ORIGINAL ARTICLE

Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis

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ABSTRACT

BACKGROUND

The Janus kinase inhibitor upadacitinib is a potential treatment for psoriatic arthritis. The efficacy and safety of upadacitinib as compared with adalimumab, a tumor necrosis factor α inhibitor, in patients who have an inadequate response to nonbiologic disease-modifying antirheumatic drugs are unclear.

METHODS

In a 24-week, phase 3 trial, we randomly assigned patients in a 1:1:1:1 ratio to receive oral upadacitinib at a dose of 15 mg or 30 mg once daily, placebo, or subcutaneous adalimumab (40 mg every other week). The primary end point was an American College of Rheumatology 20 (ACR20) response (≥20% decrease in the number of tender and swollen joints and ≥20% improvement in at least three of five other domains) at week 12 with upadacitinib as compared with placebo. Secondary end points included comparisons of upadacitinib with adalimumab.

RESULTS

A total of 1704 patients received an active drug or placebo. The percentage of patients who had an ACR20 response at week 12 was 70.6% with 15-mg upadacitinib, 78.5% with 30-mg upadacitinib, 36.2% with placebo (P<0.001 for both upadacitinib doses vs. placebo), and 65.0% with adalimumab. The difference between groups for 15-mg upadacitinib as compared with adalimumab was 5.6 percentage points (95% confidence interval [CI], −0.6 to 11.8) and for 30-mg upadacitinib as compared with adalimumab was 13.5 percentage points (95% CI, 7.5 to 19.4). Both upadacitinib doses were noninferior to adalimumab for the ACR20 response at week 12; the 30-mg dose but not the 15-mg dose was superior to adalimumab. The incidence of adverse events through week 24 was 66.9% with 15-mg upadacitinib, 72.3% with 30-mg upadacitinib, 59.6% with placebo, and 64.8% with adalimumab. There were serious infections in 1.2%, 2.6%, 0.9%, and 0.7% of the patients, respectively. Hepatic disorders occurred in 9.1% of patients in the 15-mg upadacitinib group and 12.3% in the 30-mg upadacitinib group, but grade 3 increases in aminotransferase levels occurred in 2% of patients or fewer in all groups.

CONCLUSIONS

The percentage of patients with psoriatic arthritis who had an ACR20 response at week 12 was significantly higher with 15-mg or 30-mg upadacitinib than with placebo. The 30-mg dose but not the 15-mg dose was superior to adalimumab. Adverse events were more frequent with upadacitinib than with placebo. (Funded by AbbVie; SELECT-PsA 1 ClinicalTrials.gov number, NCT03104400.)

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Upadacitinib is an oral, reversible Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis.[1-5] Adalimumab is a tumor necrosis factor α inhibitor used to treat rheumatoid arthritis and psoriatic arthritis. In one trial involving patients with rheumatoid arthritis, upadacitinib at a dose of 15 mg once daily was superior to adalimumab at week 12 in the percentage of patients who had at least 50% improvement according to the American College of Rheumatology (ACR) criteria and in the percentage of patients who had a score of 3.2 or less on the Disease Activity Score for 28 joints (range, 0 to 9.4, with higher scores indicating more disease activity).[2] We conducted SELECT-PsA 1, a double-blind, phase 3 trial comparing upadacitinib with placebo and with adalimumab as an active comparator in patients with psoriatic arthritis who had an inadequate response or unacceptable side effects with nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Methods

Patients

Eligible patients were 18 years of age or older, had received a diagnosis of psoriatic arthritis, fulfilled the Classification Criteria for Psoriatic Arthritis,[6] and had historical or current plaque psoriasis. All the patients had at least 3 swollen joints (of 66 tested) and at least 3 tender joints (of 68 tested) at baseline, the presence at screening of one or more erosions on the hands or feet on radiography (as determined by central imaging review) or a high-sensitivity C-reactive protein level that was greater than the laboratory-defined upper limit of the normal range, and an inadequate response or unacceptable side effects with at least one nonbiologic DMARD. Stable treatment with nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and no more than two nonbiologic DMARDs was permitted but not required. Patients were excluded if they had previous exposure to biologic therapies or JAK inhibitors. Details regarding inclusion and exclusion criteria are provided in Section S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design

The trial was conducted at 281 sites in 45 countries and was initiated in April 2017; the last patient completed week 24 in December 2019 (Table S1 in the Supplementary Appendix). Results for efficacy and safety are presented through week 24 (with the primary end point at week 12). The extension period is ongoing, with up to 3 years of total anticipated trial participation (Fig. S1).

Patients were randomly assigned by means of an interactive-response system in a 1:1:1:1 ratio to receive oral upadacitinib at a dose of either 15 mg or 30 mg once daily, placebo followed by upadacitinib at a dose of 15 mg or 30 mg once daily (1:1 ratio) starting at week 24, or subcutaneous adalimumab at a dose of 40 mg every other week. Randomization was stratified according to the extent of psoriasis (≥3% vs. <3% of body-surface area), current use or nonuse of at least one nonbiologic DMARD, the presence or absence of dactylitis, and the presence or absence of enthesitis.

Starting at week 16, patients who did not have at least 20% improvement in tender and swollen joint counts as compared with baseline at weeks 12 and 16 could initiate background treatment with DMARDs, NSAIDs, acetaminophen, low-potency opioids, or glucocorticoids or adjust the dose if they were already receiving the drug. During the 24-week placebo-controlled period, investigators, patients, and the sponsor were unaware of the trial group assignments.

Trial Oversight

The trial was conducted according to the International Council for Harmonisation guidelines and the principles of the Declaration of Helsinki. All the patients provided written informed consent. The trial protocol, available at NEJM.org, was approved by an independent ethics committee or institutional review board at each site.

The trial was sponsored by AbbVie, which provided upadacitinib, adalimumab, and placebo. Representatives of AbbVie designed the trial, participated in the collection and interpretation of the data, and paid for professional writing assistance, in addition to managing the data collection, maintaining the trial database, and performing the statistical analysis. Confidentiality agreements were in place between the authors and AbbVie. Data were collected by the investigators, their teams, and AbbVie. All the authors contributed to the development of the manuscript with the assistance of a professional medical writer, including interpretation of the data, and approved the final draft for submission. The authors vouch for the completeness and accuracy

of the data, for the fidelity of the trial to the protocol, and for the accurate reporting of adverse events.

END POINTS

The primary end point was at least 20% improvement according to the ACR criteria (ACR20 response) with upadacitinib as compared with placebo at week 12. This end point represents a decrease from baseline of at least 20% in the number of tender and swollen joints and an improvement of at least 20% in at least three of five other domains (an assessment of disease activity on a numerical rating scale by both the patient and the physician, an assessment of disability level based on a patient questionnaire, the patient's assessment of pain on a numerical rating scale, and high-sensitivity C-reactive protein level).

There were 14 multiplicity-controlled secondary end points: the change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score (ranging from 0 to 3, with higher scores indicating greater disability) at week 12[7]; the percentage of patients with a score of 0 or 1 and at least a 2-point decrease from baseline on the Static Investigator Global Assessment (sIGA) of Psoriasis (ranging from 0 to 4, with higher scores indicating more severe skin involvement) at week 16,[8] which was assessed in patients who had a baseline score of at least 2; the percentage of patients with a decrease from baseline of at least 75% in the score on the Psoriasis Area and Severity Index (PASI; ranging from 0 to 72, with higher scores indicating more severe disease) (PASI75 response) at week 16,[9] which was assessed in patients who had an affected body-surface of at least 3% at baseline; the change from baseline in the modified total Sharp–van der Heijde Score (ranging from 0 to 528, with higher scores indicating greater damage) at week 24; the percentage of patients with minimal disease activity (determined by fulfilling five of seven criteria: a tender-joint count of ≤1; a swollen-joint count of ≤1; a PASI score of ≤1 or an affected body-surface area of ≤3%; a score on the patient's assessment of pain of ≤1.5 [ranging from 0 to 10, with higher scores indicating more pain]; a score on the patient's global assessment of disease activity of ≤2 [ranging from 0 to 10, with higher scores indicating more disease activity]; a HAQ-DI score of ≤0.5; and a score on the Leeds Enthesitis Index [LEI] of ≤1 [ranging from 0 to 6, with higher scores indicating more affected sites]) at week 24[10]; the percentage of patients with resolution of enthesitis (LEI score, 0) at week 24,[11] which was assessed in patients with a baseline LEI score greater than 0; noninferiority of upadacitinib to adalimumab for the ACR20 response at week 12; the change from baseline in the score on the 36-Item Short Form Health Survey Physical Component Summary (SF-36 PCS; norm-based scores were used, with higher scores indicating better health-related quality of life) at week 12[12]; the change from baseline in the score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue; ranging from 0 to 52, with higher scores indicating less fatigue) at week 12[13]; superiority of upadacitinib to adalimumab for the ACR20 response at week 12; the percentage of patients with resolution of dactylitis (score of 0 on the Leeds Dactylitis Index [LDI; higher scores indicate more affected sites]) at week 24,[14] which was assessed in patients with a baseline LDI score greater than 0; superiority of upadacitinib to adalimumab for the change from baseline in the patient's assessment of pain (see above) at week 12; superiority of upadacitinib to adalimumab for the change from baseline in the HAQ-DI score at week 12; and the change from baseline in the score on the Self-Assessment of Psoriasis Symptoms (ranging from 0 to 110, with higher scores indicating greater severity of symptoms) at week 16.[15] Additional end points, which were not adjusted for multiplicity, are shown in Table S2. The comparisons of upadacitinib with placebo and with adalimumab that are included here were prespecified.

Changes were made to the protocol and statistical analysis plan during the conduct of the trial to address regulatory-agency feedback regarding the method for noninferiority testing for upadacitinib as compared with adalimumab and for ordering of multiplicity-controlled end points on the basis of data from other trials. All changes were made before the database lock and unmasking of data. The primary and secondary end points were not altered, with the exception of revision of change from baseline in enthesitis to resolution of enthesitis and change from baseline in dactylitis to resolution of dactylitis, removal of the Hochberg test to adjust for multiple comparisons, and revision of the ordering of change in the FACIT-Fatigue score and resolution of dactylitis. Amendments are provided in Section S3 in the Supplementary Appendix.

SAFETY

Adverse event reporting and clinical laboratory testing were performed by investigators who were unaware of the trial group assignments, and safety results are reported through week 24. An independent, external cardiovascular adjudication committee, whose members were unaware of the trial group assignments, adjudicated deaths and cardiovascular events using prespecified definitions.

STATISTICAL ANALYSIS

Efficacy analyses were conducted in the modified intention-to-treat population, which included all the patients who had undergone randomization and had received at least one dose of upadacitinib, placebo, or adalimumab. A sample size of 1640 patients was planned to provide at least 90% power to detect a difference between upadacitinib and placebo for the primary end point and for most key secondary end points and at least 85% power for evaluating the noninferiority and superiority of each upadacitinib dose as compared with adalimumab with respect to the ACR20 response at week 12. The trial was not powered to compare upadacitinib with adalimumab regarding the change from baseline in pain and in the HAQ-DI score. All power and sample-size calculations were performed at a two-sided significance level of 0.025, with a dropout rate of 10% taken into account.

The overall type I error rate for the calculations of the primary end point and the 14 ranked secondary end points was controlled with the use of a two-part sequential graphical multiple-testing procedure. Part 1 started with the primary end point, with the use of $\alpha \div 2$ (α was 0.0499) for each dose followed by a prespecified hierarchical α transfer path that included downstream transfer along the end-point sequence within each dose as well as cross-dose transfer between each upadacitinib dose (Fig. S2). Part 2 was tested only if the results for all end points for both doses in Part 1 were significant. If the results for some end points in Part 1 were not significant, then no α was passed to part 2 of the analysis. The end points in part 2 were tested with the use of level α in a fixed sequence. Once the results for an end point were deemed to be significant, its significance level was transferred to subsequent end points following the prespecified order. When the hierarchical analysis failed, subsequent end points were not tested and only point estimates with multiplicity-unadjusted 95% confidence intervals are given.

For binary end points, trial groups were compared with the use of the Cochran–Mantel–Haenszel test, with adjustment for current DMARD use for each upadacitinib dose as compared with placebo. Imputation of nonresponse was used for the handling of missing data. Between-group differences in the percentage of patients with a response and the associated 95% confidence intervals with the use of normal approximation for the between-group difference are presented. For the percentage of patients with an ACR20 response at week 12, the noninferiority of each upadacitinib dose to adalimumab was assessed with the use of Koch's three-group approach; noninferiority was achieved if upadacitinib preserved at least 50% of the placebo-subtracted adalimumab effect. Additional details are provided in Section S4 in the Supplementary Appendix. The original plan for noninferiority comparison of upadacitinib with adalimumab for the ACR20 response at week 12 used a margin of 15 percentage points, and this analysis is also presented.

For nonradiographic continuous end points, analyses were conducted with the use of a mixed-effects model for repeated measures (MMRM) with fixed effects of treatment, visit, treatment-by-visit interaction, current DMARD use (yes vs. no), and the corresponding baseline value as a covariate. Missing data were handled by means of MMRM, with the assumption of missing data at random. Least-squares mean differences and the associated 95% confidence intervals are provided with the use of MMRM. Prespecified sensitivity analyses that used the tipping-point method were performed for the change from baseline in the HAQ-DI score. Post hoc sensitivity analyses were performed for the SF-36 PCS and FACIT-Fatigue scores (Table S3). The confidence intervals for differences between groups for additional secondary end points and sensitivity analyses were not adjusted for multiplicity, and no clinical inferences can be drawn from those data. Additional details are provided in the statistical analysis plan, available with the protocol at NEJM.org.

RESULTS

PATIENTS

Of the 1705 patients who underwent randomization, 1704 received at least one dose of an active drug or placebo (429 received the 15-mg dose of upadacitinib, 423 received the 30-mg dose of upadacitinib, 423 received placebo, and 429 received adalimumab) (Fig. S3). Overall, 1548 patients (90.8%) completed week 24 while receiving upadacitinib, placebo, or adalimumab. The demographic and clinical characteristics of the patients at baseline were similar across groups (Table 1).

EFFICACY

At week 12, an ACR20 response (primary end point) occurred in 303 patients (70.6%) receiving the 15-mg dose of upadacitinib, in 332 (78.5%) receiving the 30-mg dose of upadacitinib, in 153 (36.2%) receiving placebo, and in 279 (65.0%) receiving adalimumab (Fig. 1A and Table 2). The between-group differences were as follows: 15-mg dose of upadacitinib as compared with placebo, 34.5 percentage points (95% confidence interval [CI], 28.2 to 40.7; P<0.001); 30-mg dose of upadacitinib as compared with placebo, 42.3 percentage points (95% CI, 36.3 to 48.3; P<0.001); 15-mg dose of upadacitinib as compared with adalimumab, 5.6 percentage points (95% CI, −0.6 to 11.8; the hierarchical analysis failed at this point, so no P value is given); and 30-mg dose of upadacitinib as compared with adalimumab, 13.5 percentage points (95% CI, 7.5 to 19.4; P<0.001).

On the basis of Koch's three-group noninferiority method, the adalimumab effect preservation was 119.4% (95% CI, 98.0 to 147.9) with the 15-mg dose of upadacitinib and 146.6% (95% CI, 122.8 to 180.4) with the 30-mg dose of upadacitinib, findings that showed noninferiority of both doses to adalimumab, because the lower boundary of the 95% confidence interval was above the prespecified threshold of 50%. The originally prespecified analysis that used a noninferiority margin of 15 percentage points gave similar results to the Koch analysis (Fig. S4). The 30-mg dose of upadacitinib was superior to adalimumab in achieving an ACR20 response, but the 15-mg dose of upadacitinib was not superior to adalimumab, which prevented the testing of significance for secondary end points lower in the end-point hierarchy.

Additional end points of clinical importance in psoriatic arthritis that were analyzed in the statistical hierarchy and for which results were significantly better with both doses of upadacitinib than with placebo were the change from baseline in the HAQ-DI score, the percentage of patients with a score on the sIGA of Psoriasis of 0 or 1 and at least a 2-point decrease from baseline, the percentage of patients with a PASI75 response, the change from baseline in the modified total Sharp–van der Heijde Score, the percentage of patients in whom minimal disease activity was achieved and resolution of enthesitis occurred, and the change from baseline in the SF-36 PCS and FACIT-Fatigue scores (Table 2 and Figs. S5 through S10, S12, and S13). Sensitivity analyses for the change from baseline in the HAQ-DI, SF-36 PCS, and FACIT-Fatigue scores yielded similar results (Table S3).

End points that could not be analyzed owing to failure of the hierarchy at the point of ACR20 response with upadacitinib at a dose of 15 mg as compared with adalimumab include resolution of dactylitis comparing upadacitinib with placebo and the change from baseline in the patient's assessment of pain with upadacitinib as compared with adalimumab, the change from baseline in the HAQ-DI score as compared with adalimumab, and the change from baseline in the Self-Assessment of Psoriasis Symptoms as compared with placebo. Responses to adalimumab as compared with upadacitinib are shown in Table 2 and Figures S5 through S10, S12, and S13.

ACR50 and ACR70 responses are of special interest to the field of rheumatology, and comparisons of the 15-mg and 30-mg doses of upadacitinib with placebo and with adalimumab for these end points were prespecified; however, confidence intervals were not adjusted for multiple comparisons, and no conclusions can be drawn from the results. The results of the comparisons of the two doses of upadacitinib with placebo with respect to ACR50 and ACR70 responses were generally in the same direction as those for the primary end point and for the comparison of the 30-mg dose of upadacitinib with adalimumab. No significant differences were noted in the comparison of the 15-mg dose of upadacitinib with adalimumab for the ACR50

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Upadacitinib, 15 mg (N=429)	Upadacitinib, 30 mg (N=423)	Placebo (N=423)	Adalimumab (N=429)
Female sex — no. (%)	238 (55.5)	236 (55.8)	211 (49.9)	222 (51.7)
Age — yr	51.6±12.2	49.9±12.4	50.4±12.2	51.4±12.0
White race — no. (%)†	386 (90.0)	377 (89.1)	377 (89.1)	375 (87.4)
Body-mass index ≥25 — no. (%)‡	342 (79.7)	319 (75.4)	329 (77.8)	334 (77.9)
Duration of psoriatic arthritis — yr	6.2±7.4	5.9±6.4	6.2±7.0	5.9±7.1
Any nonbiologic DMARD at baseline — no. (%)§	353 (82.3)	346 (81.8)	347 (82.0)	347 (80.9)
Methotrexate alone	279 (65.0)	268 (63.4)	267 (63.1)	270 (62.9)
Methotrexate + another nonbiologic DMARD	20 (4.7)	27 (6.4)	26 (6.1)	16 (3.7)
Nonbiologic DMARD other than methotrexate	54 (12.6)	51 (12.1)	54 (12.8)	61 (14.2)
Glucocorticoid use at baseline — no. (%)	73 (17.0)	71 (16.8)	70 (16.5)	72 (16.8)
Tender-joint count of 68 joints	20.4±14.7	19.4±13.3	20.0±14.3	20.1±13.8
Swollen-joint count of 66 joints	11.6±9.3	10.6±7.1	11.0±8.2	11.6±8.8
High-sensitivity C-reactive protein >ULN — no. (%)¶	324 (75.5)	324 (76.6)	324 (76.6)	308 (71.8)
HAQ-DI score‖	1.2±0.7	1.1±0.6	1.1±0.6	1.1±0.6
Score for patient's assessment of pain**	6.2±2.1	5.9±2.1	6.1±2.1	6.0±2.1
Affected body-surface area ≥3% — no. (%)	214 (49.9)	210 (49.6)	211 (49.9)	211 (49.2)
PASI score††	9.8±10.0	9.5±8.8	11.2±11.4	9.4±8.5
Score on the sIGA of Psoriasis — no. (%)‡‡				
0	34 (7.9)	21 (5.0)	24 (5.7)	34 (7.9)
1	73 (17.0)	78 (18.4)	86 (20.3)	65 (15.2)
2	170 (39.6)	173 (40.9)	167 (39.5)	181 (42.2)
3	133 (31.0)	128 (30.3)	119 (28.1)	132 (30.8)
4	19 (4.4)	23 (5.4)	27 (6.4)	17 (4.0)
Presence of enthesitis — no. (%)§§	270 (62.9)	267 (63.1)	241 (57.0)	265 (61.8)
Presence of dactylitis — no. (%)¶¶	136 (31.7)	127 (30.0)	126 (29.8)	127 (29.6)

* Plus–minus values are means ±SD. Upadacitinib at either dose was administered orally once daily, and adalimumab was administered subcutaneously at a dose of 40 mg every other week. DMARD denotes disease-modifying antirheumatic drug.

† Race was reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Permitted concomitant nonbiologic DMARDs included methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychloroquine, bucillamine, and iguratimod.

¶ The upper limit of the normal range (ULN) for C-reactive protein is 2.87 mg per liter.

‖ Scores on the Health Assessment Questionnaire–Disability Index (HAQ-DI) range from 0 to 3, with higher scores indicating worse disability.

** Scores for the patient's assessment of pain were on a numerical rating scale from 0 to 10, with higher scores indicating greater severity of pain.

†† Shown is the score on the Psoriasis Area and Severity Index (PASI; range, 0 to 72, with higher scores indicating greater severity of psoriasis) among patients with an affected body-surface area of at least 3%.

‡‡ Scores on the Static Investigator Global Assessment (sIGA) of Psoriasis range from 0 to 4, with higher scores indicating more severe skin involvement.

§§ The presence of enthesitis was defined by a score greater than 0 on the Leeds Enthesitis Index (range, 0 to 6, with higher scores indicating more affected sites).

¶¶ The presence of dactylitis was defined by a score greater than 0 on the Leeds Dactylitis Index (higher scores indicate more affected sites).

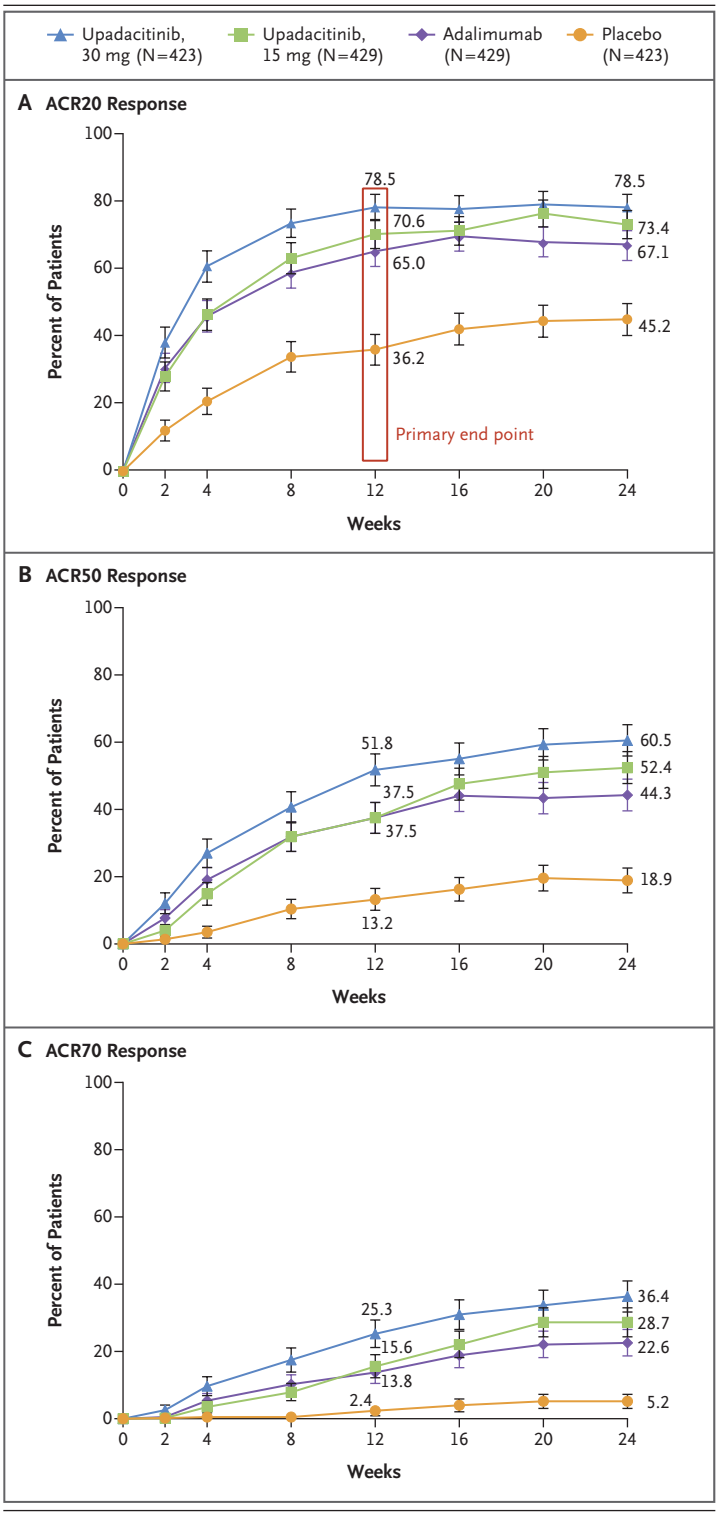

Figure 1. ACR20, ACR50, and ACR70 Responses over a Period of 24 Weeks.

Patients were randomly assigned to receive oral upadacitinib at a dose of 15 mg or 30 mg once daily, placebo, or subcutaneous adalimumab at a dose of 40 mg every other week. Panel A shows the percentage of patients with at least 20% improvement in the American College of Rheumatology (ACR) response criteria (ACR20 response). P<0.001 for the comparisons of the two upadacitinib doses with placebo with respect to the ACR20 response at 12 weeks (primary end point) and for the comparison of the 30-mg dose of upadacitinib with adalimumab. The noninferiority criterion was met for both upadacitinib doses as compared with adalimumab. Panel B shows the percentage of patients with at least 50% improvement in ACR response criteria (ACR50 response), and Panel C shows the percentage of patients with at least 70% improvement (ACR70 response). Missing data were imputed as nonresponse. I bars indicate 95% confidence intervals.

or ACR70 response at 12 weeks; confidence intervals at 12 and 24 weeks are shown in Table S4. Results for additional end points, including different time points for the primary and secondary end points, are shown in Figure 1 and Figures S5 through S14.

SAFETY

Through week 24, the incidences of adverse events and serious adverse events, including serious infections, were similar with the 15-mg dose of upadacitinib and adalimumab but were more frequent with the 30-mg dose of upadacitinib (Table 3). The most common adverse event was upper respiratory tract infection (Table S5). The incidence of serious infections was 1.2% with the 15-mg dose of upadacitinib, 2.6% with the 30-mg dose of upadacitinib, 0.9% with placebo, and 0.7% with adalimumab. Up to week 24, opportunistic infections included one case of candida urethritis with the 15-mg dose of upadacitinib and one case each of *Pneumocystis jirovecii* pneumonia and cytomegalovirus with the 30-mg dose of upadacitinib. Herpes zoster was diagnosed in four patients receiving the 15-mg dose of upadacitinib, in five receiving the 30-mg dose of upadacitinib, in three receiving placebo, and in none receiving adalimumab. Cancer occurred in one patient each in the 15-mg upadacitinib and placebo groups and in three patients each in the 30-mg upadacitinib and adalimumab groups; the types of cancer are shown in Table 3. No major adverse cardiovascular events were reported with upadacitinib. One pulmonary embolism was reported with the 30-mg dose of upadacitinib; one

Table 2. Primary and Secondary End Points.*

End Point	Upadacitinib, 15 mg (N=429)	Upadacitinib, 30 mg (N=423)	Placebo (N=423)	Adalimumab (N=429)
Primary				
ACR20 response at wk 12 — no. (%)†	303 (70.6)	332 (78.5)	153 (36.2)	279 (65.0)
Difference vs. placebo — percentage points (95% CI)	34.5 (28.2 to 40.7); P<0.001	42.3 (36.3 to 48.3); P<0.001		
Secondary				
Least-squares mean change in HAQ-DI score at wk 12 (95% CI)	−0.42 (−0.47 to −0.37) [404]	−0.47 (−0.52 to −0.42) [398]	−0.14 (−0.18 to −0.09) [392]	−0.34 (−0.38 to −0.29) [406]
Least-squares mean difference vs. placebo (95% CI)	−0.28 (−0.35 to −0.22); P<0.001	−0.34 (−0.40 to −0.27); P<0.001		
Score on the sIGA of Psoriasis of 0 or 1 and a decrease of ≥2 points from baseline at wk 16 — no./total no. (%) ‡	135/322 (41.9)	175/324 (54.0)	34/313 (10.9)	127/330 (38.5)
Difference vs. placebo — percentage points (95% CI)	31.1 (24.7 to 37.5); P<0.001	43.1 (36.7 to 49.6); P<0.001		
PASI75 response at wk 16 — no./total no. (%) §	134/214 (62.6)	131/210 (62.4)	45/211 (21.3)	112/211 (53.1)
Difference vs. placebo — percentage points (95% CI)	41.3 (32.8 to 49.8); P<0.001	41.1 (32.5 to 49.6); P<0.001		
Least-squares mean change in mTSS at wk 24 (95% CI)¶	−0.04 (−0.16 to 0.07) [391]	0.03 (−0.08 to 0.15) [383]	0.25 (0.13 to 0.36) [372]	0.01 (−0.11 to 0.13) [384]
Least-squares mean difference vs. placebo (95% CI)	−0.29 (−0.44 to −0.14); P<0.001	−0.21 (−0.36 to −0.06); P=0.007		
Minimal disease activity at wk 24 — no. (%)‖	157 (36.6)	192 (45.4)	52 (12.3)	143 (33.3)
Difference vs. placebo — percentage points (95% CI)	24.3 (18.8 to 29.8); P<0.001	33.1 (27.4 to 38.8); P<0.001		
Resolution of enthesitis at wk 24 — no./total no. (%)**	145/270 (53.7)	154/267 (57.7)	78/241 (32.4)	125/265 (47.2)
Difference vs. placebo — percentage points (95% CI)	21.3 (13.0 to 29.7); P<0.001	25.3 (16.9 to 33.7); P<0.001		
ACR20 response at wk 12: noninferiority of upadacitinib to adalimumab — no. (%)	303 (70.6)	332 (78.5)	153 (36.2)	279 (65.0)
Percentage of adalimumab effect preserved (95% CI)††	119.4 (98.0 to 147.9); P<0.001	146.6 (122.8 to 180.4); P<0.001		
Least-squares mean change in SF-36 PCS score at wk 12 (95% CI)‡‡	7.9 (7.1 to 8.6) [405]	8.9 (8.1 to 9.7) [398]	3.2 (2.4 to 4.0) [394]	6.8 (6.1 to 7.6) [410]
Least-squares mean difference vs. placebo (95% CI)	4.7 (3.7 to 5.7); P<0.001	5.7 (4.7 to 6.7); P<0.001		
Least-squares mean change in FACIT-Fatigue score (95% CI)§§	6.3 (5.4 to 7.2) [404]	7.1 (6.2 to 8.0) [398]	2.8 (1.9 to 3.7) [394]	5.7 (4.8 to 6.6) [410]
Least-squares mean difference vs. placebo (95% CI)	3.5 (2.4 to 4.7); P<0.001	4.3 (3.1 to 5.5); P<0.001		
ACR20 response at wk 12: superiority of upadacitinib to adalimumab — no. (%)	303 (70.6)	332 (78.5)	153 (36.2)	279 (65.0)
Difference vs. adalimumab — percentage points (95% CI)	5.6 (−0.6 to 11.8)¶¶	13.5 (7.5 to 19.4); P<0.001		

Resolution of dactylitis at wk 24 — no./total no. (%)‖‖	104/136 (76.5)	101/127 (79.5)	50/126 (39.7)	94/127 (74.0)
Difference vs. placebo — percentage points (95% CI)	36.8 (25.7 to 47.9)	39.8 (28.8 to 50.9)		
Least-squares mean change in patient's assessment of pain at wk 12: superiority of upadacitinib to adalimumab (95% CI)***	−2.3 (−2.5 to −2.0) [404]	−2.7 (−2.9 to −2.5) [398]	−0.9 (−1.2 to −0.7) [392]	−2.3 (−2.5 to −2.1) [406]
Least-squares mean difference vs. adalimumab (95% CI)	0.0 (−0.3 to 0.3)	−0.5 (−0.7 to −0.2)		
Change in HAQ-DI score at wk 12: superiority of upadacitinib to adalimumab	−0.42 (−0.47 to −0.37) [404]	−0.47 (−0.52 to −0.42) [398]	−0.14 (−0.18 to −0.09) [392]	−0.34 (−0.38 to −0.29) [406]
Least-squares mean difference vs. adalimumab (95% CI)	−0.08 (−0.15 to −0.01)	−0.14 (−0.20 to −0.07)		
Least-squares mean change in Self-Assessment of Psoriasis Symptoms score at wk 16 — (95% CI)†††	−25.3 (−27.3 to −23.4) [396]	−28.1 (−30.0 to −26.1) [395]	−8.2 (−10.2 to −6.3) [388]	−22.7 (−24.7 to −20.8) [407]
Least-squares mean difference vs. placebo (95% CI)	−17.1 (−19.6 to −14.6)	−19.8 (−22.3 to −17.3)		

* The primary and secondary efficacy end points were subject to a graphical testing procedure to control for the global type I error. For continuous end points, the number of patients with available data is shown in brackets.

† Patients with an American College of Rheumatology 20 (ACR20) response had a decrease from baseline of at least 20% in the number of tender and swollen joints and an improvement of at least 20% in at least three of five other domains.

‡ Results were assessed in patients with baseline score of at least 2.

§ A PASI75 response indicates a decrease of at least 75% from baseline in the PASI score. Results were assessed in patients with an affected body-surface area of at least 3% at baseline.

¶ Values for the modified total Sharp–van der Heijde Score (mTSS) range from 0 to 528, with higher scores indicating greater damage.

‖ Minimal disease activity was determined by fulfilling five of seven criteria: a tender-joint count of 0 or 1; a swollen-joint count of 0 or 1; a PASI score of 0 or 1 or an affected body-surface area of 3% or less; a score on the patient assessment of pain of 1.5 or less (range, 0 to 10, with higher scores indicating more pain); a score on the patient's global assessment of disease activity of 2 or less (range, 0 to 10, with higher scores indicating more disease activity); a HAQ-DI score of 0.5 or less; and a score on the Leeds Enthesitis Index of 0 or 1.

** Resolution of enthesitis was defined by a score of 0 on the Leeds Enthesitis Index. Results were assessed in patients with a baseline score greater than 0.

†† The percentage of adalimumab effect preserved was based on Koch's three-group noninferiority approach and calculated as [(upadacitinib − placebo) ÷ (adalimumab − placebo) × 100%].

‡‡ Norm-based scores were used for the score on the 36-Item Short Form Health Survey Physical Component Summary (SF-36 PCS), with higher scores indicating better health-related quality of life.

§§ Scores on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) range from 0 to 52, with higher scores indicating less fatigue.

¶¶ For the secondary end points, hierarchical testing failed at the end point of "ACR20 response at week 12: superiority of upadacitinib to adalimumab" in the comparison of the 15-mg dose of upadacitinib with adalimumab.

‖‖ Resolution of dactylitis was defined by a score of 0 on the Leeds Dactylitis Index. Results were assessed in patients with a baseline score greater than 0.

*** The patient's assessment of pain was determined on the same scale as in the criterion for minimal disease activity.

††† Scores on the Self-Assessment of Psoriasis Symptoms range from 0 to 110, with higher scores indicating greater severity of symptoms.

Table 3. Safety Summary through Week 24.*

Event or Variable	Upadacitinib, 15 mg (N=429)	Upadacitinib, 30 mg (N=423)	Placebo (N=423)	Adalimumab (N=429)
Patients with adverse events — no. (%)				
Any adverse event	287 (66.9)	306 (72.3)	252 (59.6)	278 (64.8)
Serious adverse event	14 (3.3)	26 (6.1)	13 (3.1)	16 (3.7)
Adverse event leading to discontinuation of placebo, upadacitinib, or adalimumab	13 (3.0)	21 (5.0)	13 (3.1)	22 (5.1)
Death	0	0	1 (0.2)	0
Infection	169 (39.4)	183 (43.3)	140 (33.1)	146 (34.0)
Serious	5 (1.2)	11 (2.6)	4 (0.9)	3 (0.7)
Opportunistic	1 (0.2)	2 (0.5)	0	0
Herpes zoster†	4 (0.9)	5 (1.2)	3 (0.7)	0
Active tuberculosis	0	0	0	0
Hepatic disorder	39 (9.1)	52 (12.3)	16 (3.8)	67 (15.6)
Cancer‡	1 (0.2)	3 (0.7)	1 (0.2)	3 (0.7)
Nonmelanoma skin cancer	0	2 (0.5)	1 (0.2)	0
Cancer other than nonmelanoma skin cancer	1 (0.2)	1 (0.2)	0	3 (0.7)
Lymphoma	0	0	0	0
Anemia	3 (0.7)	20 (4.7)	4 (0.9)	1 (0.2)
Neutropenia	4 (0.9)	21 (5.0)	1 (0.2)	10 (2.3)
Lymphopenia	6 (1.4)	15 (3.5)	5 (1.2)	1 (0.2)
Elevated creatine kinase level	38 (8.9)	41 (9.7)	6 (1.4)	24 (5.6)
Renal dysfunction	0	0	1 (0.2)	0
Major adverse cardiovascular event§	0	0	1 (0.2)	2 (0.5)
Venous thromboembolism¶	0	1 (0.2)	1 (0.2)	2 (0.5)
Least-squares mean change in laboratory measures from baseline to wk 24				
Hemoglobin — g/dl	−0.7±9.8	−2.7±9.6	0.0±7.7	2.7±9.2
Neutrophils — $\times 10^{-9}$/liter	−0.515±1.939	−0.834±1.856	0.052±1.659	−1.015±1.695
Lymphocytes — $\times 10^{-9}$/liter	0.064±0.527	0.143±0.604	0.095±0.419	0.443±0.575
Platelets — $\times 10^{-9}$/liter	−2.1±57.7	6.7±58.7	−4.7±55.4	−20.3±50.6
LDL cholesterol — mmol/liter	0.408±0.790	0.447±0.809	0.025±0.619	0.034±0.634
HDL cholesterol — mmol/liter	0.223±0.270	0.249±0.294	0.003±0.230	0.080±0.270
ALT — U/liter	6.1±20.7	7.9±23.4	−1.0±16.9	5.0±19.7
AST — U/liter	5.7±13.8	7.1±12.5	−1.1±15.3	2.9±13.2
Creatinine — μmol/liter	4.7±10.1	6.3±8.8	1.6±8.8	4.1±39.3
Creatine kinase — U/liter	85.2±110.8	140.0±342.8	20.0±331.3	25.8±105.3

* Plus–values are means ±SD. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*. Laboratory data were graded with the use of the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03. Changes in laboratory variables are reported on the basis of single measurements. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, HDL high-density lipoprotein, and LDL low-density lipoprotein.

† All cases of herpes zoster were nonserious and mild or moderate in severity, without ophthalmic, central nervous system, or other internal organ involvement.

‡ In the placebo group, one patient had basal-cell carcinoma. In the 15-mg upadacitinib group, one patient had neuroendocrine carcinoma. In the 30-mg upadacitinib group, two patients had basal-cell carcinoma and one had a malignant lung neoplasm. In the adalimumab group, one patient each had colon cancer, ovarian cancer, and uterine cancer.

§ Major adverse cardiovascular events were defined as nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes and were adjudicated by an independent committee whose members were unaware of the trial group assignments.

¶ Venous thromboembolism was defined as deep-vein thrombosis or pulmonary embolism. Cases were adjudicated by an independent committee whose members were unaware of the trial group assignments.

case of deep-vein thrombosis was reported with placebo and two cases with adalimumab. One death, adjudicated to be of unknown cause, was reported with placebo.

Mean hemoglobin, neutrophil, lymphocyte, and platelet levels remained within normal limits from baseline through week 24 in all trial groups (Table S6 and Fig. S17). Anemia and lymphopenia adverse events were reported at similar incidences with the 15-mg dose of upadacitinib and placebo but were more frequent with the 30-mg dose of upadacitinib (Table 3). Neutropenia adverse events were more common with upadacitinib than with placebo. Overall, the frequency of laboratory abnormalities of grade 3 or higher was no more than 2.1% (Table S7). One patient each had a grade 3 decrease in hemoglobin level or platelet count after discontinuation of the 30-mg dose of upadacitinib. The frequency of grade 3 decreases in neutrophil and lymphocyte levels was higher in the 30-mg upadacitinib group than in the other groups.

The incidence of adverse events involving hepatic disorders was 9.1% in the 15-mg upadacitinib group, 12.3% in the 30-mg upadacitinib group, 3.8% in the placebo group, and 15.6% in the adalimumab group. Most increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels were of grade 2 or less. Grade 3 elevations in ALT levels occurred in 0.9% with the 15-mg dose of upadacitinib, 1.2% with the 30-mg dose of upadacitinib, 1.7% with placebo, and 0.9% with adalimumab. Grade 3 elevations in AST levels occurred in 0%, 0.7%, 0.5%, and 0.2% with the 15-mg dose of upadacitinib, the 30-mg dose of upadacitinib, placebo, and adalimumab, respectively. One patient in the 30-mg upadacitinib group had a grade 4 increase in the AST level at a single time point. No patients met Hy's law criteria suggestive of drug-induced liver injury. Grade 3 or 4 increases in creatine kinase levels were more common with upadacitinib than with adalimumab and placebo; no patients had rhabdomyolysis. Increases in levels of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were observed more often with upadacitinib than with placebo (Fig. S18). The ratio of LDL cholesterol to HDL cholesterol and the ratio of total cholesterol to HDL cholesterol did not change substantially through week 24.

DISCUSSION

This trial compared upadacitinib at a dose of 15 mg or 30 mg once daily with placebo and used adalimumab as an active comparator over a period of 24 weeks in patients with psoriatic arthritis who had an inadequate response to nonbiologic DMARDs. The results for most musculoskeletal end points were significantly better with upadacitinib than placebo. The 15-mg and 30-mg doses of upadacitinib were noninferior to adalimumab with respect to the ACR20 response at week 12; the 30-mg dose, but not the 15-mg dose, was superior to adalimumab with respect to the ACR20 response. Results were better with both upadacitinib doses than with placebo in other aspects of psoriatic arthritis, including objective measures of psoriasis activity, achievement of minimal disease activity and resolution of enthesitis, physical function, fatigue, quality of life, and inhibition of radiographic progression. Additional outcomes, including resolution of dactylitis, patient-reported improvement in psoriasis symptoms, and additional comparisons with adalimumab, could not be analyzed owing to failure of the hierarchical analysis.

There are limited data on which to base assumptions for comparisons of upadacitinib with adalimumab. This resulted in challenges in selecting end points comparing upadacitinib with adalimumab, in powering comparisons between upadacitinib doses and with adalimumab, and in selecting a noninferiority margin. Because the sample size was similar to the collective sample sizes of the adalimumab and placebo groups in previous trials, the inclusion of placebo, adalimumab, and upadacitinib groups allowed estimation of the adalimumab treatment effect as compared with placebo to establish noninferiority. At the time of trial design, the appropriate end point for comparison with an active comparator was undefined and ACR20 response was the generally accepted primary end point for studies involving patients with psoriatic arthritis.

The safety profile of upadacitinib was generally similar to that reported previously in trials involving patients with rheumatoid arthritis, but direct comparisons of adverse events between trials for these two diseases cannot be made.[1-5] Serious infections were more frequent with the 30-mg dose of upadacitinib than with placebo or adalimumab. The incidences of herpes zoster

were similar and were approximately 1% for both doses of upadacitinib and placebo. Dose-dependent elevations in creatine kinase levels were reported with upadacitinib. Adverse events involving hepatic disorders were observed with upadacitinib, and grade 3 increases in ALT or AST levels were reported in 2% or less of patients across all groups. Dose-dependent increases in LDL and HDL cholesterol levels were observed with upadacitinib without changes in serum lipid ratios. No major adverse cardiovascular events were reported with upadacitinib. One pulmonary embolism occurred with the 30-mg dose of upadacitinib. Owing to the 24-week duration of the placebo-controlled portion of this trial, limited safety conclusions can be made for events that could emerge with longer use of upadacitinib or adalimumab.

In this trial, upadacitinib at a dose of 15 mg or 30 mg once daily was more effective than placebo in most measures of psoriatic arthritis activity and inhibited radiographic progression of disease. Both upadacitinib doses were noninferior to adalimumab; the 30-mg dose but not the 15-mg dose of upadacitinib was superior to adalimumab with respect to the ACR20 response at week 12. There were more adverse events with either dose of upadacitinib than with placebo and more serious adverse events with the 30-mg dose of upadacitinib. Longer and larger trials are required to determine the effect and risks of upadacitinib and its effects as compared with other drugs used to treat psoriatic arthritis.

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