WICIUN, Olympia, SKONIECZNA, Karolina, ORDON, Kacper, BADZIĄG, Magdalena, SZULC, Paulina, KURCZOBA, Laura, KŁOSSOWSKA, Martyna and KĄDZIOŁKA, Olga. Janus Kinase Inhibitors in the Treatment of Crohn's Disease and Ulcerative Colitis: A Review. Quality in Sport. 2025;41:60398. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.41.60398
https://apcz.umk.pl/QS/article/view/60398

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 17.04.2025. Revised: 30.04.2025. Accepted: 12.05.2025. Published: 12.05.2025.

Janus Kinase Inhibitors in the Treatment of Crohn's Disease and Ulcerative Colitis: A Review

Authors:

1. **Olimpia Wiciun [OW]**
   Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz
   https://orcid.org/0000-0002-1264-0481
   wiciunolimpia@gmail.com
2. **Karolina Skonieczna [KS]**
   Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz
   https://orcid.org/0009-0009-0153-7444
   karolina.skonieczna05@gmail.com
3. **Kacper Ordon [KO]**
   Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz
   https://orcid.org/0009-0000-1764-3422
   kacper.ordon1c@wp.pl

4. **Magdalena Badziąg [MB]**
   University Clinical Center in Gdansk, Poland
   80-952 Gdansk, Debinki 7
   https://orcid.org/0009-0008-8598-1034
   badziagmagdalena@gmail.com
5. **Paulina Szulc [PS]**
   Dr Jan Biziel's University Hospital No. 2
   Ujejskiego 75, 85-168 Bydgoszcz
   https://orcid.org/0009-0007-7614-9214
   paulinaszulc210@gmail.com
6. **Martyna Kłossowska [MK]**
   Baltic Clinic Sp. z o.o.
   ul. Wielkokacka 2, 81-611 Gdynia, Poland
   https://orcid.org/0009-0002-7444-1637
   marklossowska@gmail.com
7. **Laura Kurczoba [LK]**
   Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz
   https://orcid.org/0009-0004-1330-991X
   laurakurczoba@vp.pl
8. **Olga Kądziołka [OK]**
   Independent Public Health Care Facility in Szamotuły, Sukiennicza 13, 64-500 Szamotuły
   https://orcid.org/0009-0006-1052-4504
   olgkadz9393@gmail.com

Abstract

Introduction and purpose: Insufficient efficacy and adverse effects of classical therapies for inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, have prompted the search for new, more targeted treatment methods. Janus kinase (JAK) inhibitors are a new group of oral drugs that modulate the proinflammatory cytokine signaling pathway. The aim of this review is to present the state of knowledge on the efficacy and safety of currently registered JAK inhibitors in the treatment of IBD.

Review Methods: A systematic search of the PubMed database was conducted, focusing on publications from the last five years as well as selected key earlier studies. The search strategy included relevant keywords related to Janus kinase (JAK) inhibitors and inflammatory bowel disease (IBD). The most pertinent articles aligned with the study objective were reviewed and included.

State of knowledge: JAK inhibitors, such as tofacitinib, upadacitinib, and filgotinib, have shown high efficacy in the treatment of moderate to severe UC and CD, especially in patients with insufficient biological therapy response. Clinical studies confirm their efficacy in inducing and maintaining remission and improving endoscopic findings. The most common adverse events are infections (including herpes zoster), and elevation of creatine kinase and lipids. The safety profile remains acceptable, although it requires monitoring, especially at higher doses, and further investigation.

Summary: JAK inhibitors are an effective and promising therapeutic option for IBD, offering a rapid onset of action and good symptom control. Despite the favorable clinical effects, an individual approach to treatment and monitoring for adverse effects are necessary, especially with long-term use.

Key words: Janus kinase inhibitors, Crohn’s disease, ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic inflammatory diseases of the digestive system. It is characterized by symptoms such as abdominal pain, chronic diarrhea with blood, mucus, pus, rectal bleeding, weight loss, fatigue, and sometimes fever, and if left untreated, can lead to serious complications, including gastrointestinal haemorrhage, narrowing of the lumen due to the formation of post-inflammatory fibrous scar tissue, abscesses, fistulas, peritonitis, and even cancer. [1] These diseases cause a decrease in the quality of life and an economic burden on health systems. [2]

Epidemiological data indicate that due to the increasing incidence of IBD in developing countries (primarily in East Asian countries), the global number of patients will continue to increase. [3]

The exact cause of these diseases has not been confirmed yet, but they are associated with genetic mutations, environmental factors along with a disturbed intestinal microbiome and an abnormal immune response [4]. Inflammatory bowel disease has been included in the group of Immune Mediated Inflammatory Diseases, which also includes rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondylarthritis, atopic dermatitis, alopecia areata. Although different in terms of pathophysiology, all these diseases are

characterized by inadequate synthesis of proinflammatory cytokines. The common ones for CD and UC are: TNF-α**,** IL-1β, IL-6. [5,6,7] In turn, it has been shown that in the case of Crohn's disease, there is an increased activity of T helper cells: Th1 and Th17 and increased production of IL-12, IL-23, IFN-γ and IL-17. At the same time, ulcerative colitis is usually associated with Th2 and Th9 activity with an overproduction of IL-13, IL-5 and IL-9. [2,8] The knowledge of these inflammatory mediators has allowed the development of medications that neutralize these molecules, thereby reducing inflammation, which includes biological therapy. [5]

At the end of the 20th century, the introduction of anti-TNF-α drugs to the market revolutionized the treatment of inflammatory bowel disease. These drugs proved to be much more effective in achieving clinical remission than aminosalicylates, corticosteroids, or immunomodulators. [9] However, over time, it was observed that some patients lost the expected response to treatment due to the development of antibodies against the administered drug, or patients began to experience side effects which lead to the discontinuation of the implemented treatment. [10,11,12] To avoid immunogenicity, immunomodulatory drugs can be used, but such a choice of therapy is burdened with the risk of developing serious infection or even malignancy. [9] In the treatment of IBD, drugs targeting the interleukin 12/23 axis (ustekinumab) and lymphocyte tracking (vedolizumab) are also available. Despite lower immunogenicity in relation to TNF-α antagonists [13], these drugs are administered parenterally, which additionally burdens the healthcare system and patients. [9] The goal of an effective IBD treatment is long-term clinical remission, prevention of complications and achieving mucosal healing in the endoscopic image, which is associated with less frequent disease relapse. [11] Considering the unsatisfactory results of IBD treatment in some patients, a new type of drug, Janus kinase (JAK) inhibitors, was included in the therapy. They were first used in rheumatology, and in 2018 the European Medicines Agency approved their use in the treatment of IBD. [14] Small Molecule Drugs (SMD), which include JAK inhibitors, are low molecular weight drugs that easily diffuse through cell membranes and are quickly absorbed into the circulatory system. The main advantages of these drugs are oral administration, rapid onset of action, short half-life, which is helpful in the event of infection or surgery and the need to temporarily discontinue the drug, as well as the lack of specific antibody formation. [9] JAK inhibitors act by blocking the signalling pathway, as opposed to most biological therapies which work by binding to a single cytokine receptor or the cytokine itself. [15] JAK inhibitors are a novel, promising group of drugs in the treatment of IBD, especially in patients who have not achieved or stopped having clinical improvement with

biological therapy. The aim of this review is to present the state of knowledge on the efficacy and safety of currently registered JAK inhibitors in the treatment of IBD.

Methods

A systematic search of the PubMed database was conducted, focusing on publications from the last five years as well as selected key earlier studies. The search strategy included relevant keywords related to Janus kinase (JAK) inhibitors and inflammatory bowel disease (IBD). Clinical trials, systematic reviews, and meta-analyses that provided relevant information on the efficacy and safety of tofacitinib, upadacitinib, and filgotinib in the treatment of ulcerative colitis and Crohn's disease were included in the analysis. The most relevant articles in line with the aim of the study were selected.

2. State of knowledge

2.1 JAK and JAK/STAT pathway

To understand how JAK inhibitors work, it is necessary first to learn what Janus kinases are and the pathway they participate in. The JAK family includes JAK1, JAK2, JAK3 and TYK2 (tyrosine kinase 2) [11]. These are tyrosine kinases associated with intracellular regions of class I and II cytokine receptors. The name of these kinases is derived from the property of JAKs, which is the presence of two kinase domains, one of which has enzymatic properties and the other controls the action of the first one by negative feedback. They have, therefore, been compared to the Roman god of duality - Janus, with two faces [16]. Three members of the Janus kinase family, JAK1, JAK2, and TYK2, are found in all cell types, while JAK3 is found in hematopoietic cells. [11]

The JAK/STAT pathway is composed of three main elements: a cell surface receptor, at least two Janus kinases, and Signal Transducer and Activator of Transcription (STAT) proteins. [16] The STAT family consists of seven proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. [17] The binding of a cytokine to the receptor causes conformational changes in the receptor, which results in the phosphorylation of JAK tyrosine residues, which allows the recruitment and phosphorylation of STAT proteins. Then, the phosphorylated STATs undergo dimerization and, in this form, move to the cell nucleus to activate transcription of the cytokine-encoding gene. [5]

It has been confirmed that more than 50 cytokines can activate the JAK/STAT pathway, influencing various regulatory and metabolic functions and participating in haematopoiesis and immune response. [17]

JAK inhibitors block the JAK/STAT pathway by competitively binding to JAK at the ATP binding site, preventing JAK phosphorylation, STAT recruitment, and gene transcription with cytokine synthesis. The ATP binding site on JAK is type-specific, allowing for selective JAK inhibitor binding. [18]

Depending on the type of Janus kinases inhibited, there are selective inhibitors and those that block all types of Janus kinases (pan-JAK inhibitors). The advantage of selective JAK inhibitors is the possibility of achieving symptom relief, and reducing inflammation, using lower doses of the medication with reduced side effects, as opposed to pan-JAK inhibitors. [9]

2.2 Tofacitinib

Tofacitinib was the first JAK inhibitor approved for the treatment of ulcerative colitis, introduced in 2018. [19] It is classified as a pan-JAK inhibitor but preferentially inhibits JAK1 and JAK3 [11] and is mainly used in patients with an unsatisfactory response to biological therapy. [20] Due to previously reported adverse events with tofacitinib in treating rheumatoid diseases, a number of studies were conducted to establish the safety of this medication in patients with IBD.

Phase III clinical trial OCTAVE evaluated the efficacy of tofacitinib treatment in patients with moderate-to-severe ulcerative colitis. A total of 1139 patients were enrolled in the induction phase (OCTAVE Induction 1 and 2), receiving tofacitinib at a dose of 10 mg twice daily or placebo. The first end point was clinical remission after 8 weeks of therapy. Maintenance treatment (OCTAVE Sustain) included 593 patients who received tofacitinib at a dose of 5 mg or 10 mg twice daily or placebo for 52 weeks. The results of the study were satisfactory. In the OCTAVE Induction 1 study, remission after 8 weeks occurred in 18.5% of patients compared to 8.2% of patients in the placebo group ($p=0.007$). In the OCTAVE Induction 2 study, remission was achieved in 16.6% of patients compared to 3.6% of patients in the placebo group ($p<0.001$), while in the OCTAVE Sustain study, remission at 52 weeks was observed in 34.3% of patients in the tofacitinib 5 mg group and in 40.6% of patients in the tofacitinib 10 mg group compared to 11.1% of patients in the placebo group ($p<0.001$). In addition, at week 52 mucosal healing was achieved in 37.4% of patients in the tofacitinib 5

mg maintenance dose group, 45.7% of patients in the tofacitinib 10 mg group compared to 13.1% of patients in the placebo group ($p<0.001$). Adverse events reported more frequently in the study group than in the placebo group included general infections, herpes zoster virus infection, cardiovascular events, and increased lipid and creatine kinase levels. [21]

The next step was a study assessing the safety and tolerability of long-term (up to 7 years) tofacitinib in patients with moderate or severe ulcerative colitis (OCTAVE Open). A total of 944 patients were qualified for the study, 175 of whom received tofacitinib at a dose of 5 mg and 769 patients receiving 10 mg tofacitinib, both twice daily. Comparing other medications used to treat UC, including biological drugs, tofacitinib showed a similar safety profile. This study confirmed that the risk of herpes zoster infection is higher, but as many as 90.4% of infected patients had a mild course of this disease. In addition, in the 36th month of the study, the effectiveness of UC therapy was assessed in the endoscopic image. It was noted that in the group of patients receiving tofacitinib at a dose of 5 mg and in the group of patients receiving tofacitinib 10 mg, endoscopic improvement was achieved in 93% and 86.3% of patients, respectively. [22]

Ollech et al., in the pragmatic prospective real-world study published in 2024, assessed the efficacy and safety of tofacitinib during an 8-week induction phase in patients with UC. Disease activity was evaluated at the baseline and after 8 weeks of tofacitinib treatment by the Mayo Score, faecal calprotectin, endoscopic Mayo sub-score, and sigmoidal bowel wall through intestinal ultrasound. Thirty patients were included in the study, of whom 27 completed the entire trial. One patient developed localized herpes zoster which resolved spontaneously. Tofacitinib induction for 8 weeks in patients with UC was shown to be associated with improvement in all aspects of the disease and no new side effects were noted, which is consistent with previous studies. The study authors emphasize the role of prospective studies of tofacitinib in real-world conditions to better evaluate tofacitinib therapy. [23]

Patients with UC may develop Acute Severe Ulcerative Colitis (ASUC). This form of UC can affect up to 25% of patients, who may progress to toxic megacolon, colectomy, or even death. Unfortunately, many patients do not respond to standard corticosteroid or biological therapies, so there is still a need to find effective drugs that will protect patients with ASUC from dangerous complications. [31][24] The multicenter, prospective TRIUMPH study, involving five Canadian hospitals, evaluated the efficacy of tofacitinib in patients with ASUC. The study included 24 adult patients with new or previously diagnosed UC who had disease progression and developed ASUC. All participants of the study underwent sigmoidoscopy for endoscopic evaluation and got a minimum score of 10 according to

Modified Trulove-Witts Severity Index (MTWSI) despite receiving intravenous corticosteroids at a dose of 50 mg prednisone daily for at least three days. One-third of patients were noted to have been nonresponsive to prior anti-TNF therapy. Patients were then given 10 mg tofacitinib twice daily and were assessed using the MTWSI, partial Mayo scores, and serum C-reactive protein daily during their hospitalization. On day seven, 14 out of 24 patients (58.3%) achieved a clinical response. The median time to significant clinical improvement was also shown to be approximately 2.43 days. During the entire study, 5 participants (21%) reported adverse events such as headache, tachycardia, nausea, or decreased appetite, but all were mild. [25]

In a phase II clinical trial, tofacitinib was administered to patients with Crohn's disease twice daily at a dose of 10 mg or 5 mg twice daily. Remission was achieved in 43% and 43.5% of patients, respectively, compared with a placebo group with a remission rate of 36.7%. The study showed that tofacitinib was ineffective in treating Crohn’s disease. [26]

There is a need for more prospective studies on the efficacy and safety of tofacitinib in moderate to severe UC. According to the updated American Gastroenterological Association (AGA) guidelines, tofacitinib should only be used in patients who have failed or lost clinical response to anti-TNFs. In turn, the American College of Gastroenterology and ECCO guidelines from 2022 recommend the inclusion of tofacitinib as a first-line drug in patients with UC after a thorough analysis of the patient's exposure to adverse events. Due to the low availability of biological therapy in India, studies on the use of tofacitinib in biological therapy-naive patients suffering from UC are being conducted, which may help in better evaluation of tofacitinib as a first-line drug. [27]

2.3 Filgotinib

Filgotinib is another drug from the group of JAK inhibitors blocking JAK1. In contrast to tofacitinib, filgotinib is used once daily. The phase 2b/3, double-blind, randomised, placebo-controlled trial (SELECTION) was the first study to assess the efficacy and safety of filgotinib in adult patients with UC. The study included induction phases A and B and the maintenance study, which included a total of 2040 patients with UC. Data was collected from 341 centers from forty countries. Induction study A included 659 patients, who were divided into three groups receiving filgotinib at a dose of 100 mg, 200 mg, or a placebo, respectively. Induction phase B included 689 patients who were divided the same way as in induction phase A. Clinical remission was assessed using Mayo endoscopic, rectal bleeding and stool

frequency subscores. At week 10 of the study, clinical improvement with filgotinib treatment in induction phase A was demonstrated in 26.1% of patients receiving filgotinib at a dose of 200 mg compared to 15.3% in the control group (absolute difference 10.8%, 95% CI 2.1-19.5, p=0.0157), and in induction phase B in 11.5% of patients receiving 200 mg of the drug compared to 4.2% in the placebo group (absolute difference 7.2%, 95% CI 1.6-12.8, p=0.0103). Patients in both induction phases receiving filgotinib at a dose of 100 mg did not achieve statistically significant differences in clinical remission compared to the placebo group. The maintenance study included 391 patients from induction phase A and 273 from induction phase B, and 93 remained in the placebo group. The treatment's efficacy was assessed at week 58 of the study. Clinical remission was demonstrated in 37.2% of patients in the filgotinib 200 mg group compared to 11.2% in the placebo group (absolute difference 26.0%, 95% CI 16.0-35.9, p<0.0001) and in 23.8% of patients in the filgotinib 100 mg group compared to 13.5% in the placebo group (absolute difference 10.4%, 95% CI 0.0-20.7, p=0.0420). Additionally, in both induction and maintenance studies, patients in the filgotinib 100 mg and 200 mg groups achieved endoscopic improvement. The incidence of adverse events in the induction and maintenance studies was similar in all groups. The most common adverse events were nasopharyngitis, headache and worsening of UC in both Induction and Maintenance Phase trials. Most adverse events were mild or moderate. Elevation in blood lipid levels and creatine kinase were observed in the filgotinib groups, but no cases of rhabdomyolysis were reported. [28]

Subsequently, the ongoing SELECTION long-term extension (LTE) study was initiated to evaluate the long-term efficacy and safety of treatment with filgotinib in patients with UC. In the published interim analysis, 86 patients were enrolled in the study who received either filgotinib 100 mg or filgotinib 200 mg during the induction phase. Patients discontinued treatment until clinical deterioration and then received filgotinib 200 mg. Efficacy was assessed at week 48 of the study and showed that 45.1% of patients receiving filgotinib 200 mg and 51.4% of patients receiving filgotinib 100 mg achieved clinical remission. Additionally, no new adverse events were reported during the study. [29]

In the cohort study by Gros et al., the first real-world experience on the use of filgotinib in patients with UC in clinical practice was presented. The study included 91 patients, 89 of whom received filgotinib at a dose of 200 mg and 2 patients received filgotinib at a dose of 100 mg. During the study, clinical, biochemical and faecal parameters were assessed with significant improvement of these parameters at weeks 12 and 24. Adverse events were reported by 15 (16.5%) patients, including headache, fatigue, mild nausea and

arthralgia in 5 patients, while 8 (8.8%) patients had to temporarily discontinue treatment due to 5 respiratory tract infections, one facial Herpes Zoster and two mild COVID-19 infections. In 2 patients, treatment was discontinued completely for reasons most likely unrelated to filgotinib treatment. No increase in lipid levels was observed in this study, but this may have been due to the fact that 15.4% of patients had low lipid levels prior to the study. [30]

A randomized, double-blind, placebo-controlled phase II study to evaluate the efficacy and safety of filgotinib in the treatment of moderate-to-severe Crohn's disease (FITZROY) was conducted in 2014 and 2015. The study included 172 patients with active Crohn's disease and the intention-to-treat, of whom 128 received filgotinib 200 mg and the remaining 44 received placebo. At week 10 of the study, clinical remission was observed in 60 (47%) patients compared with 10 (23%) in the placebo group (absolute difference 24%, 95% CI 9-39, p=0.0077). Patients were then assigned to one of three groups: filgotinib 200 mg, filgotinib 100 mg, or placebo. Adverse events were reported by 114 (75%) patients in the filgotinib group and 45 (67%) patients in the placebo group, and serious adverse events were reported by 14 (9%) patients in the fligotinib group and 3 (4%) patients in the placebo group. Filgotinib therapy was observed to be associated with an increase in HDL and LDL levels between weeks 0 and 20 of filgotinib treatment. The study demonstrated that filgotinib is an effective and safe treatment for patients with active CD. [31]

A recently published phase III, double-blind, randomized, placebo-controlled trial (DIVERSITY) evaluated the efficacy and safety of induction and maintenance therapy with filgotinib in patients with moderate-to-severe CD. The study enrolled 1,372 adult patients who were assigned to induction study A (biologic-naive and later biologic-experienced patients) or B (biologic-experienced patients) and received oral filgotinib 200 mg, filgotinib 100 mg, or placebo for 11 weeks. Patients receiving filgotinib who had a two-item patient-reported outcome (PRO2) clinical remission or endoscopic remission were then assigned to receive the induction dose during the maintanance study in the week 10 of the study. Further clinical and endoscopic were assessed at week 58. Clinical remission was evaluated using the EU-specific (PRO2) and non-EU-specific (CDAI) scales. Induction study A did not demonstrate significant PRO2 clinical remission in patients receiving filgotinib 200 mg versus placebo (absolute difference 6.9%, 95% CI 1.4-15.2, p=0.0963), however induction study B demonstrated statistically significant clinical improvement in patients receiving filgotinib 200 mg versus placebo (absolute difference 11.9%, 95% CI 3.7-20.2, p=0.0039). In both induction studies, endoscopic response was not achieved. In turn, significant PRO2 clinical remission (absolute difference 16.8%, 95% CI 2.0-31.6, p=0.0382) and endoscopic remission (absolute

difference 20.6%, 95% CI 8.2-33.1, p=0.0038) were achieved in filgotinib group compared to the placebo in the maintenance study at week 58. The study did not demonstrate significant clinical or endoscopic improvement with the 100 mg dose of filgotinib in any study. The most common adverse events reported by patients in the induction study included: abdominal pain, arthralgia, an exacerbation, flare or worsening of CD, headache, nasopharyngitis nausea and pyrexia, while in the maintenance study, in addition to those reported in the induction study (except for the headache), abdominal distension, upper abdominal pain, anaemia and flatulence were also noted as the most common adverse events. In the induction studies, a few serious treatment-emergent adverse events (TEAEs) were reported in patients receiving filgotinib: Herpes Zoster infection, major adverse cardiovascular event, and gastrointestinal perforation (unrelated to treatment). In the maintenance study, the following serious TEAEs were reported: exacerbation, flare or worsening of CD, Herpes Zoster infection, malignancy of unknown origin (lung metastases), non-melanoma skin cancer, deep vein thrombosis, and gastrointestinal perforation. Despite not meeting the PRO2 clinical and endoscopic remission in the induction studies (EU specific analyses), the DIVERSITY study demonstrated the efficacy of filgotinib 200 mg in the maintenance studies. Filgotinib treatment was well tolerated by patients and the safety of filgotinib in patients with CD was comparable to the safety profile in different indications. [32]

2.4 Upadacitinib

Upadacitinib is a once daily JAK inhibitor with the strongest selectivity towards JAK1. [20] In March 2022, the US Food and Drug Administration approved upadacitinib as a medication for the treatment of moderate-to-severe UC in patients with an inadequate or poor tolerance of TNF inhibitors. [33] Sandborn et al. in the multicenter, double-blind, phase 2b trial evaluated the safety and efficacy of upadacitinib as an induction therapy for patients with moderate to severe active UC (U-ACHIEVE). Participants received upadacitinib at a dose of 7.5 mg, 15 mg, 30 mg, 45 mg, or placebo. Clinical assessment took place at week 8 of the study, which demonstrated statistically significant clinical and endoscopic improvement among patients in each upadacitinib-receiving group compared with placebo. During the study, a moderate Herpes Zoster infection and a case of pulmonary embolism (severe adverse event) and deep venous thrombosis (mild adverse event) were reported in patients receiving 45 mg of upadacitinib. Significantly increased lipid levels and creatine kinase were also observed in

patients receiving upadacitinib compared to placebo. No cases of gastrointestinal perforation or death were reported. [34]

To well evaluate the efficacy and safety of upadacitinib in patients with moderate to severe UC over the long term, a phase 3, multicentre, randomised, double-blind, placebo-controlled study was conducted. The trial was divided into two induction studies (U-ACHIEVE substudy 2 [UC1] and U-ACCOMPLISH [UC2]) and a maintenance study (U-ACHIEVE substudy 3 [UC3]). Patients who achieved a clinical response with upadacitinib 45 mg at week 8 or 16 of the induction study (UC1 or UC2) and patients with clinical remission from phase 2b (U-ACHIEVE substudy 1) were eligible for the maintenance study. In the maintenance study, patients received upadacitinib 15 mg, 30 mg or placebo once daily for 52 weeks. At week 8 of the induction studies, clinical remission was achieved by statistically more patients receiving upadacitinib compared with placebo (absolute difference 21.6%, 95% CI 15.8-27.4, $p<0.0001$ for UC1; absolute difference 29%, 95% CI 23.2-34.7, $p<0.0001$ for UC2). Additionally, in the upadacitinib, 45 mg once daily group, all secondary endpoints were met in both UC1 and UC2, such as improvement in disease activity, symptoms, endoscopic and histological response, QOL, faecal calprotectin, and serum C-reactive protein. Adverse event reporting was comparable in the upadacitinib 45 mg group versus placebo in UC1 but it was more common in patients in the upadacitinib 45 mg group in UC2. The most frequently reported side effects were nasopharyngitis, creatine kinase elevation (UC1) and acne (UC1 and UC2). Cases of Herpes Zoster infection (1 case in UC1 and 2 cases in UC2) occurred in both induction studies. Additionally, mild-to-moderate neutropenia and lymphopenia were reported significantly more often in patients receiving upadacitinib compared to placebo. Clinical assessment at week 52 of the maintenance study showed a higher percentage of patients with clinical remission in the upadacitinib 15 mg group (absolute difference 30.7%, 95% CI 21.7-39.8, $p<0.0001$) and upadacitinib 30 mg group (absolute difference 39%, 95% CI 29.7-48.2, $p<0.0001$) compared to placebo. In addition, the upadacitinib groups showed a durable effect of clinical remission, clinical and endoscopic response compared to placebo. In the UC3 study, the frequency of reported adverse events was comparable in all groups, and the most frequently reported were: worsening of UC, nasopharyngitis, creatine kinase elevation, arthralgia and upper respiratory tract infection. In both upadacitinib groups, there were a total of 6 events of Herpes Zoster infections (non-serious), invasive breast cancer both in placebo and 15 mg upadacitinib groups and two non-melanoma skin cancers in upadacitinib 30 mg patients. There were also several cases of vein thrombosis, hepatic events and elevated levels of alanine transaminase, aspartate transaminase, creatine kinase and

cholesterol in patients receiving upadacitinib. The study demonstrated the efficacy in achieving clinical remission and the safety of upadacitinib in patients with moderate-to-severe UC with no new serious adverse events. [35]

The aim of a recently published real-world observational study was to assess the safety and efficacy of upadacitinib in biological-naive and biological-exposed patients with moderate-to-severe UC along with examining the correlation between an intestinal ultrasound (IUS) and Total Mayo Score (TMS), fecal calprotectin (FC) and endoscopic remission. The study included 76 adult patients with the diagnosis of UC who had received upadacitinib 45 mg daily for 8 weeks. In the final week of the study, no statistically significant differences were found in clinical, endoscopic and biochemical response between biological-naive and biological-exposed patients. Clinical remission was achieved by 78.9% of naive patients versus 71.4% of exposed patients ($p=0.053$) which confirmed the efficacy of upadacitinib in inducing remission in both biological-naive and biological-exposed patients. There was no serious or new adverse events reported during the study. Additionally, it was confirmed that the intestinal ultrasound is effective in the assessment of UC activity. [36]

Systematic review and meta-analysis by Taxonera et al. collected data from twenty-four studies, including 1388 patients with active UC, to evaluate the real-world effectiveness and safety of upadacitinib. The study showed that clinical response and remission were observed respectively in 78.7% and 68.4% patients at week 8. Mean faecal calprotectin and the mean C-reactive protein decreased significantly. Additionally, previous use of biological therapy or other JAK inhibitors did not affect the clinical response after upadacitinib treatment. The review confirms the compatibility in the safety profile of the medication including the long-term data from the phase 3 open-label extension study (U-ACTIVATE). [37]

Upadacitinib was evaluated for efficacy and safety in the treatment of patients with moderate-to-severe CD with poor response or intolerance to immunosuppressants or TNF antagonists in a double-blind, phase 2 trial (CELEST). Patients were divided into six groups receiving twice daily (bid) placebo, upadacitinib at the dose of: 3 mg, 6 mg, 12 mg, 24 mg or 24 mg once daily. Clinical assessment was performed at week 12 or 16. Clinical remission was observed in 13%, 27% ($p<0.1$), 22% and 14% of patients receiving upadacitinib 3 mg, 6 mg, 12 mg, 24 mg bid and 24 mg once daily respectively, versus 11% of patients in the placebo group. Endoscopic remission was achieved in 10% ($p<0.1$), 8%, 8% ($p<0.1$), 22% ($p<0.01$), 14% ($p<0.05$) and 0% of patients from groups receiving upadacitinib 3 mg, 6 mg, 12 mg, 24 mg bid and 24 mg once daily and placebo, respectively. Adverse events were more

frequently observed in patients receiving higher doses of upadacitinib, but most of them were classified as mild or moderate. The most commonly reported AEs included headache, worsening of CD, fatigue, upper respiratory tract infection, urinary tract infection, nausea vomiting and acne. During the induction and maintenance study, several cases of serious infections and nonserious Herpes Zoster infection events were observed. This study showed the efficacy and safety of upadacitinib in the induction study. [38]

A phase 3, double-blinded, randomized, placebo-controlled trial was conducted to assess the efficacy and safety of upadacitinib as induction and maintenance therapy in patients with moderate to severe CD. The study involved two 12-week-long induction trials (U-EXCEL and U-EXCEED) and one 52-week-long maintenance study (U-ENDURE). The induction phase could have been prolonged up to 12 extra weeks to achieve clinical response in patients and qualify them for the maintenance phase of study. In U-EXCEL and U-EXCEED trials, patients received upadacitinib 45 mg once daily or placebo, whereas, in the maintenance phase, the patients received upadacitinib 15 mg, 30 mg, or placebo. Through week 12 both induction studies showed a significantly higher percentage of patients with clinical response and clinical remission in upadacitinib group compared to placebo (U-EXCEL clinical remission 49.5% vs. 29.1%, $p<0.001$; U-EXCEED 38.9% vs. 21.1%, $p<0.001$) as well as endoscopic response (U-EXCEL 45.5% vs. 13.1%, $p<0.001$; U-EXCEED 34.6% vs. 3.5%, $p<0.001$), respectively. Additionally, in both induction trials, significantly more patients receiving upadacitinib 45 mg achieved rapid symptom relief at week 2 and CDAI clinical remission at week 4 than placebo. In the maintenance study, the rate of clinical prescription in patients receiving upadacitinib 15 mg, 30 mg and placebo was 37.3%, 47.6% and 15.1%, respectively ($p<0.001$ for both comparisons of upadacitinib groups with placebo). At week 52, both CDAI clinical and endoscopic remission remained at a higher percentage of patients receiving upadacitinb 15 mg or 30 mg compared to placebo. In the induction studies, the most frequently reported adverse events in patients receiving 45 mg upadacitinib were acne and anaemia in U-EXCEL and nasopharyngitis, headache, worsening of CD, and upper respiratory infections in U-EXCEED. There were a few cases of serious infections (1.1% and 2.8% of patients receiving upadacitinib 45 mg compared to 1.7% and 1.8% of placebo in U-EXCEL and U-EXCEED, respectively). A total of 15 cases of nonserious herpes zoster infection was observed in upadacitinib-receiving patients compared with 0 cases in the placebo group in both induction studies. A higher percentage of patients receiving 45 mg of upadacitinib had neutropenia and creatine kinase elevation compared with placebo. In the maintenance study, the exacerbation of CD was the most frequently reported adverse event among all the groups.

Serious infections were noted at similar rates in upadacitinib groups and placebo. However, herpes zoster infections happened more frequently in patients receiving upadacitinib 30 mg than in those who received upadacitinib 15 mg. There were several cases of gastrointestinal perforation, hepatic vein thrombosis, metastatic ovarian, colon, and invasive lobular breath cancer in patients receiving upadacitinib. Neutropenia and creatine kinase elevation were observed more frequently in patients receiving upadacitinib 30 mg. This study showed that upadacitinib is effective in achieving and maintaining clinical remission and endoscopic response in patients with moderate to severe CD. A study evaluating the long-term safety of upadacitinib is still ongoing. [39]

In the meta-analysis by Niu et al., which included eight studies and collected 2818 patients with CD or UC treated with upadacitinib, significant efficacy in achieving clinical remission and response in both groups of patients with moderate to severe CD and UC was demonstrated. The safety profile was assessed as favourable for the treatment of both diseases. [40]

Conclusions

Janus kinase inhibitors represent a novel and promising class of drugs in the treatment of inflammatory bowel disease, particularly in patients who have not responded or have lost response to biological therapies. The big advantage of these drugs is their oral administration, quick onset of action and low immunogenicity.

This manuscript provides an overview of clinical trials and meta-analyses, ranging from the earliest studies to the most recent data. JAK inhibitors have demonstrated high efficacy in both inducing and maintaining clinical and endoscopic remission in patients with moderate to severe ulcerative colitis and Crohn's disease. The safety profile of JAK inhibitors, however, raises some concerns. The most common adverse events include infections and increased levels of creatine kinase and lipids. Less frequently reported are venous thrombosis, skin cancer, and cardiovascular complications. The incidence of side effects is dose-dependent, and most of them were mild to moderate. Meta-analyses and real-world evidence further confirm their effectiveness and acceptable safety profile, irrespective of prior biological exposure. Nevertheless, due to their relatively recent introduction into clinical practice in the treatment of IBD, long-term safety data are still needed.

Disclosure

Authors' Contributions

Conceptualization Olimpia Wiciun, Karolina Skonieczna

Methodology Kacper Ordon

Software Martyna Kłossowska

Check Karolina Skonieczna, Kacper Ordon, Laura Kurczoba

Formal analysis Laura Kurczoba

Investigation Karolina Skonieczna

Resources Olga Kądziołka

Data curation Paulina Szulc

Writing-rough preparation Kacper Ordon

Writing-review and editing Olimpia Wiciun

Visualization Magdalena Badziąg

Supervision Karolina Skonieczna

Project administration Olimpia Wiciun, Paulina Szulc, Martyna Kłossowska

All authors have read and agreed with the published version of the manuscript

Declarations

Funding Statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

References:

1. M'Koma AE. Inflammatory Bowel Disease: Clinical Diagnosis and Surgical Treatment-Overview. *Medicina (Mex)*. 2022;58(5):567. doi:10.3390/medicina58050567

2. Ortega MA, García-Montero C, Fraile-Martinez O, et al. Immune-Mediated Diseases from the Point of View of Psychoneuroimmunoendocrinology. *Biology*. 2022;11(7):973. doi:10.3390/biology11070973

3. Wang R, Li Z, Liu S, Zhang D. Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the Global Burden of Disease Study 2019. *BMJ Open*. 2023;13(3):e065186. doi:10.1136/bmjopen-2022-065186

4. Zhang YZ. Inflammatory bowel disease: Pathogenesis. *World J Gastroenterol*. 2014;20(1):91. doi:10.3748/wjg.v20.i1.91

5. Antonioli L, Armuzzi A, Fantini MC, Fornai M. JAK inhibitors: an evidence-based choice of the most appropriate molecule. *Front Pharmacol*. 2024;15:1494901. doi:10.3389/fphar.2024.1494901

6. Francescone R, Hou V, Grivennikov SI. Cytokines, IBD, and Colitis-associated Cancer: *Inflamm Bowel Dis*. 2015;21(2):409-418. doi:10.1097/MIB.0000000000000236

7. Souza RF, Caetano MAF, Magalhães HIR, Castelucci P. Study of tumor necrosis factor receptor in the inflammatory bowel disease. *World J Gastroenterol*. 2023;29(18):2733-2746. doi:10.3748/wjg.v29.i18.2733

8. Guan Q, Zhang J. Recent Advances: The Imbalance of Cytokines in the Pathogenesis of Inflammatory Bowel Disease. *Mediators Inflamm*. 2017;2017:1-8. doi:10.1155/2017/4810258

9. Harris C, Cummings JRF. JAK1 inhibition and inflammatory bowel disease. *Rheumatology*. 2021;60(Supplement_2):ii45-ii51. doi:10.1093/rheumatology/keaa896

10. Kapizioni C, Desoki R, Lam D, et al. Biologic Therapy for Inflammatory Bowel Disease: Real-World Comparative Effectiveness and Impact of Drug Sequencing in 13 222 Patients within the UK IBD BioResource. *J Crohns Colitis*. 2024;18(6):790-800. doi:10.1093/ecco-jcc/jjad203

11. Cai Z, Wang S, Li J. Treatment of Inflammatory Bowel Disease: A Comprehensive Review. *Front Med*. 2021;8:765474. doi:10.3389/fmed.2021.765474

12. Qiu Y, Chen B li, Mao R, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNFα dose intensification in Crohn's disease. *J Gastroenterol*. 2017;52(5):535-554. doi:10.1007/s00535-017-1324-3

13. Ashraf H, Bodapati A, Hanif A, et al. Safety and Efficacy of Biologic Therapies (Ustekinumab and Vedolizumab) in the Treatment of Inflammatory Bowel Disease (IBD): A Systematic Review. *Cureus*. Published online November 6, 2023. doi:10.7759/cureus.48338

14. Garrido I, Lopes S, Macedo G. Hit the Road JAK! The Role of New Oral Treatment in Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2021;27(12):2010-2022. doi:10.1093/ibd/izab037

15. Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J Med Chem*. 2014;57(12):5023-5038. doi:10.1021/jm401490p

16. Agashe RP, Lippman SM, Kurzrock R. JAK: Not Just Another Kinase. *Mol Cancer Ther*. 2022;21(12):1757-1764. doi:10.1158/1535-7163.MCT-22-0323

17. Xue C, Yao Q, Gu X, et al. Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer. *Signal Transduct Target Ther*. 2023;8(1):204. doi:10.1038/s41392-023-01468-7

18. Jun YK, Yoon H. [Small Molecule Therapy for Inflammatory Bowel Disease: JAK Inhibitors and S1PR Modulators]. *Korean J Gastroenterol Taehan Sohwagi Hakhoe Chi*. 2024;84(2):51-64. doi:10.4166/kjg.2024.064

19. Nogami A, Asonuma K, Okabayashi S, et al. Real-World Comparative Effectiveness and Safety of Filgotinib and Upadacitinib for Ulcerative Colitis: A Multicentre Cohort Study. *United Eur Gastroenterol J*. 2024;12(10):1357-1366. doi:10.1002/ueg2.12704

20. Purnak T, Ertan A. Optimal Management of Patients with Moderate-to-Severe Inflammatory Bowel Disease. *J Clin Med*. 2024;13(23):7026. doi:10.3390/jcm13237026

21. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med*. 2017;376(18):1723-1736. doi:10.1056/NEJMoa1606910

22. Sandborn WJ, Lawendy N, Danese S, et al. Safety and efficacy of tofacitinib for treatment of ulcerative colitis: final analysis of OCTAVE Open, an open-label, long-term extension study with up to 7.0 years of treatment. *Aliment Pharmacol Ther*. 2022;55(4):464-478. doi:10.1111/apt.16712

23. Ollech JE, Eran-Banai H, Goren I, et al. Tofacitinib is an effective treatment for moderate to severe ulcerative colitis, and intestinal ultrasound can discriminate response from non-response: a pragmatic prospective real-world study. *Ann Med*. 2024;56(1):2358183. doi:10.1080/07853890.2024.2358183

24. Pellegrino R, Imperio G, De Costanzo I, et al. Small Molecules in the Treatment of Acute Severe Ulcerative Colitis: A Review of Current Evidence. *Pharmaceuticals*. 2025;18(3):308. doi:10.3390/ph18030308

25. Narula N, Pray C, Hamam H, et al. Tofacitinib for Hospitalized Acute Severe Ulcerative Colitis Management (The TRIUMPH Study). *Crohns Colitis 360*. 2024;7(1):otaf013. doi:10.1093/crocol/otaf013

26. Panés J, Sandborn WJ, Schreiber S, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut*. 2017;66(6):1049-1059. doi:10.1136/gutjnl-2016-312735

27. Banerjee R, Sharma V, Patel R, et al. Tofacitinib use in ulcerative colitis: An expert consensus for day-to-day clinical practice. *Indian J Gastroenterol*. 2024;43(1):22-35. doi:10.1007/s12664-023-01507-9

28. Feagan BG, Danese S, Loftus EV, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *The Lancet*. 2021;397(10292):2372-2384. doi:10.1016/S0140-6736(21)00666-8

29. Vermeire S, Feagan BG, Peyrin-Biroulet L, et al. Withdrawal and Re-treatment with Filgotinib in Ulcerative Colitis: *Post Hoc* Analyses of the Phase 2b/3 SELECTION and SELECTIONLTE Studies. *J Crohns Colitis*. 2024;18(1):54-64. doi:10.1093/ecco-jcc/jjad123

30. Gros B, Goodall M, Plevris N, et al. Real-world Cohort Study on the Effectiveness and Safety of Filgotinib Use in Ulcerative Colitis. *J Crohns Colitis*. 2025;19(1):jjad187. doi:10.1093/ecco-jcc/jjad187

31. Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *The Lancet*. 2017;389(10066):266-275. doi:10.1016/S0140-6736(16)32537-5

32. Vermeire S, Schreiber S, Rubin DT, et al. Efficacy and safety of filgotinib as induction and maintenance therapy for Crohn's disease (DIVERSITY): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Gastroenterol Hepatol*. 2025;10(2):138-153. doi:10.1016/S2468-1253(24)00272-3

33. Law CCY, Kayal M, Mehandru S, Colombel JF. A critical review of upadacitinib for the treatment of adults with moderately to severely active ulcerative colitis. *Expert Rev Gastroenterol Hepatol*. 2023;17(2):109-117. doi:10.1080/17474124.2023.2172399

34. Sandborn WJ, Ghosh S, Panes J, et al. Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis. *Gastroenterology*. 2020;158(8):2139-2149.e14. doi:10.1053/j.gastro.2020.02.030

35. Danese S, Vermeire S, Zhou W, et al. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *The Lancet*. 2022;399(10341):2113-2128. doi:10.1016/S0140-6736(22)00581-5

36. Kaniewska M, Lewandowski K, Krogulecki M, et al. Efficacy of Upadacitinib Induction Treatment in Moderate-to-Severe Ulcerative Colitis Including Intestinal Ultrasound Assessment: A Multicenter, Real-World Observational Study. *J Clin Med*. 2025;14(5):1695. doi:10.3390/jcm14051695

37. Taxonera C, García-Brenes MA, Machín M, et al. Real-World Effectiveness and Safety of Upadacitinib in Patients with Ulcerative Colitis: A Systematic Review and Meta-Analysis. *J Clin Med*. 2025;14(7):2232. doi:10.3390/jcm14072232

38. Sandborn WJ, Feagan BG, Loftus EV, et al. Efficacy and Safety of Upadacitinib in a Randomized Trial of Patients With Crohn's Disease. *Gastroenterology*. 2020;158(8):2123-2138.e8. doi:10.1053/j.gastro.2020.01.047

39. Loftus EV, Panés J, Lacerda AP, et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med*. 2023;388(21):1966-1980. doi:10.1056/NEJMoa2212728

40. Niu C, Zhang J, Napel M, et al. Systematic Review with Meta-analysis: Efficacy and Safety of Upadacitinib in Managing Moderate-to-Severe Crohn's Disease and Ulcerative Colitis. *Clin Drug Investig*. 2024;44(6):371-385. doi:10.1007/s40261-024-01364-0