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The role of upadacitinib in the treatment of moderate-to-severe active rheumatoid arthritis

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***Abstract*:** Despite recent promising developments in the treatment of rheumatoid arthritis (RA), a substantial proportion of patients still cannot achieve the treatment targets: low disease activity and remission. Janus kinase (JAK) inhibitors have the potential to fill this important gap with their high efficiency, rapid onset of action, and acceptable safety profile. The fact that the previously approved two JAK inhibitors, tofacitinib and baricitinib, inhibit more than one JAK molecule raised the question whether a safer profile can be possible by inhibiting fewer JAK molecules. Upadacitinib, a JAK 1 selective molecule developed in this context has been evaluated in the SELECT phase-III study program and demonstrated a high and rapid efficacy in monotherapy as well as in combination with csDMARDs both in csDMARD-naive RA patients and in patients refractory to csDMARD and bDMARD treatments. Upadacitinib 15 mg once daily displayed a similar safety profile except for increased creatine phosphokinase (CPK) levels and herpes zoster (HZ) risk compared to its active comparators methotrexate (MTX) and adalimumab. Most of the CPK elevations were asymptomatic, and most of the HZ cases were not serious. Along with the randomized-controlled studies and meta-analysis results, upadacitinib 15 mg once daily has a favorable efficacy/safety profile. Long-term extensions of current studies and real-world data will be important to fully appreciate its potential in the treatment of RA.

Keywords: rheumatoid arthritis, treatment, upadacitinib

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Introduction

In the last 20 years, the management of rheumatoid arthritis (RA) was revolutionized by a significant improvement in targeted therapies. In this context, biological treatments targeting cytokines have resulted in a dramatic progress due to their effectiveness and good safety profiles. Targeting the Janus kinase (JAK) pathway, which is an important component of the intracellular message system in the action pathways of these cytokines, was introduced more recently. The oral route of intake of these small molecules targeting this pathway also signifies a separate advantage. However, this inhibition, which affects many cytokine pathways at the same time, raised toxicity concerns. Tofacitinib, the first widely used JAK inhibitor, has prompted additional developments in this area also to address safety concerns. In addition, the widespread use of baricitinib with its acceptable risk profiles further increased interest in this area. The fact that both tofacitinib and baricitinib inhibit more than one JAK molecules raised the question of whether a safer profile might be possible by inhibiting preferentially only one JAK molecule. In this context, the development of selective JAK inhibitors was started. The assumption that JAK2, 3 and tyrosine kinase 2 (Tyk2) inhibition might be more frequently associated with unwanted actions made JAK1 an attractive target in terms of selective inhibition. With this proposal, early phase trials of selective Jak1 inhibitors, such as upadacitinib, filgotinib, and itacitinib, were initiated in recent years to identify the efficacy and safety of these

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agents and to define their potential role in treatment of inflammatory and autoimmune diseases. Early phase (phase I–II) studies provided evidence for efficacy and safety of upadacitinib in refractory populations of RA patients with inadequate response or intolerance to methotrexate (MTX) or tumor necrosis factor (TNF) inhibitors and they allowed informed selection of the appropriate dose by balancing the optimal benefit–risk profile for further evaluation in phase-III trials.[1–4] Upadacitinib has extensively been evaluated in several phase-III trials (Table 1) demonstrating a favorable efficacy/safety profile.[5–11] Accordingly, upadacitinib was approved at a dosage of 15 mg per day for treatment of RA by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and other regulatory bodies.[12,13]

Effectiveness of upadacitinib in phase-III studies

Select next

This study was conducted with 661 patients with moderately-to-severely active RA who did not have an adequate response to conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs).[5] While the patients continued their background csDMARD treatments, they were recruited into the upadacitinib 15 mg, 30 mg, or placebo arms (221, 219, and 221 patients, respectively). The two primary endpoints were the proportion of patients achieving 20% improvement in American College of Rheumatology criteria (ACR20) response and a 28-joint disease activity score using C-reactive protein (DAS28-CRP) $\leqslant 3.2$ response at the end of 12 weeks. At Week 12, the proportions of patients achieving the ACR20 response were (64%, 66%, and 36%) and DAS28-CRP were (48%, 48%, and 17%) in patients receiving upadacitinib 15 mg, 30 mg, and placebo, respectively ($p < 0{\cdot}0001$ for each dose *vs* placebo for both endpoints). At Week 12, ACR50 and ACR70 response rates were also significantly greater than placebo in both the 15 and 30 mg upadacitinib arms ($p < 0.0001$). The onset effect was rapid with the ACR20 response rates of 22% in the 15-mg group, 28% in the 30-mg group, and 9% in the placebo group at Week 1 ($p < 0.0001$ for each dose *vs* placebo). For ACR50 and 70 significant differences were evident by Week 2. At the end of 12 weeks, significant improvements were demonstrated in upadacitinib arms compared to placebo, in a number of patient-reported outcomes (PROs) including quality-of-life parameter short form-36 (SF-36) physical component summary (PCS), health assessment questionnaire—disability index (HAQ-DI), Patient Global Assessment of Disease Activity (PtGA), duration and severity of morning stiffness, the Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT-F), and Work Instability Scale for RA (RA-WIS).[14]

Select beyond

A total of 499 active RA patients who were refractory to at least one previous bDMARD treatment or who were intolerant to bDMARD treatment were included in the study.[6] One patient randomized to the 15-mg upadacitinib group was excluded from the study before treatment. About 25% of the patients have already used three different biological treatments. As in the SELECT NEXT study, two separate parameters, the ratio of patients achieving the ACR20 response and the DAS28-CRP $\leqslant 3.2$ response at Week 12, were accepted as the primary endpoints. At the end of the 12 weeks, in the upadacitinib 15-mg, 30-mg, and placebo groups, ACR20 rates were 65%, 56%, and 28%, whereas the ratios of patients achieving DAS28-CRP were 43%, 42%, and 14%, respectively ($p < 0.0001$ for each dose *vs* placebo, for both endpoints). At Week 12, ACR50 rates were significantly higher for both upadacitinib doses of 15 and 30 mg compared to placebo (34%; 36% *vs* 12%, respectively, $p < 0.0001$ for both comparisons). For ACR70, the response rates of the upadacitinib 30 mg arm were significantly higher than placebo (23% *vs* 7%; $p < 0.0001$), while the upadacitinib 15-mg arm did not reach a statistical significance *versus* placebo (12% *vs* 7%; ($p = 0.1104$). The onset of effect was rapid with significant decreases in ACR20 evident at Week 1, compared to placebo. The efficacy was maintained over 24 weeks and also patients switched to upadacitinib arms at Week 12 achieved similar responses as patients initially assigned to upadacitinib. This study confirmed also significant response rates in most of the quality-of-life parameters compared to placebo.[15] Remarkably, in this population that had been refractory to sometimes even several biologics, data were very similar to patients in the SELECT NEXT trial encompassing csDMARD failure participants.

Table 1. Summary of the phase-III studies of upadacitinib.

	SELECT-NEXT[5]	SELECT-BEYOND[6]	SELECT-MONOTHERAPY[7]	SELECT-EARLY[8]	SELECT-COMPARE[9]	SELECT-SUNRISE[10]	SELECT-CHOICE[11]
Population	csDMARD-IR	bDMARD-IR	MTX-IR	MTX-naive	MTX-IR	csDMARD-IR	bDMARD-IR
Background	csDMARDs	csDMARDs	None (monotherapy)	None (monotherapy)	MTX	csDMARDs	csDMARDs
Comparator	Placebo	Placebo	MTX	MTX	Placebo ADA	Placebo	IV abatacept
Number of patients randomized to each treatment group	UPA 15 mg QD *N* = 221 UPA 30 mg QD *N* = 219 Placebo: *N* = 221	UPA 15 mg QD *N* = 165 UPA 30 mg QD *N* = 165 Placebo: *N* = 169	UPA 15 mg QD *N* = 217 UPA 30 mg QD *N* = 215 cMTX: *N* = 216	UPA 7.5 mg QD[a] *N* = 55 UPA 15mg QD *N* = 317 UPA 30mg QD *N* = 315 MTX: *N* = 315	UPA 15 mg QD *N* = 651 ADA (40 mg eow): *N* = 327 Placebo: *N* = 651	UPA 7.5mg QD *N* = 49 UPA 15 mg QD *N* = 49 UPA 30 mg QD *N* = 50 Placebo: *N* = 49	UPA 15 mg QD *N* = 303 UPA 30 mg QD *N* = 44 IV abatacept *N* = 309 Did not receive trial drug: *N* = 1
Primary endpoint	ACR20[b] and LDA[c] at Week 12	ACR20[b] and LDA[c] at Week 12	ACR20[b] and LDA[c] at Week 14	ACR20[d]/ACR50[b] at Week 12; CR[b] and ΔmTSS[d] at Week 24	ACR20[b] and CR[c] at Week 12	ACR20 at Week 12	Change in DAS28-CRP (non-inferiority) at Week 12
Results[e]	ACR20 64% UPA *vs* 36% PBO LDA 48% UPA *vs* 17% PBO	ACR20 65% UPA *vs* 28% PBO LDA 43% UPA *vs* 14% PBO	ACR20 68% UPA *vs* 41% MTX LDA 45% UPA *vs* 19% MTX	ACR50 52% UPA *vs* 28% PBO CR 48% UPA *vs* 19% PBO	ACR20 71% UPA *vs* 36% PBO *vs* 63% ADA CR 29% UPA *vs* 6% PBO *vs* 18% ADA	ACR20 83.7% UPA *vs* 42.9% PBO	Change in DAS28-CRP; −2.52 UPA *vs* −2.00 IV abatacept

Δ, change from baseline; ACR20/50, American College of Rheumatology criteria 20/50 response; ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic drug; cMTX, continuing methotrexate; CR, clinical remission (based on DAS28-CRP); csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; DAS28-CRP, 28 joint Disease Activity Score with C-reactive protein; eow, every other week; IR, inadequate response; IV, intravenous; LDA, low disease activity (based on DAS28-CRP); mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; QD, once daily; UPA, upadacitinib.

[a]Japanese patients only.

[b]Primary endpoint for the Food and Drug Administration.

[c]Primary endpoint for the European Medicines Agency.

[d]Primary endpoint for the Pharmaceuticals and Medical devices Agency.

[e]For the 15 mg upadacitinib dose.

Select early

This study was conducted in predominantly early (median disease duration at base line was 0.5 years) RA patients with moderate-to-severe disease activity who were naive for or had a limited exposure period to MTX (⩽3 weeks).[8] A total of 947 patients were randomized 1:1:1 to upadacitinib 15 mg, 30 mg, or MTX (7.5–20 mg/week) arms, and 89% of them (840 patients) completed the 24-week treatment period. The two primary endpoints were the proportion of patients with ACR50 response at Week 12 and DAS28-CRP <2.6 achievement at Week 24. Significant responses were obtained in both upadacitinib 15-mg and 30-mg arms compared to MTX (52%; 56% respectively *vs* 28% for ACR50% and 48%; 50% *vs* 19% for DAS28-CRP ($p<0.001$ for both endpoints)). Differences between both doses of upadacitinib and MTX, in terms of all ACR response rates, ACR core components, and DAS28-CRP $\leqslant 3.2$ responses were significant from Week 2 (first post-baseline visit), and this was maintained until Week 24 ($p<0.001$). Both upadacitinib doses displayed significant and clinically meaningful improvements in multiple PROs *versus* MTX. The proportions of patients without radiographic progression (modified total Sharp score $\leqslant 0$) were significantly higher in the upadacitinib 15-mg and 30-mg arms compared to MTX (88%; 89% respectively *vs* 78% ($p<0.01$)).

Select monotherapy

This study was designed to evaluate the efficacy and safety of upadacitinib monotherapy *versus* continuing MTX in moderately or severely active RA patients with an inadequate response to MTX therapy.[7] About 648 MTX-IR RA patients were randomized to upadacitinib 15-mg, 30-mg, and MTX monotherapy arms. Following Week 14, patients assigned to continue MTX were re-randomized to the upadacitinib 15- and 30-mg groups. The primary endpoints were the proportion of patients achieving ACR20 or low disease activity (LDA) defined by DAS28-CRP of 3.2 or lower at Week 14. Around 598 (92%) patients completed Week 14, and outcomes of all patients who received at least one dose of study drug were assessed. At the end of Week 14, both endpoints were met: in the upadacitinib 15-mg, 30-mg, and continued MTX groups, ACR20 rates were 68%, 71%, and 41% respectively, whereas the ratios of patients achieving DAS28-CRP 3.2 or lower were 45%, 53%, and 19%, respectively ($p<0.0001$ for each dose *vs* continued MTX, for both endpoints). Onset of efficacy was rapid with greater improvements from baseline in all ACR core components and DAS28-CRP for both doses of upadacitinib compared to continued MTX from Week 2 onwards. At Week 14, improvements in HAQ-DI were significantly better for both doses of upadacitinib *versus* continued MTX. Moreover, the proportions of patients achieving minimum clinically important difference for HAQ-DI were again significantly higher in both upadacitinib groups *versus* MTX. Furthermore, SF36 physical component score and duration of morning stiffness significantly improved in the upadacitinib 15-mg and 30-mg groups compared to MTX.

Select compare

The aim of this head-to-head study was to assess the efficacy and safety of upadacitinib in RA patients with an inadequate response to MTX compared to placebo and adalimumab.[9] A total of 1629 RA patients were randomized to receive upadacitinib 15 mg once daily, placebo, or adalimumab 40 mg every other week while continuing treatment with background MTX. Two separate parameters, the proportion of patients achieving ACR20 response and DAS28-CRP <2.6 response at Week 12 compared to placebo, were chosen as the primary endpoints. The study was also powered to test the non-inferiority and superiority of upadacitinib compared to adalimumab in terms of clinical and functional outcomes. The study also evaluated the effects of study drugs on radiographic progression at Week 26. At the end of 12 weeks, both primary endpoints were met compared to placebo with 71% of patients achieving ACR20 in the upadacitinib group *versus* 36% in placebo group and with 29% of patients achieving a DAS28-CRP score of <2.6 in the upadacitinib group *versus* 6% in the placebo group (both $p\leqslant 0.001$). Upadacitinib was superior to adalimumab in terms of ACR50 response rate (45% *vs* 29%; $p\leqslant 0.001$), DAS28-CRP score of $\leqslant 3.2$ (29% *vs* 18%; $p\leqslant 0.001$), change in pain severity score (–32.1 *vs* –25.6; $p\leqslant 0.001$) and change in HAQ-DI score (–0.6 *vs* –0.49; $p\leqslant 0.01$). At the end of 26 weeks, significantly more patients receiving upadacitinib achieved LDA or remission compared to placebo or adalimumab by a variety of composite measures ($p\leqslant 0.001$). Radiographic progression was significantly reduced in patients receiving upadacitinib compared to placebo ($p\leqslant 0.001$), whereas this was similar between upadacitinib and adalimumab

(nominal $p = 0.448$). At Week 12, upadacitinib resulted in significantly greater improvements in SF-36 PCS and FACIT-F scores and duration of morning stiffness ($p \leq 0.001$ for each).

In the 48-week extension of this study, patients with less than 20% improvement in the number of tender or swollen joints at Weeks 14, 18, or 22, or patients with a Clinical Disease Activity Index (CDAI) score of >10 at Week 26, were switched/rescued without washout from placebo or adalimumab to upadacitinib or upadacitinib to adalimumab while continuing background MTX.[16] At Week 26, all remaining placebo patients were also switched to upadacitinib. During this 48-week extension period, switching to the alternative medication after inadequate response to adalimumab or upadacitinib resulted in clinically meaningful responses in a significant number of patients. Improvements in LDA, clinical remission, pain, and function were maintained with upadacitinib and remained superior *versus* adalimumab. After 6 months of switch treatment, CDAI remission/LDA rates were 15/53% and DAS28 (CRP) < 2.6/≤3.2 were 35/56% in patients rescued from adalimumab to upadacitinib, whereas CDAI remission/LDA rates were 5/41% and DAS28(CRP) < 2.6/≤3.2 were 21/40% in patients rescued from upadacitinib to adalimumab.

Select sunrise

Unlike other global studies, this study was a phase-IIb/III dose-ranging study in Japanese patients alone, and it was designed to determine the efficacy and safety dose response of upadacitinib in active RA patients with an inadequate response to csDMARDs.[10] Patients were randomized to receive upadacitinib 7.5, 15, 30 mg, or placebo once daily in combination with csDMARDs. About 187 of 197 randomized patients completed the double-blind period. At the end of 12 weeks, significantly more patients receiving upadacitinib 7.5, 15, or 30 mg met the primary endpoint ACR20 *versus* placebo (75.5%, 83.7%, 80.0% *vs* 42.9%, respectively; $p < 0.001$). Onset of efficacy was rapid with significant differences evident from Week 1 onward. Although upadacitinib 15 and 30 mg also displayed significant differences over placebo across all definitions of LDA and remission, the 7.5-mg dose was not superior to placebo in reaching these more stringent endpoints such as remission defined by Simplified Disease Activity Index (SDAI) or CDAI. In line with other global studies, upadacitinib at the 15-mg dose showed the most favorable benefit–risk profile also in the Japanese population.

Select choice

This trial was a 24-week, phase-III, head-to-head study comparing the efficacy and safety of upadacitinib with intravenous abatacept in patients with RA refractory to bDMARDs.[11] Patients continued background csDMARDs. The primary endpoint, change in DAS-28 CRP values at Week 12, was –2.52 and –2.00, respectively, for upadacitinib and abatacept (difference, −0.52 points; 95% confidence interval (CI) −0.69 to −0.35; $p < 0.001$ for non-inferiority; $p < 0.001$ for superiority). While 30% of patients receiving upadacitinib reached remission, this rate was 13.3% in patients receiving abatacept (based on DAS28-CRP; <2.6) (difference, 16.8 percentage points; 95% CI: 10.4–23.2; $p < 0.001$ for superiority). At the end of 12 weeks, upadacitinib was superior to abatacept in terms of both for the change in DAS28-CRP and the achievement of remission, however, was associated with more serious adverse events. Remarkably, the reduction in the number of swollen joints was similar in both groups, but there was also a significant reduction of CDAI and SDAI in the upadacitinib group compared to abatacept.

Safety of upadacitinib in phase-III studies

A recent article evaluated the short-term and long-term integrated safety of upadacitinib.[17] Short-term analyses were based on phase-III clinical data (Week 12 for SELECT-BEYOND, SELECT-NEXT, and SELECT-EARLY; Week 14 for SELECT-MONOTHERAPY; and Weeks 14–48 for SELECT-COMPARE). In the short-term risk analyses of upadacitinib 15 mg, malignancy excluding non-melanoma skin cancer (NMSC), major adverse cardiovascular events (MACE), and venous thromboembolic events (VTE) were similar compared with the active comparators placebo, MTX, and adalimumab. However, serious infections were more frequently reported in patients in the upadacitinib 15 mg treatment group compared with placebo in combination with background csDMARDs. Upadacitinib 15 mg displayed a higher rate of serious infections compared to adalimumab at week 14; however, rates were similar at Week 48. Serious infections were similar to patients

receiving upadacitinib 15 mg monotherapy and MTX monotherapy. Regarding herpes zoster (HZ) infections upadacitinib 15 mg had higher rates compared to its comparators in short-term analysis.

Long-term integrated safety analysis of upadacitinib included 2629 patients who received at least one dose of upadacitinib 15 mg (4565.8 patient-years (PY); median exposure: 101.9 weeks), 314 patients who received MTX (456.0 PY; median exposure: 92.6 weeks), and 579 patients who received adalimumab (768.6 PY; median exposure: 78.6 weeks; Figure 1). The data were extracted from the phase-III SELECT clinical program, including five randomized, double-blind, controlled trials.[5–9] Safety was analyzed compared to active comparators up to a cut-off date of 30 June 2019. The most common adverse events (AEs) (⩾5 E/100 PYs) reported with upadacitinib 15 mg were upper respiratory tract infection, nasopharyngitis, urinary tract infection, bronchitis, increased creatine phosphokinase (CPK), and increased alanine aminotransferase (ALT).[18] Rates of death were comparable across treatment groups and based on standardized mortality ratio (SMR) analysis, the number of deaths in patients with RA exposed to upadacitinib was not higher than the general population.[17,18]

Treatment-emergent adverse events (TEAEs) were summarized for pooled upadacitinib 15 mg (five trials; median exposure 101.9 weeks), MTX (one trial; median exposure 92.6 weeks), and adalimumab (one trial; median exposure 78.6 weeks). AEs of special interest were reported as exposure-adjusted event rates (EAERs; events/100 patient-years (E/100 PY). In long-term analysis, the EAER of serious infection in patients receiving upadacitinib was comparable with the EAER of patients treated with adalimumab and MTX ((3.2 E/100 PY (95% CI: 2.7–3.7)); 3.9 E/100 PY (95% CI: 2.6–5.6)) and (3.1 E/100 PY (95% CI: 1.7–5.2), respectively; Figure 1) and remained stable over time.[19] Patients with RA who were ⩾75 years old and/or smokers were noted to have hazard ratios >1. Pneumonia was the most common type of serious infection. Ratios of opportunistic infections in patients treated with upadacitinib 15 mg and adalimumab were similar (0.7 E/100 PY (95% CI: 0.5–1.0)) and (0.4 E/100 PY (95% CI: 0.1–1.1), respectively; Figure 1), and the majority of them were non-serious oral candidiasis. Latent and active tuberculosis rates were comparable in patients treated with upadacitinib 15 mg, MTX, and adalimumab. In long-term analysis, a total of 142 patients receiving upadacitinib 15 mg experienced HZ with a higher rate (3.4 E/100 PY (95% CI: 2.9–4.0)) compared to patients receiving placebo, MTX, or adalimumab[19,20] (Figure 1). However, in the majority (71%), a single dermatome was affected and most of events were non-serious (95%) without any central nervous system involvement in the 15 mg upadacitinib group. A prior history of HZ and age ⩾65 years was associated with an increased risk of HZ. The rate of HZ appeared to be higher in Japanese patients compared to patients from other geographical regions.[10] The EAER for malignancy excluding NMSC in patients receiving upadacitinib 15 mg group was 0.9 E/100 PY (95% CI: 0.6–1.2) and similar to patients receiving adalimumab (0.7 E/100 PY (95% CI: 0.2–1.5)) and MTX (0.7 E/100 PY (95% CI: 0.1–1.9)) (Figure 1). The number of malignancies excluding NMSC in patients treated with upadacitinib was not significantly higher than expected when compared to general population and comparable to previous data of tofacitinib and tocilizumab.[17,18,21–23] In the long-term analysis, EAER of MACE in patients receiving upadacitinib 15 mg was comparable to patients treated with adalimumab and MTX (0.5 E/100 PY (95% CI: 0.3–0.7); 0.4 E/100 PY (95% CI: 0.1–1.1) and 0.4 E/100 PY (95% CI: 0.1–1.6), respectively; Figure 1) and remained stable over time.[18] Like the other JAK inhibitors, upadacitinib treatment increased both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels proportionally resulting in a constant ratio between them. Also the EAER for VTEs in patients exposed to upadacitinib 15 mg were similar to patients treated with adalimumab or MTX (0.5 E/100 PY (95% CI: 0.3–0.7); 0.5 E/100 PY (95% CI: 0.1–1.3) and 0.4 E/100 PY (95% CI: 0.1–1.6), respectively; Figure 1).[18] All patients who experienced a VTE or MACE had at least one known risk factor.

Upadacitinib treatment resulted in an increased incidence of CPK elevations compared to placebo, MTX, and adalimumab, as observed also in other JAK inhibitors. Most cases of CPK elevations were asymptomatic without any reported case of rhabdomyolysis and did not require treatment discontinuation.[17] While a higher incidence of transaminase elevations was observed in patients receiving upadacitinib 15 mg in the short-term placebo-controlled study period,

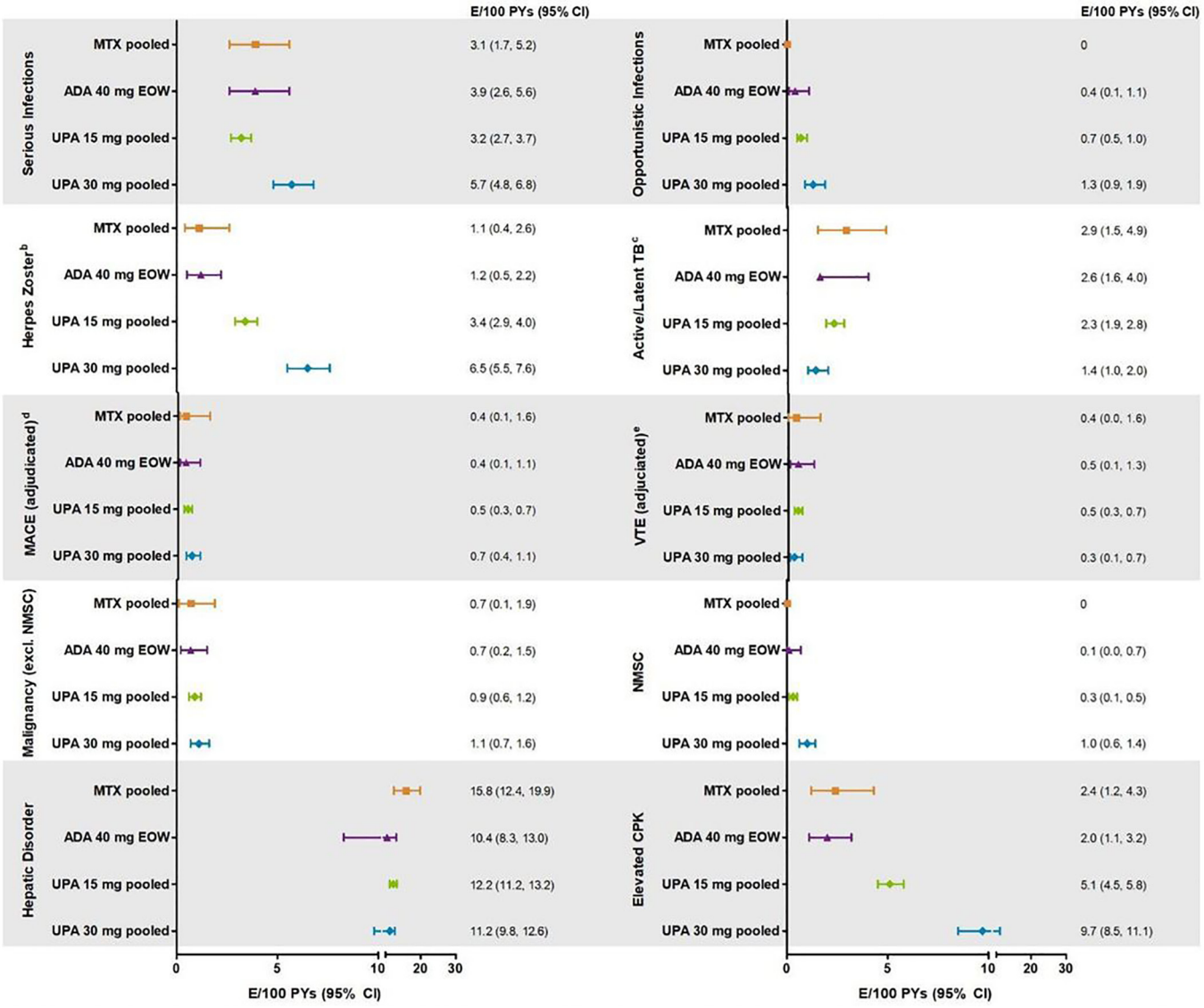

Figure 1. Overall AESIs in patients treated with upadacitinib compared to active controls[a] (reproduced with permission from Cohen et al.[18]).
MTX pooled: *N* = 314, PYs = 456.0; ADA 40 mg EOW: *N* = 579, PYs = 768.6; UPA 15 mg pooled: *N* = 2629, PYs = 4565.8; UPA 30 mg pooled: *N* = 1204, PYs = 2309.7.
ADA, adalimumab; AE, adverse event; CPK, creatine phosphokinase; CV, cardiovascular; E, events; EOW, every other week; MACE, major adverse cardiovascular event; MI, myocardial infarction; MTX, methotrexate; NMSC, non-melanoma skin cancer; PBO, placebo; PYs, patient-years; QD, once daily; TB, tuberculosis; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism.
[a]Patients who switched from PBO. ADA or MTX to UPA were included in the UPA analysis set from the start of UPA, while those who switched from upadacitinib to ADA were included in the ADA data set from the start of ADA. There was no switch between UPA doses in any study. MTX monotherapy censored at time of rescue to combination therapy (either UPA + MTX or addition of csDMARD).
[b]Most HZ cases were non-serious (95.9%) and single dermatome (74.4%).
[c]There were six cases of active TB on UPA (0.1 E/100 PYs)and one on ADA.
[d]MACE was defined as CV death, non-fatal MI, and non-fatal stroke.
[e]VTE was defined as deep vein thrombosis and pulmonary embolism.

long-term safety data showed similar rates in those receiving upadacitinib 15 mg, MTX, and adalimumab. Transaminase elevations were mostly transient and asymptomatic in the upadacitinib 15-mg arm. Upadacitinib 15 mg had only little effect on mean hemoglobin level, and Grades 3 and 4 decreases were transient in most cases and did not lead to drug discontinuation.[5,6,7,9] However, Grade 3 and 4 decreases were more common with the 30 mg dosage. Upadacitinib resulted in a higher frequency of Grades 2 and 3 neutropenia compared to

placebo, and decreases were greater in UPA (to a greater extent in the 30-mg dosage) groups compared to MTX.[24] Neutrophil counts decreased over the first 8 weeks and then plateaued.

Treatment with UPA was associated with a mean increase in absolute lymphocyte count (ALC) over the initial 36 weeks of treatment, followed by small decreases afterwards.[25] During the short-term placebo-controlled period of the studies, there were no differences in ALC between upadacitinib 15 mg and placebo.[24] The 30 mg dosage caused a higher frequency of decreases in ALC count compared to upadacitinib 15 mg. The MTX alone period and long-term upadacitinib period displayed similar results. In the Japanese study, 3 out of 10 patients with Grade 4 lymphocyte decreases discontinued the study drug and three had infectious events (pneumonia, infectious enteritis, and *Pneumocystis jirovecii* pneumonia, 1 event each, approximately − 16 to 5 days around the onset of lymphopenia).[26]

Discussion

Upadacitinib has been extensively evaluated in several randomized placebo-controlled trials with long-term follow-up periods demonstrating a favorable efficacy and safety profile. However, it is difficult to draw clear conclusions from the currently available data regarding the advantages or disadvantages of selective JAK inhibitors in terms of efficacy and/or safety to non-selective compounds in the absence of head-to-head studies of JAK inhibitors with long-term follow-up or in the absence of long-term registry data. In a recent systematic review and network meta-analysis (NMA), comparative efficacy and safety of JAK inhibitors and most of the available bDMARDs were evaluated in RA patients with an inadequate response to at least one DMARD.[27] ACR20, DAS28, and HAQ-DI were used as efficacy outcomes and discontinuations due to AEs for safety. Upadacitinib, tocilizumab, and certolizumab pegol showed relatively good efficacy in these three efficacy outcomes and increasing the doses of JAK inhibitors (baricitinib 4 mg *versus* 2 mg, tofacitinib 10 mg *versus* 5 mg, and upadacitinib 30 mg *versus* 15 mg) did not appear to provide significant additional benefits. In terms of safety based on discontinuations for AEs, all active drugs displayed a favorable safety without any significant differences compared with placebo except certolizumab pegol and rituximab. Again, in another NMA, the comparative efficacy of three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) as monotherapy or combination therapy among csDMARD-IR patients with moderate-to-severe RA were evaluated. ACR 20/50/70 responses and clinical remission (defined as DAS28-CRP < 2.6) were evaluated at Weeks 12 and 24 using Bayesian NMA.[28] Upadacitinib 15 mg once daily displayed numerically higher efficacy both in terms of ACR response and clinical remission. Moreover, in an additional NMA, evaluating the relative efficacy and tolerability of tofacitinib, baricitinib, upadacitinib, and filgotinib compared to adalimumab in MTX-IR RA patients, treatment with baricitinib 4 mg + MTX and upadacitinib 15 mg + MTX resulted in significantly higher ACR response rates, without any significant differences between the intervention groups in terms of safety.[29] Also, in RA patients with an inadequate response to cs- or b-DMARDs, upadacitinib 15 mg + MTX and upadacitinib 30 mg + MTX were more efficacious then tofacitinib 10 mg + MTX and tofacitinib 5 mg + MTX, without any significant risks of serious AEs, in another NMA.[30] These data suggest an efficacy advantage without safety flaws for upadacitinib especially in DMARD-resistant RA patients, where most needed.

At the same time, in patients with RA who are resistant to and cannot tolerate MTX, the effectiveness of upadacitinib monotherapy over MTX is an important data.[7] The advantage of this work is that it has MTX as a comparator rather than placebo and answers an important question in the treatment of RA.[31] Upadacitinib has undergone an extensive and detailed clinical trial program and its efficacy has been demonstrated in both treatment-naive and resistant RA patients to both MTX and csDMARD therapies. It also demonstrated significant efficacy when compared head-to-head with csDMARDs and biological DMARDs such as MTX, adalimumab, and abatacept. Both monotherapy and its combination with csDMARDs have proven to be effective. Its efficacy was comparable between the 15 and 30-mg doses, but serious AEs and discontinuations tended to be higher with 30 mg, resulting in the choice and approval of the 15 mg dose in the treatment. The side effect profile was as expected from the known side-effects of other class members, particularly with more frequent HZ infections and increase in CPK levels.[32–34] In line with these findings, the selective Jak-1 inhibitor upadacitinib 15 mg once daily has been approved in the United States and Europe for patients with moderately-to-severely active RA who are intolerant of or have had an inadequate

response to MTX either as monotherapy or in combination with MTX or other non-bDMARDs, depending on local labeling. Approval of upadacitinib also as monotherapy has the advantage in patients with RA who have an intolerance or contraindication to MTX.

In conclusion, upadacitinib is an interesting and additional treatment option in patients with RA with an inadequate response to both cs- and bDMARDs with a favorable efficacy and safety profile. However, JAK-inhibition still represents quite a new treatment option for inflammatory rheumatic diseases such as RA, at least in most parts of the world. Keeping in mind the recent warnings for the pan-JAK inhibitor tofacitinib with respect to malignancies, cardiovascular, and thrombotic events, which, however, were based on one single and not yet published study (https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-initial-clinical-trial-results-increased-risk-major-adverse-cardiovascular), it is of utmost importance to clarify, if there is a drug or class-specific safety concern. Of note, similar safety signals have not appeared from registers so far. Thus, the final positioning of compounds like upadacitinib will depend on long-term extensions of already initiated trials together with real-world data and head-to-head comparisons. Currently, EULAR and other societies place JAK inhibitors at the same level as biologic DMARDs after failure of traditional synthetic DMARDs such as MTX in the treatment of rheumatoid arthritis. Provided that JAK inhibitors will not disappoint us with striking and so far unrecognized safety issues, it is easy to imagine a future scenario, where this class of drugs will step forward to challenge the positioning of our today's gold standard MTX.

Conflict of interest statement

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