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ORIGINAL RESEARCH

Effectiveness, Safety, and Health-Related Quality of Life in Moderate-to-Severe Atopic Dermatitis Treated with Lebrikizumab: A 16-Week Nationwide Retrospective Cohort Study

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin condition that significantly affects the quality of life (QoL). Lebrikizumab, a biologic drug targeting interleukin-13,

demonstrated efficacy and safety in clinical trials. However, real-world data remain limited, largely restricted to Asian populations.
Methods: This 16-week retrospective multicenter study included 78 adults from a predominantly white cohort with moderate-to-severe AD treated with lebrikizumab throughout 2024. Patients were both naïve and experienced with biologics or Janus kinase inhibitors (bio/JAKi-naïve or -experienced). The primary outcome for disease severity and therapeutic response was measured using the Eczema Area and Severity Index (EASI). Secondary outcomes included the Dermatology Life Quality Index (DLQI), itch- and sleep-numerical rating scales (NRS), body surface area (BSA), Investigator Global Assessment (IGA), SCORing Atopic Dermatitis (SCORAD), and Patient-Oriented Eczema

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Measure (POEM). Atopic Dermatitis Control Tool (ADCT) and minimal disease activity (MDA) were used to estimate disease control, and Hospital Anxiety and Depression Scales to monitor mental health status.

***Results*:** At week 16, benefits in disease severity were observed for EASI (−15.8 ± 9.4, $p < 0.0001$) and EASI head and neck (−2.0 ± 1.7, $p < 0.0001$). QoL significantly improved in 70% of patients (DLQI reduction of −12.6 ± 9.3, $p < 0.0001$), accompanied by decreased pruritus (Itch-NRS reduction of −4.6 ± 3.2, $p < 0.0001$) and better sleep quality (sleep-NRS reduction of −4.1 ± 3.4, $p < 0.0001$). A 76% reduction in BSA score was recorded, 85% of subjects improved their IGA index, with 62% achieving a score of 0–1, and SCORAD and POEM assessments significantly improved ($p < 0.0001$). Patients perceived a better control of the disease (ADCT, −10.9 ± 7.1, $p < 0.0001$), and 14% of patients achieved MDA. Anxiety and depression levels decreased. Four mild adverse events were registered.

***Conclusions*:** This is one of the first real-world multicenter studies in a predominantly adult white population showing that lebrikizumab is effective, safe and improves symptoms, QoL, and mental health in moderate-to-severe AD bio/JAKi-naïve and -experienced patients.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis is a chronic inflammatory skin condition that can impact quality of life. Lebrikizumab, a new biological drug, proved to be effective and safe. This is one of the first studies investigating the benefit of lebrikizumab use in routine clinical practice in predominantly white adults. The study included 78 adults who were treated with lebrikizumab for 16 weeks between January and December 2024. Some patients had never used biologic treatments before, while others had been treated using different therapies. Different evaluations of the benefit of treatment were performed by physicians and patients, assessing the severity of the disease, including skin appearance, itchiness, and how much of the body was affected. The impact on the quality of life and mental health, including itch levels, sleep quality, anxiety and depression states, and overall control over the disease was also evaluated. After 16 weeks, most patients reported major improvements. The severity of their skin symptoms and itch reduced significantly, and 76% had less body surface area affected. About 70% of patients reported an improvement in their quality of life. Itch and sleep improved, anxiety and depression levels decreased, and patients felt more in control of their condition. Only three mild side effects and one relapse were reported. Overall, this study shows that lebrikizumab is safe and effective for the treatment of moderate-to-severe atopic dermatitis in white patients.

Keywords: Biologics; Monoclonal antibodies; IL-13 inhibitor; Skin disease; Atopic dermatitis; Lebrikizumab; Multi-failure

Key Summary Points

Why carry out this study?

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a high disease burden.

The continuous development of novel targeted therapies is essential to ensure effective disease control while maintaining a favorable safety profile.

While lebrikizumab has shown promise in clinical trials, real-world data remain limited and are largely restricted to patients of Asian ethnic background.

What did the study ask?

The study aimed to assess the real-world effectiveness, safety, and impact on QoL and mental health of lebrikizumab in patients with moderate-to-severe AD in a predominantly white population.

What were the study outcomes?

After 16 weeks of treatment, lebrikizumab significantly improved AD symptoms, QoL, and mental health, with mild adverse events.

What has been learned from the study?

Lebrikizumab is effective and well-tolerated across both bio/JAKi-naïve and experienced patients, providing substantial improvements even in difficult-to-treat areas like the head and neck.

These findings support the use of lebrikizumab as a valid treatment option for moderate-to-severe AD and may guide clinicians in tailoring biologic therapies on the basis of patient phenotype and treatment history.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritus and a detrimental impact on patients' quality of life (QoL). It affects 2–7% of adults worldwide [1, 2], with a prevalence of 8% in the Italian adult population [3]. AD is a multifactorial disorder characterized by the interplay of genetic factors, immune dysregulation, skin barrier dysfunction, microbiome imbalance, and environmental factors [2]. Type 2 inflammatory response is mainly responsible for AD pathogenesis, with interleukin (IL)-13 and IL-4 overexpression causing skin barrier dysfunction, inflammation, and pruritus [4, 5]. The condition typically begins in childhood but frequently continues into adulthood. The presentation and severity of skin lesions differ according to age, race, and ethnicity [6]. Moderate-to-severe AD in adults is characterized by persistent or recurrent symptoms affecting mainly flexural areas of the body, hands, neck, and face. Inflammation and itching often lead to scratching, resulting in skin lichenification, crusting, and infections [7, 8]. Intense pruritus is responsible for sleep deprivation, significantly affecting patients' health-related quality of life (HRQoL) and impairing their daily activities.

Typically, topical treatments, including corticosteroids, are the first-line options for flare-ups [9]. However, European and Italian guidelines advise systemic therapies, such as immunosuppressive drugs and biologic drugs, for patients with moderate-to-severe disease who are unable to manage AD symptoms through topical treatments. This is particularly true for those affected over extensive body areas, to minimize the corticosteroid intake [10, 11]. Recently, biologic therapies have been developed to more effectively target the IL-4R, IL-13, or Janus kinase (JAK) signaling pathways, which play a crucial role in AD pathogenesis [9]. Additionally, biologics have demonstrated a more advantageous safety profile compared to alternative systemic therapies [12].

Lebrikizumab is a novel monotherapy that specifically targets IL-13, selectively inhibiting only the IL-4Rα/IL-13Rα1 heterodimer formation, thereby blocking this signaling pathway, while still allowing IL-13 to interact with IL-13Rα2, thus preserving its endogenous regulation [13]. In 2023, it received European Medicines Agency approval for use in adults with moderate-to-severe AD [13]. Phase II and III clinical trials demonstrated that lebrikizumab

effectively alleviates AD symptoms in moderate-to-severe disease, improving its severity across all body areas and all Eczema Area and Severity Index (EASI) clinical signs in the short and long term [14–16].

To date, only two real-world studies have investigated the effect of lebrikizumab in Japanese patients [17, 18]. In addition, two real-world studies suggest that switching from other biologics to lebrikizumab is effective and safe for Japanese patients [19, 20]. However, considerable heterogeneity of AD exists among different ethnic groups, leading to important therapeutic implications and requiring treatment strategies tailored to the patient's specific clinical characteristics [21].

Considering the recognized disparities between patient populations in randomized controlled trials (RCTs) and real-world studies, along with the AD heterogeneity across ethnic groups, the real-world effectiveness of lebrikizumab requires further exploration.

This real-world multicenter study investigated the effectiveness and safety of lebrikizumab, as well as its impact on the patients' QoL and mental health, predominantly involving the adult white population.

METHODS

Study Design and Patient Population

This multicenter retrospective cohort study collected data on 78 adult patients across 26 Italian tertiary referral hospitals. Patients were eligible if aged ≥ 18 years, were diagnosed with moderate-to-severe AD according to the European Academy of Dermatology guidelines [10], and had received subcutaneous injections of lebrikizumab at a dose of 500 mg at weeks 0 and 2, followed by 250 mg every 2 weeks until week 16 between January 1, 2024 and December 31, 2024. Participants were either naïve to biologic drugs or JAK inhibitors (hereafter defined as "bio/JAKi-naïve") or had previously received type 2-targeted biologics or JAK inhibitors (hereafter defined as "bio/JAKi-experienced"). Identification of eligible cases was achieved through the retrospective review of both electronic health records and specific datasets from the participating sites. Patients were excluded if they had a follow-up period of less than 16 weeks. This study aims to provide an analysis of baseline characteristics and study endpoints at the 4 and 16 weeks of follow-up.

Ethical Approval

The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cohort studies [22], and the principles outlined in the Declaration of Helsinki. Ethical approval was granted by an institutional review board (Ethics Approval Committee Lombardia 3, protocol number Lebri-AD-2024). All patients provided written informed consent.

Data Collection

Data on patients' demographics, medical history, clinical features, including AD phenotype [23] and involved skin areas, previous and current AD treatments, and baseline disease severity parameters, were collected. Data from outcome assessments were evaluated at baseline (defined as the initiation of lebrikizumab therapy), 4 weeks, and 16 weeks post baseline. The effectiveness of lebrikizumab on disease severity was assessed by the physicians through the EASI, both in overall form, with scores ranging from 0 (no eczema) to 72 (severe eczema), and specifically for the head and neck region (EASI H&N), with scores ranging from 0 to 7.2 [24].

Patient-reported outcomes (PROs) related to overall mental health were assessed using the Dermatology Life Quality Index (DLQI) self-administered questionnaire [25]. To assess HRQoL, pruritus severity and sleep quality were evaluated using numerical rating scales (NRS) [26, 27].

Secondary outcomes to assess effectiveness included the body surface area (BSA) to evaluate skin involvement [28], and the Investigator Global Assessment (IGA) [29]. The SCORing Atopic Dermatitis (SCORAD) score was used to evaluate objective and subjective symptoms by

the physicians and patients, respectively [30]. Additionally, patients' self-evaluation of disease severity was assessed through the Patient-Oriented Eczema Measure (POEM) [31]. Patient-reported disease control was evaluated using the Atopic Dermatitis Control Tool (ADCT) self-administered questionnaire [32]. Minimal disease activity (MDA) assessment was performed by evaluating both PROs and clinician-reported outcomes to investigate the impact of treatment on disease management [33]. MDA was defined as the achievement of EASI 90 or an EASI score ≤ 3, a DLQI score of 0 or 1, and an itch-NRS score of 0 or 1. Mental health was investigated by monitoring the states of anxiety and depression through the Hospital Anxiety and Depression Scales (HADS-A and HADS-D) [34]. Safety was assessed by examining the occurrence of adverse events (AEs) associated with the study treatment.

Primary and Secondary Outcomes

The primary outcome was the percentage change in EASI from baseline to week 16. Key secondary outcomes included (i) the percentage change in EASI H&N, IGA, SCORAD, NRS-pruritus, NRS-sleep, DLQI, POEM, HADS-A, HADS-D, and ADCT from baseline to week 16; (ii) the proportion of patients achieving MDA at week 16; (iii) the incidence of treatment-related AEs.

Statistical Analysis

Patients who completed the 16 weeks of treatment with lebrikizumab were included. Data from all sites were pooled and summarized. Continuous data are presented as mean and standard deviation (SD). Categorical data were presented by absolute and relative frequencies. Bilateral 95% confidence limits of the change response from baseline were presented as appropriate. In particular, a paired-samples *t* test was used when the response change was normally distributed (evaluated with the Shapiro–Wilk test) to calculate the 95% confidence interval (CI) on the mean change. Otherwise, the Wilcoxon signed-rank test was employed to calculate the 95% CI on the median change. All statistical analysis was performed with SAS software 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Population

The baseline characteristics of the study population are presented in Table 1. A total of 78 patients were treated over a period of 16 weeks with lebrikizumab. The most frequent reasons for switching to lebrikizumab included loss ($n = 29$, 37.2%) or lack of response to previous treatments ($n = 19$, 24.4%) and the presence of AEs to previous treatments ($n = 14$, 17.9%).

The majority ($n = 63$, 80.8%) were white, 42 (53.9%) were female and 36 (46.1%) were male. The mean age was 37.6 ± 15.7 years, while the mean age at AD onset was 17.9 ± 22.1 years, with a disease duration of 19.7 ± 14.5 years. The most frequent AD phenotypes were "classical/flexural" and "generalized inflammatory", reported in 47 (60.3%) and 14 (18.0%) cases, respectively. Four patients reported involvement exclusively of the "head and neck" region. However, these body areas were the most affected overall, reported by 63 (80.8%) and 57 (73.1%) individuals, respectively. Familiarity with AD was reported in 13 (16.7%) subjects, while 17 (21.8%) reported familiarity with other atopic diseases. Comorbidities were present in 46 (59.0%) patients, with the most frequent atopic comorbidities being atopy ($n = 44$, 56.4%), allergies ($n = 39$, 50.0%), allergic rhinitis ($n = 34$, 43.6%), and allergic conjunctivitis ($n = 23$, 29.5%). The majority of patients ($n = 49$, 62.8%) had previously received biologic or JAKi treatment (bio/JAKi-experienced), including 18 patients (23.1%) who had received JAKi therapy prior to starting lebrikizumab, while 29 subjects (37.2%) patients were bio/JAKi-naïve. Previous topical therapy was used by 41 (52.6%) patients (30 used topical corticosteroids and 11 topical calcineurin inhibitors).

Table 1 Demographic and clinical characteristics of the study population ($n = 78$)

Patient characteristics	*n* (%)
Age, years (mean ± SD)	37.6 ± 15.7
Sex	
Female	42 (53.9)
Male	36 (46.1)
BMI, (kg/m^2) (mean ± SD)	23.7 ± 4.6
Currently smoking	17 (21.8)
Regular alcohol consumption	2 (2.6)
Ethnicity	
White	63 (80.8)
African American	1 (1.3)
Asian	2 (2.6)
Hispanic/Latino	7 (9.0)
Missing	5 (6.4)
AD history	
Age at disease onset (mean ± SD)	17.9 ± 22.1
Disease duration at study start	19.7 ± 14.5
AD phenotype*	
Classical/flexural	47 (60.3)
Generalized inflammatory	14 (18.0)
Head and neck	4 (5.1)
Generalized lichenoid	3 (3.9)
Prurigo nodularis-like	3 (3.9)
Portrait	2 (2.6)
Hand eczema	2 (2.6)
Nummular eczema-like	1 (1.3)
Erythrodermic	1 (1.3)
Psoriasiform	1 (1.3)
Body areas involved	
Head	63 (80.8)
Neck	57 (73.1)
Hands	33 (42.3)
Feet	6 (7.79)
Other	73 (93.6)
Familiarity with AD	13 (16.7)
Familiarity with other atopic diseases	17 (21.8)
Comorbidities	46 (59.0)
AD-related comorbidities	
Atopy	44 (56.4)
Allergies	39 (50.0)
Allergic rhinitis	34 (43.6)
Asthma	19 (24.4)
Allergic conjunctivitis	23 (29.5)
Food allergies	15 (19.2)
Nasal polyps	2 (2.6)
Bio/JAKi-experienced at treatment start	49 (62.8)
JAKi-experienced	18 (23.1)
Upadacitinib	12 (15.4)
Abrocitinib	4 (5.1)
Baricitinib	2 (2.6)
Non-JAKi-experienced	31 (39.7)
Dupilumab	22 (28.2)
Traklokinumab	7 (8.9)
Missing	2 (2.6)
Bio/JAKi-naïve at treatment start	29 (37.2)
Previous topical therapy (TCS or TCI)	41 (52.6)

Each patient could have more than one comorbidity

AD atopic dermatitis, *bio/JAKi* biologic drug or Janus kinase inhibitor, *BMI* body mass index, *n* number, *SD* standard deviation, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroid

*Only the predominant phenotype per patient was reported

Lebrikizumab Effectiveness: The EASI Score

The effectiveness of lebrikizumab, evaluated through the EASI score, showed a marked improvement in reducing disease severity from baseline to week 16. The scores revealed a mean change from baseline of −13.5 ± 9.4 (95% CI −15.0 to −10.0, $p<0.0001$), reflecting a 60.0% reduction by week 4, and a mean change from baseline of −15.8 ± 9.4 (95% CI −17.9 to −13.7, $p<0.0001$), equating to a reduction of 75.4% by week 16 (Fig. 1a).

Assessment of the most affected areas of head and neck, using the EASI H&N, reflected the overall EASI outcomes. The scores indicate a significant mean change of −1.6 ± 1.4 (95% CI −2.0 to −1.0, $p<0.0001$), with a 43% reduction at week 4 and mean change from baseline of −2.0 ± 1.7 (95% CI −2.4 to −1.6, $p<0.0001$), with a 57% reduction at week 16 (Fig. 1b).

Of the 61 subjects evaluated for EASI at week 4, 22 (28.1%) achieved EASI 75, 9 (11.5%) reached EASI 90, and 6 (7.7%) attained EASI 100 responses, respectively. At week 16 ($n=78$), the EASI 75, EASI 90, and EASI 100 responses were achieved by 48 (61.5%), 22 (28.2%), and 7 (9.0%) patients, respectively (Fig. 1c).

Treatment Impact on Health-Related QoL

PROs through the DLQI questionnaire revealed a marked improvement in their HRQoL following 4 and 16 weeks of lebrikizumab treatment. The reduction in DLQI score from baseline to week 4 ($n=43$) was 54% and to week 16 ($n=48$) was 70% (Fig. 2a, Table S1).

Significant improvements in pruritus and sleep quality were also observed following lebrikizumab treatment. The mean itch-NRS score improved from baseline ($n=77$) to week 4 ($n=61$), and further improved at week 16 ($n=76$), with a reduction from baseline of −4.4 ± 2.9 (95% CI −5.0 to −4.0, $p<0.0001$) and −4.6 ± 3.2 (95% CI −5.0 to −4.0, $p<0.0001$), respectively (Fig. 2b, Table S2). Sleep-NRS scores revealed a mean change of −3.6 ± 3.2 (95% CI −4.5 to −2.8, $p<0.0001$) at week 4 and of −4.1 ± 3.4 (95% CI −5.0 to −3.0, $p<0.0001$) at week 16 (Fig. 2c).

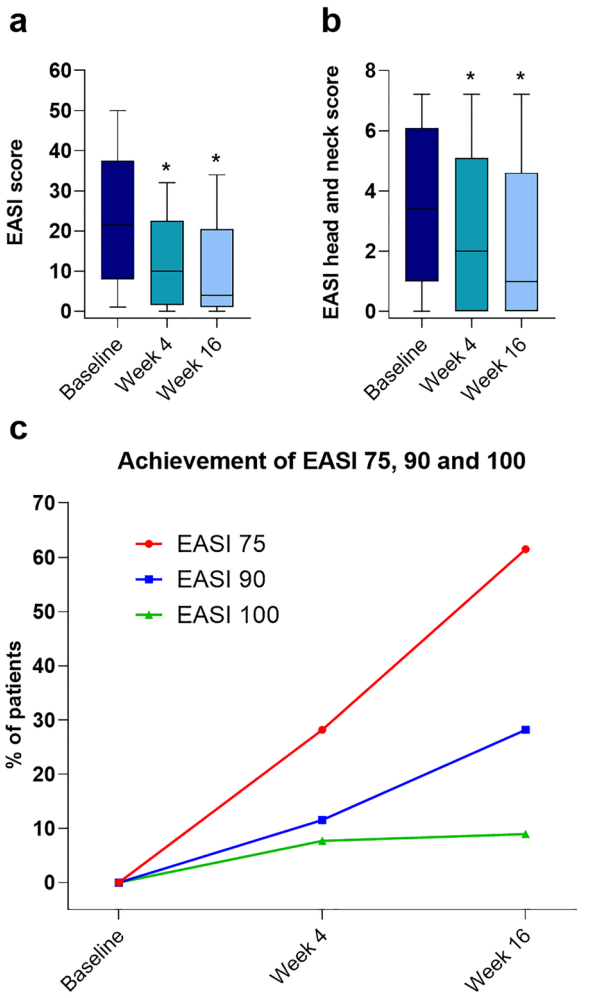

Fig. 1 Eczema Area and Severity Index (EASI) scores. **a** Whole-body EASI scores; **b** EASI Head and Neck scores; **c** achievement of EASI 75, 90, and 100. The boxes represent the interquartile range, the horizontal line within each box indicates the median, the whiskers extend to the minimum and maximum values within the dataset. Statistical significance is shown against baseline values; *$p < 0.001$

At baseline ($n=28$), on average, patients perceived "no control" of AD. After 4 weeks of treatment ($n=25$), the perception improved to "not well-controlled", achieving a "better control" of AD at week 16 ($n=30$), with a reduction from baseline of the ADCT score of −9.2 ± 5.8 (95% CI −11.7 to −6.7, $p<0.0001$) at week 4 and of −10.9 ± 7.1 (95% CI −13.7 to −8.2, $p<0.0001$) at week 16 (Fig. 2d).

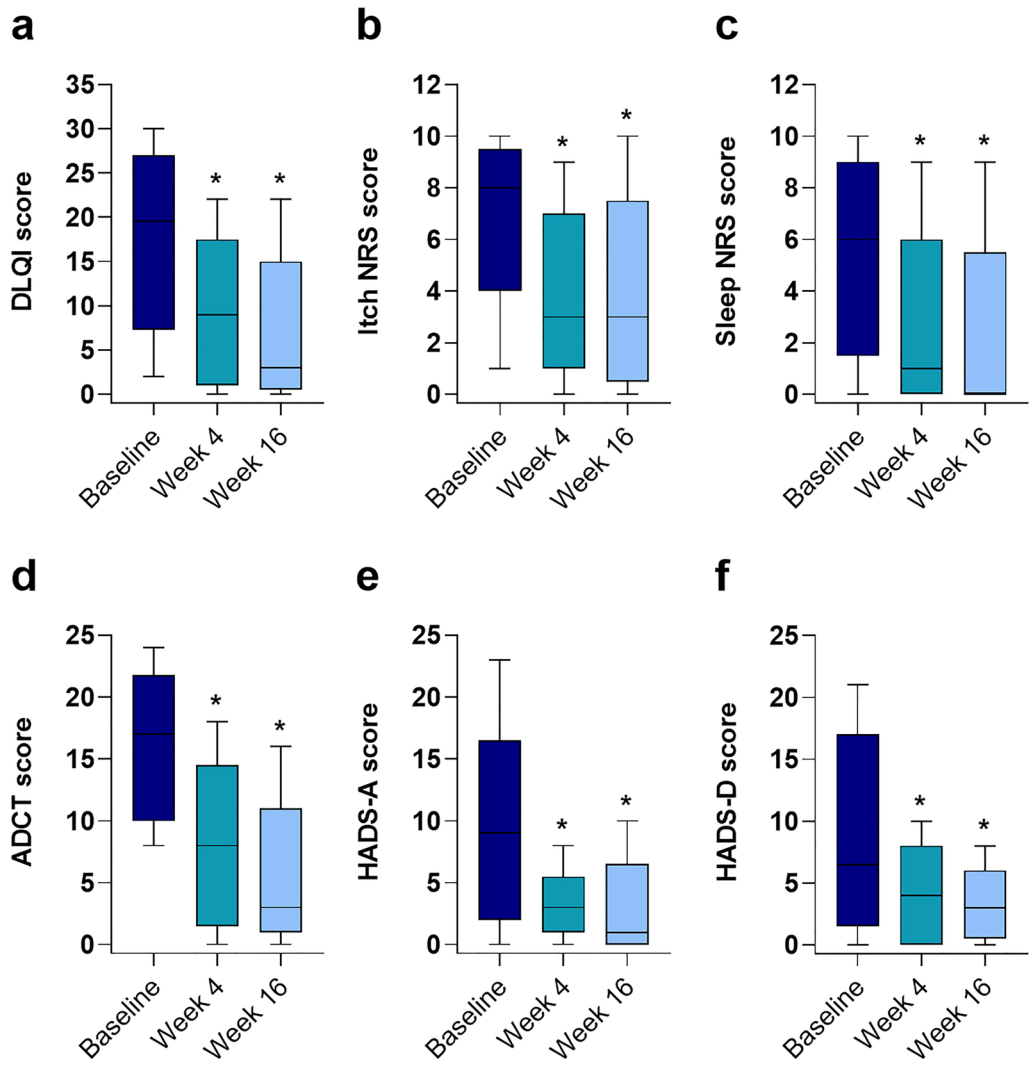

Fig. 2 Health-related quality of life assessments and disease control. **a** Dermatology Life Quality Index (DLQI) scores; **b** itch numerical rating scales (NRS) scores; **c** sleep NRS scores; **d** Atopic Dermatitis Control Tool (ADCT) scores; **e** Hospital Anxiety and Depression Scale (HADS), anxiety subscale (HADS-A) scores; **f** HADS depression subscale (HADS-D) scores. The boxes represent the interquartile range, the horizontal line within each box indicates the median, the whiskers extend to the minimum and maximum values within the dataset. Statistical significance is shown against baseline values; $^{*}p < 0.001$

Treatment Impact on Mental Health

The HADS-A and HADS-D mean scores at baseline ($n = 18$) were 8.2 ± 5.5 and 8.1 ± 6, respectively. After 4 weeks of treatment, the mean HADS-A score was 2.8 ± 2.3 ($n = 13$) and mean HADS-D score was 3.8 ± 3.4 ($n = 14$). The outcomes remained stable at week 16 ($n = 17$, mean scores 2.2 ± 2.9 and 3.2 ± 2.8, respectively) with a mean change from baseline of -6.5 ± 5.1 (95% CI -9.1 to -3.9, $p < 0.0001$) for HADS-A (Fig. 2e) and a mean change from baseline of -5.4 ± 5.5 (95% CI -8.2 to -2.5, $p < 0.001$) for HADS-D (Fig. 2f).

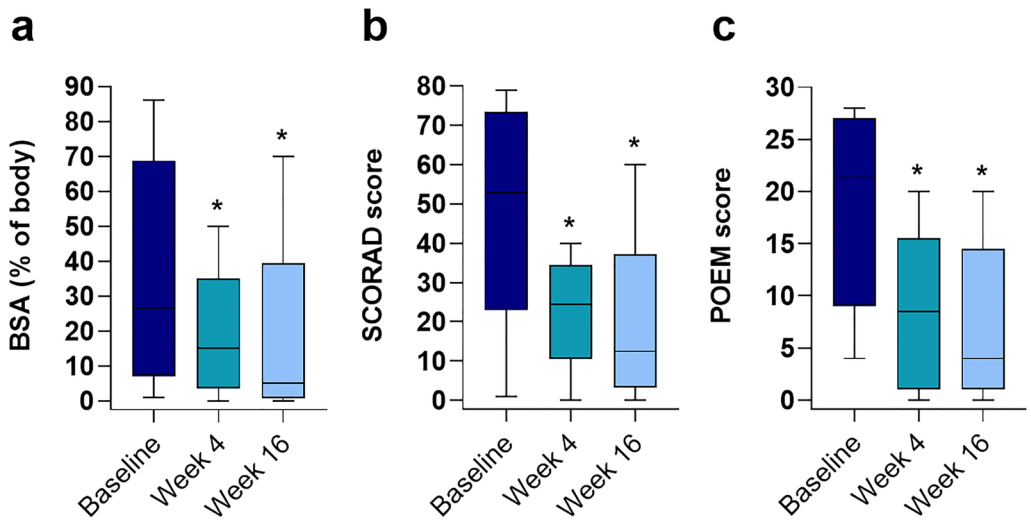

Fig. 3 Objective and subjective symptom scoring. **a** Body surface area (BSA); **b** SCORing Atopic Dermatitis (SCORAD); **c** Patient-Oriented Eczema Measure (POEM). The boxes represent the interquartile range, the horizontal line within each box indicates the median, the whiskers extend to the minimum and maximum values within the dataset. Statistical significance is shown against baseline values $^{*}p < 0.001$

Lebrikizumab Effectiveness: Secondary Objective and Subjective Assessments

The skin involvement was assessed through the BSA score and revealed an improvement in mean BSA score from baseline ($n=56$), to week 4 ($n=41$) and week 16 ($n=52$). The scores showed a mean change from baseline of −20.1 ± 20.1% (95% CI −20.0 to −10.0, $p<0.0001$), reflecting a 55.0% reduction at week 4, and a mean change from baseline of −23.7 ± 21.3% (95% CI −29.6 to −17.7, $p<0.0001$), reflecting a 76% reduction at week 16 (Fig. 3a).

The global clinical assessment, performed using the IGA, revealed that at baseline ($n=73$), most patients presented an IGA score of 3–4 ($n=64$, 87.7%). Fifty-seven patients were evaluated both at baseline and at week 4, and 29.8% ($n=17$) reached an IGA of 0–1. Out of the 68 patients evaluated both at baseline and at week 16, 85% ($n=58$) improved their IGA index, with 62% ($n=42$) achieving a score of 0–1 (Tables 2 and S3).

Mean SCORAD score significantly improved from baseline ($n=19$) to week 4 ($n=18$), showing a mean change of −31.0 ± 18.8 (95% CI −40.4 to −21.6, $p<0.0001$) and a reduction of 58%. The evaluation further improved at week 16 ($n=18$), registering a mean change from baseline of −40.7 ± 18.8 (95% CI −50.0 to −31.3, $p<0.0001$) and a reduction of 75% (Fig. 3b).

The POEM showed a mean change of −12.4 ± 6.6 (95% CI −14.0 to −7.0, $p<0.0001$), with a reduction of 61% at week 4, and a mean change of −13.0 ± 8.8 (95% CI −16.0 to −10.0, $p<0.0001$), with a reduction of 69% at week 16 (Fig. 3c).

MDA was achieved by four (9.5%) patients at week 4 ($n=42$) and by seven (14.6%) patients at week 16 ($n=48$).

The recorded use of topical therapies at week 16 decreased from 30 patients to 11 using topical corticosteroids, and from 11 patients to 5 using topical calcineurin inhibitors.

Stratification by Bio/JAKi-Naïve and -Experienced Cohorts

Results were stratified by bio/JAKi-naïve ($n=29$) and bio/JAKi-experienced ($n=49$) patients, as reported in Table S4.

The EASI score at baseline differed by subgroup, with a mean score of 19.2 ± 10.9 for the bio/JAKi-experienced cohort, and a mean score

Table 2 Shifts in disease severity reported as mean IGA score at baseline, week 4, and week 16

	Total IGA score at baseline					
	Clear *n* (%)	**Almost clear *n* (%)**	**Mild *n* (%)**	**Moderate *n* (%)**	**Severe *n* (%)**	**Total *n* (%)**
IGA score at week 4						
Clear	0	0	0	1 (3.0)	4 (21.1)	5 (8.8)
Almost clear	0	0	5 (100.0)	5 (15.2)	2 (10.5)	12 (21.1)
Mild	0	0	0	20 (60.6)	6 (31.6)	26 (45.6)
Moderate	0	0	0	7 (21.2)	7 (36.8)	14 (24.6)
Severe	0	0	0	0	0	0
Patients (total *n*)	0	0	5	33	19	57
IGA score at week 16						
Clear	0	0	1 (12.5)	4 (11.1)	3 (13.0)	8 (11.8)
Almost clear	0	0	3 (37.5)	20 (55.6)	11 (47.8)	34 (50.0)
Mild	0	0	3 (37.5)	8 (22.2)	5 (21.7)	16 (23.5)
Moderate	0	1 (100.0)	1 (12.5)	4 (11.1)	3 (13.0)	9 (13.2)
Severe	0	0	0	0	1 (4.3)	1 (1.5)
Patients (total *n*)	0	1	8	36	23	68

Only patients with a mean IGA score at baseline and week 4 or at baseline and week 16 are considered. Percentages were computed within each IGA category at baseline. IGA categories were defined as follows: 0, "clear"; 1, "almost clear"; 2, "mild signs"; 3, "moderate signs"; and 4, "severe signs"

IGA Investigator Global Assessment, *n* number

of 23.8 ± 7.5 for the bio/JAKi-naïve group. No notable difference was recorded between bio/JAKi-experienced (9.0 ± 6.6) and bio/JAKi-naïve (9.2 ± 6.8) patients after 4 ($n = 38$ and $n = 23$, respectively) and 16 weeks [5.2 ± 4.80 ($n = 49$) and 5.1 ± 6.4 ($n = 29$), respectively] of treatment.

Instead, the EASI H&N scores showed that bio/JAKi-naïve patients improved from a mean score of 2.8 ± 2.2 at baseline ($n = 28$) to 1.3 ± 1.7 at week 4 ($n = 24$) and 1.0 ± 1.5 at week 16 ($n = 28$). In the bio/JAKi-experienced group, EASI H&N scores decreased from 4.1 ± 1.8 at baseline ($n = 39$) to 2.6 ± 2.1 at week 4 ($n = 32$) and 1.9 ± 1.9 at week 16 ($n = 40$).

Patients' perception of the improvements in their overall HRQoL was comparable between bio/JAKi-naïve and -experienced cohorts. The mean DLQI score at baseline was 19.2 ± 7.5 for bio/JAKi-naïve patients ($n = 20$) and 17.2 ± 7.8 for bio/JAKi-experienced patients ($n = 28$), which improved to 7.6 ± 6.3 and 9.5 ± 6.2 at week 4 ($n = 19$ and $n = 24$, respectively), and to 4.6 ± 5.9 for bio/JAKi-naïve ($n = 20$) and 5.9 ± 5.4 for bio/JAKi-experienced patients ($n = 28$) at week 16.

The reported improvements in pruritus levels and sleep quality were also comparable in both cohorts (bio/JAKi-experienced and -naïve) after 4 weeks of treatment, shifting from an itch-NRS score of 7.5 ± 2.1 and 7.9 ± 2.0, respectively, to scores of 3.3 ± 2.3 and 3.5 ± 2.2, respectively. Sleep-NRS scores went from 5.3 ± 3.5 and 6.3 ± 3.2, respectively, to scores of 2.0 ± 2.5 and

1.8 ± 2.0, respectively. Interestingly, at week 16, the bio-experienced group ($n = 47$) showed greater benefits from the treatment, achieving an itch-NRS of 2.7 ± 2.4 and a sleep-NRS of 1.2 ± 2.2. Whereas the bio/JAKi-naïve cohort ($n = 29$) reached an itch-NRS of 3.6 ± 2.9 and a sleep-NRS of 2.1 ± 2.8. Additional outcomes data stratified by bio/JAKi-naïve and -experienced status are reported in Table S4.

Safety

Among the 78 patients treated for 16 weeks, four (5.1%) experienced treatment-related AEs, most commonly conjunctivitis ($n = 3$; 3.8%), followed by facial redness ($n = 1$; 1.3%). No AE led to study drug discontinuation.

DISCUSSION

This multicenter study presents real-world evidence on the effectiveness, patient-reported outcomes, safety, and impact on HRQoL and mental health of lebrikizumab within a predominantly white population suffering from moderate-to-severe AD. It offers important insights into clinical outcomes after 16 weeks of treatment in a cohort of 78 adults, including both bio/JAKi-naïve and -experienced patients.

Substantial improvements in disease severity were observed, as reflected by outcomes assessed by clinicians and self-reported outcomes by patients across all clinical measures. In particular, by week 16, lebrikizumab significantly reduced the overall disease burden and skin involvement, as assessed by the physicians, changing from an average of "moderate-to-severe" AD to a "mild-to-clear" condition for most patients (EASI, IGA, and BSA scores), with marked benefit observed in the head and neck region (EASI H&N scores), a recognized difficult-to-treat area due to its high exposure to environmental factors, including UV radiation, allergens, *Malassezia* spp. colonization, and irritants from cosmetic products, which may exacerbate AD symptoms, and the potential for AEs from topical corticosteroids [35].

The improvements noted in objective evaluations were mirrored by outcomes derived from the patients' self-reported symptoms and disease burden (SCORAD, POEM, and itch- and sleep-NRS scores).

Since lebrikizumab has only recently been approved [3], only two other real-world studies currently exist that have investigated its effectiveness and safety over 24 weeks in systemic treatment-naïve or -experienced Japanese patients. These studies showed improvements in both cohorts, with greater benefits observed for the naïve patients [17, 18]. In addition, two other real-world studies involving a limited number of Japanese patients ($n = 13$) showed that lebrikizumab is effective and well tolerated in patients with moderate-to-severe AD switching from other biologics [19, 20]. However, these studies were only conducted on Japanese patients, limiting the extrapolation of these findings to other populations. Indeed, ethnic background is one of the factors that contributes to the heterogeneity of AD, characterized by various genetic and clinical phenotypes, thus carrying important implications for disease evaluation and therapeutic programs [21]. For instance, the most relevant genetic factor for AD, filaggrin mutations, is nearly twice as prevalent in the white population compared to Asian patients and is very rare in the African population [21].

Overall, the benefits observed in patients receiving lebrikizumab in this real-world study corroborate with outcomes observed in clinical trials [14, 36–40]. Our data shows that improvements in AD symptoms and HRQoL were observed after just 4 weeks of treatment, with further improvements seen at 16 weeks. In line with our findings, RCTs have demonstrated positive outcomes for lebrikizumab after 16 weeks of treatment, with benefits remaining stable for 1 year in patients undergoing maintenance therapy [41, 42]. Importantly, a significant proportion of the real-world cohort in the current investigation consisted of bio/JAKi-experienced individuals (63%), an important distinction from RCTs, which usually only include bio-naïve patients. These factors highlight the practical relevance of the findings of this study, as in real-life clinical practice, physicians often treat

patients with a history of multiple systemic therapies and concurrent medications.

It is worth emphasizing that the current analysis revealed that both bio/JAKi-experienced and bio/JAKi-naïve patients responded similarly in terms of disease severity and HRQoL, with notable improvement seen for bio/JAKi-naïve patients in the head and neck region (EASI H&N). Consequently, these outcomes reveal that lebrikizumab can be considered an effective first-line treatment option and serves as a strong and robust choice for AD therapy in patients with varying disease histories and therapeutic backgrounds.

The favorable clinical response to lebrikizumab observed in patients with H&N AD (reflected by an improvement in EASI H&N scores) may suggest a predominant role of IL-13 in driving inflammation in this region [43]. By selectively inhibiting IL-13, lebrikizumab preserves IL-4-mediated immunoregulatory functions and may mitigate the type 22 immune deviation implicated in dupilumab-associated facial dermatitis [44]. Furthermore, IL-13 blockade has been shown to enhance epidermal barrier integrity and promote microbial diversity, including a reduction in *Staphylococcus aureus* colonization, a mechanism particularly relevant to the sebaceous-rich skin of the head and neck [45]. It is worth noting that emerging evidence also suggests that additional immune pathways, such as IL-31 and Th17/Th22, may contribute to H&N-predominant AD [46, 47].

The potential advantages of biologics targeting IL-13 are supported by reports of patients experiencing favorable outcomes when switching from dupilumab to either tralokinumab or lebrikizumab, both of which target IL-13 at different epitopes [19, 48, 49]. Although head-to-head comparisons of AD biologic monotherapies are still limited, available RCTs suggest that lebrikizumab may provide some advantages over tralokinumab after 16 weeks of treatment and appears to offer long-term outcomes comparable to those of dupilumab, potentially with the added benefit of less frequent dosing [12, 50].

Moreover, our study reported only two cases of conjunctivitis after 16 weeks of lebrikizumab. This observation aligns with the biological role of IL-4 in mucosal immunity, including goblet cell differentiation and mucin production. As IL-4 inhibition by dupilumab may impact ocular surface homeostasis, selective IL-13 inhibitors, such as lebrikizumab, could potentially help preserve some of these protective mechanisms, which may contribute to the lower incidence of conjunctivitis [8].

Further validation through comparative studies and long-term real-world experience is required to better define optimal patient selection and the role of IL-13 inhibitors within the broader treatment algorithm for AD.

Study Limitations

The main limitations of this study are the small sample size, despite its multicenter design, absence of a control group, and the short treatment duration of 16 weeks. The small sample size also limited formal comparative exploratory analyses in specific subgroups of patients receiving different prior treatments. In particular, comparisons between bio/JAKi-naïve and -experienced patients were exploratory only, as subgroup sizes were small and imbalanced and baseline disease severity differed, making formal statistical testing inappropriate and *p* values potentially misleading. In addition, as a result of the retrospective design, data for some PRO measures were not available in a subset of patients. Nevertheless, with the recent approval of lebrikizumab, this study remains the largest real-life cohort in a white population to date. However, since the majority of patients were white, this limits the extrapolation of data to other ethnic groups. Many patients have experienced prior biologic or JAK inhibitors therapies, limiting causal inference. Moreover, approximately half of patients previously used concomitant therapies for the management of AD, such as local corticosteroids or calcineurin inhibitors, which may have introduced confounding. Although these limitations hinder the strict randomization of clinical trials, they capture the complexities of routine practice and the typical patient population within the real-world setting of dermatological practices.

CONCLUSION

This is one of the first real-world studies supporting the clinical effectiveness and safety of lebrikizumab in the treatment of moderate-to-severe AD in a predominantly adult white population, including patients with prior biologic/JAK inhibitors exposure. Long-term analyses will further help to clarify the benefits of lebrikizumab therapy for managing moderate-to-severe AD.

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Data Availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Luigi Gargiulo has been a consultant and/or speaker and has participated to advisory boards for Abbvie, Amgen, Almirall, Novartis, Johnson and Johnson, Eli Lilly, Sanofi, Pierre Fabre, BMS, Leo Pharma, UCB, and Pfizer; Caterina Foti has conflict of interest with AbbVie, Almirall, Amgen, Eli Lilly, Incyte, Leo Pharma, Novartis, and Sanofi; Mariateresa Rossi has served as advisory board member and received honoraria for lectures from Almirall, AbbVie, Sanofi, LEO Pharma, Pfizer, Eli Lilly, L'Oréal, Galderma; Serena Giacalone has received honoraria from AbbVie, Johnson and Johnson, Almirall, Sanofi, Leo Pharma, and Novartis. Mariateresa Rossi is an Editorial Board member of *Dermatology and Therapy* and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Cataldo Patruno acted as

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Ethical Approval. The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for cohort studies and the principles outlined in the Declaration of Helsinki. Ethical approval was granted by an institutional review board (Ethics Approval Committee Lombardia 3, protocol number Lebri-AD-2024). All patients provided written informed consent to participate in the study and for publication.

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