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ORIGINAL ARTICLE

Effect of abrocitinib and dupilumab on eosinophil levels in patients with moderate-to-severe atopic dermatitis

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Abstract

Background: Eosinophilia is common in patients with atopic dermatitis (AD). Abrocitinib, an oral Janus kinase-1 inhibitor and dupilumab, an anti–interleukin-4 receptor-α antibody, are approved for moderate-to-severe AD. Dupilumab has been associated with transient eosinophilia.

Objectives: To assess the effect of abrocitinib and dupilumab on eosinophils in patients from the phase 3 JADE COMPARE (NCT03720470) and JADE EXTEND (NCT03422822) trials.

Methods: In JADE COMPARE, patients received once-daily oral abrocitinib (200/100 mg), placebo or subcutaneous dupilumab (300 mg, biweekly) with background topical therapy. In the ongoing long-term JADE EXTEND study (Data cutoff: April 22, 2020), dupilumab-treated patients from JADE COMPARE received once-daily abrocitinib (200/100 mg) with background topical therapy. The proportion of patients with

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eosinophilia and hypereosinophilia, and association of eosinophilia with clinical efficacy was assessed. Adverse events (AEs) were also assessed.

Results: Of the 837 patients in JADE COMPARE, 58 (25.7%), 47 (19.7%) and 51 (21.1%) had eosinophilia at baseline in the abrocitinib 200 mg, abrocitinib 100 mg and dupilumab groups, respectively. At Week 16, eosinophilia decreased with abrocitinib 200 mg (9.3%) and abrocitinib 100 mg (19.0%) but not dupilumab (21.5%); no cases of hypereosinophilia were observed with abrocitinib 200 mg compared with abrocitinib 100 mg (1.9%) and dupilumab (2.3%). Decreases in median eosinophil counts were greater with abrocitinib 200 mg (difference, $-100/mm^3$) and abrocitinib 100 mg ($-70/mm^3$) than dupilumab ($+25/mm^3$) or placebo ($+30/mm^3$) at Week 16. Similar trends were observed in patients with comorbid asthma and allergic rhinitis. Eosinophilia decreased from baseline to Week 12 in dupilumab-treated patients who switched to abrocitinib in JADE EXTEND. Decreased eosinophil counts with abrocitinib correlated positively with improvements in AD severity, itch and sleep loss. No eosinophilia-associated AEs occurred.

Conclusions: Abrocitinib decreased eosinophilia in patients with moderate-to-severe AD who had baseline eosinophilia. Resolution of eosinophilia was associated with abrocitinib clinical efficacy.

KEYWORDS

atopic dermatitis, clinical trials, eosinophil disorders

INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease associated with intense pruritus and impaired quality of life.[1,2] Pro-inflammatory eosinophils play an important role in mediating the inflammatory response in AD.[3] Under normal conditions, eosinophils localize to specific organs, excluding the skin and reside at low levels in the blood.[4] In AD, T helper type 2 (Th2) responses in skin are characterized by interleukin (IL)−4, IL-5 and IL-13 release.[5,6] IL-4 facilitates eotaxin-3 production, the main chemokine that mediates chemotaxis of eosinophils from the vasculature to sites of inflammation.[7] IL-5 stimulates eosinophil proliferation, differentiation and maturation,[8] whereas IL-13, a central mediator of inflammation in AD, promotes eosinophil survival and activation.[9,10] The activity of these cytokines is mediated via the Janus kinase (JAK)-signal transducer and activator of transcription pathway, specifically JAK1/JAK2 (IL-5) and JAK1/tyrosine kinase 2 (IL-13).[8–10]

Approximately 30% of patients with moderate-to-severe AD have blood eosinophilia (eosinophil count $>500/mm^3$), with some categorized as having hypereosinophilia (eosinophil count $>1500/mm^3$).[11–14] In an observational study, the mean (SD) eosinophil count at baseline in patients with moderate-to-severe AD was $290 \pm 205.7/mm^3$ compared with $153.3 \pm 113.7/mm^3$ in healthy individuals.[15] A real-world study reported a mean eosinophil count of $460 \pm 400/mm^3$ at baseline in patients with AD.[12] Eosinophil levels can be associated with AD severity, with numerically higher counts observed in patients with severe disease.[15–17]

Dupilumab, a monoclonal anti–IL-4 receptor α antibody that blocks the effects of IL-4 and IL-13, is approved for treatment-resistant moderate-to-severe AD.[18] Dupilumab was associated with a transient increase in eosinophil levels both in clinical trials and real-world studies.[12–14,19–24] Patients with very high levels of circulating eosinophils tended to remain asymptomatic, with no increase in associated adverse events (AEs).[13,20] However, the clinical consequence of this increase is not fully understood, and other studies have proposed that increased eosinophil levels after treatment with dupilumab are associated with the incidence of conjunctivitis in patients with AD.[22,23,25] As such, eosinophilic conditions are a precaution for use of dupilumab[18,26] and may prompt discontinuation in some patients with moderate-to-severe AD.[13]

JAK selective inhibitors such as tofacitinib, ruxolitinib and upadacitinib have been shown to reduce

pathologically elevated eosinophil counts in patients with hypereosinophilic syndrome with cutaneous involvement, and in patients with AD.[27,28] Abrocitinib is an oral, once-daily, JAK1-selective inhibitor approved for the treatment of adult[29–32] and adolescent patients with moderate-to-severe AD.[29,30] The efficacy and safety of abrocitinib was established in multiple randomized controlled clinical trials.[33–37] In the phase 3 JADE COMPARE trial, abrocitinib 200 mg with background topical therapy rapidly improved itch, compared with dupilumab and placebo, in patients with moderate-to-severe AD.[33,34] In addition, abrocitinib 200 and 100 mg significantly decreased the severity and extent of AD as assessed by Investigator's Global Assessment (IGA) and Eczema Area and Severity Index score (EASI) compared with placebo at Weeks 12 and 16.[33] The effect of abrocitinib treatment on circulating eosinophil levels in patients with AD is not known. This post hoc analysis investigated the effect of abrocitinib and dupilumab on eosinophil levels and the clinical consequences of eosinophilia in patients with moderate-to-severe AD from JADE COMPARE and the long-term extension study JADE EXTEND. The effect of abrocitinib and dupilumab treatment on eosinophil count in patients with comorbid inflammatory diseases (asthma and allergic rhinitis) was also examined.

METHODS

Study design and treatment

JADE COMPARE (NCT03720470) was a phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled clinical trial designed to compare the efficacy and safety of abrocitinib, dupilumab and placebo in combination with background topical therapy in patients with moderate-to-severe AD.[33] Details of the study design have been previously described.[33] Briefly, eligible patients were ≥18 years of age and had an IGA score ≥3, EASI score ≥16, percentage of treatable body surface area (%BSA) ≥10, and Peak Pruritus Numerical Rating Scale (PP-NRS; © Regeneron Pharmaceuticals, Inc., and Sanofi [2017]) score ≥4 for at least 1 year and an inadequate response to topical medicated therapy or requirement for systemic therapy to control AD ≤6 months before screening. Patients were randomly assigned 2:2:2:1 to receive once-daily (QD) oral abrocitinib (200 or 100 mg), dupilumab 300 mg subcutaneous injection once every 2 weeks (Q2W) (following a 600-mg loading dose) or placebo for 16 weeks. All patients used background medicated topical therapy once daily throughout the study.

Patients who completed the JADE COMPARE study or the phase 3 JADE MONO-1[35] and JADE MONO-2[36] studies could enroll in JADE EXTEND (NCT03422822), an ongoing, phase 3 long-term extension study.

Study population

This post hoc analysis included two separate patient populations:

1. Patients treated with abrocitinib, dupilumab and placebo in JADE COMPARE
2. Patients treated with dupilumab in JADE COMPARE who entered JADE EXTEND, where they were randomly assigned to receive double-blind treatment with either abrocitinib 200 or 100 mg in combination with topical medications for AD as needed. This was a planned, interim analysis of data from JADE EXTEND (data cutoff date: April 22, 2020).

Assessments

Circulating eosinophil levels in blood samples were measured at baseline and Weeks 2, 4, 8, 12 and 16 in JADE COMPARE and at baseline and Weeks 2, 4 and 12 in JADE EXTEND. Eosinophil counts of ≤500/mm^3 were defined as normal, >500/mm^3 to ≤1500/mm^3 as eosinophilia, and >1500/mm^3 as hypereosinophilia. To understand the relationship between comorbid conditions and eosinophilia, least–squares mean (LSM) change from baseline in eosinophil count was evaluated by comorbid condition in JADE COMPARE. The presence of comorbid conditions at baseline (i.e., asthma and allergic rhinitis) was based on medical history.[33]

Assessments in JADE COMPARE included the proportion of patients with eosinophilia from baseline to Week 16; absolute eosinophil counts at baseline and Weeks 2, 4, 8, 12 and 16; and LSM change in eosinophil count from baseline to Week 16. Correlation analyses were performed to evaluate the relationship between baseline eosinophil levels and change from baseline to Week 16 in the efficacy endpoints of EASI, IGA, PP-NRS and SCORing Atopic Dermatitis-Visual Analog Scale (SCORAD-VAS) for sleep loss and pruritus. The relationship between change from baseline to Week 16 in eosinophil levels and change from baseline to Week 16 in the aforementioned efficacy endpoints was also assessed.

Assessments in JADE EXTEND included the proportions of patients with eosinophilia or hypereosinophilia

after switching from dupilumab in JADE COMPARE to abrocitinib in JADE EXTEND at baseline and Weeks 2, 4 and 12. Due to the small number of patients with hypereosinophilia entering JADE EXTEND from the dupilumab treatment arm of JADE COMPARE, patients with eosinophilia or hypereosinophilia were pooled for this analysis. Correlation analyses were performed to evaluate the relationships between baseline eosinophil levels in JADE COMPARE and change from baseline to Week 12 IGA, EASI and PP-NRS scores in JADE EXTEND. The relationship between change from baseline to Week 12 eosinophil levels and change from baseline to Week 12 IGA, EASI and PP-NRS scores in JADE EXTEND was also assessed.

Safety endpoints were assessed in JADE COMPARE via all-cause AEs and serious adverse events (SAEs).

Statistical analysis

The full analysis set and safety analysis set were identical and comprised all randomly assigned patients who received ≥1 dose of study drug. Baseline was defined as the last measurement before first dosing (Day 1), and the proportion of patients with eosinophilia was assessed by treatment group in the overall population, asthma status and allergic rhinitis status. Median eosinophil counts were assessed by treatment group (abrocitinib 200 mg, abrocitinib 100 mg, placebo and dupilumab) only. No formal statistical testing was conducted to compare the treatment groups; all comparisons were descriptive.

LSM change from baseline in eosinophil levels was evaluated by asthma status and allergic rhinitis status using a mixed model for repeated measures, with fixed factors of treatment, visit, treatment-by-visit interaction, baseline value and an unstructured covariance matrix.

In each treatment group, 95% CIs were reported. Correlation analyses were performed using Pearson's product-moment correlation coefficients. A correlation coefficient of equal to or less than −0.3 was considered a negative correlation, and equal to or greater than 0.3 was considered a positive correlation.

The LSM change from baseline analyses were conducted using SAS version 9.4 (SAS Institute Inc). For safety analyses, AEs and SAEs were coded using the Medical Dictionary for Regulatory Activities, version 22.1J.

Ethics and patient consent

The study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice guidelines and was approved by the institutional review board or ethics committee at each trial site. Patients provided written informed consent before enrollment.

RESULTS

Baseline characteristics

A total of 837 patients were randomly assigned to treatment in JADE COMPARE (placebo: $n = 131$; abrocitinib 100 mg: $n = 238$; abrocitinib 200 mg: $n = 226$; dupilumab 300 mg: $n = 242$; Supporting Information: Figure S1). Of the patients in the JADE COMPARE dupilumab group, 203 were randomly assigned to receive abrocitinib in JADE EXTEND (abrocitinib 100 mg: $n = 130$; abrocitinib 200 mg: $n = 73$). Patient demographics and baseline disease characteristics were comparable across treatment groups in JADE COMPARE (Table 1). Common comorbid conditions at baseline were asthma ($n = 260$; 31.1%) and allergic rhinitis ($n = 139$; 16.6%); 210 patients (25.1%) had eosinophilia or hypereosinophilia.

Effect of abrocitinib treatment on eosinophilia in patients with moderate-to-severe AD from JADE COMPARE

At baseline, the proportion of patients with eosinophilia were comparable between the treatment arms (Figure 1). Abrocitinib rapidly decreased the proportion of patients with eosinophilia compared with placebo as early as Week 2 after treatment; abrocitinib treatment response occurred in a dose-dependent manner. Dupilumab had little effect on the proportion of patients with eosinophilia. The magnitude of decrease was greatest in the abrocitinib 200-mg group; there were no cases of hypereosinophilia at Weeks 12 and 16 following treatment with abrocitinib 200 mg.

Absolute eosinophil counts were highly variable across all groups at Week 16 after treatment (Figure 2). There was a trend for lower eosinophil counts at Week 16 in patients who received active treatment. Decreases from baseline in median eosinophil counts were greater with abrocitinib 200mg (difference, $-100/mm^3$) and

TABLE 1 Patient demographics and baseline disease characteristics in JADE COMPARE (safety analysis set).

	Placebo *n* = 131	Abrocitinib 100 mg QD *n* = 238	Abrocitinib 200 mg QD *n* = 226	Dupilumab 300 mg Q2W *n* = 242	Total *N* = 837
Mean (SD) age, years	37.4 (15.2)	37.3 (14.8)	38.8 (14.5)	37.1 (14.6)	37.7 (14.7)
Female, *n* (%)	54 (41.2)	118 (49.6)	122 (54.0)	134 (55.4)	428 (51.1)
Duration of AD, mean (SD), years	21.4 (14.4)	22.7 (16.3)	23.4 (15.6)	22.8 (14.8)	22.7 (15.4)
%BSA, mean (SD)	48.9 (24.9)	48.1 (23.1)	50.8 (23.0)	46.5 (22.1)	48.5 (23.1)
IGA score, *n* (%)					
Moderate (3)	88 (67.2)	153 (64.3)	138 (61.1)	162 (66.9)	541 (64.6)
Severe (4)	43 (32.8)	85 (35.7)	88 (38.9)	80 (33.1)	296 (35.4)
EASI, mean (SD)	31.0 (12.6)	30.3 (13.5)	32.1 (13.1)	30.4 (12.0)	30.9 (12.8)
PP-NRS, mean (SD)	7.1 (1.8)	7.1 (1.7)	7.6 (1.5)	7.3 (1.7)	7.3 (1.7)
SCORAD, mean (SD)	67.9 (12.0)	66.8 (13.8)	69.3 (12.7)	67.9 (11.4)	67.9 (12.6)
Comorbid condition at baseline, *n* (%)					
Asthma	45 (34.4)	72 (30.3)	68 (30.1)	75 (31.0)	260 (31.1)
Allergic rhinitis	23 (17.6)	47 (19.7)	30 (13.3)	39 (16.1)	139 (16.6)
Eosinophilia status at baseline, *n* (%)					
Eosinophilia[a]	31 (23.7)	47 (19.7)	58 (25.7)	51 (21.1)	187 (22.3)
Hypereosinophilia[b]	4 (3.1)	10 (4.2)	3 (1.3)	6 (2.5)	23 (2.7)

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale (PP-NRS © Regeneron Pharmaceuticals, Inc., and Sanofi [2017]); QD, once daily; Q2W, once every 2 weeks; SCORAD, SCORing Atopic Dermatitis; %BSA, percentage of treatable body surface area.

[a]Eosinophilia was defined as eosinophil count $>0.5 \times 10^3/mm^3$ ($>500/mm^3$ and $\leq 1500/mm^3$).

[b]Hypereosinophilia was defined as eosinophil count $>1.5 \times 10^3/mm^3$ ($>1500/mm^3$).

abrocitinib 100 mg (difference, $-70/mm^3$) than dupilumab (difference, $+25/mm^3$) or placebo ($+30/mm^3$).

Effect of abrocitinib on eosinophil levels in patients with comorbid asthma and allergic rhinitis from JADE COMPARE

In JADE COMPARE, 92 patients (35.4%) with comorbid asthma and 45 patients (32.4%) with comorbid allergic rhinitis at baseline also had eosinophilia at baseline. At Week 2 through Week 16, the proportion of patients with eosinophilia in the subset with comorbid asthma was lower in the abrocitinib 200-mg group compared with the other treatment groups (Figure 3a), and a similar trend was observed in the subset with allergic rhinitis (Figure 3b). Reductions from baseline in eosinophil counts at Weeks 2 through 16 after abrocitinib 200 mg treatment were greater with abrocitinib compared with placebo, regardless of whether the patient had comorbid asthma or allergic rhinitis at baseline (Supporting Information: Figure S2a–d). Dupilumab treatment did not decrease eosinophil counts relative to placebo; in patients with comorbid allergic rhinitis at baseline, eosinophil counts were increased from baseline by Week 2 and remained elevated through Week 16 of treatment with dupilumab.

Relationship between eosinophil levels and clinical efficacy at Week 16 of JADE COMPARE

To investigate the use of baseline eosinophil count as a potential predictor of response to treatment, correlation analyses were performed. Baseline eosinophil count was negatively associated with improvement in EASI score at Week 16 with abrocitinib 200 mg ($r = -0.35$; 95% CI −0.46 to −0.22) and dupilumab 300 mg ($r = -0.40$; 95% CI −0.50 to −0.28), but not with abrocitinib 100 mg or placebo (Table 2). No association was observed between baseline eosinophil count and change from baseline in IGA, PP-NRS or SCORAD-VAS at Week 16 with abrocitinib at either dose, placebo or dupilumab.

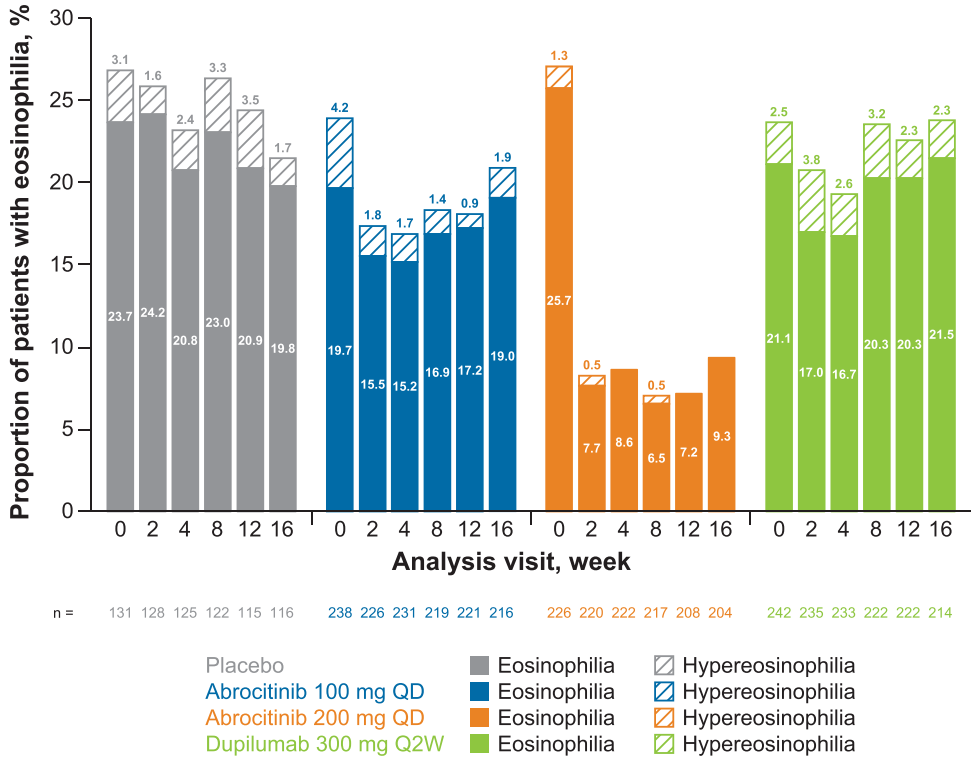

FIGURE 1 Proportion of patients with eosinophilia from baseline to Week 16 by treatment (safety analysis set). Eosinophilia was defined as eosinophil count $>0.5 \times 10^3/mm^3$ ($>500/mm^3$ and $\leq 1500/mm^3$). Hypereosinophilia was defined as eosinophil count $>1.5 \times 10^3/mm^3$ ($>1500/mm^3$). QD, once daily; Q2W, once every 2 weeks.

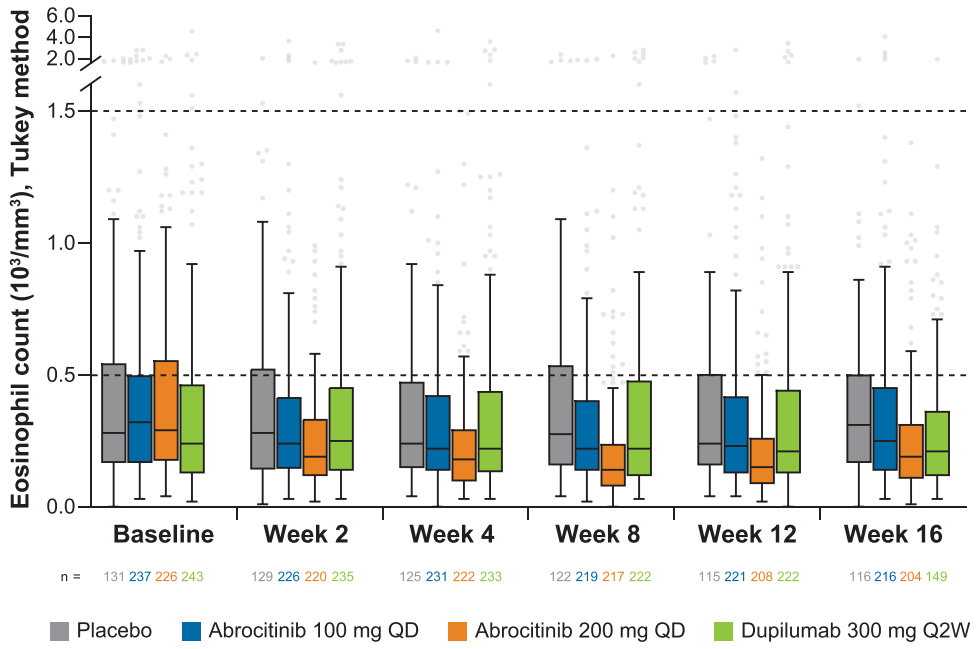

FIGURE 2 Median circulating eosinophil levels from baseline to Week 16 by treatment in the overall patient population (safety analysis set). Eosinophilia was defined as eosinophil count $>0.5 \times 10^3/mm^3$ ($>500/mm^3$ and $\leq 1500/mm^3$). Hypereosinophilia was defined as eosinophil count $>1.5 \times 10^3/mm^3$ ($>1500/mm^3$). Box plot indicates median and 25th/75th percentiles; outliers and whiskers were calculated using the Tukey method. QD, once daily; Q2W, once every 2 weeks.

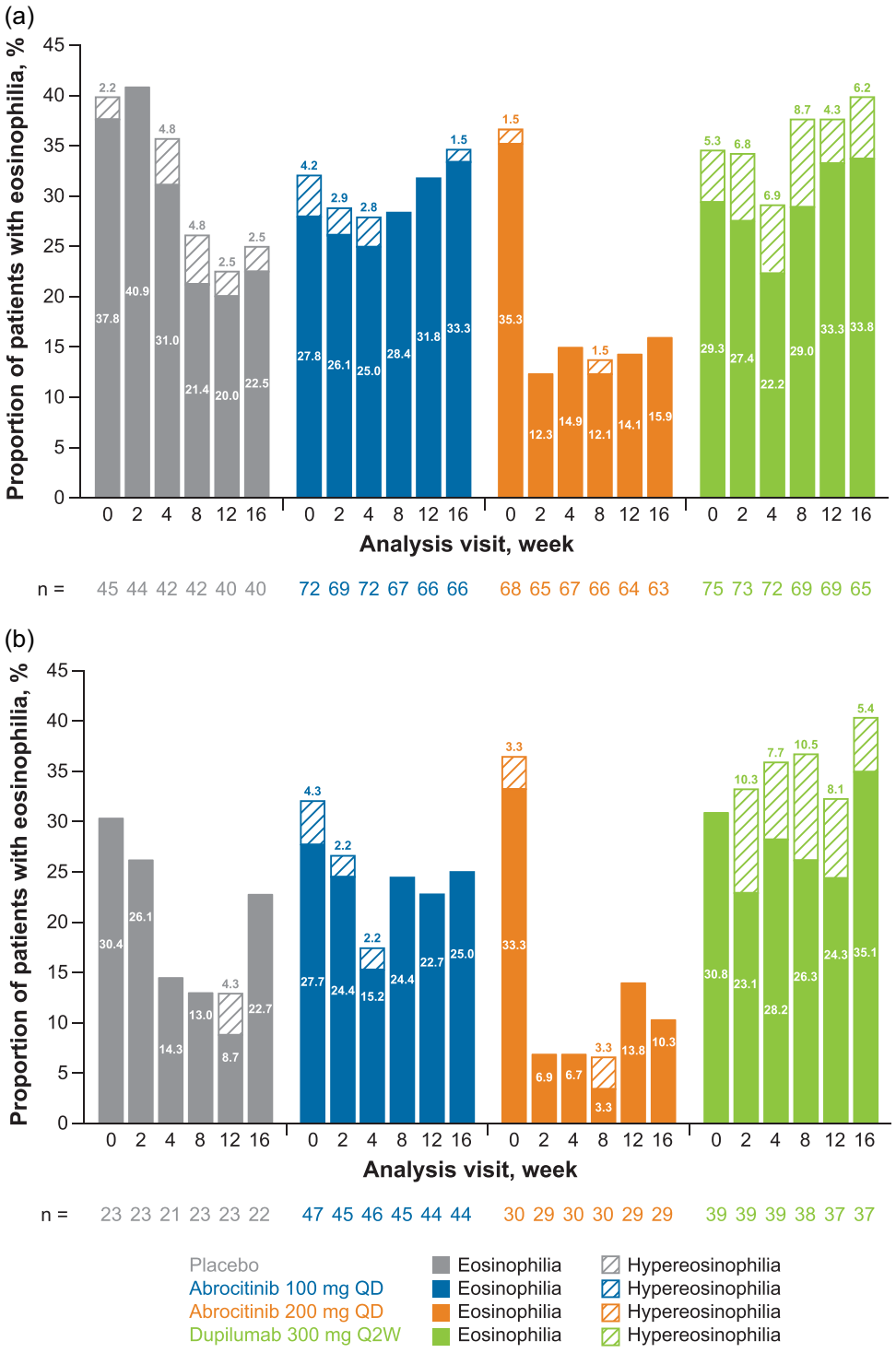

FIGURE 3 Proportion of patients from JADE COMPARE with (a) asthma and (b) allergic rhinitis at baseline who had eosinophilia or hypereosinophilia (safety analysis set). Eosinophilia was defined as eosinophil count >0.5 $\times 10^3$/mm^3 (>500/mm^3 and ≤1500/mm^3). Hypereosinophilia was defined as eosinophil count >1.5 $\times 10^3$/mm^3 (>1500/mm^3). QD, once daily; Q2W, once every 2 weeks.

There was no correlation observed between the change from baseline in eosinophil counts at Week 16 and change from baseline in most of the efficacy endpoints at Week 16; a modest correlation was observed with EASI improvement score in the abrocitinib 200-mg group ($r = 0.32$; 95% CI 0.20–0.44) and SCORAD-VAS sleep loss score in the abrocitinib 100-mg group ($r = 0.30$; 95% CI 0.17–0.42) (Table 2).

TABLE 2 Correlation between eosinophil count and change from baseline in Week 16 efficacy endpoints[a] in JADE COMPARE (safety analysis set).

	Change from baseline at Week 16	Correlation (95% CI)			
		Placebo	Abrocitinib 100 mg QD	Abrocitinib 200 mg QD	Dupilumab 300 mg Q2W
Baseline eosinophil count[a]	IGA	0.09 (−0.09 to 0.27)	0.01 (−0.13 to 0.14)	−0.14 (−0.27 to −0.01)	−0.10 (−0.23 to 0.03)
	EASI	−0.07 (−0.25 to 0.12)	−0.26 (−0.38 to −0.13)	**−0.35 (−0.46 to−0.22)**	**−0.40 (−0.50 to −0.28)**
	PP-NRS	−0.08 (−0.29 to 0.14)	−0.01 (−0.17 to 0.15)	−0.03 (−0.19 to 0.13)	−0.20 (−0.34 to −0.05)
	SCORAD-VAS sleep loss	−0.08 (−0.26 to 0.11)	−0.07 (−0.20 to 0.07)	−0.20 (−0.32 to −0.06)	−0.23 (−0.35 to −0.10)
Change from baseline in eosinophil count at Week 16[b]	IGA	0.14 (−0.05 to 0.32)	0.17 (0.04 to 0.30)	0.23 (0.10 to 0.36)	0.18 (0.05 to 0.31)
	EASI	0.20 (0.01 to 0.37)	0.26 (0.13 to 0.38)	**0.32 (0.20 to 0.44)**	0.28 (0.15 to 0.40)
	PP-NRS	0.18 (−0.04 to 0.38)	0.25 (0.10 to 0.39)	0.17 (0.01 to 0.32)	0.08 (−0.07 to 0.23)
	SCORAD-VAS sleep loss	0.22 (0.03 to 0.38)	**0.30 (0.17 to 0.42)**	0.21 (0.07 to 0.34)	0.14 (0.01 to 0.27)

Note: Values ≥0.3 were considered a positive correlation and values ≤0.3 were considered a negative correlation and are shown in bold.

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus-Numerical Rating Scale; QD, once daily; Q2W, once every 2 weeks; SCORAD-VAS, SCORing Atopic Dermatitis-Visual Analog Scale.

[a]Safety analysis set.

[b]Full analysis set.

Effect of abrocitinib on eosinophilia in dupilumab-treated patients from JADE COMPARE who enrolled in JADE EXTEND

A total of 203 patients treated with dupilumab in JADE COMPARE entered the JADE EXTEND study and were randomly assigned to receive abrocitinib 100 mg ($n = 130$) or abrocitinib 200 mg ($n = 73$); 30 of 130 patients (23.1%) in the abrocitinib 100-mg group and 18 of 73 patients (24.7%) in the abrocitinib 200-mg group had eosinophilia or hypereosinophilia at baseline in EXTEND. After switching from dupilumab in JADE COMPARE to abrocitinib treatment in JADE EXTEND, reductions from baseline in eosinophil counts were observed from Week 2 through Week 24 in a dose-dependent manner (Supporting Information: Figure S3). The proportion of patients with eosinophilia or hypereosinophilia decreased rapidly at Week 2 and continued to decrease through Week 12 in both abrocitinib treatment groups (Figure 4).

Relationship between eosinophil levels and clinical efficacy at Week 12 in JADE EXTEND

The relationship between eosinophil count and improvements in EASI, IGA and PP-NRS at Week 12 of JADE EXTEND were assessed using correlation analyses. Baseline eosinophil counts were negatively associated with Week 12 EASI scores in JADE EXTEND in the abrocitinib 200 mg ($r = –0.37$; 95% CI –0.55 to –0.14) and abrocitinib 100 mg ($r = –0.46$; 95% CI –0.59 to –0.30) treatment groups (Supporting Information: Table S1). No associations were observed between baseline eosinophil counts and change from baseline in IGA or PP-NRS score at Week 12 with abrocitinib at either dose.

In the abrocitinib 200 mg group, change from baseline to Week 12 of JADE EXTEND in eosinophil count was positively associated with Week 12 IGA ($r = 0.39$; 95% CI 0.16 to 0.58) and EASI scores ($r = 0.44$; 95% CI 0.21 to 0.61; Supporting Information: Table S1). A modest but positive

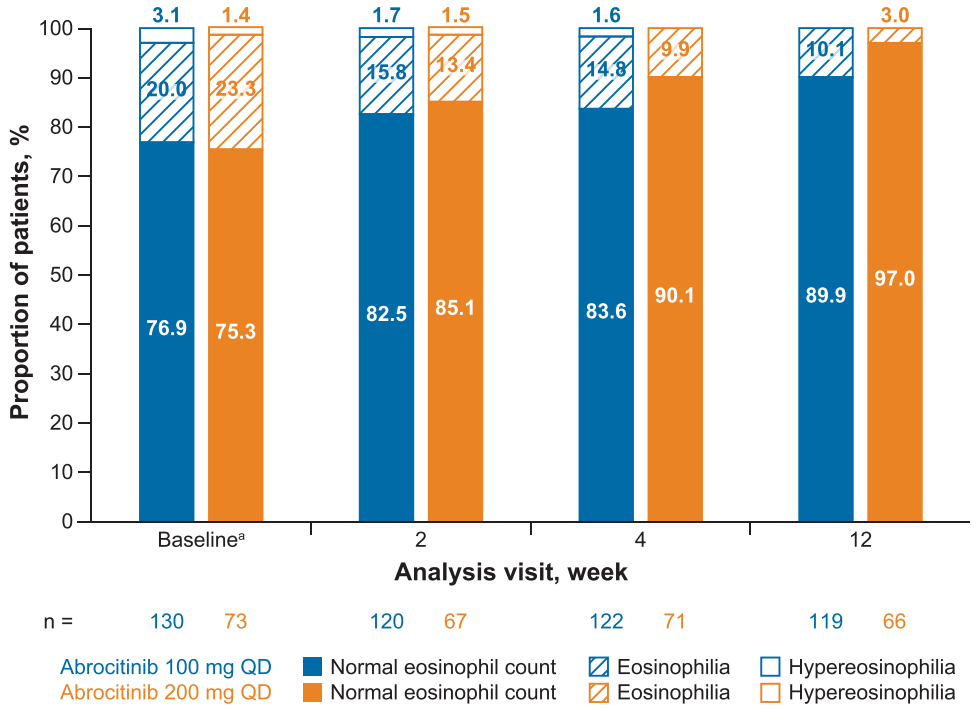

FIGURE 4 Eosinophilia status in patients treated with dupilumab from JADE COMPARE after switching to abrocitinib treatment in the long-term JADE EXTEND study (safety analysis set). Normal eosinophil count was defined as $\leq 0.5 \times 10^3/mm^3$ ($\leq 500/mm^3$). Eosinophilia was defined as eosinophil count $>0.5 \times 10^3/mm^3$ ($>500/mm^3$ and $\leq 1500/mm^3$). Hypereosinophilia was defined as eosinophil count $>1.5 \times 10^3/mm^3$ ($>1500/mm^3$). [a]Baseline in JADE EXTEND. QD, once daily.

correlation was also observed with the PP-NRS score at Week 12 ($r = 0.30$; 95% CI 0.06 to 0.50; Supporting Information: Table S1). In the abrocitinib 100 mg group, change from baseline in eosinophil count was positively associated with EASI score at Week 12 ($r = 0.48$; 95% CI 0.32–0.61); no correlations were observed between change from baseline in eosinophil count and IGA or PP-NRS (Supporting Information: Table S1).

Safety

To assess for any possible eosinophilia-associated clinical consequences, we investigated whether safety events in JADE COMPARE were associated with elevated circulating eosinophil counts. AEs were mainly mild or moderate, and no AEs or SAEs were attributed to eosinophilia. A detailed summary of the abrocitinib safety profile has been published previously.[33]

DISCUSSION

In this post hoc analysis of JADE COMPARE, abrocitinib 200 mg was associated with rapid resolution of eosinophilia in patients with moderate-to-severe AD. In contrast, eosinophil levels did not decrease in patients treated with dupilumab for the duration of this analysis (16 weeks after treatment). A similar trend was observed in the subset with comorbid asthma and allergic rhinitis; rapid resolution of hypereosinophilia was observed as early as Week 2 after treatment with abrocitinib 200 mg but not dupilumab.

The mechanism by which abrocitinib and dupilumab exert their clinical effect on eosinophilia has not been fully elucidated. It is likely that JAK inhibition with abrocitinib disrupts IL-5 signaling, leading to subsequent inhibition of eosinophil development and activation, which suggests a direct or indirect role of JAK1 in eosinophil biology.[8] Consistent with our findings, other JAK inhibitors have also been shown to resolve hypereosinophilia, including dramatic decreases in blood eosinophil counts in patients with hypereosinophilic syndrome with cutaneous involvement after treatment with tofacitinib, a JAK 1/3 inhibitor, and ruxolitinib, a JAK1/2 inhibitor.[27]

Increases in circulating eosinophils induced by dupilumab may be due to inhibition of IL-4 and IL-13, which in turn increases IL-5, promoting eosinophil proliferation and activation[8,38] and suppressing the production of eotaxin-3 and/or reduces IL-13-positive Langerhans cell-mediated CCL5 production, which precludes chemotaxis

of eosinophils from the vasculature to the inflamed tissue.[7,39,40]

Consistent with this hypothesis, clinical and real-world studies have reported elevated eosinophil counts in patients with moderate-to-severe AD after treatment with dupilumab.[12–14,19–24] In a retrospective real-world cohort of patients from France with moderate-to-severe AD, 9.0% developed hypereosinophilia (≥1500/mm^3) soon after initiating treatment with dupilumab, followed by a subsequent decrease of circulating eosinophils.[41] Similarly, in a recent prospective study of a Dutch cohort, the proportion of patients with eosinophilia increased at Week 16 after dupilumab treatment before decreasing to baseline levels at Week 52.[14]

The clinical implications of elevated eosinophils in patients with moderate-to-severe AD remain to be fully elucidated. Some studies of dupilumab-treated patients found that increased eosinophil levels had no clinically meaningful impact on adverse events,[13,20] whereas in other studies, they were associated with a history of allergic conjunctivitis and food allergies[22] and an increased risk of dupilumab-associated conjunctivitis,[42,43] supporting the interplay between AD, conjunctivitis and circulating eosinophil counts.[22,23,25] Furthermore, a recent analysis of dupilumab efficacy by eosinophilic endotypes in patients with moderate-to-severe AD from the TREATgermany clinical registry demonstrated a more robust treatment effect in the subset with low-eosinophilic endotype compared with high-eosinophilic endotype.[44] This suggests a potential impact of eosinophil levels on the magnitude of treatment benefit, although further study is warranted to help guide disease management in these patients.

There were no eosinophilia-associated AEs observed in our analysis. Reduced levels of circulating eosinophils at Week 16 of JADE COMPARE had a modest correlation with improvements in EASI and SCORAD-VAS sleep loss score with both abrocitinib doses but not with dupilumab or placebo. This is consistent with a retrospective study of patients with AD treated with dupilumab, in which patients who achieved an EASI-75 response at Week 16 had a numerically greater percentage change from baseline in eosinophil count.[45] Interestingly, in patients who were treated with dupilumab in JADE COMPARE and subsequently received abrocitinib in the long-term JADE EXTEND study, lower eosinophil levels were associated with improvements in EASI, IGA and PP-NRS, suggesting that abrocitinib-mediated decreases in eosinophils could contribute, at least in part, to improvement in signs and symptoms of AD. Our findings are in line with previous evidence that suggests a contributing role for eosinophils in the pathophysiology of AD[46] mediated by secretion of IL-31, a cytokine associated with pruritus in AD,[47–49] and expression of receptors for substance P, which has been associated with scratching behavior in mice.[50] Thus, eosinophils could potentially modulate pruritus via interactions with the peripheral nervous system.

This analysis was limited by its post hoc nature and small sample sizes. The comparisons between abrocitinib and dupilumab were descriptive and not subjected to formal statistical testing. Finally, the data presented here are from a 16-week study (i.e., JADE COMPARE) and an interim analysis (data cutoff April 22, 2020) of the ongoing long-term JADE EXTEND study. Final analysis of the EXTEND study will further inform the impact of abrocitinib on circulating eosinophil counts.

CONCLUSIONS

In summary, abrocitinib decreased the proportion of patients with eosinophilia in JADE COMPARE and JADE EXTEND. Decreases in eosinophil levels occurred early after treatment with abrocitinib and were sustained through Week 16 in a dose-dependent manner, irrespective of the status of comorbid asthma and allergic rhinitis at baseline. Abrocitinib at the 200-mg dose resolved all cases of hypereosinophilia by Week 12 and may thus provide a therapeutic alternative for patients who discontinue dupilumab treatment due to hypereosinophilia. Resolution of eosinophilia with abrocitinib appeared to be associated with clinical efficacy, as was evident by improvements in AD severity, itch and sleep loss, although further studies are needed to better understand the link between decreased circulating eosinophils and abrocitinib efficacy.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, and data analysis and interpretation. Fan Zhang performed the statistical analyses. All authors participated in drafting and revising the manuscript and approved the final version for submission.

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CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

ETHICS STATEMENT

This study was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonization Good Clinical Practice guidelines and was approved by the institutional review board or ethics committee at each trial site. All patients in this manuscript have given written informed consent for participation in the study and the use of their de-identified, anonymized, aggregated data and their case details (including photographs) for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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