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ORIGINAL RESEARCH

Real-World Effectiveness of Dupilumab in Atopic Dermatitis Patients: Analysis of an Electronic Medical Records Dataset

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ABSTRACT

Introduction: While the efficacy of dupilumab for the treatment of adults with moderate-to-severe atopic dermatitis (AD) has been demonstrated in several clinical trials, patients in such trials may not necessarily reflect the real-world clinical practice setting. This study evaluated the real-world effectiveness of dupilumab in adults with moderate-to-severe AD based on physician global assessment, percent body surface area affected, and patient-reported itch.

Methods: From Modernizing Medicine's Electronic Medical Assistant dermatology-specific electronic medical records, adults (≥ 18 years) were identified with a diagnosis of AD and ≥ 1 dupilumab prescription (index event) between 1 April 2017 and 31 January 2019. Three cohorts were identified based on 3-month pre-index (1) Investigator Global Assessment (IGA) score ≥ 3, (2) an itch severity numerical rating scale (NRS) score ≥ 3, and (3) body surface area (BSA) affected ≥ 10%. Changes from pre-index on the outcome within each cohort were evaluated at 4 months post-index. Patients were also stratified for evaluation of outcomes by baseline demographic (sex, age) and prior AD treatments (topical therapy only or no treatment, any systemic therapy).

Results: More than 70% of the 435 AD patients with baseline IGA score ≥ 3 improved to an IGA score of ≤ 2 at month 4 post-dupilumab initiation, including 42.8% who achieved IGA 0/1 (clear/minimal). Among 112 patients with a pre-index itch severity NRS ≥ 3, scores were reduced from mean (SD) 7.0 (2.4) pre-index to 2.8 (2.8) at month 4 ($p < 0.0001$); 70.5% of patients had a reduction ≥ 3 points. In the BSA cohort ($n = 387$), affected BSA was significantly reduced from a pre-index mean (SD) of 39.3% (26.1%) to 16.3% (21.2%) at month 4 ($p < 0.0001$). Significant improvements in IGA, itch NRS, and BSA were observed regardless of

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demographic (age and sex) or clinical characteristics such as treatment history (all $p < 0.0001$ compared with pre-index).
Conclusions: Consistent with outcomes observed in clinical trials, patients treated with dupilumab in real-world clinical settings achieved clinically meaningful improvements in severity and extent of AD and severity of itch comparable to those reported in clinical trials at a similar time point.

Keywords: Atopic dermatitis; Dupilumab; Real-world effectiveness; Itch; Body surface area affected; Investigator global assessment

Key Summary Points

Why carry out this study?

The efficacy of dupilumab for treatment of adults with moderate-to-severe atopic dermatitis has been demonstrated in clinical trials, but results from real-world clinical practice can additionally confirm the benefits of treatment.

What was learned from the study?

Enrolled patients had moderate-to-severe atopic dermatitis based on thresholds for clinician-assessed Investigator Global Assessment and body surface area affected, and patient-reported itch severity.

Regardless of prior treatment history, patients initiated on dupilumab in real-world clinical settings achieved clinically meaningful improvements in severity and extent of atopic dermatitis (Investigator Global Assessment, body surface area affected) and itch severity that were comparable to those reported in clinical trials at a similar time point.

INTRODUCTION

Interleukins 4 (IL-4) and 13 (IL-13) are key drivers of type 2 immune responses that contribute to the pathogenesis of atopic dermatitis (AD) [1]. Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13 and modulates the downstream pathways regulated by these cytokines [2, 3]. Dupilumab is approved in the USA (Dupixent) for patients aged ≥ 6 years with moderate-to-severe AD not adequately controlled with topical therapies, as add-on maintenance treatment in patients ≥ 12 years with moderate-to-severe asthma with an eosinophilic phenotype or oral corticosteroid-dependent asthma, and as add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis [4]. The efficacy of dupilumab for the treatment of AD has been demonstrated in several clinical trials in patients with moderate-to-severe AD. Those trials showed that dupilumab not only reduced the clinical signs and symptoms of AD and improved patient-reported outcomes relative to placebo [5–11] but also resulted in clinically relevant effects on disease biomarkers and reversal of AD-associated epidermal abnormalities [12, 13]. However, patients in clinical trials may not necessarily reflect the patient population likely to be treated in routine clinical practice. Thus, it is important to evaluate the real-world effectiveness of treatment and to determine whether the effects observed in the clinical setting support those reported in clinical trials. Several real-world studies have reported on the effectiveness of dupilumab [14–27], but these studies either evaluated small populations or were from a limited number of study sites.

Electronic medical records (EMR) are increasingly being utilized as a source of real-world data for large populations. The purpose of the current analysis is to evaluate the real-world effectiveness of dupilumab in adults with moderate-to-severe AD over a time period comparable to that of dupilumab clinical trials, using a large, dermatology-specific structured

EMR database and clinically relevant outcomes of clinician assessment of global AD severity, percentage body surface area affected, and patient-reported itch severity.

METHODS

Data source

Data for this retrospective observational study were derived from Modernizing Medicine's Electronic Medical Assistant (EMA) dermatology-specific EMR database. This database is the most widely used dermatology-specific EMR platform in the USA, containing structured, real-world data from over 30% of US dermatologists. All patient-level data were fully anonymized to ensure confidentiality and compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Use of dermatology-specific EMR enables extraction of AD assessments, where available, including severity using the six-point Investigator Global Assessment scale (IGA; 0 = clear to 5 = very severe), and itch severity, which was assessed using a numerical rating scale (NRS) based on the question "How intense is your itching, 0 being no itch, 10 being the most severe itch possible?" Information on percent of body surface area (BSA) affected is also available in the database. These measures were used for both identification of cohorts and for evaluation of effectiveness.

Study populations

From the EMR database, patients were identified who had a diagnosis of AD (ICD-10 codes L20.0, L20.81, L20.82, L20.83, L20.84, L20.89, L20.9) and received ≥ 1 dupilumab prescription(s) between 1 April 2017 and 31 January 2019 (representing the initial approval in adults); the date of the first dupilumab prescription was defined as the index date, and patients were required to be ≥ 18 years of age at index. The study period was from 1 April 2016 to 31 May 2019 to capture outcomes assessment at 12 months pre-index (baseline) and 4 months post-index, defined as 120–149 days after the initial prescription. For inclusion in the analysis, patients were required to have IGA, itch severity NRS, and BSA recorded in the EMR within 3 months pre-index and any time during the 120–149-day post-index period. Inclusion criteria were based on availability of the outcomes independent of whether the patient discontinued treatment, since they had to have at least one treatment with dupilumab, i.e., treatment was initiated during the specified time frame. From this population, three cohorts were identified for analysis based on the most recently recorded IGA, itch severity NRS, and BSA scores within the 3-month pre-index period: (1) patients with moderate-to-severe AD defined as IGA ≥ 3, (2) patients with moderate-to-severe itch, defined as NRS score ≥ 3 [28], and (3) patients with BSA $\geq 10\%$.

Effectiveness

Effectiveness was evaluated based on changes from baseline at 4 months post-index on the IGA, itch severity NRS, and BSA scores in the three populations, respectively. The proportion of patients with post-index IGA 0/1 was determined, as was the proportion of patients with IGA scores ≥ 1 and ≥ 2 points lower than baseline; a change ≥ 1 point has been considered to be clinically relevant [29, 30]. Similarly, for the itch severity NRS, in addition to the mean change in score, the proportion of patients who improved by a ≥ 3-point reduction in score from baseline was determined, as were the proportions of patients with post-index scores stratified by itch severity strata of 0–3 (mild), 4–6 (moderate), and 7–10 (severe) [28]; severity strata were used rather than NRS scores because data cells with ≤ 5 patients in the Modernizing Medicine's EMR database are masked to ensure patient privacy. A ≥ 3-point reduction can be considered clinically meaningful based on empirically derived thresholds from a similar NRS [31].

Effectiveness in the cohorts was further evaluated among patients stratified by treatment history during the baseline period, and sex and age. Two distinct treatment history

strata were defined: one stratum consisted of patients with either a history of topical therapy only (topical corticosteroids, topical calcineurin inhibitors, and phosphodiesterase 4 inhibitor) or no treatment, and the other stratum consisted of those who had history of use of any systemic therapy (systemic corticosteroids, immunosuppressants, and phototherapy). Age strata were 18–34 years, 35–54 years, and ≥ 55 years.

In the BSA cohort, patients were stratified by quartiles of BSA affected (10%–25%, 26%–50%, 51%–75%, and 76%–100%).

Statistical analysis

Results were analyzed descriptively, with mean and standard deviation (SD) generated as measures for continuous variables, and count (frequency) and percentages generated for categorical variables. Statistical comparisons of changes in severity of AD and itch outcomes from pre- and post-index were performed using two-sided paired *t*-tests or Wilcoxon signed-rank tests at 0.05 significance level. The mean percent change in itch severity NRS score was derived from the percent change calculated across the individual patients. For BSA quartiles, least-squares (LS) mean change from baseline and 95% confidence intervals (95% CI) were estimated using analysis of covariance (ANCOVA) adjusted for age, gender, baseline IGA, and binary baseline therapies of interest (topical corticosteroids; topical calcineurin inhibitors; PDE-4 inhibitors; systemic steroids; immunosuppressants); confidence intervals that do not include 0 would map to $p < 0.05$.

All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Cohort characteristics

From an initial population of 1,446,601 patients identified with AD, 22,914 were initiated on dupilumab during the study period. Among these patients who met the inclusion criteria of age ≥ 18 years, and were eligible for subgroup analysis based on Modernizing Medicine's EMR patient privacy criteria (n = 21,408), the identified cohorts, which partially overlapped, included 435 patients with IGA ≥ 3 (mean [SD] age 47.4 [18.4] years, 48.3% male, 49.4% white), 112 patients with NRS ≥ 3 (mean [SD] age 48.7 [17.3] years, 50.0% male, 40.5% white), and 387 patients with BSA ≥ 10% (mean [SD] age 45.5 [17.8] years, 48.6% male, 44.4% white) (Table 1). These three cohorts served as the final dataset for analysis.

Topical corticosteroids were the most widely used therapy prior to the index date (77.0%, 83.0%, and 72.4% in the IGA, NRS, and BSA cohorts, respectively) followed by systemic steroids (42.3%, 44.6%, and 38.8%, respectively) (Table 1). A history of systemic immunosuppressants was observed in 15.2%, 12.5%, and 12.4% of the IGA, NRS, and BSA cohorts, respectively.

Change in AD severity

At baseline in the IGA ≥ 3 cohort, 41.6% and 58.4% had IGA scores of 3 (moderate) and 4/5 (severe/very severe) AD, respectively (Fig. 1). At month 4 after initiation of dupilumab, disease severity was reduced in the majority of patients in the cohort with baseline IGA ≥ 3 as indicated by differences in the distribution of patients across the IGA scores post-index relative to pre-index (Fig. 1). Among these patients, 72.0% improved to an IGA score of ≤ 2 post-dupilumab initiation, including 42.8% who achieved IGA 0/1 (clear/minimal). A reduction in score ≥ 1 point from baseline was observed in 81.8% of patients, and almost two-thirds (62.8%) had a reduction of ≥ 2 points.

When stratified by history of treatment, patterns of improvement in AD severity were comparable to that observed among all patients with baseline IGA score ≥ 3 (Fig. 1); 44.2% of those who used topical corticosteroids only or no therapy and 41.5% of those who used systemic therapy achieved a score of 0/1. Additionally, the proportions of these patients with reductions in IGA scores ≥ 1 and ≥ 2 points reflected that of the overall population

Table 1 Demographic and clinical characteristics

Variable	Baseline IGA ≥ 3 (*n* = 435)	Baseline NRS ≥ 3 (*n* = 112)	Baseline BSA ≥ 10 (*n* = 387)
Age, years, mean (SD)	47.4 (18.4)	48.7 (17.3)	45.5 (17.8)
Age distribution, *n* (%)			
18–34 years	133 (30.6)	25 (22.3)	128 (33.1)
35–44 years	55 (12.6)	23 (20.5)	61 (15.8)
45–54 years	79 (18.2)	17 (15.2)	63 (16.3)
55–64 years	89 (20.5)	28 (25.0)	73 (18.9)
≥ 65 years	79 (18.2)	19 (17.0)	62 (16.0)
Sex, *n* (%)			
Male	210 (48.3)	56 (50.0)	188 (48.6)
Female	225 (51.7)	56 (50.0)	199 (51.4)
Race, *n* (%)			
White	215 (49.4)	45 (40.5)	172 (44.4)
African American	38 (8.7)	9 (8.1)	34 (8.8)
Asian	31 (7.1)	8 (7.2)	24 (6.2)
Other/unknown	151 (34.7)	50 (44.6)	157 (40.6)
Geographic region, *n* (%)			
Northeast	83 (19.1)	23 (20.5)	41 (10.6)
Midwest	58 (13.3)	18 (16.1)	66 (17.1)
South	207 (47.6)	44 (39.3)	162 (41.9)
West	87 (20.0)	27 (24.1)	118 (30.5)
Body surface area, %, mean (SD) [*n*]	37.2 (26.5) [361]	38.8 (26.8) [60]	39.3 (26.1) [387]
Atopic comorbidities, *n* (%)			
Asthma	137 (31.5)	31 (27.7)	96 (24.8)
Allergic rhinitis	124 (28.5)	28 (25.0)	96 (24.8)
Other AD-related comorbidities, *n* (%)			
Skin infections	88 (20.2)	30 (26.8)	61 (15.8)
Treatment history, *n* (%)[a]			
No treatment	66 (15.2)	10 (8.9)	78 (20.2)
Topical corticosteroids	335 (77.0)	93 (83.0)	280 (72.4)
Topical calcineurin inhibitors	130 (29.9)	33 (29.5)	122 (31.5)
Phosphodiesterase 4 inhibitor	92 (21.2)	29 (25.9)	78 (20.2)

Table 1 continued

Variable	Baseline IGA ≥ 3 (n = 435)	Baseline NRS ≥ 3 (n = 112)	Baseline BSA ≥ 10 (n = 387)
Systemic steroids	184 (42.3)	50 (44.6)	150 (38.8)
Systemic immunosuppressants[b]	66 (15.2)	14 (12.5)	48 (12.4)
Phototherapy	30 (6.9)	7 (6.3)	25 (6.5)

BSA body surface area, *NRS* itch severity numerical rating scale, *PGA* Physician Global Assessment, *SD* standard deviation
[a]Percentages exceed 100% since some patients had a history of multiple therapies
[b]Systemic immunosuppressants include mycophenolate, azathioprine, cyclosporine, and methotrexate

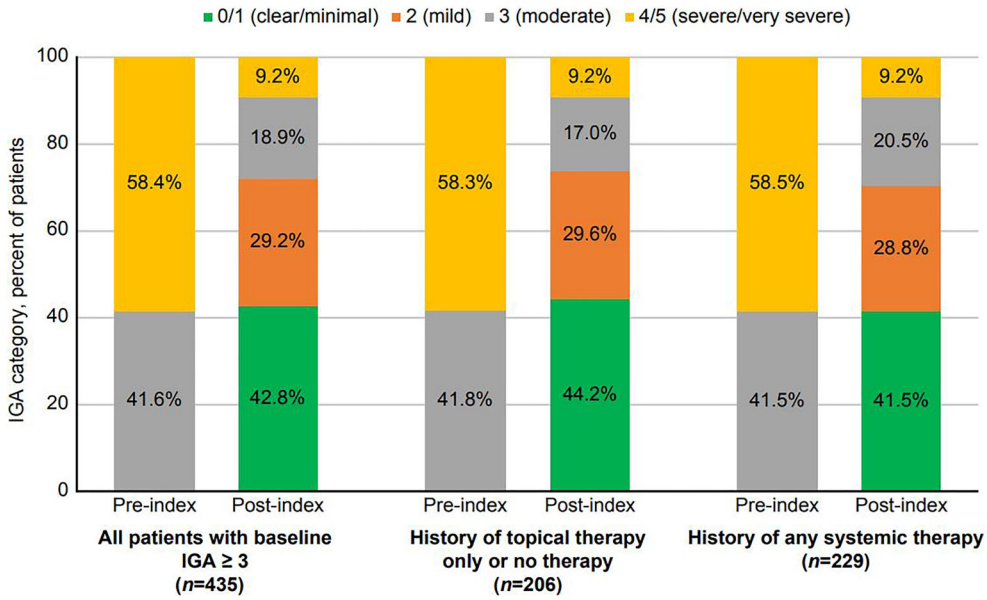

Fig. 1 Atopic dermatitis disease severity, assessed using the Investigator Global Assessment (IGA) scale, before and at 4 months after initiating treatment with dupilumab (index event), among patients with pre-index scores ≥ 3 on IGA

(Table 2). Similar effectiveness with regard to proportions of patients with post-index IGA score 0/1 and ≥ 1- and ≥ 2-point reductions in IGA scores were also observed across all strata regardless of sex and age (Table 2), with these proportions comparable to that observed in the total population.

Change in itch severity

In the total cohort of patients with a baseline itch severity NRS score ≥ 3, the mean (SD) pre-index score, 7.0 (2.4), was significantly reduced to 2.8 (2.8) ($p < 0.0001$) at 4 months after initiation of dupilumab therapy (Table 3); the mean percent change in score showed a reduction of 54.9%. This reduction was driven by a shift in distribution from higher severity levels during the pre-index period, with 70.5% reporting scores in the "mild range" at month 4 (Fig. 2), including almost one-quarter of the patients (24.1%) with no itch.

Across demographic and clinical strata, the mean change in NRS score from pre- to post-index ranged from −3.6 to −4.9 points

Table 2 Atopic dermatitis severity, assessed using the Investigator Global Assessment (IGA) at 4 months after initiating treatment with dupilumab (index event), among patients with pre-index IGA score ≥ 3 by clinical and demographic characteristics

Population	Number (%) of patients post-index		
	IGA score 0/1	≥ 1-point reduction in IGA score	≥ 2-point reduction in IGA score
Treatment history			
Topical therapy only or no treatment (n = 206)[a]	91 (44.2)	167 (81.1)	133 (64.6)
Any systemic therapy (n = 229)[b]	95 (41.5)	189 (82.5)	140 (61.1)
Sex			
Male (n = 210)	84 (40.0)	166 (79.1)	124 (59.1)
Female (n = 225)	102 (45.3)	190 (84.4)	149 (66.2)
Age			
18–34 years (n = 133)	52 (39.1)	109 (82.0)	83 (62.4)
35–54 years (n = 134)	54 (40.3)	107 (79.9)	83 (61.9)
≥ 55 years (n = 168)	80 (47.6)	140 (83.3)	107 (63.7)

[a]Includes topical corticosteroids, topical calcineurin inhibitors, and phosphodiesterase 4 inhibitor
[b]Includes systemic corticosteroids, immunosuppressants, and phototherapy

(Table 3). Additionally, 70.5% of patients in the overall cohort had a pre- to post-index decrease ≥ 3 points, and these proportions ranged from 68.1% to 72.5% across age, sex, and treatment history strata (Table 3).

Change in body surface area affected

As shown in Table 4, there was a significant reduction in BSA from a pre-index mean (SD) of 39.3% (26.1%) to 16.3% (21.2%) at month 4 post-index ($p < 0.0001$), with similar reductions observed when stratified by age, sex, and treatment history (all $p < 0.0001$). When stratified by baseline BSA quartile (Fig. 3), the LS mean change from baseline was higher with increasing quartile, and ranged from –4.4% (95% CI –8.9%, 0.2%) for patients in the 10–25% quartile to –60.9% (95% CI –68.1%, –53.7%) for patients in the 76–100% quartile.

DISCUSSION

This study, through its use of a dermatology-specific EMR database to identify cohorts of patients defined as having moderate-to-severe AD based on established severity thresholds, adds to the expanding body of evidence supporting the effectiveness of dupilumab in the real-world clinical setting. Evaluation of dupilumab treatment outcomes was from both the clinician's perspective using a global severity assessment (IGA) and an objective assessment of BSA, and the patient's perspective based on the hallmark symptom of itch. Furthermore, the analyses included stratification by treatment history, with evaluation conducted at a time point that allowed for comparison with clinical trial data. On all outcomes, the results showed that the majority of patients achieved benefits after initiation of dupilumab therapy that were statistically significant, clinically meaningful, and consistent with improvements in AD observed at similar time points in the

Table 3 Itch severity numerical rating scale (itch NRS) scores before and at 4 months after initiating treatment with dupilumab (index event)

Population	Pre-index NRS score, mean (SD)	Post-index NRS score, mean (SD)	Change, mean (SD)	Percent change, mean (SD)	Post-index reduction ≥ 3 points, *n* (%)
All patients with pre-index NRS ≥ 3 (n = 112)	7.0 (2.4)	2.8 (2.8)	−4.2 (3.6)*	54.9 (55.4)	79 (70.5)
Patients with pre-index NRS ≥ 3 by treatment history					
Topical therapy only or no treatment (n = 51)[a]	6.7 (2.3)	2.8 (3.1)	−3.9 (4.1)*	50.1 (72.8)	36 (70.6)
Any systemic therapy (n = 61)[b]	7.2 (2.5)	2.8 (2.5)	−4.4 (3.1)*	58.8 (35.2)	43 (70.5)
Patients with pre-index NRS ≥ 3 by sex					
Male (n = 56)	7.0 (2.4)	3.1 (3.1)	−3.8 (3.7)*	51.3 (58.0)	39 (69.6)
Female (n = 56)	7.0 (2.5)	2.5 (2.4)	−4.6 (3.5)*	58.4 (53.0)	40 (71.4)
Patients with pre-index NRS ≥ 3 by age group					
18–34 years (n = 25)	6.5 (2.3)	2.8 (2.4)	−3.6 (2.5)*	58.3 (36.2)	18 (72.0)
35–54 years (n = 40)	7.3 (2.6)	2.5 (2.8)	−4.9 (4.2)*	53.1 (74.2)	29 (72.5)
≥ 55 years (n = 47)	7.0 (2.4)	3.0 (3.0)	−3.9 (3.4)*	54.5 (45.3)	32 (68.1)

IGA Investigator Global Assessment

[a]Includes topical corticosteroids, topical calcineurin inhibitors, and phosphodiesterase 4 inhibitor

[b]Includes systemic corticosteroids, immunosuppressants, and phototherapy

*$p < 0.0001$

dupilumab clinical trials [5, 7, 9–11] and other real-world studies [14–24, 26].

IGA is a relevant efficacy endpoint in clinical trials as it considers global physician assessment of disease and may be less cumbersome than multi-item measures [32]. In the IGA cohort, 59.1–66.2% of patients had a ≥ 2-point reduction in score, which resulted in substantial proportions of the patients achieving an IGA score of clear or minimal AD (39.1–47.6%) regardless of strata and 42.8% overall. These proportions may be considered comparable to what was observed in phase 3 clinical trials, which used a combined endpoint of IGA 0/1 plus a ≥ 2-point reduction in score, and reported that 36–40% of patients met this endpoint after 16 weeks of dupilumab treatment [7, 9, 10]. It should be noted that the IGA in dupilumab clinical trials was based on a 0–4-point scale rather than the 0–5-point scale in this study. However, the additional discrimination associated with the wider scale was related to expansion of scores representing severe (4) and very severe (5), and thus patients at higher severity required a greater point reduction to achieve IGA 0/1 in this analysis compared with clinical trials. The IGA has been reported in few real-world studies, with proportions of patients who achieved a clear/minimal score ranging from 38% to 60% within 3–4 months after dupilumab initiation [18, 33, 34], although the study populations were small.

Both the absolute and percent reduction in itch severity were substantial, and 68.1–72.5%

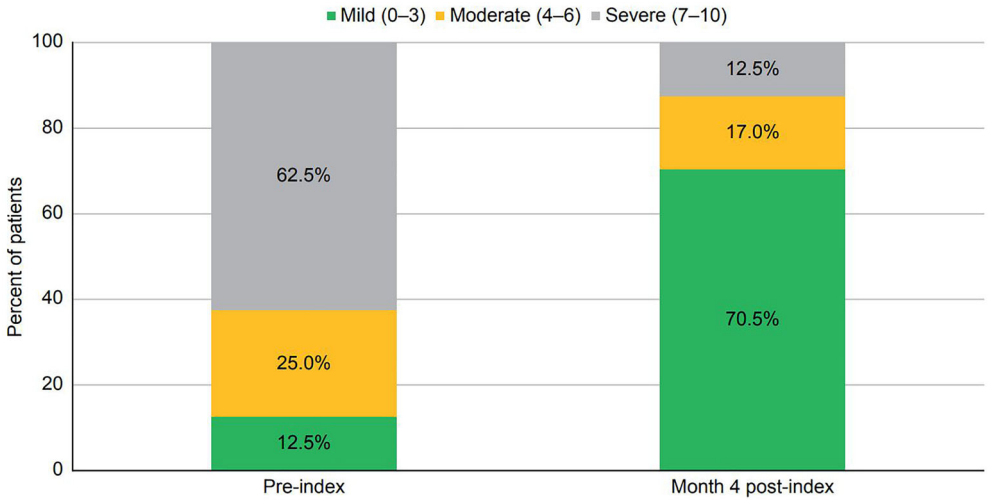

Fig. 2 Distribution of itch severity on an itch severity numerical rating scale (NRS), before and at 4 months after initiating treatment with dupilumab (index event) among patients with pre-index NRS score ≥ 3 ($n = 112$)

of patients across age, sex, and treatment history strata had a clinically meaningful improvement of ≥ 3 points. These effects of dupilumab on itch are consistent with what has been reported after 16 weeks of dupilumab treatment in phase 3 clinical trials with regard to magnitude of reduction (44.3–56.2%) and clinical relevance (47–66% of patients with reductions ≥ 3 points) [7, 9, 10]. Importantly, the observed effects of dupilumab in reducing AD severity and itch were independent of sex and age, and appeared to be comparable regardless of treatment history.

The BSA affected by AD was also significantly reduced in the post-index period after initiation of dupilumab therapy. Notably, patients who had a higher percentage of BSA affected at baseline were characterized by greater absolute reductions. However, it should also be noted that the change in the lowest quartile may reflect a floor effect with regard to baseline, since these patients may have had less room for improvement. As with the other outcomes, improvements in BSA were similar regardless of demographic characteristics and treatment history.

Interpretation of these results should consider several study limitations, including that certain data elements, such as those evaluated in this study, are optional fields in EMRs and may not be populated at each visit for all patients. Consequently, only a small proportion of patients had these outcomes recorded in the EMR prior to and after the initiation of dupilumab therapy. In this regard, the absence of multi-item measures such as the Eczema Area and Severity Index (EASI) or Scoring of Atopic Dermatitis (SCORAD) may also be considered a limitation, but since these measures are time consuming, they are infrequently used in daily clinical practice and are even less likely to be captured in EMR than the ones reported in this study. These limitations further suggest that more routine recording in the EMR of AD severity from the clinician and patient perspectives should be encouraged as part of regular clinical visits. Assessment of itch severity in dupilumab clinical trials was the average of daily scores for a week, whereas a single time point was used in the current analysis. Treatment exposure was based on prescription orders, and whether the prescription was actually filled and appropriately used by the patient could not be confirmed. However, the use of an intention-to-treat approach provided a conservative estimate of real-world dupilumab effectiveness. While information on treatment history was available, concomitant medication use throughout the study period was not captured. Nevertheless, this analysis showed that substantial and clinically relevant

Table 4 Body surface area (BSA) affected before and at 4 months after initiating treatment with dupilumab (index event)

Population	Pre-index BSA, mean (SD)	Post-index BSA, mean (SD)	Absolute change, mean (SD)
All patients with pre-index BSA ≥ 10% (n = 387)	39.3 (26.1)	16.3 (21.2)	−23.0 (28.1)*
Patients with pre-index BSA ≥ 10% by treatment history			
Topical therapy only or no treatment (n = 203)[a]	38.3 (25.9)	17.5 (22.9)	−20.8 (28.3)*
Any systemic therapy (n = 184)[b]	40.3 (26.4)	14.9 (19.2)	−25.4 (27.7)*
Patients with pre-index BSA ≥ 10% by sex			
Male (n = 188)	40.8 (25.9)	18.2 (22.8)	−22.6 (29.0)*
Female (n = 199)	37.8 (26.3)	14.4 (19.5)	−23.4 (27.2)*
Patients with pre-index BSA ≥ 10% by age group			
18–34 years (n = 128)	43.5 (27.8)	16.5 (21.5)	−27.1 (30.1)*
35–54 years (n = 124)	34.4 (26.0)	18.1 (23.1)	−16.3 (27.9)*
≥ 55 years (n = 135)	39.7 (24.0)	14.4 (19.0)	−25.3 (25.2)*

[a]Includes topical corticosteroids, topical calcineurin inhibitors, and phosphodiesterase 4 inhibitor
[b]Includes systemic corticosteroids, immunosuppressants, and phototherapy
*$p < 0.0001$

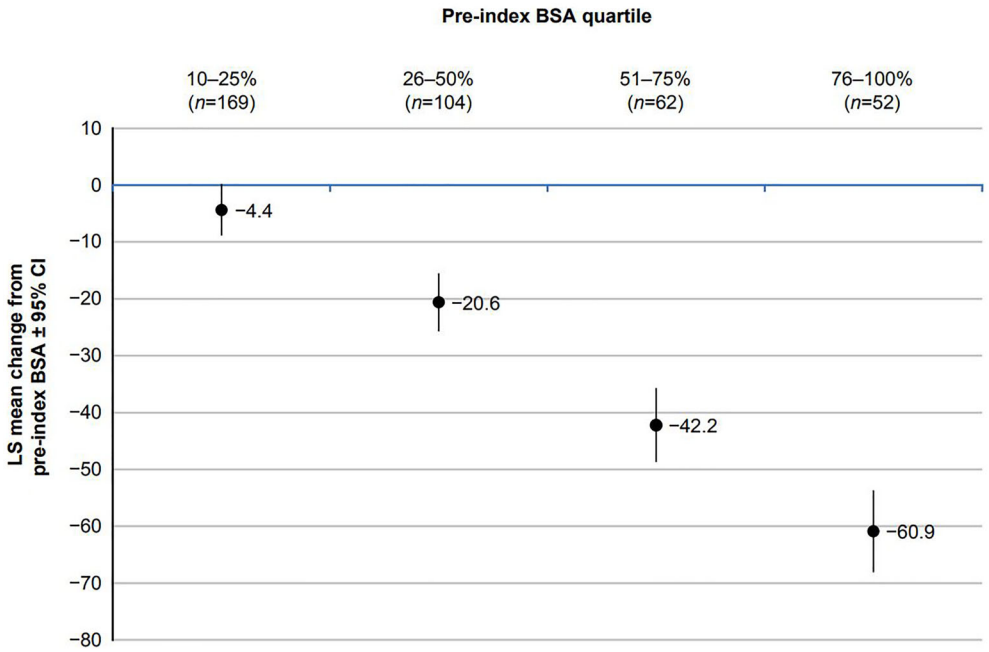

Fig. 3 Change in total body surface area (BSA) affected by atopic dermatitis 4 months after initiating treatment with dupilumab (index event) by pre-index quartile of affected BSA. Confidence intervals that include 0 are indicative of p-value ≥ 0.05; intervals that do not include 0 would map to $p < 0.05$. *CI* confidence interval, *LS* least squares

improvements from baseline were observed at the post-index assessment after initiation of dupilumab.

CONCLUSIONS

The results of this study largely corroborate the findings from the dupilumab clinical trial program. These results showed that, in adults with moderate-to-severe AD treated with dupilumab in routine clinical practice, significant and clinically meaningful improvements in clinician-assessed global AD severity were consistently achieved by the majority of patients, with significant and substantial reductions in patient-reported itch severity as well as in BSA affected. These improvements included substantial proportions of patients achieving clear/minimal AD and no or mild itch, comparable to improvements seen in dupilumab clinical trials.

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REFERENCES

1. Gittler JK, Shemer A, Suarez-Farinas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012;130(6):1344–54.

2. Brandt EB, Sivaprasad U. Th2 Cytokines and Atopic Dermatitis. J Clin Cell Immunol. 2011;2(3)

3. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016;15(1):35–50.

4. Dupixent® [dupilumab injection for subcutaneous use] prescribing information. Regeneron Pharmaceuticals Inc., Tarrytown, NY; sanofi-aventis U.S. LLC, Bridgewater, NJ. June 2020.

5. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo controlled, dose-ranging phase 2b trial. Lancet. 2016;387(10013):40–52.

6. Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). J Am Acad Dermatol. 2016;75(3):506–15.

7. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335–48.

8. Simpson EL. Dupilumab improves general health-related quality of life in patients with moderate-to-severe atopic dermatitis: pooled results from two randomized, controlled phase 3 clinical trials. Dermatol Ther (Heidelb). 2017;7:243–8.

9. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork M, Radin A, et al. Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-

controlled, randomized phase 3 clinical trial (LIBERTY AD CAFE). Br J Dermatol. 2017;178(4):897–902.

10. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287–303.

11. Cork MJ, Eckert L, Simpson EL, Armstrong A, Barbarot S, Puig L, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. J Dermatolog Treat. 2019;31(6):606–14.

12. Hamilton JD, Suarez-Farinas M, Dhingra N, Cardinale I, Li X, Kostic A, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014;134(6):1293–300.

13. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol. 2019;143(1):155–72.

14. Ruiz-Villaverde R, Dominguez-Cruz J, Armario-Hita JC, Martinez-Pilar L, Alcantara-Luna S, Pereyra-Rodriguez JJ. Dupilumab: short-term effectiveness and security in real clinical practice - A retrospective multicentric study. J Eur Acad Dermatol Venereol. 2019;33(1):e21–2.

15. Armario-Hita JC, Pereyra-Rodriguez J, Silvestre JF, Ruiz-Villaverde R, Valero A, Izu-Belloso R et al. Treatment of moderate-to-severe Atopic dermatitis with dupilumab in real clinical practice. A multicentre, retrospective case series. Br J Dermatol. 2019;181(5):1072–4.

16. Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz JD, Reguiai Z, et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. J Am Acad Dermatol. 2019;81(1):143–51.

17. Olesen CM, Holm JG, Norreslet LB, Serup JV, Thomsen SF, Agner T. Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral center. J Eur Acad Dermatol Venereol. 2019;33(8):1562–8.

18. de Wijs LEM, Bosma AL, Erler NS, Hollestein LM, Gerbens LAA, Middelkamp-Hup MA, et al. Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data. Br J Dermatol. 2020;182(2):418–26.

19. Marron SE, Tomas-Aragones L, Moncin-Torres CA, Gomez-Barrera M, Alcalde-Herrero VM, Garcia-Latasa de Aranibar FJ. Adult patients with atopic dermatitis treated with dupilumab in routine clinical practice: preliminary data at week 16. Neuropsychiatry (London). 2019;9(2):2255–61.

20. Wang C, Kraus CN, Patel KG, Ganesan AK, Grando SA. Real-world experience of dupilumab treatment for atopic dermatitis in adults: a retrospective analysis of patients' records. Int J Dermatol. 2020;59(2):253–6.

21. Nettis E, Ferrucci SM, Ortoncelli M, Pellacani G, Foti C, Di Leo E et al. Use of Dupilumab for 543 Adult Patients with Moderate-To-Severe Atopic Dermatitis: A Multicenter, Retrospective Study. J Investig Allergol Clin Immunol. 2022;32(2):124–32.

22. Fargnoli MC, Esposito M, Ferrucci S, Girolomoni G, Offidani A, Patrizi A et al. A 48-week update of a multicentre real-life experience of dupilumab in adult patients with moderate-to-severe atopic dermatitis. J Dermatolog Treat. 2022;33(2):1146–9.

23. Bosma AL, de Wijs LEM, Hof MH, van Nieuwenhuizen BR, Gerbens LAA, Middelkamp-Hup MA, et al. Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry. J Am Acad Dermatol. 2020;83(5):1375–84.

24. Uchida H, Kamata M, Kato A, Mizukawa I, Watanabe A, Agematsu A, et al. One-year real-world clinical effectiveness, safety and laboratory safety of dupilumab in Japanese adult patients with atopic dermatitis: A single-center retrospective study. J Am Acad Dermatol. 2021;84(2):547–50.

25. Sears AV, Woolf RT, Gribaleva E, Abdelrahman W, Robbie S, Menon B, et al. Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: A single centre, prospective one-year observational cohort study of the first 100 patients treated. Br J Dermatol. 2021;184(4):755–7.

26. Kreeshan FC, Al-Janabi A, Warren RB, Hunter HJA. Real-World experience and laboratory monitoring of dupilumab in patients with moderate to severe atopic dermatitis in a tertiary centre. Dermatol Ther (Heidelb). 2021;11(1):149–60.

27. Georgakopoulos JR, Felfeli T, Drucker AM, Jo CE, Piguet V, Yeung J. Two-year efficacy, safety, and drug survival of dupilumab for atopic dermatitis: A real-world Canadian multicenter retrospective study. JAAD Int. 2021;4:67–9.

28. Vakharia PP, Chopra R, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for five patient-reported outcomes in adults with atopic dermatitis. Br J Dermatol. 2018;178(4):925–30.

29. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99–106.

30. Silverberg JI, Lei D, Yousaf M, Janmohamed SR, Vakharia PP, Chopra R, et al. What are the best endpoints for Eczema Area and Severity Index and Scoring Atopic Dermatitis in clinical practice? A prospective observational study. Br J Dermatol. 2020;184(5):888–95.

31. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbe A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761–9.

32. Chopra R, Silverberg JI. Assessing the severity of atopic dermatitis in clinical trials and practice. Clin Dermatol. 2018;36(5):606–15.

33. Jo CE, Georgakopoulos JR, Ladda M, Ighani A, Mufti A, Drucker AM, et al. Evaluation of long-term efficacy, safety, and reasons for discontinuation of dupilumab for moderate-to-severe atopic dermatitis in clinical practice: A retrospective cohort study. J Am Acad Dermatol. 2020;82(6):1530–2.

34. Quint T, Brunner PM, Sinz C, Steiner I, Ristl R, Vigl K et al. Dupilumab for the treatment of atopic dermatitis in an austrian cohort-real-life data shows rosacea-like folliculitis. J Clin Med. 2020;9(4).