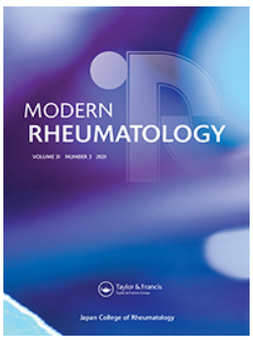

Modern Rheumatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/imor20

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To cite this article: Tsutomu Takeuchi, Maureen Rischmueller, Ricardo Blanco, Ricardo M Xavier, Yukitaka Ueki, Tatsuya Atsumi, Su Chen, Alan Friedman, Aileen L Pangan, Vibeke Strand & Ronald F van Vollenhoven (2021) Upadacitinib monotherapy versus methotrexate monotherapy in methotrexate-naïve Japanese patients with rheumatoid arthritis: a sub-analysis of the Phase 3 SELECT-EARLY study, Modern Rheumatology, 31:3, 534-542, DOI: 10.1080/14397595.2020.1847776

To link to this article: https://doi.org/10.1080/14397595.2020.1847776

MODERN RHEUMATOLOGY
2021, VOL. 31, NO. 3, 534–542
https://doi.org/10.1080/14397595.2020.1847776

Japan College of Rheumatology
MODERN RHEUMATOLOGY
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ORIGINAL ARTICLE

Upadacitinib monotherapy versus methotrexate monotherapy in methotrexate-naïve Japanese patients with rheumatoid arthritis: a sub-analysis of the Phase 3 SELECT-EARLY study

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ABSTRACT

Objective: To assess upadacitinib monotherapy versus methotrexate (MTX) in MTX-naïve Japanese patients with rheumatoid arthritis (RA) from the Phase 3 SELECT-EARLY study.

Methods: Japanese patients were randomized 2:1:1:1 to upadacitinib 7.5, 15, or 30 mg daily or MTX 7.5 mg/week (titrated to ≤15 mg/week). Efficacy endpoints included the proportion of patients reporting 20% improvement in American College of Rheumatology criteria (ACR20) at week 12 and change from baseline in modified Total Sharp Score (mTSS) at week 24. Other efficacy outcomes were also assessed at weeks 12 and/or 24. Safety was assessed over 24 weeks.

Results: Of 138 Japanese patients enrolled, significantly more patients treated with upadacitinib 7.5 and 15 mg, but not 30 mg, reported ACR20 responses versus MTX at week 12. Significantly smaller changes from baseline in mTSS were observed with upadacitinib 15 and 30 mg, but not 7.5 mg, versus MTX at week 24. Upadacitinib demonstrated an acceptable safety profile; herpes zoster occurred in 3.6%, 7.4%, and 7.1% of patients treated with upadacitinib 7.5, 15, and 30 mg, respectively.

Conclusion: Similar to the global study population, upadacitinib demonstrated clinical efficacy superior to placebo in the Japanese subpopulation. Among upadacitinib-treated patients, herpes zoster was least common with 7.5 mg.

ARTICLE HISTORY
Received 2 September 2020
Accepted 1 November 2020

KEYWORDS
DMARD; Japan; methotrexate; rheumatoid arthritis; upadacitinib

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease characterized by persistent synovitis that progressively leads to joint damage and deformity [1,2]. The estimated prevalence of RA ranges from 0.33% to 1.1% worldwide [3] and in Japan was reported to be 0.6% to 1.0% [4]. Management guidelines recommend treatment with disease-modifying antirheumatic drugs (DMARDs) immediately following diagnosis of RA, with the goal of achieving sustained clinical remission or low disease activity (LDA) using a treat-to-target approach [5,6]. Due to its long-term efficacy and safety data and relatively low costs, the conventional synthetic (cs)DMARD methotrexate (MTX) is recommended as an initial treatment for patients with RA [5–7]. However, only a minority of patients achieve the treatment goal of LDA or remission with MTX [8–11] and in Japanese patients it may be associated with serious and unique adverse events, (AEs) such as pneumocystis pneumonia and lymphoproliferative disorders, which are less commonly seen in other populations [7]. If patients fail to show an initial response to MTX, or for those intolerant to MTX, guidelines recommend a number of alternative approaches, including addition of a second csDMARD, a biologic (b)DMARD, or a targeted synthetic (ts)DMARD [6].

Janus kinases (JAKs; JAK1, JAK2, JAK3, and TYK2) mediate the intracellular signaling of multiple cytokines that play a role in the pathogenesis of RA [12]. Upadacitinib, a potent, oral, JAK1-selective inhibitor [13], met all primary and key secondary endpoints across a variety of RA patient populations in five pivotal Phase 3 randomized controlled trials (RCT) [14–18]. The SELECT-EARLY MTX-controlled trial [18] was designed to study the safety and efficacy of upadacitinib 15 mg and 30 mg once daily (qd) as monotherapy in patients with moderately to severely active RA and poor prognostic features who were either naïve to or had

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Supplemental data for this article can be accessed here.

limited exposure to MTX. SELECT-EARLY also included a subset of Japanese patients, 40% of whom were randomized to receive upadacitinib 7.5 mg once daily. Here we present a subgroup analysis of the Japanese patients enrolled in the SELECT-EARLY RCT. The results of this substudy through week 24 (including the primary endpoints) are reported.

Materials and methods

Patients

The SELECT-EARLY trial has been reported previously [18]. In brief, this was an international, multicenter Phase 3 RCT of adult patients (≥18 years of age) with active RA, with symptoms consistent with RA for ≥6 weeks and fulfilling the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) 2010 classification criteria for RA [19]. Active disease was defined as ≥6 swollen joints (based on 66 joint counts; SJC66) and ≥6 tender joints (based on 68 joint counts; TJC68) at screening and baseline visits, with a high-sensitivity C-reactive protein (hsCRP) concentration ≥5 mg/L. In addition, patients had either ≥1 bone erosion on X-ray (by local reading) or positivity for both rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP) autoantibodies at screening. Eligible patients were naïve to MTX or had received no more than three weekly doses of MTX and completed a 4-week MTX washout prior to the first dose of study drug. Patients who had received prior csDMARD(s) other than MTX were also eligible, provided they had completed a predefined washout period. Patients were ineligible for inclusion in the study if they were intolerant to MTX or had prior exposure to any JAK inhibitor or bDMARD.

The trial was conducted according to the International Conference on Harmonization of Technical Regulations for Pharmaceuticals for Human Use guidelines, applicable regulations, and the Declaration of Helsinki. All study-related documents were approved by independent ethics committees and institutional review boards. All patients provided written informed consent. This trial is registered with ClinicalTrials.gov, identifier: NCT02706873.

Study design

SELECT-EARLY comprised two periods: a 48-week, double-blind, active-comparator-controlled phase followed by an open-label, long-term extension period of up to 4 years (Figure 1). In the global study, 947 patients were randomized 1:1:1 to receive either upadacitinib (15 or 30 mg qd as monotherapy) or weekly MTX [18]. In the Japanese substudy, 138 patients were randomized 2:1:1:1 to receive either qd upadacitinib 7.5 mg (Japanese patients only), 15 mg, or 30 mg as monotherapy or weekly MTX. MTX dosing was initiated at 7.5 mg/week with titration up to 10 mg/week at week 4 and to 15 mg/week, as tolerated, by week 8. The minimum final dose of MTX was 7.5 mg/week, provided intolerance to >7.5 mg/week was documented. The upadacitinib 7.5 mg qd arm was included in the Japanese substudy to meet the requirements of the Pharmaceuticals and Medical Devices Agency, Japan. As this dose was not studied in the global population, additional Japanese patients were included in this arm of the substudy. Rescue therapy (nonsteroidal anti-inflammatory drugs, low-potency analgesics, low-dose glucocorticoids [oral ≤10 mg/day prednisone equivalent or prednisone equivalent ≤0.5 mg/kg/day for three consecutive days] but not DMARDs) was offered to patients who did not report ≥20% improvement from baseline in both TJC and SJC at two consecutive visits beginning at week 12.

Efficacy, vital signs, and laboratory assessments were measured at baseline and at weeks 2, 4, 8, 12, 16, 20, and 24. Patient-reported outcomes (PROs) including the

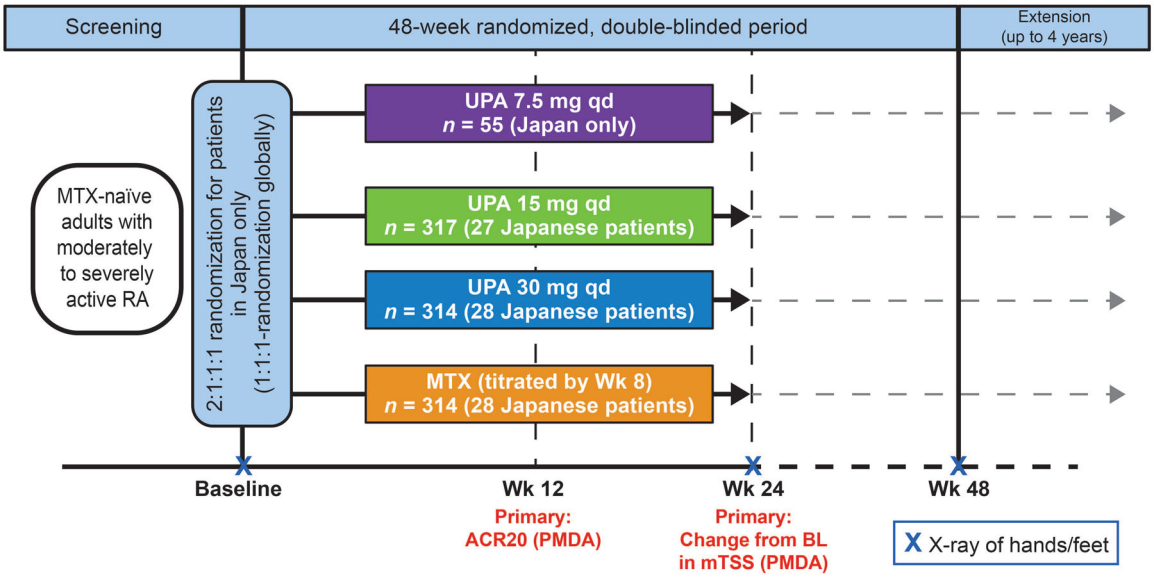

Figure 1. SELECT-EARLY global study design. ACR20: 20% improvement in American College of Rheumatology criteria; BL: baseline; mTSS: modified Total Sharp Score; MTX: methotrexate; PMDA: Pharmaceuticals and Medical Devices Agency; qd: once daily; RA: rheumatoid arthritis; UPA: upadacitinib; Wk: week.

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, Health Assessment Questionnaire-Disability Index (HAQ-DI), and physical health status measured by physical component summary of the 36-item Short Form Survey (SF-36 PCS), were measured at baseline and at weeks 12 and 24. AEs were measured throughout the study. Bilateral X-rays of hands and feet were completed during screening and at week 24.

Study outcomes

For Japan/Pharmaceuticals and Medical Devices Agency (PMDA) regulatory purposes, primary endpoints of the SELECT-EARLY global analysis were the proportion of patients who reported ≥20% improvement in the ACR criteria (ACR20 response) at week 12 and change from baseline in radiographic progression measured by the modified Total Sharp Score (mTSS) at week 24. Secondary endpoints included: changes from baseline in 28-Joint Disease Activity Score based on CRP (DAS28[CRP]) and HAQ-DI at week 12; the proportion of patients reporting LDA (DAS28[CRP] ≤ 3.2, Simplified Disease Activity Index [SDAI] ≤ 11, or Clinical Disease Activity Index [CDAI] ≤ 10) at week 12; the proportion of patients reporting clinical remission (DAS28[CRP] < 2.6, SDAI ≤3.3, or CDAI ≤2.8) at week 24; change from baseline in SF-36 PCS at week 12; ≥50% improvement in the ACR criteria, and ≥70% improvement in the ACR criteria (ACR50 and ACR70 responses) at week 12; and proportion of patients with no radiographic progression (defined as change from baseline in mTSS ≤0) at week 24. The proportion of patients reporting clinically meaningful change in HAQ-DI – minimum clinically important difference (MCID; decrease from baseline of ≥0.22) [20] – was also assessed. Patients' assessments of pain as well as Patient (PtGA) and Physician Global Assessment (PGA) of disease activity were evaluated by visual analog scales. These efficacy endpoints assessed in the SELECT-EARLY global population as described above were also assessed in this Japanese subpopulation.

Safety evaluations included AEs, physical examinations, vital signs, electrocardiograms, and clinical laboratory tests (hematology, chemistry, and urinalysis); these were monitored throughout the study and for 30 days after study-drug discontinuation. Treatment-emergent adverse events (TEAEs), defined as any AE with an onset on or after the first dose of study drug or up to 30 days after the last dose of study drug, were coded using the preferred terms from the Medical Dictionary for Regulatory Activities (version 19.1). AEs of special interest were infections, including serious infections, opportunistic infections, herpes zoster, and tuberculosis; malignancy and lymphoproliferative disorders; gastrointestinal perforations, major adverse cardiovascular events (MACE); lipid profile changes; anemia and hemoglobin effects; decreased neutrophil and lymphocyte counts; increased serum creatinine and renal dysfunction; hepatic events and increased hepatic transaminases; and increased creatine phosphokinase (CPK).

Statistical analysis

Efficacy analyses of this Japanese substudy were conducted using the Japanese analysis set (JAS) population, which included all randomized patients in the substudy who received at least one dose of study drug. Safety analyses of this Japanese substudy were carried out using the safety analysis set, which consisted of all patients in the substudy who received at least one dose of study drug and were based on treatments actually received. For binary endpoints (excluding the radiographic endpoint), each upadacitinib arm was compared with the MTX arm, and *p*-values were constructed using the chi-square test, with nonresponder imputation (NRI) used for missing data. Patients who met the rescue criteria at week 16 or 20 were treated as nonresponders at visits post-rescue. For continuous endpoints (excluding the radiographic endpoint), analysis of covariance (ANCOVA) with treatment as the fixed factor and corresponding baseline value as the covariate was used to assess significance. Data post-rescue in patients who met the rescue criteria at week 16 or 20 were overwritten by last observation carried forward. For the radiographic binary endpoint at week 24 (% with no radiographic progression [mTSS ≤ 0]), the upadacitinib and MTX arms were compared, and *p*-values were constructed using the chi-square test, with linear extrapolation analysis. The continuous radiographic endpoint was analyzed using ANCOVA with linear extrapolation analysis, with treatment as the fixed factor and the corresponding baseline value as the covariate. For this Japanese substudy, no multiplicity adjustments were applied, and only nominal *p*-values were provided for all efficacy analyses, including mTSS-related endpoints. The nominal *p*-values should be interpreted with caution due to limited sample size.

Results

Patient disposition and baseline demographics

In this substudy, 138 patients from 46 study sites in Japan were randomized to receive either once weekly MTX ($n = 28$) or once daily upadacitinib (7.5 mg: $n = 55$; 15 mg: $n = 27$; and 30 mg: $n = 28$). All randomized patients received at least one dose of study drug and most patients ($n = 128$, 92.8%) completed treatment up to week 24 (Figure 2). The most common primary reason for study drug discontinuation during this period was an AE ($n = 5$; 3.6%). The mean dose of MTX in the MTX treatment group was 14 mg/week at week 24, which was lower than that reported for the global population (19.2 mg/week [18]).

Patient demographics were generally well balanced across the treatment arms at baseline (Table 1). Most patients were female, with a body mass index <25 kg/m^2, and aged 58 to 60 years. Baseline disease characteristics were also well balanced across groups, except for mean duration of RA diagnosis, which was longer in the upadacitinib groups (1.9 to 2.3 years) compared with the MTX group (0.9 years). Disease activity and physical function scores were consistent with moderately to severely active RA, as indicated by mean

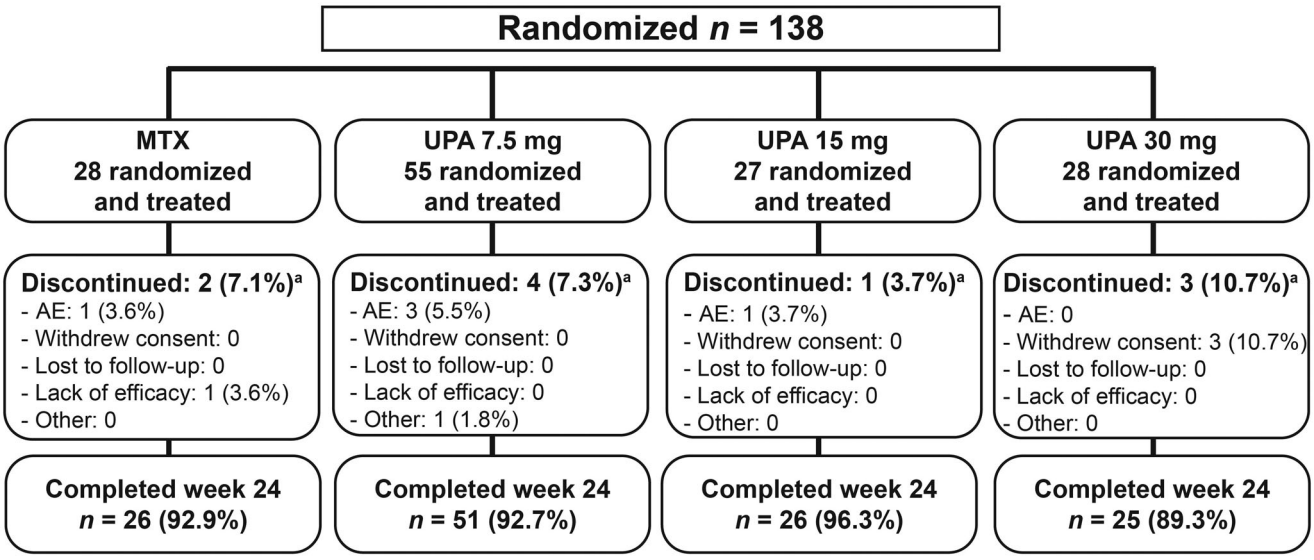

Figure 2. Patient disposition in the Japanese population. AE: adverse event; MTX: methotrexate; UPA: upadacitinib. [a]Only primary reasons for discontinuation are listed.

Table 1. Baseline demographics and disease characteristics in the Japanese population.

	MTX ($n = 28$)	UPA 7.5 mg qd ($n = 55$)	UPA 15 mg qd ($n = 27$)	UPA 30 mg qd ($n = 28$)
Age, years, mean (SD)	57.9 (12.1)	59.7 (13.8)	59.8 (10.4)	59.3 (12.9)
Female, *n* (%)	18 (64.3)	36 (65.5)	18 (66.7)	19 (67.9)
BMI, kg/m^2, mean (SD)	24.3 (5.0)	22.1 (3.3)	22.8 (2.7)	22.2 (3.7)
Oral glucocorticoid use, *n* (%)	12 (42.9)	25 (45.5)	11 (40.7)	12 (42.9)
Dose, mg, mean (SD)[a]	3.3 (1.5)	3.6 (1.6)	3.5 (1.4)	4.2 (2.9)
Duration of RA symptoms, years, mean (SD)	1.7 (2.0)	3.4 (7.5)	3.3 (7.1)	3.8 (6.8)
Duration of RA diagnosis, years, mean (SD)	0.9 (1.5)	2.3 (5.8)	2.0 (5.8)	1.9 (4.7)
RF- and ACCP-positive, *n* (%)	22 (78.6)	42 (76.4)	23 (85.2)	18 (64.3)
DAS28(CRP), mean (SD)	5.5 (0.8)	5.5 (0.9)	5.6 (1.1)	5.5 (0.9)
DAS28(CRP) >5.1, *n* (%)	22 (78.6)	38 (69.1)	17 (63.0)	17 (60.7)
SDAI, mean (SD)[b]	35.7 (10.8)	36.0 (11.9)	36.8 (14.5)	35.9 (11.6)
CDAI, mean (SD)[b]	33.1 (10.3)	34.1 (11.2)	34.3 (13.8)	33.8 (11.2)
TJC68, mean (SD)	17.3 (9.5)	18.0 (11.8)	19.8 (13.2)	16.8 (9.0)
SJC66, mean (SD)	15.9 (6.3)	14.7 (8.2)	12.9 (8.3)	13.9 (7.0)
PtGA, 0–100 mm VAS, mean (SD)	65.1 (18.8)	64.1 (21.4)	61.6 (23.9)	65.2 (14.2)
PGA, 0–100 mm VAS, mean (SD)[b]	68.9 (18.6)	63.3 (19.3)	64.4 (20.3)	69.8 (13.2)
Pain, 0–100 mm VAS, mean (SD)	60.7 (20.5)	64.1 (21.2)	63.7 (22.5)	65.9 (17.3)
hsCRP, mg/L, mean (SD)	25.9 (28.3)	18.5 (17.6)	25.0 (25.1)	20.4 (16.3)
mTSS, mean (SD)[c]	9.4 (28.8)	15.9 (39.1)	9.8 (19.4)	18.1 (41.8)
Erosion score[c]	4.8 (15.3)	8.4 (21.2)	5.3 (10.2)	9.2 (20.9)
JSN score[c]	4.6 (14.1)	7.5 (18.3)	4.4 (9.7)	8.9 (21.3)
HAQ-DI, mean (SD)	1.4 (0.6)	1.3 (0.6)	1.4 (0.7)	1.2 (0.6)

ACCP: anti-cyclic citrullinated peptide; BMI: body mass index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28(CRP): 28-Joint Disease Activity Score based on CRP; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high-sensitivity CRP; JSN: joint space narrowing; mTSS: modified Total Sharp Score; MTX: methotrexate; PtGA: Patient's Global Assessment; PGA: Physician's Global Assessment; qd: once daily; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; SDAI: Simplified Disease Activity Index; SJC66: swollen joint count 66; TJC68: tender joint count 68; UPA: upadacitinib; VAS: visual analog scale. Patients who had a missing baseline value or whose values were unknown for a variable were not counted in the denominator for that measure.
[a]Based on prednisone equivalent dose (number of patients: $n = 11$ [MTX], $n = 24$ [UPA 7.5 mg], $n = 10$ [UPA 15 mg], $n = 12$ [UPA 30 mg]).
[b]$n = 54$ in the UPA 7.5 mg group.
[c]$n = 26$ in the UPA 15 mg group.

baseline TJC68, SJC66, and DAS28(CRP) (Table 1). Similar to the global population, the Japanese patients also had risk factors for structural progression, i.e. RF and A-CCP positivity was documented in 76.1% of patients, with a mean mTSS of 13.8. At baseline, 43.5% of patients were receiving oral corticosteroids.

Efficacy endpoints

At week 12, ACR20 was reported by significantly more patients receiving upadacitinib 7.5 mg and 15 mg (85.5% [$p<.01$] and 85.2% [$p<.05$], respectively) compared with MTX (57.1%; Figure 3). While upadacitinib 30 mg resulted in a numerically higher response rate (78.6%) compared with MTX, the difference versus MTX did not reach statistical significance ($p=.086$) due to the small sample size. All three upadacitinib doses showed clinically meaningful and significant improvements in other clinical efficacy endpoints versus MTX, despite the small sample size (Table 2). This included the proportion of patients reporting ACR50, ACR70, and LDA (defined by DAS28[CRP] ≤ 3.2, SDAI ≤ 11, or CDAI ≤ 10) at week 12, as well as remission

(defined by DAS28[CRP] < 2.6, SDAI ≤3.3, or CDAI ≤2.8) at week 24. Significant improvements were also observed with all three upadacitinib doses compared with MTX in mean change from baseline in DAS28(CRP), and reported in HAQ-DI and SF-36 PCS at week 12. The proportion of patients reporting improvements ≥ MCID in HAQ-DI was significantly greater with upadacitinib 15 mg versus MTX at week 24 ($p<.05$) and was significantly greater with other upadacitinib doses versus MTX at other time points (Supplementary Figure 1). Some dose-dependent effects were observed, including lower rates of ACR50, ACR70, and DAS28(CRP) remission with upadacitinib 7.5 mg versus the other doses, although these should be interpreted with caution due to the relatively low patient numbers.

Despite the small sample size of the JAS population, change in mTSS from baseline at week 24 was significantly smaller with upadacitinib 15 mg and 30 mg (0.24 and 0.19, respectively; both $p<.05$) compared with MTX (2.64); however, the increase from baseline with upadacitinib 7.5 mg (0.95), although numerically smaller versus MTX, was not significant ($p=.063$; Figure 3; Supplementary Figure 2). The proportion of patients with no radiographic progression at week 24 (change from baseline in mTSS ≤0) was significantly greater with upadacitinib 7.5, 15, and 30 mg versus MTX (82.4%, 80.8%, and 79.2% versus 46.2%, respectively; $p<.05$).

Safety

The overall proportion of patients with AEs was greater among those receiving upadacitinib 30 mg compared with MTX and upadacitinib 7.5 and 15 mg (Table 3). Serious adverse events (SAEs) were reported in 5 patients in the 7.5 mg group, 1 patient in the 15 mg group, and 4 patients in the 30 mg group. No SAE was reported in more than 1 patient. One death was reported in the upadacitinib 30 mg group; this was a case of sudden death that was adjudicated as a MACE.

Infections were the most common AE of special interest and were most common in the upadacitinib 30 mg group. Serious and opportunistic infections were infrequent, and there were no cases of active tuberculosis. Herpes zoster was reported in 3.6%, 7.4%, and 7.1% of patients in the 7.5, 15, and 30 mg groups, respectively, and in no patients in the MTX group. All events of herpes zoster were considered nonserious by the investigators. The incidence of CPK elevation appeared to be dose-dependent, with higher rates seen in the upadacitinib 30 mg group, while anemia appeared to be unrelated to dose. No patient experienced rhabdomyolysis or polymyositis. In addition, no patient experienced a malignancy, a gastrointestinal perforation, or a venous thromboembolic event (Table 3).

Mean values of laboratory parameters were within normal limits at baseline across all treatment groups, and some remained so to week 24 (Table 3). The proportions of patients with Grade 3 or 4 decreases in hemoglobin were similar between the MTX and upadacitinib 30 mg groups, with fewer or no patients having Grade 3 or 4 decreases in the other upadacitinib dose groups. Grade 3 decreases in lymphocytes were highest in the MTX group (28.6%) followed by the upadacitinib 15, 30, and 7.5 mg groups (18.5%, 14.3%, and 10.9%, respectively); no Grade 4 decreases in lymphocytes were reported in any treatment group. Few patients had Grade 3 or 4 decreases in leukocyte or neutrophil values, or Grade 3 or 4 elevations in alanine transaminase or aspartate transaminase, and there were no Grade 3 or 4 decreases in platelet values in any treatment group.

Discussion

SELECT-EARLY was a global Phase 3 study assessing upadacitinib monotherapy compared with MTX monotherapy in MTX-naïve patients with RA [18]. Here we assessed the

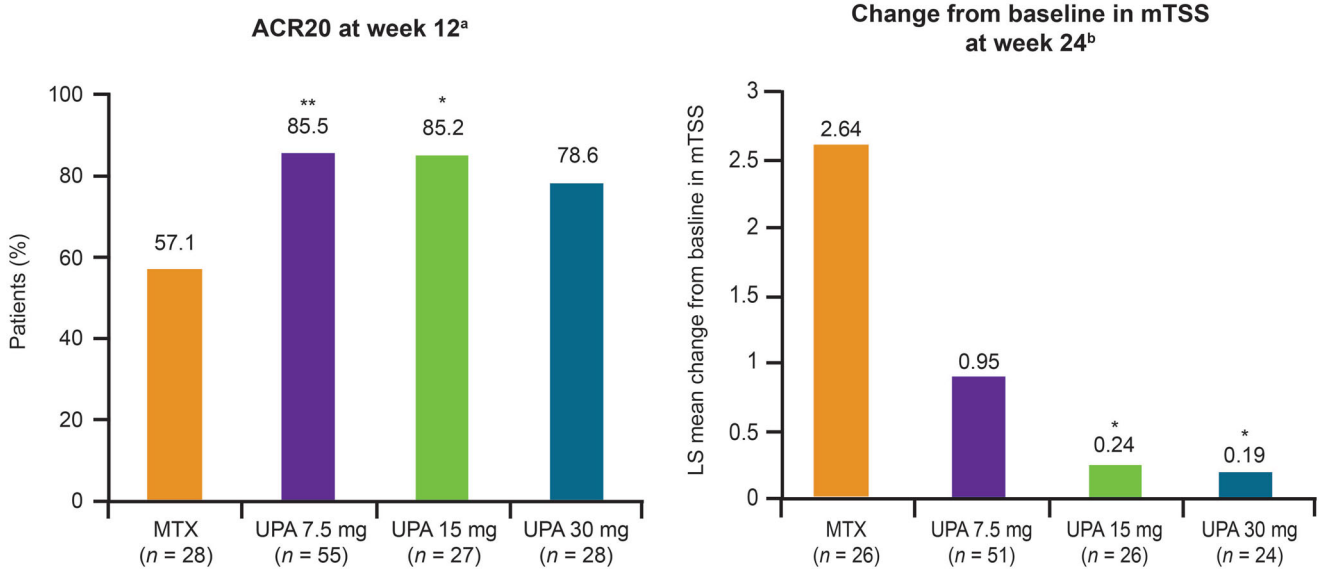

Figure 3. Primary endpoints[c] for SELECT-EARLY in the Japanese population. ACR20: 20% improvement in American College of Rheumatology criteria; LS: least squares; mTSS: modified Total Sharp Score; MTX: methotrexate; NRI: nonresponder imputation; PMDA: Pharmaceuticals and Medical Devices Agency; UPA: upadacitinib. *$p<.05$, **$p<.01$ versus MTX. [a]NRI. [b]Linear extrapolation analysis. [c]PMDA-defined.

Table 2. Additional efficacy endpoints at week 12[a] in the Japanese population.

	MTX ($n = 28$)	UPA 7.5 mg qd ($n = 55$)	UPA 15 mg qd ($n = 27$)	UPA 30 mg qd ($n = 28$)
LS mean (95% CI) change from baseline in DAS28(CRP)[b]	−1.54[c] (−1.95 to −1.14)	−2.89[d] (−3.18 to −2.60)***	−3.29[c] (−3.70 to −2.88)***	−3.39[e] (−3.81 to −2.98)***
LS mean (95% CI) change from baseline in HAQ-DI[b]	−0.24[c] (−0.41 to −0.06)	−0.75[f] (−0.87 to −0.63)***	−0.95[g] (−1.12 to −0.78)***	−0.93[e] (−1.11 to −0.75)***
LS mean (95% CI) change from baseline in SF-36 PCS[b]	3.43[c] (0.40 to 6.47)	9.51[f] (7.38 to 11.64)**	10.01[g] (7.02 to 13.00)**	9.92[c] (6.88 to 12.97)**
ACR50, *n* (%)[h]	6 (21.4)	33 (60.0)***	18 (66.7)***	20 (71.4)***
ACR70, *n* (%)[h]	0	19 (34.5)***	14 (51.9)***	18 (64.3)***
DAS28(CRP) ≤3.2, *n* (%)[h]	5 (17.9)	38 (69.1)***	21 (77.8)***	22 (78.6)***
DAS28(CRP) <2.6, *n* (%)[h,i]	5 (17.9)	37 (67.3)***	19 (70.4)***	23 (82.1)***
SDAI ≤11, *n* (%)[h]	7 (25.0)	35 (63.6)***	17 (63.0)**	22 (78.6)***
SDAI ≤3.3, *n* (%)[h,i]	1 (3.6)	19 (34.5)**	10 (37.0)**	13 (46.4)***
CDAI ≤10, *n* (%)[h]	8 (28.6)	35 (63.6)**	17 (63.0)*	22 (78.6)***
CDAI ≤2.8, *n* (%)[h,i]	2 (7.1)	19 (34.5)**	11 (40.7)**	13 (46.4)**
Proportion of patients with change from baseline in mTSS ≤0, *n* (%)[i,j]	12[c] (46.2)	42[k] (82.4)**	21[c] (80.8)**	19[l] (79.2)*

ACR50/70: 50%/70% improvement in American College of Rheumatology; CDAI: Clinical Disease Activity Index; CI: confidence interval; CRP: C-reactive protein; DAS28(CRP): 28-Joint Disease Activity Score based on CRP; HAQ-DI: Health Assessment Questionnaire-Disability Index; LOCF: last observation carried forward; LS: least squares; mTSS: modified Total Sharp Score; MTX: methotrexate; NRI: nonresponder imputation; PCS: physical component summary; qd: once daily; SDAI: Simplified Disease Activity Index; SF-36: 36-item Short Form Survey; UPA: upadacitinib.

*$p < .05$, **$p < .01$, ***$p < .001$ versus MTX.

[a]Unless specified. [b]LOCF analysis. [c]$n = 26$. [d]$n = 52$. [e]$n = 25$. [f]$n = 53$. [g]$n = 27$. [h]NRI. [i]Week 24. [j]Linear extrapolation analysis. [k]$n = 51$. [l]$n = 24$.

efficacy and safety of upadacitinib in Japanese patients enrolled in SELECT-EARLY, with inclusion of a 7.5 mg dosing group at the request of the Japanese regulatory authority. Similar to the global population, and despite the small sample size of the JAS population, upadacitinib improved clinical, radiographic, and patient-reported endpoints compared with MTX over 24 weeks in Japanese patients and showed an acceptable safety profile with no new signals.

Although MTX is the recommended initial treatment for patients with RA, including those of Japanese descent, it has several limitations. MTX treatment results in remission, the primary treatment target in early RA, in only a minority of patients (<20% in this study), and less than half report LDA (despite pre-specified MTX dose escalation) [9,10]. In addition, it may not be an appropriate treatment in some patient populations (e.g. patients with significant alcohol intake), and its use is associated with the relatively frequent occurrence of nonserious, but inconvenient, AEs such as nausea and other gastrointestinal symptoms, oral ulcers, alopecia, and general malaise [21]. More serious AEs with MTX can include hepatotoxicity, myelosuppression, and interstitial pneumonitis. However, it should be noted that the rates of remission with MTX monotherapy in this study appeared to be lower than those observed in other studies in Japanese patients with RA [9,10]. For example, rates of DAS28(CRP) and SDAI remission with MTX monotherapy in this study were 17.9% and 3.6%, respectively, compared with 26.4% and 12.3% in the HOPEFUL-1 study [9].

As seen in the global population, the efficacy of upadacitinib appeared to plateau at 15 mg, with no further benefits observed with the 30 mg dose. Favorable efficacy was also observed in the Japan-specific 7.5 mg arm, with significant improvements observed versus MTX for all secondary endpoints. Conversely, response rates based on more stringent measures such as ACR50/70, LDA, and clinical remission, were numerically lower with the 7.5 mg dose compared with the higher doses of upadacitinib. In addition, no significant effect on prevention of radiographic progression was observed with upadacitinib 7.5 mg. However, the proportion of patients with no radiographic progression was significantly greater with all upadacitinib doses versus MTX. Therefore, the non-significant change in mTSS observed with upadacitinib 7.5 mg versus MTX may be in part due to the small sample size of the JAS population, which may have been affected by outliers.

The safety of upadacitinib in Japanese patients in this study was generally comparable with the global population. Similar to the global population, AEs such as CPK elevation and infection were more common in the 30 mg group compared with 7.5 and 15 mg. Herpes zoster reactivation, which has been reported more frequently in Japanese than in global patients receiving JAK inhibitors [22–24], was reported in 3.6%, 7.4%, and 7.1% of patients in the upadacitinib 7.5, 15, and 30 mg groups, respectively; all cases were nonserious. The reasons why herpes zoster occurs more frequently among Japanese and Asian populations than among other populations is unknown, although genetic predisposition, regional differences in reporting, and other cultural or medical factors could be involved [23,24]. Other AEs of special interest, such as serious infections and opportunistic infections, were infrequent, and there were no cases of gastrointestinal perforation, malignancy, or venous thromboembolism. For most laboratory parameters, Grades 3 and 4 changes occurred infrequently and were similar across all treatment groups; however, Grade 3 decreases in lymphocytes occurred more frequently with MTX compared with upadacitinib treatment groups. There were no Grade 4 decreases in lymphocytes and no cases of lymphoma or lymphopenia were reported with upadacitinib.

A major limitation of this Japanese subgroup analysis was the relatively low numbers of patients in each group; results must, therefore, be interpreted with caution. In addition, SELECT-EARLY only included patients with risk factors for radiographic progression, so the findings may not be generalizable to all MTX-naïve patients with RA.

Table 3. Safety in the Japanese population.

Event, *n* (%) unless otherwise stated	MTX (*n* = 28)	UPA 7.5 mg qd (*n* = 55)	UPA 15 mg qd (*n* = 27)	UPA 30 mg qd (*n* = 28)
Any AE	19 (67.9)	43 (78.2)	20 (74.1)	26 (92.9)
Any SAE	0	5 (9.1)	1 (3.7)	4 (14.3)
Any AE leading to discontinuation of study drug	1 (3.6)	5 (9.1)	1 (3.7)	0
Deaths	0	0	0	1 (3.6)
Infection	12 (42.9)	27 (49.1)	10 (37.0)	16 (57.1)
Serious infection	0	2 (3.6)	1 (3.7)	1 (3.6)
Opportunistic infection[a]	0	1 (1.8)	1 (3.7)	1 (3.6)
Herpes zoster	0	2 (3.6)	2 (7.4)	2 (7.1)
Active tuberculosis	0	0	0	0
Hepatic disorder	1 (3.6)	4 (7.3)	5 (18.5)	1 (3.6)
Renal dysfunction	0	1 (1.8)	0	0
Anemia	1 (3.6)	3 (5.5)	0	4 (14.3)
Elevated CPK	0	2 (3.6)	2 (7.4)	6 (21.4)
Gastrointestinal perforation	0	0	0	0
Malignancy (including NMSC)	0	0	0	0
MACE (adjudicated)	0	0	0	1 (3.6)
VTE (adjudicated)	0	0	0	0
Laboratory variables[b]				
Hemoglobin (g/L)				
Mean (SD) change from baseline to week 24[c]	3.1 (13.3)	5.6 (8.9)	5.6 (10.4)	−0.7 (14.5)
Grade 3 (70 to <80 or decreased 21 to <30)	2 (7.1)	1 (1.8)	0	1 (3.6)
Grade 4 (<70 or decreased ≥30)	1 (3.6)	0	0	2 (7.1)
Platelets ($\times 10^9$/L)				
Mean (SD) change from baseline up to week 24[c]	−27.9 (58.9)	−33.9 (52.2)	−52.9 (84.3)	−19.1 (72.1)
Grade 3 (20 to <50)	0	0	0	0
Grade 4 (<20)	0	0	0	0
Leukocytes ($\times 10^9$/L)				
Mean (SD) change from baseline up to week 24[d]	−0.4 (1.6)	−1.7 (1.5)	−1.4 (2.2)	−1.5 (2.5)
Grade 3 (1.0 to <2.0)	0	0	0	1 (3.6)
Grade 4 (<1.0)	0	0	0	1 (3.6)
Neutrophils ($\times 10^9$/L)				
Mean (SD) change from baseline up to week 24[d]	−0.4 (1.5)	−1.7 (1.5)	−1.3 (2.1)	−1.6 (2.1)
Grade 3 (0.5 to <1.0)	0	1 (1.8)	0	1 (3.6)
Grade 4 (<0.5)	0	0	0	0
Lymphocytes ($\times 10^9$/L)				
Mean (SD) change from baseline up to week 24[d]	−0.0 (0.4)	0.1 (0.5)	0.0 (0.5)	0.3 (0.9)
Grade 3 (0.5 to <1.0)	8 (28.6)	6 (10.9)	5 (18.5)	4 (14.3)
Grade 4 (<0.5)	0	0	0	0
ALT (U/L)				
Mean (SD) change from baseline up to week 24[c]	6.8 (13.8)	5.9 (22.4)	11.7 (12.9)	4.2 (8.1)
Grade 3 (3.0 to <8 ×ULN)	0	0	0	0
Grade 4 (>8 ×ULN)	1 (3.6)	0	1 (3.7)	0
AST (U/L)				
Mean (SD) change from baseline up to week 24[e]	4.6 (12.0)	7.9 (13.5)	10.2 (7.8)	5.5 (5.8)
Grade 3 (3.0 to <8 ×ULN)	1 (3.6)	0	0	0
Grade 4 (>8 ×ULN)	0	0	1 (3.7)	0

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; MACE: major adverse cardiovascular event; MTX: methotrexate; NMSC: non-melanoma skin cancer; qd: once daily; SAE: serious adverse event; SD: standard deviation; ULN: upper limit of normal; UPA: upadacitinib; VTE: venous thromboembolism.

[a]MedDRA 19.1 preferred terms for cases of opportunistic infection: oral candidiasis (UPA 7.5 mg), pneumonia cryptococcal (UPA 15 mg), and cytomegalovirus test positive (UPA 30 mg).

[b]Grading is based on OMERACT criteria.

[c]$n = 26$, $n = 51$, $n = 26$, $n = 25$, respectively.

[d]$n = 26$, $n = 52$, $n = 26$, $n = 25$, respectively.

[e]$n = 26$, $n = 51$, $n = 25$, $n = 25$, respectively.

In conclusion, this sub-analysis confirmed the efficacy and safety profile of upadacitinib monotherapy in MTX-naïve Japanese patients with active RA, and was comparable with that observed in the global population. Here, upadacitinib 7.5 mg daily was shown to be a clinically effective treatment with a favorable side effect profile, making it a suitable therapeutic option to consider for some patients.

Acknowledgments

AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Laura Chalmers, PhD and Frances Smith, PhD of 2 the Nth (Cheshire, UK), and was funded by AbbVie.

Conflict of interest

T Takeuchi has received grants from AbbVie GK, Asahi-Kasei Pharma Corporation, Astellas Pharma Inc., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., JCR Pharma Co, Ltd., Mitsubishi Tanabe Pharma Co., Nippon Kayaku Co. Ltd., and Takeda Pharmaceutical Co., Ltd. Personal/speaker fees from A2 Healthcare

Corporation, AbbVie GK., Astellas Pharma Inc., AYUMI Pharmaceutical Corporation, Boehringer-Ingelheim Co. Ltd., Bristol-Myers K.K., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., Gilead Sciences, Inc., Kissei Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Co., Nippon Kayaku Co., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Pfizer Japan Inc., SRL. Inc., Taiho Pharmaceutical Co. Ltd., Taisho Pharmaceutical Co. Ltd., and the Uehara Memorial Foundation. Consultancy fees from A2 Healthcare Corporation, AbbVie GK., Astellas Pharma Inc., Boehringer-Ingelheim Co. Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Gilead Sciences Inc., Nippon Kayaku Co., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Taisho Pharmaceutical Co. Ltd. M Rischmueller has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, and UCB; consulting/speaker fees from AbbVie, Bristol-Myers Squibb, CSL Behring, Eli Lilly, Gilead, Janssen Cilag, Novartis, Pfizer, Sanofi, and UCB. R Blanco has received grants/research support from AbbVie, MSD, and Roche; consulting fees/participation in company-sponsored speaker's bureau from AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck Sharp & Dohme, Pfizer, and Roche. RM Xavier has received consultant/speaker fees from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and Roche; research grants from AbbVie, Eli Lilly, Janssen, and Pfizer. Y Ueki has received speaker fees from AbbVie GK, Asahi Kasei Pharma Corp., Astellas Pharma Inc., Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Ono Pharmaceutical Co., Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd. T Atsumi has received research grants and/or honoraria for meetings from AbbVie Inc., Alexion Inc., Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Eisai, Eli Lilly Japan K.K., Gilead Sciences Inc., Mitsubishi Tanabe Pharma Co., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., Takeda Pharmaceutical Co., Ltd., and UCB Japan Co. Ltd. S Chen, A Friedman, and AL Pangan are all employees of AbbVie and may hold stock or options. V Strand is a consultant for AbbVie, Amgen, Arena, Asana, AstraZeneca, Bayer, Blackrock, Bioventus, BMS, Boehringer Ingelheim, Celgene, Celltrion, Concentric Analgesics, Crescendo/Myriad Genetics, EMD Serono, Equilium, Eupraxia, Flexion, Galapagos, Genentech/Roche, Gilead, GSK, Horizon, Ichnos, Inmedix, Janssen, Kiniksa, Kypha, Lilly, Merck, MiMedx, MyoKardia, Novartis, Pfizer, Regeneron, Samsung, Samumed, Sandoz, Sanofi, Servier, Setpoint, SKK, Tonix, and UCB. RF van Vollenhoven has received research support (institutional grants) from BMS, GSK, Lilly, and UCB; support for educational programs (institutional grants) from Pfizer and Roche. Consultancy, for which institutional and/or personal honoraria were received from AbbVie, AstraZeneca, Biogen, Biotest, Celgene, Galapagos, Gilead, Janssen, Pfizer, Servier, and UCB. Speaker, for which institutional and/or personal honoraria were received from AbbVie, Galapagos, Janssen, Pfizer, and UCB.

Data sharing statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review, and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023–38.
2. Sobue Y, Kojima T, Funahashi K, Okui N, Takahashi N, Asai S, et al. Relationship between disease activity of rheumatoid arthritis and development of locomotive syndrome: a five-year longitudinal cohort study. Mod Rheumatol. 2020;1–7. Online ahead of print.
3. Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: rheumatoid arthritis. J Autoimmun. 2010;35(1):10–4.
4. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). Mod Rheumatol. 2014;24(1):33–40.
5. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016;68(1):1–25.
6. Smolen JS, Landewé R, Bijlsma J, Burmester G, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685–99.
7. Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K, et al. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. Mod Rheumatol. 2019;29(1):31–40.
8. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54(1):26–37.
9. Takeuchi T, Hisashi Y, Naoki I, Nobuyuki M, Masaya M, Tsukasa M, et al. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. Ann Rheum Dis. 2014;73(3):536–43.
10. Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomized, parallel-group certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016;75(1):75–83.
11. Yamanaka H, Tanaka E, Nakajima A, Furuya T, Ikari K, Taniguchi A, et al. A large observational cohort study of rheumatoid arthritis, IORRA: providing context for today's treatment options. Mod Rheumatol. 2020;30(1):1–6.
12. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205–19.
13. Parmentier JM, Voss J, Graff C, Schwartz A, Argiriadi M, Friedman M, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). BMC Rheumatol. 2018;2:23.
14. Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, 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(10139):2503–12.
15. Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, 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(11):1788–800.

16. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, 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(10139):2513–24.
17. Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JI, 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(10188):2303–11.
18. van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed M-EF, Chen S, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naïve patients with moderately to severely active rheumatoid arthritis (SELECT-EARLY): a randomized, double-blind, active-comparator, multi-center, multi-country trial. Arthritis Rheumatol. 2020;72(10):1607–20.
19. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010; 69(9):1580–8.
20. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheum. 1993;20: 557–60.
21. Summary of Product Characteristics for Methotrexate 2.5 mg tablets USP [Last accessed 18 December 2019]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf.
22. Harigai M, Takeuchi T, Smolen JS, Winthrop KL, Nishikawa A, Rooney TP, et al. Safety profile of baricitinib in Japanese patients with active rheumatoid arthritis with over 1.6 years median time in treatment: an integrated analysis of Phases 2 and 3 trials. Mod Rheumatol. 2020;30(1):36–43.
23. Winthrop KL, Curtis JR, Lindsey S, Tanaka Y, Yamaoka K, Valdez H, et al. Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. Arthritis Rheumatol. 2017; 69(10):1960–8.
24. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014; 66(10):2675–84.