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CLINICAL SCIENCE

Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response

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ABSTRACT

Background In SELECT-COMPARE, a randomised double-blind study, upadacitinib 15 mg once daily was superior to placebo or adalimumab on background methotrexate (MTX) for treating rheumatoid arthritis signs and symptoms and inhibited radiographical progression versus placebo at 26 weeks. Here we report 48-week safety and efficacy in patients who continued their original medication or were rescued to the alternative medication for insufficient response.

Methods Patients on MTX received upadacitinib 15 mg, placebo or adalimumab for 48 weeks. Rescue without washout, from placebo or adalimumab to upadacitinib or upadacitinib to adalimumab occurred if patients had <20% improvement in tender joint count (TJC) or swollen joint count (SJC) (weeks 14/18/22) or Clinical Disease Activity Index (CDAI) >10 (week 26); remaining placebo patients were switched to upadacitinib at week 26. Efficacy was analysed by randomised group (non-responder imputation), as well as separately for rescued patients (as observed). Treatment-emergent adverse events per 100 patient-years were summarised.

Results Consistent with responses through week 26, from weeks 26 to 48, responses by randomised group including low disease activity, clinical remission and improvements in pain and function remained superior for upadacitinib versus adalimumab; radiographical progression remained lower for upadacitinib versus placebo (linear extrapolation). Although both switch groups responded, a higher proportion of patients rescued to upadacitinib from adalimumab achieved CDAI ≤10 at 6 months postswitch versus patients rescued from upadacitinib to adalimumab. Safety at week 48 was comparable to week 26.

Conclusion Upadacitinib+MTX demonstrated superior clinical and functional responses versus adalimumab+MTX and maintained inhibition of structural damage versus placebo+MTX through week 48. Patients with an insufficient response to adalimumab or upadacitinib safely achieved clinically meaningful responses after switching to the alternative medication without washout.

Key messages

What is already known about this subject?
► In patients with rheumatoid arthritis (RA) who do not respond sufficiently to biologic disease-modifying antirheumatic drug (bDMARD) treatment with Janus kinase inhibitors (JAKi) is efficacious.
► Switching of therapies including switching from a JAKi to a bDMARD may be required to achieve treatment goals.
► In the SELECT-COMPARE study, through 6 months, upadacitinib demonstrated significant improvements in RA signs and symptoms versus placebo and adalimumab and inhibited radiographical progression versus placebo.

What does this study add?
► Consistent with responses through week 26, between weeks 26 and 48 of the SELECT-COMPARE study, responses by randomised group including low disease activity, clinical remission and improvements in pain and function remained superior for upadacitinib versus adalimumab and radiographical progression remained lower for upadacitinib versus placebo. Safety at week 48 was comparable to findings through week 26.
► The SELECT-COMPARE study design incorporated blinded treatment switches within the first 6 months that allocated patients who were not sufficiently responding to randomised treatment to the alternative advanced therapy (ie, insufficient responders to upadacitinib were switched without washout to adalimumab and insufficient responders to adalimumab were switched without washout to upadacitinib). Both switch groups responded, but a higher proportion of patients rescued to upadacitinib from adalimumab achieved Clinical Disease Activity Index ≤10 at 6 months postswitch versus patients rescued from upadacitinib to adalimumab.

Key messages

How might this impact on clinical practice?
► A clinically significant number of patients with an insufficient response to adalimumab or upadacitinib safely achieved clinically meaningful responses after switching to the alternative medication without washout.
► Responses were maintained with upadacitinib treatment over 48 weeks and were consistently significantly better with upadacitinib than with adalimumab.
► No new safety findings were observed with longer-term exposure to upadacitinib or in the period following the switch from adalimumab to upadacitinib.

INTRODUCTION

The goal of treatment for rheumatoid arthritis (RA) is to maximise patient outcomes including preventing structural damage and subsequent loss of function. A treat-to-target strategy optimises treatment until clinical remission (or low disease activity (LDA)) is achieved and maintained, which improves long-term prognosis.[1–3] Methotrexate (MTX) is the recommended initial treatment; however, in patients who are intolerant or have an inadequate response, a second conventional synthetic disease-modifying antirheumatic drug (csDMARD), biologic DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD) should be added.[4 5]

Upadacitinib, an oral Janus kinase (JAK) inhibitor engineered to have greater selectivity towards JAK1 than JAK2, JAK3, or TYK2, has demonstrated efficacy in five phase III trials.[6–10] The primary results of SELECT-COMPARE through 26 weeks demonstrated that 15 mg of upadacitinib once daily was superior to placebo and adalimumab for clinical and functional outcomes, including clinical remission and LDA, and was superior to placebo for inhibition of radiographical progression in MTX inadequate responders.[10] Here we report blinded long-term safety and efficacy for upadacitinib versus adalimumab through 48 weeks from SELECT-COMPARE. Importantly, SELECT-COMPARE was uniquely designed to explore a randomised, blinded switch to a JAK inhibitor from a tumour necrosis factor (TNF) inhibitor in patients with insufficient response (and vice versa) without a washout period; similar data have not been reported to date.

PATIENTS AND METHODS

Patients
Inclusion criteria have been described previously.[10] Patients were ≥18 years of age with RA receiving stable MTX background therapy with continued active joint disease, had a high-sensitivity C-reactive protein (hsCRP) ≥5 mg/L and evidence of erosive disease and/or seropositivity.

Study design
Patients were blindly randomised 2:2:1 to upadacitinib 15 mg once daily, placebo or adalimumab (Humira) 40 mg every other week, with stable background MTX (online supplementary figure 1). Blinded rescue treatment, without washout but with background MTX, from placebo and adalimumab to upadacitinib, and upadacitinib to adalimumab occurred at weeks 14, 18 or 22 for patients with <20% improvement from baseline in tender or swollen joints. At week 26, all remaining placebo patients and those not meeting LDA by Clinical Disease Activity Index (CDAI ≤10) receiving adalimumab were rescued to upadacitinib, while those receiving upadacitinib were rescued to adalimumab.

Patients provided written informed consent. AbbVie sponsored the study and collaborated with the academic authors to design the study. AbbVie and the academic authors analysed the data, interpreted the results and prepared, reviewed and approved the final version; AbbVie provided writing support. All the authors approved the final submission and attest to its accuracy.

Assessments
Efficacy through week 48 was assessed by initial randomised group for: meeting improvement in American College of Rheumatology (ACR) response criteria (ACR20/50/70), change from baseline in individual components of ACR response, proportions achieving LDA defined by CDAI ≤10 or Simplified Disease Activity Index (SDAI ≤11); clinical remission defined by CDAI (≤2.8) or SDAI (≤3.3), ACR/European League Against Rheumatism Boolean remission (swollen 28-joint count (SJC28) ≤1, tender 28-joint count (TJC28) ≤1, hsCRP ≤1 (mg/dL), patient's global assessment of disease activity (PGA) ≤1 (on a 0–10 cm Visual Analogue Scale), DAS28(CRP) <2.6 or ≤3.2 and change from baseline in 36-Item Short Form Survey (SF-36) physical component summary (PCS) and morning stiffness duration. For rescued patients, the achievement of CDAI remission and LDA, DAS28(CRP) <2.6 and ≤3.2 were assessed 3 and 6 months (±2 weeks) postswitch.

Assessments of X-rays of hands and feet were conducted at baseline, weeks 14 (for rescued patients), 26 and 48 and included mean change from baseline in van der Heijde's modification of the Total Sharp Score (mTSS),[11 12] joint space narrowing (JSN), Erosion Score (ES) and the proportion of patients with no radiographical progression (defined as change from baseline in mTSS ≤0) versus placebo. Similar to the first reading session of the 6 month X-rays, radiographs were also reviewed by two independent readers blinded to treatment and sequence at a second session at week 48 (reported here).

Safety reports are based on available data as of 6 July 2018, when all patients completed their 48-week visit. As of this cut-off date, safety data for some patients extends past week 48 as patients could subsequently continue into a long-term extension (LTE). Investigator-reported treatment-emergent adverse events (AEs) are summarised for events occurring while exposed to upadacitinib or adalimumab, based on the treatment received at the time of the event ('any upadacitinib', 'any adalimumab'). Exposure-adjusted event rates (EAER) are reported (events/100 patient-years (PY)), and exposure adjusted incidence rates (EAIR) are reported for deaths, major adverse cardiovascular events (MACE) and venous thromboembolic events (VTEs). AEs were coded per the Medical Dictionary for Regulatory Activities (MedDRA), V.19.1, and AEs and laboratory changes were graded using the Rheumatology Common Toxicity Criteria V.2.0.[13] Changes in creatine phosphokinase (CPK) and creatinine were graded using the Common Toxicity Criteria of the National Cancer Institute.[13 14] Cardiovascular events including MACE and VTE were blindly adjudicated by an independent, external Cardiovascular Adjudication Committee using predefined event definitions. Laboratory changes from baseline to each visit are reported in patients on continuous upadacitinib or adalimumab through the week 48 visit.

Statistical analysis
Efficacy is reported by the three initial randomised groups. Analyses were conducted in the full analysis set, including all randomised patients who had received at least one dose of study drug. For binary endpoints, treatments were compared using the
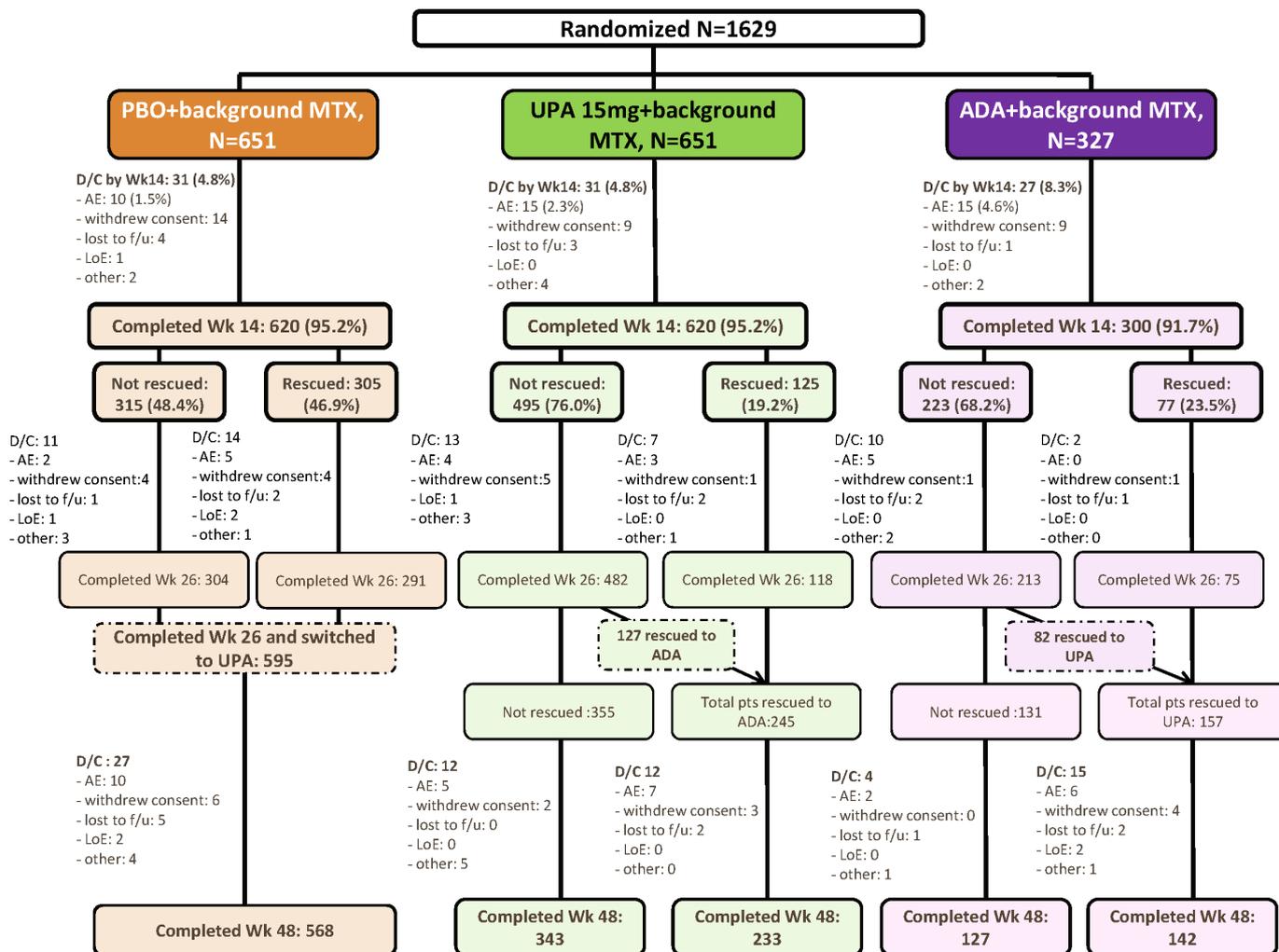
Figure 1 Disposition of patients through week 48. At weeks 14, 18 and 22, patients who had <20% improvement in 66 swollen joint count or 68 tender joint count were rescued. At week 26, patients with CDAI >10 were rescued. Regardless of CDAI low disease activity achievement at week 26, all remaining PBO patients were switched to UPA. ADA, adalimumab; AE, adverse events; CDAI, Clinical Disease Activity Index; PBO, placebo; MTX, methotrexate; UPA, upadacitinib.

Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factor of prior bDMARD use (yes, no). Non-responder imputation (NRI) was used for missing data and for observations after rescue for patients rescued at weeks 14, 18 or 22; last observation carried forward (LOCF) was used for observations after rescue for patients rescued at week 26. For continuous endpoints, analyses were conducted using the analysis of covariance (ANCOVA) model including treatment, the corresponding baseline value and the stratification factor of prior bDMARD use (yes, no). LOCF was used for observations after rescue treatment for patients rescued at weeks 14–26. For the radiographical endpoints, ANCOVA and CMH analyses were conducted as above. Linear extrapolation was used for missing data and rescue/switch handling.

For patients who switched treatments, as-observed analyses were conducted. Data on the proportions of patients achieving LDA or remission by CDAI, DAS28(CRP) ≤3.2, DAS28(CRP) <2.6, at 3 and 6 months (±2 weeks) after rescue are summarised.

RESULTS
Disposition
One thousand six hundred and twenty-nine patients were randomised at baseline (figure 1). Among 651 randomised to

upadacitinib, 252 (39%) were rescued to adalimumab (125 (19%) for <20% improvement in SJC or TJC between weeks 14 and 22 and 127 (20%) at week 26 for CDAI >10). Among 327 patients randomised to adalimumab, a higher proportion compared with upadacitinib were rescued (159 (49%): 77 (24%) for <20% improvement in SJC or TJC and 82 (25%) for CDAI >10 at week 26). Among 651 randomised to placebo, 305 (47%) were rescued for <20% improvement in SJC or TJC; 303 were switched to upadacitinib 15 mg at week 26 per protocol.

Efficacy by randomised groups
Over 48 weeks, upadacitinib was superior versus adalimumab for ACR20/50/70 responses (online supplementary figure 2); ACR20/50/70 at week 48 was achieved by 65/49/36% and 54/40/23% of patients randomised to upadacitinib and adalimumab (both plus background MTX), respectively (p<0.01 for upadacitinib vs adalimumab). Similar significant results were observed for each ACR core component except SJC (online supplementary figure 3). At week 48, mean improvements from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) were −0.73 and −0.60 (p<0.01) with 62% versus 52% achieving the minimum clinically important difference (less than or equal to −0.22, p<0.01) for upadacitinib versus
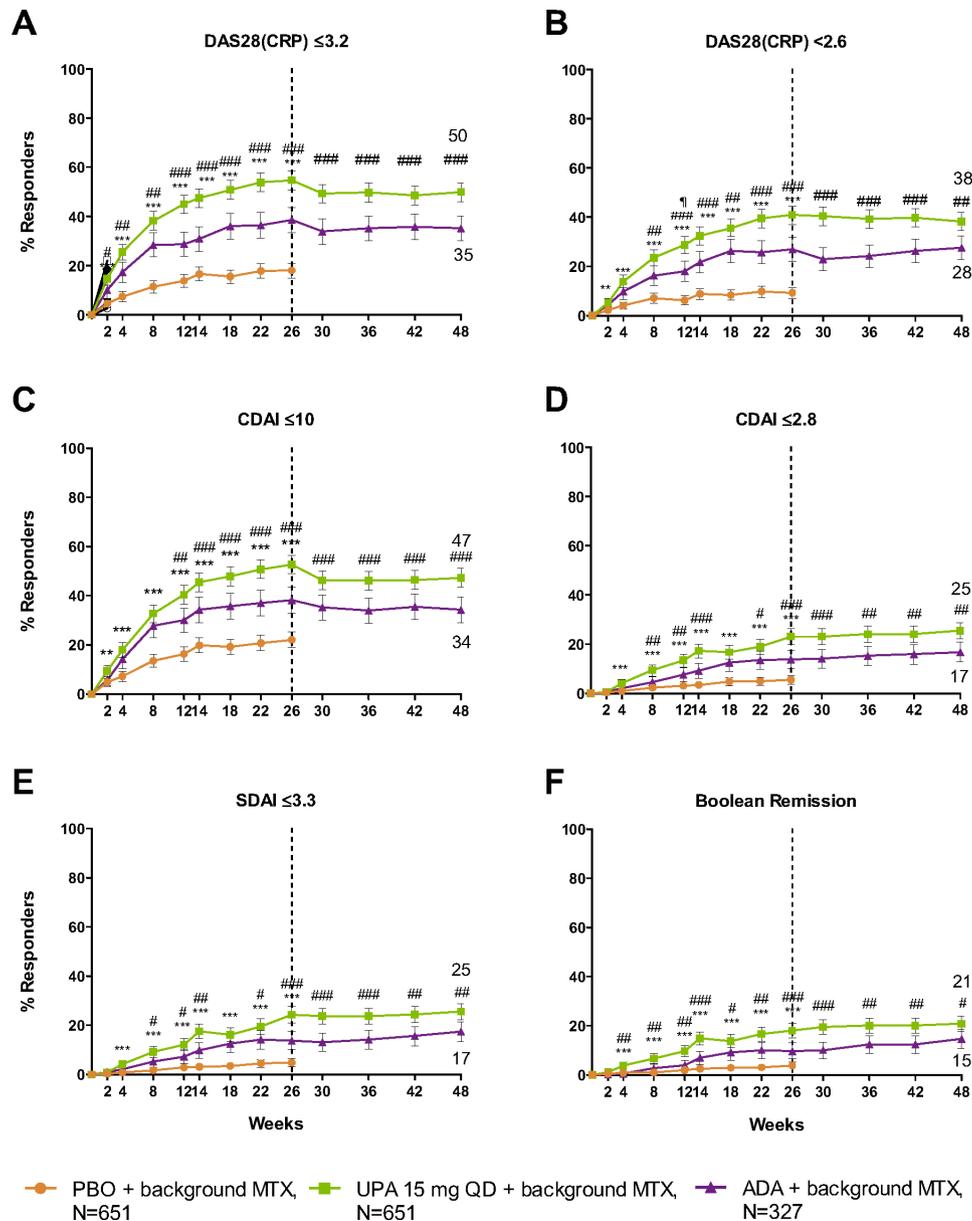
Figure 2 Proportions of patients achieving disease activity states over 48 weeks (NRI). Vertical line at week 26 indicates the end of the PBO-controlled period. Treatment groups are by initial randomisation. *p≤0.05; **p≤0.01; ***p≤0.001 for comparison of UPA versus PBO; #p≤0.05; ##p≤0.01; ###, p≤0.001 for comparison of UPA versus ADA. Error bars reflect 95% CI.¶Indicates multiplicity-controlled comparisons of UPA versus PBO. Observations after rescue were handled using NRI (patients rescued at weeks 14–22) and LOCF (patients rescued at week 26) for binary endpoints. ADA, adalimumab; CDAI, Clinical Disease Activity Index; DAS28(CRP), 28-joint Disease Activity Score based on C-reactive protein; LOCF; last observation carried forward; MTX, methotrexate; NRI, non-responder imputation; PBO, placebo; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.

adalimumab, respectively. At week 48, upadacitinib was superior to adalimumab for the reduction in pain (−36.7 vs −32.1, p<0.05), with continued higher improvements in SF-36 PCS, Functional Assessment of Chronic illnesses Therapy-Fatigue (FACIT-F) and duration of morning stiffness (SF-36 PCS: 9.8 vs 8.1, p<0.01; FACIT-F: 10.2 vs 8.9, p<0.05; morning stiffness: −101.7 vs −95.5; online supplementary figure 4).

LDA and clinical remission by CDAI, SDAI and Boolean remission, as well as DAS28(CRP) <2.6/≤3.2, were consistently and statistically significantly superior for upadacitinib versus adalimumab through week 48 (figure 2 and online supplementary figure 5); at week 48, CDAI LDA was achieved by 47% versus 34% of patients randomised to upadacitinib and adalimumab (p<0.001), respectively, CDAI remission by 25% versus 17% (p<0.01) and

Boolean remission by 21% versus 15% (p<0.05). DAS28(CRP) <2.6 was achieved by 38% versus 28% of patients randomised to upadacitinib and adalimumab, respectively (p<0.01).

At week 48, based on initial randomised group, using linear extrapolation, mean change from baseline in mTSS, JSN and ES continued to be significantly lower on upadacitinib versus placebo (p<0.001, figure 3A, B). Significantly more patients randomised to upadacitinib (86%) or adalimumab (88%) had no radiographic progression versus placebo (74%) (p≤0.001). Results were consistent using 'as-observed' analyses (online supplementary figure 6).

Efficacy in the switch population

Of the 651 and 327 patients randomised to upadacitinib and adalimumab, 251 (38.6%) were rescued to adalimumab versus
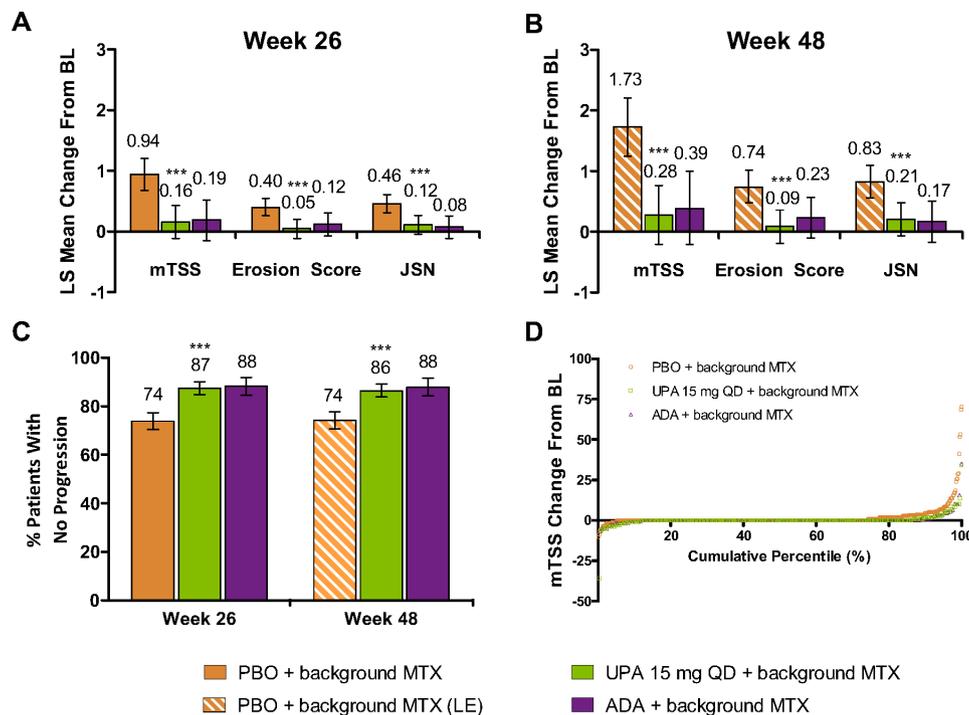
Figure 3 Radiographic progression through week 48 (linear extrapolation). Treatment groups are by initial randomisation. Results based on reading session 2. *p≤0.05; **p≤0.01; ***p≤0.001 for comparison of UPA versus PBO. Error bars reflect 95% CI. For the PBO group, all data at week 48 were imputed by linear extrapolation. X-ray data collected at treatment switching or at discontinuation of PBO (for patients who discontinued PBO) were used for extrapolation. Specifically, for PBO patients who switched to UPA at week 26, the week 26 X-ray was used for extrapolation to impute the data at week 48. For patients randomised to UPA or ADA who were rescued, data at week 48 were also imputed by linear extrapolation using X-ray data collected at treatment switching. Statistical analysis comparing UPA to ADA was not prespecified; nominal p values were not significant. ADA, adalimumab; BL, baseline; JSN, joint space narrowing; PBO, placebo; mTSS, modification of the total Sharp Score; MTX, methotrexate; UPA, upadacitinib.

159 (48.6%) to upadacitinib per the predefined criteria. The demographics of these patients were similar to the overall randomised population. A similar proportion (~90%) of patients in both rescued groups remained in the study at 6 months postswitch (figure 1). Following 6 months of switch treatment in patients rescued from adalimumab to upadacitinib, CDAI remission/LDA was achieved by 15/53% and DAS28(CRP) <2.6/≤3.2 by 35/56%; in patients rescued from upadacitinib to adalimumab, CDAI remission/LDA was achieved in 5/41% and DAS28(CRP) <2.6/≤3.2 was achieved in 21/40%. Improvements in SDAI, HAQ-DI and absolute changes in CDAI, SDAI and DAS28(CRP) were consistent with these results (table 1).

After rescue, responses in many patients were rapid and continued to improve, with a consistently higher magnitude for those switched to upadacitinib from adalimumab versus those switched to adalimumab from upadacitinib (figure 4). Responses in patients who were initially randomised and continued adalimumab or upadacitinib through week 48 were high.

Table 1 Clinical and functional responses in patients who switched treatments, 3 and 6 months postswitch (as observed)

n/N (%)	UPA 15 mg once daily to ADA (N=251)		ADA to UPA 15 mg once daily (N=159)	
	3 months postswitch	6 months postswitch	3 months postswitch	6 months postswitch
DAS28(CRP) ≤3.2	71/233 (30.5)	91/230 (39.6)	77/150 (51.3)	82/147 (55.8)
DAS28(CRP) <2.6	34/233 (14.6)	49/230 (21.3)	45/150 (30.0)	51/147 (34.7)
CDAI ≤10	74/242 (30.6)	95/234 (40.6)	58/148 (39.2)	77/146 (52.7)
CDAI ≤2.8	8/242 (3.3)	12/234 (5.1)	13/148 (8.8)	22/146 (15.1)
SDAI ≤11	69/231 (29.9)	96/229 (41.9)	64/144 (44.4)	77/145 (53.1)
SDAI ≤3.3	9/231 (3.9)	11/229 (4.8)	12/144 (8.3)	26/145 (17.9)
Mean change from baseline (95% CI)*				
HAQ-DI	−0.56 (−0.64 to −0.48)	−0.58 (-0.66 to −0.49)	−0.69 (−0.79 to −0.60)	−0.73 (−0.83 to −0.63)
DAS28(CRP)	−2.13 (−2.3 to −1.96)	−2.40 (−2.58 to −2.22)	−2.74 (−2.96 to −2.52)	−2.88 (−3.11 to −2.65)
CDAI	−24.94 (−26.86 to −23.01)	−27.28 (−29.35 to −25.21)	−27.01 (−29.63 to −24.56)	−29.47 (−32.23 to −26.71)
SDAI	−25.80 (−27.84 to −23.76)	−28.30 (−30.45 to −26.15)	−28.57 (−31.31 to −25.84)	−31.02 (−33.86 to −28.19)

*Mean change from baseline at randomisation.
ADA, adalimumab; CDAI, Clinical Disease Activity Index; DAS28(CRP), 28-joint disease activity score based on C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.
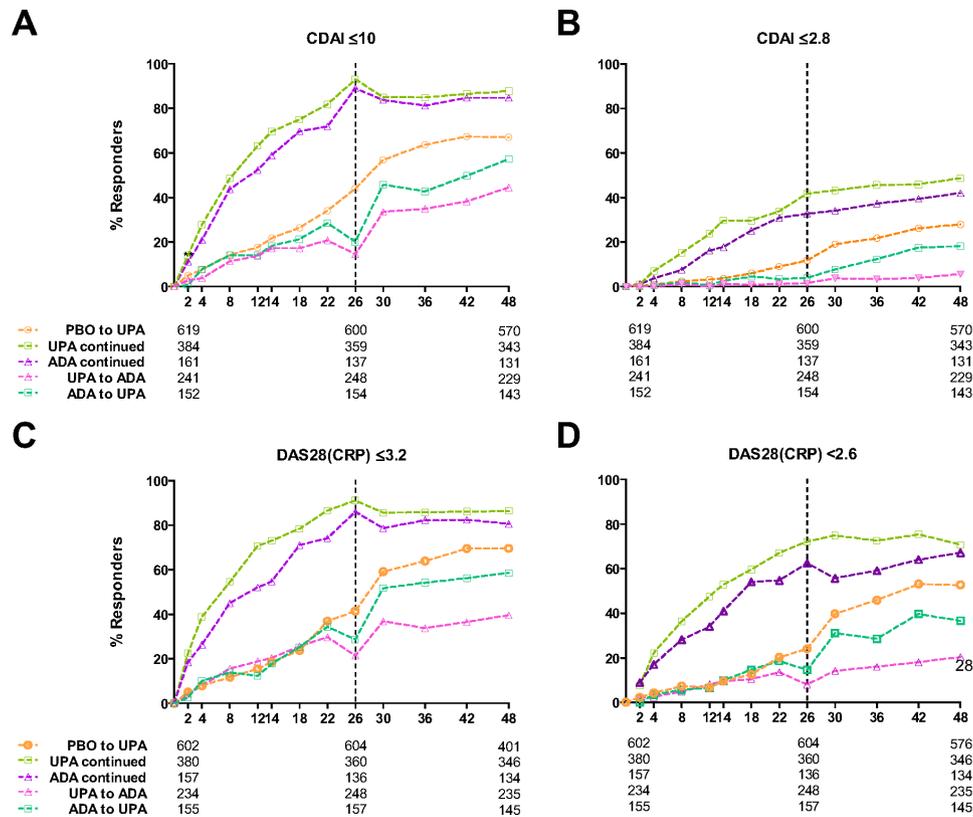
Figure 4 Proportions of patients who were switched from ADA to UPA 15 mg once daily or vice versa achieving disease activity states over 48 weeks (as observed). Vertical line at week 26 indicates the end of the PBO-controlled period. Numbers of patients at selected visits are indicated below the graphs. Groups are by sequence of treatments. ADA, adalimumab; CDAI, Clinical Disease Activity Index; DAS28(CRP), 28-joint Disease Activity Score based on C-reactive protein; PBO, placebo; UPA, upadacitinib.

Safety

The cumulative exposures for upadacitinib and adalimumab were 1243.3 and 467.8 PYs, respectively. Through the cut-off date, the EAER for AEs leading to discontinuation and serious AEs were higher in the adalimumab versus upadacitinib group (table 2). The most frequently reported TEAEs (≥7.5E/100 PY) with upadacitinib were upper respiratory tract infection, urinary tract infection, nasopharyngitis and increased alanine aminotransferase (ALT), while the most frequently reported TEAEs with adalimumab were urinary tract infection and worsening of RA. EAER were similar on upadacitinib and adalimumab for serious infections (4.1 and 4.3, respectively)

Table 2	Exposure adjusted event rates for TEAE (E/100 PYs (95% CI))	
	Upadacitinib 15 mg once daily, N=1417, PY=1243.3	**Adalimumab, N=579, PY=467.8**
Any AE	266.4 (257.4 to 275.6)	294.8 (279.4 to 310.8)
Serious AE	12.9 (11.0 to 15.1)	15.6 (12.2 to 19.6)
AE leading to discontinuation of study drug	7.4 (6.0 to 9.1)	11.1 (8.3 to 14.6)
Infection	86.8 (81.7 to 92.1)	79.1 (71.2 to 87.6)
Serious infection	4.1 (3.1 to 5.4)	4.3 (2.6 to 6.6)
Opportunistic infection	0.7 (0.3 to 1.4)	0.6 (0.1 to 1.9)
Herpes zoster	3.1 (2.2 to 4.2)	1.3 (0.5 to 2.8)
Hepatic disorder*	17.7 (15.4 to 20.2)	13.9 (10.7 to 17.7)
Gastrointestinal perforation†	0.2 (0 to 0.7)	0
Any malignancy (excluding NMSC)	0.4 (0.1 to 0.9)	0.6 (0.1 to 1.9)
NMSC	0.2 (0 to 0.7)	0.2 (0 to 1.2)
MACE (adjudicated)‡	0.4 (0.1 to 0.9)	0.4 (0.1 to 1.5)
Venous thromboembolic events (adjudicated)‡	0.3 (0.1 to 0.8)	1.1 (0.3 to 2.5)
Deaths‡§	0.4 (0.1 to 0.9)	0.9 (0.2 to 2.2)

*Hepatic disorders: majority were based on asymptomatic alanine aminotransferase/aspartate aminotransferase elevations.
†Gastrointestinal perforations were identified through Standardised Medical Dictionary for Regulatory Activities query.
‡Exposure-adjusted incidence rates.
§Deaths included non-treatment emergent deaths.
AE, adverse event; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PYs, patient years; TEAE, treatment-emergent adverse events.

and opportunistic infections (0.7 and 0.6), with oral candidiasis being the most common opportunistic infection. The EAER for active tuberculosis were 0.1 and 0.2 for upadacitinib and adalimumab, respectively. The event rate of herpes zoster (HZ) was higher on upadacitinib than adalimumab (table 2). No HZ event was meningoencephalopathic or involved non-cutaneous internal organs except one event on upadacitinib, reported as ophthalmic and led to study drug discontinuation. Most HZ events were non-serious and involved 1–2 dermatomes.

The event rate of malignancies was similar with upadacitinib and adalimumab, and no notable pattern or types of malignancies were observed (online supplementary material). NMSCs were two basal cell carcinomas and one squamous cell carcinoma on upadacitinib, and one basal cell carcinoma on adalimumab; no cases of treatment-emergent lymphoma were reported (table 2). Three events on upadacitinib were classified as 'gastrointestinal (GI) perforation'; however, none were spontaneous GI perforations but rather events of peritonitis with appendicitis in setting of a fallopian tube abscess, anal abscess and anal fistula. Most hepatic events reported were asymptomatic elevations of ALT and AST; most did not lead to premature discontinuation of study drug.

The EAIR for adjudicated MACE were the same on upadacitinib and adalimumab (0.4 n/100 PY) (table 2 and online supplementary material). The EAIR for adjudicated VTE were 0.3 n/100 PY and 1.1 n/100 PY on upadacitinib and adalimumab, respectively; all patients had more than one risk factor besides RA, including family history of VTE, obesity, hypertension and smoking. On upadacitinib, there was one patient with a deep vein thrombosis (DVT), two patients with pulmonary embolism (PE) and one patient with both DVT and PE. On adalimumab, there were four patients with PE and one patient with a DVT. Nine deaths were reported (table 2 and online supplementary material). All patients with events adjudicated as cardiovascular death had known cardiovascular risk factors.

Overall, through week 48 in patients on continuous adalimumab or upadacitinib on a group level, the mean levels of haemoglobin, neutrophils, lymphocytes and platelets continued to remain similar to the first 26 weeks and within the normal ranges (online supplementary figure 7). Mean elevations in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed on upadacitinib versus adalimumab, although ratios of LDL-C:HDL-C and total cholesterol:HDL-C remained steady (online supplementary figure 8 and data not shown). There were a few patients in both arms who had greater than or equal to grade 3 changes in laboratory parameters including decreases in haemoglobin, neutrophils and platelet counts (online supplementary table 1). The proportions of patients with grades 3 and 4 lymphocyte decreases were higher for upadacitinib versus adalimumab; there was no clear association between low lymphocyte counts or low neutrophil counts and the rates of infections, including serious and opportunistic infections, and HZ. Grade 3/4 elevations in ALT/AST were not common, occurring more on upadacitinib than adalimumab or placebo; no Hy's law cases were reported. Greater than or equal to grade 3 increases in CPK occurred in a few patients, more frequently on upadacitinib. Most patients were asymptomatic except two (one with muscle weakness, one with muscle pain) who had single grade 3 CPK increases after vigorous activity; the increases normalised without study drug interruption. No patient had rhabdomyolysis or discontinued due to increased CPK.

Switch safety

Among patients who were rescued from upadacitinib to adalimumab or vice versa, the proportion (95% CI) of patients with serious AEs and serious infections through 6 months postrescue was consistent with those observed for adalimumab and upadacitinib during comparable periods: for serious AEs and serious infections in patients rescued to upadacitinib, 8.8 (95% CI 5.32 to 14.24) and 3.8 (95% CI 1.74 to 7.99), respectively; for patients rescued to adalimumab, it was 6.7 (95% CI 4.25 to 10.54) and 3.8 (95% CI 0.85 to 4.56).

DISCUSSION

In this 48-week trial, clinical responses, including LDA and clinical remission by multiple validated metrics, as well as functional, pain, quality of life and fatigue responses, in patients randomised to upadacitinib plus MTX were superior to adalimumab plus MTX and were maintained consistently through 48 weeks, with a similar impact on radiographic inhibition and consistent with observations up to week 26.[11] Safety over 48 weeks remained consistent with observations during the first 26 weeks, including events observed after protocol-directed immediate treatment switches between upadacitinib and adalimumab despite a lack of washout. Furthermore, patients who had an insufficient response to initial treatment with upadacitinib or adalimumab and switched without washout to the other therapy were able to improve clinically with many able to achieve the treat-to-target goal of either clinical remission or at minimum LDA after 3 or 6 months of therapy.

Through 48 weeks, treatment with upadacitinib was associated with consistently higher levels of LDA and clinical remission than adalimumab, with approximately one-half and one-quarter of patients achieving LDA and clinical remission, respectively, by various composite definitions. Interestingly, the unique rescue rule based on CDAI LDA at week 26, when coupled with NRI imputation, affected the pattern of responses differently across endpoints in a consistent manner between the upadacitinib and adalimumab arms. LDA rates decreased slightly at week 30 before improving again, as patients not meeting CDAI LDA at week 26 had their week 26 (non-responder) status carried forward through week 48. Conversely, remission rates were stable or continued to increase from weeks 26 to 48 as non-rescued patients who had not yet achieved remission at week 26, although in LDA, had a chance to do so through week 48.

The SELECT-COMPARE study design uniquely incorporated a blinded rescue, with an immediate switch, for patients with an insufficient response to upadacitinib, adalimumab or placebo at or before week 26, as advocated by the treat-to-target principles. The proportion of patients rescued at week 14 is consistent with what has been observed in other clinical trials using similar rescue criteria.[15–17] In contrast to those trials, SELECT-COMPARE had three additional rescue visits including rescue for patients who did not meet LDA based on CDAI at week 26 explaining why the overall proportion of patients rescued was higher than in other clinical studies. Importantly, although clinical trials of JAK inhibitors have demonstrated robust outcomes in patients who were switched from a TNF-inhibitor for an inadequate response to a JAK inhibitor,[7 18 19] there is a lack of data on the outcomes of patients who are switched from a JAK inhibitor to a TNF inhibitor for the same reasons. This is the first prospective, blinded, randomised controlled trial which evaluated this scenario. While this study was not powered to assess which switch strategy is more efficacious, among patients who were rescued

from upadacitinib to adalimumab, the response rate increased after switch, although to a lesser extent than for patients rescued from adalimumab to upadacitinib. Still, further appropriately powered studies, including other bDMARDs and tsDMARDs, are needed to answer this important clinical question. In SELECT-COMPARE, the proportions of patients, on a group level, achieving clinical remission and LDA postswitch appeared slightly lower than those observed among the naive populations over the first 26 weeks. However, the results in patients rescued to upadacitinib from adalimumab were consistent with the observations in a previous study of upadacitinib in bDMARD-IR patients.[7]

This study addresses an important question relevant to clinical practice, where patients are often switched between treatments with different mechanisms of action without washout of a prior immunosuppressant. Based on the limited switch data in this study, no additional safety concerns were observed; however, larger studies are needed to more thoroughly evaluate this issue. Adalimumab was included as a long-term safety comparator, and patients and investigators remained blinded to switch between adalimumab and upadacitinib up to week 48. Treatment-emergent AEs, including serious and opportunistic infections, malignancies, MACE and VTE, appeared comparable between upadacitinib and adalimumab in this data set, except for the known HZ signal observed in patients receiving JAK inhibition.[18 20] The types of serious infections reported were generally consistent with those anticipated in a population of patients with moderately to severely active RA. Most opportunistic infections reported with upadacitinib exposure and all opportunistic infections with adalimumab exposure were non-serious mucosal candida infections. Rates of VTEs were within the reported range for the general RA population.[21 22] An integrated analysis across the five phase III SELECT studies will better characterise the overall AE profile of upadacitinib, in particular for rare events such as malignancies, NMSC and VTE.

Limitations of this 48-week study include that placebo was permitted only until week 26 (for ethical reasons) and that the rescue arms were not powered or designed to enable a valid statistical comparison for efficacy between the switch arms. Furthermore, only one bDMARD was used as a comparator; different results may have been observed had other bDMARDs been included.

In summary, responses were maintained with upadacitinib treatment over 48 weeks and were consistently significantly better than with adalimumab. The significant inhibition of radiographical progression at week 26 was maintained at week 48 and was comparable to adalimumab. Patients with insufficient response to either upadacitinib or adalimumab can benefit from switching to the other therapy. No new safety findings were observed with longer term exposure to upadacitinib, or in the period following the switch from adalimumab to upadacitinib.

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