INVITED REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2023.57966
Rheumatology Quarterly 2024;2(4):147-57

UPADACITINIB IN ACTION: EFFICACY AND SAFETY IN THE TREATMENT OF RHEUMATOID ARTHRITIS, PSORIATIC ARTHRITIS, AND AXIAL SPONDYLOARTHRITIS

Fatma Başıbüyük, İsmail Sarı

Dokuz Eylül University Faculty of Medicine, Department of Rheumatology, İzmir, Turkey

Abstract

This review examines the efficacy, safety, and pharmacokinetics of upadacitinib (UPA) for treating rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA). This review analyzes the results of multiple clinical trials and provides a comprehensive overview of UPA's effectiveness in improving disease activity, reducing symptoms, and preventing joint damage. The review also highlights the safety profile of UPA, including the increased risk of herpes zoster, non-melanoma skin cancer, and elevated creatine phosphokinase levels. In addition, the review discusses the pharmacokinetics of UPA, emphasizing its rapid absorption and limited plasma protein binding. Overall, UPA appears to be a promising therapeutic option for patients with RA, PsA, and axSpA, particularly those with inadequate response to other therapies.

Keywords: Upadacitinib, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis

INTRODUCTION

Recent technological advancements have revolutionized our understanding and management of inflammatory rheumatic conditions. Among these breakthroughs, Janus kinases (JAKs) have emerged as pivotal components in signal transduction pathways, providing promising avenues for treating these diseases. The JAK enzyme family, comprising cytoplasmic protein tyrosine kinases (TYKs), has revealed new therapeutic possibilities for addressing unmet needs for treating inflammatory rheumatic diseases (1-3).

The JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2. These kinases bind to transmembrane cytokine receptors, initiating downstream signaling cascades that ultimately activate transcription factors such as signal transducer and activator of transcription (STAT) proteins. JAKs play a role in various physiological processes, including immune defense, hematopoiesis, and development. Dysregulation of JAK activity has been implicated in the pathogenesis of various diseases, particularly immune-mediateddiseases. The JAK/STAT pathway plays a critical role in such diseases because cytokine signaling considerably impacts their development and progression (1-3).

Upadacitinib (UPA), or ABT-494, is an oral JAK inhibitor and targeted synthetic disease-modifying antirheumatic drug (tsDMARD) with selective activity toward JAK1 over JAK2, JAK3, and TYK2 (4). It is the first JAK1-selective inhibitor developed on the basis of the hypothesis that JAK1 inhibition would result in fewer adverse effects. Cellular assays have confirmed its selectivity, with UPA demonstrating >40-fold greater selectivity for JAK1 than for JAK2, 130-fold greater selectivity for JAK1 than

Address for Correspondence: İsmail Sarı, Dokuz Eylül University Faculty of Medicine, Department of Rheumatology, İzmir, Turkey
Phone: +90 530 592 97 55 **E-mail:** ismailsari35@gmail.com **ORCID ID:** orcid.org/0000-0001-7737-4180
Received: 16.05.2023 **Accepted:** 22.05.2023

for JAK3, and 190-fold greater selectivity for JAK1 than for TYK2 (4). Both the Food and Drug Administration (FDA) and European Medical Agency (EMA) have approved UPA for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). In addition, the FDA and EMA have approved it for treating ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-AxSpA) (5).

In this review, we provide a comprehensive overview of UPA application for treating RA, AS, and axSpA, with a focus on its efficacy and safety profile.

Rheumatoid Arthritis

RA is a chronic autoimmune disorder that primarily affects synovial joints, causing inflammation, progressive joint damage, deformity, and functional impairment. This systemic condition affects approximately 0.5-1% of the global population, with a higher prevalence in women than in men. Although the exact cause remains uncertain, the development of RA involves a complex interplay of genetic, environmental, and hormonal factors.

Patients with RA often experience joint pain, stiffness, and swelling, which significantly affect their quality of life and daily activities. In addition, the disease may involve extra-articular tissues, leading to complications such as rheumatoid nodules, vasculitis, and organ involvement. Early diagnosis and aggressive treatment are crucial to control inflammation, alleviate symptoms, and prevent joint damage. Initial treatment typically involves conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), which demonstrate a 60-70% drug survival rate at one year of treatment (6,7). However, approximately one-third of patients require the use of biological or tsDMARDs to achieve better disease control.

The efficacy of UPA in RA was assessed in two Phase 2 studies, BALANCE I and BALANCE II, which involved patients with moderate to severe RA and lasted 12 weeks each (8,9).

BALANCE I included 276 patients with RA on stable methotrexate (MTX) doses who had an inadequate response to at least one anti-tumor necrosis factor agent (TNF-IR) (8). They were randomized to receive immediate-release ABT-494 (UPA) at 3, 6, 12, or 18 mg twice daily or a matching placebo. The primary endpoint, American College of Rheumatology (ACR)20 response (20% improvement per the ACR criteria), at week 12 showed rates of 53%, 58%, 71%, 67%, and 34%, respectively, with all active treatment doses being significant compared with placebo (8). Secondary endpoints included ACR50 and ACR70, which demonstrated significance for all doses except the 3 mg bid dose. Additional secondary endpoints, low disease activity (LDA) based on disease activity score (DAS)28-C-reaktif protein (CRP) ≤3.2 and clinical disease activity index (CDAI) ≤10, revealed that only the 12 mg bid dose was significant for DAS28-CRP ≤3.2, while none of the doses were significant for CDAI ≤10. Remission rates based on DAS28-CRP <2.6 and CDAI ≤2.8 showed significance only for the 12 mg bid dose and none of the doses, respectively (8).

BALANCE II involved 300 active RA patients with inadequate responses to MTX (MTX-IR), who received immediate-release UPA at various doses or placebo while maintaining stable MTX doses (9). ACR20, ACR50, and ACR70 response rates were significant for all doses compared with placebo, except for the 12 mg bid dose in ACR70. LDA based on DAS28 ≤3.2 and CDAI ≤10 were significant at all doses compared with placebo. Remission rates for DAS28 <2.6 were significant for all doses except the 24 mg once daily, while none of the doses reached significance based on CDAI ≤2.8 (9). The most common adverse events (AEs) included headache, nausea, upper respiratory tract infection (URTI), and urinary tract infection. Infection rates increased with higher UPA doses, but none were severe. In patients with inadequate responses or intolerance to anti-TNF agents, the addition of UPA to MTX led to rapid, dose-dependent improvements in RA signs and symptoms (9). Table 1 summarizes the primary and secondary endpoints of both studies.

In BALANCE I, significant findings were observed for ACR20, ACR50, and ACR70 response rates with active treatment doses (except 3 mg bid), indicating improvement compared with placebo. Significant results were also observed for LDA (DAS28-CRP ≤3.2) with the 12 mg bid dose. No significant differences were found for CDAI ≤10 or remission rates based on CDAI ≤2.8. In BALANCE II, all doses (except 12 mg bid) showed significant improvements in ACR20, ACR50, and LDA (DAS28 ≤3.2 and CDAI ≤10) compared with placebo. ACR70 response rates were significant for all doses except 12 mg bid. Remission rates based on DAS28 <2.6 were significant for all doses except 24 mg once daily (QD). However, no significant differences were found for remission rates based on CDAI ≤2.8.

The BALANCE studies provided a solid foundation for advancing to Phase III trials, as both studies assessed efficacy and found no safety concerns. In BALANCE I, a dosage of 6 mg of UPA taken twice daily demonstrated near-maximum efficacy. The BALANCE II study revealed an additional benefit with a dosage of 12 mg taken twice daily. Based on these results, daily equivalent doses of 15 mg and 30 mg of UPA in the extended-release form, administered once daily, were selected for Phase III studies (10).

UPA has been evaluated in the SELECT Phase III RA program, which includes six multicenter, randomized, double-blind, placebo-controlled studies. Five of these studies were conducted

Table 1. Summary of primary and secondary endpoints in the BALANCE-I and BALANCE-II studies at 12 weeks

Dose	ACR20	ACR50	ACR70	DAS28-CRP ≤3.2	CDAI ≤10	DAS28-CRP <2.6	CDAI ≤2.8
BALANCE I							
Placebo	34	16	4	25	25	13	7
3 mg bid	53	24	13	33	27	24	9
6 mg bid	58	36	26	36	31	26	11
12 mg bid	71	42	22	49	40	33	13
18 mg bid	67	38	22	42	40	27	16
BALANCE II							
Placebo	46	18	6	20	20	14	6
3 mg bid	62	38	22	48	40	36	4
6 mg bid	68	46	28	52	38	36	12
12 mg bid	80	50	16	46	40	34	14
18 mg bid	64	40	26	46	46	40	6
24 mg QD	76	39	22	41	35	22	14

ACR: American College of Rheumatology, CDAI: Clinical disease activity index, DAS-28: Disease activity score 28, CRP: C-reaktif protein, QD: Once daily

in patients with MTX-IR or other csDMARDs. In four of these studies, UPA was tested in combination with either MTX or csDMARDs. Two of these studies were placebo-controlled trials without active comparators [SELECT-NEXT in a csDMARD-inadequate response (IR) population and SELECT-BEYOND in a biological DMARD-IR population] (11,12), whereas the other two studies included an active comparator (SELECT-COMPARE in a MTX-IR population and SELECT-CHOICE in a biological DMARD-IR population) (13,14). Another study was conducted with UPA as monotherapy in patients with an inadequate response to MTX, known as the SELECT-MONOTHERAPY trial (15). The final study, the SELECT-EARLY trial, was conducted in MTX-naive patients, in whom UPA was evaluated as monotherapy (16). Table 2 summarizes the key domains of the SELECT studies.

The SELECT-NEXT trial focused on the csDMARD-IR population and found that UPA 15 mg and 30 mg both led to significant improvements in ACR20 response rates, with 64% and 66% response rates, respectively, at week 12 (11). Additionally, both doses of UPA resulted in a DAS28-CRP ≤3.2 response rate of 48%, which was higher than the 17% response rate seen in the placebo group. It is important to note that patients in this trial were permitted to continue their background csDMARD therapy (11). In the SELECT-BEYOND trial, which targeted the biological disease-modifying antirheumatic drug (bDMARD)-IR population, UPA 15 mg and 30 mg demonstrated higher ACR20 response rates of 65% and 56%, respectively, at week 12 compared with the placebo group's 28% response rate (12). Similarly, the percentages of patients achieving DAS28-CRP ≤3.2 with UPA 15 mg and 30 mg were 43% and 42%, respectively, compared with only 14% in the placebo group. Patients in this trial continued their stable csDMARD therapy (12). The SELECT-COMPARE trial focused on the MTX-IR population and compared UPA 15 mg with adalimumab (ADA) 40 mg and placebo (13). At week 12, UPA 15 mg exhibited a strong ACR20 response rate of 71% and a DAS28-CRP ≤3.2 response rate of 45%, outperforming ADA 40 mg, which had lower response rates of 63% and 29%, respectively. In comparison, the placebo group showed the lowest response rates, with an ACR20 response rate of 36% and a DAS28-CRP ≤3.2 response rate of 15% at week 12. All patients in this trial received background MTX (13).

In the SELECT-CHOICE trial, which lasted 24 weeks, patients were treated with either oral UPA 15 mg once daily or intravenous ABA, along with stable synthetic DMARDs (14). At week 12, the ACR 20 response rate was higher in the UPA group (76%) than in the ABA group (66%), and this trend continued at week 24 (79% vs. 74%, respectively). In terms of DAS28-CRP ≤3.2 response rates, UPA was superior to ABA at both the 12-week mark (50% vs. 29%) and the 24-week mark (63% vs. 48%) (14).

In the SELECT-MONOTHERAPY trial, patients with active RA despite stable MTX were assigned to receive UPA 15 or 30 mg once daily or to continue MTX at their previous dose (15). The group that received UPA 15 mg had a 68% ACR20 response and 45% DAS28-CRP ≤3.2 response at week 14, whereas the UPA 30 mg group showed a 71% ACR20 response and 53% DAS28-CRP ≤3.2 response at the same time point. Comparatively, in the

Table 2. Summary of phase III clinical trials evaluating upadacitinib for the treatment of RA (11-16)

Study name	Study design	Population	Background therapy	Upadacitinib arms	Comparator	The type of treatment	Sample size	Primary endpoint
Next	12-week, multicenter, randomized, double-blind study	csDMARD-IR	csDMARD	15 mg QD, 30 mg QD	Placebo	Combination	661	ACR20 at week 12; DAS28-CRP ≤3.2 at week 12
Beyond	12-week, multicenter, randomized, double-blind study	bDMARD-IR	csDMARD	15 mg QD, 30 mg QD	Placebo	Combination	499	ACR20 at week 12; DAS28-CRP ≤3.2 at week 12
Compare	26-week, multicenter, randomized, double-blind study	MTX -IR	MTX	15 mg QD	Placebo	Combination	1629	ACR20 at week 12; DAS28-CRP >2.6 at week 12
Choice	24-week, multicenter, randomized, double-blind study	bDMARD-IR	csDMARD	15 mg QD, 30 mg QD	ADA 40 mg/2 weeks	Combination	612	Change in DAS28-CRP levels at week 12 (non-inferiority)
Monotherapy	14-week, multicenter, randomized, double-blind study	MTX -IR	Not applicable	15 mg QD	MTX	Monotherapy	648	ACR20 at week 14; DAS28-CRP ≤3.2 at week 14
Early	48-week, multicenter, randomized, double-blind study	Naive or limited exposure to MTX	Not applicable	15 mg QD	Not applicable	Monotherapy	947	ACR50 at week 12; DAS28-CRP ≥2.6 at week 24

RA: Rheumatoid arthritis, csDMARD: Conventional synthetic disease-modifying antirheumatic drugs, IR: Inadequate responses, ACR: American College of Rheumatology, DAS-28: Disease activity score 28, CRP: C-reaktif protein, bDMARD: Biological disease-modifying antirheumatic drug, MTX: Methotrexate, ADA: Adalimumab, QD: Once daily

same trial, the group that continued MTX treatment had a 42% ACR20 response and a 20% DAS28-CRP ≤3.2 response at week 14 (15).

The SELECT-EARLY trial aimed to evaluate the efficacy of UPA as monotherapy in patients with predominantly early RA who were either new to or had limited exposure to MTX (16). The trial comprised a 48-week active comparator-controlled period, followed by a long-term extension period of up to 4 years. The results showed that the ACR20 response rates at week 12 were higher in patients receiving UPA at both doses (76% and 77% for UPA 15 and UPA 30, respectively) than in those receiving MTX (54%). Similarly, the DAS28-CRP ≤3.2 response rates at week 12 were also higher in the UPA groups (53% and 55% for UPA 15 and UPA 30, respectively) than in the MTX group (28%). Both endpoints were statistically significant in the UPA groups compared with MTX (16).

The SELECT-SUNRISE trial was a dose-ranging study conducted in Japan and involved patients who were previously on stable csDMARDs (17). They were randomly assigned to receive UPA 7.5, 15, or 30 mg once daily or a matching placebo for a 12-week double-blind period. The primary endpoint of the trial was to measure the ACR20 response. At week 12, a higher percentage of patients receiving UPA at all doses (7.5 mg, 15 mg, and 30 mg) achieved the ACR20 response compared with those receiving placebo (76%, 84%, and 80% vs. 43%). The DAS28-CRP ≤3.2 response rates at week 12 were also significantly higher in patients receiving UPA (53%, 69%, and 72%) than in those receiving placebo (18%) (17). Following the initial 12-week study, patients were enrolled in a blinded extension period. Recently, the 84-week results of this extension study were reported (18). During this period, placebo patients were randomly assigned to UPA 7.5, 15, or 30 mg doses, whereas former UPA patients

continued the same dose scheme. The ACR20 response rates for patients initially randomized to UPA demonstrated continued improvement or maintenance over time up to week 84. In contrast, patients initially randomized to placebo showed improvements in ACR20 response after switching to UPA at week 12. At week 84, ACR20 response rates were 85.7%, 77.6%, and 58.0% for patients continuing UPA 7.5 mg, 15, and 30 mg, respectively. These response rates were similar for patients who had switched to UPA at week 12. Similar trends were observed in patients who achieved DAS28-CRP ≤3.2 response rates at 84 weeks. In summary, patients who switched from placebo to UPA at week 12 showed efficacy improvements up to week 84 that were comparable to those observed in patients initially randomized to UPA (18). Table 3 summarizes the key outcome variables for each of the SELECT trials.

In the SELECT-NEXT trial, both doses of UPA demonstrated significant improvements in each outcome variable compared with placebo. In SELECT-BEYOND, all outcome variables except for ACR70 with UPA 15 mg were significantly better than those with placebo. In SELECT-COMPARE, UPA outperformed ADA and placebo in each outcome variable at both time points. In SELECT-CHOICE, no significant differences were found between UPA and ABA for each outcome variable at both time points, except for the remission rate based on DAS28 at week 12, which favored UPA over ABA. In SELECT-MONOTHERAPY, both UPA doses significantly outperformed MTX for each outcome variable. Finally, in SELECT-EARLY, both UPA doses showed significant improvements at both time points for all variables compared with placebo. It is noteworthy that CDAI LDA and remission rates were only presented for week 24.

The SELECT-EARLY and SELECT-COMPARE trials evaluated radiographic progression in patients with RA receiving UPA (19). The results showed that UPA monotherapy or in combination with background MTX was more effective than MTX monotherapy in inhibiting the progression of structural joint damage in MTX-naive patients with RA. In MTX-IR patients with RA, UPA plus MTX

Table 3. Key outcome variables for SELECT phase III trials (11-16)

Dose	ACR20	ACR50	ACR70	DAS28-CRP ≤3.2	CDAI ≤10	DAS28-CRP <2.6	CDAI ≤2.8
SELECT NEXT, % of patients achieving response at 12 weeks							
Placebo	36	15	6	17	19	10	3
15 mg	64	38	21	48	40	31	9
30 mg	66	43	27	48	42	28	12
SELECT BEYOND, % of patients achieving response at 12 weeks							
Placebo	28	20	11	14	14		
15 mg	65	34	12	43	32		
30 mg	56	36	23	42	34		
SELECT COMPARE, % of patients achieving response (weeks 12 and 26 respectively)							
Placebo	36, 36	15, 21	5	14, 18	16, 22	6, 9	3, 6
UPA	71, 67	45, 54	25	45, 55	40, 53	29, 41	13, 23
ADA	63, 57	29, 42	13	29, 39	30, 38	18, 27	8, 14
SELECT CHOICE, % of patients achieving response (weeks 12 and 26 respectively)							
UPA	76, 79	46, 59	21, 37	50, 63	41, 58	30, 46	8, 21
ABA	66, 74	34, 49	14, 26	29, 48	35, 52	13, 31	3, 14
SELECT MONOTHERAPY, % of patients achieving response at 14 weeks							
15 mg	68	42	23	45	35	28	13
30 mg	71	52	33	53	47	41	19
MTX	41	15	3	19	25	8	1
SELECT EARLY, % of patients achieving response (weeks 12 and 24 respectively)							
15 mg	77, 79	52, 60	32, 45	53, 60	56	48, 48	28
30 mg	75, 78	56, 66	37, 50	55, 65	61	50, 50	29
MTX	54, 59	28, 33	14, 19	28, 32	38	18, 18	11

ACR: American College of Rheumatology, DAS-28: Disease activity score 28, CRP: C-reaktif protein, CDAI: Clinical disease activity index, UPA: Upadacitinib, ADA: Adalimumab, ABA: Abatacept, MTX: Methotrexate

was more effective in inhibiting the progression of structural joint damage than placebo plus MTX, with a mean change from baseline in the modified total Sharp score (mTSS) of 0.28 for UPA plus MTX compared with 1.73 for placebo plus MTX at week 48 ($p<0.05$). The mean change from baseline in mTSS was 0.39 for ADA plus MTX. Furthermore, significantly reduced progression of joint space narrowing and erosion scores with UPA plus MTX vs. placebo plus MTX were observed at 6 months and 1 year ($p<0.05$). Overall, these results suggest that UPA may be an effective treatment option for preventing the progression of joint damage in patients with RA (19).

In conclusion, studies evaluating the efficacy and safety of UPA for treating RA have provided valuable insights into its potential as a therapeutic option. UPA has demonstrated significant improvements in various outcome variables, including ACR response rates, disease activity scores, and radiographic progression, compared with placebo and other active comparators. The BALANCE studies, as well as the SELECT Phase III trials, have consistently shown that UPA, either as monotherapy or in combination with conventional synthetic or biological DMARDs, effectively reduces disease activity and improves patient outcomes. Notably, UPA exhibited dose-dependent efficacy, with the 15 and 30 mg daily doses generally demonstrating superior results. Furthermore, these studies have established the safety profile of UPA, with manageable AEs and no significant safety concerns. The positive results from these trials provide a solid foundation for considering UPA as a valuable treatment option for patients with RA, particularly those who have an inadequate response to other therapies.

Psoriatic Arthritis

PsA is a chronic inflammatory rheumatic disease characterized by joint inflammation and skin lesions. Although it often occurs in individuals with pre-existing psoriasis, it can also manifest independently. Despite extensive research, the exact cause of PsA remains unknown. However, emerging evidence suggests that the JAK/STAT pathway plays a critical role in PsA pathogenesis. The JAK/STAT pathway is responsible for regulating immune responses and inflammatory processes, making it an intriguing target for therapeutic interventions. As a result, JAK inhibitors have emerged as promising and innovative therapies for PsA, offering new possibilities for managing this complex condition (20). Currently, several studies have shown the efficacy of these treatments in PsA. The EMA approved UPA for treating active PsA in patients who are intolerant to DMARDs or have had an inadequate response to one or more DMARDs or conventional therapy. The SELECT-PsA1 trial, a randomized, double-blind, placebo-controlled phase 3 study, involved 1704 patients with PsA (21). Participants were eligible if they were 18 years or older, diagnosed with PsA, and had an inadequate response to at least one non-biologic DMARD. The study compared the efficacy of UPA 15 or 30 mg once daily with placebo or ADA 40 mg every other week. Patients with prior exposure to biological therapies or JAK inhibitors were excluded. The primary endpoint was an ACR20 response with UPA versus placebo at week 12. At this point, both UPA doses exhibited non-inferiority to ADA and superiority to placebo, with ACR20 response rates of 70.6% and 78.5% for UPA 15 mg and 30 mg, respectively, compared with 36.2% for placebo and 65% for ADA ($p<0.001$ for both UPA doses vs. placebo) (21). ACR50 response rates were 13.2% for placebo, 37.5% for ADA, 37.5% for UPA 15 mg, and 51.8% for UPA 30 mg. ACR70 response rates at week 12 were 15.6% for UPA 15 mg, 25.3% for UPA 30 mg, 13.8% for ADA, and 2.4% for placebo. At week 24, ACR20 response rates were 45.2% for placebo, 67.1% for ADA, 73.4% for UPA 15 mg, and 78.5% for UPA 30 mg. ACR50 response rates were 18.9% for placebo, 44.3% for ADA, 52.4% for UPA 15 mg, and 60.5% for UPA 30 mg. ACR70 response rates were 5.2% for placebo, 22.6% for ADA, 28.7% for UPA 15 mg, and 36.4% for UPA 30 mg (21).

The SELECT-PSA1 trial results include findings from 1- and 2-year follow-up periods (22,23). During the 56-week study, approximately 17% of the patients discontinued treatment, with 20% of them ceasing due to insufficient efficacy. Notably, patients who switched from placebo to active drugs experienced response rate improvements similar to those who started with active drugs (22). Efficacy was evaluated by measuring ACR20, 50, and 70 response rates for three different drugs at week 56: UPA 15 mg (73.7%, 57.1%, and 35.2%, respectively), UPA 30 mg (74.4%, 60.4%, and 39.7%, respectively), and ADA (68.5%, 51.3%, and 31.2%, respectively) (22). In the second year, these rates wereas follows: UPA 15 mg (69%, 53.6%, and 38%, respectively), UPA 30 mg (69.5%, 59.3%, and 43.5%, respectively), and ADA (63.4%, 47.1%, and 29.4%, respectively) (23). Regarding enthesitis resolution, 59.3%, 57.8%, and 54% of patients receiving UPA 15, UPA 30, and ADA 40 mg, respectively, experienced improvement by week 56, while 53.3%, 52.2%, and 49.1% did so by week 104. Regarding dactylitis, 75%, 74.8%, and 74% of patients achieved resolution by week 56, and 69.9%, 71.7%, and 72.4% achieved resolution by week 104, respectively (23).

The SELECT-PsA2 trial was conducted with 641 patients to assess the effectiveness of once-daily UPA 15or 30 mg compared with placebo in patients with PsA who were refractory or intolerant to biological DMARDs (24). Eligible patients were 18 years or older with active PsA, had a diagnosis of PsA with symptom onset for at least 6 months, had a history or current plaque psoriasis, had at least three swollen and tender joints at baseline, and had an inadequate response or intolerance to at least one biological DMARD. The primary endpoint was the ACR20 response at week 12. Both UPA doses demonstrated superior efficacy to placebo in achieving ACR20 response at week 12, with response rates of

56.9% and 63.8% for UPA 15 and 30 mg, respectively, compared with 24.1% for placebo ($p<0.05$ for both UPA doses vs. placebo). At week 24, the response rates for ACR20, 50, and 70 wereas follows: UPA 15 mg (59.2%, 38.4%, and 19.4%, respectively), UPA 30 mg (61.5%, 36.2%, and 23.9%, respectively), and placebo (20.3%, 9.4%, and 0.9%, respectively). Both UPA doses were statistically significant compared with placebo. Other secondary endpoints at week 24, such as improvement in enthesitis [Leeds Enthesitis Index (LEI); UPA 15 mg 43%, UPA 30 mg 45%, and placebo 15%] and dactylitis [Leeds Dactylitis Index (LDI); UPA 15 mg 58%, UPA 30 mg 68%, and placebo 28%], were also significant compared with placebo (24).

By week 56, approximately 25% of the patients had to discontinue medication due to various factors, primarily AEs. Approximately 19% of these discontinuations resulted from insufficient efficacy (25). At the same time, the proportion of patients achieving ACR20/50/70 was 59.7%, 40.8%, and 24.2% for UPA 15 mg and 59.2%, 38.5%, and 26.6% for UPA 30 mg, respectively. Responses at week 56 for both placebo-to-UPA groups were similar to those who received UPA from the beginning. In patients with dactylitis at baseline, complete resolution (LDI =0) was observed in 50.9% and 58.0% of patients treated with UPA 15 mg and 30 mg, respectively, by week 56. Additionally, for those with enthesitis at baseline, complete resolution (LEI =0) was achieved in 42.9% and 42.8% of patients for the 15 and 30 mg dosages, respectively (25).

In both SELECT-PsA 1 and SELECT-PsA 2 studies, axial involvement was also assessed (26). At baseline, the determination of axial involvement was made by the investigator's judgment (yes or no), considering all available clinical information such as duration and characteristics of back pain, age of onset, and any previous lab investigations or imaging, if accessible. Axial involvement was present in 30.9% of patients in SELECT-PsA 1 and 35.7% in SELECT-PsA 2. In SELECT-PsA 1, Ankylosing spondylitis disease activity score inactive disease (ASDAS ID) was achieved in higher percentages by week 12 for UPA 15 mg and ADA compared with placebo (23%, 29.9%, and 6.2%, respectively), as well as by week 24 (41.7%, 35.4%, and 13.1%, respectively). In SELECT-PsA 2, ASDAS ID was attained in 17.1% and 28.9% of UPA 15 mg patients by weeks 12 and 24, whereas for placebo, the percentages were 6.7% and 2.7%, respectively (26).

In summary, based on the controlled trials (Table 4), UPA at both doses proved effective in managing PsA. In addition to improving

Table 4. Key outcome variables for SELECT PsA-1 and SELECT PsA-2 phase III trials (21-26)

Dose	ACR20	ACR50	ACR70	ASDAS ID
SELECT PsA-1, % of patients achieving response (weeks 12 and 24 respectively)				
Placebo	36.2/45.2	13.2/18.9	2.4/5.2	6.2/13.1
15 mg	70.6/73.4	37.5/52.4	15.6/28.7	23/41.7
30 mg	78.5/78.5	51.8/60.5	25.3/36.4	
ADA	65/67.1	37.5/44.3	13.8/22.6	29.9/35.4
SELECT PsA-1, % of patients achieving response at one to two year follow up periods (weeks 56 and the second year respectively)				
15 mg	73.7/69	57.1/53.6	35.2/38	
30 mg	74.4/69.5	60.4/59.3	39.7/43.5	
ADA	68.5/63.4	51.3/41.7	31.2/29.4	
SELECT PsA-2, % of patients achieving response at 12 week				
Placebo	35.1			6.7
15 mg	56.9			17.1
30 mg	63.8			
SELECT PsA-2, % of patients achieving response at 24 week				
placebo	20.3	9.4	0.9	2.7
15 mg	59.2	38.4	19.4	28.9
30 mg	61.5	36.2	23.9	
SELECT PsA-2, % of patients achieving response at 56 week				
15 mg	59.7	40.8	24.2	
30 mg	59.2	38.5	26.6	

PsA: Psoriatic arthritis, ACR: American college of rheumatology, ASDAS ID: Ankylosing spondylitis disease activity score inactive disease, ADA: Adalimumab

arthritis symptoms, significant responses were observed across various domains, including enthesitis, dactylitis, and axial disease.

Axial Spondyloarthritis

UPA is effective in treating both AS and nr-axSpA patients with axSpA. The SELEXT-AXIS-1 trial, a placebo-controlled study, was conducted on patients with active AS who were unresponsive to NSAIDs (27). Exclusion criteria included previous exposure to any JAK inhibitor or biological therapy. Participants were randomized to receive either UPA 15 mg or placebo for 14 weeks. At week 14, a significantly higher percentage of patients in the UPA group achieved an Assessment of Spondylarhtritis International Society (ASAS)40 response compared with the placebo group (52% vs. 26%). Additionally, a greater proportion of patients in the UPA group reached ASDAS LDA (49% vs. 11%) and ASDAS inactive disease (16% vs. 0%) compared with those receiving the placebo. Furthermore, Spondyloarthritis Sesearch Concertium of Canada (SPARCC) magnetic resonance imaging (MRI) spine and sacroiliac joint scores showed greater improvement from baseline to week 14 in patients treated with UPA than in those given the placebo (27).

Of the 187 patients, 178 (95%) completed week 14 on the study drug and proceeded to the open-label extension (28). The most common reasons for discontinuation between weeks 14 and 64 were lack of efficacy (5.6%) and AEs (2.2%). Comparable proportions of patients in both groups (continuous UPA or placebo-to-UPA) achieved ASAS40 response or ASDAS indicating LDA at week 64. The primary efficacy endpoint of ASAS40, initially at 52% at week 14, continued to increase in the continuous group, reaching 72% by week 64. A similar pattern of improvement was observed for ASDAS LDA (70%), ASDAS ID (34%), and ASAS partial remission (40%) (28). The recently published second-year results of the study revealed that 144 patients (77%) completed week 104 (29). Between weeks 64 and 104, the rates of lack of efficacy and AEs were 0.7% and 4.1%, respectively. In the continuous UPA group, at week 104, ASAS40 was 66%, ASDAS LDA 62%, and ASDAS ID 33%. The mean baseline mSASSS was 8.1±11.6 units, with a mean change of 0.7 [95% confidence intervale (CI): 0.3 to 1.1] after two years. In the continuous UPA group, the mean (95% CI) decrease from baseline to week 14 in the SPARCC MRI spine inflammation score was -7.2 (-10.2 to -4.2), which was sustained through week 104 [-7.3 (-10.8 to -3.7)]. Similar results were observed in the SPARCC MRI sacroiliac joint inflammation score, with a mean decrease from baseline to week 14 of -6.1 (-8.5 to -3.7) and a consistent reduction through week 104 [-5.3 (-7.6 to -3.1)] (29).

The SELECT-AXIS 2 study employed a master protocol and a common screening platform to determine patient eligibility for two separate phase 3, randomized, double-blind, placebo-controlled multicenter trials: bDMARD-IR AS and active nr-axSpA resistant to NSAIDs (30,31). The bDMARD-IR AS study aimed to assess the efficacy and safety of once-daily UPA 15 mg versus placebo, with the primary endpoint being ASAS40 response at week 14 (30). The majority of participants had prior exposure to one TNF inhibitors (TNFi) (74%), followed by one interleukin (IL)-17i (13%). ASAS40 response at week 14 was observed in 45% of the UPA group compared with 18% in the placebo group. UPA also demonstrated superior ASAS40 treatment effects in subgroups of patients who had received either one (46% vs. 20%) or two (36% vs. 4%) prior bDMARDs, as well as in those with previous exposure to TNFi (47% vs. 22%) or IL-17i (37% vs. 4%). In addition, UPA improved objective inflammation markers, as indicated by hsCRP and SPARCC MRI spine and sacroiliac joint inflammation scores. ASDAS LDA rates were 44% vs. 10%, and ASDAS-ID rates were 13% vs. 2%, both in favor of UPA (30).

In the nr-axSpA study, participants were required to exhibit at least one objective sign of active inflammation during the screening phase, as evidenced by MRI of the sacroiliac joints or high-sensitivity CRP levels above the upper limit of normal. Patients must have had an inadequate response to at least two NSAIDs or demonstrated intolerance or contraindication for NSAIDs. Enrollment permitted previous treatment with one bDMARD for a minimum of 20% and a maximum of 35% of participants who had discontinued the prior bDMARD because of lack of efficacy (after ≥12 weeks at an adequate dose) or intolerance (31). The primary endpoint was the proportion of patients who achieved an ASAS40 response at week 14. ASAS40 responses were observed in 45% of the UPA group and 23% of the placebo group, whereas ASAS partial remission rates were 19% and 8%, respectively. Comparing baseline and 14-week SPARCC MRI scores for the spine and sacroiliac joint, the UPA group showed reductions of -0.79 and -2.49, whereas the placebo group experienced increases of 0.34 and 0.57 units, respectively (31).

In summary, the SELECT-AXIS studies demonstrated the benefits of UPA in patients with AS and nr-axSpA (Table 5), regardless of whether they were biologic-naïve or had previous experience with biological treatments.

Table 5. Key outcome variables for SELECT AXIS-1 and SELECT AXIS-2 phase III trials (27-31)

Dose	ASAS40	ASDAS LDA	ASDAS ID	ASAS PR
SELECT AXIS-1, % of patients achieving response at 14 weeks				
Placebo	26	11	0	
15 mg	52	49	16	
SELECT AXIS-1, % of patients achieving response (weeks 64 and 104 respectively)				
15 mg	72/66	70/62	34/33	40/40
SELECT AXIS-2 (bDMARD-IR AS study), % of patients achieving response at 14 weeks				
Placebo	18	10	2	6.7
15 mg	45	44	13	17.1
SELECT AXIS-2 (nr-axSpA study), % of patients achieving response at 14 weeks				
placebo	23			8
15 mg	45			19

ASAS: Assessment of Spondylarhtritis International Society,ASDAS: Ankylosing spondylitis disease activity score, LDA: Low disease activity, ID: Inactive disease, PR: Partial remission, bDMARD: Biologic disease-modifying antirheumatic drug, IR: Inadequate responses, AS: Spondylitis, nr-axSpA: Non-radiographib axial spondyloarthritis

Safety

The safety profile of UPA in RA has been investigated in various studies, including the SELECT phase III clinical studies and a systematic review and meta-analysis of JAK inhibitors (32,33). The SELECT trials found an increased risk of herpes zoster in patients receiving UPA compared with those receiving ADA, with hazard ratios of 2.997 (vs. MTX) and 3.221 (vs. ADA). The integrated safety analysis reported acceptable safety profiles with no new risks compared with other JAK inhibitors (32). In the systematic review and meta-analysis, JAK inhibitors, including UPA, were significantly associated with an increased risk of AEs [relative risk (RR) 1.09, 95% CI 1.05-1.13], herpes zoster (RR 2.57, 95% CI 1.43-4.62), and URTI (RR: 1.32, 95% CI: 1.07-1.63) compared with placebo. Both the 15 and 30 mg doses of UPA were linked to an increased risk of AEs (15 mg QD: RR 1.14, 95% CI 1.02-1.27; 30 mg QD: RR 1.15, 95% CI 1.02-1.30). The risk of herpes zoster was higher in patients receiving UPA, although the effect was not statistically significant (15 mg QD: RR: 1.41, 95% CI: 0.44-4.45; 30 mg QD: RR: 2.96, 95% CI: 0.59-14.83) (33).

In a safety study of UPA involving over 6,000 patients with RA, PsA, AS, and atopic dermatitis (AD), the overall occurrence of AEs was comparable between upadacitinib 15 mg QD and ADA 40 mg EOW among RA patients (205.5 vs. 203.6 events per 100 patient-years) (34). UPA showed a slightly lower rate of serious AEs (12.4 events per 100 patient-years) than ADA (13.7 events per 100 patient-years) in RA patients, whereas in PsA patients, both treatments had similar rates of serious AEs (11.1 vs. 9.0 events per 100 patient-years). The mortality rate was low and similar for both treatments in patients with RA (0.8 vs. 0.9 events per 100 patient-year). Patients with RA and PsA treated with UPA experienced higher incidences of herpes zoster (1.6-3.6 events per 100 patient-years), non-melanoma skin cancer (0-0.8 events per 100 patient-years), and increased creatine phosphokinase levels (4.4-7.9 events per 100 patient-years) compared with those on active comparators (34). The rates of serious infections, major cardiovascular events (MACE), venous thromboembolism, and malignancies were generally lower in patients with AS and AD. Acne rates rose only in AD patients (34). The study supports UPA as having an acceptable safety profile for treating RA, PsA, AS, and AD, with similar rates of malignancy (excluding non-melanoma skin cancer), MACE, and venous thromboembolism between UPA and active comparators (ADA and MTX). Known differences in the side effect profile of JAK inhibitors, such as increased rates of herpes zoster, elevated creatine phosphokinase levels, and NMSC, have also been observed (34).

Pharmacokinetics

Numerous investigations have explored the pharmacokinetics of UPA, including both human and in vitro studies (35,36). It is rapidly absorbed from the gastrointestinal tract, reaching peak concentration (C_{max}) within approximately 1 hour. The drug exhibits limited plasma protein binding, with less than 50% bound. Its primary metabolism involves the CYP3A4 enzyme. *In vitro* experiments have shown that it does not inhibit drug-metabolizing enzymes or transporters at clinically relevant concentrations (35,36). No significant QTc prolongation was associated with therapeutic doses. The average terminal

elimination half-life ranges from 8 to 14 hours. When examining the influence of food on its pharmacokinetics, Cmax decreased by 23%, but the area under the curve (AUC) remained unchanged compared with fasting conditions (36).

Regarding dose adjustments, the extended-release formulation has an average terminal elimination half-life of 9-14 hours. Dose modifications based on factors such as age, sex, body weight, race, and ethnicity are generally not required for most patients. Mild or moderate renal impairment does not necessitate dose adjustment, whereas severe renal impairment requires a recommended dose of 15 mg once daily. Similarly, individuals with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment do not require dose adjustment. However, the drug should not be administered to patients with severe hepatic impairment (Child-Pugh C). These considerations are particularly important for specific patient populations, including those with renal or hepatic failure (37).

In summary, these studies have shown that upadacitinib is associated with an increased risk of herpes zoster, non-melanoma skin cancer, and elevated creatine phosphokinase levels in patients with RA and PsA. However, the overall occurrence of AEs and serious AEs were generally comparable to those of active comparators, such as ADA and MTX. The rates of serious infections, MACE, venous thromboembolism, and malignancies were typically lower in patients with AS and AD. Collectively, these findings support an acceptable safety profile for Upadacitinib in treating RA, PsA, AS, and AD, while acknowledging known differences in the side effect profile of JAK inhibitors.

CONCLUSION

In conclusion, studies evaluating the efficacy and safety of UPA for treating RA, PsA, and axSpA have provided valuable insights into its potential as a therapeutic option. UPA has demonstrated significant improvements in various outcome variables, including ACR response rates, disease activity scores, and radiographic progression, compared with placebo and other active comparators. Studies have consistently shown that UPA, either as monotherapy or in combination with conventional synthetic or biological DMARDs, effectively reduces disease activity and improves patient outcomes. Furthermore, these studies have established the safety profile of UPA, with manageable AEs and no significant safety concerns. The positive results from these trials provide a solid foundation for considering UPA as a valuable treatment option for patients with RA, PsA, and axSpA, particularly those who have an inadequate response to other therapies.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.B., İ.S., Concept: F.B., İ.S., Design: F.B., İ.S., Literature Search: F.B., İ.S, Writing: F.B., İ.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Fragoulis GE, McInnes IB, Siebert S. JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. Rheumatology 2019;58:43-54.
2. Benucci M, Bernardini P, Coccia C, et al. JAK inhibitors and autoimmune rheumatic diseases. Autoimmun Rev 2023;22:103276.
3. Yamaoka K, Oku K. JAK inhibitors in rheumatology. Immunol Med 2023:1-10.
4. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). BMC Rheumatol 2018;2:23.
5. Boyce EG, Rogan EL, M CL. Upadacitinib for the treatment of rheumatoid arthritis: an extensive review. Ann Pharmacother 2023;57:450-62.
6. Aletaha D, Stamm T, Kapral T, et al. Survival and effectiveness of leflunomide compared with methotrexate and sulfasalazine in rheumatoid arthritis: a matched observational study. Ann Rheum Dis 2003;62:944-51.
7. Lie E, van der Heijde D, Uhlig T, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:671-6.
8. Kremer JM, Emery P, Camp HS, et al. A Phase IIb Study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. Arthritis Rheumatol 2016;68:2867-77.
9. Genovese MC, Smolen JS, Weinblatt ME, et al. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Rheumatol 2016;68:2857-66.
10. Serhal L, Edwards CJ. Upadacitinib for the treatment of rheumatoid arthritis. Expert Rev Clin Immunol 2019;15:13-25.
11. Burmester GR, Kremer JM, van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:2503-12.
12. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to

biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513-24.

13. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol 2019;71:1788-800.
14. Rubbert-Roth A, Enejosa J, Pangan AL, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. N Engl J Med 2020;383:1511-21.
15. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303-11.
16. van Vollenhoven R, Takeuchi T, Pangan AL, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. Arthritis Rheumatol 2020;72:1607-20.
17. Kameda H, Takeuchi T, Yamaoka K, et al. Efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE): a placebo-controlled phase IIb/III study. Rheumatology 2020;59:3303-13.
18. Kameda H, Takeuchi T, Yamaoka K, et al. Efficacy and safety of upadacitinib over 84 weeks in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE). Arthritis Res Ther 2021;23:9.
19. Peterfy CG, Strand V, Friedman A, et al. Inhibition of structural joint damage progression with upadacitinib in rheumatoid arthritis: 1-year outcomes from the SELECT phase 3 program. Rheumatology 2022;61:3246-56.
20. Fonseca D, Nogueira M, Torres T. Upadacitinib for the treatment of psoriatic arthritis. Drugs Context 2023;12:2022-11-6.
21. McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. N Engl J Med 2021;384:1227-39.
22. McInnes IB, Kato K, Magrey M, et al. Upadacitinib in patients with psoriatic arthritis and an inadequate response to non-biological therapy: 56-week data from the phase 3 SELECT-PsA 1 study. RMD Open 2021;7:e001838.
23. McInnes IB, Kato K, Magrey M, et al. Efficacy and safety of upadacitinib in patients with psoriatic arthritis: 2-year results from the phase 3 SELECT-PsA 1 study. Rheumatol Ther 2023;10:275-92.
24. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis 2021;80:312-20.
25. Mease PJ, Lertratanakul A, Papp KA, et al. Upadacitinib in patients with psoriatic arthritis and inadequate response to biologics: 56-week data from the randomized controlled phase 3 SELECT-PsA 2 study. Rheumatol Ther 2021;8:903-19.
26. Baraliakos X, Ranza R, Ostor A, et al. Efficacy and safety of upadacitinib in patients with active psoriatic arthritis and axial involvement: results from two phase 3 studies. Arthritis Res Ther 2023;25:56.
27. van der Heijde D, Song IH, Pangan AL, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 2019;394:2108-17.
28. Deodhar A, van der Heijde D, Sieper J, et al. Safety and efficacy of upadacitinib in patients with active ankylosing spondylitis and an inadequate response to non-steroidal antiinflammatory drug therapy: one-year results of a double-blind, placebo-controlled study and open-label extension. Arthritis Rheumatol 2022;74:70-80.
29. van der Heijde D, Deodhar A, Maksymowych WP, et al. Upadacitinib in active ankylosing spondylitis: results of the 2-year, double-blind, placebo-controlled SELECT-AXIS 1 study and open-label extension. RMD Open 2022;8:e002280.
30. van der Heijde D, Baraliakos X, Sieper J,et al. Efficacy and safety of upadacitinib for active ankylosing spondylitis refractory to biological therapy: a double-blind, randomised, placebo-controlled phase 3 trial. Ann Rheum Dis 2022;81:1515-23.
31. Deodhar A, Van den Bosch F, Poddubnyy D, et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2022;400:369-79.
32. Cohen SB, van Vollenhoven RF, Winthrop KL, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis 2021;80:304-11.
33. Wang F, Sun L, Wang S, et al. Efficacy and safety of tofacitinib, baricitinib, and upadacitinib for rheumatoid arthritis: a systematic review and meta-analysis. Mayo Clin Proc 2020;95:1404-19.
34. Burmester GR, Cohen SB, Winthrop KL, et al. Safety profile of upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. RMD Open 2023;9:e002735.
35. Mohamed MF, Klunder B, Othman AA. Clinical Pharmacokinetics of Upadacitinib: Review of Data Relevant to the Rheumatoid Arthritis Indication. Clin Pharmacokinet 2020;59:531-44.
36. Veeravalli V, Dash RP, Thomas JA, Babu RJ, Madgula LMV, Srinivas NR. Critical assessment of pharmacokinetic drug-drug interaction potential of tofacitinib, baricitinib and upadacitinib, the three approved janus kinase inhibitors for rheumatoid arthritis treatment. Drug Saf 2020;43:711-25.
37. Sanmarti R, Corominas H. Upadacitinib for patients with rheumatoid arthritis: a comprehensive review. J Clin Med 2023;12:1734.