Attenuating the atopic march: Meta-analysis of the dupilumab atopic dermatitis database for incident allergic events

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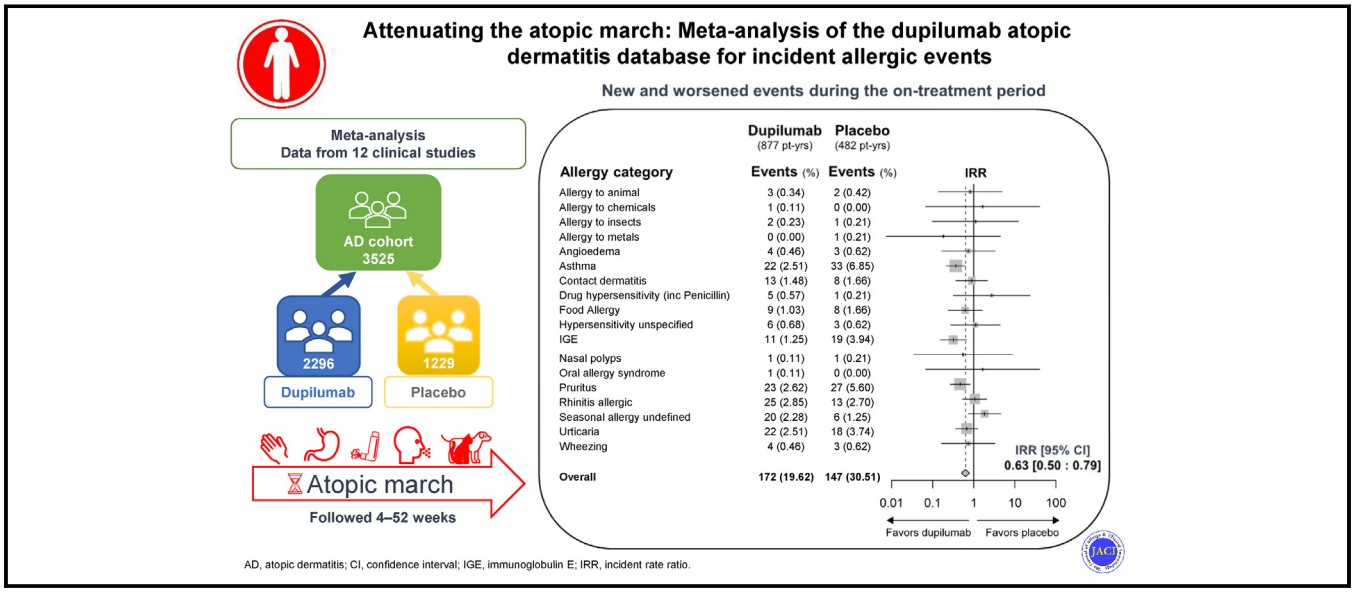
GRAPHICAL ABSTRACT



Background: Atopic march refers to the sequential development of allergic diseases from infancy through adolescence, typically beginning with atopic dermatitis (AD), followed by food allergy and then airway diseases, later evolving to broader or worsened spectrum of allergic diatheses. No intervention has shown to alter its course.

Objective: We sought to determine the rate of acquisition of new or worsened allergic events for dupilumab versus placebo in patients with AD.

Methods: Allergy-associated events from 12 clinical trials were grouped into 17 allergy categories, and IgE changes from baseline were defined. A new/worsened event was considered one step of atopic march. Treatment effect was assessed by incidence rate ratios (IRRs), dupilumab versus placebo, by meta-analysis.

Results: The duration of pooled AD studies was 4 to 52 weeks (1359 patient-years; n = 2296 dupilumab, n = 1229 placebo, median age 35 years). The median age at AD onset was 2 years. Baseline allergic disease burden was comparable between groups. Dupilumab reduced the risk of new/worsening allergies by 34% (IRR 0.66; 95% confidence interval [CI], 0.52-0.84) and new allergies by 37% (IRR 0.63; 95% CI, 0.48-0.83) versus placebo. Including IgE category shift, the IRR for combined new/worsening allergies was reduced by 54% (IRR 0.46; 95% CI, 0.36-0.57). These treatment benefits did not reverse on treatment discontinuation in off-treatment follow-up.

Conclusions: The acquisition/worsening of allergic conditions suggestive of atopic march was observed in a pooled adult/adolescent AD study population with inadequately controlled AD. Treatment with dupilumab reduced new/worsened allergy events versus placebo; inclusion of IgE category change increased the apparent benefit. (J Allergy Clin Immunol 2022;■■■:■■■-■■■.)

Key words: *Atopic march, dupilumab, dermatitis, atopic, food hypersensitivity, eczema, antibodies, monoclonal, asthma, rhinitis, allergic, IgE responsiveness, atopic, meta-analysis*

From Regeneron Pharmaceuticals, Inc, Tarrytown.

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Disclosure of potential conflict of interest: All authors are employees of and stakeholders in Regeneron Pharmaceuticals, Inc.

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Abbreviations used
AD: Atopic dermatitis
CI: Confidence interval
EASI: Eczema Area and Severity Index
IRR: Incidence rate ratio
TEAE: Treatment-emergent adverse event

Atopic march has been defined as the serial acquisition of new and worsened allergies after a first instance of clinically important allergic diathesis.[1-7] Allergic immune responses are characterized by the presence of allergen-specific IgE,[8] T-helper cell subsets, and antigen-specific T_H2 cells[9] that produce a pattern of cytokines (IL-4, IL-5, and IL-13). Innate immune cells (group 2 innate lymphoid cells, or ILC2) magnify the production of cytokines (IL-4, IL-5, IL-9, and IL-13) and contribute to the generation of the allergic immune response, constituting an important contributor to type 2 inflammation.

The risk of atopic march is higher in children who produce IgE antibodies in response to environmental triggers than in those who do not. IgE-associated allergic sensitization is an important factor in atopic march, and the relationship of increasing IgE concentrations with acquisition of allergic conditions may depend on genetic and environmental factors.[1,10] The presence of one allergic condition is a risk factor for developing others, increasing allergic disease burden.[2,11]

The presence and severity of atopic dermatitis (AD) positively correlates with the risk of developing food hypersensitivities, typically present from an early age.[2,12] While food-specific IgE antibodies were reported in a small number of infants with AD 3 months after birth, up to 10% of infants at the age of 1 year[3] and almost 15% of children under 6 years of age with AD exhibited food hypersensitivities.[13] AD is also strongly associated with IgE responses to inhalant allergens as well as the development of asthma and allergic rhinitis.[2] About one third of people with AD develop asthma, while two thirds develop allergic rhinitis during their lives.[1,12,14,15] Multiple longitudinal studies provide evidence of atopic march between AD and subsequent allergies.[1,12,16-22]

The main predictors of later atopic diseases, such as asthma, are IgE sensitization and early onset and severity of AD,[23,24] both dependent on type 2 inflammatory signals, most critically IL-4. Modulation of IL-4 signaling[25,26] therefore may represent an important therapeutic approach to target the drivers of atopic march. Dupilumab, a monoclonal antibody designed to block IL-4R, has been shown to provide efficacy in the treatment of moderate-to-severe AD, allergic asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis, all known to be driven largely by type 2 inflammation.[27-30]

In this analysis, we evaluated whether dupilumab would attenuate the acquisition of new allergic conditions or the worsening of existing allergic conditions for participants involved in our large AD clinical trial database compared to those treated with placebo. Using meta-analytical methodology, applied to the entire pooled AD clinical database treated for 4 to 52 weeks, we determined the progression of allergic disease after infancy in this highly atopic population of adolescents and adults.

METHODS

Study design

To qualify for meta-analyses of adverse events for the objectives, the studies must have been randomized, placebo-controlled, double-blind, parallel-grouped trials of dupilumab in the treatment of AD. Twelve such studies completed as of June 2019 were identified, conducted in both adolescent and adult subjects.[31-42] To qualify for enrollment onto the studies, all subjects had moderate-to-severe AD at baseline not adequately controlled with topical medications, an Investigator's Global Assessment severity score of at least 3 (5-point scale; graded 0-4), and generally an Eczema Area and Severity Index (EASI) score of 16 or higher (maximum of 72). The dupilumab dosing regimens in the 12 studies ranged from 100 mg every 4 weeks to 300 mg weekly, with most patients, including all dupilumab-treated patients in the larger pivotal trials, receiving 300 mg weekly or every 2 weeks. The majority of trials studied dupilumab as monotherapy, while 1 long-term study added dupilumab or placebo to topical corticosteroids. The treatment duration ranged from 4 to 52 weeks. Patients may have been treated on a rescue basis with topical corticosteroids while continuing to receive the study drug. However, if patients were rescued with systemic corticosteroids, nonsteroidal immunosuppressants, or phototherapy, study drug was discontinued. An overview of the study design of the individual trials is shown in Table E1 in this article's Online Repository at www.jacionline.org.

End points

In order to track new allergic conditions or determine the impact on existing allergic diatheses, separate from the main effects on AD (which was the primary end point of these studies), we assessed allergic treatment-emergent adverse events (TEAEs). Medical Dictionary for Regulatory Activities–preferred terms from baseline medical history, a specific atopic disease questionnaire, and allergic TEAEs were pooled to identify allergic events across all studies and treatment groups. Because all subjects had AD, this term and terms that mapped to AD were not included for assessment of atopic march. All subjects had moderate-to-severe AD at study initiation; improvement would imply efficacy, while deterioration would have been considered treatment failure that led to rescue therapy.

The selected preferred terms were then assigned to allergy categories to combine terms referring to similar allergic events. The selection process and categorization were performed independently by a board-certified allergist who was unaware of the trial and treatment assignment. A list of allergy categories and associated preferred terms is provided in Table E2 in the Online Repository at www.jacionline.org.

New allergic TEAEs were defined as events not present at the time of study entry (ie, not captured in the list of current or past medical conditions), and worsened TEAEs were defined as allergic conditions that had been identified in the medical history or were present at study entry that had worsened during the course of the studies. This approach to capturing adverse events is a standard of controlled clinical trials. New and worsened IgE categories were defined on the basis of the category shifts from baseline during treatment period, as shown in Table E3 in the Online Repository at www.jacionline.org. IgE categories were analyzed by both 1- and 2-step increases. One-step increases constituted the minimal amount that might be deemed to represent an important change that was prespecified. Though these minimal changes were substantial, as a sensitivity analysis, we included a more conservative 2-step increase to assess the contribution of IgE changes to atopic march (Table E3). Each new or worsening event in a category was considered to be 1 step of atopic march. Any single term coded from a category constituted an end point. Multiple terms from 1 allergic TEAE event category (eg, different pollen reports of pollen sensitization) were deemed to represent a single change in that category (ie, allergy to plants). Thus, a subject deemed to have acquired new sensitizations, such as having grass allergy at baseline and newly reporting tree allergy, was not considered to have acquired a new allergic diathesis and was instead considered to have worsened allergy. If the allergic manifestation involved a different organ (eg, asthma), it was considered a new category of allergy.

TABLE I. Demographic information between placebo and dupilumab arms combining all studies

Characteristic	Variable	Dupilumab (n = 2296)	Placebo (n = 1229)
Age (years)	Mean (SD)	36.2 (14.5)	36.5 (14.5)
	Median (Q1, Q3)	34.0 (24.0, 46.0)	35.0 (24.0, 47.0)
Age at onset (years)	Mean (SD)	9.1 (13.8)	9.1 (14.3)
	Median (Q1, Q3)	2.0 (1.0, 12.0)	2.0 (1.0, 10.0)
Allergic burden	Mean (SD)	3.4 (2.6)	3.4 (2.6)
	Median (Q1, Q3)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)
Sex	Male, no. (%)	1352 (58.9)	706 (57.4)
	Female, no. (%)	944 (41.1)	523 (42.6)
Region	North America, no. (%)	1017 (44.3)	561 (45.6)
	Europe, no. (%)	973 (42.4)	508 (41.3)
	Asia, no. (%)	268 (11.7)	138 (11.2)
	Oceania, no. (%)	38 (1.7)	22 (1.8)
Race	White, no. (%)	1647 (71.7)	865 (70.4)
	Asian, no. (%)	426 (18.6)	232 (18.9)
	Black, no. (%)	153 (6.7)	96 (7.8)
	Other, no. (%)	70 (3.0)	36 (2.9)

Q, Quartile; *SD,* standard deviation.

Statistical analysis

In the meta-analyses, patients were analyzed as treated in the dupilumab or placebo arms from the 12 trials. Demographic and baseline allergic burden and age at AD onset were summarized by treatment groups, dupilumab versus placebo. Mean, standard deviation, median, and interquartile range were used for continuous variables. Percentage of each level was summarized for all categorical variables. In addition, analysis of variance adjusting for study was used to assess baseline allergic burden between treatment groups. Association of baseline burden with baseline IgE was evaluated by negative binomial regression. Time to end of treatment between treatment groups was analyzed by the log-rank test, stratified by study.

Incidence rate ratio (IRR) was defined as the number of events divided by exposure (patient-years) comparing dupilumab to placebo. To account for differential treatment duration across studies and individuals due to early dropout, IRR was used as the metric to quantify the treatment effect in the meta-analyses. All dupilumab dose levels were combined in the meta-analyses, as no apparent dose–response trend with respect to rates of allergic TEAE events was observed. Both fixed-effect models (assuming homogeneity of treatment effects across studies) and random-effect models (assuming heterogeneity of treatment effects across studies) were used for the meta-analyses. Heterogeneity of treatment effects was evaluated using the I^2 statistic, and an I^2 value of ≥50% was considered to indicate significant heterogeneity.[43] Results of fixed-effect models were reported if no heterogeneity was present; otherwise, results of random-effect models were reported. When we pooled the treatment effects in the meta-analysis, the inverse of the variance was used to determine the weight of each study. Analyses were performed separately for the on-treatment period (from the date of first exposure to the end of treatment) and for the entire study period (from the date of first exposure to treatment to study end date—ie, both the on-treatment period and the off-treatment follow-up period) for combined new and worsening allergic TEAE events, new allergic TEAE events alone, combined new and worsening allergic TEAE events, and new and worsening IgE events.

Descriptive subgroup analyses were completed for the variables of age, age at AD onset, region, race, severity of AD, baseline IgE, presence of asthma at baseline, and baseline burden to assess level of varying treatment effects.

The analyses were all performed by R software (R Project; www.r-project.org), and the R package 'meta' was used for the meta-analyses.[44]

RESULTS

The pooled analysis data set included 3525 subjects (n = 2296, dupilumab; n = 1229, placebo). Among the placebo subgroups, the total treatment period was 482 patient-years; the total dupilumab exposure was 877 patient-years. Patient demographics were balanced between the dupilumab and placebo groups in the combined data set (Table I; data for individual studies are presented in Table E4 in the Online Repository at www.jacionline.org). The mean age was 36 years (median, 35 years; range, 12-88 years). The median age at onset of AD was 2 years (mean, 9.1 years; range, 0-80 years), and the mean duration of AD was 27 years. Baseline allergic burden was comparable between treatment groups across studies ($P = .672$), and the average baseline concomitant allergic burden was 3.4 categories (excluding AD). Increased burden rate was significantly associated with increased IgE (IRR 1.17; 95% confidence interval [CI], 1.14-1.20; $P < .001$; see Table E5 in the Online Repository at www.jacionline.org).

Log-rank test stratified by study indicated that there was differential dropout between placebo and dupilumab, as significantly more subjects in the placebo group dropped out before the scheduled end-of-treatment period than in the dupilumab group ($P < .001$). In 10 of 12 trials, time on treatment with dupilumab was greater than placebo. For the pooled data set, a small imbalance in dropout rates (yielding approximately 5% less time on dupilumab vs placebo) may have led to a slightly more conservative estimate of treatment benefit for dupilumab in reducing rates of new and worsened allergy, because events in the placebo arm would have been artificially constrained by less time on randomized treatment.

As can be seen in Fig 1, among the 17 categories contributing to allergic TEAE events, asthma, pruritus, and urticaria were especially notable contributors to the overall positive treatment effect of dupilumab. There were very few IgE events that were new, likely as a result of the small number of these subjects with AD with a baseline IgE level of <30 IU/mL at study entry. However, the statistically significant reduction in IgE events (demonstrated as a 1- or 2-step increase) in dupilumab versus placebo was driven by worsening of IgE in the placebo arm, attenuated in the dupilumab arm, leading to an IRR of 0.32 (95% CI, 0.15-0.67; Fig 1, *A*). Further examination of allergen-specific IgE data from the largest study where this was available, R668-AD-1224, demonstrated a reduction in new as well as in new and worsened allergen-specific IgEs with treatment of dupilumab from baseline to end

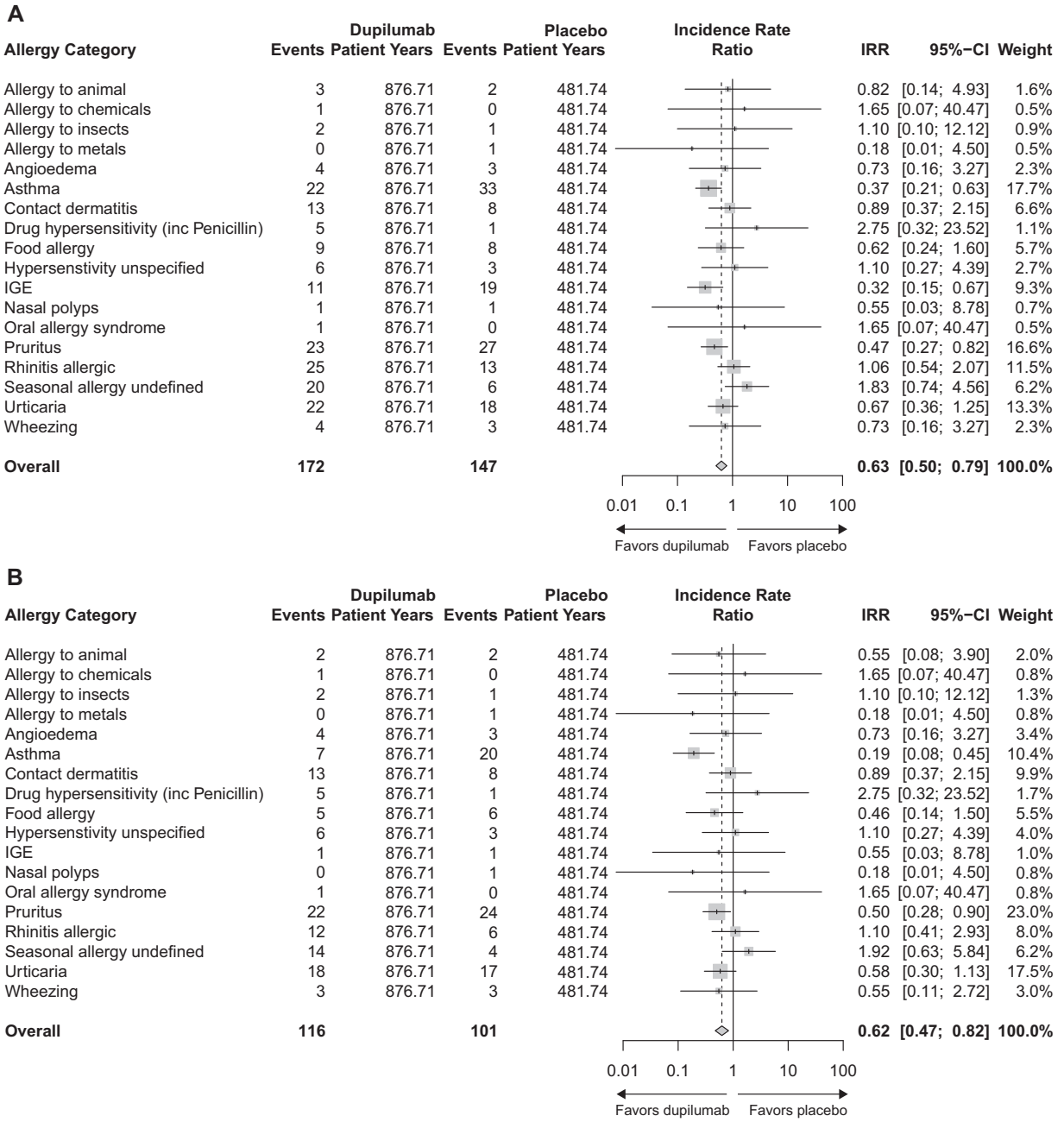


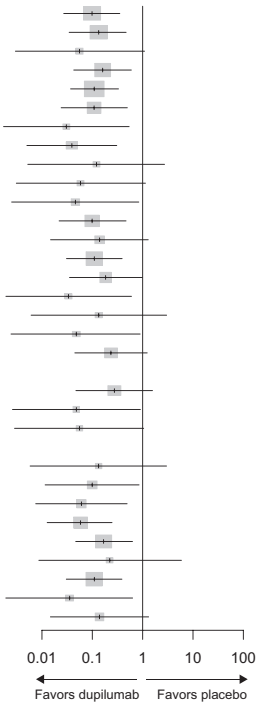
FIG 1. Forest plots **(A)** by allergy category for new and worsened events during the on-treatment period, and **(B)** by allergy category for new events during the on-treatment period.

of study compared to subjects treated with placebo, suggesting attenuation of acquisition of allergenic sensitivity in those treated with dupilumab versus those receiving placebo (Fig 2).

The treatment effect across all studies indicates an overall IRR favoring dupilumab (Fig 3). During the treatment period, dupilumab reduced the risk of new or worsened allergies by 34% (IRR 0.66; 95% CI, 0.52-0.84, Fig 3, *A*) and new allergies by 37% (IRR 0.63; 95% CI, 0.48-0.83, Fig 3, *B*), respectively, versus placebo. When IgE category shift (1-step increase) was taken into consideration, a greater reduction in IRR for combined new/worsening allergic TEAEs of 54% (IRR 0.46; 95% CI, 0.37-0.56, Fig 3, *C*) was observed. Applying the more conservative 2-step definition of IgE change resulted in an IRR reduction of new or worsened allergies of 39% (IRR 0.61; 95% CI, 0.49-0.76, Fig 3, *D*). The longest and most data-dense study (R668-AD-1224) alone showed a statistically significant reduction in allergic TEAE events by dupilumab treatment (IRR 0.59; 95% CI, 0.41-0.85, Fig 3, *A*) for new and worsened allergies during the on-treatment period. A sensitivity analysis that excluded all skin events demonstrated results consistent with the primary analytic

A

Antigen–specific IgE	Dupilumab Events	Dupilumab N	Placebo Events	Placebo N	OR	95%–CI
Alder Grey t2 IgE (kU/L)	3	218	17	142	0.10	[0.03; 0.36]
Alternar Ten/Alter, IgE (kU/L)	3	335	14	220	0.13	[0.04; 0.47]
Asperg. fumig. m3 IgE (kU/L)	0	71	5	50	0.06	[0.00; 1.07]
Bermuda Grass g2 IgE (kU/L)	3	260	11	166	0.16	[0.05; 0.60]
C. Silver Birch t3 IgE (kU/L)	4	333	21	216	0.11	[0.04; 0.33]
Cat Dander IgE (kU/L)	2	327	11	212	0.11	[0.02; 0.51]
Cladosporium IgE (kU/L)	0	259	9	167	0.03	[0.00; 0.56]
Cockroach German IgE (kU/L)	1	256	14	159	0.04	[0.01; 0.31]
Com Sting Nettle w20 IgE (kU/L)	0	37	2	25	0.13	[0.01; 2.73]
Cult. Oat g14 IgE (kU/L)	0	84	5	61	0.06	[0.00; 1.12]
CypressIt. Fun. t23 IgE (kU/L)	0	121	6	81	0.05	[0.00; 0.86]
D. farianae (mite) IgE (kU/L)	2	274	12	181	0.10	[0.02; 0.47]
D. pter (mite) IgE (kU/L)	1	77	4	47	0.14	[0.02; 1.31]
Dog Dander IgE (kU/L)	3	329	16	214	0.11	[0.03; 0.40]
Elm t8 IgE (kU/L)	2	136	6	81	0.19	[0.04; 0.95]
English Plantain w9 IgE (kU/L)	0	125	8	83	0.04	[0.00; 0.62]
Eucalyptus t18 IgE (kU/L)	0	96	2	68	0.14	[0.01; 2.92]
Japanese Cedar t17 IgE (kU/L)	0	72	6	51	0.05	[0.00; 0.88]
Johnson Grass g10 IgE (kU/L)	2	147	5	93	0.24	[0.05; 1.28]
Melaleuca/Bottleb, IgE (kU/L)	0	23	0	17		
Oak White t7 IgE (kU/L)	2	159	4	92	0.28	[0.05; 1.56]
Orchard Grass g3 IgE (kU/L)	0	87	6	62	0.05	[0.00; 0.90]
Oriental Cockroach IgE (kU/L)	0	71	5	49	0.06	[0.00; 1.05]
Ox-eye/Marguerite, IgE (kU/L)	0	23	0	15		
Peren. Rye Grass g5 IgE (kU/L)	0	37	2	27	0.14	[0.01; 2.95]
Ragweed Short/Com IgE (kU/L)	1	187	6	120	0.10	[0.01; 0.86]
Sage. Mugwort w6 IgE (kU/L)	1	286	10	187	0.06	[0.01; 0.49]
Staph Enterotoxin A IgE (kU/L)	2	380	21	255	0.06	[0.01; 0.25]
Staph Enterotoxin B IgE (kU/L)	3	380	11	255	0.18	[0.05; 0.64]
Sw. Vernal Grass g1 IgE (kU/L)	0	73	1	52	0.23	[0.01; 5.85]
Timothy (Phleump.) IgE (kU/L)	3	225	16	147	0.11	[0.03; 0.39]
Wall Pellitory w19 IgE (kU/L)	0	138	8	94	0.04	[0.00; 0.64]
White Ash t15 IgE (kU/L)	1	118	4	71	0.14	[0.02; 1.31]



B

Antigen–specific IgE	Dupilumab Events	Dupilumab N	Placebo Events	Placebo N	OR	95%–CI
Alder Grey t2 IgE (kU/L)	1	218	5	142	0.13	[0.01; 1.09]
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Com Sting Nettle w20 IgE (kU/L)	0	37	1	25	0.22	[0.01; 5.57]
Cult. Oat g14 IgE (kU/L)	0	84	2	61	0.14	[0.01; 2.99]
CypressIt. Fun. t23 IgE (kU/L)	0	121	3	81	0.09	[0.00; 1.81]
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Johnson Grass g10 IgE (kU/L)	1	147	2	93	0.31	[0.03; 3.49]
Melaleuca/Bottleb, IgE (kU/L)	0	23	0	17		
Oak White t7 IgE (kU/L)	1	159	1	92	0.58	[0.04; 9.32]
Orchard Grass g3 IgE (kU/L)	0	87	1	62	0.23	[0.01; 5.85]
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Sage. Mugwort w6 IgE (kU/L)	1	286	2	187	0.32	[0.03; 3.60]
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Staph Enterotoxin B IgE (kU/L)	1	380	4	255	0.17	[0.02; 1.49]
Sw. Vernal Grass g1 IgE (kU/L)	0	73	0	52		
Timothy (Phleump.) IgE (kU/L)	1	225	2	147	0.32	[0.03; 3.60]
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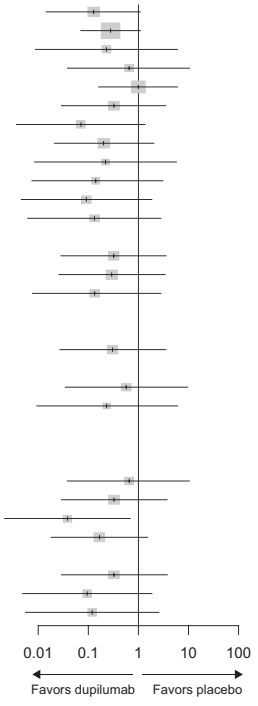

FIG 2. Forest plot by antigen-specific IgE for study R668-AD-1224. For 1-step analysis, for each antigen, new event was defined as below lower limit of quantification (LLOQ) at baseline and above LLOQ at week 52; worsened event was defined as above LLOQ at baseline and increases by at least 1-fold at week 52. For 2-step analysis, for each antigen, new event was defined as below LLOQ at baseline and at least 2 times as large as LLOQ at week 52; worsened event was defined as above LLOQ at baseline and increases by at least 2-fold at week 52. **(A)** One-step analysis for new and worsened allergic events. **(B)** One-step analysis for new allergic events only. **(C)** Two-step analysis for new and worsened allergic events. **(D)** Two-step analysis for new allergic events only. Antigen-specific IgE were tested by region-specific allergen panels; not all patients were tested for all antigens, which led to different sample sizes for different antigens. Percentage of missing (not shown) data was comparable between treatment groups for all antigens. *OR,* Odds ratio.

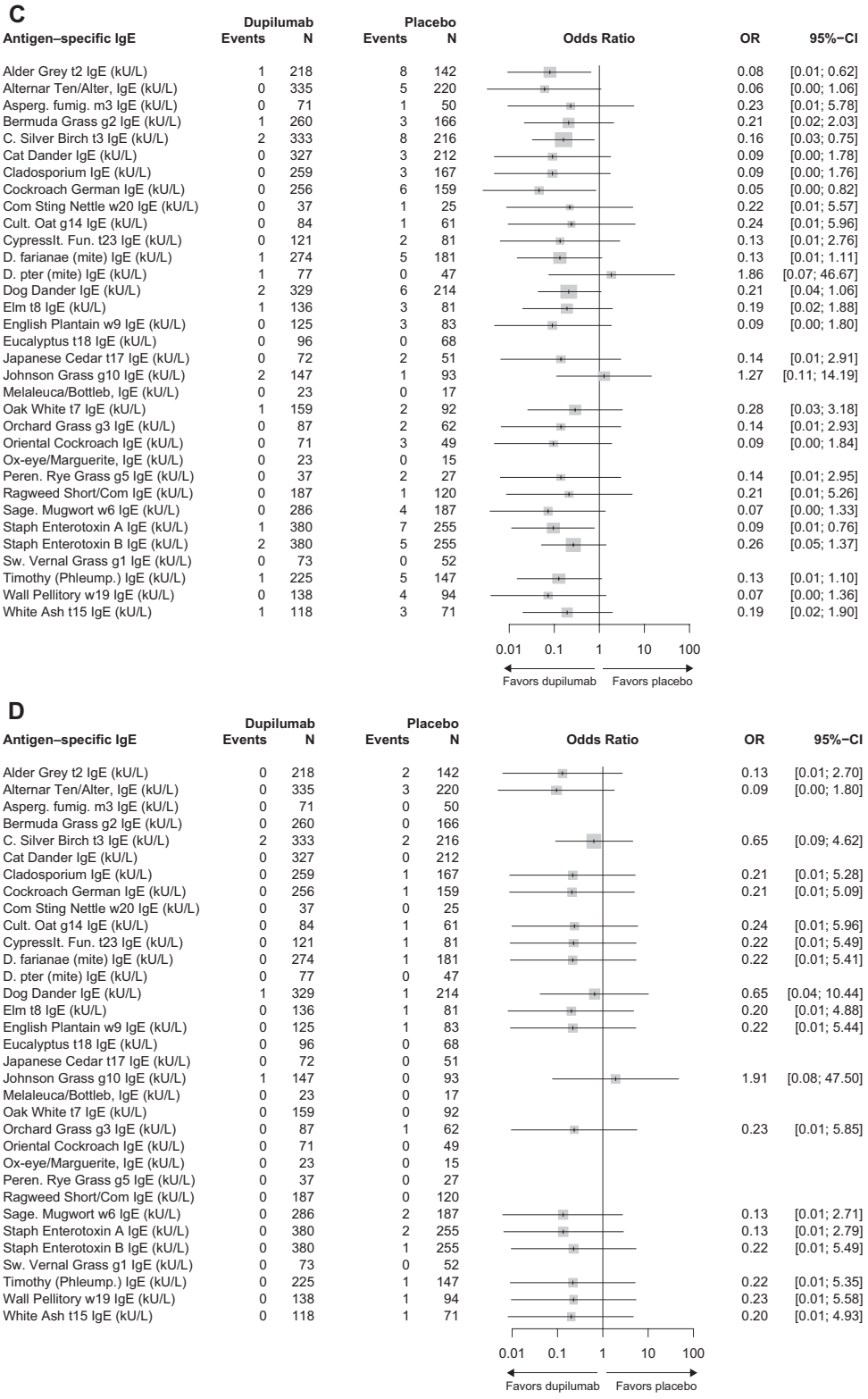

FIG 2. (*Continued*).

approach and a maintained reduction in the incidence rate of new and worsened allergic events in those treated with dupilumab. Additionally, the treatment effects were consistent across all studies after removing the clinical trials that included topical corticosteroids (see Fig E1 in the Online Repository at www.jacionline.org).

When analyzed over the entire study period (including both on-treatment and off-treatment follow-up periods), the treatment effect

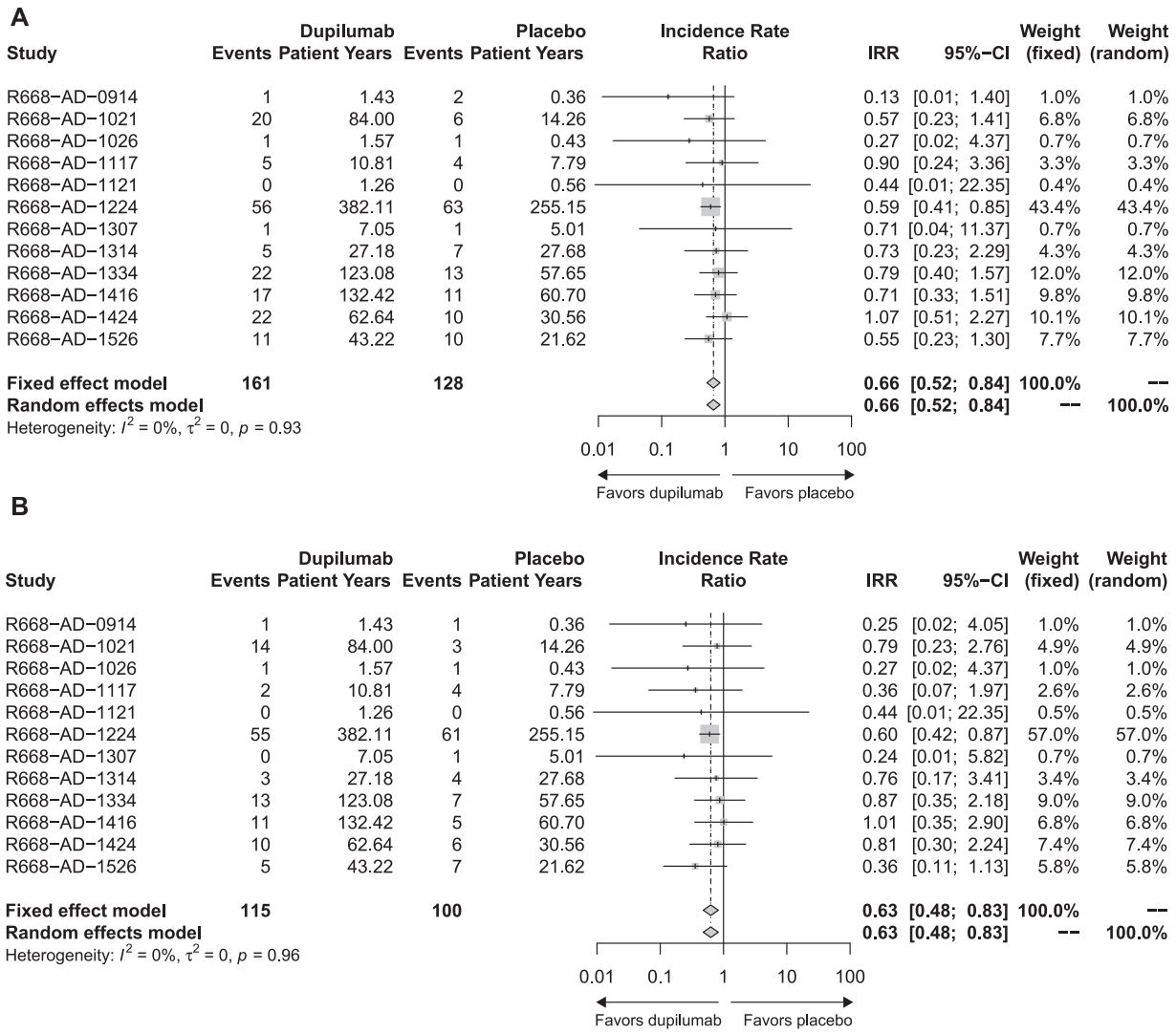

FIG 3. Forest plots **(A)** by study for new and worsened allergic events during the on-treatment period, **(B)** by study for new allergic events during the on-treatment period, **(C)** by study for new and worsened allergic events (includes IgE 1-step increases) during the on-treatment period, and **(D)** by study for new and worsened allergic events (includes IgE 2-step increases) during the on-treatment period.

of dupilumab was moderated (new + worsened: IRR 0.72; 95% CI, 0.58-0.90, Fig E2, *A,* in the Online Repository at www.jacionline.org; new: IRR 0.69; 95% CI, 0.54-0.88, Fig E2, *B*) due to diminished treatment effect during the off-treatment period. However, although the treatment effects of dupilumab on further preventing atopic march were moderated during the off-treatment period, they were not reversed (see Fig E3 in the Online Repository).

A difference in effect according to age at onset of AD (with earlier life emergence and consequent greater amount of time to develop additional allergic diatheses over a lifetime), the severity of AD on study entry (perhaps indicating enhanced type 2 disease), and the coexistence of asthma (suggesting that a second step in atopic march had already been observed) were assessed. In addition, the role of demographic features (age, gender, race, ethnicity) and environment (geography), as well as the relationship to baseline IgE and baseline allergic burden, were examined.

As shown in Fig E4 in the Online Repository at www.jacionline.org, on the basis of shifts in point estimates across these subgroup analyses, treatment benefit seemed to be greater for younger patients (age <18 years), those with early onset of AD (before age 2 years), those with more severe AD at baseline, and those with baseline asthma versus no asthma. Sensitivity analyses suggested that treatment benefits were continuously observed from later age at AD onset up through onset as late as 12 years of age (data not shown). Patients in North America and Europe had a greater number of allergic conditions at baseline and demonstrated stronger treatment benefits versus those from Asia/Oceania. This difference across geographies carried through in part to the analysis across ethnicities, where a greater effect of treatment was seen in White versus Asian participants. In addition, patients with baseline IgE levels between 375 and 2000 IU/mL seemed to benefit more than others. Treatment effect analyzed by baseline IgE quartiles and baseline EASI quartiles are shown in Fig E5 in the Online Repository. Also, treatment benefit seemed to be greater for patients with greater allergic burden at baseline (≥2 concomitant allergic conditions).

A higher allergic burden was observed in patients with higher IgE levels and more severe AD assessed by EASI scores at

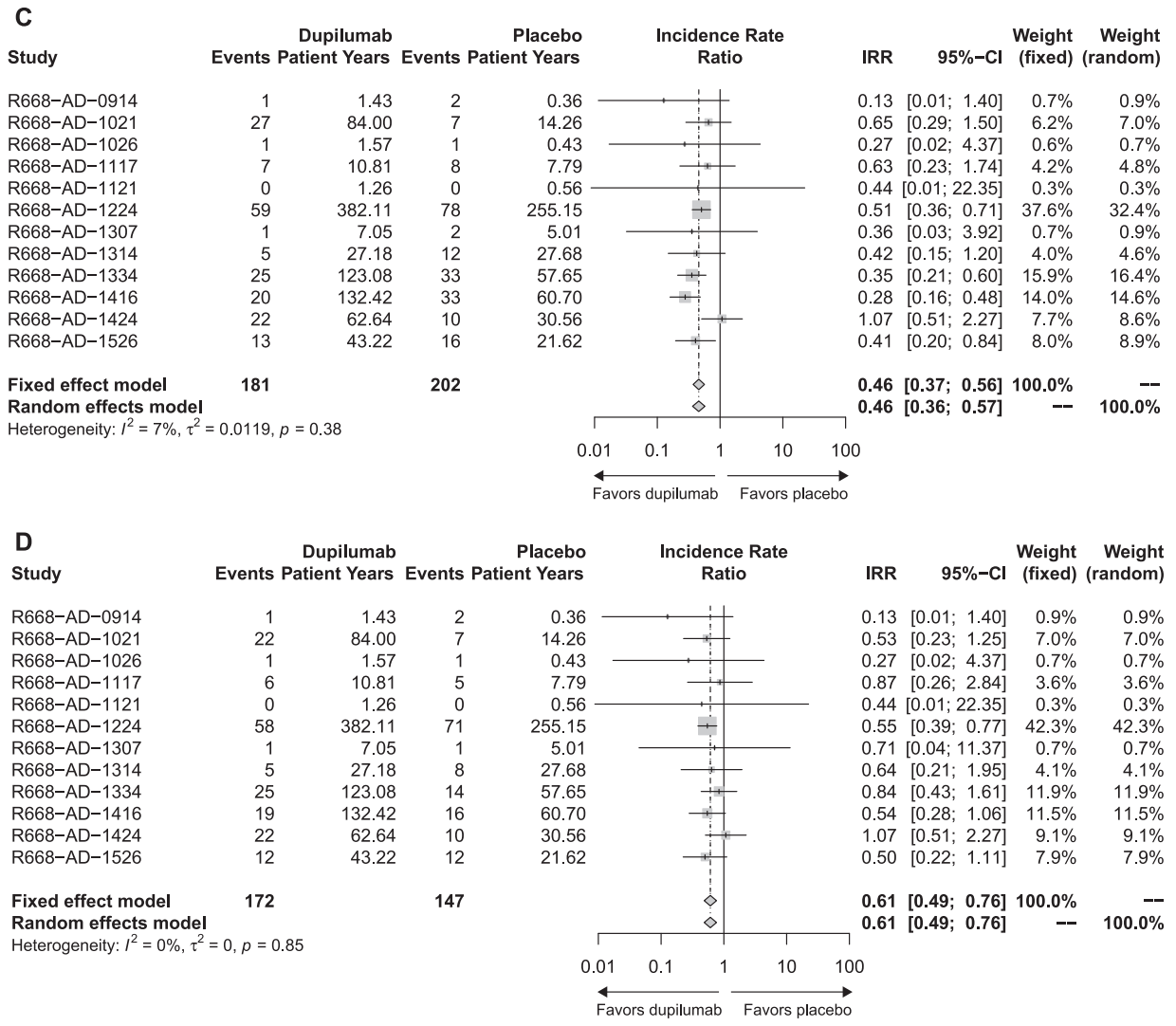

FIG 3. (*Continued*).

baseline (Table E5). Dupilumab substantially reduced IgE levels and EASI scores over the course of treatment across all levels of IgE and EASI scores (see Table E6 in the Online Repository at www.jacionline.org). The changes in IgE levels and EASI scores from end-of-treatment to end-of-study across trials are shown in Table E7 in the Online Repository. Although higher allergic burden provides a greater opportunity to demonstrate treatment benefit, the clear-cut, though moderated, effect on atopic march at the highest levels of IgE suggests the possibility that reaching threshold reductions of IgE as a reflection of blockade of IL-4/IL-13 biologic activity plays a role in the degree of its attenuation. It follows that those individuals with the highest IgE levels at baseline may require longer duration of treatment to obtain the IgE threshold that would maximally attenuate atopic march.

DISCUSSION

Individuals with AD demonstrate an increased propensity for the development of other allergic diseases, with the existence of atopic march supported by cross-sectional and longitudinal research, as well as experimental evidence from animal models.[20,21,45-48] The typical type and pattern of sequential development of allergic disease suggests an underlying progressive atopic diathesis, as opposed to a simple, chance manifestation of single allergic conditions occurring throughout life.[1,22,23] The classical sequence observed in atopic march presents first in the skin as AD, followed by the gastrointestinal tract as food allergy, and can then progress to the upper and lower airways as allergic rhinitis and asthma, respectively, in modestly variable sequence.[2,23] Many argue that AD is not a causal factor for atopic march but mostly represents the first clinical manifestation of the IgE atopic response.[1] Other analyses of the AD and asthma dupilumab clinical trial databases showed a markedly greater number of concomitant allergies in those with AD versus those with asthma, suggesting that AD may reflect stronger type 2 immune influences promoting atopic disease compared to other allergic conditions (in preparation).

It has been conventionally thought that atopic march is a process that begins in early infancy and extends into childhood. However, it has been more recently noted that sensitization to allergens as well as first presentation of AD, and new aeroallergen and food hypersensitivities can develop in late adolescence and

adulthood.[3,13,17,22,49] New manifestations of allergy, such as asthma, urticaria/angioedema, allergic sinusitis, and sensitivity to a variety of chemicals and drugs on exposure of the skin and mucosal surfaces may be acquired progressively over the course of time, from childhood into adulthood.[2,6,17,22,50,51]

The current analyses were performed on the largest and most comprehensive clinical trial database of moderate-to-severe AD. We believe that we have shown for the first time, in a large pooled study population of mostly adults (mean age, 36 years; median age, 35 years; range, 12-88 years) and generally consistent across the individual component studies, evidence of atopic march in adults, separated in time from their most active period of allergy acquisition in childhood. This was uncovered despite the relatively short follow-up period (mean, 0.390 years; median, 0.290 years; range, 0.003-1.018 years). Furthermore, this analysis showed that dupilumab can interfere with atopic march. Dupilumab reduced both the incidence of new allergies and worsening of preexisting allergic conditions compared to controls treated with standard of care.

Shifts in point estimates across subgroup analyses revealed that the treatment benefit of dupilumab appeared greater for younger patients (<18 years), those with early onset of AD (<2 years), those with more severe AD at baseline, and those with baseline asthma versus no asthma (Fig E4). Greater treatment benefit was also observed in the atopic White population compared with the Asian population. This is likely due to the larger number of allergies at baseline in the White group, providing a greater potential for worsening, and therefore a greater opportunity to demonstrate a treatment benefit. Of note, previous studies have shown differences in the number and severity of allergic conditions between ethnic groups.[52-57]

A persistent, albeit attenuated, effect was observed with discontinuing dupilumab therapy in off-treatment periods; however, no rebound in allergic events was noted after dupilumab treatment had been discontinued, as evidenced by continued treatment benefits observed in follow-up periods after discontinuation of therapy. Thus, although larger and longer trials will be needed to further confirm these findings, dupilumab treatment may provide some prolonged disease modification, at least over the follow-up duration of these studies (beyond 5 dupilumab half-lives). An even longer follow-up will be required to assess the durability of this potential effect on atopic march. In addition, longer duration of dupilumab treatment will be needed to assess the full impact in those with the highest IgE levels and the greatest allergic burden. Finally, further study of patients who have less severe AD and who are younger would provide insight into the generalizability of dupilumab's effects on atopic march in newly developed or milder AD.

Dupilumab treatment showed significant improvement in disease severity, with remarkable reduction in serum total IgE levels. Interestingly, a nonmonotonic relationship was observed for treatment effect and baseline serum IgE levels (Fig E4). Although dupilumab treatment effects were demonstrated with improvement in disease severity irrespective of IgE level at baseline, the greatest treatment effect was observed in patients whose baseline IgE levels were between 375 and 2000 IU/mL, defined empirically and prospectively as thresholds. When baseline IgE was analyzed by quantiles, the data showed a similar trend (Fig E5). Whether this occurred by chance or reflects a difference in intensity of type 2 inflammation, with low- or intermediate-grade intensities more easily quenched than very severe type 2 inflammatory responses, or whether the relationship of dupilumab to IgE in those with highest IgE levels might demonstrate greater effects with longer duration of dupilumab exposure, is not known. The effects of dupilumab were more pronounced for those with more active atopic march irrespective of IgE, marked by other indicators of degree of allergy sensitization, such as earlier age at onset or greater severity of AD, presence of asthma, and higher allergic burden at study start, while the nonmonotonic relationship between IRR and IgE by quantile also extended to EASI scores at baseline (Fig E5). Because EASI and IgE are highly correlated, this may also reflect differences in exposure response, whereby the strongest type 2 inflammatory signals may require longer exposure to dupilumab to optimally demonstrate benefit. Larger and longer clinical trials focused on this question may be required to confirm this result.

Other agents have unsuccessfully been used to attempt to modify allergic disease progression in atopic march. Pimecrolimus, a calcineurin inhibitor that downregulates IL-2–induced T-cell activation and inhibits cytokine activation pathways, including production of IL-4 and IL-10 by T_H2 cells,[58] was assessed in a study designed to evaluate effects on atopic march by administration at first manifestation of AD in infancy to assess effect on asthma incidence by 6 years of age.[21] An unexpectedly high discontinuation rate (48%) reduced the power of the study, which was also confounded by the use of emollients and the topical corticosteroid fluticasone, and the asthma end point could not be tested because the study was stopped at year 3.[21] Other trials have used prophylactic antihistamines, pre- and postnatal probiotics, and ceramide-dominant emollients to attempt to abrogate atopic march, without success.[59,60]

This analysis across the entire adolescent and adult AD clinical database determined that dupilumab reduced the acquisition of new or the worsening of preexisting allergic conditions in a large AD clinical trial database in a highly atopic population. This provided important evidence that dupilumab may be effective in reducing allergic burden in these individuals over the course of time, reflecting a potential for disease modification in slowing the atopic march. Specifically designed larger trials of longer duration across an even broader spectrum of age and disease severity will be required to confirm whether dupilumab can completely and durably exert these effects correcting the underlying immune skew towards type 2 inflammation, which underlies the atopic march.

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Clinical implications: Atopic march is associated with progressive allergic disease burden, and there are no disease-modifying treatments. Dupilumab was associated with fewer new/worsening allergies in AD and may attenuate atopic march.

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