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Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Upadacitinib is an oral selective Janus kinase inhibitor to treat rheumatoid arthritis. The efficacy and safety of upadacitinib as compared with abatacept, a T-cell costimulation modulator, in patients with rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs (DMARDs) are unclear.

METHODS

In this 24-week, phase 3, double-blind, controlled trial, we randomly assigned patients in a 1:1 ratio to receive oral upadacitinib (15 mg once daily) or intravenous abatacept, each in combination with stable synthetic DMARDs. The primary end point was the change from baseline in the composite Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP; range, 0 to 9.4, with higher scores indicating more disease activity) at week 12, assessed for noninferiority. Key secondary end points at week 12 were the superiority of upadacitinib over abatacept in the change from baseline in the DAS28-CRP and the percentage of patients having clinical remission according to a DAS28-CRP of less than 2.6.

RESULTS

A total of 303 patients received upadacitinib, and 309 patients received abatacept. From baseline DAS28-CRP values of 5.70 in the upadacitinib group and 5.88 in the abatacept group, the mean change at week 12 was −2.52 and −2.00, respectively (difference, −0.52 points; 95% confidence interval [CI], −0.69 to −0.35; P<0.001 for noninferiority; P<0.001 for superiority). The percentage of patients having remission was 30.0% with upadacitinib and 13.3% with abatacept (difference, 16.8 percentage points; 95% CI, 10.4 to 23.2; P<0.001 for superiority). During the treatment period, one death, one nonfatal stroke, and two venous thromboembolic events occurred in the upadacitinib group, and more patients in the upadacitinib group than in the abatacept group had elevated hepatic aminotransferase levels.

CONCLUSIONS

In patients with rheumatoid arthritis refractory to biologic DMARDs, upadacitinib was superior to abatacept in the change from baseline in the DAS28-CRP and the achievement of remission at week 12 but was associated with more serious adverse events. Longer and larger trials are required in order to determine the effect and safety of upadacitinib in patients with rheumatoid arthritis. (Funded by AbbVie; SELECT-CHOICE Clinicaltrials.gov number, NCT03086343.)

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Upadacitinib is an oral, reversible Janus kinase (JAK) inhibitor with selectivity for JAK1 over JAK2, JAK3, and tyrosine kinase 2[1] that has been approved for the treatment of rheumatoid arthritis.[2-6] Studies have shown remission with the use of upadacitinib in approximately 30% of patients regardless of previous treatment, including those who had not previously received methotrexate or who had had treatment failure with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or biologic DMARDs.[2-6] Abatacept, a drug approved for the treatment of rheumatoid arthritis, modulates T-cell costimulation by binding to CD80 and CD86 receptors on antigen-presenting cells, thereby inhibiting T-cell proliferation and B-cell stimulation. The efficacy and safety of abatacept have been shown in phase 3 trials involving patients with active rheumatoid arthritis and an inadequate response to methotrexate or biologic DMARDs.[7-12]

Multiple head-to-head trials comparing a tumor necrosis factor (TNF) inhibitor with another biologic DMARD have been conducted in patients with rheumatoid arthritis with an inadequate response to conventional synthetic DMARDs.[10,12-15] The SELECT-CHOICE trial, a phase 3, double-blind trial involving patients with an inadequate response to biologic DMARDs, was designed to compare the efficacy and safety of a JAK inhibitor (upadacitinib) with those of a biologic DMARD (abatacept), each in combination with stable background conventional synthetic DMARDs.

Methods

Patients

We recruited patients 18 years of age or older with a diagnosis of rheumatoid arthritis for at least 3 months who also met the 2010 American College of Rheumatology (ACR)–European League against Rheumatism classification criteria for rheumatoid arthritis.[16] Patients had moderate-to-severe active disease (defined as a swollen-joint count [SJC] of ≥6 out of 66 and a tender-joint count [TJC] of ≥6 out of 68 in conjunction with a high-sensitivity C-reactive protein [hs-CRP] level of ≥3 mg per liter) despite treatment for at least 3 months with at least one biologic DMARD or had had unacceptable side effects from at least one biologic DMARD. In accordance with the protocol, patients had to have been receiving conventional synthetic DMARDs for at least 3 months and taking a stable dose of up to two conventional synthetic DMARDs for at least 4 weeks before entry. Patients were excluded if they had previous exposure to a JAK inhibitor or abatacept or had a history of inflammatory joint disease other than rheumatoid arthritis. A complete list of eligibility criteria is provided in Section S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design

We conducted a randomized, double-blind, phase 3, active-comparator–controlled trial at 120 sites in 28 countries (Section S1). Patients were randomly assigned by means of an interactive response technology system in a 1:1 ratio to receive either extended-release oral upadacitinib (15 mg once daily) or intravenous abatacept (at day 1 and weeks 2, 4, 8, 12, 16, and 20 [500 mg in patients with a body weight of <60 kg, 750 mg in those with a weight of 60 to 100 kg, and 1000 mg in those with a weight of >100 kg]). Patients in the upadacitinib group also received placebo intravenous infusions, and patients in the abatacept group also received oral placebo. All biologic DMARDs must have been discontinued with the use of a protocol-specified washout period, and biologic therapies were prohibited during the trial. Patients were to continue protocol-specified stable background conventional synthetic DMARDs, nonsteroidal antiinflammatory drugs, acetaminophen, or oral or inhaled glucocorticoids. Starting at week 12, patients who did not have at least a 20% decrease in both the TJC and the SJC as compared with baseline at two consecutive visits were to have background medications adjusted or added. All the patients who completed week 24 were eligible to remain in an open-label, long-term extension period of the trial for up to 5 years, receiving upadacitinib at a dose of 15 mg once daily under the same trial registration as the randomized trial (Fig. S1 in the Supplementary Appendix).

Randomization was stratified according to the number of previous biologic DMARDs and geographic region. The trial extension is ongoing; data presentation includes the 24-week double-blind period during which investigators, patients, and the sponsor were unaware of the treatment assignments.

According to the initial protocol, we planned

to evaluate upadacitinib at a dose of 30 mg once daily; the protocol was amended to assess upadacitinib at a dose of 15 mg on October 12, 2017, on the basis of the results from other phase 3 trials of upadacitinib in patients with rheumatoid arthritis showing that the 30-mg dose provided minimal incremental benefit over the 15-mg dose. (The initial and amended protocols are available at NEJM.org.) A total of 44 patients had been assigned to either upadacitinib at a dose of 30 mg once daily or intravenous abatacept under the initial protocol; of these, patients who completed week 24 could remain in the open-label, long-term extension period of the trial while receiving upadacitinib at a dose of 30 mg once daily. The efficacy and safety results from these patients are not included in the analyses presented here; they are presented separately in Tables S6 and S7.

TRIAL OVERSIGHT

The trial was conducted according to the International Council for Harmonisation guidelines, applicable regulations and guidelines governing the conduct of clinical trials, and the principles of the Declaration of Helsinki. All the patients provided written informed consent. The trial protocol was approved by independent ethics committees and institutional review boards. AbbVie designed the trial, participated in the collection and interpretation of the data, and paid for professional writing assistance. AbbVie performed the statistical analysis according to the prespecified statistical analysis plan. Confidentiality agreements were in place between the authors and AbbVie. Abatacept was manufactured by Bristol Myers Squibb and purchased by AbbVie through commercial sources. 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, review of drafts, and approval of the final draft for submission. The authors vouch for the accuracy and completeness of the data and the reporting of adverse events and for the fidelity of the trial to the protocol.

END POINTS

The primary end point was the change from baseline in the Disease Activity Score for 28 joints (DAS28-CRP) at week 12, tested for the noninferiority of upadacitinib to abatacept. The DAS28-CRP is a continuous but nonlinear composite measure ranging from 0 to 9.4, with higher scores indicating more active disease. The score is calculated on the basis of a continuous scale of combined measures of the TJC of 28 joints (TJC28); the SJC of 28 joints (SJC28); the patient's global assessment of disease activity (PtGA) on a visual-analogue scale ranging from 0 to 100, with higher scores indicating greater disease activity; and the hs-CRP level measured in milligrams per liter. The formula is

$$\begin{aligned}\text{DAS28-CRP} = {} & 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \\ & \times \sqrt{(\text{SJC28})} + 0.36 \times \ln(\text{hs-CRP} + 1) + 0.014 \\ & \times \text{PtGA} + 0.96,\end{aligned}$$

where $\sqrt{}$ is square root and ln is natural log. The level of disease activity was categorized as follows: a DAS28-CRP of less than 2.6 indicated remission; 2.6 to less than 3.2, low disease activity; 3.2 to 5.1, moderate disease activity; and more than 5.1, high disease activity.[17]

Key secondary end points at week 12 were the superiority of upadacitinib over abatacept in the change from baseline in the DAS28-CRP and superiority in the percentage of patients having clinical remission based on the DAS28-CRP, defined as a score of less than 2.6. There were 14 prespecified exploratory end points as listed and defined in the protocol and Table S1.

SAFETY

Adverse events, physical examination findings, vital-sign measurements, electrocardiographic results, and clinical laboratory results (hematologic, chemical, and urologic) were monitored for the entire trial duration. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 22.0. The Rheumatology Common Toxicity Criteria, version 2.0,[18] were used to grade adverse events and laboratory changes, except for creatine kinase and creatinine, which were graded with the use of the Common Toxicity Criteria of the National Cancer Institute.[19] An external data monitoring committee reviewed the safety data. An independent, external cardiovascular adjudication committee whose members were unaware of the treatment assignments adjudicated reported cardiovascular events (including major adverse cardiovascular events and venous thromboem-

bolic events) and all deaths as defined in the charter of that committee.

STATISTICAL ANALYSIS

A sample of 550 patients was planned to provide the trial with at least 90% power for testing the noninferiority of upadacitinib to abatacept for the change from baseline in the DAS28-CRP at week 12 with a margin of 0.6, with the assumption of a true difference between upadacitinib and abatacept in this outcome of 0.5 with an assumed standard deviation of 2.0 (at a two-sided 0.05 level accounting for withdrawal of 10% of the patients). The 0.6 margin was based on the meta-analysis of treatment effect of biologic agents on the DAS28 in patients who had an inadequate response to biologics.[20,21]

The overall type I error rate of the primary and ranked key secondary end points was controlled with the use of a step-down approach, in which significance could be claimed for a lower-ranked end point only if the previous end point in the sequence showed a significant difference between the two groups. A post hoc analysis of the mean change from baseline in the TJC28 and SJC28 components of the DAS28-CRP was performed. Results for the prespecified exploratory end points and post hoc analyses were not adjusted for multiple comparisons, and unadjusted confidence intervals are presented, from which no clinical inferences can be drawn.

Efficacy and safety analyses were conducted in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of upadacitinib at a dose of 15 mg once daily or abatacept under the amended protocol. For binary end points, treatments were compared with the use of the Cochran–Mantel–Haenszel test, with adjustment for the main stratification factor of previous failed biologic DMARD. Imputation of nonresponse was used for the handling of missing data. For continuous end points, analyses were conducted with the use of the analysis-of-covariance model with treatment group as the fixed factor and with the corresponding baseline value and the main stratification factor as covariates. Multiple imputation with the fully conditional specification method was used for missing data. Additional details are provided in Section S3 and in the statistical analysis plan, available with the protocol at NEJM.org.

RESULTS

PATIENTS

From May 2017 through September 2019, a total of 613 patients underwent randomization; 612 received at least one dose of a trial drug (303 received upadacitinib, and 309 received abatacept) (Fig. 1). Approximately 90% of the patients completed week 24. The percentage of patients who discontinued treatment did not differ substantially between the two treatment groups. Baseline demographic characteristics, disease characteristics, and the severity of disease activity for all the patients in the modified intention-to-treat population did not differ substantially between the two treatment groups (Table 1).

EFFICACY

Primary and Key Secondary End Points

At baseline, the mean DAS28-CRP was 5.70 in the upadacitinib group and 5.88 in the abatacept group. At week 12, the mean change from baseline in the DAS28-CRP was −2.52 points and −2.00 points, respectively (difference, −0.52 points; 95% confidence interval [CI], −0.69 to −0.35; P<0.001 for noninferiority; P<0.001 for superiority) (Table 2 and Fig. S2). Results of subgroup analyses of the primary end point according to baseline disease characteristics and stratification factors are shown in Figure S3.

The percentage of patients having remission according to a DAS28-CRP of less than 2.6 was 30.0% with upadacitinib and 13.3% with abatacept (difference, 16.8 percentage points; 95% CI, 10.4 to 23.2; P<0.001) (Table 2). Similar results were obtained from the post hoc analysis that used multiple imputation for missing data (Table S2). The change from baseline over a period of 24 weeks in the DAS28-CRP core components is shown in Figure 2. At week 12, the mean changes from baseline for the components of the primary end point for upadacitinib and abatacept, respectively, were −10.49 and −9.32 for the TJC28, −7.73 and −7.31 for the SJC28, −33.85 and −28.35 for the PtGA, and −12.34 mg per liter and −7.13 mg per liter for the hs-CRP level; 95% confidence intervals are shown in Table 2. The percentage of patients who did not have at least a 20% decrease in both the TJC and the SJC as compared with baseline at two consecutive visits starting at week 12 was 5.0% for upadacitinib and 5.8% for abatacept; 1.7% and

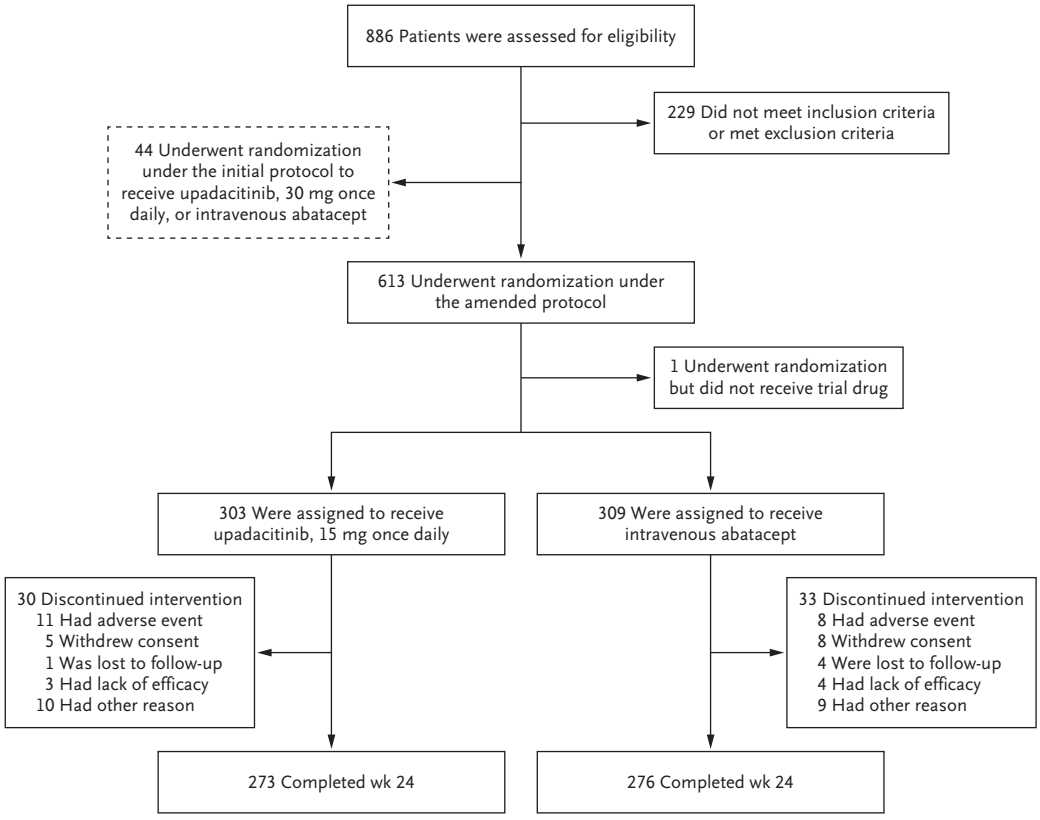

Figure 1. Screening, Randomization, and Follow-up to Week 24.

In the initial protocol, upadacitinib was to be evaluated at a dose of 30 mg once daily (box with dashed lines). The protocol was amended to assess upadacitinib at a dose of 15 mg after other phase 3 trials involving patients with rheumatoid arthritis showed that the 30-mg dose provided minimal incremental benefit over the 15-mg dose.

2.3% of the patients in the respective groups had their background medications adjusted.

Exploratory End Points

Results for exploratory end points that do not include the hs-CRP level were generally in the same direction as the results for the primary end point. The percentage of patients having remission according to the DAS28 based on the erythrocyte sedimentation rate (DAS28-ESR) at week 12 is shown in Figure S6, and the percentage of patients having remission according to the Clinical Disease Activity Index (CDAI) at week 12 is shown in Figure S7. Results for additional prespecified exploratory end points, including the percentage of patients who had a response according to ACR criteria, other measures of remission and low disease activity, and patient-reported outcomes, are shown in Figures S4 through S11.

SAFETY

Throughout the 24-week trial period, the incidences of serious adverse events, adverse events leading to discontinuation of the trial drug, and severe adverse events were numerically higher with upadacitinib than with abatacept (Table 3). Serious adverse events were reported in 10 patients (3.3%) receiving upadacitinib and in 5 patients (1.6%) receiving abatacept (Table S3). Serious infections occurred in 3 patients (1.0%) receiving upadacitinib and in 1 patient (0.3%) receiving abatacept. Opportunistic infections were reported in 4 patients receiving upadacitinib (3 patients with oral candidiasis and 1 patient with esophageal candidiasis) and in 1 receiving abatacept (oral candidiasis). Herpes zoster infection occurred in 8 patients (4 in each treatment group; 1.3%); no cases were serious, and most affected a single dermatome. Three patients prematurely

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

Characteristic	Upadacitinib (N=303)	Abatacept (N=309)
Female sex — no. (%)	249 (82.2)	253 (81.9)
Duration of rheumatoid arthritis — yr	12.4±9.5	11.8±8.3
Age — yr	55.3±11.4	55.8±11.9
Race — no. (%)†		
White	288 (95.0)	285 (92.2)
Black	7 (2.3)	14 (4.5)
American Indian or Alaska Native	1 (0.3)	2 (0.6)
Asian	5 (1.7)	6 (1.9)
Multiple	2 (0.7)	2 (0.6)
Geographic region — no. (%)		
North America	72 (23.8)	73 (23.6)
South America and Central America	98 (32.3)	99 (32.0)
Western Europe	43 (14.2)	45 (14.6)
Eastern Europe	77 (25.4)	77 (24.9)
Asia	4 (1.3)	4 (1.3)
Other	9 (3.0)	11 (3.6)
Body-mass index — no. (%)‡		
<25	96 (31.7)	88 (28.5)
≥25	207 (68.3)	221 (71.5)
Oral glucocorticoid use at baseline — no. (%)	169 (55.8)	158 (51.1)
Positive for rheumatoid factor and anti–cyclic citrullinated peptide antibodies — no. (%)	189 (62.4)	201 (65.0)
No. of previous biologic DMARDs — no. (%)		
0§	4 (1.3)	2 (0.6)
1	206 (68.0)	202 (65.4)
2	64 (21.1)	70 (22.7)
3	29 (9.6)	35 (11.3)
Tender-joint count of 28 joints	14.40±6.49	15.63±6.53
Swollen-joint count of 28 joints	10.45±4.72	11.26±5.09
Patient's global assessment of disease activity — mm¶	66.82±19.92	69.61±20.83
C-reactive protein — mg/liter	15.95±18.48	17.38±21.12
DAS28-CRP‖	5.70±0.90	5.88±0.94
DAS28-ESR‖	6.36±0.92	6.57±0.99
Clinical Disease Activity Index**	38.54±11.37	40.74±12.05

* Plus–minus values are means ±SD. Patients were randomly assigned to receive oral upadacitinib (15 mg once daily) or intravenous abatacept. Percentages may not total 100 because of rounding. DMARD denotes disease-modifying antirheumatic drug.
† Race was reported by the patient. The categories shown are those that were used when data on race were collected.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ These patients had not received any of the protocol-specified biologic DMARDs before trial entry.
¶ Values range from 0 to 100 mm (visual-analogue scale), with higher values indicating more disease activity.
‖ Values for the 28-joint Disease Activity Score, which is based on the C-reactive protein level (DAS28-CRP) or on the erythrocyte sedimentation rate (DAS28-ESR), range from 0 to 9.4, with higher values indicating more active rheumatoid arthritis.
** Values range from 0 to 76, with higher scores indicating greater disease activity.

Table 2. Primary and Key Ranked Secondary End Points and Change from Baseline in DAS28-CRP Components at Week 12.

Variable	Upadacitinib (N=303)	Abatacept (N=309)	Difference (95% CI)	P Value
Primary and key secondary end points				
Primary end point: change from baseline in DAS28-CRP, assessed for noninferiority of upadacitinib to abatacept				
No. of patients with available data	287	285		
Change (95% CI)	−2.52 (−2.66 to −2.37)	−2.00 (−2.14 to −1.85)	−0.52 (−0.69 to −0.35)	<0.001
First key secondary end point: change from baseline in DAS28-CRP, assessed for superiority of upadacitinib over abatacept				
No. of patients with available data	287	285		
Change (95% CI)	−2.52 (−2.66 to −2.37)	−2.00 (−2.14 to −1.85)	−0.52 (−0.69 to −0.35)	<0.001
Second key secondary end point: percentage of patients with clinical remission according to DAS28-CRP of <2.6, assessed for superiority				
No. of patients with available data	287	285		
Percentage (95% CI)	30.0 (24.9 to 35.2)	13.3 (9.5 to 17.1)	16.8 (10.4 to 23.2)*	<0.001
Change from baseline in DAS28-CRP components†				
Tender-joint count of 28 joints				
No. of patients with available data	290	295		
Change (95% CI)	−10.49 (−11.16 to −9.82)	−9.32 (−9.97 to −8.66)	−1.17 (−1.96 to −0.39)	
Swollen-joint count of 28 joints				
No. of patients with available data	290	295		
Change (95% CI)	−7.73 (−8.20 to −7.26)	−7.31 (−7.77 to −6.85)	−0.41 (−0.97 to 0.14)	
Patient's global assessment of disease activity				
No. of patients with available data	290	294		
Change (95% CI) — mm	−33.85 (−37.06 to −30.63)	−28.35 (−31.51 to −25.19)	−5.49 (−9.27 to −1.71)	
High-sensitivity C-reactive protein				
No. of patients with available data	287	286		
Change (95% CI) — mg/liter	−12.34 (−13.75 to −10.93)	−7.13 (−8.52 to −5.73)	−5.21 (−6.87 to −3.56)	

* The difference is shown in percentage points.
† Because of a lack of a prespecified statistical plan for adjustment for multiple testing, no clinical inferences can be drawn from these data.

discontinued the trial drug owing to herpes zoster infection (2 patients receiving upadacitinib and 1 patient receiving abatacept). Hepatic disorders were reported in 23 patients (7.6%) receiving upadacitinib and in 5 patients (1.6%) receiving abatacept; most cases were elevations in the alanine aminotransferase or aspartate aminotransferase level and were nonserious. No cancers or gastrointestinal perforations were reported during the 24 weeks.

One major adverse cardiovascular event (nonfatal stroke) was reported in a patient in the upadacitinib group who had a history of cerebrovascular accident (Section S4). Two venous thromboembolic events were reported in the upadacitinib group: deep-vein thrombosis in a patient with hypertension and obesity, and pulmonary embolism in a patient who had a previous pulmonary embolism (Section S5). Non–treatment-emergent deaths were defined as deaths

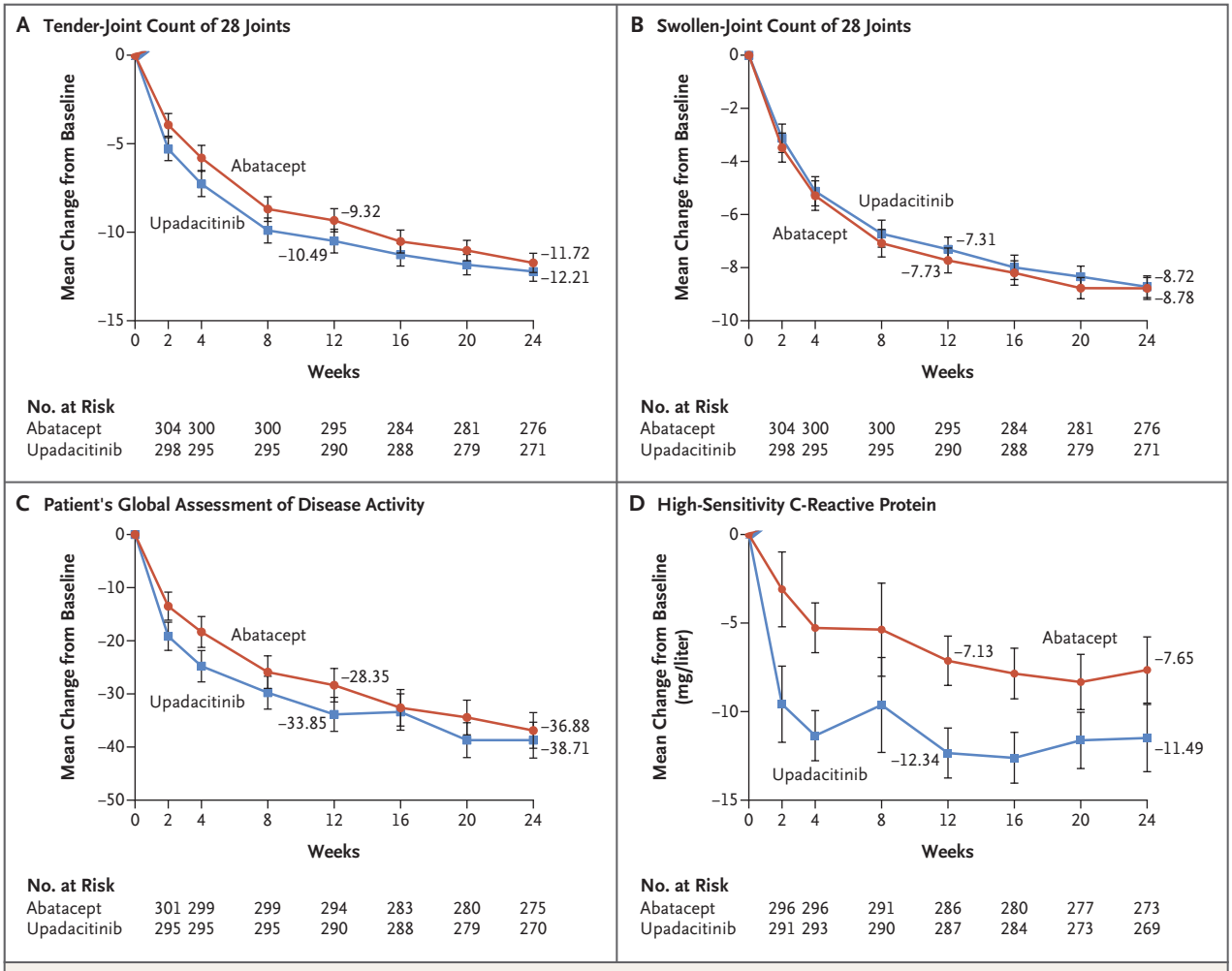

Figure 2. Mean Change from Baseline over a Period of 24 Weeks in the Core Components of the DAS28-CRP.

Values for the Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP) are determined on the basis of a continuous scale of combined measures of the tender-joint count of 28 joints (Panel A), the swollen-joint count of 28 joints (Panel B), the patient's global assessment of disease activity, and the high-sensitivity C-reactive protein level (Panel D). Values for the patient's global assessment of disease activity are determined on the basis of a visual-analogue scale ranging from 0 to 100, with higher scores indicating greater disease activity. The I bars indicate 95% confidence intervals.

that occurred more than 70 days after the last dose of abatacept or more than 30 days after the last dose of upadacitinib. Three deaths occurred: one treatment-emergent death in the upadacitinib group (due to cardiac arrest after an initial hospitalization with pneumonia) and one non–treatment-emergent death in each of the treatment groups (both adjudicated as having an undetermined or unknown cause of death). These deaths are described in detail in Section S6.

The mean values for key hematologic variables (levels of hemoglobin, lymphocytes, neutrophils, and platelets) were within the normal laboratory reference range at baseline and at all visits for both treatment groups (Fig. S12). A higher percentage of patients had grade 3 or 4 decreases in hemoglobin or lymphocyte levels with upadacitinib than with abatacept. Grade 3 decreases in the neutrophil level were observed in a similar percentage of patients in each treatment group (Table S4).

One case of a grade 3 increase and two cases of a grade 4 increase in the creatine kinase level were reported with upadacitinib; all three patients were asymptomatic, and none had rhabdomyolysis or discontinued upadacitinib owing to

Table 3. Adverse Events through Week 24.

Event	Upadacitinib (N=303)		Abatacept (N=309)	
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*
Any adverse event	209	69.0 (59.9–79.0)	189	61.2 (52.8–70.5)
Serious adverse event	10	3.3 (1.6–6.1)	5	1.6 (0.5–3.8)
Adverse event leading to discontinuation of trial drug	14	4.6 (2.5–7.8)	9	2.9 (1.3–5.5)
Death*	2	0.7 (0.1–2.4)	1	0.3 (0.0–1.8)
Treatment-emergent	1	0.3	0	
Non–treatment-emergent	1	0.3	1	0.3
Serious infection	3	1.0 (0.2–2.9)	1	0.3 (0.0–1.8)
Opportunistic infection	4	1.3 (0.4–3.4)	1	0.3 (0.0–1.8)
Herpes zoster infection	4	1.3 (0.4–3.4)	4	1.3 (0.4–3.3)
Hepatic disorder	23	7.6 (4.8–11.4)	5	1.6 (0.5–3.8)
Gastrointestinal perforation	0		0	
Cancer, including nonmelanoma skin cancer	0		0	
Major adverse cardiovascular event†	1	0.3 (0.0–1.8)	0	
Venous thromboembolic event†	2	0.7 (0.1–2.4)	0	

* Treatment-emergent deaths were defined as deaths that occurred after the first dose and within 30 days after the last dose of upadacitinib or within 70 days after the last dose of abatacept. Non–treatment-emergent deaths were defined as deaths that occurred more than 30 days after the last dose of upadacitinib or more than 70 days after the last dose of abatacept.

† These events were adjudicated by an independent, external cardiovascular adjudication committee whose members were unaware of the treatment assignments.

the increase in the creatine kinase level. Grade 3 elevations in the alanine aminotransferase level occurred in 2.6% of the patients receiving upadacitinib and in no patients receiving abatacept. Grade 3 elevations in the aspartate aminotransferase level were reported in 2.6% of the patients receiving upadacitinib, and grade 4 elevations were reported in 0.3%; in the abatacept group, grade 3 elevations in the aspartate aminotransferase level were reported in 0.3% of the patients. No patients met Hy's law criteria suggestive of drug-induced liver injury.

Changes in laboratory values from baseline to week 24 are shown in Table 4. Through week 24, the mean change from baseline in levels of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were greater with upadacitinib than with abatacept (Fig. S13). There was no meaningful change in the ratio of LDL cholesterol to HDL cholesterol and the ratio of total cholesterol to HDL cholesterol through week 24 (Table S5).

DISCUSSION

In our phase 3 trial, upadacitinib, a JAK inhibitor, was compared with abatacept, a T-cell costimulation inhibitor, in patients with rheumatoid arthritis who had had inadequate responses to biologic DMARDs. The DAS28 composite score is a measure of disease activity that is used to assess individual treatment response, with a decrease of 1.2 considered to be a significant change for an individual patient.[22,23] Whether this decrease can be applied to determine differences between treatment groups has not been established. Our trial examined the mean change in the DAS28-CRP at the group level in both active-treatment groups, as has been done in other trials involving patients with rheumatoid arthritis.[24,25] Upadacitinib, when administered with stable conventional DMARDs, was superior to abatacept in the mean change from baseline in the DAS28-CRP at week 12 (–2.52 vs. –2.00), with a difference of –0.52 points (95% CI, –0.69

Table 4. Change in Laboratory Values from Baseline to Week 24.*

Variable	Upadacitinib (N = 303)	Abatacept (N = 309)
	least-squares mean change	
Hemoglobin — g/dl	−0.4±9.5	2.7±8.8
Neutrophil count — $\times 10^{-9}$/liter	−1.08±2.31	−0.90±2.10
Lymphocyte count — $\times 10^{-9}$/liter	0.02±0.62	0.16±0.82
Platelet count — $\times 10^{-9}$/liter	−9.6±64.2	−17.1±64.3
LDL cholesterol — mmol/liter	0.37±0.76	0.05±0.68
LDL cholesterol — % change	15.81±28.31	4.16±24.15
HDL cholesterol — mmol/liter	0.20±0.39	0.05±0.28
HDL cholesterol — % change	16.23±27.40	5.10±20.79
ALT — U/liter	3.5±21.2	0.0±10.2
AST — U/liter	5.4±17.8	1.1±8.2
Creatinine — μmol/liter	4.6±9.7	2.2±9.4
Creatine kinase — U/liter	86.4±247.4	20.0±52.4

* Plus–values are means ±SD. 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.

to −0.35). Upadacitinib was also superior with regard to the percentage of patients having remission according to a DAS28-CRP of less than 2.6 at week 12.

Of the components of the DAS28-CRP, the SJC28 did not differ substantially between the two treatment groups; the findings for the other components were generally in the same direction as the findings for the primary end point, but no conclusions can be made regarding them because of the lack of a statistical plan for multiple testing. The finding that remission according to the DAS28-CRP occurred in 30.0% of the patients in the upadacitinib group is consistent with the findings of other phase 3 trials of upadacitinib involving patients with rheumatoid arthritis who had not previously received methotrexate or who had had an inadequate response to methotrexate, conventional synthetic DMARDs, or biologic DMARDs.[2-6] A higher percentage of patients having remission according to the DAS28-CRP with upadacitinib than with abatacept was observed at week 12.

JAK inhibitors are involved in the interleukin-6 signaling pathway and have an effect on CRP[26]; therefore, we did exploratory analyses of remission measures that do not incorporate hs-CRP levels, such as remission according to the DAS28-ESR and remission according to the CDAI, both of which showed results in the same direction as the results for the primary end point. Abatacept also showed efficacy and safety results similar to previously reported results of abatacept in patients with rheumatoid arthritis and an inadequate response to TNF inhibitors.[7,11]

More adverse events were reported with upadacitinib than with abatacept. Two adjudicated venous thromboembolic events, one major adverse cardiac event, and a higher percentage of patients with grade 3 or 4 elevations in hepatic enzyme and creatine kinase levels were reported with upadacitinib. The frequency of herpes zoster infection did not differ between the treatment groups. One death during the treatment period was reported in a patient who received upadacitinib, and one death after the trial period was reported in each of the treatment groups.

In patients with rheumatoid arthritis refractory to previous biologic DMARD therapy, upadacitinib was superior to abatacept with regard to remission but was associated with more adverse events and serious adverse events. Additional data from longer and larger trials are needed to better understand long-term outcomes and safety of upadacitinib as compared with other drugs for the treatment of rheumatoid arthritis.

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