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Review On The Efficacy And Safety Of Upadacitinib In The Treatment Of Rheumatoid Arthritis

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ABSTRACT:

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory joint disease affecting approximately 0.5-1% of adults worldwide, leading to significant bone and cartilage loss, functional disability, and decreased quality of life. Traditional treatments, including methotrexate and biologic DMARDs, often face limitations in efficacy and safety. Upadacitinib (Rinvoq™), a selective Janus kinase (JAK) inhibitor targeting JAK1 and JAK3, offers a novel therapeutic approach for moderate to severe RA, particularly in patients intolerant to or unresponsive to previous treatments. This drug prevents pro-inflammatory cytokine signaling, reduces inflammation, and inhibits joint damage, leading to improved clinical outcomes. Upadacitinib is approved by the US FDA and EMA and has shown significant efficacy in clinical trials, with rapid onset of action, substantial improvements in disease activity measures (ACR responses, DAS28-CRP remission), and reduced structural joint damage over time. The drug has a favorable safety profile, with long-term studies indicating consistent efficacy and no new safety concerns. Overall, upadacitinib represents a promising option for managing RA, particularly in difficult-to-treat patient populations.

Keywords: Rheumatoid arthritis, Upadacitinib, Janus kinase (JAK) inhibitor

Introduction:

The chronic inflammatory joint disease known as rheumatoid arthritis (RA) is linked to increasing bone and cartilage loss. About 0.5% of adults worldwide suffer from RA, which can cause functional disability, decreased mobility, and a lower quality of life.[1]

RA is a chronic autoimmune disease and characterized by inflammation, joint damage, and disability. Traditional treatments with methotrexate and biologic DMARDs often reveal limitations concerning efficacy, safety, and convenience. Upadacitinib, an oral JAK inhibitor, is a novel treatment approach for RA. RA causes progressive damage to bone and cartilage, and it is associated with significant levels of disability, reduced quality of life, and an increased risk of comorbidities . The incidence of RA is between 0.5% and 1% worldwide, making it one of the most common chronic inflammatory diseases in adults.[2]

Upadacitinib, also known by its brand name RinvoqTM, is a selective JAK inhibitor which acts specifically against JAK1 and JAK3 while reversibly inhibiting TYK2 to a much lesser degree. Inhibiting these enzymes thus prevents the signaling of pro-inflammatory cytokines which leads to a reduction in inflammation and joint damage.[3]

Approval and Indications:

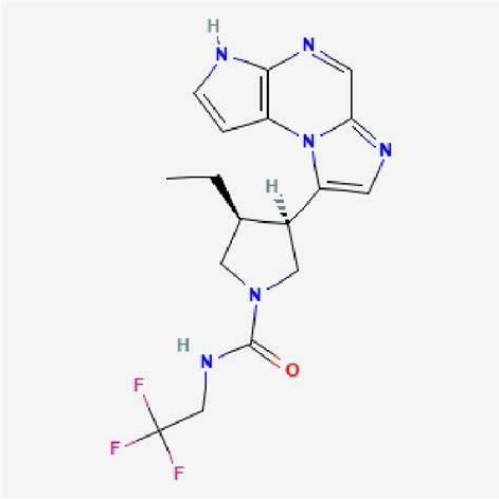
US FDA and EMA-approved upadacitinib in adults with moderate to severe RA who had previously failed on or were intolerant to methotrexate.

Upadacitinib is presently being assessed in clinical trials for the treatment of additional inflammatory disorders and is undergoing regulatory review by different organizations worldwide.JAK1 is strongly inhibited by upadacitinib, whereas JAK2, JAK3, and TYK2 are less effectively inhibited. Upadaci tinib was developed on the theory that greater potency against JAK1 could optimize RA efficacy while minimizing side effects on physiological processes involving JAK enzymes (e.g., hematopoiesis and immunological function). After the extended-release formulation is administered, upadacitinib has a terminal half-life of 9–14 hours with dose-proportional pharmacokinetics and biphasic elimination[4].

Chemical Name: (3S,4S)-3-(4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)cyclohexyloxy)pyrrolidine-1-carboxylic acid (2-(1-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)cyclopropyl)amide)

Molecular Formula: C27H35N7O3

Molecular Weight: 499.61 g/mol[5]



MECHANISM OF ACTION:

Upadacitinib is a selective Janus kinase (JAK) inhibitor that blocks the activity of JAK enzymes, specifically:

●JAK1

●JAK3 (to a lesser extent)

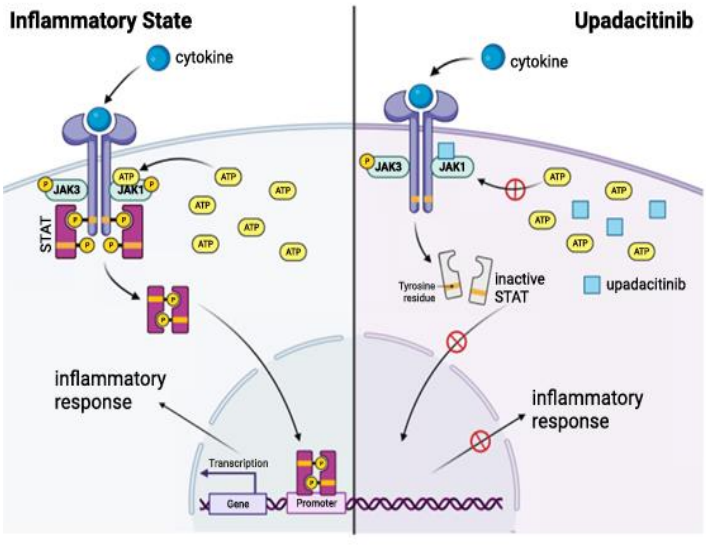
The JAK–STAT pathways consist of four JAK kinases and seven STATs (STAT1–6, including homologs STAT5a and STAT5b). A cytokine binding to its receptor initiates the signaling cascade as well as the subsequent association/rearrangement of the receptor subunits. This rearrangement enables JAK activation by transphosphorylation and, upon activation, JAKs phosphorylate the receptors. This phosphorylation allows STATs to bind to the receptor and become phosphorylated by activated JAKs. The phosphorylated STATs (pSTATs) are unable to form either homo- or heterodimers and consequently cannot translocate into the nucleus where they bind to their respective promoter elements. By binding to the promoter elements, they are able to regulate transcription of target genes. Since each cytokine receptor recruits

and utilizes a unique combination of JAK kinases, these combinations present an important aspect in the therapeutic target Getting of JAKs in various diseases.

It acts as an ATP-competitive JAK inhibitor, competing with ATP and blocking the nucleotide binding to inhibit kinase activity and the phosphorylation of downstream effectors. Therefore, STAT dimers are not formed and the translocation to the nucleus and the promotor binding are inhibited. The enzyme assays showed that upadacitinib inhibits JAK1 with half-maximal inhibitory concentration (IC50)of 0.043 μM, JAK2 (IC50 = 0.12 μM), JAK3 (IC50 = 2.3 μM), and TYK2 (IC50 = 4.7 μM).16 In cellular assays, upadacitinib showed greater than 40-, 130-, and 190-fold selectivity for JAK1 vs JAK2, JAK3, and TYK2, respectively, in a set of engineered cell lines used to measure cellular potency and selectivity of upadacitinib for each individual kinase.

The pharmacokinetic–pharmacodynamic analyses that characterized the relationships between upadacitinib plasma exposures and in vivo pharmacodynamic effects showed a greater potency of inhibition of IL- 6- induced pSTAT3 (as a measure of JAK1 activity) than IL- 7- induced pSTAT5 (as a measure of JAK1/3 activity) for Upadacitinib. The potency ratio for inhibition of IL- 6- induced pSTAT3 relative to IL- 7- induced pSTAT5 (based On ratio of estimated EC50 values) is 2.0, consistent with the higher potency towards the inhibition of JAK1 compared to JAK3 observed in vitro).

Together, these studies show that upadacitinib potently inhibits JAK1 and is less active against the remaining isoforms, JAK2, JAK3, and TYK2.7,16 Since different receptors are associated with distinct JAKs, selective blockade of one JAK can prevent a specific biologic function or the critical cytokines responsible for each immune-mediated inflammatory disease while leaving other JAK-dependent cytokines free to signal in an intact manner. However, despite the concomitant significantly higher exposure and activity levels of upadacitinib against JAK1 versus JAK2, JAK3, and TYK2, the compound has roughly equivalent potency against nine of twelve these diseases.Tinib is a selective JAK1 antagonist, JAK enzymes act in synergistic combination and may therefore have some kind of biological effects on all pairings involving JAK1[6]



Pharmacokinetics characteristics :

Numerous studies have assessed the pharmacokinetic properties of upadacitinib in both healthy participants and RA patients utilizing the immediate-release and Several studies have assessed the pharmacokinetic properties of upadacitinib utilizing both the immediate-release and extended-release formulations in both healthy volunteers and RA patients. The latter formulation was eventually marketed, has been utilized during the phase III program, and permits a once-daily dosing.The extended-release formulation's primary pharmacokinetic properties and the part that inherent variables like age, ethnicity, and hepatic and renal impairment play in the The primary extended-release formulation pharmacokinetic properties and the contribution of inherent variables including age, ethnicity, and hepatic and renal impairment to upadacitinib pharmacokinetic[5]

The drug has an oral bioavailability of 38-45%, indicating that 38 to 45 percent of the dose enters the bloodstream after oral administration. It reaches peak plasma concentration (Tmax) within 1-2 hours, meaning the highest level of the drug in the blood occurs during this time frame. Additionally, there is no significant food effect on its bioavailability, so the drug can be taken with or without food without impacting its absorption.[7,8]

The drug has a volume of distribution (Vd) of 383-456 liters, indicating extensive distribution throughout body tissues. It binds to plasma proteins, primarily albumin, at a rate of 52-58%. The primary metabolic pathway for the drug involves CYP3A4, with CYP2C19 contributing to a lesser extent, resulting in inactive metabolites. The drug has a half-life (t1/2) of 8-12 hours, reflecting how long it takes for the plasma concentration to decrease by half. Its clearance (CL) rate is 12-15 liters per hour, indicating how efficiently the drug is eliminated from the body, while less than 1% of the dose is excreted unchanged through the kidneys.[7,9,10]

Over the therapeutic dose range, upadacitinib plasma exposures are dose-proportional. When upadacitinib extended-release formulation is taken orally, it is absorbed with a median time to achieve maximum plasma concentration (Tmax) of 2-4 hours.19. Upadacitinib administered once daily results in steady-state plasma concentrations with little buildup in as little as four days.14 Upadacitinib's average terminal elimination half-life was between 8 and 14 hours. In urine (24%) and feces (38%), upadacitinib is mostly eliminated as the unaltered parent drug, although upadacitinib metabolism accounts for around 34% of drug excretion.14 Upadacitinib's pharmacokinetics have been demonstrated to be similar in every patient population that has been studied thus far.While the primary metabolite, ac, makes up around 13% of the whole plasma, the parent molecule, upadaci tinib, is responsible for approximately 79% of the total plasma's pharmacologic activity. Upadacitinib does not have any known active metabolites[6]

The main pharmacokinetics characteristics of extended release of upadacitinib

CHARACTERISTIC:	
Absorption	tmax median:2 -4 h
Distribution	Protein binding 52%
Metabolism	Mainly CYP3A4 and minor contribution of CYP2D6
Elimination	Predominantly as the unchanged substance in urine (24%)and feces (38%) Terminal elimination half- life; mean: 9-14 hr

Pharmacodynamics :

Janus kinase (JAK) enzymes, particularly JAK1, are selectively inhibited as the mechanism of action
- Prevents pro-inflammatory cytokine signaling, such as TNF-α, IL-1, and IL-6.

Impact on Cytokines: - Reduces inflammatory cytokine levels (TNF-α, IL-1, and IL-6).
IL-10 and IL-22, two anti-inflammatory cytokines, are elevated.

Effects of Immunomodulation: - Prevents T-cell and B-cell activation
Decreases the invasion of inflammatory cells in synovial tissue.

Clinical Impact: Lowers DAS28-CRP, a measure of RA disease activity.
Enhances bodily performance (HAQ-DI).

Prevents the advancement of structural joint deterioration on radiographs.[11,12]

Parameters of Pharmacodynamics:

43 nM is the half-maximal inhibitory concentration (IC50) for JAK1.

JAK1's inhibitory constant, Ki, is 14 nM.

For IL-6 inhibition, the half-maximal effective concentration (EC50) is 120 nM.

Targeted DMARDs have been developed as a result of our improved understanding of the pathophysiology of RA through the identification of important cells and cytokines. TNF, interferon, interleukin (IL)-1, IL-2, IL-6, IL-8, and IL-17 are among the numerous cytokines implicated in the pathophysiology of RA. Intracellular enzymes known as Janus kinases (JAKs) carry cytokine or growth factor signals that are involved in a variety of cellular functions, such as immune surveillance, hematopoiesis, and inflammatory reactions. JAK1, JAK2, JAK3, and TYK2 are the four members of the JAK family of enzymes that phosphorylate and activate signal transducers and activators of transcription (STATs) in pairs. Cellular function and gene expression are subsequently altered by this phosphorylation. JAKi are useful treatments for RA because they inhibit the activity of the JAK enzyme, which stops cytokine signaling and action. To investigate if higher JAK1 selectivity over other JAK family members might result in a more advantageous benefit-risk profile,

upadacitinib was created. Upadacitinib reduces effects on reticulocytes and natural killer cells while specifically targeting JAK1-dependent cytokines including IL-6 and interferon.[5]

Development:

1. Discovery: Upadacitinib was discovered by AbbVie scientists using a structure-based design approach.
2. Optimization: Lead optimization focused on improving potency, selectivity, and pharmacokinetics.
3. Preclinical testing: In vitro and in vivo studies evaluated efficacy, safety, and pharmacodynamics.[2,7,]

Preclinical Characterization:

In Vitro Studies:

1. Enzyme assays: Upadacitinib demonstrated potent inhibition of JAK1 and JAK3.
2. Cell-based assays: Inhibited cytokine-induced STAT phosphorylation and cellular proliferation.
3. Cytokine inhibition: Blocked IL-6, IL-1, TNF-α, IL-12, and IL-23 signaling.

In Vivo Studies:

1. Mouse collagen-induced arthritis (CIA) model: Upadacitinib reduced joint inflammation and damage.
2. Rat adjuvant-induced arthritis (AIA) model: Demonstrated efficacy in reducing disease severity.
3. Pharmacokinetic/pharmacodynamic (PK/PD) modeling: Predicted human dose and exposure.[8,10]

CLINICAL TRIALS:

- Long-term Safety and Efficacy of Sirukumab: This study evaluates the long-term safety and efficacy of sirukumab in participants with rheumatoid arthritis who are unresponsive to treatment with modifying antirheumatic drugs or anti-TNF alpha agents [1].
- Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis: This study determines if hydroxychloroquine is safe and effective for preventing the onset of rheumatoid arthritis in individuals with elevations of an autoantibody.
- A Study to Evaluate Response Markers to Treat Rheumatoid Arthritis: This study defines pharmacogenomics markers and clinical phenotype features associated with response to RA treatments [1].
- A Study of the Effect of Intestine Bacteria on Rheumatoid Arthritis: This study understands how bacteria in the intestines interact with the inflammation process in patients with rheumatoid arthritis [1].
- Somatic Mutation in Rheumatoid Arthritis: This study determines whether somatic mutations in T cells contribute to the pathogenesis of rheumatoid arthritis[6,13,14]

EFFICASY ASSESMENT:

Primary Endpoints:

1. ACR20/50/70 response
2. DAS28-CRP remission/low disease activity
3. HAQ-DI improvement
4. Radiographic progression inhibition

SELECT-EARLY Study (NCT02721489):

1. ACR50 response at Week 12: 43% (upadacitinib 15 mg) vs. 23% (placebo)
2. DAS28-CRP remission at Week 24: 29% (upadacitinib 15 mg) vs. 12% (placebo)
3. HAQ-DI improvement at Week 12: -0.53 (upadacitinib 15 mg) vs. -0.23 (placebo)

SELECT-MONOTHERAPY Study (NCT02706951):

1. ACR50 response at Week 24: 44% (upadacitinib 15 mg) vs. 23% (methotrexate)
2. DAS28-CRP remission at Week 24: 25% (upadacitinib 15 mg) vs. 13% (methotrexate)
3. HAQ-DI improvement at Week 12: -0.51 (upadacitinib 15 mg) vs. -0.28 (methotrexate)

SELECT-NEXT Study (NCT02675426):

1. ACR50 response at Week 12: 45% (upadacitinib 15 mg) vs. 22% (placebo)
2. DAS28-CRP remission at Week 24: 26% (upadacitinib 15 mg) vs. 13% (placebo)
3. HAQ-DI improvement at Week 12: -0.49 (upadacitinib 15 mg) vs. -0.25 (placebo)

SELECT-BEYOND Study (NCT02706873):

1. ACR50 response at Week 12: 41% (upadacitinib 15 mg) vs. 22% (placebo)
2. DAS28-CRP remission at Week 24: 24% (upadacitinib 15 mg) vs. 12% (placebo)
3. HAQ-DI improvement at Week 12: -0.46 (upadacitinib 15 mg) vs. -0.26 (placebo)

Overall Efficacy:

1. Upadacitinib demonstrated significant improvements in ACR20/50/70 response, DAS28-CRP remission, and HAQ-DI improvement.
2. Consistent efficacy across different patient populations (methotrexate-naive, biologic-experienced).
3. Radiographic progression inhibition observed.[8,10,15,16]

Safety Assessments:

1. Adverse Event (AE) reporting
2. Serious Adverse Event (SAE) reporting
3. Laboratory assessments (hematology, biochemistry, urinalysis)
4. Vital sign monitoring (blood pressure, pulse rate)
5. Physical examinations
6. Electrocardiogram (ECG) monitoring
7. Infection monitoring (serious infections, opportunistic infections)
8. Malignancy monitoring
9. Cardiovascular event monitoring (major adverse cardiovascular events, MACE)
10. Liver function test (LFT) monitoring

Safety Endpoints:

1. Incidence of AEs and SAEs
2. Discontinuation rate due to AEs
3. Time to first AE or SAE
4. Change from baseline in laboratory parameters (hematology, biochemistry)
5. Change from baseline in vital signs (blood pressure, pulse rate)

Safety Monitoring:

1. Regular safety updates to regulatory agencies
2. Periodic safety review meetings
3. Safety signal detection and evaluation
4. Risk management plan implementation[8,9,10,16]

Clinical Trials Safety Data:

SELECT-EARLY Study (NCT02721489)

1. AE incidence: 64.1% (upadacitinib 15 mg) vs. 55.6% (placebo)
2. SAE incidence: 5.5% (upadacitinib 15 mg) vs. 3.4% (placebo)
3. Discontinuations due to AEs: 4.5% (upadacitinib 15 mg) vs. 2.5% (placebo)

SELECT-MONOTHERAPY Study (NCT02706951)

1. AE incidence: 65.1% (upadacitinib 15 mg) vs. 59.2% (methotrexate)
2. SAE incidence: 4.9% (upadacitinib 15 mg) vs. 3.4% (methotrexate)
3. Discontinuations due to AEs: 5.1% (upadacitinib 15 mg) vs. 3.4% (methotrexate)

SELECT-NEXT Study (NCT02675426)

1. AE incidence: 63.2% (upadacitinib 15 mg) vs. 56.3% (placebo)
2. SAE incidence: 5.1% (upadacitinib 15 mg) vs. 3.5% (placebo)
3. Discontinuations due to AEs: 4.3% (upadacitinib 15 mg) vs. 2.6% (placebo)

Post-Marketing Safety Surveillance:

1. FDA Adverse Event Reporting System (FAERS)
2. EMA Pharmacovigilance Risk Assessment Committee (PRAC)
3. Periodic safety update reports (PSURs)

Risk Management Plan:

1. Identification of safety risks (serious infections, MACE, malignancies)
2. Mitigation strategies (dose adjustment, monitoring, patient education)
3. Communication plan (healthcare provider education, patient information)[5,6,15,16,1718,]

Benefit Assessment:

Improvement of Disease Status

Enhancement of the Condition At week 12, upadacitinib 15 mg plus baseline csDMARDs/methotrexate was better than a placebo across composite indices for clinical response and overall disease status (SELECT-NEXT, SELECT COMPARE, and SELECT-BEYOND) in patients who were either csDMARD/methotrexate IR or bDMARD-IR. Significantly more patients received ACR responses (except for ACR70 at week 12 in SELECT-BEYOND), remission, and LDA by all measures when compared to placebo. Weeks 48 and 60 saw an improvement in the responses (SELECT-NEXT and SELECT-BEYOND). In patients who were methotrexate-naïve (SELECT-EARLY) or methotrexate-IR (SELECT-MONOTHERAPY), upadacitinib monotherapy outperformed methotrexate at weeks 12 or 14, respectively, on a number of clinical response and disease status markers.In both cases, this was maintained until week 48. Notably, upadacitinib, either alone or in combination, showed a quick commencement of action, with statistically significant responses as early as week 2 when compared to methotrexate or a placebo, respectively.

Inhibition of Progression of Structural Joint Damage.

In addition to disease activity and safety, EULAR guidelines state that treatment decisions should be based on the progression of structural damage. One key way that DMARDs differ from purely symptomatic antirheumatic medications, like non-steroidal anti-inflammatory drugs, is by inhibiting structural damage. Both the methotrexate-naïve and methotrexate-IR populations (SELECT-EARLY and SELECT-COMPARE) had their radiographic progression evaluated as part of the upadacitinib development program. When compared to placebo + methotrexate, upadacitinib + methotrexate significantly slowed the progression of structural joint damage in methotrexate-IR patients at week 26, with a much higher percentage of patients showing no radiographic progression. Up until week 48, structural joint deterioration was kept at bay.Similarly, compared to methotrexate monotherapy, upadacitinib monotherapy in patients who had never taken methotrexate demonstrated a statistically significant decrease in the progression of structural joint damage. Additionally, a significantly higher proportion of patients had no radiographic progression at week 24, with progression inhibition maintained through week 48.

Radiographic Benefits:
1. Inhibition of structural joint damage
2. Reduced joint space narrowing
3. Decreased erosions

Additional Patient Reported Outcomes
1. Improved quality of life
2. Reduced fatigue
3. Improved sleep quality
4. Enhanced emotional well-being
5. Increased productivity.

Clinical Benefits:
1. Rapid and sustained improvement in disease activity
2. Reduced joint pain and swelling
3. Improved physical function and mobility
4. Slowed disease progression
5. Reduced risk of joint damage and erosion[7,8,10,15,18],

CONCLUSION:

When used to treat rheumatoid arthritis, upadacitinib has demonstrated encouraging outcomes, especially in individuals who have not reacted well to tumor necrosis factor inhibitors (TNFis) or biologic disease-modifying antirheumatic medications (bDMARDs). Upadacitinib has been shown in studies to provide clinically significant effectiveness responses over a 24-week period, while maintaining safety levels that are comparable to those of the entire bDMARD-IR patient population. Upadacitinib has been reported to have a stable safety profile with no new hazards arising after five years in terms of long-term safety and efficacy. Furthermore, at the five-year mark, upadacitinib showed statistically greater clinical responses than adalimumab, suggesting a favorable benefit-risk profile for long-term therapy of rheumatoid arthritis.[19,20,21]

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