Expert Opinion on Biological Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iebt20

Current treatment goals are achieved by the majority of patients with atopic dermatitis treated with tralokinumab: results from a multicentric, multinational, retrospective, cohort study

A Chiricozzi, SM Ferrucci, L Di Nardo, N Gori, A Balato, M Ortoncelli, M Maurelli, M Galluzzo, M Munera Campos, T Seremet, G Caldarola, C De Simone, E Ippoliti, T Torres, S Gkalpakiotis, C Conrad, JM Carrascosa, L Bianchi, G Argenziano, S Ribero, G Girolomoni, AV Marzano, K Peris & MEDaCoTRA Study Group

To cite this article: A Chiricozzi, SM Ferrucci, L Di Nardo, N Gori, A Balato, M Ortoncelli, M Maurelli, M Galluzzo, M Munera Campos, T Seremet, G Caldarola, C De Simone, E Ippoliti, T Torres, S Gkalpakiotis, C Conrad, JM Carrascosa, L Bianchi, G Argenziano, S Ribero, G Girolomoni, AV Marzano, K Peris & MEDaCoTRA Study Group (2023) Current treatment goals are achieved by the majority of patients with atopic dermatitis treated with tralokinumab: results from a multicentric, multinational, retrospective, cohort study, Expert Opinion on Biological Therapy, 23:12, 1307-1315, DOI: 10.1080/14712598.2023.2292627

To link to this article: https://doi.org/10.1080/14712598.2023.2292627

EXPERT OPINION ON BIOLOGICAL THERAPY
2023, VOL. 23, NO. 12, 1307–1315
https://doi.org/10.1080/14712598.2023.2292627

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

Current treatment goals are achieved by the majority of patients with atopic dermatitis treated with tralokinumab: results from a multicentric, multinational, retrospective, cohort study

A Chiricozzi [a,b], SM Ferrucci[c], L Di Nardo[a,b], N Gori[a,b], A Balato[d], M Ortoncelli[e], M Maurelli [f], M Galluzzo [g,h], M Munera Campos[i], T Seremet[j], G Caldarola [a,b], C De Simone[a,b], E Ippoliti[a,b], T Torres [k], S Gkalpakiotis[l], C Conrad[j], JM Carrascosa[i], L Bianchi[g,h], G Argenziano[d], S Ribero[e], G Girolomoni[f], AV Marzano[c,m], K Peris[a,b] and MEDaCoTRA Study Group

[a]Dermatologia, Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [b]UOC di Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [c]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [d]Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy; [e]Section of Dermatology, Department of Medical Sciences, University of Turin, Turin, Italy; [f]Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy; [g]Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy; [h]Dermatology Unit, Fondazione Policlinico "Tor Vergata", Rome, Italy; [i]Department of Dermatology, Germans Trias i Pujol University Hospital (HUGTP), Autonomous University of Barcelona (UAB), Badalona, Spain; [j]Department of Dermatology, Lausanne University Hospital CHUV and University of Lausanne, Lausanne, Switzerland; [k]Department of Dermatology, Centro Hospitalar Universitário de Santo António, University of Porto, Porto, Portugal; [l]Department of Dermatovenereology, Third Faculty of Medicine, Charles University and Kralovske Vinohrady University Hospital, Prague, Czech Republic; [m]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

ABSTRACT

Background: Tralokinumab is a human monoclonal antibody targeting interleukin-13 that is approved for the treatment of moderate-severe atopic dermatitis. Studies analyzing the efficacy and safety of tralokinumab in a real-world setting are scarce.

Research design and methods: A European, multicentric, real-world, retrospective cohort study was defined to assess the effectiveness and safeness profile of tralokinumab, investigating the achievement of pre-specified treatment goals; and to detect potential differences in terms of effectiveness and safeness across some selected patient subcohorts.

Results: A total of 194 adult patients were included in this study. A significant improvement in physician-assessed disease severity was detected at each follow-up visit as compared with baseline and similar trend was observed for patient-reported outcomes and quality of life. No meaningful difference in effectiveness was found when considering patient age (<65 versus ≥65 years), neither dissecting patient cohort in dupilumab-naive vs dupilumab-treated subjects. Among tralokinumab-treated patients, 88% achieved at least one currently identified real-world therapeutic goal at week 16.

Conclusions: This retrospective multicenter study confirmed the effectiveness and safeness of tralokinumab throughout 32 weeks of observation, showing the achievement of therapeutic goals identified in both trial and real-world settings in a large proportion of tralokinumab-treated patients.

ARTICLE HISTORY
Received 25 September 2023
Accepted 5 December 2023

KEYWORDS
Atopic dermatitis; eczema; tralokinumab; IL-13 inhibitor; Treatment goals

1. Introduction

Atopic dermatitis (AD) is one of the most common inflammatory skin conditions, with a prevalence of 20% in children and 7–14% in adults [1]. AD is clinically characterized by intense, persistent and debilitating itching, often leading to sleep deprivation, anxiety, depression, impairment in productivity, and reduction in health-related quality of life [2]. More than a third of AD cases are considered to be moderate-to-severe and often require systemic treatment to achieve adequate control [3]. However, long-term management of AD has been challenging for several years due to a lack of therapeutic options, mainly limited to traditional systemic immunosuppressants (e.g. cyclosporine, methotrexate, and azathioprine), which are burdened by toxicity [3]. Recent advances in clarifying the pathogenic role of type II inflammation in AD, led to the development of new target therapies, including two biologics (dupilumab and tralokinumab) and three small molecules (upadacitinib, baricitinib, and abrocitinib), which have revolutionized the therapeutic management of AD [4–6].

Tralokinumab is the first fully human monoclonal antibody that specifically targets interleukin (IL)-13 with high affinity, thus preventing it from binding to both IL-13 Rα1 and IL-13 Rα2 [7].

Notably, the Phase III ECZTRA 3 and ECZTRA 7 studies demonstrated significantly greater efficacy of tralokinumab plus topical corticosteroids (TCS) than placebo plus TCS in reducing disease signs and symptoms in an adult population

CONTACT A Chiricozzi chiricozziandrea@gmail.com Università Cattolica del Sacro Cuore, Dermatologia, Rome, Italy
MEDaCoTRA Study Group: G Coscarella[1,2], F Antonelli[1,2],M Talamonti[8], N Macagno[5], C Paganini[7], LMastorino[5].

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14712598.2023.2292627

with moderate-to-severe AD over 32 and 24 weeks of observation, respectively [8,9].

In addition, these studies confirmed a favorable safety profile of tralokinumab, similarly to placebo, with the majority of reported adverse events being mild to moderate in severity and not leading to treatment discontinuation [8,9].

To date, studies analyzing the efficacy and safety of tralokinumab in a real-world setting are scarce [10–13]. So far, no real-world studies evaluated the therapeutic response considering the therapeutic goals that have been recently proposed to assess, through a multidimensional approach, the treatment response in AD.

Indeed, an international expert panel identified, *via* an e-Delphi consensus process, a list of objective treatment goals that were selected to comprehensively evaluate the clinical response to systemic treatments for AD, based on the achievement of specific scores of validated and recommended tools (e.g. SCORAD, EASI, DLQI, Peak Pruritus NRS, or POEM), after 3 and 6 months of therapy [14,15]. Additional treatment goals were considered within the tralokinumab trial program that result similar to those proposed for the real-world setting [8].

The aims of this European, multicentric, real-world, retrospective cohort study were: 1) to assess the effectiveness and safeness profile of tralokinumab up to 32 weeks, investigating the achievement of pre-specified treatment goals; 2) to detect potential differences in terms of effectiveness and safeness across some selected patient subcohorts.

2. Patients and methods

This European, multicentric, real-world, retrospective, cohort study included adult patients affected by moderate-to-severe AD under treatment with tralokinumab for at least 16 weeks, referring to the outpatient clinics of 10 European dermatology centers between October 2022 and July 2023. Tralokinumab was prescribed at the standard dose of 600 mg at the baseline followed by 300 mg every 2 weeks. All subjects were encouraged to use moisturizers on a daily basis, while topical corticosteroids or calcineurin inhibitors were allowed on an as-needed basis.

The following clinical and demographic characteristics were collected at baseline: age, gender, history and severity of AD, clinical phenotypes, and topographic distribution of lesions according to Silvestre Salvador JF et al16, serum total IgE levels, eosinophil count, prior systemic therapies for AD, atopic and non-atopic comorbidity and related treatments.

At the baseline and at each subsequent visit conducted at weeks 4, 16, and 32, with minor variations depending on each center timetable, disease severity was evaluated using Eczema Area and Severity index (EASI) with a score ranging from 0 to 72, and a six points Investigator Global Assessment (IGA) with a scale ranging from 0 to 5. In addition, pruritus severity was measured using a 0–10 numerical rating scale (itch-NRS), sleep disturbances/sleeplessness by a 0–10 NRS scale (sleep-NRS), and patient's quality of life by the Dermatology Life Quality Index (DLQI).

Safety was evaluated through physical examination and laboratory tests. Any abnormal physical condition and alteration in blood test results was defined as adverse event (AE). Physicians collected this information every 16 weeks or more frequently in response to clinical needs throughout the study period. This study was approved by the Local Ethics Committee – Comitato Etico Territoriale Lazio Area 3, Prot ID: 5909. Permission was obtained from each center involved to use their patient records for the purposes of this study. Patient records were anonymized. Written informed consent was obtained from patients, whereby they also gave consent for their anonymized data to be used for research and publication purposes.

2.1. Statistical analysis

Summary statistics were generated and expressed as mean and standard deviation, or numbers and frequencies. AD extent and severity were evaluated at baseline, weeks 4, 16 and 32 by defining absolute scores, including physician-measured (EASI, v-IGA) and patient-reported scores (DLQI, itch-NRS, and sleep-NRS scores). We also evaluated the proportion of patients achieving clinically meaningful treatment goals, established in the real-world and trial setting, that included: 50%, 75%, and 90% improvement in baseline EASI score (EASI50, EASI 75 and EASI 90, respectively), a minimum 4-point improvement in DLQI score and a minimum 3-point improvement in itch-NRS versus baseline, and absolute EASI ≤ 7, absolute DLQI score ≤5, absolute itch-NRS ≤4.

For binary endpoints, the McNemar's test has been used to assess differences in proportions between paired data. For continuous endpoints, changes from baseline were analyzed using a repeated-measurements model (paired t-test or analysis of variance-ANOVA, as needed) at each follow-up visit. Results were stratified according to age at tralokinumab initiation and previous exposure to dupilumab. Multivariable logistic regression analysis was conducted to characterize the study population accessing to tralokinumab. All data management and analysis were performed using STATA BE/17.

3. Results

3.1. Patient characteristics

A total of 194 adult patients, 110 (56.7%) males and 84 (43.3%) females, with a mean (±SD) age at treatment initiation of 42.0 ± 19.1, who were diagnosed as moderate-to-severe AD and treated with tralokinumab, were analyzed. Disease and patients' characteristics with indication of prior systemic therapies are reported in Table 1.

Mean (±SD) age at diagnosis was 21.4 (±26.6) years, with a mean (±SD) disease duration of 21.7 (±15.1) years. Persistent and relapsing AD patterns were recorded in 58.9% (99/168) and 10.1% (17/168), respectively, while late onset AD pattern was seen in 30.9% (52/168). Early onset (<18 years) of disease was observed in 62.1% (108/174) of patients, adult AD onset (18–64 years) in 25.3% (44/174) and elderly AD onset (≥65 years) in 12.6% (22/174).

Head/neck AD involvement occurred in 70.6% (84/119) of patients, while hand eczema in 9.2% (11/119) of patients. Elevated IgE level (IgE ≥100 kU/L) and eosinophilia (>500 cells/mm^3) were recorded in 76.9% (80/104) and 40.2% (39/

Table 1. Baseline disease and patients' characteristics, subdividing the study population into young and elderly, and bio-experienced versus bio-naive.

Patients characteristics		Overall population $N = 194$	Young population (≤65 years) $N = 159$	Elderly population (>65 years) $N = 35$	P value*	Dupilumab-experienced $N = 38$	Dupilumab naïve $N = 133$	P value§
Gender n(%)	Male	110 (56.7)	93 (58.5)	17 (48.6)	0.284	23(60.5)	76(57.1)	0.709
	Female	84(43.3)	66 (41.5)	18 (51.4)		15(39.5)	57(42.9)	
Age at disease onset n(%)	Early (<18 years)	108 (62.1)	105(73.4)	3(9.7)	**<0.0001**	22(61.1)	72(62.6)	0.955
	Adult (18–65)	44(25.3)	36(25.2)	8(25.8)		9(25.0)	26(22.6)	
	Elderly (>65)	22(12.6)	2(1.4)	20(64.5)		5(13.9)	17(14.8	
IgE (IU/mL) n(%)	Abnormal (>100 IU/mL	80(76.9)	16(19.1)	8(40.0)	0.05	13(72.2)	60(76.9)	0.674
	Normal (<100 IU/mL)	24(23.1)	68(80.9)	12(60.0)		5(27.8)	18(23.1)	
Eosinophilia (cell/mm^3)	Abnormal (>500 cells/mm^3)	39(40.2)	51(62.2)	7(46.7)	0.259	7(50.0)	32(40.0)	
	Normal (<500 cells/mm^3)	58(59.8)	31(37.8)	8(53.3)		7(50.0)	48(60.0)	
Current allergic comorbidities ($N = 153$)	Rhinitis	77 (50.3)	69(55.2)	8(28.6)	**0.011**	8(17.8)	37(82.2)	0.829
	Asthma	48(31.4)	44(35.2)	4(14.3)	**0.031**	11(15.7)	59(84.3)	0.738
	Conjunctivitis	40 (26.1)	37(29.6)	3(10.7)	**0.040**	5(12.8)	34(87.2)	0.437
Other comorbidities	Cardiovascular disease	21(50.0)	6(31.6)	15(65.2)	**0.030**	9(45.0)	11(55.0)	1.000
	History of cancer	4(9.5)	3(75.0)	1(25.0)	0.392	1(25.0)	3(75.0)	0.397
Disease phenotype n(%)	Flexural	159 (82.0)	138(86.8)	21(60.0)	**0.002**	30(80.1)	107(80.5)	0.571
	Nummular	19(9.8)	11(6.9)	8(22.9)		4(10.5)	14(10.5)	
	Prurigo-like	12(6.2)	7(4.4)	5(14.3)		4(10.5)	8(6.0)	
	Erythrodermic	4(2.1)	3(1.9)	1(2.9)		0(0.0)	4(3.0)	
Head/neck involvement n(%)	Yes	84(70.6)	75(79.8)	9(36.0)	**<0.0001**	23(74.2)	42(64.6)	0.348
	No	35(29.4)	19(20.2)	16(64.0)		8(25.8)	23(35.4)	
Hand involvement n(%)	Yes	11(9.2)	9(9.6)	2(8.0)	0.809	4(12.9)	5(7.7)	0.413
	No	108 (90.8)	85(90.4)	23(92.0)		27(87.1)	60(92.3)	
EASI (mean ±SD)		21.6(9.2)	22.0(8.7)	19.8(10.9)	0.192	17.9(11.7)	22.4(8.4)	**0.009**
Itch-NRS (mean ±SD)		7.3(2.4)	7.3(2.3)	7.4(2.7)	0.785	6.7(3.1)	7.3(2.1)	0.175
Sleep-NRS (mean ±SD)		5.0(3.7)	4.9(3.7)	5.9(3.5)	0.187	4.8(3.9)	4.6(3.5)	0.743
DLQI (mean ±SD)		10.8(6.1)	10.6(6.1)	11.7(6.4)	0.415	8.8(5.0)	11.4(6.6)	**0.042**
vIGA-1		8(5.89	7(5.8)	1(5.9)	0.563	5(21.7)	2(1.9)	**<0.0001**
vIGA-2		24(7.4)	21(17.4)	3(17.6)		4(17.4)	18(16.8)	
vIGA-3		53(38.4)	46(38.0)	7(41.2)		5(21.7)	45(42.1)	
vIGA-4		51(37)	46(38.0)	5(29.4)		7(30.4)	42(39.2)	
vIGA-5		2(1.4)	1(0.8)	1(5.9)		2(8.7)	0(0.0)	

*P value for the comparison between young and elderly study groups. Statistically significant p values are in bold.
§P value for the comparison between bio-experienced and bio-naive study groups. Statistically significant p values are in bold.
The sum does not always matched the total due to missing data.

97) of patients, respectively. The most frequent AD phenotype was flexural eczema (82.0%, 159/194).

Patients with active allergic comorbidities were 56.1% (97/173), being rhinitis 79.4% (77/97) and asthma 49.5% (48/97) the most frequent ones, followed by conjunctivitis (40.2%, 39/97) and food allergy (12.3%, 11/97). Patients with early onset of disease showed more often (73.6%, 67/91) allergic comorbidities ($p = 0.004$) and head/neck (73.2%, 60/82) AD involvement ($p < 0.0001$) compared to adults (17.6%, 16/91, and 20.7%, 17/82, respectively) or elderly subjects (8/91, 8.8% and 5/82, 6.1%, respectively).

Based on the age at treatment initiation (<65 versus ≥65 years old), elderly patients [18.4% (35/194)] showed a significantly lower number of atopic comorbidities (either conjunctivitis $p = 0.040$, asthma $p = 0.031$, or rhinitis $p = 0.011$) and more frequent head/neck involvement ($p < 0.0001$) than younger patients.

Cardiovascular diseases (hypertension and/or IMA, coronary/aortic stenosis, dilated cardiomyopathy) were significantly more frequent among elderly (≥65 years) patients (65.2% versus 311.6% of those aged <65 years, respectively, $p = 0.030$). Other recorded comorbidities included type 2 diabetes in 16.7% (7/42), history of neoplastic disease (colon cancer, lung cancer, melanoma) in 9.5% (4/42) of patients, one case of thyroid disorder and one case of alopecia areata.

Previous systemic treatments were recorded in 86.6% patients (148/171), including non-steroidal immunosuppressants (79.0% of cases 117/148), with cyclosporin as the most frequently prescribed conventional systemic immunosuppressant (77.0%, 114/148), followed by methotrexate (10.1%, 15/148) and azathioprine (3.4%, 5/148). Prior use of targeted therapies included dupilumab (25.7%, 38/148), JAK-inhibitors (upadacitinib) (9/148, 6.1%), and omalizumab (3/148, 2.0%). Multiple systemic treatments (at least two) were recorded in 62.8% (93/148) of patients. Dupilumab-experienced patients were more likely to show relapsing AD (OR = 3.5, 95%CI = 1.0–12.13, $p = 0.043$) and to be aged ≥65 years (OR = 7.2, 95%CI = 1.9–25.7, $p = 0.003$; Table 2), than dupilumab-naïve patients. The main (74.3%, 26/35) reason for discontinuing dupilumab was ineffectiveness, while adverse events caused treatment interruption in 25.7% of cases (9/35).

3.2. Assessment of AD severity throughout the observation period

Disease burden at the baseline was defined by a mean (±SD) EASI score of 21.6 ± 9.2, mean (±SD) DLQI of 10.8 ± 6.1, mean (±SD) itch-NRS of 7.3 ± 2.4, mean (±SD) sleep-NRS of 5.0 ± 3.7. The majority of patients presented an IGA 3 (53/138, 38.4%), with IGA 4 being documented in 37.0% (51/138), IGA 2 in 7.4% (24/138), IGA 1 in 5.8% of (8/138), and IGA 5 in 1.4% of patients. Baseline EASI score was greater in patients showing head/neck involvement than in those without head/neck AD (20.9 ± 9.4 versus 14.7 ± 9.8, $p = 0.001$), and it was found significantly higher in erythrodermic than in other phenotypes ($p = 0.002$). In addition, we found significantly higher EASI ($p = 0.009$) and DLQI ($p = 0.042$) scores in bio-naïve than dupilumab-experienced patients, although the only two patients presenting IGA5 were previously treated with dupilumab ($p < 0.0001$) (Table 1).

A significant improvement in mean EASI score compared to baseline was detected at each follow-up visit during tralokinumab administration (Table 3). A similar trend was observed for patient-reported outcomes, including itch-NRS, sleep-NRS, and DLQI, with significant improvements from baseline to week 16 and sustained until week 32. The proportion of patients achieving EASI75 continued to increase through week 32 (from 42% at week 16 to 76% at week 32), while EASI90 response rates achieved a plateau at week 16 without meaningful improvements thereafter. Similarly, the proportion of patients obtaining absolute DLQI score ≤5 and itch-NRS score ≤4 significantly increased through the whole treatment period. DLQI score ameliorated by more than 4 points in 46.5% (60/129) of patients at week 4, 50% (43/86) at week 16 and 52% (13/25) at week 32, while itch-NRS score improved by more than 3 points from baseline to week 16 but these improvements were not sustained throughout the whole observation period (Table 3).

3.3. Comparing tralokinumab effectiveness among different patient subcohorts

No difference in effectiveness was also found when considering the whole patient cohort according to age at tralokinumab initiation (<65 versus ≥65 years), except for the significantly more frequent DLQI scoring ≤5 at week 16 in patients ≥65 years old (57.1% versus 55.7%, $p = 0.005$) (Supplementary Table S2). Whereas no difference could be demonstrated between dupilumab-naive vs dupilumab-treated subjects in terms of effectiveness at week 4 and 16, an EASI75 response was significantly more frequent within dupilumab-naïve patient subcohort at week 32 (93.7% versus 44.4%, $p = 0.006$). Dissecting patient population by patient's age at the disease onset (early AD onset [<18 years old] vs late AD onset [≥18 years old]), we did not detect any significant difference in terms of treatment response, except for two effectiveness parameters assessed at week 4 (Supplementary Table S4). The absolute itch Absolute itch-NRS score ≤4 that was achieved by a significantly greater percentage of early AD onset patients (56.9% vs. 37.5%, $p = 0.03$). This improvement in itch disturbances was associated with a significantly lower mean sleep-NRS value in early AD onset patients (1.9 ± 2.1 vs. 3.9 ± 3.6, $p = 0.0002$; Supplementary Table S2). Considering AD localization in special areas, we evaluated the impact of head/neck involvement that negatively affected the effectiveness of tralokinumab, obtaining significantly lower rates of EASI 75 and EASI 90 responses, with a significantly smaller reductions of different disease severity scores (Supplementary Table S2). Overall head/neck involvement reduced treatment response at both week 4 and week 16, whereas this negative impact was not detected when considering hand involvement (Supplementary Table S2).

Table 2. Multivariable analysis to characterize bio-experienced patients (number of obs = 158, prob > chi2 = 0.0133, pseudo R2 = 0.0920).

Prior use of dupilumab		OR	Std. Err.	P>|z|	[95% conf. interval]
Age at tralokinumab initiation (years)	≤65	ref			
	>65	7.2	4.676	**0.003**	1.997–25.747
Sex	Female	ref			
	Male	1.1	0.466	0.882	0.452–2.514
AD pattern	Persistent	ref			
	Late	0.4	0.277	0.189	0.114–1.533
	Relapsing	3.5	2.226	**0.043**	1.038–12.136
Compassionate access to tralokinumab	No	ref			
	Yes	1.3	0.576	0.612	0.514–3.088

Abbreviations OR:odds ratio; Std.Err.:Standard Error; 95% conf. interval:95% confident interval.

3.4. Current therapeutic goals were achieved by the vast majority of tralokinumab-treated patients.

Among tralokinumab-treated patients, 88% achieved at least one currently identified real-world therapeutic goal at week 16, and 81% of patients obtained one physician-measured endpoint of AD severity (absolute EASI ≤ 7 or EASI75) combined with patient-reported endpoints of AD symptoms or quality of life (absolute DLQI ≤ 5, absolute itch-NRS ≤4, or DLQI ≥ 4-point reduction from baseline, itch-NRS ≥3-point reduction from baseline; Figure 1). Overall, 35% (30/86) and 25% (21/85) of tralokinumab-treated patients reached all the three therapeutic goals described by absolute scores (EASI ≤7, absolute itch-NRS ≤4, and absolute DLQI ≤ 5) or improved scoring from baseline (EASI75, DLQI ≥ 4-point reduction, itch-NRS ≥3 points reduction), respectively.

About one third of patients (31%) achieved all therapeutic endpoints commonly used in the trial setting, i.e. EASI50, itch-NRS ≥3-point reduction, DLQI ≥ 4 points reduction at week 16. Specifically, an EASI50 response was largely achieved by 86% of patients, while both DLQI ≥ 4-point and itch-NRS ≥3 points reductions were obtained by half of patients (Supplementary Figure S1).

3.5. Safety and reason of treatment discontinuation

Early treatment discontinuation occurred in 7.0% (9/129) of patients, 2 of them were due to ineffectiveness, while adverse events like injection site reaction (4/9, 44.4%) or flu-like symptom (4/9, 44.4%) were reported in the other cases, without specifying their causative relationship with therapy discontinuation. After 16 weeks of tralokinumab administration, the percentage of treatment discontinuation slightly increased to 12.5% (11/88). AEs reported at week 16 included 4 ocular disturbances (3 conjunctivitis and 1 dry eye disease), 1 psoriasis, 3 injection site hematoma, 1 facial redness, 1 visual blurring and 1 defluvium. At week 32 only 1 case of therapy discontinuation was recorded as lost-to-follow-up and unrelated to AEs.

4. Discussion

The recent introduction of new targeted therapies revolutionized the therapeutic approach in AD, providing long-term stable control of clinical signs and symptoms and valuable tolerability. In this scenario, the development of new biologic drugs (tralokinumab, lebrikizumab, the last not yet approved) that inhibit IL-13 signaling, which is central to the pathogenesis of AD, provided valid and additional therapeutic options, exhibiting significant clinical efficacy in the trial setting [7].

Overall, this retrospective multicenter study confirmed the effectiveness and safeness of tralokinumab throughout 32 weeks of observation in a relatively large real-word patient cohort.

Significant reductions from baseline in both patient-reported (Itch and Sleep NRS and DLQI) and physician-reported (EASI, IGA) outcomes were observed as early as week 4 and were maintained throughout the 32 weeks of treatment.

Notably, the proportion of patients achieving EASI75 continued to increase through week 32 (from 42% at week 16 to 76% at week 32). In the ECZTRA 3 study, the proportion of EASI75 responders increased from 56% at week 16 to 70% at week 32 [8]. This observation is clinically relevant, indicating that week 16 May be too early to evaluate the full effect of tralokinumab.

Since a multidimensional disease such as AD cannot be adequately captured by a single outcome, we conducted a comprehensive evaluation of clinical response, using both specific treatment goals proposed by De Bruin-Weller M et al.[14] and its update[15] along with therapeutic targets identified in the clinical trial setting [8,9].

Notably, by week 16, over 88% of patients treated with tralokinumab achieved at least one of the therapeutic goals proposed by De Bruin-Weller M et al. and approximately one-third of patients achieved all therapeutic goals [14,15], reflecting a multidimensional improvement induced by tralokinumab.

Similarly to ECZTRA 3, approximately one-third of patients achieved all three endpoints of interest at week 16, namely EASI 50, itch-NRS ≥3 and DLQI ≥ 4. Indeed, an improvement in disease domains correlating positively with patients' quality of life, pruritus, sleep, and DLQI was observed within the first 4 weeks of treatment, with further amelioration through week 32.

We investigated treatment response across different patient subcohorts and no difference in clinical response was observed according to age at the treatment initiation (<65 vs

Table 3. Outcomes of effectiveness detected throughout the 32-week observation period.

Outcomes of effectiveness	*Baseline (N = 194)*	*Week 4 (N = 150)*	*P value (95%CI)*	*Week 16 (N = 95)*	*P value (95%CI)*	*Week 32 (N = 29)*	*P value (95%CI)*
vIGA-4 (severe disease) n(%)	51(36.9)	11(10.5)	0.0007[§]	2(2.6)	<0.0001[§]	0(0.0)	0.0010[§]
EASI (mean ±SD)	21.6(9.2)	8.7(7.8)	<0.0001*	6.2(7.3)	<0.0001*	3.8(4.7)	<0.0001*
Absolute EASI score ≤ 7, *n* (%)	23(11.9)	79(52.7)	<0.0001[§] (0.00–0.08)	70(73.7)	<0.0001[§] (0.00–0.06)	25(86.2)	<0.0001[§] (0.001–0.28)
EASI75 n(%)	-	63(42.0)	-	59(62.8)	<0.0001[ς] (0.00–0.17)	22(75.9)	0.0075[ς] (0.02–0.75)
EASI90 n(%)	-	32(21.3)	-	32(34.0)	0.0046[ς] (0.06–0.72)	13(44.8)	0.083[ς] (0.05–1.33)
DLQI (mean ±SD)	10.8(6.1)	6.7(5.3)	<0.0001*	5.7(5.6)	<0.0001*	3.6(3.9)	0.0004*
Absolute DLQI score ≤ 5, n (%)	38(21.6)	58(44.9)	<0.0001[§] (0.09–0.47)	48(55.8)	<0.0001[§] (0.03–0.36)	18(72.0)	0.0126[§] (0.02–0.83)
≥4 points reduction of absolute DLQI *n* (%)	-	60(46.5)	-	43(50.0)	0.065[ς] (0.02–1.07)	13(52.0)	0.414[ς] (0.04–3.49)
Itch-NRS (mean ±SD)	7.3(2.4)	4.6(2.6)	<0.0001*	4.2(2.9)	<0.0001*	4.1(3.3)	0.0034*
Absolute itch-NRS score ≤ 4, *n* (%)	30(15.5)	73(48.3)	<0.0001[§] (0.03–0.22)	51(53.7)	<0.0001[§] (0.03–0.28)	15(51.7)	0.076[§] (0.07–1.09)
≥3 points reduction of itch-NRS, *n* (%)	-	73(48.3)	-	48(50.5)	0.157[ς] (0.15–1.44)	14(42.3)	0.739[§] (0.16–3.72)
Sleep-NRS (mean ±SD)	5.0(3.7)	2.6(2.9)	<0.0001*	2.2(2.8)	<0.0001*	1.2(2.3)	0.0035*
≥4point sleep-NRS improvement		45(31.7)		31(32.9)		9(31.0)	

*paired t test for the comparison between each follow-up visit and baseline.
[§]McNemar test for the comparison between each follow-up visit and baseline.
[ς]McNemar test for the comparison between each follow-up visit and week 4.

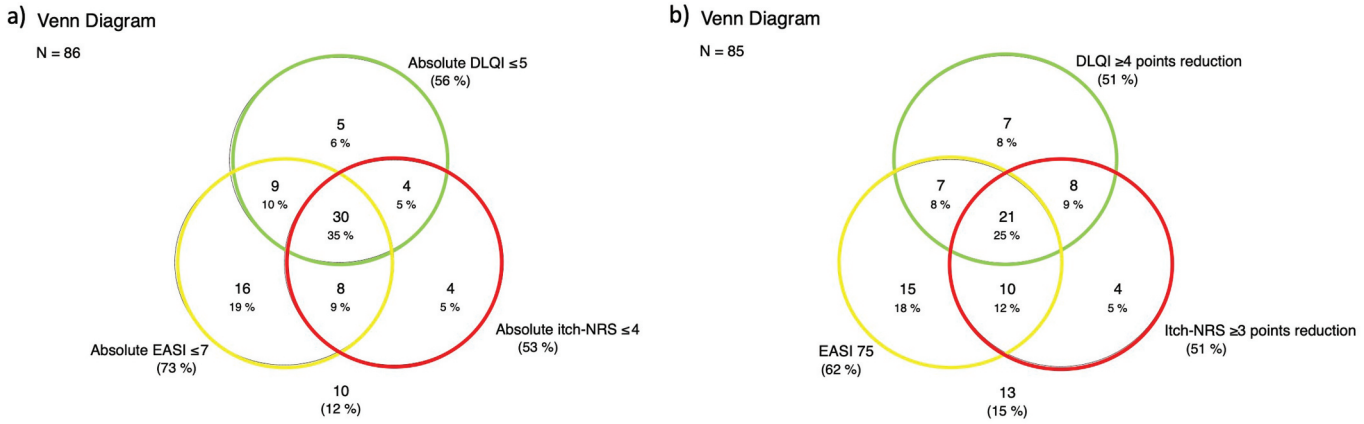

Figure 1. Therapeutic goals achieved at week 16 a) by meaning of clinically relevant absolute scored and b) clinically relevant improvement from baseline. The overlap between circles represents the combination of efficacy endpoints. Non-overlapping areas represent the achievement of a unique, non-combined endpoint. The space outside the circles represents patients achieving none of the therapeutic goals. In brackets are indicated the % of total. *DLQI* Dermatology life quality index, *EASI* eczema Area and severity index, *EASI-75* at least 75% improvement in EASI, *NRS* numeric rating scale.

≥65 years). Patient's age at AD onset negatively but partially affected therapeutic response in terms if itch and sleep disturbances, with early AD onset that was significantly associated with better outcomes. Considering AD localization in special areas, head/neck involvement significantly reduced the effectiveness of tralokinumab whereas no impact on treatment response was detected in patients with hand involvement (compared with patients without these affected sites). Lower responses were also observed with dupilumab in patients with head/neck AD localization whereas upadacitinib was suggested to obtain higher responses in patients with this affected body area, unresponsive to dupilumab [16,17].

Several lines of evidence indicate that elderly patients with AD exhibit a predominantly Th2/Th17/Th22 skewed mixed inflammation, whereas children and young adults with AD typically present a Th2-mediated inflammation [18]. Based on these observations, the clinical response could likely differ according to the age of the patient. However, our study, in line with results from a recently published post-hoc analysis of phase 3 trials in adults aged 65 years and older, confirms that tralokinumab is equally effective in treating moderate-to-severe AD in elderly patients [19]. In contrast to clinical trials, our study includes a significant proportion of patients who have previously received targeted therapy for AD. In our patient population, 25.7% (38/148) had previously used dupilumab, which was discontinued in 25 patients due to ineffectiveness and in 9 patients due to the occurrence of AEs.

In comparison to our study, an analysis of the first 100 patients enrolled from 39 sites across Germany in the observational TRACE study detected a slightly higher percentage of bio-naïve subjects (4 out of 5) among those who started tralokinumab, confirming that tralokinumab is typically prescribed as first-line systemic treatment in the real world, in accordance with European Dermatology Forum guidelines [20].

In our study, bio-naïve patients reported a significantly worse disease burden at baseline (higher EASI and DLQI scores) compared with dupilumab-experienced patients. Therapeutic responses between these two subgroups did not significantly differ with the exception of higher percentage of EASI75 response detected among bio-naïve sub-group at week 32 (93.7% versus 44.4%, $p = 0.006$), although considering the small number of patients analyzed at this time point, this finding should be carefully interpreted.

Likewise, a multicenter study involving 85 individuals, 32% (27/85) of whom were not naïve to biologicals or Janus kinase inhibitors, revealed a significantly higher percentage of EASI75 responders among naïve vs. non-naïve patients (67% vs. 41%) [12]. In addition, a Belgian multicentric study including with a limited patient cohort detected a higher response at 16 weeks among patients who had not previously been treated with immunomodulatory agents [13]. Nevertheless, the scarce number of bio-experienced patients enrolled in that study (6 out of 21) may have limited the validity of the results [13].

Indeed, further studies comprising larger sub-cohorts of patients for longer periods of observation are needed to elucidate the aforementioned issue.

A good safety profile was observed in this study throughout the 32 weeks of treatment, with most of the AEs reported as mild and not requiring treatment discontinuation. Interestingly, no differences in safety were reported in elderly patients compared to non-elderly ones, suggesting tralokinumab being well tolerated in this sub-cohort of frail

patients, which is scarcely represented in clinical trials. This aspect could be notably relevant for the positioning of tralokinumab in the therapeutic algorithm as it may represent a valid option in elderly patients, whose management may result challenging. Indeed, in this peculiar patient subpopulation the number of alternative therapeutic therapies is limited as the prescription of JAK-inhibitors is recommended with caution prioritizing the use of other agents if available.

Allergic conjunctivitis was reported in 2% of patients, which is consistent with the literature and confirms a lower incidence of ocular adverse events compared to dupilumab, that ranges between 17.9% and 48.6% in real-world studies [21–23].

The main limitation of the study lies in its retrospective nature. In addition, in real-life experience, there may be variability in visit schedules between centers or missing follow-up visits, which may affect data collection.

5. Conclusions

This study suggested that tralokinumab is a valid therapeutic option in the treatment of AD as it is able to achieve the therapeutic goals identified in both trial and real-world settings. A large proportion of tralokinumab-treated patients obtained at least one therapeutic goal. In addition, about one-third of patients after 16 weeks of treatment achieved all therapeutic goals, reflecting a multidimensional amelioration induced by tralokinumab. The favorable safety and efficacy profile is widely observed across different patient subcohorts such as elderly patients or dupilumab-experienced patients. The safety of tralokinumab may strengthen its positioning as valid therapy in the management of elderly patients. The preserved effectiveness in dupilumab-experienced patients tralokinumab is an additional finding that may have relevant clinical implications. Indeed, these results suggest that tralokinumab may be equally effective either as a first-line treatment in patients who are naïve to immunomodulatory treatment or as a second-line treatment in patients who experience ineffectiveness or adverse reactions to dupilumab.

Funding

This paper was not funded.

Declaration of interest

L Bianchi declares to have acted as a speaker and consultant for AbbVie, Novartis, Janssen-Cilag, Pfizer, UCB, and LeoPharma, outside the submitted work. A Chiricozzi has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer, and Sanofi Genzyme, outside the submitted work. C Conrad has been scientific adviser and/or clinical study investigator for AbbVie, Actelion, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli-Lilly, Incyte, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Samsung, Sanofi, and UCB. Silvia Ferrucci has been principal investigator in clinical trials for ABBVIE, Almirall, Galderma, Leo Pharma, Sanofi, Amgen, Novartis, Bayer and received honoraria for lectures for Novartis and Menarini. M Galluzzo declares to have acted as speakers and/or consultants for AbbVie, Almirall, Eli-Lilly, Janssen-Cilag, LeoPharma, Novartis and Sanofi, outside the submitted work. G Girolomoni has received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Samsung, and Sanofi. N Gori served as advisory board member and received honoraria for lectures for AbbVie, Sanofi, and Leo-Pharma. AV Marzano reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Boehringer-Ingelheim, Novartis, Pfizer, Sanofi, Janssen, and UCB. Michela Ortoncelli has received research grant/travel for AbbVie, Almirall, Amgen, Leo Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi Genzyme UCB Pharma, Pierre Fabre, and Sun Pharma. K Peris has served on advisory board, received honoraria for lectures and/or research grants for Abbvie, Almirall, Lilly, Galderma, Leo Pharma, Pierre Fabre, Novartis, Sanofi, Sun Pharma, Janssen. S Ribero has received research grant/travel for AbbVie, Almirall, Amgen, Leo Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi Genzyme UCB Pharma, Pierre Fabre, and Sun Pharma. T Torres has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Almirall, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz, and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Ethics statement

Approval of this study was obtained by the Local Ethics Committee – Comitato Etico Territoriale Lazio Area 3, Prot ID: 5909. Permission was obtained from each center involved to use their patient records for the purposes of this study. Patient records were anonymized. Written informed consent was obtained from patients, whereby they also gave consent for their anonymized data to be used for research and publication purposes.

Author contributions

All authors contributed significantly to this work, in details: Chiricozzi A. for study conception and design, and article writing; Ferrucci SM, Balato A, Ortoncelli M, Maurelli M, Galluzzo M, Munera Campos M, Seremet T, Caldarola G, De Simone C, for Ippoliti E for patient management and data collection; Di Nardo L for statistical analysis and data interpretation; Torres T, Gkalpakiotis S, and Gori N for article drafting and data interpretation; Conrad C, Carrascosa JM, Bianchi L, Argenziano G, Ribero S, Girolomoni G, Marzano AV, Peris K for critical revision of the draft and supervision;

The submitted manuscript has been read, reviewed, and approved by all the authors. All have agreed on the journal to which the article will be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage.

All authors agreed to take responsibility and be accountable for the contents of the article and to share responsibility to resolve any questions raised about the accuracy or integrity of the published work.

Data availability statement

Enquiries related to the data generated or analyzed during this study can be directed to the corresponding author.

ORCID

A Chiricozzi http://orcid.org/0000-0002-6739-0387
M Maurelli http://orcid.org/0000-0001-7492-8010
M Galluzzo http://orcid.org/0000-0002-3424-5175
G Caldarola http://orcid.org/0000-0002-8837-9232
T Torres http://orcid.org/0000-0003-0404-0870

References

1. Bylund S, Kobyletzki LB, Svalstedt M, et al. Prevalence and incidence of atopic dermatitis: a systematic review. Acta Derm Venereol. 2020;100(12):adv00160. doi: 10.2340/00015555-3510
2. Gori N, Chiricozzi A, Marsili F, et al. National information campaign revealed disease characteristic and burden in adult patients suffering from atopic dermatitis. J Clin Med. 2022;11(17):5204. doi: 10.3390/jcm11175204
3. Siegels D, Heratizadeh A, Abraham S, et al. Systemic treatments in the management of atopic dermatitis: a systematic review and meta-analysis. Allergy. 2021;76(4):1053–1076. doi: 10.1111/all.14631
4. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. J Eur Acad Dermatol Venereol. 2022;36(9):1409–1431. doi: 10.1111/jdv.18345
5. Wollenberg A, Kinberger M, Arents B, et al. First update of the living European guideline (EuroGuiderm) on atopic eczema. J Eur Acad Dermatol Venereol. 2023;37(11):e1283–7. doi: 10.1111/jdv.19269
6. Gori N, Sernicola A, Tolino E, et al. Analysis of predictive factors influencing dupilumab continuation rate in adult patients with atopic dermatitis: results from an Italian multicenter study. J DermatolTreat. 2023;34(1):2230685. doi: 10.1080/09546634.2023.2230685
7. Chiricozzi A, Gori N, Maurelli M, et al. Biological agents targeting interleukin-13 for atopic dermatitis. Expert Opin Biol Ther. 2022;22(5):651–659. doi: 10.1080/14712598.2022.2035356
8. Silverberg JI, Adam DN, Zirwas M, et al. Tralokinumab plus topical corticosteroids as needed provides progressive and sustained efficacy in adults with moderate-to-severe atopic dermatitis over a 32-week period: an ECZTRA 3 post hoc analysis. Am J Clin Dermatol. 2022;23(4):547–559. doi: 10.1007/s40257-022-00702-2
9. Gutermuth J, Pink AE, Worm M, et al. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7). Br J Dermatol. 2022;186(3):440–52. doi:10.1111/bjd.20832
10. Gargiulo L, Ibba L, Vignoli CA, et al. Tralokinumab rapidly improves subjective symptoms and quality of life in patients with moderate-to-severe atopic dermatitis: a real-life 16-week experience. J DermatolTreat. 2023;34(1):2216815. doi: 10.1080/09546634.2023.2216815
11. Pezzolo E, Schena D, Gambardella A, et al. Survival, efficacy and safety of tralokinumab after 32 and 52 weeks of treatment for moderate-to-severe atopic dermatitis in adults: a multicentre real-world study. J Eur Acad Dermatol Venereol. [2023 Jul 22]. Online ahead of print. doi: 10.1111/jdv.19382
12. Pereyra-Rodríguez JJ, Herranz P, Ruiz-Villaverde R, et al. Treatment of severe atopic dermatitis with tralokinumab in clinical practice: Short-term effectiveness and safety results. Clin Exp Dermatol. 2023;48(9):991–997. doi: 10.1093/ced/llad153
13. De Greef A, Ghislain PD, Bulinckx A, et al. Real-life experience of tralokinumab for the treatment of adult patients with severe atopic dermatitis: a multicentric prospective study. Clin Drug Investig. 2023;43(4):299–306. doi: 10.1007/s40261-023-01258-7
14. Bruin-Weller M D, Biedermann T, Bissonnette R, et al. Treat-to-target in atopic dermatitis: An international consensus on a set of core decision points for systemic therapies. Acta Derm Venereol. 2021;101(2):adv00402. doi: 10.2340/00015555-3751
15. Bruin-Weller M D, Deleuran M, Biedermann T, et al. The treat-to-target project in atopic dermatitis: One year on. Acta Derm Venereol. 2023;103:adv5382. doi: 10.2340/actadv.v103.5382
16. Chiricozzi A, Gori N, Di Nardo L, et al. Therapeutic impact and management of Persistent head and neck atopic dermatitis in dupilumab-treated patients. Dermatology. 2022;238(4):717–724. doi: 10.1159/000519361
17. Gori N, Ippoliti E, Peris K, et al. Head and neck atopic dermatitis: Still a challenging manifestation in the biologic era. Expert Opin Biol Ther. 2023;23(7):575–577. doi:10.1080/14712598.2023.2224499
18. Wang S, Zhu R, Gu C, et al. Distinct clinical features and serum cytokine pattern of elderly atopic dermatitis in China. J Eur Acad Dermatol Venereol. 2020;34(10):2346–2352. doi: 10.1111/jdv.16346
19. Merola JF, Butler DC, Mark T, et al. Safety and efficacy of tralokinumab in older adults with moderate-to-severe atopic dermatitis: A secondary analysis. JAMA Dermatol. 2023;159(10):1119–1123. doi:10.1001/jamadermatol.2023.2626
20. Thaçi D, Kleinheinz A, Anastasiadou DM, et al. A global, observational, cohort study of patients with atopic dermatitis to evaluate tralokinumab real-world clinical use (TRACE): Baseline characteristics from the first 100 patients in Germany. Br J Dermatol. 2023;188(3). doi: 10.1093/bjd/ljad162.038
21. Chiricozzi A, Di Nardo L, Gori N, et al. Dupilumab-associated ocular adverse events are predicted by low tear break-up time and correlate with high IL-33 tear concentrations in patients with atopic dermatitis. Exp Dermatol. 2023;32(9):1531–1537. doi: 10.1111/exd.14859
22. Touhouche AT, Cassagne M, Berard E, et al. Incidence and risk factors for dupilumab associated ocular adverse events: A real-life prospective study. J Eur Acad Dermatol Venereol. 2021;35(1):172–179. doi: 10.1111/jdv.16724
23. Faiz S, Giovannelli J, Podevin C, 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):143–151. doi: 10.1016/j.jaad.2019.02.053