Factors Associated With Persistent Efficacy of Abrocitinib Without Flare: A Multivariable Analysis of the JADE-REGIMEN Study

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BACKGROUND

- Atopic dermatitis (AD) is a chronic skin disease that presents with eczematous lesions and intense pruritus[1,2]
- Patients with moderate-to-severe AD have a chronic, relapsing course that warrants systemic maintenance therapy in order to control disease and reduce the number and severity of flares[1]
- An important consideration when using long-term therapy is to use the lowest possible drug dose to reduce the risk for adverse events[1]
- JADE REGIMEN (NCT03627767) evaluated the efficacy and safety of continuous abrocitinib, dose reduction, or withdrawal of abrocitinib after induction of response with once-daily oral abrocitinib 200 mg in patients with moderate-to-severe AD[3]
- Predicting risk for disease flare can inform selection of appropriate maintenance therapy for patients with moderate-to-severe AD who achieve skin clearance after 12 weeks of induction monotherapy with abrocitinib 200 mg

OBJECTIVES

- To evaluate patient factors associated with a higher probability of persistent clinical response with different abrocitinib doses, with no protocol-defined flare, during a 40-week maintenance period
- To create a nomogram, based on the patient factors identified above, to predict the probability of flare for individual patients with AD

METHODS

Patients

- Patients eligible to enroll in JADE REGIMEN were aged ≥12 years with moderate-to-severe AD (Investigator's Global Assessment [IGA] score ≥3, Eczema Area and Severity Index [EASI] ≥16, percentage of body surface area (%BSA) affected ≥10, and Peak Pruritus Numerical Rating Scale [PP-NRS, © Regeneron Pharmaceuticals, Inc. and Sanofi, 2017] ≥4 at baseline)
- Patients had a clinical diagnosis of chronic AD for ≥1 year and a recent history (within ≤6 months) of inadequate response

Study Design

- JADE REGIMEN was a responder-enriched, placebo-controlled, double-blind, phase 3 randomized withdrawal study with rescue treatment in patients experiencing flare
- The study comprised 3 periods (**Supplemental Figure S1**)
  - A 12-week, open-label induction period in which patients received once-daily oral abrocitinib 200 mg
  - At the end of the12-week period, responders (defined as those who achieved IGA score 0 or 1 with ≥2-grade improvement [IGA 0/1] and ≥75% improvement in EASI [EASI-75]) were randomly assigned in a 1:1:1 ratio to receive abrocitinib 200 mg, abrocitinib 100 mg, or placebo by mouth once daily for 40 weeks
  - Patients who experienced protocol-defined flare (≥50% loss of week 12 EASI response and IGA score ≥2) were offered rescue treatment (abrocitinib 200 mg plus topical medicated therapy) for 12 weeks to attempt to recapture response

Efficacy Endpoints

- The primary endpoint of JADE REGIMEN was loss of response (flare) during the maintenance period

Statistical Analysis

Regression model

- In this post hoc analysis, a multivariable logistic regression model with fixed and random effects was fit to determine factors associated with not experiencing flare by week 52
  - Fixed effects (factors) considered were randomly allocated treatment, age (<18 vs ≥18 years), race, weight, prior use of systemic agents, duration of AD, onset of response in induction (early vs late), EASI score at baseline, IGA score at randomization, %BSA affected (≤50 vs >50) at baseline, and improvement in EASI at randomization
  - Variability relating to region of enrollment (Asia, Eastern Europe/Russia, Latin America, United States/Canada, or Western Europe) was accounted for using random effects
- To achieve the most parsimonious model, backward elimination and stepwise model selection procedures were applied with entry and exit criteria based on a *P* value threshold of 5%

Generation of nomogram

- Results of the multivariate regression model were used to create a nomogram to estimate the probability of not experiencing flare
  - Each factor was assigned points based on the relative contribution to flare probability
  - The sum of points was transferred to a "total points" scale from which the corresponding probability of not experiencing flare could be extrapolated

RESULTS

Demographics and Baseline Disease Characteristics

- 1233 patients were treated with abrocitinib 200 mg in the open-label induction period
- 798 patients (64.7%) achieved IGA 0/1 and EASI-75 responses and were randomly assigned to the maintenance period
- Demographics and disease characteristics of responders who experienced protocol-defined flare and those who did not experience protocol-defined flare during the maintenance period are summarized in **Supplemental Table S1**, and key patient characteristics are provided in **Table 1**
  - Patient demographics and baseline disease characteristics were comparable across treatment groups
  - Responders who did not experience flare during the maintenance period had lower affected %BSA at baseline than responders who did experience flare during maintenance, regardless of treatment arm
  - Similarly, more responders who did not experience flare during the maintenance period had no prior exposure to systemic agents than responders who did experience flare during maintenance, regardless of treatment arm

Table 1. Key Patient Characteristics by Presence or Absence of Protocol-Defined Flare During the Maintenance Period

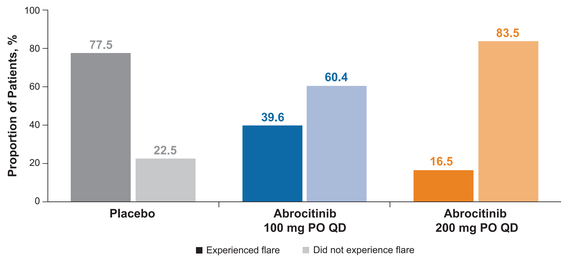
	Placebo		Abrocitinib 100 mg		Abrocitinib 200 mg	
	Flare n=207	No Flare n=60	Flare n=105	No Flare n=160	Flare n=44	No Flare n=222
EASI at randomization, median (Q1, Q3)	0.8 (0.0, 2.0)	0.8 (0.0, 2.0)	1.2 (0.3, 2.8)	0.4 (0.0, 1.3)	1.8 (0.6, 3.2)	0.6 (0.0, 1.5)
Percentage of BSA affected at baseline, n (%)						
>10% to 30%	45 (21.7)	17 (28.3)	21 (20.0)	49 (30.6)	10 (22.7)	54 (24.3)
>30% to ≤50%	78 (37.7)	24 (40.0)	32 (30.5)	53 (33.1)	11 (25.0)	74 (33.3)
>50%	84 (40.6)	19 (31.7)	52 (49.5)	58 (36.3)	23 (52.3)	94 (42.3)
Prior medication, n (%)						
None	0	0	1 (1.0)	0	0	0
Topical only	74 (35.7)	28 (46.7)	37 (35.2)	81 (50.6)	16 (36.4)	86 (38.7)
Systemic agents	133 (64.3)	32 (53.3)	67 (63.8)	79 (49.4)	28 (63.6)	136 (61.3)
Nonbiologic	121 (58.5)	31 (51.7)	57 (54.3)	73 (45.6)	26 (59.1)	123 (55.4)
Biologic	12 (5.8)	1 (1.7)	10 (9.5)	6 (3.8)	2 (4.5)	13 (5.9)
Dupilumab	9 (4.3)	0	8 (7.6)	4 (2.5)	2 (4.5)	9 (4.1)
Other biologic agent	3 (1.4)	1 (1.7)	3 (2.9)	2 (1.3)	0	6 (2.7)

%BSA, percentage of body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; Q, quartile.
Flare was defined as loss of ≥50% in EASI response at randomization and IGA score ≥2.

Factors Associated With Flare

- In total, 356 patients (44.6%) experienced protocol-defined flare during the maintenance period, which included 16.5%, 39.6%, and 77.5% of patients in the abrocitinib 200-mg, abrocitinib 100-mg, and placebo treatment arms, respectively (**Figure 1**)

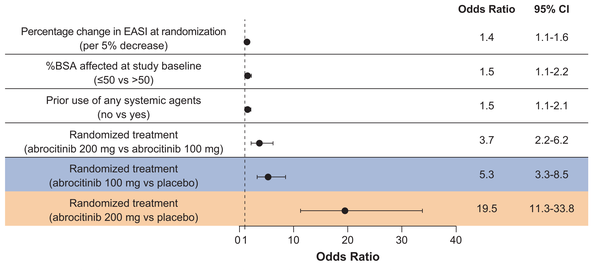
Figure 1. Abrocitinib Treatment Was Associated With Lower Proportions of Patients Who Experienced Flare During the Maintenance Period of JADE REGIMEN



EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PO, by mouth; QD, once daily.
Flare was defined as loss of ≥50% in EASI response at randomization and IGA score ≥2.

- Multivariable analysis identified continuation of abrocitinib 200-mg treatment and treatment with reduced-dose abrocitinib 100 mg as the greatest predictors that a patient will not experience flare during the maintenance period (**Figure 2**)
  - No prior use of systemic agents, lower affected %BSA at baseline, and greater EASI reduction during induction were also associated with not experiencing flare

Figure 2. Maintaining Active Treatment Is the Primary Factor Associated With Not Experiencing Flare

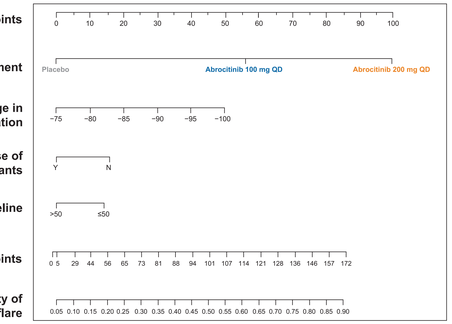


%BSA, percentage of body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.
Flare was defined as loss of ≥50% in EASI response at randomization and IGA score ≥2.

Estimating the Probability of Flare

- Factors associated with flare were incorporated into a nomogram that could be used to estimate the probability of not experiencing flare (**Figure 3**)
  - Consistent with multivariate analysis, the nomogram included the following factors in order of importance, which were assigned points that were totaled to determine the probability of not experiencing flare
    - Randomized treatment
    - Percentage improvement in EASI at randomization
    - Prior use of immunosuppressants
    - Baseline %BSA affected
  - The point summary translated into a probability of not experiencing flare of 5% to 90%
  - To see the nomogram in action, please scan the QR code

Figure 3. Nomogram for Predicting the Probability of Not Experiencing Flare



%BSA, percentage of body surface area; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; QD, once daily.
Flare was defined as loss of ≥50% in EASI response at randomization and IGA score ≥2.

CONCLUSIONS

- Multivariable analysis of JADE REGIMEN data indicated that maintenance treatment with abrocitinib reduced the risk for flare in patients with AD in a dose-dependent manner
- Other factors associated with maintaining response to treatment without flare included no previous exposure to systemic agents, lower extent of BSA involvement at baseline, and greater percentage change in EASI response during induction
- Through inclusion in a nomogram, these findings may assist clinicians with abrocitinib maintenance dosing decisions in the future

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