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Dupilumab Treatment Improves Lichenification in Atopic Dermatitis in Different Age and Racial Groups

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ABSTRACT

Background: Lichenification, common in moderate to severe atopic dermatitis (AD) at any age, is often difficult to treat. This analysis assessed dupilumab vs placebo in AD lichenification by age and race-defined groups.

Methods: This post hoc analysis included pooled data from 5 clinical trials of dupilumab (NCT03054428, NCT03345914, NCT02277743, NCT02277769, NCT02395133), including 1,997 patients aged 6 to 88 years of all races with moderate to severe AD.

Results: Placebo/dupilumab randomized groups analyzed by age (n=1,535) included 123/244 children, 85/166 adolescents, and 460/457 adults; groups analyzed by self-reported racial background (n=1,902) included 132/234 Asian, 74/112 Black/African American, and 427/923 White patients. Dupilumab treatment resulted in nominally significant reductions vs placebo in Global Individual Signs Score lichenification from week 1 (adults/adolescents) or week 2 (children) through week 16. Lichenification measured by SCORing Atopic Dermatitis and Eczema Area and Severity Index improved similarly. By week 16, dupilumab significantly improved lichenification, with nominal significance vs placebo across all racial groups.

Conclusion: Dupilumab treatment resulted in rapid and sustained improvement in lichenification across anatomic regions in all ages. Lichenification improved to a similar extent across racial groups.

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INTRODUCTION

Lichenification, associated with disease chronicity in moderate to severe atopic dermatitis (AD), is a skin sign characterized by skin thickening with demarcated skin lines and leathery aspect, partially resulting from repetitive scratching and rubbing due to pruritus.[1-3] AD lichenification can occur at any age and is more prevalent in patients from South-Eastern Asian or African racial backgrounds.[3,4]

Chronic lichenified AD lesions are histologically characterized by epidermal hyperplasia with acanthosis and elongation of the rete ridges, hyperkeratosis, and minimal spongiosis, with an increase in epidermal IgE-bearing dendritic cells.[5] The dermal mononuclear cell infiltrate is dominated by macrophages and mast cells, usually fully granulated. There may be some increase in collagen, manifesting as fibrosis in the upper dermis, including the papillae.[5,6]

Type 2 inflammation induces epidermal hyperplasia with acanthosis directly through overexpression of interleukin (IL)-4 and IL-13.[7] Dupilumab, a fully human monoclonal antibody, specifically binds to a single target, the IL-4 receptor alpha (IL-4Rα), and inhibits signaling of both IL-4 and IL-13. Dupilumab has been shown to modulate markers of epidermal hyperplasia and keratinocyte proliferation in clinical trials[8,9] and real-world studies.[10]

MATERIALS AND METHODS

Study Design

This post hoc analysis included pooled data from 5 double-blind, placebo-controlled studies of dupilumab conducted in patients aged 6 years and older with moderate and severe AD. Detailed methodology and primary results (including safety) have been reported.[11-14] LIBERTY AD PEDS (NCT03345914) included children (aged 6–11 years) with severe AD, randomized to placebo or

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dupilumab (300 mg every 4 weeks [q4w] or 100/200 mg every 2 weeks [q2w] by baseline weight) with concomitant topical corticosteroids (TCS).[11] LIBERTY AD ADOL (NCT03054428) included adolescents (aged 12–17 years) with moderate to severe AD, randomized to placebo or dupilumab monotherapy (300 mg q4w or 200/300 mg q2w by baseline weight).[12] LIBERTY AD SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769) included adults with moderate to severe AD inadequately controlled by TCS, randomized to placebo or dupilumab (300 mg q2w or 300 mg weekly [qw]).[13] In LIBERTY AD SOLO–CONTINUE (NCT02395133), patients who achieved an Investigator's Global Assessment (IGA) score of 0 or 1 or 75% improvement in Eczema Area and Severity Index (EASI75) at week 16 in SOLO 1/2 were subsequently re-randomized to placebo or dupilumab for an additional 36 weeks.[14] This analysis included patients who received dupilumab 300 mg q2w for the initial 16 weeks and were randomized to continue their original dosing regimen for 36 weeks and patients who received dupilumab 300 mg qw or q2w for the initial 16 weeks and were then re-randomized to placebo for 36 weeks. Analyses by age included only the q2w regimen from SOLO 1/2, whereas analyses by racial subgroup included both the q2w and qw regimens.

Endpoints

Lichenification was assessed by 3 different measures: overall by Global Individual Signs Score (GISS), in a pre-defined target lesion by SCORing Atopic dermatitis (SCORAD), and by anatomic region using EASI. Study endpoints were mean scores from baseline to week 16 (or week 52 for SOLO-CONTINUE) by age and mean percent change in GISS, SCORAD, and EASI lichenification scores from baseline to week 16 by racial group.

Statistical Analyses

Data were analyzed using an analysis of covariance model with baseline measurement as a covariate, and treatment and randomization strata (region [North America vs Europe] and baseline weight group [<30 kg vs ≥30 kg]) as fixed factors. Patients who missed an assessment or received rescue treatment were considered nonresponders (censored), and missing data were imputed using multiple imputation. All significance values are nominal.

RESULTS

Baseline Demographics and Disease Characteristics

Analyses by age included 1,535 patients (placebo/dupilumab, adults: n=460/n=457; adolescents: n=85/n=166; children: n=123/n=244; Table 1). Analyses by racial background included 1,902 patients: 366 self-identified as Asian (placebo/dupilumab, n=132/n=234), 186 as Black/African American (n=74/n=112), and 1,350 as White (n=427/n=923; Table 2). Across age and racial subgroups, baseline GISS, SCORAD, and EASI upper and lower extremities scores corresponded to severe lichenification (Table 2; Figures 1-3). Lichenification severity was higher in the African American vs Asian and White subgroups (Table 2).

TABLE 1.

Baseline Characteristics							
	6-11 years		12-17 years		≥18 years		
	Placebo + TCS (n=123)	Dupilumab 300 mg q4w or 100/200 mg q2w +TCS (n=244)	Placebo (n=85)	Dupilumab 300 mg q4w or 200/300 mg q2w (n=166)	Placebo (n=460)	Dupilumab 300 mg q2w (n=457)	Dupilumab 300 mg qw (n=462)
Age (study start), years	8.3 (1.8)	8.5 (1.7)	14.5(1.8)	14.5 (1.7)	38.4 (14.0)	38.3 (14.4)	38.2 (14.5)
Sex, male, n (%)	61 (49.6)	122 (50.0)	53 (62.4)	95 (57.2)	250 (54.3)	267 (58.4)	281 (60.8)
Race, n (%)							
Asian	13 (10.6)	15 (6.1)	13 (15.3)	25 (15.1)	106 (23.0)	98 (21.4)	96 (20.8)
Black/African American	23 (18.7)	39 (16.0)	15 (17.6)	15 (9.0)	36 (7.8)	23 (5.0)	35 (7.6)
White	77 (62.6)	177 (72.5)	48 (56.5)	109 (65.7)	302 (65.7)	320 (70.0)	317 (68.6)
Other	9 (7.3)	10 (4.1)	6 (7.1)	15 (9.0)	8 (1.7)	8 (1.8)	8 (1.7)
Weight, kg	31.5 (10.8)	31.5 (10.1)	64.4 (21.5)	65.7 (22.3)	76.2 (18.3)	76.8 (18.4)	77.6 (18.9)
Duration of AD, years	7.2 (2.2)	7.3 (2.4)	12.3 (3.4)	12.2 (3.1)	28.8 (14.4)	27.9 (15.2)	27.6 (15.4)
EASI (range 0–72)	39.0 (12.0)	37.3 (11.7)	35.5 (14.0)	35.5 (14.3)	34.0 (14.4)	32.4 (13.3)	32.5 (13.3)
PP-NRS (range 0–10)	7.7 (1.5)	7.8 (1.6)	7.7 (1.6)	7.5 (1.7)	7.4 (1.8)	7.4 (1.8)	7.3 (1.9)
SCORAD (range 0–103)	72.9 (12.0)	74.0 (11.4)	70.4 (13.3)	70.2 (14.0)	68.8 (14.5)	67.1 (13.7)	67.5 (13.3)
IGA (range 0–4)	4.0 (0.0)	4.0 (0.1)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
GISS (range 0–12)	10.2 (1.5)	10.2 (1.4)	9.5 (1.8)	9.4 (1.8)	9.1 (1.8)	9.0 (1.8)	8.9 (1.7)

All data are mean (standard deviation) unless otherwise noted.
AD, atopic dermatitis; EASI, Eczema Area and Severity Index; GISS, Global Individual Signs Score; IGA, Investigator's Global Assessment; PP-NRS, Peak weekly average Pruritus Numerical Rating Scale; q2/4w, every 2/4 weeks; qw, weekly; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroids.

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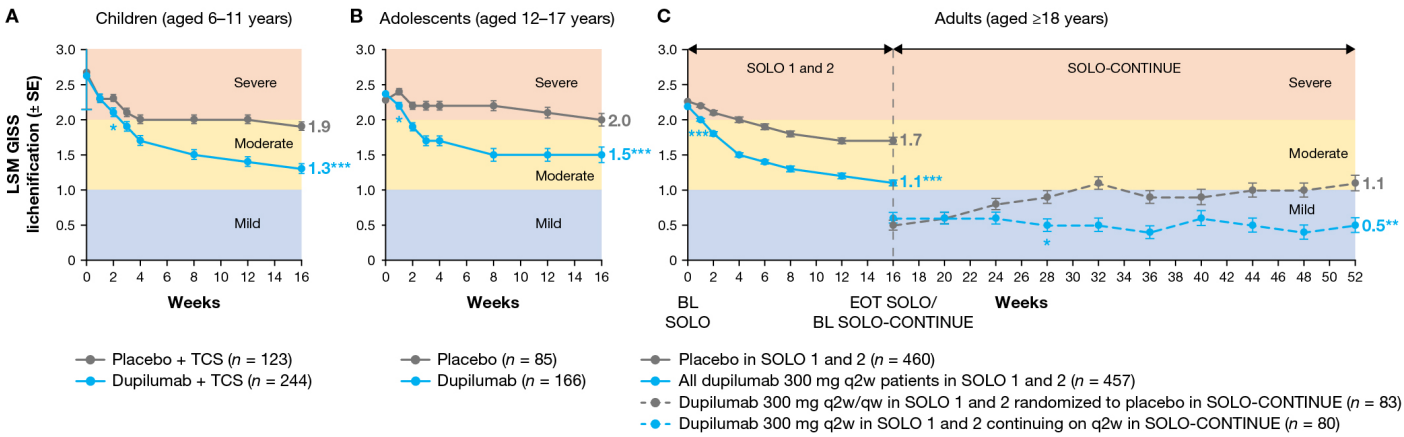
TABLE 2.

Percent Change from Baseline in Lichenification Scores at Week 16															
	Asian					Black/African American					White				
	Placebo ±TCS (n=132)		Dupilumab ±TCS (n=234)			Placebo ±TCS (n=74)		Dupilumab ±TCS (n=112)			Placebo ±TCS (n=427)		Dupilumab ±TCS (n=923)		
	Baseline	Week 16	Baseline	Week 16	*P* value	Baseline	Week 16	Baseline	Week 16	*P* value	Baseline	Week 16	Baseline	Week 16	*P* value
GISS lichenification (0–3)	2.4 (0.7)	−15.1 (4.4)	2.3 (0.7)	−45.5 (3.1)	<0.0001	2.5 (0.6)	−19.9 (5.8)	2.6 (0.6)	−41.6 (4.1)	0.0021	2.3 (0.6)	−22.6 (2.8)	2.3 (0.7)	−47.7 (2.0)	<0.0001
SCORAD lichenification (0–3)	2.4 (0.7)	−14.9 (4.7)	2.3 (0.6)	−43.9 (3.4)	<0.0001	2.6 (0.5)	−23.1 (5.5)	2.5 (0.7)	−42.6 (4.1)	0.0034	2.3 (0.6)	−23.1 (2.9)	2.2 (0.7)	−47.4 (2.1)	<0.0001
EASI lichenification (0–3)															
Head	2.1 (0.7)	−18.4 (6.2)	2.0 (0.7)	−43.3 (4.5)	0.0004	1.9 (0.8)	−29.0 (8.0)	2.1 (0.8)	−54.1 (6.8)	0.0152	2.0 (0.7)	−32.5 (3.6)	1.9 (0.7)	−51.9 (2.6)	<0.0001
Trunk	2.0 (0.7)	−27.1 (6.0)	2.1 (0.7)	−58.8 (4.9)	<0.0001	2.2 (0.8)	−40.6 (6.9)	2.2 (0.7)	−62.8 (5.3)	0.0121	2.0 (0.7)	−36.7 (3.2)	1.9 (0.7)	−65.5 (2.0)	<0.0001
Upper extremities	2.3 (0.7)	−15.0 (5.7)	2.2 (0.7)	−48.0 (3.8)	<0.0001	2.6 (0.6)	−26.6 (6.2)	2.6 (0.6)	−46.8 (4.5)	0.0061	2.4 (0.6)	−25.6 (3.6)	2.3 (0.6)	−51.8 (2.3)	<0.0001
Lower extremities	2.2 (0.7)	−14.2 (5.9)	2.2 (0.7)	−50.2 (4.1)	<0.0001	2.6 (0.6)	−22.0 (6.7)	2.6 (0.6)	−48.0 (5.1)	0.0018	2.3 (0.7)	−27.6 (3.4)	2.3 (0.7)	−54.7 (2.4)	<0.0001

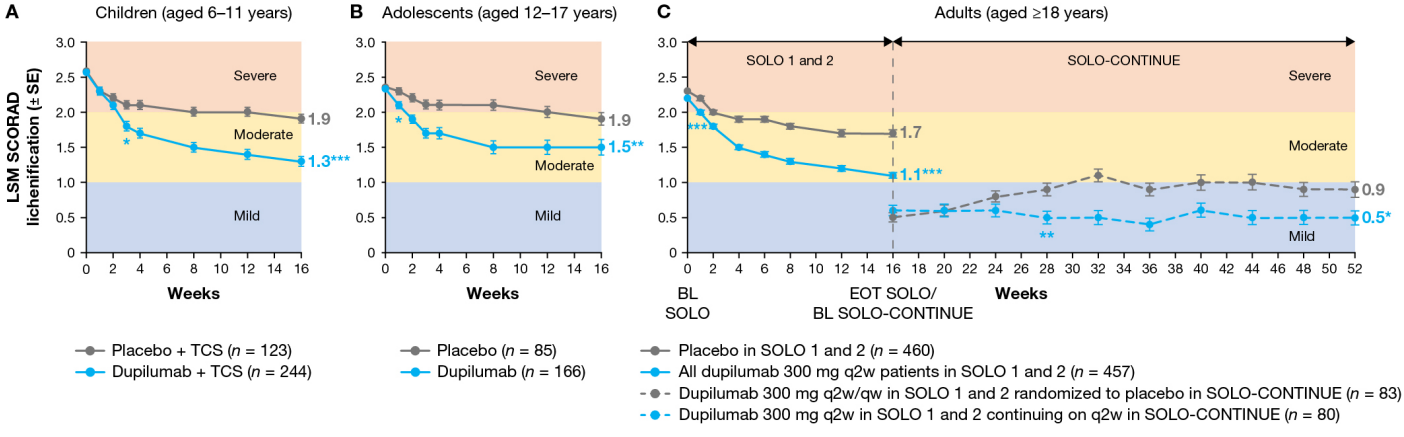
Baseline values are mean (standard deviation); week 16 values are least squares mean % change (standard error). All *P* values are nominal.
EASI, Eczema Area and Severity Index; GISS, Global Individual Signs Score; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroids.

FIGURE 1. GISS lichenification score in (A) Children, (B) Adolescents, and (C) Adults.



*P<0.05; **P<0.001; ***P<0.0001 (*P* values shown at the first significant time point and week 16; all P values are nominal).
BL, baseline; EOT, end of treatment; GISS, Global Individual Signs Score; LSM, least squares mean; q2w, every 2 weeks; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

FIGURE 2. SCORAD lichenification score in (A) Children, (B) Adolescents, and (C) Adults.



*P<0.05; **P<0.001; ***P<0.0001 (*P* values shown at the first significant time point and week 16; all *P* values are nominal).
BL, baseline; EOT, end of treatment; LSM, least squares mean; q2w, every 2 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

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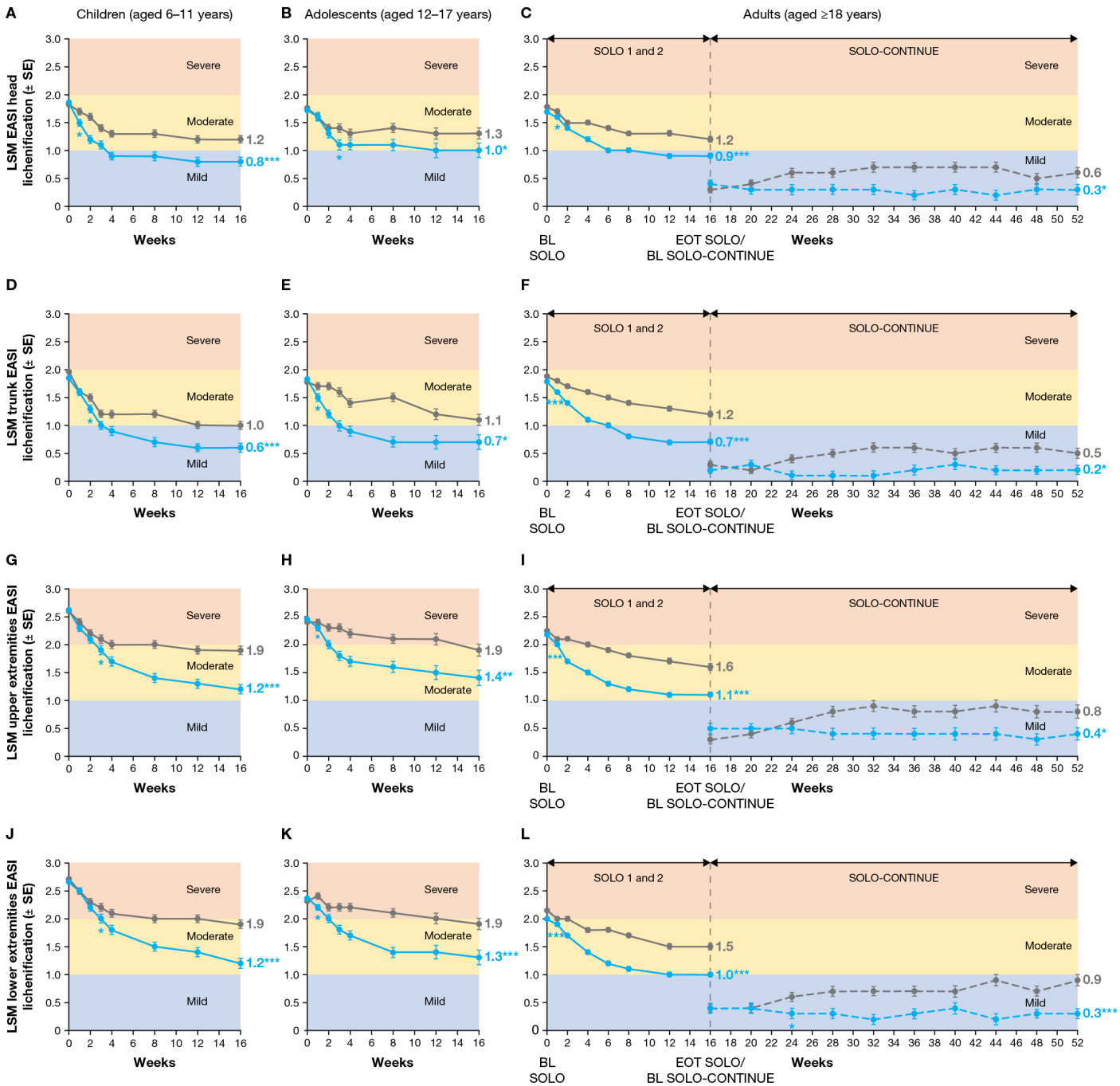
FIGURE 3. EASI score for lichenification in 4 anatomic regions by age group.



*P<0.05; **P<0.001; ***P<0.0001 (P values shown at the first significant time point and week 16; all P values are nominal).
BL, baseline; EASI, Eczema Area and Severity Index; EOT, end of treatment; LSM, least squares mean; q2w, every 2 weeks; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.

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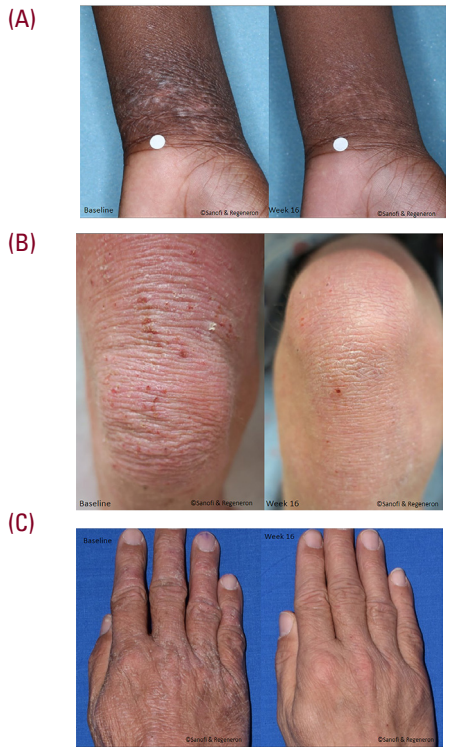
FIGURE 4. Clinical photographs of representative lichenification in (A) Black/African American child, (B) White adolescent, and (C) Asian adult patient with moderate to severe atopic dermatitis treated with dupilumab.



Efficacy

Progressive improvement of lichenification was observed across age groups and anatomic regions in dupilumab-treated patients, with statistically differentiated mean improvements vs placebo at week 16 (Figures 1–3). Improvements measured by GISS started at week 1 in adults (P<0.0001 vs placebo) and adolescents (P<0.05 vs placebo) and week 2 in children (P<0.05 vs placebo) and increased progressively to week 16 (Figure 1). SCORAD and EASI lichenification showed similar results (Figures 2 and 3). Across ages, the mean lichenification scores improved from moderate to mild in head, neck, and trunk regions, and from severe to moderate in upper and lower extremities, with nominally significant differences between treatment groups at week 16 (all P<0.0001; Figure 3). In adults, starting with moderate to severe EASI lichenification scores at baseline across anatomic regions, 16 weeks of dupilumab treatment led to EASI lichenification scores ranging between 0.7 to 1.1 (none–mild) in all body areas (Figure 3). Improvements were comparable between racial subgroups and nominally significant vs placebo at week 16 for all assessments (Table 2).

Adults treated with dupilumab 300 mg q2w for up to 1 year maintained consistently low lichenification scores across anatomic regions, whereas patients who were re-randomized to placebo showed a slight worsening in lichenification (Figures 1-3).

Lichenification Case Examples

Figure 4 shows clinical images of study participants of different ages and racial backgrounds, who had baseline scores close to the population mean scores and are representative of improvements after dupilumab treatment.

DISCUSSION

Lichenification secondary to AD often takes months or years to resolve with traditional therapeutic approaches and, in some cases, can be entirely treatment-refractory.[15-17] In this study, patients with AD experienced substantial improvement during 16-week dupilumab treatment. Reductions in lichenification were steady throughout the treatment period, with improvements starting from the first dupilumab dose, and were similar across racial subgroups.

The clinical presentation and underlying molecular features of AD are highly heterogeneous in age and racial groups.[4,18-21] Consistent with previous studies,[3,19] we observed a higher baseline degree of lichenification in the Black/African American group. However, the amplitude of improvement post-treatment did not vary with race. Reductions in lichenification occurred promptly following dupilumab initiation across age and racial subgroups. As scratching related to pruritus is considered to contribute substantially to the development of lichenification in AD and significant improvement in pruritus after the first dose of dupilumab was previously reported across ages,[22] breaking the itch-scratch cycle can directly contribute to the rapid improvement. Nevertheless, additional direct mechanisms to reduce lichenification should be considered.

Dupilumab has been shown to reduce epidermal hyperplasia of lesional skin vs placebo, including reduced epidermal thickness observed in biopsies in adults (–44% vs +4% with placebo at week 16; P<0.01)[9] and by non-invasive optical coherence tomography in pediatric patients.[23] Furthermore, dupilumab treatment led to reduced expression of epidermal hyperplasia *K16* and *Mki67* genes and of epidermal proliferation markers in patients with AD.[8,9,24] The rapid effect of dupilumab on epidermal hyperplasia can be explained by the blocking of IL-4 and IL-13, known to induce acanthosis,[7] added to potential indirect effects of dupilumab on the IL-22 and IL-17 axes, as IL-22 is also known to mediate IL-23–induced dermal inflammation and acanthosis.[25]

Secondary lichenification in AD may, in addition to epidermal changes, involve dermal components, such as collagenosis and fibrosis. Fibroblasts in AD are characterized by an inflammatory Th2 phenotype, further contributing to papillary dermal fibrosis and skin thickening.[26] IL-4Rα, expressed on fibroblasts, initiates ERK and Akt signaling pathway activation, with subsequent fibroblast proliferation, differentiation, and increased production of type I/III collagen, fibronectin, and fibrinogen, as well as reduced proteolysis of extracellular matrix components.[27-29] Dupilumab treatment can reverse overexpression of both

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fibronectin and fibrinogen in adults and adolescents with moderate to severe AD.[30] Additionally, IL-4 and IL-13 have been shown to induce production by fibroblasts of the matricellular protein periostin, which plays pathogenic roles in chronic allergic inflammation and skin fibrosis in allergic diseases.[31] Periostin was found highly expressed in the dermis of patients with AD and lichenification, and serum levels of periostin in AD increase proportionally with disease severity.[32] Interestingly, periostin may link itch and fibrosis, acting as a pruritogen via direct stimulation of nerve fibers.[33]

CONCLUSION

In conclusion, dupilumab treatment promoted rapid and sustained improvement in lichenification across all body regions in children, adolescents, and adults; and resulted in comparable improvements in lichenification across self-identified racial subgroups. These results highlight the importance of both IL-4 and IL-13 in the pathogenesis of lichenification in AD.

DISCLOSURES

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Data Availability Statement: Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the indication has been approved by major health authorities, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Requests should be submitted to https://vivli.org/.

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