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Clinical science

Impact of initial therapy with upadacitinib or adalimumab on achievement of 48-week treatment goals in patients with rheumatoid arthritis: *post hoc* analysis of SELECT-COMPARE

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Abstract

Objectives: Evaluate the importance of treatment sequencing in SELECT-COMPARE, assessing potential differences between starting upadacitinib or adalimumab therapy following inadequate MTX response.

Methods: Patients from SELECT-COMPARE were randomized to upadacitinib 15 mg once daily, placebo or adalimumab 40 mg. Per protocol, patients with <20% improvement in tender or swollen joint counts (weeks 14, 18, 22) or failure to achieve Clinical Disease Activity Index (CDAI) low disease activity (LDA) at week 26 were blindly switched from upadacitinib to adalimumab or vice versa. Treatment outcomes, including clinical remission/LDA, physical function, pain and a novel combined endpoint for deep response, were evaluated through 48 weeks and corresponding time-averaged response rates determined. Data were analysed by initial randomized group regardless of any subsequent switch in therapy.

Results: This *post hoc* analysis included 651 patients initially randomized to upadacitinib (of whom 252 switched to adalimumab) and 327 patients initially randomized to adalimumab (of whom 159 switched to upadacitinib). At week 48, patients randomized to either therapy demonstrated similar achievement of most treatment endpoints. Greater improvements in the total time spent in a lower disease state were observed for initial upadacitinib *vs* initial adalimumab therapy across most clinical and patient-reported outcomes through 48 weeks, and the median time to DAS28(CRP) <2.6/≤3.2 occurred 6–8 weeks earlier among those randomized to upadacitinib.

Conclusion: Following a modified treat-to-target strategy, rates of CDAI remission/LDA and DAS28(CRP) <2.6/≤3.2 at 48 weeks were similar, regardless of starting therapy. However, patients initially receiving upadacitinib reached treatment targets more quickly and spent more time in clinical targets over the initial 48 weeks of treatment.

Trial registration: ClinicalTrials.gov, https://clinicaltrials.gov, NCT02629159

Keywords: JAK inhibitors, bDMARD, clinical trials, RA, treatment strategy, treat-to-target

Rheumatology key messages

- Patients randomized to either upadacitinib or adalimumab therapy achieved similar clinical responses at week 48.
- Patients initiating on upadacitinib *vs* adalimumab attained treatment targets more quickly.
- Through 48 weeks, upadacitinib-randomized *vs* adalimumab-randomized patients spent more overall time in improved diseased states.

Introduction

The development and clinical use of TNF inhibitors (TNFis) and other biologic DMARDs (bDMARDs) with other mechanisms of action have transformed the management of RA over the past two decades [1, 2]. The introduction of oral targeted synthetic DMARDs (tsDMARDs), including Janus kinase inhibitors (JAKis), provide yet another alternative for patients who do not sufficiently respond to conventional

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synthetic DMARDs (csDMARDs) or bDMARDs [3]. Current guidelines from the ACR and EULAR include both JAKis and bDMARDs as viable second-line treatments in patients with active RA refractory to MTX [1, 2], although different regulatory agencies have contrasting perspectives in this regard, with the US Food and Drug Administration recently limiting approved use of JAKis to patients who have failed or are intolerant to one or more TNFi [4].

Treatment strategy plays a critical role in the management of RA. The treat-to-target (T2T) approach, which sets a primary goal of sustained remission or at least low disease activity (LDA) in a patient who cannot achieve remission, by a validated metric including examination of joints, has been shown to improve both clinical and functional outcomes [5]. For T2T to be successful, it is necessary to perform frequent monitoring of disease activity, with appropriate modification of medications if there is not satisfactory improvement in disease activity towards the target goal [2].

In the SELECT-COMPARE phase 3 trial, which enrolled patients with active RA despite MTX treatment, a higher proportion of patients randomized to the JAKi upadacitinib 15 mg once daily achieved remission or LDA by multiple metrics as well as DAS28(CRP) $<2.6/\leq3.2$ at week 26 compared with those randomized to placebo or adalimumab [6]. The unique study design of SELECT-COMPARE incorporated a modified T2T approach, in which patients who did not respond or showed an insufficient response to initial therapy [defined as not achieving Clinical Disease Activity Index (CDAI) LDA at week 26] with upadacitinib or adalimumab were blindly switched to the alternative therapy without washout. Clinical improvements were observed in both treatment switch groups through 48 weeks [7]. What has not been examined, however, is whether there is an effect of the initial therapy on achieving T2T goals. Here, we evaluate the effect of treatment order (i.e. whether the initial therapy was a JAKi or TNFi) via a *post hoc* analysis of 1-year treatment outcomes in patients who initiated treatment following randomization either to upadacitinib or adalimumab, regardless of whether they continued the same treatment or later switched to adalimumab or upadacitinib per T2T suggestions, respectively.

Methods

Patients

Study eligibility criteria and baseline demographics have been previously reported [6]. Briefly, patients who met 2010 ACR/EULAR classification criteria [8] with active RA, defined as having at least six swollen and six tender joints despite receiving MTX 15–25 mg/week, or $\geq$10 mg/week if intolerant of higher doses, for at least 3 months prior to baseline, were enrolled.

Ethics approval

SELECT-COMPARE (NCT02629159) was conducted in accordance with International Council for Harmonization guidelines, applicable regulations and the Declaration of Helsinki. Study-related protocols were approved by independent ethics committees and institutional review boards. Patients provided written informed consent to participate in the trial.

Study design and treatment

SELECT-COMPARE included a 48-week double-blind, active comparator-controlled period, followed by an ongoing long-term extension of up to 9 years (for a total study duration of 10 years; supplementary Fig. S1, available at *Rheumatology* online). Patients on background MTX were randomized 2:2:1 to upadacitinib 15 mg once daily, placebo (not included in the present analysis) or adalimumab 40 mg every other week. Double-blind rescue from upadacitinib to adalimumab or adalimumab to upadacitinib occurred at weeks 14, 18 and 22 in patients with <20% improvement from baseline in swollen or tender joint counts or at week 26 in patients who did not achieve LDA, as determined by CDAI $\leq$10. Initiation or modification of background RA medications (including CS, NSAIDs, acetaminophen/paracetamol) was allowed per investigator's discretion starting at week 26.

Efficacy and safety assessments

Efficacy assessments were conducted through 48 weeks and included the proportion of patients achieving clinical remission (defined by CDAI $\leq$2.8) or LDA (defined by CDAI $\leq$10) [9], DAS28(CRP) <2.6 or $\leq$3.2 [10, 11], Boolean remission [12], HAQ-Disability Index <0.5 (HAQ-DI; range 0–3) [13], patient's assessment of pain <20 (on 100 mm visual analogue scale) and $\geq$50% improvement from baseline, and a novel composite measure of 'deep response' (combining CDAI $\leq$2.8, HAQ-DI <0.5 and pain <20) that was developed and assessed in this analysis.

Safety assessments were based on available data up to week 48 for each patient. Treatment-emergent adverse events per 100 patient-years (PY) were summarized by initial randomization to upadacitinib or adalimumab, regardless of any subsequent switch in treatment. All safety data are reported as exposure-adjusted event rates.

Statistical analysis

All patients initially randomized to upadacitinib or adalimumab (both with background MTX), regardless of rescue between weeks 14–26, were included in this *post hoc* analysis. Efficacy data through 48 weeks were analysed by originally assigned randomized treatment group: randomized upadacitinib (includes continuous upadacitinib users as well as patients who were rescued to adalimumab) and randomized adalimumab (includes continuous adalimumab users as well as patients switched to upadacitinib). Non-responder imputation was applied for any missing response variables, and patients who prematurely discontinued were considered as non-responders for all subsequent visits after discontinuation. In contrast to the primary results from the study [6], patients who switched from upadacitinib to adalimumab (or vice versa) were still eligible to be considered as responders post-switch. Moreover, while the rescue strategies were prespecified, the analyses performed for this paper are *post hoc*, with nominal *P*-values provided throughout.

Summary statistics (n and the percentage of patients who responded) were generated for the above efficacy endpoints up to week 48. Time-averaged response rates were computed as the area under the curve of response rate standardized by the length of the study (48 weeks) and were used to evaluate the percentage of time patients spent in each response state [e.g. achieving response for the entire 48-week period would correspond to 100% (rate = 1.0)]. Time to initial CDAI

remission/LDA or DAS28(CRP) <2.6/≤3.2 response was estimated by the Kaplan–Meier method, and the log-rank test was used to evaluate whether the time to response differed between the groups. The median time for patients to attain CDAI LDA and DAS28(CRP) <2.6/≤3.2 was estimated. Of note, the median time to CDAI remission could not be calculated given that at least half of patients must achieve the response to determine median time and fewer than half of patients achieved remission; instead, the time needed for 25% of patients to achieve CDAI remission was determined. Differences in the numbers needed to treat (NNT) for initial upadacitinib *vs* initial adalimumab therapy were also calculated for ≥50% improvement in pain at weeks 12 and 48, as well as the 48-week average ≥50% improvement in pain (determined as the average ≥50% improvement in pain value from week 0 through week 48). Maintenance of response was defined as having never lost response at any visit during ~6 months (22–26 weeks) follow-up after initially attaining response before or at week 26. The predictive ability of key baseline characteristics and patient demographics (including age, gender, BMI, prior bDMARD use, duration of RA diagnosis, oral steroid use at baseline, disease activity scores at baseline, CRP, seropositivity, tender and swollen joint counts at baseline, patient's global assessment of disease activity, physician's global assessment of disease activity and HAQ-DI) was evaluated using concordance (c)-index.

Results

Patient disposition

Of the 1629 patients randomized, 651 received upadacitinib 15 mg once daily and 327 received adalimumab 40 mg every other week. Demographic and disease characteristics of the patients randomized to upadacitinib or adalimumab were balanced across treatment arms, as previously reported [6]. Through week 22, 19% and 24% of patients randomized to upadacitinib and adalimumab, respectively, were rescued to the other therapy (Fig. 1A). At week 26, a lower proportion of patients were again rescued in the randomized upadacitinib group (19% rescued to adalimumab) *vs* the randomized adalimumab group (25% rescued to upadacitinib) (Fig. 1B). In total, 39% of patients randomized to upadacitinib switched to adalimumab, whereas 49% of patients randomized to adalimumab switched to upadacitinib.

CDAI and DAS28(CRP) response

At week 48, similar proportions of patients initially randomized to upadacitinib or adalimumab therapy achieved CDAI remission/LDA or DAS28(CRP) <2.6/≤3.2 (Fig. 2A and B). However, patients initially randomized to upadacitinib demonstrated improvements more quickly than those randomized to adalimumab [by week 12, for instance, 13/41% *vs* 8/30% attained CDAI remission/LDA (nominal $P < 0.01$), while 29/45% and 18/29% achieved DAS28(CRP) <2.6/≤3.2

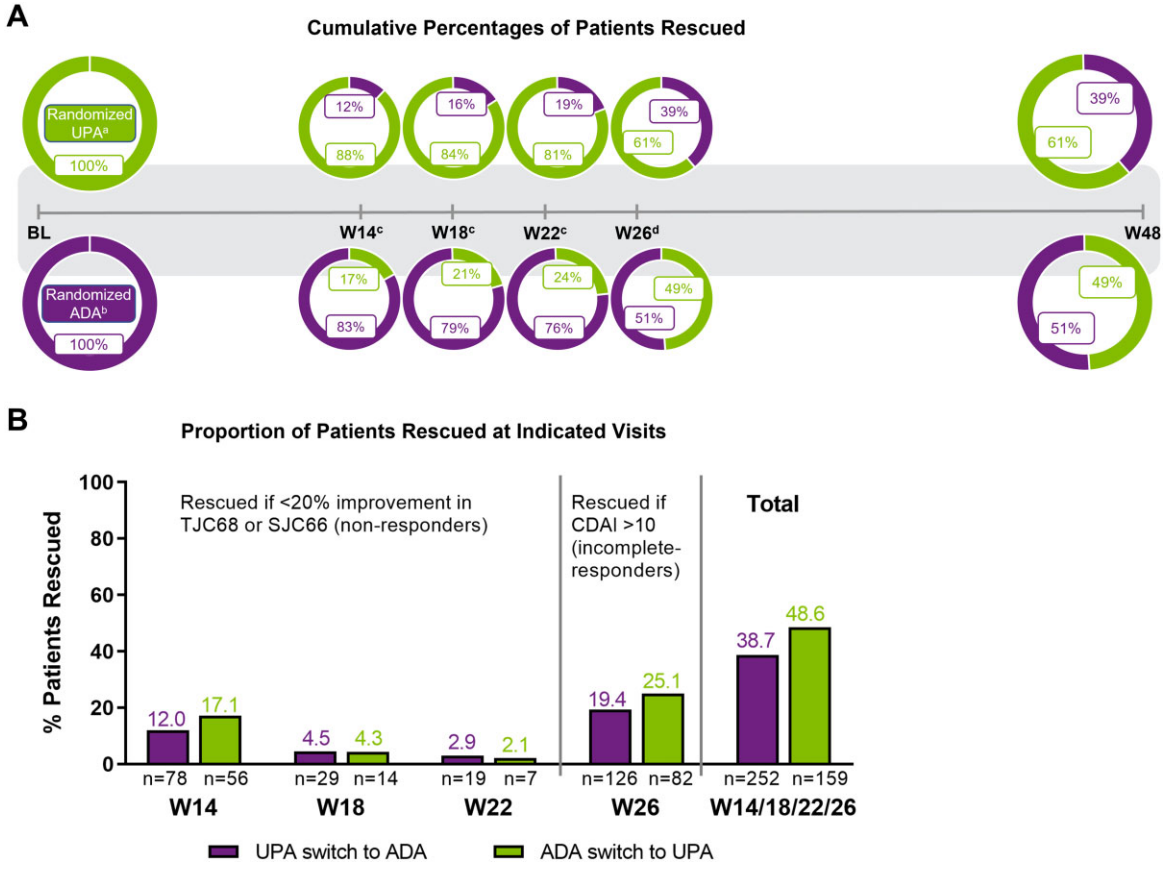

Figure 1. Proportions of patients over time contributing to the randomized upadacitinib and randomized adalimumab groups

(**A**) Circle charts indicate the percentages of patients in each group who were originally assigned to upadacitinib (green; $n = 651$) or adalimumab (purple; $n = 327$) and then either remained on that treatment or switched to the alternate therapy. [a]Randomized upadacitinib includes continuous upadacitinib users as well as patients who switched to adalimumab. [b]Randomized adalimumab includes continuous adalimumab users as well as patients who switched to upadacitinib. [c]Patients with less than 20% improvement from baseline in SJC or TJC were rescued at weeks 14, 18 and 22. [d]At week 26, patients who failed to achieve CDAI low disease activity were rescued. (**B**) Percent rescue based on the total number of patients randomized. ADA: adalimumab; BL: baseline; CDAI: Clinical Disease Activity Index; SJC: swollen joint count; TJC: tender joint count; UPA: upadacitinib; W: week.

(nominal $P < 0.001$), respectively]. Moreover, the time needed for 25% of patients to achieve CDAI remission was shorter among patients randomized to upadacitinib *vs* adalimumab (18 weeks *vs* 26 weeks), and the median time to CDAI LDA occurred 4 weeks earlier among those who initiated on upadacitinib (median time: 14 and 18 weeks, respectively). Similarly, the median time to achievement of DAS28(CRP) $<2.6/\leq 3.2$ was 6–8 weeks earlier among patients initially receiving upadacitinib *vs* adalimumab [median time to DAS28(CRP) $<2.6/\leq 3.2$ was 18/12 weeks *vs* 26/18 weeks]. When comparing the total time patients spent within a disease activity state (i.e. the time-averaged response rate), patients randomized to upadacitinib spent longer time in remission or LDA compared with those randomized to adalimumab. Specifically, the time-averaged response rates for CDAI remission among those randomized to upadacitinib and adalimumab, respectively, were 0.19 *vs* 0.14 (nominal $P = 0.012$), meaning that patients initially treated with upadacitinib were in CDAI remission 19% of the time over 48 weeks compared with 14% of the time among those initially treated with adalimumab (Fig. 2C). Likewise, patients randomized to upadacitinib spent more time in CDAI LDA and DAS28(CRP) $<2.6/\leq 3.2$ over 48 weeks [for randomized upadacitinib *vs* randomized adalimumab, the time-averaged response rates were as follows: CDAI LDA, 0.47 *vs* 0.41 (nominal $P = 0.009$); DAS28(CRP) <2.6, 0.36 *vs* 0.29 (nominal $P = 0.002$); and DAS28(CRP) ≤ 3.2, 0.50 *vs* 0.43 (nominal $P = 0.004$)] (Fig. 2D). Consistent results were also observed for $\geq 50\%$ improvement from baseline in CDAI and DAS28(CRP), with patients randomized to upadacitinib spending more total time in improved disease activity states over 48 weeks than those randomized to adalimumab (nominal $P < 0.05$) (supplementary Fig. S2, available at *Rheumatology* online).

Physical function and pain

Generally similar results were observed for HAQ-DI and patient's assessment of pain. Although comparable percentages of patients attained HAQ-DI <0.5 or pain scores <20 (on 100 mm visual analogue scale) at week 48 (Fig. 3A and B), patients randomized to upadacitinib spent more total time in the improved disease state through 48 weeks. Specifically, the time-averaged responses for those randomized to upadacitinib and adalimumab, respectively, were 0.28 *vs* 0.21 for HAQ-DI <0.5 (nominal $P = 0.004$) and 0.38 *vs* 0.33 (nominal $P = 0.037$) for pain <20 (Fig. 3C and D). In contrast, patients spent a similar proportion of time with $\geq 50\%$ improvement in pain over 48 weeks regardless of whether upadacitinib or adalimumab was the initial therapy and showed similar attainment of $\geq 50\%$ improvement in pain at week 48 (61% on randomized upadacitinib *vs* 62% on randomized adalimumab) (supplementary Fig. S3, available at *Rheumatology* online). NNTs for $\geq 50\%$ improvement in pain for initial upadacitinib *vs* initial adalimumab treatment numerically favoured upadacitinib at week 12 (NNT 7.4, which means that approximately seven patients would need to initially receive upadacitinib to get one additional patient who does better than they would when receiving initial adalimumab therapy). At week 48, the NNT showed a marginally negative correlation with randomized upadacitinib *vs* adalimumab (NNT –250), although the overall 48-week average NNT for $\geq 50\%$ improvement in pain numerically favoured initial upadacitinib over initial adalimumab (NNT 33).

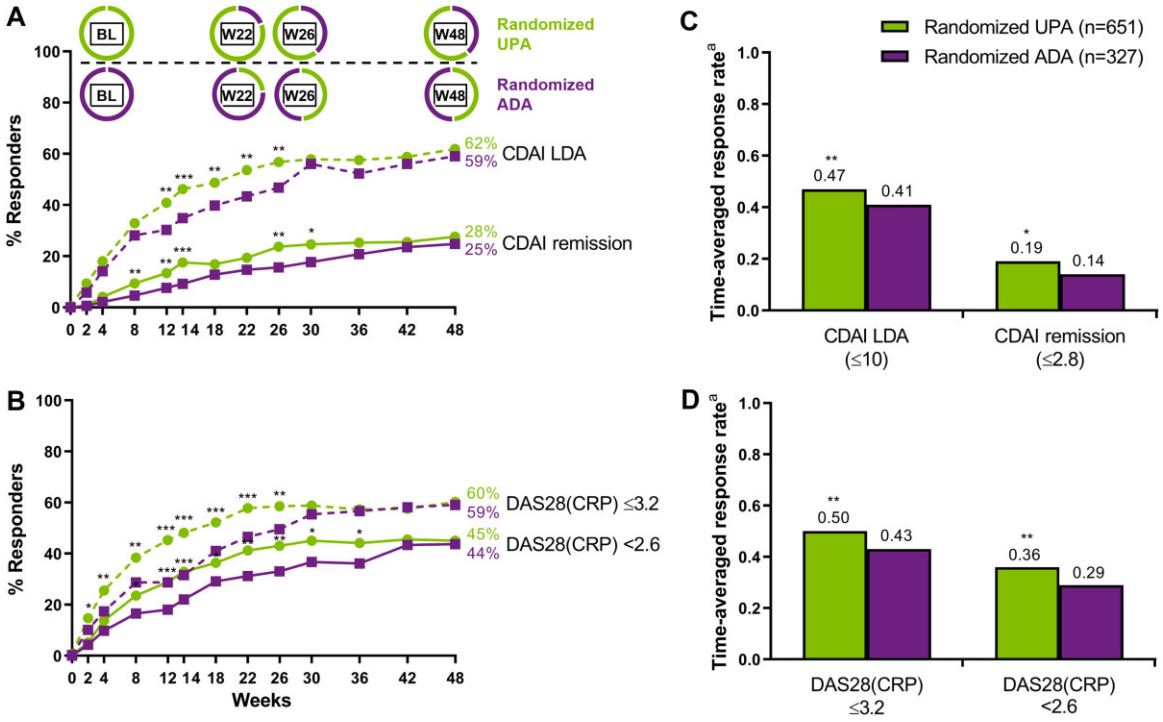

Figure 2. Achievement of CDAI and DAS28(CRP) over 48 weeks by randomized therapy with upadacitinib or adalimumab

*Nominal $P < 0.05$, **$P < 0.01$, ***$P < 0.001$ comparing upadacitinib *vs* adalimumab as initial therapy. Blinded rescue from upadacitinib to adalimumab or adalimumab to upadacitinib occurred at weeks 14, 18 and 22 for patients with <20% improvement in TJC or SJC and at week 26 for CDAI >10. Data were analysed by original randomized group (upadacitinib or adalimumab) regardless of any subsequent switch in therapy; non-responder imputation was applied. [a]Calculated as area under the curve of response rate standardized by length of study (48 weeks). ADA: adalimumab; CDAI: Clinical Disease Activity Index; DAS28(CRP): disease activity score in 28 joints; LDA: low disease activity; SJC: swollen joint count; TJC: tender joint count; UPA: upadacitinib; W: week.

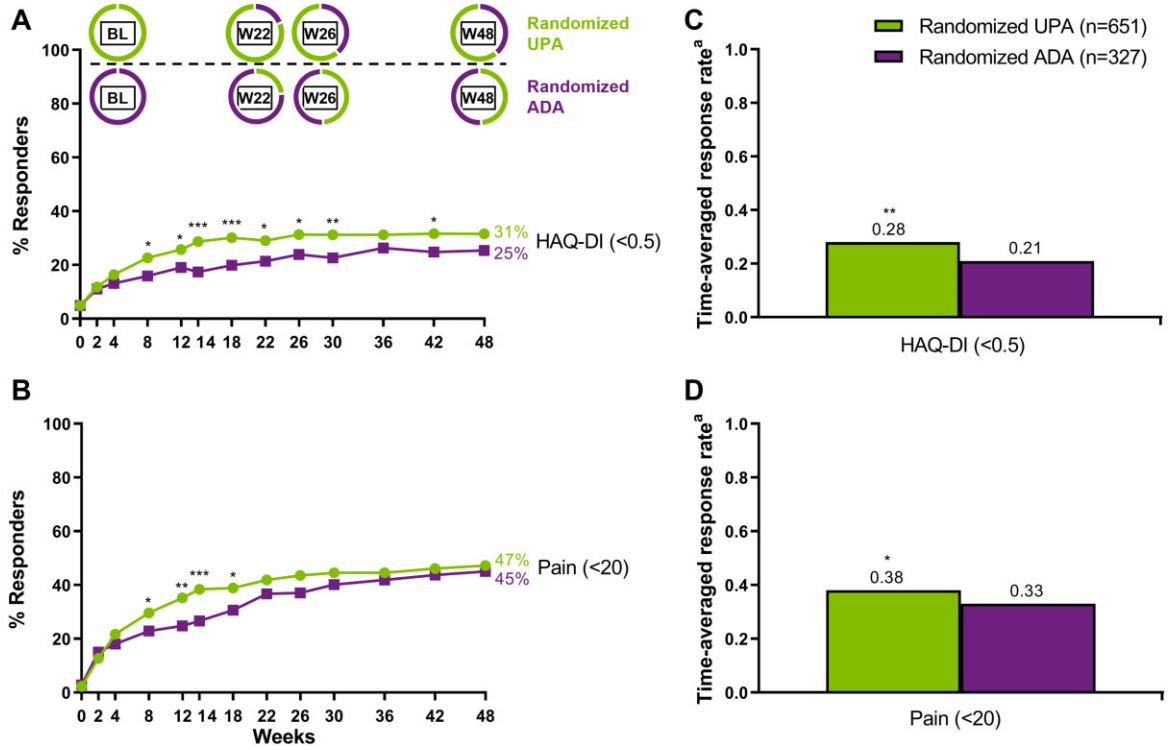

Figure 3. Achievement of HAQ-DI <0.5 and pain <20 over 48 weeks by randomized therapy with upadacitinib or adalimumab

*Nominal $P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for upadacitinib vs adalimumab as initial therapy. Treatment groups are by initial randomization (upadacitinib or adalimumab) regardless of any subsequent switch in therapy; non-responder imputation was applied. [a]Calculated as area under the curve of response rate standardized by length of study (48 weeks). HAQ-DI: 0 to 3 scale; patient's assessment of pain: 0 to 100 mm scale. ADA: adalimumab; HAQ-DI: HAQ-Disability Index; LDA: low disease activity; UPA: upadacitinib; W: week.

Deep response and Boolean remission

Over 48 weeks, a slightly higher proportion of patients randomized to upadacitinib achieved a novel combined endpoint indicative of a deep response (defined as CDAI ≤2.8, HAQ-DI <0.5 and pain score <20) at each time point compared with those randomized to adalimumab (18% *vs* 13% at week 48; nominal $P = 0.049$) (Fig. 4A). The time-averaged response rate over 48 weeks for this combined endpoint was also higher for those initially randomized to upadacitinib than adalimumab (0.12 *vs* 0.08; nominal $P = 0.005$) (Fig. 4B).

Higher proportions of patients randomized to upadacitinib achieved the stringent Boolean-based definition of remission from week 4–30, with both treatment strategies showing similar responses from week 36–48 (at week 48, 23% and 21% achieved Boolean remission on randomized upadacitinib and adalimumab, respectively; supplementary Fig. S4, available at *Rheumatology* online). Patients initially receiving upadacitinib demonstrated an improved time-averaged response rate compared with those randomized to adalimumab (0.15 *vs* 0.11; nominal $P = 0.006$).

Maintenance of response

In keeping with the time-averaged response data, patients randomized to upadacitinib showed consistently better maintenance of response earlier in their treatment time course than those randomized to adalimumab across all examined endpoints (Fig. 5). After achieving an initial clinical response, similar proportions of patients randomized to either therapy maintained their week 26 CDAI and DAS28(CRP) responses during 6-month follow-up, with a numerical trend favouring initial upadacitinib treatment across most disease activity measures (Fig. 6). For instance, a numerically higher proportion of patients maintained CDAI remission/LDA on initial upadacitinib *vs* initial adalimumab (35/44% *vs* 23/36%) and DAS28(CRP) ≤3.2 (39% *vs* 35%), whereas the same proportion of patients (30%) maintained DAS28(CRP) <2.6 responses regardless of starting therapy.

Predictors of response

Baseline disease activity weakly predicted CDAI remission and LDA at week 48 but was not predictive of ≥50% improvement in CDAI achievement at week 48 (supplementary Table S1, available at *Rheumatology* online). Overall, there were no clear predictors among examined variables (including age, gender, BMI, duration of RA, oral steroid use at baseline, HAQ-DI and other disease activity measurements) that could identify responders to either treatment approach.

Safety

Exposure-adjusted event rates were generally similar in patients who initiated with either upadacitinib or adalimumab for any adverse event (AE; 300 events/100 PY and 274 events/100 PY), serious AEs (12 events/100 PY and 19 events/100 PY), AEs leading to discontinuation of study drug (9 events/100 PY and 11 events/100 PY) and deaths (0.8 events/100 PY for both) (supplementary Fig. S5, available at *Rheumatology* online).

Discussion

While many therapeutic options are now available for RA, there is no information to guide clinicians on which treatment

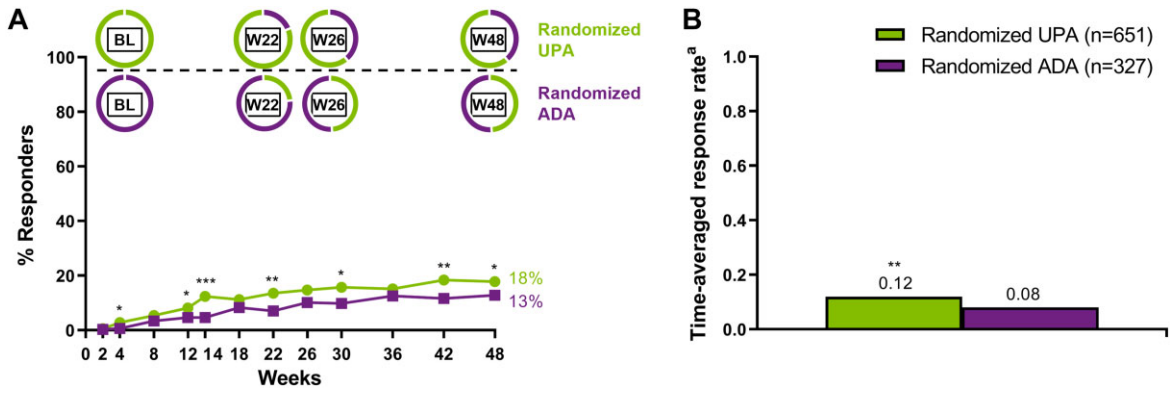

Figure 4. Achievement of deep response over 48 weeks by randomized therapy with upadacitinib or adalimumab

*Nominal $P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for upadacitinib *vs* adalimumab as initial therapy. Treatment groups are by initial randomization (upadacitinib or adalimumab) regardless of any subsequent switch in therapy; non-responder imputation was applied. [a]Calculated as area under the curve of response rate standardized by length of study (48 weeks). Composite novel endpoint for 'deep response' includes CDAI ≤2.8, HAQ-DI <0.5 and pain <20. ADA: adalimumab; BL: baseline; CDAI: Clinical Disease Activity Index; DAS28(CRP): disease activity score in 28 joints; HAQ-DI: HAQ-Disability Index; LDA: low disease activity; UPA: upadacitinib; W: week.

should be initially used following an inadequate response to csDMARD therapy. Current treatment guidelines of the professional societies highlight the parity of approved bDMARDs and tsDMARDS to obtain desirable treatment outcomes [1, 2]. SELECT-COMPARE offers a unique opportunity to investigate the importance of treatment sequencing in RA with respect to clinical efficacy and identify potential advantages of upadacitinib or adalimumab as a patient's initial therapy after csDMARDs.

When employing a protocol-directed treatment switch following a modified T2T strategy, rates of CDAI remission or LDA were ∼25% and ∼60%, respectively, at week 48 and similar between patients initially randomized to upadacitinib or adalimumab, although higher numbers of patients randomized to adalimumab required rescue to upadacitinib. Despite achieving comparable disease activity targets at week 48, patients randomized to upadacitinib reached treatment targets more quickly than those randomized to adalimumab and spent more time in clinical remission or LDA by multiple clinical metrics over the study period. Similar benefits were observed for initial upadacitinib *vs* initial adalimumab in key indicators of patient functional ability, as assessed by HAQ-DI, and patients in the initial upadacitinib group experienced more time with reduced pain (<20) over 48 weeks, although the time-averaged response rates for ≥50% improvement in pain were comparable regardless of starting therapy. Patients who were initially treated with upadacitinib also showed numerically better trends in sustaining an initially good clinical response during a 6-month follow-up period.

Loss of physical function and control over pain are among the most significant unmet needs in RA [14, 15]. Further, patient-reported outcomes, including HAQ-DI and pain, have a major effect on patient satisfaction and persistence with therapy [16]. In the interest of more holistically addressing these domains, we developed a novel endpoint for 'deep response' that combines normal physical function (HAQ-DI <0.5 [17]) and pain relief (patient's assessment of pain <20) together with clinical control (CDAI ≤2.8). Although this is not a validated metric, it is notable that higher proportions of patients randomized to upadacitinib *vs* adalimumab achieved the combined endpoint for deep response at 48 weeks, with correspondingly greater time spent in the improved disease state compared with patients randomized to adalimumab.

In terms of the radiographic hallmarks of RA, upadacitinib 15 mg and adalimumab therapy were previously shown to reduce radiographic progression compared with placebo at 6 months [18], and both treatments continued to inhibit structural progression through 2 years in SELECT-COMPARE [19].

JAK inhibition has been previously suggested to require a shorter time for pain relief and control of clinical symptoms [20, 21] as also observed in this analysis for upadacitinib compared with adalimumab. Faster achievement of clinical targets is particularly relevant in daily clinical practice settings as it is associated with persistence on therapy and is a strong predictor of long-term outcomes [22–25]. In this study, patients initially treated with upadacitinib achieved treatment endpoints more rapidly than those who initiated on adalimumab. Indeed, the median time for patients to achieve CDAI LDA was 4 weeks sooner among patients randomized to upadacitinib *vs* adalimumab, with attainment of DAS28(CRP) <2.6/≤3.2 also occurring 6–8 weeks earlier among those who initiated on upadacitinib.

Early achievement of treatment targets, with a primary goal of remission, not only leads to better physical function and patient quality of life [23, 26] but also could decrease the risk of adverse events of special interest (AESI) associated with chronic systemic inflammation. As a systemic inflammatory disease that can involve other tissues and organs in addition to the joints, RA patients have been observed to have an increased risk of heart disease, venous thromboembolism (VTE) and other disorders [27–30]. In turn, early resolution of inflammation and deeper response are associated with reduced risk of MACE, VTE, malignancies and serious infection [27, 31–33]. Thus, optimizing the treatment sequence to allow faster attainment of sustained remission, or perhaps at least LDA, could play an important role in decreasing these RA comorbidities.

Recently, potential safety issues were reported in ORAL Surveillance, a post-marketing safety study of another JAKi (tofacitinib) involving an older population enriched for patients with cardiovascular (CV) risk factors (≥50 years of age with one or more CV risk factor) [34]. Numerically higher rates of several AESIs, including CV disease and malignancies,

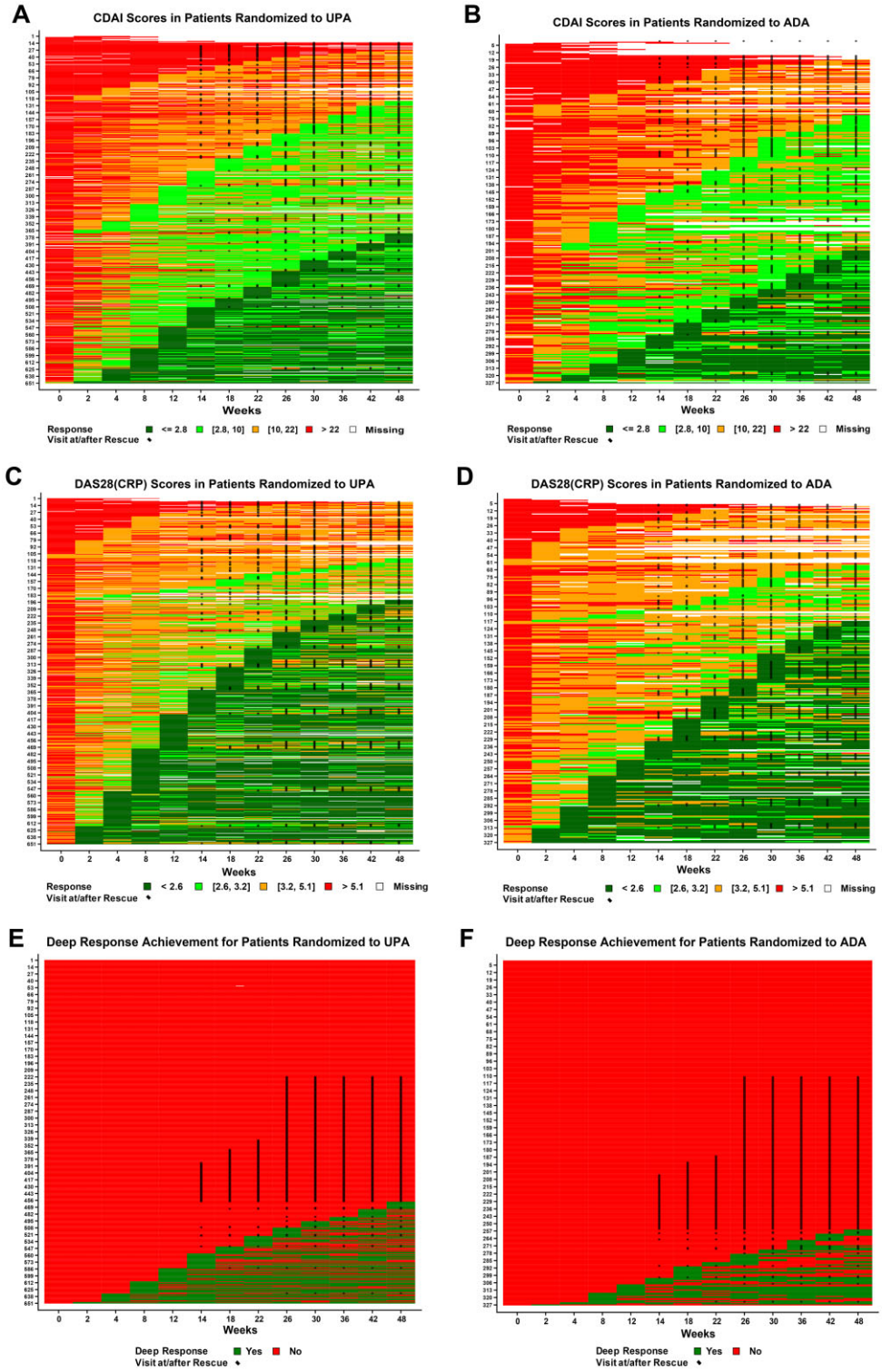

Figure 5. Heat map of CDAI, DAS28(CRP), and deep response activity among patients randomized to upadacitinib or adalimumab

Treatment groups are by initial randomization (upadacitinib or adalimumab) regardless of any subsequent switch in therapy. An asterisk indicates that patients were on rescue therapy when disease activities were evaluated. 'Deep response' is a composite endpoint that includes CDAI ≤2.8, HAQ-DI <0.5 and pain <20. ADA: adalimumab; CDAI: Clinical Disease Activity Index; DAS28(CRP): disease activity score in 28 joints; HAQ-DI: HAQ-Disability Index; LDA: low disease activity; UPA: upadacitinib; W: week.

were observed in patients receiving tofacitinib *vs* a TNFi. In contrast to ORAL Surveillance, SELECT-COMPARE enrolled a population of typical RA patients and did not enrich for patients at risk for CV events, nor was SELECT-COMPARE powered to show safety differences *vs* adalimumab. However, in keeping with the importance of tight disease control and inflammation reduction, a recent *post hoc* analysis of ORAL Surveillance suggests that one of the risk

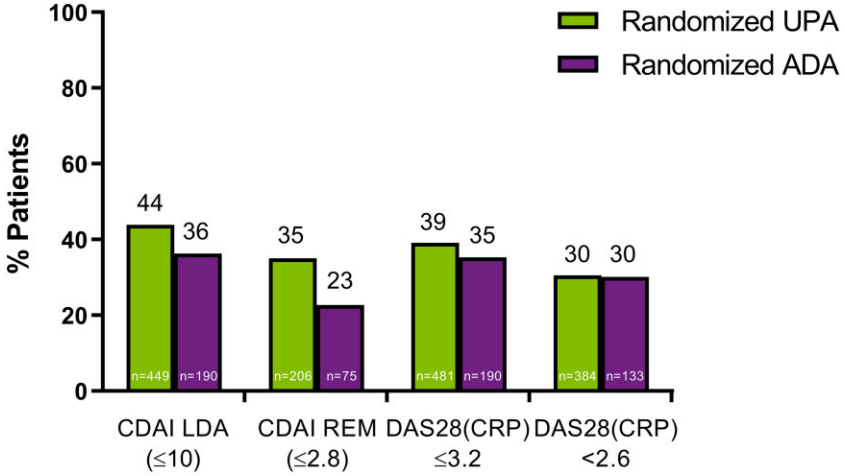

Figure 6. Proportion of patients maintaining week 26 CDAI and DAS28(CRP) responses during 6-month follow-up

Data reported as observed. Maintaining response defined as never losing response at any visit during approximately 6 months (22–26 weeks) follow-up after first achieving response before or at week 26. *n* indicates the number of patients who achieved response at or before week 26. Treatment groups are by initial randomization (upadacitinib or adalimumab) regardless of any subsequent switch in therapy. ADA: adalimumab; CDAI: Clinical Disease Activity Index; DAS28(CRP): disease activity score in 28 joints; LDA: low disease activity; REM: remission; UPA: upadacitinib.

factors for some of these AESIs, including MACE and VTE, was related to disease activity, with patients in remission experiencing lower levels of these AEs compared with those with active RA [35].

The overall rate of AEs, serious AEs and deaths were similar with either upadacitinib or adalimumab as the initiating therapy in this study. Although AESIs were not evaluated here, overall safety has been reported previously for SELECT-COMPARE and in an integrated phase 3 safety analysis of upadacitinib [6, 19, 36]. In brief, safety over 3 years was generally comparable between upadacitinib 15 mg and adalimumab for malignancies, MACE, VTE and deaths, while higher rates of some AEs such as herpes zoster and CPK elevation were reported on upadacitinib [19]. These publications, however, did not address the effect of disease activity or other known risk factors for these events.

A limitation of this study is that patients were analysed by their original randomized group (upadacitinib or adalimumab) regardless of any subsequent switch in therapy. Separate analyses of those who remained on their initial treatment assignment without switch was not conducted here; however, a prior report from SELECT-COMPARE demonstrated consistent numerically higher attainment of CDAI remission/LDA and DAS28(CRP) $<2.6/\leq 3.2$ through 48 weeks among those who stayed on continuous upadacitinib *vs* adalimumab [7]. Another limitation is that this was a *post hoc* analysis not based on pre-specified endpoints and should thus be treated with caution. Further, the results of this study need to be more broadly evaluated in clinical practice settings without the constraints of a clinical trial. Despite these limitations, this study identifies early efficacy benefits of upadacitinib in favour of adalimumab, both with concomitant MTX, in a robustly controlled clinical trial setting following a modified T2T strategy.

In summary, this study demonstrates that patients initially randomized to upadacitinib *vs* adalimumab reached treatment targets more quickly and spent a greater amount of time in clinical control, along with more time with improved physical function. Our findings provide the first data evaluating the importance of treatment order with JAKi *vs* TNFi as initial therapy, suggesting that a JAKi-first strategy leads to more rapid improvements in treatment outcomes following csDMARD failure. This study, combined with an in-depth review of the safety profiles, should help physicians in selecting an optimal treatment plan for each patient.

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Data availability 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 datasets), and other information (e.g. protocols and clinical study reports, analyses plans), 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 statement. Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript, and the data will be accessible for 12 months, with possible extensions considered. For more information on the data sharing process, or to submit a request, see https://www.abbvie.com/ourscience/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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