The impact of C-reactive protein levels on the effectiveness of upadacitinib in patients with rheumatoid arthritis: a 12-month prospective, non-interventional German study

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Abstract

Objective

We investigated whether the effectiveness of upadacitinib in rheumatoid arthritis (RA) treatment is affected by baseline CRP levels in a real-world setting.

Methods

UPwArds was a prospective, non-interventional study. Patients had moderate-to-severe RA and an inadequate response or intolerance to ≥1 disease-modifying anti-rheumatic drug (DMARD). The primary endpoint was clinical remission (Clinical Disease Activity Index [CDAI] ≤2.8) at 6 months. Secondary endpoints at 12 months included clinical remission and low disease activity assessed by CDAI and Simple Disease Activity Index criteria, DAS28-CRP <2.6/≤3.2, and patient-reported outcomes. The impact of baseline CRP levels (normal vs. above the upper limit of normal [ULN]) on primary and secondary endpoints was evaluated. The effect of concomitant MTX and prior inadequate response to biologic or targeted synthetic DMARDs (b/tsDMARD-IR) on the effectiveness of upadacitinib was also assessed. Safety was evaluated through 12 months.

Results

518 patients were included in the effectiveness analyses. At 6 months, 24.4% of patients achieved the primary endpoint (CDAI ≤2.8). At 12 months, similar proportions of patients with normal CRP and CRP above the ULN at baseline achieved CDAI ≤2.8 (27.3% and 29.1%) and other key secondary endpoints. The effectiveness of upadacitinib was comparable with and without concomitant MTX and in b/tsDMARD-naive and b/tsDMARD-IR patients. The safety results were consistent with the known safety profile of upadacitinib; no new safety signals were identified.

Conclusion

Upadacitinib therapy was effective for RA in a real-world setting. Baseline CRP levels had no significant impact on the effectiveness of upadacitinib.

Key words

anti-rheumatic agents, arthritis, rheumatoid, biological therapy, Janus kinase inhibitors, observational study

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Data availability statement
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Funding and competing interests: see page 745.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that affects around 20 million people globally (1). RA leads to progressive cartilage and bone damage, which is associated with significant disability, pain, and reduced quality of life (2). Initial treatment for RA typically includes conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as MTX (3, 4). However, as the disease progresses, most patients require advanced therapies, including biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), namely Janus kinase (JAK) inhibitors; both are highly effective for inducing clinical remission and/or lowering disease activity (5, 6).

In Germany, the reversible and selective JAK inhibitor upadacitinib is indicated for the treatment of adults with moderately to severely active RA who have had an inadequate response or intolerance to ≥1 DMARD (6, 7). Upadacitinib demonstrated efficacy in the SELECT phase 3 clinical trial programme, with an acceptable and well-characterised safety profile (8-12). However, real-world data for upadacitinib are limited.

CRP is an acute-phase reactant that has been extensively used as a marker of inflammation (13). In inflammatory diseases such as RA, it is often used to monitor disease activity during treatment (14). Clinical trials of new therapies for RA, including the SELECT programme, typically enrol patients with elevated CRP or ESR. However, there is growing evidence to suggest that individual CRP/ESR levels do not always correlate with disease activity (15, 16). For example, in the SELECT-NEXT study, upadacitinib was efficacious for inducing disease remission regardless of CRP levels in patients with moderately to severely active RA with an inadequate response to csDMARDs (csDMARD-IR) (17). Therefore, the requirement for elevated CRP and/or ESR levels as inclusion criteria in clinical trials may exclude some patients with active RA from receiving appropriate treatment (16). Further research on patients with active disease without CRP elevation is needed to improve our understanding.

Therefore, we conducted a prospective, non-interventional real-world study in Germany to assess whether the effectiveness of upadacitinib monotherapy or combination therapy with MTX for the treatment of RA is affected by baseline CRP levels.

Methods

Study design and patient population

UPwArds was a prospective, multicentre, non-interventional cohort study evaluating the impact of baseline CRP level on the real-world effectiveness of upadacitinib when used as monotherapy or in combination with MTX in patients with RA who were initiating upadacitinib in German clinical practice (ClinicalTrials.gov NCT04267536) (online Supplementary Fig. S1). The decision to initiate upadacitinib was made by the treating physician prior to enrolment. Patients received upadacitinib 15 mg once daily alone or in combination with MTX according to the German label and were followed up for 12 months. Per protocol, it was planned that approximately 50% of patients should be treated with monotherapy and 50% should be treated with upadacitinib plus MTX combination therapy.

Patients were included in the study if they were aged ≥18 years, had moderately to severely active RA, a swollen joint count of ≥3 joints included in the 28-joint DAS (DAS28) (18), and had an inadequate response or intolerance to ≥1 DMARD. A CRP measurement was required at baseline or ≤4 weeks prior to baseline at a timepoint when their prednisolone equivalent dose of glucocorticoids was ≤10 mg/day for ≥7 days. Patients were not eligible if they could not be treated with upadacitinib according to the German label, had received prior upadacitinib treatment, had received treatment with sarilumab or tocilizumab within 8 weeks before the CRP level for inclusion was measured, were currently participating in interventional research, or were unwilling or unable to complete the patient-reported outcome (PRO) questionnaires.

UPwArds was conducted according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guide-

lines, applicable regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Hannover Medical School, and all patients provided written informed consent before study participation.

Outcome measures

The primary endpoint was the proportion of patients achieving clinical remission (Clinical Disease Activity Index [CDAI] ≤2.8) (19) after 6-month follow-up. Secondary endpoints assessed through 12 months included: the proportion of patients achieving clinical remission (CDAI ≤2.8); Simple Disease Activity Index (SDAI) ≤3.3; the proportion of patients with DAS28-CRP <2.6 or DAS28-ESR <2.6; the proportion of patients achieving low disease activity (LDA) defined as CDAI ≤10 or SDAI ≤11; DAS28-CRP ≤3.2 or DAS28-ESR ≤3.2; and mean change from baseline in CDAI, SDAI, DAS28-CRP and DAS28-ESR. Other secondary endpoints included PROs, such as pain, fatigue and functionality assessed through 12 months. Achievement of clinical remission or LDA by CDAI or SDAI definitions, DAS28-CRP <2.6/≤3.2 and PRO endpoints, was also assessed by treatment group (upadacitinib monotherapy or upadacitinib plus MTX). Analysis of clinical remission or LDA was also performed by prior b/tsDMARD therapy. The impact of baseline CRP levels (normal and above the upper limit of normal [ULN]) on the primary endpoint, LDA, remission, pain and fatigue, was evaluated.

Assessments

Only data that were routinely collected during a regular visit were collected and documented. Data on disease activity (physician's global assessment, patient's global assessment, tender joint count [28 joints] and swollen joint count [28 joints]) for calculation of effectiveness outcome measures, CRP level and PROs, including the functional ability questionnaire (FFbH, Funktionsfragebogen Hannover; converted into internationally used HAQ-Disability Index [HAQ-DI] values) (20), RA Impact of Disease score (RAID), pain and fatigue numeric rating scales from 0 to 10 within RAID, morning stiffness severity and duration, 12-item Short Form health status survey and Patient Health Questionnaire-9 (PHQ-9) were collected at baseline and after 1, 3, 6, 9 and 12 months.

Safety was assessed throughout the 12-month observation period by collection of adverse event (AE) data. AEs of special interest (AESIs) assessed were based on the known safety profiles of JAK inhibitors (21), and included serious infections, opportunistic infections (excluding herpes zoster and tuberculosis), herpes zoster, active tuberculosis, malignancy (excluding non-melanoma skin cancer [NMSC]), NMSC, hepatic disorder, gastrointestinal perforation, major adverse cardiovascular events, venous thromboembolism, creatine phosphokinase elevation and weight gain. Patients who discontinued upadacitinib were withdrawn from the study.

Statistical analysis

Effectiveness analyses were conducted using the intention-to-treat (ITT) population, which included all patients enrolled with ≥1 follow-up visit. Safety analyses were conducted using the safety analysis set, which included all enrolled patients.

Effectiveness rates were estimated with their corresponding (adjusted) 95% confidence intervals (CIs) and changes in categories were analysed using the McNemar-Bowker test for two and more categories, respectively. Differences between means (changes from baseline) were evaluated using one-sample *t*-tests. The Bonferroni test was used to adjust for multiple testing for secondary endpoints assessed by visit. Analyses were based on as-observed data per visit without imputation of missing data. For effectiveness and safety analyses by treatment group, patients were assigned to upadacitinib monotherapy or upadacitinib plus MTX based on MTX therapy at baseline since upadacitinib treatment was documented during follow-up visits.

The impact of baseline CRP levels on the probability of achieving clinical remission (CDAI ≤2.8) at 6 months (primary endpoint) was analysed using a multivariable logistic regression model with baseline variables (age [years], sex [male/female], ACPA [positive/negative/unknown], RF [positive/negative/unknown], BMI [kg/m^2], number of previous b/tsDMARDs [0/1–2/>2], pain, RAID score, PHQ-9 score [<10/10–15/>15], number of comorbidities, erosions [yes/no/unknown], systemic glucocorticoids [yes/no/unknown] and dosage of MTX [only in the upadacitinib plus MTX group (mg/week)]). Potential confounders were determined through bootstrapping and included in the model. Baseline variables that were selected into the model in ≥60% of the bootstrap samples were chosen as possible predictors. The variable selection was performed separately within the upadacitinib monotherapy and upadacitinib plus MTX treatment groups. Baseline CRP was evaluated using its square root-transformed values because of non-normal distribution and included in the model as a fixed variable. To account for possible termination of MTX treatment during the study, a sensitivity analysis modelling remission (CDAI ≤2.8) at 6 months was performed as a combined analysis of all patients with a generalised linear mixed-model approach and using all the variables selected within the separate upadacitinib monotherapy and upadacitinib plus MTX treatment groups. For secondary endpoints, exploratory, unadjusted analyses of effectiveness rates were performed for categorical baseline CRP (normal and above the ULN).

Safety data are reported as numbers of AEs, and exposure-adjusted event rates (EAERs; events [E]/100 patient-years [PY]) with corresponding 95% CI.

Results

Patients

Data were collected from 50 rheumatology outpatient clinics and office-based rheumatologists throughout Germany between 6 February 2020 and 1 February 2022. In total, 533 patients were enrolled, assessed at baseline and assigned to treatment groups (upadacitinib monotherapy, n=260; upadacitinib plus MTX, n=273) with data available at 6 and 12 months for 453 (85.0%) and 371 (69.6%) patients, respectively

Table I. Baseline demographics and clinical characteristics of all enrolled patients.

n (%) unless otherwise stated	UPA (n=260)	UPA + MTX (n=273)	Total (n=533)
Female	213 (81.9)	193 (70.7)	406 (76.2)
Mean (SD) age, years	57.8 (13.2)	58.0 (11.4)	57.9 (12.3)
Age ≥65	75 (28.8)	77 (28.2)	152 (28.5)
Mean (SD) BMI, kg/m^2	27.4 (5.3)	28.0 (5.8)	27.7 (5.6)
Mean (SD) RA duration, years*	9.4 (8.3)	8.6 (7.7)	9.0 (8.0)
Mean (SD) CDAI	24.8 (10.1)	25.9 (10.9)	25.4 (10.5)
Mean (SD) SDAI	26.1 (10.4)	27.1 (11.4)	26.6 (10.9)
Mean (SD) DAS28-CRP	4.6 (1.0)	4.6 (1.0)	4.6 (1.0)
Mean (SD) HAQ-DI†	1.3 (0.7)	1.3 (0.6)	1.3 (0.6)
Mean pain (SD)‡	6.2 (2.2)	6.2 (2.3)	6.2 (2.2)
Mean fatigue (SD)‡	5.6 (2.6)	5.4 (2.6)	5.5 (2.6)
RF+§	133 (67.2)	151 (67.7)	284 (67.5)
ACPA+‖	94 (69.1)	97 (62.2)	191 (65.4)
Mean (SD) CRP, mg/L	12.5 (18.4)	11.6 (17.2)	12.0 (17.8)
CRP >upper limit of normal	138 (53.1)	158 (57.9)	296 (55.5)
Any comorbidities**	200 (76.9)	209 (76.6)	409 (76.7)
History of hypertension	106 (40.8)	104 (38.1)	210 (39.4)
History of coronary heart disease	22 (8.5)	13 (4.8)	35 (6.6)
History of apoplexy	2 (0.8)	3 (1.1)	5 (0.9)
History of myocardial infarction	6 (2.3)	3 (1.1)	9 (1.7)
History of diabetes Type II	25 (9.6)	20 (7.3)	45 (8.4)
History of hyperlipidaemia	28 (10.8)	36 (13.2)	64 (12.0)
Prior b/tsDMARDs	169 (65.0)	155 (56.8)	324 (60.8)
Prior TNFis††	142 (54.6)	120 (44.0)	262 (49.2)
Prior IL-6is‡‡	47 (18.1)	42 (15.4)	89 (16.7)
Prior abatacept	32 (12.3)	29 (10.6)	61 (11.4)
Prior rituximab	12 (4.6)	13 (4.8)	25 (4.7)
Prior tsDMARDs§§	54 (20.8)	43 (15.8)	97 (18.2)
Concomitant glucocorticoids	115 (44.2)	134 (49.1)	249 (46.7)
Mean (SD) glucocorticoid dose, mg/day ‖‖	7.4 (5.3)	6.6 (4.7)	7.0 (5.0)

For UPA, UPA + MTX and total, respectively: *n=256, 269 and 525; †n=254, 268 and 522; ‡n=259, 273 and 532; §n=198, 223 and 421; ‖n=136, 156 and 292; ‖‖n=115, 134 and 249.
** Includes all comorbidities, not limited to those listed.
†† Adalimumab, etanercept, infliximab, golimumab or certolizumab pegol
‡‡ Sarilumab or tocilizumab
§§ Baricitinib or tofacitinib
b/tsDMARD: biologic/targeted synthetic disease-modifying anti-rheumatic drug; CDAI: Clinical Disease Activity Index; DAS28-CRP: DAS in 28 joints using CRP HAQ-DI: HAQ-Disability Index; IL-6i: IL-6 inhibitor; SD: standard deviation; SDAI: Simple Disease Activity Index; TNFi: TNF inhibitor; UPA: upadacitinib.

(Suppl. Fig. S2). For the upadacitinib monotherapy and upadacitinib plus MTX groups, data for 219 (84.2%) and 234 (85.7%) patients were available at 6 months, and for 178 (68.5%) and 193 (70.7%) patients at 12 months, respectively. Of the 533 patients enrolled and assessed at baseline, 518 had ≥1 follow-up visit and were included in the ITT population for effectiveness analyses. Of those 518 patients, two (0.4%) had no treatment with upadacitinib documented during follow-up visits but were included in all analyses (representing six visits in total and one AE leading to discontinuation); the other 516 patients had ≥1 dose of upadacitinib documented during follow-up visits.

Of the enrolled patients, most were male (76.2%), the mean (standard deviation [SD]) age was 57.9 (12.3) years, and the mean (SD) BMI was 27.7 (5.6 kg/m^2). The mean (SD) RA disease duration was 9.0 (8.0) years, 67.5% were RF positive, and 65.4% were ACPA positive (Table I). More than half of patients (60.8%) had received prior treatment with b/tsDMARDs and 18.2% of patients had previously received ≥1 JAK inhibitor (baricitinib and/or tofacitinib). At baseline, the overall enrolled patient population had moderate-to-severe mean (SD) disease activity (SDAI: 26.6 [10.9]; DAS28-CRP: 4.6 [1.0]; pain: 6.2 [2.2]; and HAQ-DI: 1.3 [0.6]) and 55.5% had CRP levels above the ULN.

The proportion of the total population receiving MTX decreased from 53.5% at baseline to 40.7% at 12 months. At the 12-month follow-up, the mean MTX dose in those patients still on MTX remained consistent with that at baseline (13.6 mg/week *vs*. 12.8 mg/week). Glucocorticoid use in the total population decreased from 46.7% of patients at baseline to 27.5% at 12 months. The mean systemic glucocorticoid dose fell from 7.0 mg/day prednisolone equivalent at baseline to 4.4 mg/day among patients still on glucocorticoids at 12 months.

Clinical remission and LDA

After 6 months, 24.4% (n=105/431) of patients in the overall ITT population achieved the primary endpoint of clinical remission (CDAI ≤2.8). Similar results for CDAI remission after 6 months were seen by treatment group (upadacitinib monotherapy 23.2% [n=48/207]; upadacitinib plus MTX 25.4% [n=57/224]).

In the overall ITT population, the proportions of patients achieving clinical remission after 12 months reached 28.3% (n=105/371; CDAI), 34.5% (n=128/371; SDAI) and 66.3% (n=246/371; DAS28-CRP <2.6) (Fig. 1). The proportions of patients achieving LDA after 12 months reached 77.4% (n=287/371; CDAI), 76.5% (n=284/371; SDAI) and 81.7% (n=303/371; DAS28-CRP ≤3.2) (Fig. 1). Improvements were observed in all four components of DAS28-CRP (data not shown). Similar trends in the proportions of patients achieving clinical remission and LDA by applying CDAI, SDAI and DAS28-CRP criteria were observed after 12 months in the upadacitinib monotherapy and upadacitinib plus MTX treatment groups (Fig. 2).

Clinical remission and LDA by prior b/tsDMARD treatment

Analysis of the proportions of patients achieving clinical remission and LDA by CDAI and SDAI criteria, and DAS28-CRP <2.6/≤3.2 at 12 months by prior b/tsDMARD treatment status showed that achievement of treatment targets by patients who had prior inadequate response or intolerance to b/tsDMARDs (b/tsDMARD-IR) (Fig. 3) was generally comparable to that in the overall ITT population (Fig. 1).

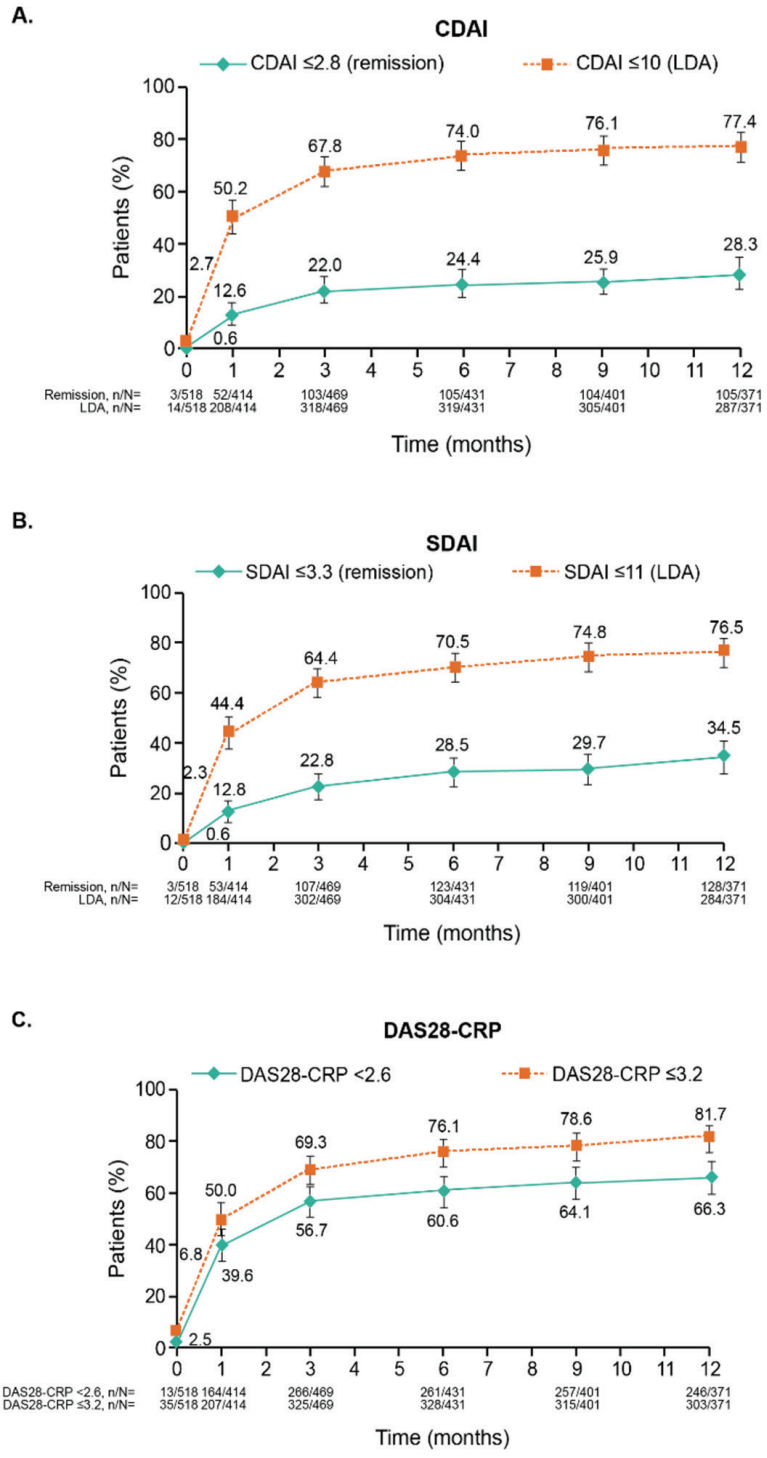

Fig. 1. Effectiveness over 12 months of upadacitinib treatment (ITT population).
A: CDAI LDA and remission. **B**: SDAI LDA and remission. **C**: DAS28-CRP ≤3.2 and <2.6. Error bars represent 95% confidence intervals.
CDAI: Clinical Disease Activity Index; DAS28-CRP: DAS in 28 joints using CRP; ITT: intent-to-treat; LDA: low disease activity; SDAI: Simple Disease Activity Index.

At 12 months, the proportions of b/tsDMARD-naive patients achieving remission, LDA and DAS28-CRP <2.6/≤3.2 were numerically higher than for b/tsDMARD-IR patients (Fig. 3) and the overall ITT population (Fig. 1).

Patient-reported outcomes

In the overall ITT population, a reduction in pain of ≥30% was reported by 58.0% (n=250/431) of patients at 6 months and by 61.7% (n=229/371) at 12 months. Moreover, a reduction in fatigue of ≥30% was reported by 45.9% (n=198/431) of patients at 6 months and by 46.1% (n=171/371) at 12 months (Suppl. Table S1). The proportion of patients with a ≥0.22 improvement in HAQ-DI was 42.2% (n=182/431) at 6 months and was maintained through 12 months (42.0% [n=156/371]) (Suppl. Table S1). Similar proportions of patients in the upadacitinib monotherapy and upadacitinib plus MTX groups achieved improvements in pain (≥30%, ≥50% and ≥70%), fatigue (≥30%, ≥50% and ≥70%) and HAQ-DI (≥0.22) at 6 and 12 months (Suppl. Table S1).

Impact of baseline CRP levels on effectiveness of upadacitinib - Factors impacting achievement of CDAI clinical remission at 6 months

In the upadacitinib monotherapy group, baseline CRP, systemic glucocorticoid use and ACPA status were found to be possible predictors for clinical remission (CDAI ≤2.8) at 6 months. Modelling of CDAI ≤2.8 at 6 months showed that use of systemic glucocorticoids at baseline was significantly associated with a lower probability of achieving remission (p=0.041) with an odds ratio (OR) for systemic glucocorticoid use (yes *vs*. no) of 0.42 (95% CI 0.19–0.94), p=0.035. Baseline ACPA status showed a tendency towards association with achieving remission (p=0.114), with ACPA-negative (22) patients having a lower probability for remission (negative *vs*. positive: OR 0.25 [95% CI 0.07–0.93]; p=0.038). In contrast, baseline CRP level was not associated with the probability of achieving remission (p=0.704).

In the upadacitinib plus MTX group, baseline CRP, RAID score, ACPA status and BMI were found to be possible predictors for achieving CDAI ≤2.8 at 6 months. Modelling of CDAI ≤2.8 at 6 months showed that RAID score (p<0.001) and ACPA status (p=0.022) were significantly associated with remission. For RAID score, the higher the score, the lower the probability for remission (OR 0.74 [95% CI 0.62–0.88]). ACPA-positive patients had a higher probability for remission (positive *vs*.

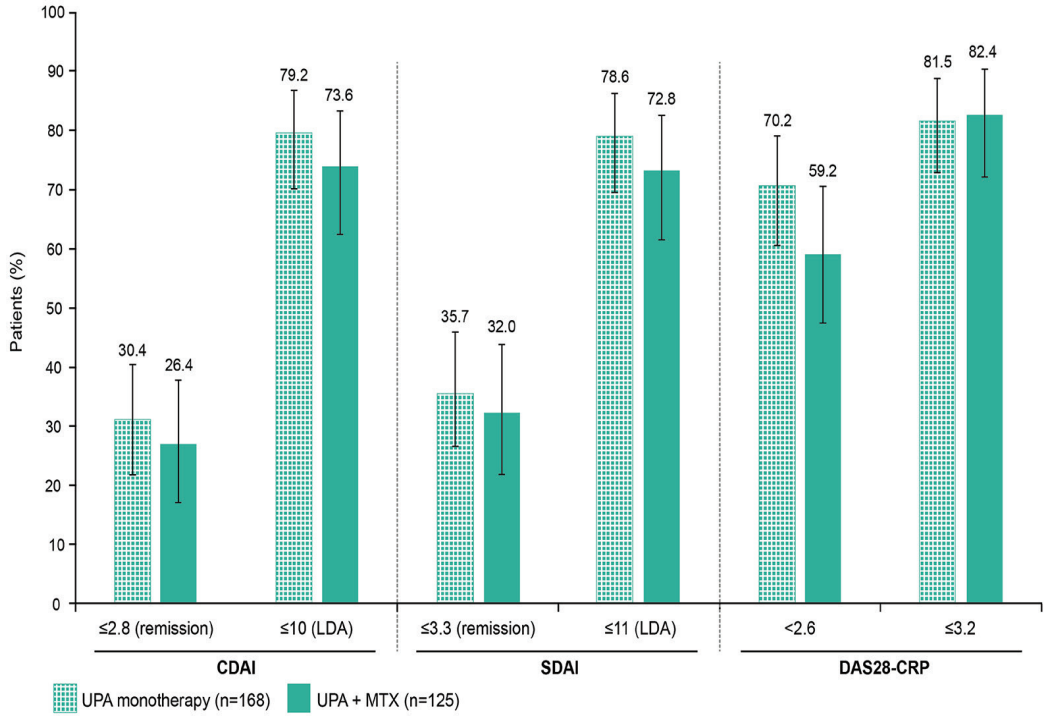

Fig. 2. Effectiveness at 12 months of upadacitinib monotherapy and upadacitinib plus MTX treatment (ITT population).
At baseline, ~50% of patients received UPA monotherapy and ~50% received UPA + MTX; however, patients switched from UPA + MTX to UPA monotherapy and *vice versa* during the study. At 12 months, 19.5% (52/266) of patients starting on UPA + MTX were on UPA monotherapy and 4.0% (10/252) of patients starting on UPA monotherapy had added MTX.
These data are from patients who consistently received UPA monotherapy or UPA + MTX throughout. Error bars represent 95% confidence intervals.
CDAI: Clinical Disease Activity Index; DAS28-CRP: DAS in 28 joints using CRP; ITT: intent-to-treat; LDA: low disease activity; SDAI: Simple Disease Activity Index; UPA: upadacitinib.

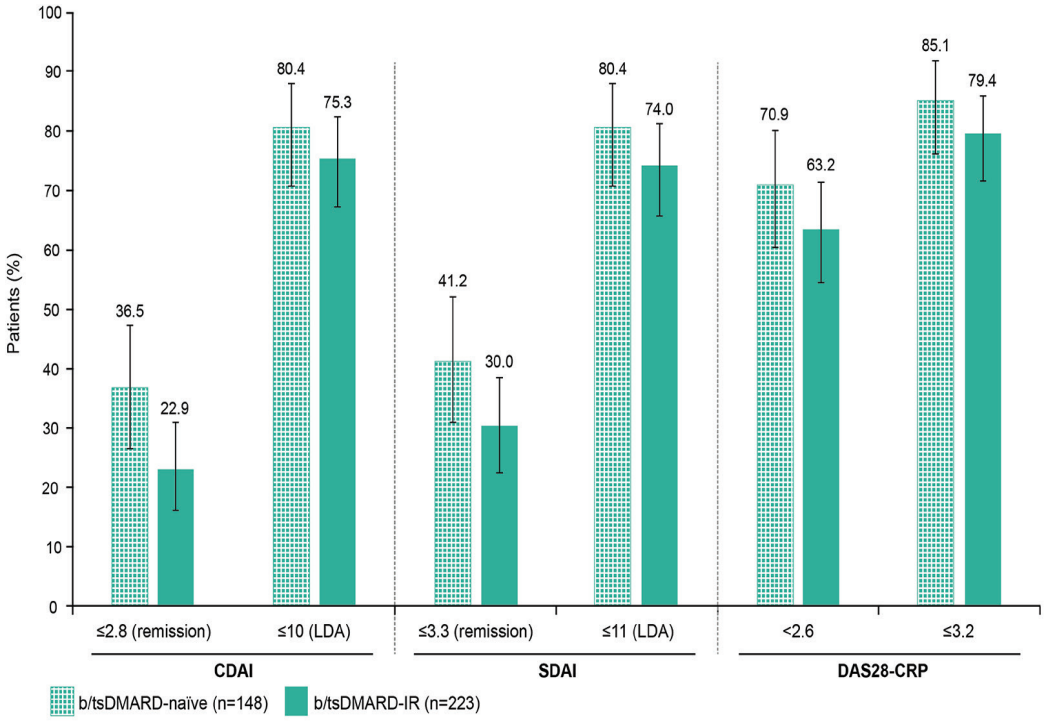

Fig. 3. Effectiveness at 12 months of upadacitinib treatment in b/tsDMARD-naive and b/tsDMARD-IR patients (ITT population).
Error bars represent 95% confidence intervals.
b/tsDMARD: biologic/targeted synthetic disease-modifying anti-rheumatic drug; CDAI: Clinical Disease Activity Index; DAS28-CRP: DAS in 28 joints using CRP; IR: inadequate response; ITT: intent-to-treat; LDA: low disease activity; SDAI: Simple Disease Activity Index.

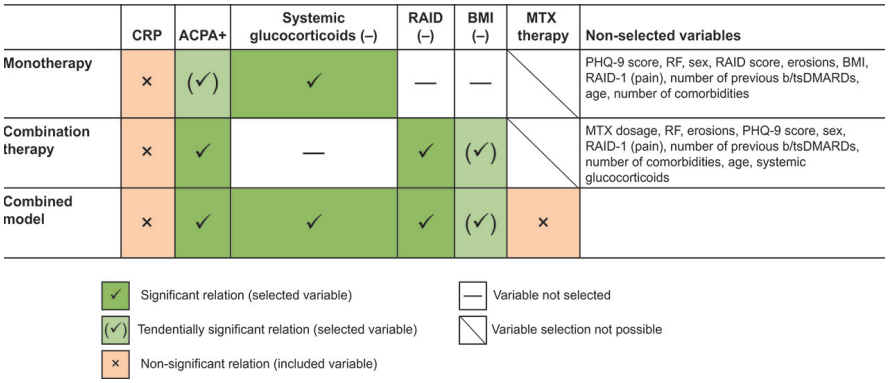

Fig. 4. Possible predictors of achieving CDAI remission at 6 months in the multivariable model (ITT population).
* Possible predictors of clinical remission were chosen baseline variables based on stepwise regression within a bootstrapping algorithm. These variables were then included in the multivariable model for clinical remission (CDAI ≤2.8) at 6 months. Variables were selected separately for the upadacitinib monotherapy and upadacitinib + MTX treatment groups. Variables for the overall ITT population included all possible predictors selected for both the upadacitinib monotherapy and upadacitinib + MTX groups.
b/tsDMARD: biologic/targeted synthetic DMARD; CDAI: Clinical Disease Activity Index; ITT: intent-to-treat; PHQ: Patient Health Questionnaire; RAID: Rheumatoid Arthritis Impact of Disease; UPA: upadacitinib.

unknown: OR 2.85 [95% CI 1.35–6.03]; p=0.006; negative *vs*. positive: OR 0.55 [95% CI 0.24–1.30]; p=0.175). BMI showed a tendency towards higher values being associated with lower probability for remission (p=0.085), whereas baseline CRP had no significant impact (p=0.408).
In the combined sensitivity analysis of all patients, of the possible predictors chosen in the separate treatment groups, ACPA status (p=0.044), systemic glucocorticoid use (p=0.034) and RAID score (p<0.001) showed significant association with achieving CDAI ≤2.8 (Fig. 4).

- Impact of CRP on achievement of CDAI clinical remission and LDA

At 12 months, CDAI remission was achieved by similar proportions of patients with normal CRP and CRP above the ULN at baseline (27.3% [95% CI 18.8–37.1] and 29.1% [95% CI 21.3–37.9], respectively) in the overall ITT population. Similar proportions of patients with normal CRP and CRP above the ULN at baseline also achieved remission as assessed by SDAI (34.5% [25.3–44.7] and 34.5% [26.1–43.5]) and DAS28-CRP <2.6 (67.9% [57.8–76.9] and 65.0% [56.0–73.4]). Additionally, LDA as assessed by CDAI (78.2% [95% CI 68.8–85.8] and 76.7% [95% CI 68.3–83.8]), SDAI (77.0% [95% CI 67.5–84.8] and 76.2% [95% CI 67.8–83.4]) and DAS28-CRP ≤3.2 (84.2% [95% CI 75.7–90.8] and 79.6% [95% CI 71.5–86.3]) was comparable between patients with normal CRP levels and CRP levels above the ULN at baseline, respectively (Table II). Similar trends in LDA as assessed by CDAI, SDAI and DAS28-CRP ≤3.2 were observed after 6 months in the overall ITT population and after 6 and 12 months in the upadacitinib monotherapy and upadacitinib plus MTX treatment groups (Table II).

- Impact of CRP levels on pain and fatigue

Improvements in patient-reported pain and fatigue by baseline CRP level (normal and above the ULN) for the overall ITT population and by treatment group after 6 and 12 months are reported in Table II. Similar proportions of patients with normal CRP levels and CRP levels above the ULN at baseline achieved a reduction of ≥30% in pain (60.6% [95% CI 50.3–70.3] and 62.6% [95% CI 53.5–71.2], respectively) and fatigue (43.6% [95% CI 33.7–54.0] and 48.1% [95% CI 39.0–57.2], respectively) after 12 months in the overall ITT population. Comparable proportions of patients achieving improvements in pain and fatigue by baseline CRP level were seen in the upadacitinib monotherapy and upadacitinib plus MTX treatment groups (Table II).

Safety

The safety analysis included all enrolled patients assessed at baseline (n=533). Ten patients (upadacitinib monotherapy, n=6; upadacitinib plus MTX, n=4; 0 PYs exposure) had no follow-up visits and no AEs documented but were included in the safety analysis. Over the 12-month follow-up period, ≥1 AE or serious AE occurred in 232 (43.5%) and 47 (8.8%) patients in the overall enrolled population, corresponding to EAERs of 104.4 and 14.5 E/100 PY, respectively. Similar rates were seen for the upadacitinib monotherapy and upadacitinib plus MTX groups (Table III). There was one death from a recurrence of breast cancer in the upadacitinib monotherapy group, which was considered not related to study treatment by the treating physician. The most common AESIs (EAERs) were hepatic function disorders (including raised liver enzymes; 3.8/100 PY), serious infections (2.9/100 PY), herpes zoster (2.7/100 PY) and weight gain (2.5/100 PY). The most common AEs leading to discontinuation were cough (6 events), nausea (4 events), dyspnoea (4 events), weight increase (4 events) and worsening of RA (4 events).

Discussion

In this 12-month, real-world, non-interventional study in patients with moderately to severely active RA treated with upadacitinib in routine clinical practice in Germany, upadacitinib monotherapy and upadacitinib plus MTX were consistently effective at inducing clinical remission (CDAI ≤2.8) after 6 months, as well as remission and LDA as assessed by CDAI and SDAI, and DAS28-CRP <2.6/≤3.2 through 12 months. The difference in remission rates at 12 months between DAS28-CRP (66.3%) and CDAI (28.3%) was not based solely on a reduction in CRP levels but was due to the effect of upadacitinib on all four components of the score reducing disease activity. Upadacitinib treatment also improved PROs of pain and fatigue at 6 months, and improvements were maintained through 12 months. Additionally, upadacitinib treatment was effective independently of CRP levels at baseline, and effective in b/tsDMARD-IR patients

Table II. Improvements in endpoints by baseline CRP levels at 6 and 12 months (ITT population).

			% (95% CI) – 6-month follow-up			% (95% CI) – 12-month follow-up		
			UPA	UPA + MTX	Total	UPA	UPA + MTX	Total
Remission	CDAI	Baseline CRP above ULN	29.2 (18.6–41.9)*	22.3 (13.7–33.0)†	25.4 (18.5–33.4)‡	30.9 (19.3–44.4)§	27.7 (17.5–39.8)‖	29.1 (21.3–37.9)**
		Normal baseline CRP	16.8 (8.5–28.4)††	29.8 (18.4–43.3)§	23.1 (15.8–31.7)‡‡	28.6 (16.8–42.8)§§	25.9 (14.5–40.3)‖‖	27.3 (18.8–37.1)****
	SDAI	Baseline CRP above ULN	34.0 (22.6–46.8)*	24.6 (15.6–35.6)†	28.8 (21.5–37.0)‡	36.2 (23.9–49.9)§	33.0 (22.1–45.5)‖	34.5 (26.1–43.5)**
		Normal baseline CRP	21.8 (12.3–34.1)††	35.1 (22.9–48.8)§	28.2 (20.3–37.2)‡‡	34.5 (21.8–49.1)§§	34.6 (21.6–49.4)‖‖	34.5 (25.3–44.7)****
	DAS28-CRP	Baseline CRP above ULN	55.7 (42.7–68.1)*	60.0 (48.3–70.9)†	58.1 (49.5–66.3)‡	64.9 (51.2–77.1)§	65.2 (52.7–76.4)‖	65.0 (56.0–73.4)**
		Normal baseline CRP	61.4 (48.1–73.6)††	66.0 (52.3–78.0)§	63.6 (54.2–72.3)‡‡	76.2 (62.3–87.0)§§	59.3 (44.4–73.0)‖‖	67.9 (57.8–76.9)****
LDA	CDAI	Baseline CRP above ULN	70.8 (58.1–81.4)*	77.7 (67.0–86.3)†	74.6 (66.6–81.5)‡	75.5 (62.5–85.9)§	77.7 (66.0–86.9)‖	76.7 (68.3–83.8)**
		Normal baseline CRP	71.3 (58.4–82.1)††	75.5 (62.5–85.9)§	73.3 (64.4–81.1)‡‡	83.3 (70.5–92.3)§§	72.8 (58.4–84.5)‖‖	78.2 (68.8–85.8)****
	SDAI	Baseline CRP above ULN	67.9 (55.2–79.0)*	73.1 (61.9–82.5)†	70.8 (62.6–78.1)‡	74.5 (61.3–85.1)§	77.7 (66.0–86.9)‖	76.2 (67.8–83.4)**
		Normal baseline CRP	69.3 (56.3–80.5)††	71.3 (57.9–82.5)§	70.3 (61.1–78.4)‡‡	82.1 (69.1–91.4)§§	71.6 (57.1–83.5)‖‖	77.0 (67.5–84.8)****
	DAS28-CRP	Baseline CRP above ULN	70.8 (58.1–81.4)*	80.8 (70.4–88.8)†	76.3 (68.4–83.0)‡	76.6 (63.6–86.8)§	82.1 (71.1–90.4)‖	79.6 (71.5–86.3)**
		Normal baseline CRP	73.3 (60.5–83.8)††	78.7 (66.0–88.4)§	75.9 (67.2–83.3)‡‡	85.7 (73.3–93.9)§§	82.7 (69.5–92.0)‖‖	84.2 (75.7–90.8)****
Pain improvement	≥30%	Baseline CRP above ULN	60.4 (47.4–72.4)*	57.7 (46.0–68.8)†	58.9 (50.3–67.1)‡	61.7 (47.9–74.3)§	63.4 (50.8–74.8)‖	62.6 (53.5–71.2)**
		Normal baseline CRP	53.5 (40.3–66.3)††	60.6 (46.9–73.3)§	56.9 (47.5–66.0)‡‡	60.7 (46.1–74.1)§§	60.5 (45.6–74.1)‖‖	60.6 (50.3–70.3)****
	≥50%	Baseline CRP above ULN	48.1 (35.5–60.9)*	48.5 (37.0–60.0)†	48.3 (39.8–56.9)‡	52.1 (38.5–65.5)§	50.9 (38.5–63.2)‖	51.5 (42.3–60.5)**
		Normal baseline CRP	41.6 (29.1–54.9)††	46.8 (33.5–60.5)§	44.1 (34.9–53.6)‡‡	46.4 (32.4–60.9)§§	40.7 (27.0–55.6)‖‖	43.6 (33.7–54.0)****
	≥70%	Baseline CRP above ULN	24.5 (14.7–36.8)*	24.6 (15.6–35.6)†	24.6 (17.7–32.5)‡	31.9 (20.2–45.5)§	25.0 (15.3–36.9)‖	28.2 (20.4–36.9)**
		Normal baseline CRP	19.8 (10.7–31.8)††	25.5 (14.9–38.7)§	22.6 (15.4–31.2)‡‡	23.8 (13.0–37.7)§§	22.2 (11.6–36.2)‖‖	23.0 (15.2–32.5)****
Fatigue improvement	≥30%	Baseline CRP above ULN	47.2 (34.6–60.0)*	49.2 (37.8–60.8)†	48.3 (39.8–56.9)‡	46.8 (33.5–60.5)§	49.1 (36.8–61.5)‖	48.1 (39.0–57.2)**
		Normal baseline CRP	42.6 (30.0–55.8)††	43.6 (30.5–57.4)§	43.1 (34.0–52.5)‡‡	42.9 (29.1–57.4)§§	44.4 (30.3–59.3)‖‖	43.6 (33.7–54.0)****
	≥50%	Baseline CRP above ULN	35.8 (24.3–48.7)*	35.4 (24.9–47.0)†	35.6 (27.7–44.1)‡	37.2 (24.8–51.0)§	36.6 (25.2–49.2)‖	36.9 (28.4–46.0)**
		Normal baseline CRP	25.7 (15.4–38.4)††	29.8 (18.4–43.3)§	27.7 (19.8–36.7)‡‡	28.6 (16.8–42.8)§§	32.1 (19.5–46.8)‖‖	30.3 (21.5–40.3)****
	≥70%	Baseline CRP above ULN	18.9 (10.2–30.4)*	19.2 (11.2–29.6)†	19.1 (13.0–26.5)‡	21.3 (11.6–34.0)§	25.9 (16.0–37.9)‖	23.8 (16.6–32.2)**
		Normal baseline CRP	11.9 (5.0–22.5)††	9.6 (3.4–20.1)§	10.8 (5.8–17.7)‡‡	20.2 (10.3–33.7)§§	16.0 (7.2–29.1)‖‖	18.2 (11.2–27.1)****

* n=106. † n=130. ‡ n=236. § n=94. ‖ n=112. ** n=206. †† n=101. ‡‡ n=195. §§ n=84. ‖‖ n=81. **** n=165.
CDAI: Clinical Disease Activity Index; CI: confidence interval; DAS28-CRP: DAS in 28 joints using CRP; ITT: intent-to-treat; LDA: low disease activity; SDAI: Simple Disease Activity Index; ULN: upper limit of normal; UPA: upadacitinib.

and b/tsDMARD-naive patients. Overall, the effectiveness and safety results of this study on the real-world effectiveness of upadacitinib are consistent with previous findings from the phase 3 SELECT clinical trial programme covering bDMARD-IR and bDMARD-naive patient populations (8–12).

In these analyses, baseline CRP level had no significant association with the achievement of clinical remission (CDAI ≤2.8) after 6 months with upadacitinib monotherapy or therapy with upadacitinib plus MTX. Exploratory unadjusted analyses also suggested that having normal CRP levels or CRP levels above the ULN at baseline had no significant effect on the proportions of patients achieving clinical remission, LDA, and improvements in pain and fatigue in patients treated with upadacitinib monotherapy or upadacitinib plus MTX in clinical practice. In contrast to this real-world study with no specific CRP level inclusion criterion, elevated CRP levels are typically an inclusion criterion in clinical trials assessing RA therapies, including the upadacitinib phase 3 SELECT programme (8-12). Thus, a substantial proportion of patients with active RA but normal CRP levels who could potentially benefit from advanced therapies are excluded from trials. Indeed, in the current study, patients with normal CRP levels at baseline accounted for 44.5% of the en-

Table III. Safety overview by upadacitinib monotherapy and upadacitinib plus MTX in all patients assessed at baseline.

	UPA (n=260) 216.7 PY		UPA + MTX (n=273) 230.6 PY		Total (n=533) 447.4 PY	
	Number of AEs	Events per 100 PY (95% CI)	Number of AEs	Events per 100 PY (95% CI)	Number of AEs	Events per 100 PY (95% CI)
Any AEs	225	103.8 (90.7–118.3)	242	104.9 (92.1–119.0)	467	104.4 (95.1–114.3)
Serious AEs	30	13.8 (9.3–19.8)	35	15.2 (10.6–21.1)	65	14.5 (11.2–18.5)
AE leading to discontinuation (total)	80	36.9 (29.3–45.9)	41	17.8 (12.8–24.1)	121	27.0 (22.4–32.3)
AE leading to discontinuation (due to AE)	61	28.1 (21.5–36.2)	26	11.3 (7.4–16.5)	87	19.4 (15.6–24.0)
AE leading to discontinuation (lack of effectiveness)	19	8.8 (5.3–13.7)	15	6.5 (3.6–10.7)	34	7.6 (5.3–10.6)
Death*	1	0.5 (0.0–2.6)	0	0 (0.0–1.6)	1	0.2 (0.0–1.2)
AEs of special interest						
Serious infections	8	3.7 (1.6–7.3)	5	2.2 (0.7–5.1)	13	2.9 (1.5–5.0)
Opportunistic infections†‡	2	0.9 (0.1–3.3)	5	2.2 (0.7–5.1)	7	1.6 (0.6–3.2)
Herpes zoster	6	2.8 (1.0–6.0)	6	2.6 (1.0–5.7)	12	2.7 (1.4–4.7)
Malignancy (excluding NMSC)§	3	1.4 (0.3–4.0)	1	0.4 (0.0–2.4)	4	0.9 (0.2–2.3)
NMSC	1	0.5 (0.0–2.6)	1	0.4 (0.0–2.4)	2	0.4 (0.1–1.6)
Hepatic disorder‖	10	4.6 (2.2–8.5)	7	3.0 (1.2–6.3)	17	3.8 (2.2–6.1)
Gastrointestinal perforation	0	0 (0.0–1.7)	0	0 (0.0–1.6)	0	0 (0.0–0.8)
MACE**	1	0.5 (0.0–2.6)	2	0.9 (0.1–3.1)	3	0.7 (0.1–2.0)
VTE††	0	0.0 (0.0–1.7)	1	0.4 (0.0–2.4)	1	0.2 (0.0–1.2)
Creatine phosphokinase elevation	0	0.0 (0.0–1.7)	1	0.4 (0.0–2.4)	1	0.2 (0.0–1.2)
Weight increased	7	3.2 (1.3–6.7)	4	1.7 (0.5–4.4)	11	2.5 (1.2–4.4)
Active tuberculosis	0	0 (0.0–1.7)	0	0 (0.0–1.6)	0	0 (0.0–0.8)

* Recurrence of breast cancer (1 event).
† Excluding herpes zoster and tuberculosis; ‡ Including fungal oropharyngitis (3 events), oral candidiasis (3 events) and oropharyngeal candidiasis (1 event); § Bladder cancer (1 event), recurrence of breast cancer (1 event), metastatic prostate cancer (1 event) and cerebellar tumour (1 event); ‖ Including liver enzymes increased; ** Defined as cardiovascular death (0 events), non-fatal myocardial infarction (1 event) or non-fatal stroke (2 events); †† Deep vein thrombosis (1 event).
AE: adverse event; CI: confidence interval; MACE: major adverse cardiovascular event; NMSC: non-melanoma skin cancer; PY: patient-years; UPA: upadacitinib; VTE: venous thromboembolic event.

rolled population. The results provide real-world evidence that patients with RA benefit from upadacitinib treatment regardless of CRP levels.

In contrast with these findings, a previous USA registry study found that the number of acute-phase reactants (including CRP) elevated at baseline was positively associated with improved CDAI and modified HAQ scores at 1 year, but that there was no association of outcomes with normal baseline levels (16). However, the results of the current study were consistent with a previous exploratory analysis of the SELECT-NEXT study in csDMARD-IR patients that required elevated CRP for inclusion, which showed that upadacitinib was effective in inducing remission regardless of the degree of elevation of CRP levels (17). Additionally, an analysis of tocilizumab treatment in RA clinical trials did not find an association between baseline CRP level and clinical response assessed by DAS28-CRP or CDAI (23). In contrast, analyses of tofacitinib efficacy by baseline CRP in clinical trials suggest that high baseline CRP levels may be associated with better response to tofacitinib (24, 25). As such, the effect of baseline CRP level on clinical response may be treatment dependent. Given the conflicting data associated with baseline CRP as a predictor of clinical response in RA and the lack of association seen for upadacitinib, it may be beneficial to patients to also consider other measures of disease activity when deciding whether to initiate advanced therapy.

The safety profile of upadacitinib in this real-world population was consistent with the upadacitinib safety profile previously reported from the SELECT clinical trial programme (26). Upadacitinib was generally well tolerated, and events of major adverse cardiovascular events, venous thromboembolic events and malignancy were rare. Altogether, no new safety risks were identified.

Limitations associated with observational studies should be considered when interpreting the current findings, such as decreasing patient numbers over time and the potential for responder bias. Additionally, while the proportions of patients in each treatment group were generally similar at baseline, 19% of patients had switched from upadacitinib plus MTX to upadacitinib monotherapy at 12 months, which might have affected the results of analyses by treatment group.

Conclusion

In conclusion, upadacitinib as monotherapy or in combination with MTX was consistently effective at inducing CDAI clinical remission and LDA, and improving pain and fatigue at 6 and 12 months in patients with moderately to severely active RA in a real-world setting. Baseline CRP level had no significant association with the probability of achieving CDAI clinical remission at 6 months in the upadacitinib monotherapy or upadacitinib plus MTX treatment groups. The safety profile in this real-world patient population was consistent with the known upadacitinib safety profile in this indication, and no new safety risks were identified.

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D. Adolf is an employee of StatConsult and may own stock or options.

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