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ORIGINAL RESEARCH

Long-term sustainability of response to upadacitinib among patients with active rheumatoid arthritis refractory to biological treatments: results up to 5 years from SELECT-BEYOND

Ronald F van Vollenhoven ,[1] Stephen Hall,[2] Alvin F Wells,[3] Sebastian Meerwein,[4] Yanna Song,[5] Oishi Tanjinatus,[5] Roy Fleischmann [6]

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For numbered affiliations see end of article.

Correspondence to
Dr Ronald F van Vollenhoven; r.vanvollenhoven@amsterdamumc.nl

ABSTRACT

Objective To evaluate the long-term sustainability of response to the Janus kinase inhibitor upadacitinib among patients with rheumatoid arthritis and an inadequate response or intolerance to biological disease-modifying antirheumatic drugs (bDMARD-IR) in the SELECT-BEYOND phase 3 trial.

Methods Patients on background conventional synthetic DMARDs (csDMARDs) were treated once daily with upadacitinib 15 mg or placebo. Patients who completed the week 24 visit could enter a long-term extension of up to 5 years. The sustainability of response was assessed based on achievement of Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Disease Activity Score 28-joint count using C-reactive protein (DAS28 (CRP)) targets and evaluated up to week 260 in all patients receiving the approved upadacitinib 15 mg dose, including those randomised to upadacitinib 15 mg and those who switched from placebo to upadacitinib 15 mg at week 12.

Results In this bDMARD-IR population, 45% (n=104/229) and 79% (n=172/219) of patients treated with upadacitinib 15 mg plus background csDMARD(s) achieved CDAI remission or CDAI low disease activity (LDA) at any point during the 5-year study, respectively. Of those who achieved CDAI remission/LDA, 25%/43% maintained their initial response through 240 weeks of follow-up after first achieving response. Most patients who lost remission or LDA were able to recapture that response by the cut-off date. Similar overall results were observed for SDAI and DAS28 (CRP). No strong predictors of response were identified.

Conclusions Over three-quarters of bDMARD-IR patients achieved CDAI LDA with upadacitinib, and almost half of those maintained LDA through 240 weeks of follow-up. Remission was achieved by nearly half of all patients and maintained in approximately a quarter of those achieving remission.

Trial registration number NCT02706847.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The ultimate treatment goal for patients with rheumatoid arthritis (RA) is sustained remission, with low disease activity (LDA) being an appropriate target for those who cannot achieve remission.

⇒ In the phase 3 SELECT-BEYOND study, which was conducted in patients with active RA and an inadequate response (IR) or intolerance to biological disease-modifying antirheumatic drugs (bDMARDs), treatment with upadacitinib 15 mg once daily plus background conventional synthetic DMARD(s) (csDMARD) demonstrated significant improvements in clinical, functional and patient-reported outcomes through 12 weeks compared with placebo treatment plus background csDMARD(s).

WHAT THIS STUDY ADDS

⇒ This study provides insights into the management of RA with upadacitinib treatment over 5 years in a clinical setting and explores potential predictors of response for patients who achieve long-term sustained clinical remission or LDA.

⇒ Approximately three-quarters of bDMARD-IR patients achieved Clinical Disease Activity Index LDA with upadacitinib 15 mg, and almost half of those maintained LDA through 240 weeks of follow-up.

⇒ Remission was achieved by nearly half of all patients receiving upadacitinib 15 mg and maintained through 240 weeks of follow-up in approximately a quarter of patients in this group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Together with the safety profile of upadacitinib, these data underscore that upadacitinib 15 mg, in combination with background csDMARD(s), is a useful treatment choice for patients with RA, particularly those who are refractory to biological treatments.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a complex pathophysiology that affects more than 23 million people globally.[1–3] The primary treatment goal for patients with RA is sustained remission, with low disease activity (LDA) considered an appropriate target for treatment-refractory patients.[4 5] Effective disease control is critical not only for symptom alleviation but also for preventing long-term structural damage and disability, improved quality of life, and reduction of systemic complications such as cardiac events.[6–8] Nonetheless, a large proportion of patients fail to achieve clinical remission with biological disease-modifying antirheumatic drugs (bDMARDs) and/or conventional synthetic DMARDs (csDMARDs), including methotrexate (MTX).[9–13] Janus kinase (JAK) inhibitors, a class of targeted synthetic DMARDs (tsDMARDs), provide an established alternative to address this treatment gap.

Upadacitinib, an oral JAK inhibitor, has been investigated across the SELECT RA clinical programme, a series of multicentre, randomised, controlled trials.[14–19] In the SELECT-BEYOND phase 3 trial, treatment with upadacitinib plus background csDMARD(s) demonstrated efficacy and safety through 12 weeks in patients with moderately to severely active RA and an inadequate response or intolerance to bDMARDs (bDMARD-IR).[15] Given the chronic nature of RA, understanding the long-term sustainability of response to treatment is crucial for optimising treatment decisions and improving outcomes for patients. Here, we evaluated the sustainability of response to upadacitinib up to 5 years among bDMARD-IR patients and explored potential predictors of response.

METHODS

Patients

Study eligibility criteria for SELECT-BEYOND (clinical trial number: NCT02706847) have been described previously.[15] Briefly, patients were ≥18 years old and met the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA.[20] All patients failed at least one previous bDMARD therapy for RA due to lack of efficacy or intolerance. Patients were also required to have been on a stable dose of csDMARD(s) for at least 4 weeks prior to the first dose of study drug and continued to receive that same dose until week 24 unless decreased for safety reasons. Exclusion criteria included prior exposure to any JAK inhibitor or a history of inflammatory joint disease other than RA. Patients with previous malignancies (except for successfully treated non-melanoma skin cancer or localised carcinoma in situ of the cervix) and patients with moderate to severe congestive heart failure, uncontrolled hypertension, recent (ie, within the past 6 months) myocardial infarction, stroke or other specific cardiovascular conditions were also excluded (detailed in online supplemental text).

Study design and treatment

Patients received upadacitinib 15 mg or 30 mg once daily or placebo, each in combination with stable background csDMARD therapy. After the 12-week placebo-controlled period, patients receiving placebo were switched to upadacitinib 15 mg or 30 mg. All patients who completed the week 24 visit could enter a long-term extension for up to 5 years of treatment. Initiation or change in background RA medications, including adding or increasing doses in up to two csDMARDs (except for the combination of MTX and leflunomide), was allowed starting at week 24 per investigators' discretion.

Assessments and statistical analysis

The proportions of patients who achieved remission (defined as Clinical Disease Activity Index (CDAI) ≤2.8 or Simplified Disease Activity Index (SDAI) ≤3.3[21]), LDA (CDAI≤10 or SDAI≤11) and Disease Activity Score 28-joint count using C-reactive protein (DAS28 (CRP)) <2.6/≤3.2[22 23]) between the first dose of upadacitinib and a maximum of 260 weeks were assessed. This post hoc analysis only evaluated data from patients receiving upadacitinib 15 mg, which is the approved dose for RA, and included those randomised to upadacitinib 15 mg and those who switched from placebo to upadacitinib 15 mg at week 12. Patients who achieved a response in any of the above-listed response criteria before or at upadacitinib 15 mg start date were excluded from the analysis of the respective response.

Changes in concomitant glucocorticoid (GC) treatment were also evaluated among patients receiving GCs at baseline. A decrease in GC treatment was defined as at least one dose decrease as compared with baseline levels (not including those who stopped treatment), whereas GC increase was defined as at least one dose increase compared with baseline. Stopped GC treatment was defined as those who stopped GC treatment at least once, with a treatment gap >45 days; maintenance of GC was defined as no dose change from baseline. Lastly, the proportion of patients not receiving concomitant GC treatment at baseline who later started GCs was determined.

Sustained response was estimated by the Kaplan-Meier method and defined as the time from when the response was first achieved while on upadacitinib to the earliest date at which the response was lost at two consecutive visits or discontinuation of the study drug due to lack of efficacy. Data for Kaplan-Meier analyses were censored at the cut-off date when all patients reached the week 260 visit or at the time of study drug discontinuation. Maintenance of response was also assessed using the Kaplan-Meier method in patients who achieved CDAI remission or LDA before or at month 6 (day 168). The proportions of patients who achieved initial CDAI, SDAI or DAS28 (CRP) responses and either remained in those disease activity states or shifted to moderate or high disease activity (HDA) at weeks 60, 120, 180 and 240 after the first-time achieving response were also evaluated. Recapture of

response was assessed in patients who lost response at two consecutive visits but later regained response. Reasons for loss of response were summarised and included those who discontinued upadacitinib due to lack of efficacy and those who remained on upadacitinib but never recaptured response by the cut-off date after having lost response at two consecutive visits. CDAI changes of 2 units (>2 CDAI) and 4.5 units (≥4.5) were assessed as different thresholds for minimal clinically important differences (MCID) for worsening of RA (as reported by Curtis *et al*[24] and Konzett *et al*[25]) among those who initially achieved a response but later lost it. The Kaplan-Meier method was also used to evaluate the sustainability of response in the subgroup of patients with an IR or intolerance to TNF inhibitors (TNF-IR). Achievement and sustainability of response were also analysed in subgroups based on exposure to previous bDMARD(s) and the number of prior bDMARD mechanisms of action (MOA) at baseline (less refractory subgroup: ≤2 prior bDMARDs and 1 failed MOA; more refractory subgroup: >2 prior bDMARDs and ≥2 failed MOA). The ability of key baseline and demographic characteristics, including age, duration of RA since diagnosis, clinical disease activity, pain, CRP levels and time to response, to predict sustained response duration (ie, how long it takes for patients to lose response based on two consecutive visits), were evaluated using Harrell's concordance (C)-index (range: 0–1, where 0.5 indicates a model that is no better at predicting an outcome than random chance, and 1 indicates perfect predictive ability). All analyses used observed cases, with discontinuation of upadacitinib due to lack of efficacy treated as a loss of response; other reasons for drug discontinuation were treated as censored observations as of the last dose date.

RESULTS

Patients

Baseline demographics and disease characteristics were balanced across placebo and upadacitinib treatment groups (online supplemental table 1). Patients had a mean disease duration of approximately 13 years since RA diagnosis and a mean CDAI score of ~41, indicating HDA at baseline. Approximately half of the patients had previous exposure to at least two or more bDMARDs. Among patients receiving concomitant GCs at baseline, 54% (68/125) maintained their initial dose, 25% (31/125) increased their dose at least once, 20% (25/125) decreased their dose at least once and 20% (25/125) stopped GC treatment at least once. Of those not receiving GC treatment at baseline, 39% (48/124) later received GC therapy during the study.

Achievement of disease activity targets and duration of response

At any point during the 5-year study, a total of 45% (n=104/229) and 79% (n=172/219) of patients receiving upadacitinib 15 mg plus background csDMARD(s) attained CDAI remission or LDA, respectively (figure 1).

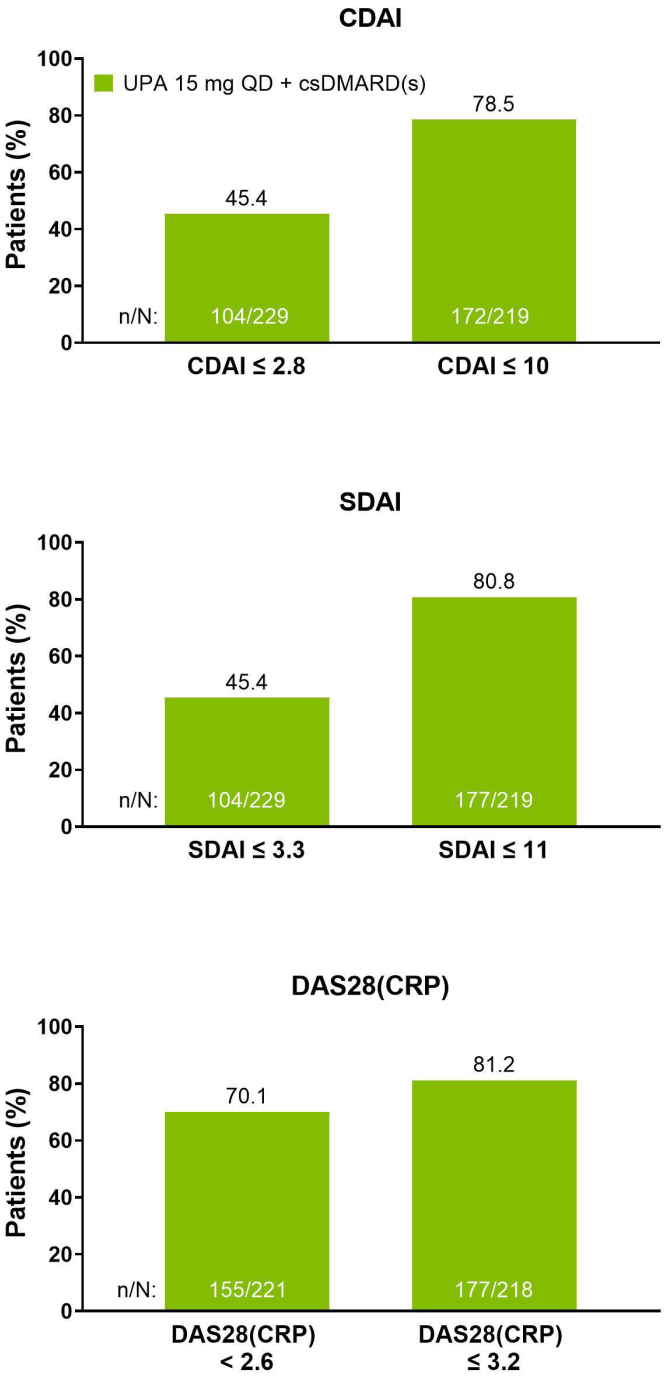

Figure 1 Proportion of patients achieving disease activity targets up to 5 years in SELECT-BEYOND. Data include patients randomised to UPA 15 mg and those who switched from placebo to UPA 15 mg at week 12. The proportions of patients achieving CDAI, DAS28 (CRP) or SDAI responses at any point during the 5-year study period are shown. CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic DMARD; DAS28 (CRP), 28-joint Disease Activity Score based on C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; QD, once daily; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.

Additionally, 45% (n=104/229) and 81% (n=177/219) attained SDAI remission or LDA, and 70% (n=155/221) and 81% (n=177/218) of patients attained DAS28 (CRP)

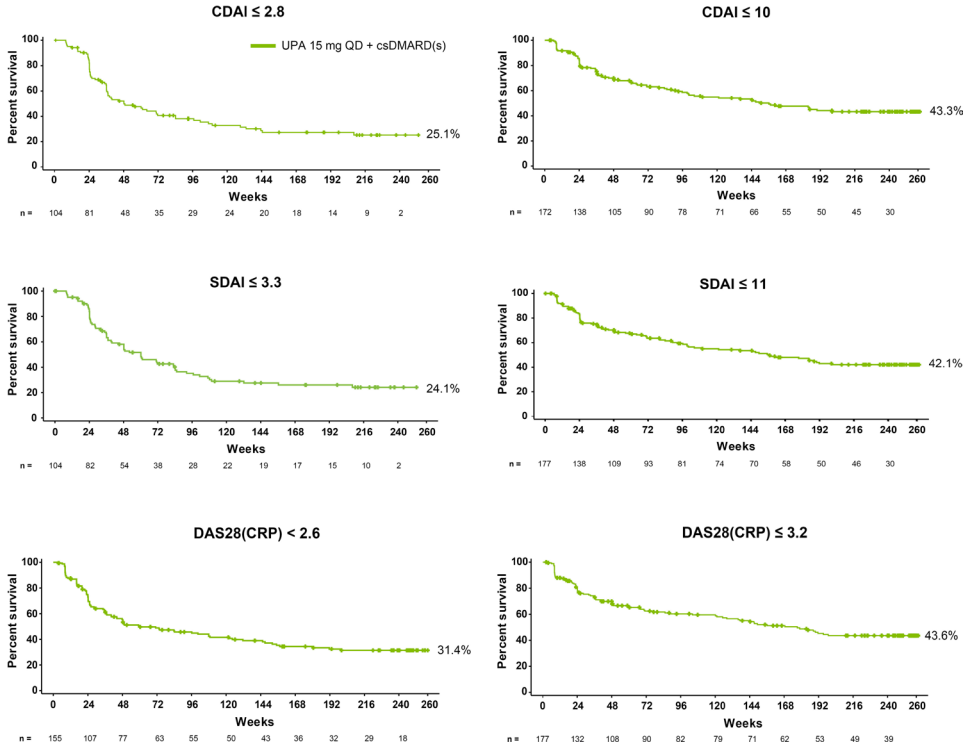

Figure 2 Kaplan-Meier analysis of time to loss of disease activity targets after the first occurrence of response. Results are for patients who had achieved CDAI remission/LDA, DAS28<2.6/≤3.2 or SDAI remission/LDA. Week 0 indicates the first occurrence of response. Data include patients randomised to UPA 15 mg and those who switched from placebo to UPA 15 mg at week 12; those receiving placebo who achieved disease activity targets before or at UPA start date were excluded from the analysis. Remission was defined as CDAI≤2.8 or SDAI≤3.3; LDA was defined as CDAI≤10 or SDAI≤11. CDAI, Clinical Disease Activity Index; DAS28 (CRP), 28-joint Disease Activity Score based on C-reactive protein; LDA, low disease activity; QD, once daily; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.

<2.6 or ≤3.2, respectively. Through 240 weeks of follow-up after reaching the initial response, 25% and 43% of patients who achieved the respective disease activity targets never lost CDAI remission or LDA at two consecutive visits with upadacitinib 15 mg treatment based on Kaplan-Meier analysis; 24% and 42% never lost SDAI remission or LDA; and 31% and 44% never lost DAS28 (CRP) <2.6 or ≤3.2 (figure 2). Patients who achieved CDAI remission or LDA maintained their initial response for a median time of 48 weeks and 156 weeks, respectively. Similarly, for SDAI remission/LDA and DAS28 (CRP) <2.6/≤3.2, the median duration of response was 60/156 weeks and 59/177 weeks, respectively. Of the 38 and 116 patients who achieved CDAI remission and LDA, respectively, within the first 6 months of the trial, 26% and 53% maintained that initial response through 240 weeks after first achieving the response based on Kaplan-Meier analysis.

Of the 44 patients who attained CDAI remission and remained on upadacitinib for at least 180 weeks after first achieving response, 27 (61%) stayed in remission, 15 (34%) were in LDA, 1 (2%) was in moderate disease activity (MDA) and 1 (2%) was in HDA (figure 3). Of the 93 patients who achieved CDAI LDA and continued upadacitinib treatment for at least 180 weeks, 29 (31%) were in remission, 43 (46%) were in LDA, 20 (22%) were in MDA and 1 (1%) was in HDA. Similar results were observed for SDAI and DAS28 (CRP) thresholds (figure 3).

Most patients who initially achieved CDAI, SDAI or DAS28 (CRP) targets but demonstrated loss of response at two consecutive visits were able to recapture the same level of response by the end of the study or premature discontinuation (figure 4). For instance, 72% (n=49/68) and 73% (n=61/84) of patients who lost their initial CDAI remission and LDA response were able to regain that response by the cut-off date, respectively. Similarly, 77% (n=53/69) and 68% (n=60/88) recaptured SDAI remission and LDA; 77% (n=73/95) and 72% (n=62/86) of patients recaptured DAS28 (CRP) <2.6/≤3.2. Of note, however, background medications of patients who lost response could be modified, with an increase or addition of up to ≤2 csDMARDs starting at week 24 per investigator's discretion, which may have contributed to their recapture of response. While the majority of these patients were able to regain response by the end of the study, many showed an MCID for CDAI worsening (based on thresholds of CDAI >2 or ≥4.5) from the visit at which the response was first achieved to the visit at which it was lost. Of those who achieved CDAI remission but later lost it, for example, 77% (n=52/68) had a CDAI change >2 while 46% (n=31/68) had a CDAI change ≥4.5 from the visit at which the response was first achieved. Additionally, 91% (n=76/84) and 75% (n=63/84) of those who

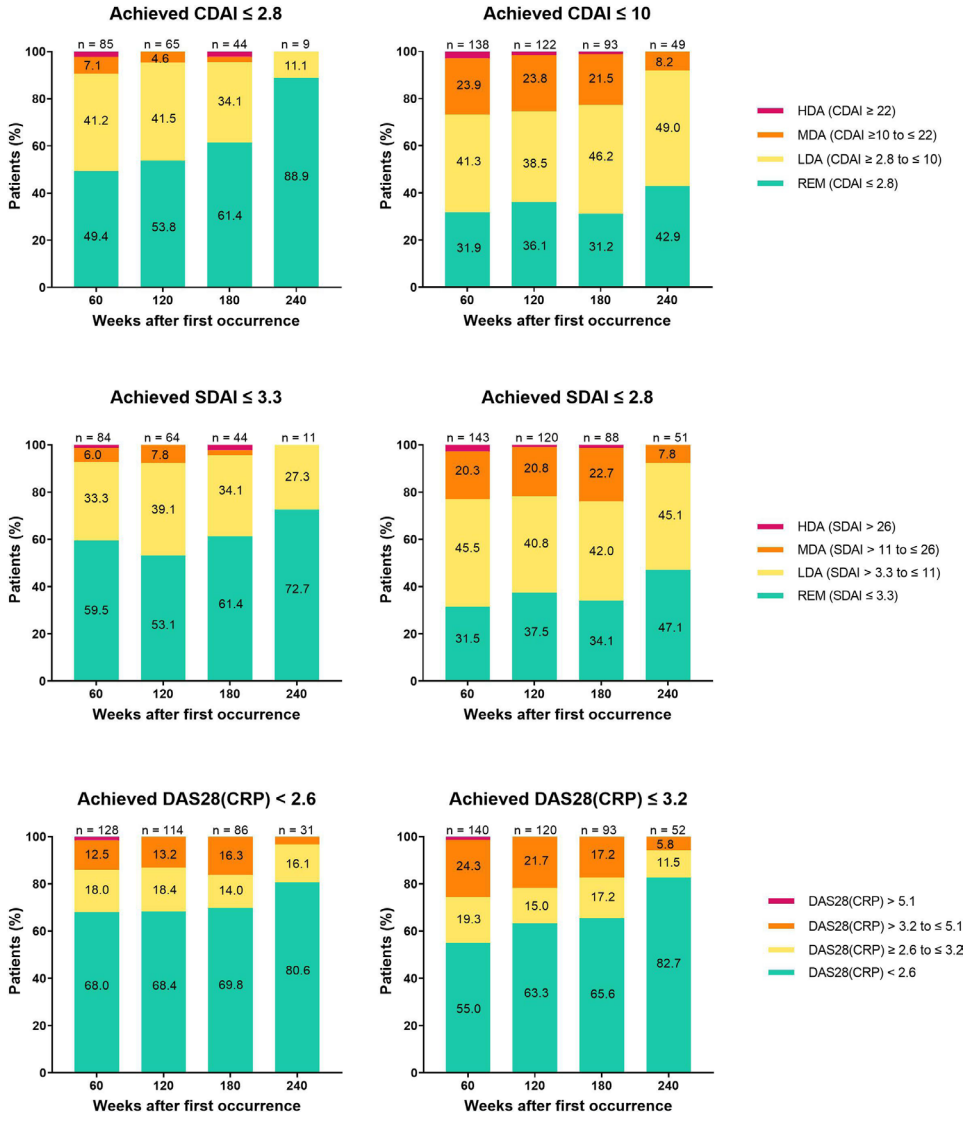

Figure 3 Proportions of patients in different disease activity states among those who achieved initial CDAI, DAS28 (CRP) or SDAI response (Observed Case). Data include patients randomised to UPA 15 mg and those who switched from placebo to UPA 15 mg at week 12; those receiving placebo who achieved disease activity targets before or at UPA start date were excluded from the analysis. Data are reported as observed case, with discontinuation of upadacitinib due to lack of efficacy treated as a loss of response (censored at the last dose date). CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic DMARD; DAS28 (CRP), 28-joint Disease Activity Score based on C-reactive protein; DMARD, disease-modifying antirheumatic drug; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; QD, once daily; REM, remission; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.

initially attained CDAI LDA but lost response had a CDAI change >2 and ≥4.5, respectively, compared with the visit when LDA was first achieved.

Of the 19 patients who first achieved CDAI remission, lost response and never regained remission by the cut-off date, 10 (53%) reached the end of the study, 4 (21%) discontinued due to an adverse event, 1 (5%) never recaptured response but remained on the study drug and later discontinued upadacitinib due to lack of efficacy and 4 (21%) discontinued due to other reasons. Of the 23 patients who did not recapture CDAI LDA, 7 (30%) reached the end of the study, 6 (26%) discontinued due to an adverse event, 2 (9%) lost response because of discontinuation of upadacitinib due to lack of efficacy, 4 (17%) never recaptured response but remained on the study drug and later discontinued upadacitinib due to lack of efficacy, 2 (9%) voluntarily withdrew before the end of the study and 2 (9%) discontinued for other reasons. Similar results were observed for patients who first achieved SDAI and DAS28 (CRP) disease activity targets but never recaptured response (detailed in online supplemental materials text).

Sustainability of response in the TNF-IR subgroup

The TNF-IR subgroup demonstrated a similar sustainability of response to the overall population of SELECT-BEYOND. Through 240 weeks of follow-up after initially achieving response, 26%/44% of TNF-IR patients who

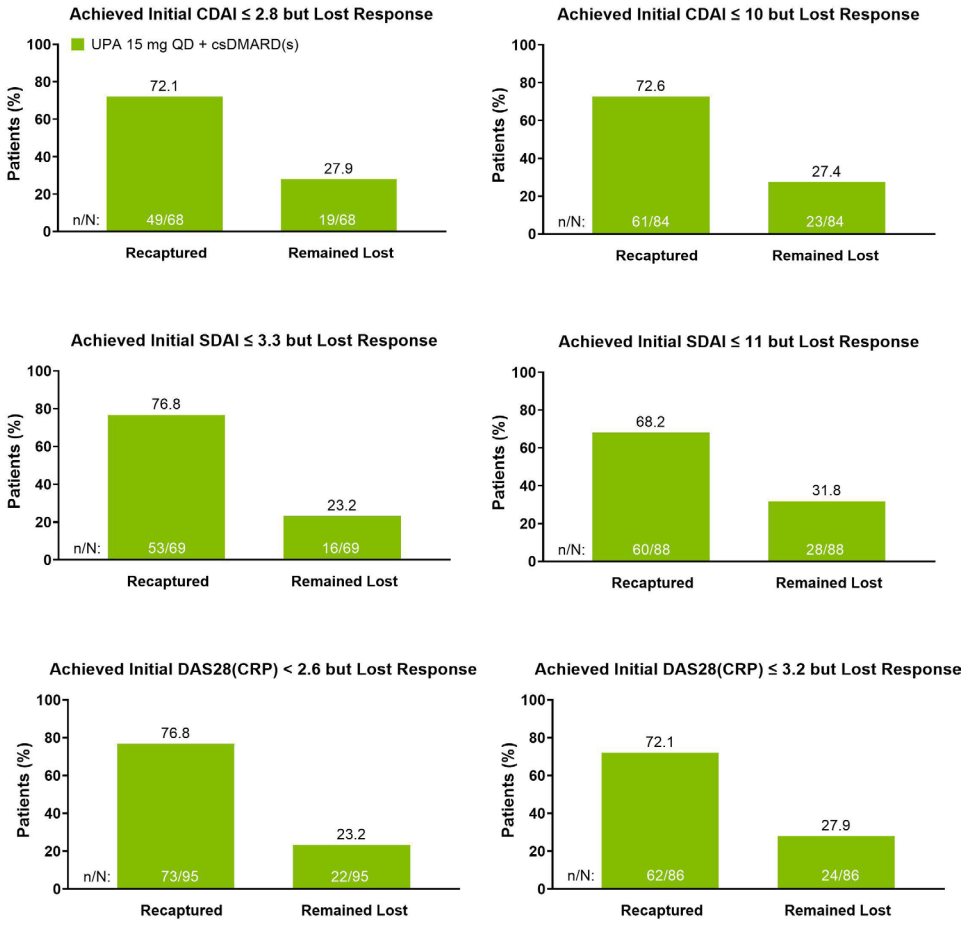

Figure 4 Proportions of patients who lost initial CDAI, DAS28 (CRP) or SDAI targets and either recaptured or failed to regain response by the cut-off date. Data include patients randomised to UPA 15 mg and those who switched from placebo to UPA 15 mg at week 12; those receiving placebo who achieved disease activity targets before or at UPA start date were excluded. CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic DMARD; DAS28 (CRP), 28-joint Disease Activity Score based on C reactive protein; DMARD, disease-modifying antirheumatic drug; QD, once daily; SDAI, Simplified Disease Activity Index; UPA, upadacitinib.

achieved disease activity responses with upadacitinib 15 mg never lost CDAI remission/LDA, 24%/43% never lost SDAI remission/LDA, and 33%/44% never lost DAS28 (CRP) <2.6/≤3.2 by our definition of loss of response (online supplemental figure 1).

Sustainability of response stratified by prior bDMARD exposure and MOA

Upadacitinib treatment demonstrated efficacy in both less refractory (≤2 prior bDMARDs and 1 MOA) and more refractory (>2 prior bDMARDs and ≥2 MOA) patients, although the cumulative achievement of disease activity targets at any point during the trial was numerically higher in the less refractory subgroup (online supplemental figure 2). Similarly, among patients who achieved a response, the less refractory subgroup showed numerically better sustainability of response than the more refractory subgroup (online supplemental figures 3 and 4).

Predictors of sustained response

Of the examined baseline and demographic characteristic variables, including age, sex, number of failed prior biological treatments, time to response, CDAI or DAS28 (CRP) scores, HAQ-DI, levels of rheumatoid factor, CRP or anti-CCP antibody, no strong predictors of sustained clinical response were observed (online supplemental table 2).

DISCUSSION

Understanding the sustainability of treatment response in managing RA can contribute to optimising treatment decisions and improving long-term outcomes for patients with the condition. The study design of SELECT-BEYOND, which allowed patients to enter a long-term extension of up to 5 years, provides an important opportunity to evaluate the long-term response to upadacitinib in patients who were previously refractory to at least one bDMARD. Notably, our results demonstrate that over three-fourths of bDMARD-IR patients with active RA achieved CDAI LDA with upadacitinib 15 mg plus background csDMARD(s), and approximately half of those maintained this response through 240 weeks of follow-up. CDAI remission was attained by approximately half of all patients treated with upadacitinib 15 mg

and was maintained in about a quarter of those patients through 240 weeks after initially achieving remission. These results were consistent in both the overall population of SELECT-BEYOND and the subgroup of TNF-IR patients.

Stringent disease control in RA is associated with better patient outcomes, including inhibition of joint damage, reduced pain, greater functional ability, improved quality of life and reduced systemic complications.[3 6 7] Although the frequency of patients achieving sustained remission has substantially improved in recent years, particularly with the application of treat-to-target treatment strategies and additional therapeutic options, it remains a challenging goal for most patients and healthcare providers.[26–28] While remission is the ideal outcome, LDA nevertheless represents a significant improvement in disease control and can lead to a better quality of life for patients. It is thus notable that in this difficult-to-treat population approximately half of patients who achieved CDAI LDA in our study maintained their initial LDA response through 240 weeks of follow-up.

Of patients who achieved treatment targets and continued upadacitinib treatment, the majority continued to maintain high levels of responsiveness throughout the 5-year trial. For instance, of those who attained CDAI remission and remained in the trial, the vast majority (95%) remained in remission or were in LDA after 180 weeks of follow-up. As a caveat, results showing the distribution of patients in different disease activity states over time are biased, given that those who respond well to treatment are more likely to continue with their treatment and thus have long-term data available. Notably, even though many patients who lost their initial CDAI remission or LDA response showed an MCID for CDAI worsening, most (68%–77%) were still able to recapture remission or LDA by the end of the study, when allowing for modification or addition of background medications. This suggests that the likelihood of recapturing remission/LDA after a flare is high if treated appropriately.

Our results are consistent with previous research suggesting that switching to a b/tsDMARD with a new MOA is more beneficial than cycling to another TNF inhibitor among patients who have previously failed TNF inhibitor therapy.[29 30] Although upadacitinib treatment showed efficacy in both subgroups, we found that higher proportions of less refractory patients (≤2 prior bDMARDs and 1 MOA) achieved disease activity targets and better sustained that response compared with those in the more refractory subgroup (>2 prior bDMARDs and ≥2 MOA). In addition to improved quality of life, controlling RA disease activity plays a crucial role in mitigating the risk of inflammation-related adverse events. RA is associated with a higher risk of major adverse cardiovascular events (MACE), certain cancers, venous thromboembolism (VTE) and serious infections.[31–34] Proper management of RA disease activity is associated with reduced risk of at least some RA comorbidities.[8 35–37] Consistent with this, upadacitinib-treated patients who did not experience MACE or VTE showed greater improvements in their time-weighted changes in disease activity compared with those who did experience MACE or VTE.[38] Although safety outcomes in patients who achieved remission or LDA were not specifically examined in this study, the safety of upadacitinib 15 mg in the overall SELECT-BEYOND population has been described through 5 years[39] and are consistent with integrated safety findings for upadacitinib across the SELECT phase 3 clinical programme, involving over 4000 patients with RA and more than 10 000 patient-years of exposure.[40 41]

While SELECT-BEYOND did not include an active comparator as a reference, there are several factors that may have affected patients' long-term sustainability of response with upadacitinib treatment. First, patients with RA prefer oral treatments vs injections.[42 43] Given that JAK inhibitors are small molecules allowing for oral administration, the simpler treatment regimen provided by upadacitinib could improve long-term medication compliance.[44] Second, small molecule inhibitors avoid the possible loss of efficacy over time that can result from the formation of neutralising or antidrug antibodies to biological treatments.[2 45]

The underlying complexity of RA makes it difficult to predict who will respond to a treatment and when. Among the variables examined in this study, no clear predictors of sustained clinical remission, LDA or DAS28 (CRP) response were identified. A previous assessment of predictors of response to upadacitinib treatment, either as monotherapy or in combination with csDMARDs, also did not identify any baseline characteristics that strongly predicted response to upadacitinib at 6 months; however, composite disease scores at week 12 did appear to be predictive of response at 6 months.[46] Ultimately, additional research into the predictors of response is needed to better tailor treatment to individual patients.

Limitations of this study include potential bias due to the inherent nature of long-term extensions, in which patients who respond well are more likely to be tolerant of the treatment and continue with the study drug. Additional limitations are the lack of a long-term placebo control and the absence of active comparators in the SELECT-BEYOND trial. The proportions of patients who recaptured response reported here could be underestimated due to the short follow-up time after lost response. For analyses of disease activity distribution over 240 weeks of follow-up (figure 3), one constraint is that the follow-up time after the first occurrence of remission or LDA differed across patients, and the numbers shown in this figure may be biased due to this. Analysis of the proportions of patients who recaptured lost response also did not take into consideration how changes in background RA medications may have contributed to the ability of these patients to regain disease control. Because the EULAR definition of difficult-to-treat RA (ie, failure of ≥2 b/tsDMARD with different MOA, after failing csDMARDs)[47] was reported after the start of the SELECT-BEYOND trial, we used slightly different criteria

in evaluating the more refractory subgroup (failure of >2 bDMARDs and ≥2 different MOA). Lastly, our findings do not address the feasibility of long-term sustained remission/LDA in real-world clinical practice, particularly in patients who were excluded from the trial based on the inclusion/exclusion criteria and those who had not failed a bDMARD. Despite these constraints, this examination of the 5-year data from SELECT-BEYOND provides insights into the long-term benefit of upadacitinib in a clinically controlled setting.

In summary, our findings show that ~80% of bDMARD-IR patients were able to achieve LDA or DAS28 (CRP) ≤3.2 at some point during the 5-year study when treated with upadacitinib 15 mg, and approximately half of those patients were able to maintain this lowered disease activity through 240 weeks of follow-up. Clinical remission was attained by 45% of all patients during the study and maintained in approximately 25% of this group through 240 weeks after initially achieving response. As suggested by the treat-to-target strategy, LDA may be a realistic goal in patients who have failed multiple therapies, and this target may be successfully achieved in most patients with upadacitinib treatment.

Author affiliations
[1]Amsterdam University Medical Centres, Amsterdam, The Netherlands
[2]Rheumatology, Emeritus Research and Monash University, Melbourne, Victoria, Australia
[3]Aurora Rheumatology and Immunotherapy Center, Franklin, Wisconsin, USA
[4]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany
[5]AbbVie, North Chicago, Illinois, USA
[6]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, USA

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval SELECT-BEYOND was conducted in accordance with International Council for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. Independent ethics committees and institutional review boards approved all study-related documents. Patients provided written informed consent.

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Data availability statement Data are available on reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports or analysis 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, Statistical Analysis Plan (SAP) and execution of a data sharing agreement (DSA). Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select 'Home'.

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ORCID iDs
Ronald F van Vollenhoven http://orcid.org/0000-0001-6438-8663
Roy Fleischmann http://orcid.org/0000-0002-6630-1477

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