseph Wu,[6] Sujatha Menon,[6] Cunshan Wang,[6] Oluwaseyi Dina,[7] Lara Fallon,[8] Keith S Kanik,[6] Désirée van der Heijde [9]

ABSTRACT

Objective To assess the efficacy/safety of tofacitinib in adult patients with active ankylosing spondylitis (AS).

METHODS

This phase III, randomised, double-blind, placebo-controlled study enrolled patients aged ≥18 years diagnosed with active AS, meeting the modified New York criteria, with centrally read radiographs, and an inadequate response or intolerance to ≥2 non-steroidal anti-inflammatory drugs. Patients were randomised 1:1 to receive tofacitinib 5mg two times per day or placebo for 16 weeks. After week 16, all patients received open-label tofacitinib until week 48. The primary and key secondary endpoints were Assessment of SpondyloArthritis international Society ≥20% improvement (ASAS20) and ≥40% improvement (ASAS40) responses, respectively, at week 16. Safety was assessed throughout.

RESULTS

269 patients were randomized and treated: tofacitinib, n=133; placebo, n=136. At week 16, the ASAS20 response rate was significantly greater with tofacitinib (56.4%, 75 of 133) versus placebo (29.4%, 40 of 136).

CONCLUSIONS

In adults with active AS, tofacitinib demonstrated significantly greater efficacy versus placebo. No new potential safety risks were identified.

Tofacitinib is effective and safe in UC patients in real practice

Journal of Crohn's and Colitis, 2021, 35–42
doi:10.1093/ecco-jcc/jjaa145
Advance Access publication September 24, 2020
Original Article

Original Article

Tofacitinib in Ulcerative Colitis: Real-world Evidence From the ENEIDA Registry

ABSTRACT

To evaluate the effectiveness and safety of tofacitinib in ulcerative colitis [UC] in real life.

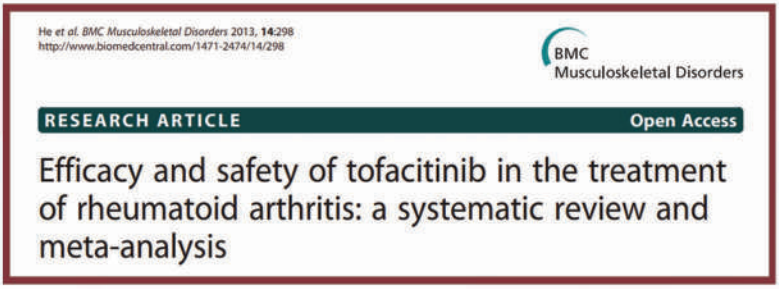
METHODS

Patients from the prospectively maintained ENEIDA registry and treated with tofacitinib due to active UC were included. Clinical activity and effectiveness were defined based on Partial Mayo Score [PMS]. Short-term response/remission was assessed at Weeks 4, 8, and 16. Results: A total of 113 patients were included. They were exposed to tofacitinib for a median time of 44 weeks. Response and remission at Week 8 were 60% and 31%, respectively. In multivariate analysis, higher PMS at Week 4 (odds ratio [OR] = 0].2; 95% confidence interval [CI] = 0].1–0.4) was the only variable associated with lower likelihood of achieving remission at Week 8. Higher PMS at Week 4 [OR = 0.5; 95% CI = 0.3–0.7] and higher PMS at Week 8 [OR = 0.2; 95% CI = 0.1–0.5] were associated with lower probability of achieving remission at Week 16.

CONCLUSIONS

Tofacitinib is effective and safe in UC patients in real practice, even in a highly refractory cohort. A relevant proportion of patients discontinue the drug over time, mainly due to primary failure.

Tofacitinib is efficacious and well tolerated in patients with MTX-resistant RA up to a period of 24 weeks


He et al. BMC Musculoskeletal Disorders 2013, 14:298
http://www.biomedcentral.com/1471-2474/14/298

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Efficacy and safety of tofacitinib in the treatment of rheumatoid arthritis: a systematic review and meta-analysis

ABSTRACT

Tofacitinib is a disease-modifying antirheumatic drug (DMARD) which was recently approved by US Food and Drug Administration (FDA). There are several randomised clinical trials (RCTs) that have investigated the efficacy and safety of tofacitinib in adult patients with rheumatoid arthritis (RA). A systematic review with a metaanalysis of RCTs was undertaken to determine the efficacy and safety of tofacitinib in treating patients with RA.

METHODS

Electronic and clinical trials register databases were searched for published RCTs of tofacitinib between 2009 and 2013. Outcomes of interest include 20% and 50% improvement in the American College of Rheumatology Scale (ACR20 and ACR50) response rates, rates of infection, the number of immunological/ haematological adverse events (AEs), deranged laboratory results (hepatic, renal, hematological tests and lipoprotein level) and the incidence of drug withdrawal.

RESULTS

Eight RCTs (n = 3,791) were reviewed. Significantly greater ACR20 response rates were observed in patients receiving tofacitinib 5 and 10 mg bid (twice daily) versus placebo at week 12, with risk ratios (RR) of 2.20 (95% CI 1.58, 3.07) and 2.38 (95% CI 1.81, 3.14) respectively. The effect was maintained at week 24 for 5 mg bid (RR 1.94; 95% CI 1.55, 2.44) and 10 mg bid (RR 2.20; 95% CI 1.76, 2.75). The ACR50 response rate was also significantly higher for patients receiving tofacitinib 5 mg bid (RR 2.91; 95% CI 2.03, 4.16) and 10 mg bid (RR 3.32; 95% CI 2.33, 4.72) compared to placebo at week 12. Patients in the tofacitinib group had significantly lower mean neutrophil counts, higher serum creatinine, higher percentage change of LDL/HDL and a higher risk of ALT/AST > 1 ULN (upper limit of normal) versus placebo. There were no significant differences in AEs and withdrawal due to AEs compared to placebo.

CONCLUSION

Tofacitinib is efficacious and well tolerated in patients with MTX-resistant RA up to a period of 24 weeks. However, haematological, liver function tests and lipoproteins should be monitored. Long-term efficacy and pharmacovigilance studies are recommended.

The efficacy of tofacitinib is superior in previously inadequate response to conventional synthetic DMARDs

ORIGINAL ARTICLE

Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis

P. Mease, S. Hall, O. FitzGerald, D. van der Heijde, J.F. Merola, F. Avila-Zapata, D. Cieślak, D. Graham, C. Wang, S. Menon, T. Hendrikx, and K.S. Kanik

BACKGROUND

We evaluated tofacitinib in patients with active psoriatic arthritis who previously had an inadequate response to conventional synthetic disease modifying antirheumatic drugs (DMARDs).

METHODS

In this 12-month, double-blind, active-controlled and placebo-controlled, phase 3 trial, we randomly assigned patients in a 2:2:2:1:1 ratio to receive one of the following regimens: tofacitinib at a 5-mg dose taken orally twice daily (107 patients), tofacitinib at a 10-mg dose taken orally twice daily (104), adalimumab at a 40-mg dose administered subcutaneously once every 2 weeks (106), placebo with a blinded switch to the 5-mg tofacitinib dose at 3 months (52), or placebo with a blinded switch to the 10-mg tofacitinib dose at 3 months (53).

RESULTS

ACR20 response rates at month 3 were 50% in the 5-mg tofacitinib group and 61% in the 10-mg tofacitinib group, as compared with 33% in the placebo group (P=0.01 for the comparison of the 5-mg dose with placebo.

CONCLUSIONS

The efficacy of tofacitinib was superior to that of placebo at month 3 in patients with psoriatic arthritis who had previously had an inadequate response to conventional synthetic DMARDs.

Tofacitinib has shown good efficacy and safety in the treatment of sJIA patients,

Tofacitinib treatment of systemic juvenile idiopathic arthritis: a case report and literature review

Meifang Zhu[1†], Yan Zhao[2†], Xiaohua Zhang[1†], Peng Zhou[1†], Jing Jin[1], Zhidan Fan[1*] and Haiguo Yu[1*]

OBJECTIVE

Systemic juvenile idiopathic arthritis (sJIA), a particularly aggressive form of childhood arthritis, is characterized by persistent systemic inflammation. The most advanced treatments include biologic agents that target the interleukin-1 (IL-1) and interleukin-6(IL-6) pathways. However, sJIA continue to pose challenging challenges for rheumatologists treating pediatric patients worldwide.

METHODS

1 children with sJIA was retrospectively collected from the Department of Rheumatology and immunology, Children's Hospital of Nanjing Medical University, Nanjing. Literature published between 2019 and 2024 was reviewed to understand the effect of tofacitinib on patients with sJIA.

RESULTS

After a month of treatment of tofacitinib, there was a significant improvement in clinical symptoms and inflammatory indicators showed a marked decrease. As of July 2023, the patient's condition was effectively in remission. The efficacy of tofacitinib treatment was remarkable.

CONCLUSION

Tofacitinib has shown good efficacy and safety in the treatment of sJIA patients, effectively controlling disease activity and relieving symptoms. The application of Janus kinase (JAK) inhibitors may offer a new treatment option for this disease.

Tofacitinib 7.8 Years of Safety Data from the Global Clinical Program

Journal of Crohn's and Colitis, 2023, **17**, 338–351
https://doi.org/10.1093/ecco-jcc/jjac141
Advance access publication 17 September 2022
Original Article

Tofacitinib for the Treatment of Ulcerative Colitis: An Integrated Summary of up to 7.8 Years of Safety Data from the Global Clinical Programme

William J. Sandborn,[a] Geert R. D'Haens,[b] Bruce E. Sands,[c] Remo Panaccione,[d] Siew C. Ng,[e] Nervin Lawendy,[f] Nicole Kulisek,[f] Irene Modesto,[g] Xiang Guo,[f] Rajiv Mundayat,[g] Chinyu Su,[f] Ivana Vranic,[h] Julian Panés[i]

ABSTRACT

Tofacitinib is an oral small molecule Janus kinase [JAK] inhibitor for the treatment of ulcerative colitis. We report an integrated summary of tofacitinib safety [exposure: ≤ 7.8 years] from the global clinical programme.

METHODS

Patients receiving tofacitinib 5 or 10 mg twice daily [BID] from completed phase [P]2/3 placebo-controlled studies, an open-label, long-term extension study [final data cut-off: August 24, 2020], and interim analysis of a P3b/4 study (interim data cut-off: February 20, 2020; Overall plus P3b/4 [2020] Cohort) were included. Proportions with adverse events [AEs] and serious AEs, and incidence rates [IRs; unique patients with events/100 patient-years] for deaths and AEs of special interest [AESI] were evaluated. Opportunistic infections, malignancies, major adverse cardiovascular events [MACE] and gastrointestinal perforations were adjudicated.

RESULTS

In total, 1157 patients received one or more dose of tofacitinib (mean duration: 946.9 days); 955/1157 [83%] received a predominant dose of 10 mg BID; 412/1157 [35.6%] received tofacitinib for >4 years; 992/1157 [85.7%] had AEs, 244/1157 [21.1%] had serious AEs and 134/1157 (11.6%) discontinued use due to AEs. IRs [95% confidence intervals] for all tofacitinib doses were: deaths, 0.23 [0.09–0.46]; serious infections, 1.69 [1.26–2.21]; herpes zoster [non-serious and serious], 3.30 [2.67–4.04]; opportunistic infections, 1.03 [0.70–1.46]; malignancies (excluding non-melanoma skin cancer [NMSC]), 0.84 [0.55–1.24]; NMSC, 0.73 [0.45–1.10]; MACE, 0.29 [0.13–0.55]; deep vein thrombosis, 0.03 [0.00–0.18]; pulmonary embolism, 0.19 [0.07–0.42]; gastrointestinal perforations, 0.10 [0.02–0.28].

CONCLUSIONS

AESI IRs were stable to 7.8 years.

COMPARISON BETWEEN JAK INHIBITORS

Feature	Tofacitinib (Xeljanz®)	Baricitinib (Olumiant®)
Drug Class	JAK inhibitor (JAK1 & JAK3; weak JAK2 inhibition)	JAK inhibitor (Selective JAK1 & JAK2)
Mechanism of Action	Inhibits JAK1 and JAK3, leading to decreased cytokine signaling involved in inflammation	Primarily inhibits JAK1 and JAK2, which are involved in cytokine-mediated immune regulation
FDA Approval Year	2012 (for RA)	2018 (for RA)
FDA-Approved Indications	- Rheumatoid Arthritis (RA) (2012) - Psoriatic Arthritis (PsA) (2017) - Ulcerative Colitis (UC) (2018) - Juvenile Idiopathic Arthritis (JIA) (2020) - Ankylosing Spondylitis (AS) (2021) - COVID-19 (Emergency Use) (2020)	- Rheumatoid Arthritis (RA) (2018) - Alopecia Areata (2022) - COVID-19 (Emergency Use) (2021)
Dosing for RA	- Oral: 5 mg twice daily (BID) OR 11 mg once daily (XR)	- Oral: 2 mg once daily
Dosing for Other Indications	- PsA & AS: 5 mg BID - UC Induction: 10 mg BID for 8 weeks, then 5 mg BID for maintenance - JIA: Weight-based dosing - COVID-19: Off-label, varies	- Alopecia Areata: 2 mg or 4 mg once daily - COVID-19: 4 mg once daily for hospitalized patients
Metabolism & Elimination	Hepatic (CYP3A4, CYP2C19) metabolism, renal elimination	Primarily renal elimination

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Tocinib 5/10 PRODUCT MONOGRAPH

TOCINIB

Brand Name	: Tocinib 5 & Tocinib 10
Generic Name	: Tofacitinib
Dosage Forms and Strengths	: Tablets: 5 mg, 10 mg
Route of Administration	: Oral
Pharmacologic Class	: Janus Kinase (JAK) Inhibitor

Zifam

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