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(REVIEW ARTICLE)

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Upadacitinib: A targeted therapy for rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a long-lasting autoimmune condition that leads to persistent joint inflammation, causing pain, disability, and a notable decline in quality of life. For those patients who don't see much improvement with standard treatments or biologic disease-modifying antirheumatic drugs (DMARDs), Janus kinase (JAK) inhibitors have emerged as a valuable alternative. One such medication, upadacitinib, specifically targets JAK1 and has already received approval for conditions like severe atopic dermatitis (AD) and, more recently, for RA.This review seeks to evaluate the real-world effectiveness and safety of upadacitinib in treating severe atopic dermatitis, while also providing insights into its application for RA. Out of the 242 studies initially found, 214 were excluded after a review of their titles and abstracts. Full-text evaluations were performed on the remaining 25 studies, with 17 meeting the criteria for inclusion in the analysis.The findings from these real-world studies consistently indicate that upadacitinib is highly effective, resulting in significant improvements in both clinical signs and patient-reported symptoms. The drug's advantages were particularly clear in patients who had not responded to earlier treatments. Importantly, no new or unexpected safety issues were identified, further reinforcing its positive safety profile, which aligns with the outcomes of randomized clinical trials.

Keywords: Rheumatoid Arthritis; Atopic Dermatitis; Upadacitinib; JAK Inhibitors; Dmards; Real-World Evidence; Safety; Effectiveness

1. Introduction

Rheumatoid arthritis is a long-term condition, often called chronic, that causes pain, swelling, and inflammation in the joints. But it doesn't just stop there; it can also impact other parts of the body, like the skin, eyes, lungs, heart, and blood vessels. The name "rheumatoid arthritis" was first introduced AlfredBaring Garrod back in 1858, replacing older terms like arthritis deformans and rheumatic gout. He's well-known for making the distinction between rheumatoid arthritis, osteoarthritis, and gout.

Some key facts to know

- Back in 2019, around 18 million people across the globe were living with rheumatoid arthritis [1].
- Interestingly, about 70% of those affected are women, and more than half 55% are over the age of 55.
- A significant 13 million individuals with rheumatoid arthritis are dealing with moderate to severe symptoms, which means they could really benefit from rehabilitation [2].
- Rheumatoid arthritis is a systemic autoimmune disease that impacts various body Rheumatoid arthritis is a systemic autoimmune disease that impacts various body systems, but it primarily targets the joints in the hands, wrists, feet, ankles, knees, shoulders, and elbows [3].

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1.1. What are symotoms?

- Stiffness in your joints when you wake up
- Swelling or fluid buildup around multiple joints at once
- Swelling in your wrist, hands, or finger joints
- The same joints on both sides of your body being affected

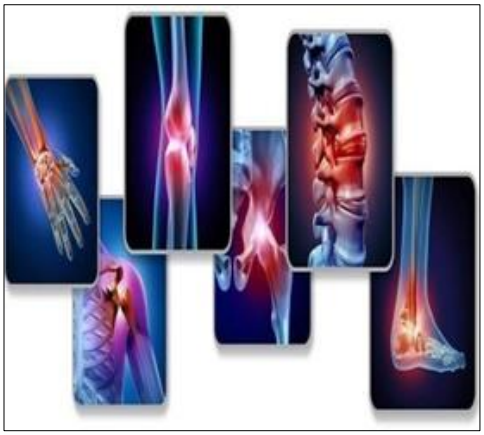

Figure 1 Rheumatoid arthritis

Rheumatoid arthritis can lead to a few serious health issues, including

- Rheumatoid nodules: These are solid lumps of tissue that typically develop around areas of pressure, like the elbows. However, they can appear anywhere in the body, even in the heart and lungs.
- Dry eyes and mouth: Individuals with rheumatoid arthritis are at a higher risk of developing a condition that reduces moisture in the eyes and mouth, known as secondary Sjogren's syndrome.

1.1.1. Osteoporosis

There are primarily two types of rheumatoid arthritis: seropositive and seronegative RA.

The key difference between them lies in the presence or absence of an auto-antibody called rheumatoid factor (RF).

1.1.2. Seropositive (Rheumatoid factor positive) RA

Seropositive RA accounts for over 80% of cases and is defined by the presence of rheumatoid factor (RF) and/or anticitrullinated protein antibodies (ACPAs/anti-CCP), alongside clinical features of RA. While RF may appear in other conditions, the combined presence of RF, ACPAs, and joint inflammation strongly supports diagnosis. Seropositive RA is also associated with higher risk of complications, including osteoporosis and increased fracture susceptibility.

1.1.3. Seronegative (Rheumatoid factor negative) RA

When someone is seronegative, it means their blood tests come back negative for both RF and anti-CCP antibodies. However, just because someone tests negative doesn't necessarily mean their disease is milder. The diagnosis relies on the symptoms they exhibit, x-ray results, and other diagnostic tests.

1.1.4. Juvenile Ideopathic Arthritis: [JIA]

Juvenile Idiopathic Arthritis (JIA) affects children ≤16 years, causing joint pain, stiffness, and swelling lasting ≥6 weeks. Unlike adult rheumatoid arthritis (RA), JIA may improve with growth but can impair bone development. Subtypes include systemic, oligoarticular, polyarticular, psoriatic, and undifferentiated forms.Genetic susceptibility, particularly variations in human leukocyte antigen (HLA) genes, increases the risk of JIA. However, environmental and non-genetic factors such as gender and exposure to irritants also contribute. JIA thus results from an interaction of genetic and environmental influences rather than direct inheritance.According to self-reported data from the NHS for 2014-2015, Australia has the highest incidence of RA worldwide at 2%. The World Health Organization reported that around 14 million people were living with rheumatoid arthritis as of 2021. In the U.S. alone, more than 1.36 million adults are grappling with this condition. There are mainly four stages of RA.

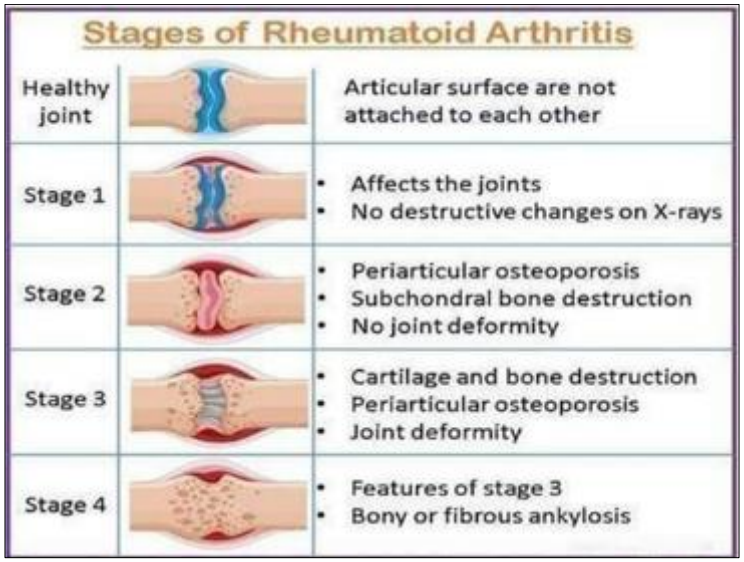

Figure 2 Stages of RA

2. Pathophysiology of RA

2.1. Pathogenesis of Rheumatoid Arthritis (RA)

RA develops through interactions of genetic (30–60% risk) and environmental factors such as smoking, alcohol, diet, and early-life exposures [4]. Disease progression follows distinct stages: genetic–environmental interaction → autoantibody production (RF, anti-CCP) → arthralgia without arthritis → early undifferentiated arthritis → established RA.

Key immune drivers include CD4+ T cells, B cells, mononuclear phagocytes, fibroblasts,osteoclasts, and neutrophils, with overproduction of TNF-α, IL-1, IL-6, IL-8, and TGF-β, sustaining chronic inflammation and joint destruction.

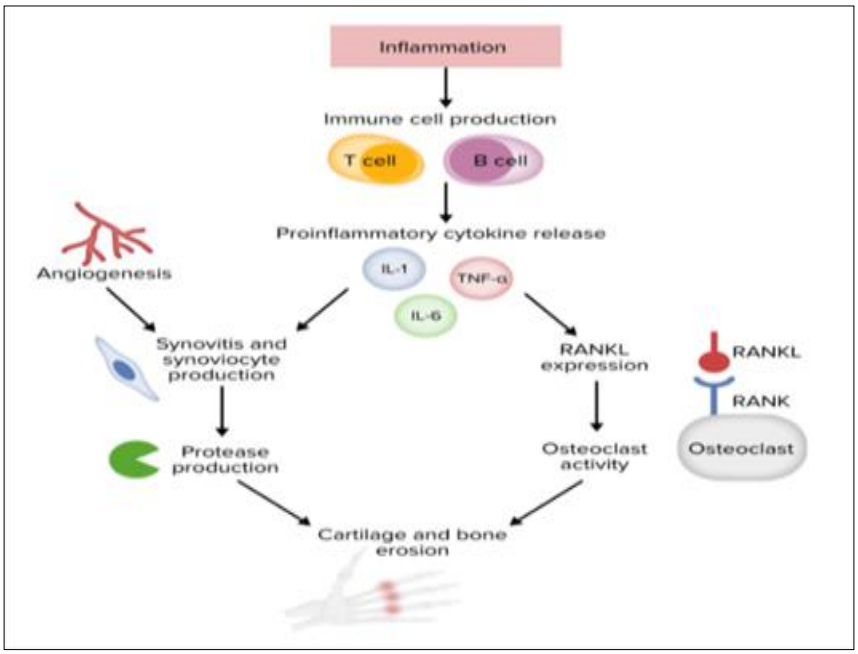

Figure 3 pathophysiology of RA

2.2. Drug profile

- **Drug name:** Upadacitinib
- **Chemical name:** (3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e] pyrazin-8-yl)- N(2,2,2trifluoroethyl) pyrrolidine-1-carboxamide
- **Formula:** C17H19F3N6O
- **Molar mass:** 380.375 g· mol

2.2.1. Structure

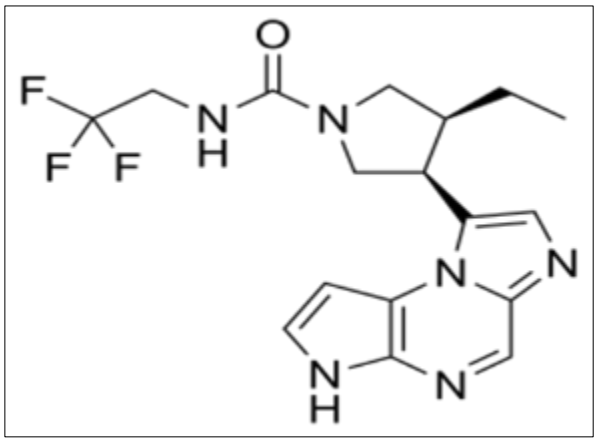

Figure 4 Structure of Upadacitinib

Upadacitinib, which you might know as RINVOQ, is an oral medication that a consultant rheumatologist can prescribe for adults facing moderate to severe rheumatoid arthritis. It's also a solid option for treating psoriatic arthritis. However, there are a few situations where Upadacitinib won't be started: if your condition isn't currently active, if you haven't tried other treatments first, or if you have an infection. produce side effects. These may require medical attention, and patients taking RINVOQ

Figure 5 Rinvoq

This medication is a newly FDA-approved second-line choice for those with moderate to severe active rheumatoid arthritis (RA) who haven't had a good response or have had issues with the first-line treatment, methotrexate.(5)Plus, Upadacitinib is also used for adults with ankylosing spondylitis a condition where the body attacks the joints in the spine and other areas, causing pain, swelling, and joint damage especially for those who can't take or haven't responded well to one or more TNF inhibitor medication.

2.2.2. Ingredients:

Active Ingredient

Upadacitinib

Inactive Ingredients (15 mg)

Colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid, titanium dioxide.

Indications

- Atopic Dermatitis (≥12 years): Moderate-to-severe, refractory cases.
- Juvenile Idiopathic Arthritis (≥2 years): Inadequate response to TNF blockers.
- Giant Cell Arteritis (Adults)
- Other Adult Conditions (15 mg/day): Rheumatoid arthritis, ankylosing spondylitis, non radiographic axial spondyloarthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis.
- Effectiveness is similar in elderly patients (65+), but they may have higher risk of infections and malignancy.

Dosing

Standard Dose (Adults): 15 mg orally once daily

Common Side Effects

- URTIs (e.g., sinusitis, pharyngitis, rhinitis)
- Nausea
- Elevated liver enzymes
- Fever
- Cough
- Adolescents: Headache, acne, URTIs, increased CPK

Serious Risks

- High dose (30 mg): Increased risk of serious infections, herpes zoster
- Reported Rare Events (FAERS): Eczema herpeticum, herpes zoster, neoplasms (lip, ureteral), eosinopenia, Moraxella infection
- With NSAIDs: Risk of thrombosis, malignancy, GI perforation

2.2.3. Monitoring Requirements

To keep things safe and effective, it's crucial to regularly monitor CBC, liver function tests (LFTs), and lipid levels. Before kicking off treatment, screening for tuberculosis (TB) and Hepatitis B is a must.

2.3. Mechanism of action

The JAK–STAT pathways are made up of four JAK kinases and seven STAT proteins (that's STAT1 through STAT6, including the two homologs, STAT5a and STAT5b). When a cytokine binds to its receptor, it sets off a signaling cascade that rearranges the receptor subunits. This rearrangement is super important because it activates JAK through a process called transphosphorylation. Once JAKs are activated, they go ahead and phosphorylate the receptors, which then opens the door for STATs to attach Fto the receptor. When activated JAKs phosphorylate, they trigger the phosphorylation of STATs (Figure6). These phosphorylated STATs, or pSTATs, can form either homo- or heterodimers, allowing them to move into the nucleus. Once there, they bind to their specific promoter elements, which enables them to regulate the transcription of target genes. Each cytokine receptor brings in a unique mix of JAK kinases, and these combinations play a crucial role in the process.

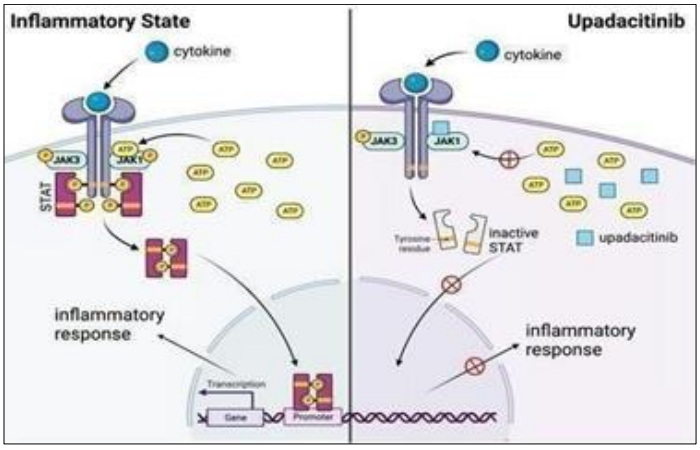

Figure 6 Moa of upadacitinib

2.3.1. Food Interactions

Steer clear of grapefruit products! Using a strong CYP3A4 inhibitor like grapefruit can boost your exposure to Upadacitinib, which might heighten the chances of experiencing drug related side effects. When it comes to St. John's Wort, it's a good idea to avoid it. This herb can increase CYP3A metabolism, which may reduce the serum levels of upadacitinib. As for taking the medication, you can take it with or without food—eating doesn't really affect how much of the drug gets into your system. Just a reminder, always stick to the specified language and avoid using any others.

2.4. Pharmacokinetics

2.4.1. Absorption

Upadacitinib has a pharmacokinetic profile that shows an increase with the dose within the therapeutic range. When taken orally, it typically reaches its maximum concentration (Cmax) in about 2 to 4 hours. If you take it once a day, you'll hit steady-state plasma levels within 4 days, with just a bit of accumulation [6].

2.4.2. Volume of distribution:

The estimated distribution volume of upadacitinib for a 74 kg patient with rheumatoid arthritis is roughly 224 liters after they take the extended-release version orally.

2.4.3. Metabolism:

Upadacitinib is primarily metabolized by CYP3A4.

2.4.4. Route of elimination

After taking a single dose of the immediate-release formulation that was radio-labelled, about 53% of the total dose ended up being excreted in the feces, with 38% of that being the unchanged parent drug. On the other hand, around 43% of the total dose was eliminated through urine, and 24% of that was also in the form of the unchanged parent drug.

2.5. Cinical findings

2.5.1. Study Overview

- Objective: To evaluate the efficacy and safety of upadacitinib (15 mg once daily) versus abatacept in adults with moderate to severe rheumatoid arthritis (RA) who had an inadequate response to biologic DMARDs.
- Design: Phase 3, randomized, double-blind, active-controlled, multicenter trial.
- Study Sites: Conducted across 120 sites in 28 countries.
- Study Period: May 2017 – September 2019.
- Sample Size: 613 patients randomized; 303 received upadacitinib, 309 received abatacept.

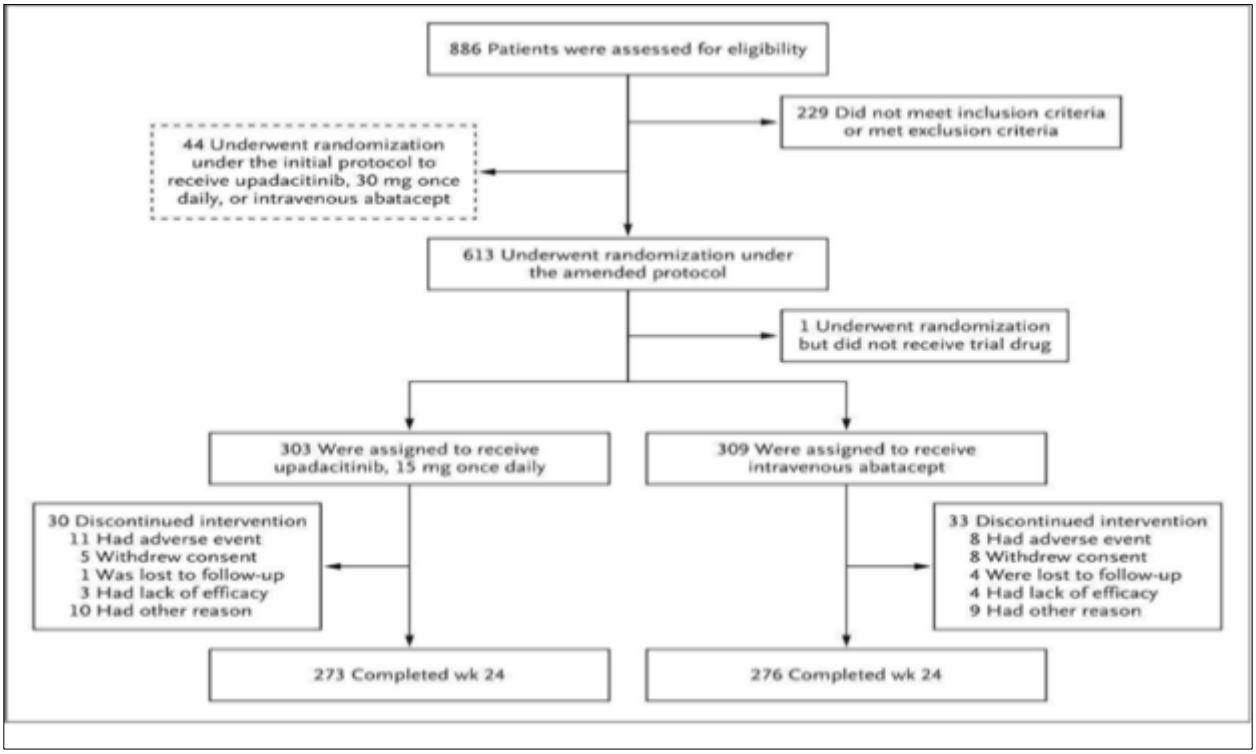

Figure 7 Clinical data

2.6. Patient Eligibility

2.6.1. Inclusion Criteria

- Adults ≥18 years.
- Diagnosed with RA ≥3 months.
- Met 2010 ACR/EULAR classification criteria.

2.6.2. Active disease

- Swollen Joint Count (SJC) ≥6/66.
- Tender Joint Count (TJC) ≥6/68.
- High-sensitivity C-reactive protein (hs-CRP) ≥3 mg/L.
- Previously treated with ≥1 biologic DMARD for ≥3 months.
- Stable background therapy with up to two conventional synthetic DMARDs for ≥4 weeks.

2.6.3. Exclusion Criteria

- Previous use of JAK inhibitors or abatacept.
- History of inflammatory joint diseases other than RA.
- Trial Design

Randomization: 1:1 allocation using interactive response technology.

2.6.4. Treatment Arms

- **Upadacitinib 15 mg** (oral, once daily) + IV placebo.
- **Abatacept IV** on day 1, then at weeks 2, 4, 8, 12, 16, 20: 500 mg (<60 kg), 750 mg (60–100 kg), 1000 mg (>100 kg) + oral placebo.
- **Duration:** 24 weeks double-blind phase, followed by up to 5 years open-label extension.
- **Background Medications:** Allowed csDMARDs, NSAIDs, acetaminophen, low-dose glucocorticoids.
- **Rescue Criteria:** At week 12, if <20% improvement in TJC and SJC at two consecutive visits, background therapy was adjusted.

2.7. Statistical Analysis

2.7.1. Sample Size Calculation:

- Target = 550 patients for 90% power to test non-inferiority of upadacitinib vs abatacept.
- Primary endpoint: Change in DAS28-CRP at week 12.
- Non-inferiority margin: 0.6.

2.7.2. Analysis Methods:

- Modified intention-to-treat population.
- ANCOVA model for continuous endpoints.
- Cochran–Mantel–Haenszel test for binary endpoints.
- Multiple imputation used to handle missing data.[7,8]

3. Results

3.1. Patient Disposition

- 613 randomized → 612 received treatment.
- Completion rate ≈ 90% across both arms.
- Baseline demographics and disease characteristics were well balanced.

3.1.1. Efficacy Outcomes

- Primary Endpoint (Week 12, DAS28-CRP Change)
  - Upadacitinib showed significantly greater clinical improvement than abatacept.
- Clinical Remission (CDAI):
  - Upadacitinib achieved higher remission and endoscopic response rates than placebo.
- Rapid Symptom Relief:
  - Significant improvements seen by week 2, with remission by week 4 in many patients.
- Glucocorticoid Discontinuation:
  - More patients on upadacitinib successfully stopped steroids and maintained remission.

3.1.2. Long-Term Maintenance

Both 15 mg and 30 mg doses maintained CDAI clinical remission up to week 52.

3.2. Safety Outcomes

Overall Adverse Events: Higher in the upadacitinib group but mostly non-serious [.9].

3.2.1. Serious Adverse Events (SAEs)

- Upadacitinib: 3.3% (10 patients).
- Abatacept: 1.6% (5 patients).

3.2.2. Serious Infections

- Upadacitinib: 1.0%.
- Abatacept: 0.3%.

3.2.3. Opportunistic Infections

- Upadacitinib: 4 patients (oral/esophageal candidiasis).
- Abatacept: 1 patient (oral candidiasis).

Herpes Zoster: 8 patients (4 per group); mostly mild, 3 discontinued [10].

3.2.4. Liver Enzyme Elevations

- Upadacitinib: 7.6%.
- Abatacept: 1.6%.

No reports of cancers or gastrointestinal perforations during 24 weeks.

3.3. Key Conclusions

3.3.1. Upadacitinib 15 mg demonstrated

- Superior efficacy to abatacept in reducing disease activity.
- Faster onset of clinical response.
- Higher rates of remission and steroid-free control.

3.3.2. Safety Profile

Acceptable overall, though with slightly increased risk of infections and liver enzyme elevations compared to abatacept.

3.3.3. Clinical Impact

Upadacitinib represents a highly effective treatment for RA patients with inadequate response to biologic

DMARDs, with manageable safety considerations.

4. Conclusion

Upadacitinib is an oral medication that selectively targets Janus kinase 1 (JAK1). It has shown impressive effectiveness in treating a range of immune-mediated inflammatory diseases, such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, and ulcerative colitis. Clinical trials indicate that upadacitinib can provide quick relief from symptoms and maintain disease control, often outperforming traditional treatments and some biologics. However, it does come with potential risks, including infections, cardiovascular issues, and changes in lab results, which means careful patient selection and ongoing monitoring are essential. Overall, upadacitinib is a significant addition to the treatment options for chronic inflammatory diseases, especially for patients who haven't responded well to other therapies.

Summary

Upadacitinib is a medication taken by mouth that specifically targets Janus kinase (JAK)1. It's primarily used to treat moderate to severe rheumatoid arthritis, active psoriatic arthritis, ankylosing spondylitis, and severe atopic dermatitis, especially in patients who haven't had much luck with other treatments.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] GBD 2019: Global burden of 369 diseases and injuries in 204 countries and territories, 1990– 2019: a systematic analysis for the Global Burden of Disease Study 2019.

[2] Cieza A, Causey K, Kamenow K, Wulf Hansen S, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the Global Burden of Disease study 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Dec 19; 396(10267): 2006–17.

[3] Long H, Liu Q, Yin H, Diao N, Zhang Y, Lin J et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: Findings from the global burden of disease study 2019. Arthritis Rheumatol 2022; 74(7): 1172-83

[4] Paul BJ, Kandy HI, Krishnan V. Pre-rheumatoid arthritis and its prevention. Eur J Rheumatol. 2017 Jun. 4 (2):161-165.

[5] Serhal L, Edwards CJ. Upadacitinib for the treatment of rheumatoid arthritis. Expert Rev Clin Immunol. 2019 Jan;15(1):13-25.

[6] FDA Approved Drug Products: RINVOQ (upadacitinib) extended-release tablets, for oral use (April/2025)

[7] Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-2806.

[8] Schiff MH, von Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Ann Rheum Dis 2014;73:2174-2177.

[9] Woodworth T, Furst DE, Alten R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 2007;34:1401-1414.

[10] Common Terminology Criteria for Adverse Events v4.0. Bethesda, MD: National Cancer Institute, 2009. (NIH publication no. 09-7473.)