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ORIGINAL RESEARCH

Tralokinumab for the Treatment of Adult Atopic Dermatitis in Special Populations

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Introduction: Even if mild forms of atopic dermatitis (AD) are usually well controlled with topical prescription drugs and emollients, the management of severe forms of the disease may be challenging, especially in special populations (SPs). These patients include groups of disadvantaged people (elderly, patients with disabilities and serious medical conditions) who are usually excluded from clinical trials. As a consequence, most of the data about the efficacy and safety of a drug in these patients derives from post-marketing experiences. In this context, the aim of our study was to retrospectively investigate the effectiveness and safety of tralokinumab in the management of AD in SPs.

Methods: A 24-weeks retrospective, dual-center study was performed enrolling patients with a diagnosis of moderate-to-severe AD undergoing treatment with tralokinumab at labelled dosage. Disease severity was assessed using Eczema Area Severity Index (EASI), Pruritus–Numerical Rating Scale (P-NRS), and Dermatology Life Quality Index (DLQI) score at baseline and after 4 weeks (W4), W16, and W24. Adverse events (AEs) were monitored at the same timepoints. Statistical significance of clinical improvement (EASI, P-NRS, DLQI) at week 4, week 16, and week 24 as compared with baseline was evaluated by using Student's *t*-test, considering significant a p-value <0.05.

Results: Our study enrolling 27 SPs patients showed a significant improvement in EASI and P-NRS since week 4, continuing to improve up to week 24. Similarly, DLQI significantly decreases at each timepoint as compared with baseline. Finally, no AEs were reported during the study period. Of interest, our cohort included oncologic patients, a patient with a history of severe infection, as well as subjects affected by severe neurological, psychiatric, pulmonary, and/or cardiovascular disease.

Discussion: Our experience showed that tralokinumab is effective and safe in elderly patients and subjects affected by severe comorbidities.

Keywords: atopic dermatitis, special populations, treatment, tralokinumab, biologics

Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease, affecting up to 25% of children and from 2.0% to 17.6% of adults worldwide.[1,2] Clinically, AD is usually characterized by eczema and itch, typically affecting the face, neck, and the flexures of the limbs.[1,2] However, several clinical phenotypes can be distinguished.[3] Moreover, AD can strongly affect patients' quality of life, thus requiring a prompt and effective treatment.[4]

As regards AD pathogenesis, the impairment of cutaneous barrier and the hyperactivation of T helper (Th) 2 cells seem to play a key role.[5] Recent knowledge on the overexpressed cytokines belonging to the Th2 pathway, such as interleukin (IL) 13 and 4, led to the development of new effective and targeted drugs, completely changing therapeutic scenario.[5] Indeed, even if mild forms of AD are usually well controlled with topical prescription drugs and emollients, the management of severe forms of the disease may be challenging.[6] In particular, the conventional systemic drugs used for AD management such as systemic immunosuppressant may be contraindicated for patients' comorbidities or the

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development of adverse events (AEs).[7] In this scenario, tralokinumab is a fully human monoclonal antibody targeting interleukin IL13, recently licensed for the treatment of moderate-to-severe AD in adult and adolescent patients 12 years and older who are candidates for systemic therapy.[8]

Despite its effectiveness and safety have been widely reported in both clinical trials and real-life experiences,[9–17] studies regarding its use on "special populations" (SPs), are scant. These populations include groups of disadvantaged people (elderly, patients with disabilities and serious medical conditions) who are usually excluded from clinical trials.[18,19] As a consequence, most of the data about the efficacy and safety of a drug in these patients derives from post-marketing experiences. It should be underlined that real-world data plays a crucial role because patients involved in clinical trials often differ from those encountered in routine clinical practice.[20] Indeed, real-life subjects exhibit a broader range of characteristics, whereas the stringent inclusion and exclusion criteria employed in clinical trials can limit the representation of diverse clinical scenarios and individual variability.[20]

In this context, the aim of our study was to evaluate the effectiveness and safety of tralokinumab for the management of SPs affected by AD.

Material and Methods

Study Population

A retrospective dual-center study was conducted, analyzing data from patients with moderate-to-severe AD who received tralokinumab treatment and attended the outpatient clinic of the Dermatology Unit at the University Federico II of Naples and University Magna Graecia of Catanzaro, Catanzaro, Italy.

The inclusion criteria comprised individuals aged ≥18 years with a diagnosis of moderate-to-severe AD who had undergone tralokinumab treatment for a minimum of 24 weeks and the presence of a comorbidity and/or age ≥65 years, which allow to consider these subjects as "SPs".

In addition to age, the following criteria were considered to categorize patients as SPs: severe cardiovascular disease, severe neurological disease, severe psychiatric disorder, severe pulmonary disorder, history of cancer, severe infection. Comorbidities were defined as "severe" when they significantly impact a patient's overall health, complicate the treatment of the primary condition, or increase the risk of adverse outcomes.

Exclusion criteria were: history of allergy to any component of tralokinumab, absence of a comorbidity and/or age <65 years which does not allow to categorize these patients as "SPs".

Tralokinumab has been administered at labelled dosage as subcutaneous injection [600 mg (four 150 mg injections) at baseline followed by 300 mg (two 150 mg injections) administered every other week] in all the patients.

For each subject, the demographic (age, sex) and clinical data (medical history, AD comorbidities, previous treatments for AD, concomitant disease, medications or procedures) were recorded.

The efficacy of tralokinumab treatment was measured evaluating AD severity using the following score: Eczema Area Severity Index (EASI), and Pruritus–Numerical Rating Scale (P-NRS). Moreover, the impact of AD on quality of life was evaluated by using Dermatology Life Quality Index (DLQI). Clinical and demographic data, as well as EASI, P-NRS and DLQI were evaluated at baseline. Moreover, AD severity scores and DLQI were also evaluated following 4 and 16 weeks of treatment.

Regarding safety data, any new clinical symptoms reported by the patient or observed during physical examinations were documented at each visit and assessed for potential side effects.

Statistical Analysis

Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Statistical significance of clinical improvement (EASI, P-NRS, DLQI) at week 4, week 16, and week 24 as compared with baseline was evaluated by using Student's *t*-test. Statistical analyses were performed using GraphPad Prism software (v.8.0; GraphPad Software Inc., La Jolla, CA, USA), with significance set at $p < 0.05$.

Additionally, data analysis employed the last observation carried forward method, wherein if a patient discontinued the study, the last available value was extrapolated forward until the end of the treatment period.

Ethical Considerations

The study adhered to the principles of the Declaration of Helsinki, and all patients provided informed consent for the collection of their personal and clinical data, authorizing the treatment of their anonymized clinical records, as was the case of the Campania region web-based platform used for biologic drug prescription (SANIARP; www.saniarp.it). Moreover, for non-interventional studies, the Directive (2001/20/EC) stipulates that they should be conducted in accordance with the Declaration of Helsinki, but they are generally exempt from the stringent requirements applied to interventional clinical trials, including the need for formal ethical approval.

Results

Demographics

A total of 112 patients were screened. Of these, 93 (83.04%) had a follow-up period of at least 24 weeks. Then, 66 (70.97%) subjects were excluded since they did not respect inclusion criteria. Finally, 27 patients [17 males (62.96%), mean age: 71.26 ± 11.32 years, range 33–87 years] were included in the study, respecting all the inclusion and exclusion criteria. Rhinitis was the commonest AD comorbidity, reported in 10 (37.04%) patients, followed by conjunctivitis (n = 4, 14.81%) and asthma (n = 2, 7.41%).

Clinical and demographical data of patients are reported in Table 1.

Twenty-three out of 27 (85.19%) subjects were over 65 years old. Of these, only 5/23 (21.74%) had not relevant concomitant disease.

Table 1 Demographic Data and Clinical Outcomes of SPs Patients Treated with Tralokinumab

Number of patients	27
Sex:	
Male	17 (62.96%)
Female	10 (37.04%)
Mean Age (years)	71.26 ± 11.32
Mean duration of Atopic Dermatitis (years)	19.85 ± 21.15
Atopic comorbidities:	
Rhinitis	10 (37.04%)
Conjunctivitis	4 (14.81%)
Asthma	2 (7.41%)
Food allergy	0 (0%)
Previous conventional treatments:	
Cyclosporine	5 (18.52%)
Systemic corticosteroids	6 (22.22%)
Phototherapy	13 (48.15%)
Methotrexate	1 (3.70%)
Dupilumab	1 (3.70%)
Baseline	
Mean EASI	25.96 ± 2.81
Mean DLQI	26.12 ± 3.19
Mean P-NRS	9.04 ± 1.46
Week 4	
Mean EASI	14.92 ± 5.67
Mean DLQI	14.52 ± 6.48
Mean P-NRS	6.28 ± 2.01

(*Continued*)

Table 1 (Continued).

Week 16	
Mean EASI	5.24 ± 4.71
Mean DLQI	5.52 ± 4.89
Mean P-NRS	4.04 ± 2.91
Week 24	
Mean EASI	3.08 ± 3.11
Mean DLQI	2.12 ± 2.51
Mean P-NRS	2.92 ± 2.41

Abbreviations: EASI, Eczema Area Severity Index; DLQI, Dermatology Life Quality Index; P-NRS, Pruritus Numerical Rating Scale.

Globally, history of cancer (prostatic cancer, breast cancer, non-Hodgkin's lymphoma, colorectal cancer, lung cancer) was found in 7 (25.93%) patients, whereas 3 (11.11%) psychiatric disorder (depression, bipolar syndrome), 2 (7.41%) neurological disorder (Parkinson's disease or epilepsy), 11 (40.74%) cardiovascular disease (ischemic heart disease, cerebral vasculopathy, idiopathic thrombosis lower limbs, ictus, pacemaker, congenital thrombophilia), 3 (11.11%) pulmonary disease (chronic obstructive pulmonary disease, pulmonary fibrosis, pulmonary emphysema), and 1 (3.70%) case of severe infection (hepatitis C) were collected, with 6 (22.22%) patients reporting more than 1 severe comorbidity.

Detailed clinical history is reported in Table 2.

Table 2 Demographic Data and Clinical History of SPs

Patient	Age	Sex	Time*	Disease	Treatment
1	68	M	2	None	NA
2	65	M	60	None	NA
3	81	M	10	Prostatic Cancer	C
4	77	M	50	Parkinson disease	C
5	77	M	30	Depression Ischemic Heart Disease Cerebral Vasculopathy	C C C
6	67	M	1	Idiopathic Thrombosis Lower Limbs	C
7	81	F	3	Ischemic Heart Disease Ictus Pulmonary Fibrosis	C CC
8	77	M	25	Ischemic Heart Disease	C
9	87	M	10	Chronic Obstructive Pulmonary Disease	C
10	73	F	6	Ischemic Heart Disease	C
11	75	F	8	Ictus	C
12	67	M	2	None	NA
13	75	F	68	Depression Ischemic Vasculopathy	C C
14	70	F	5	None	NA

(*Continued*)

Table 2 (Continued).

Patient	Age	Sex	Time*	Disease	Treatment
15	74	M	8	Prostatic Cancer	C
16	71	M	12	Meningioma Epilepsy Pulmonary Emphysema	P C C
17	82	M	62	Prostatic Cancer	C
18	79	M	3	Prostatic Cancer Non-Hodgkin's Lymphoma Lung cancer	C C C
19	74	F	4	Cerebral Embolism	C
20	85	M	7	Pacemaker	C
21	83	M	5	None	NA
22	64	F	35	Hepatitis C	P
23	56	F	25	Breast Cancer	P
24	53	F	15	Depression Bipolar Syndrome	C C
25	33	F	20	Congenital Thrombophilia	C
26	65	M	55	Colorectal Cancer	C
27	65	M	5	Ischemic Heart Disease	C

Note: *Years between disease diagnosis and tralokinumab starting.
Abbreviations: C, concomitant treatment; P, previous treatment; NA, not applicable.

All the patients with neurological, psychiatric, pulmonary, or cardiovascular disease were on various pharmacological treatments during the administration of tralokinumab. Among the 6 patients with a history of cancer, 5 received concomitant therapy. Finally, the subject with Hepatitis C was previously treated with Interferon.

Regarding previous treatments, phototherapy was the most common (n = 13, 48.15%), followed by systemic corticosteroids (n = 6, 22.22%), and cyclosporine (n = 5, 18.51%). Of interest, 1 (3.70%) patient previously failed dupilumab for conjunctivitis.

Clinical Effectiveness and Safety

At baseline, mean EASI and P-NRS were 25.96 ± 2.81 and 9.04 ± 1.46. Moreover, a high impact on quality of life was reported with a DLQI of 26.12 ± 3.19. All of the patients completed week 4, week 16 and week 24 follow-up. Clinical results were summarized in Table 1 and Figure 1.

In particular, a statistically significant reduction of EASI was observed at week 4 (14.92 ± 5.67, $p < 0.0001$), week 16 (5.24 ± 4.71, $p < 0.0001$), and week 24 (3.08 ± 3.11, $p < 0.0001$) as compared with baseline.

Similarly, P-NRS significantly decrease following 4 (6.28 ± 2.01, $p < 0.0001$), 16 (4.04 ± 2.91, $p < 0.0001$) and 24 weeks of treatment (2.92 ± 2.41, $p < 0.0001$).

As regards the impact of tralokinumab on quality of life, DLQI significantly reduced at each follow-up visit ($p < 0.0001$ for both), resulting as 14.52 ± 6.48 at week 4, 5.52 ± 4.89 at week 16, and 2.12 ± 2.51 at week 24, respectively.

Finally, no cases of tralokinumab discontinuation for inefficacy were collected, as well as no patients reported at least one AE during the study period.

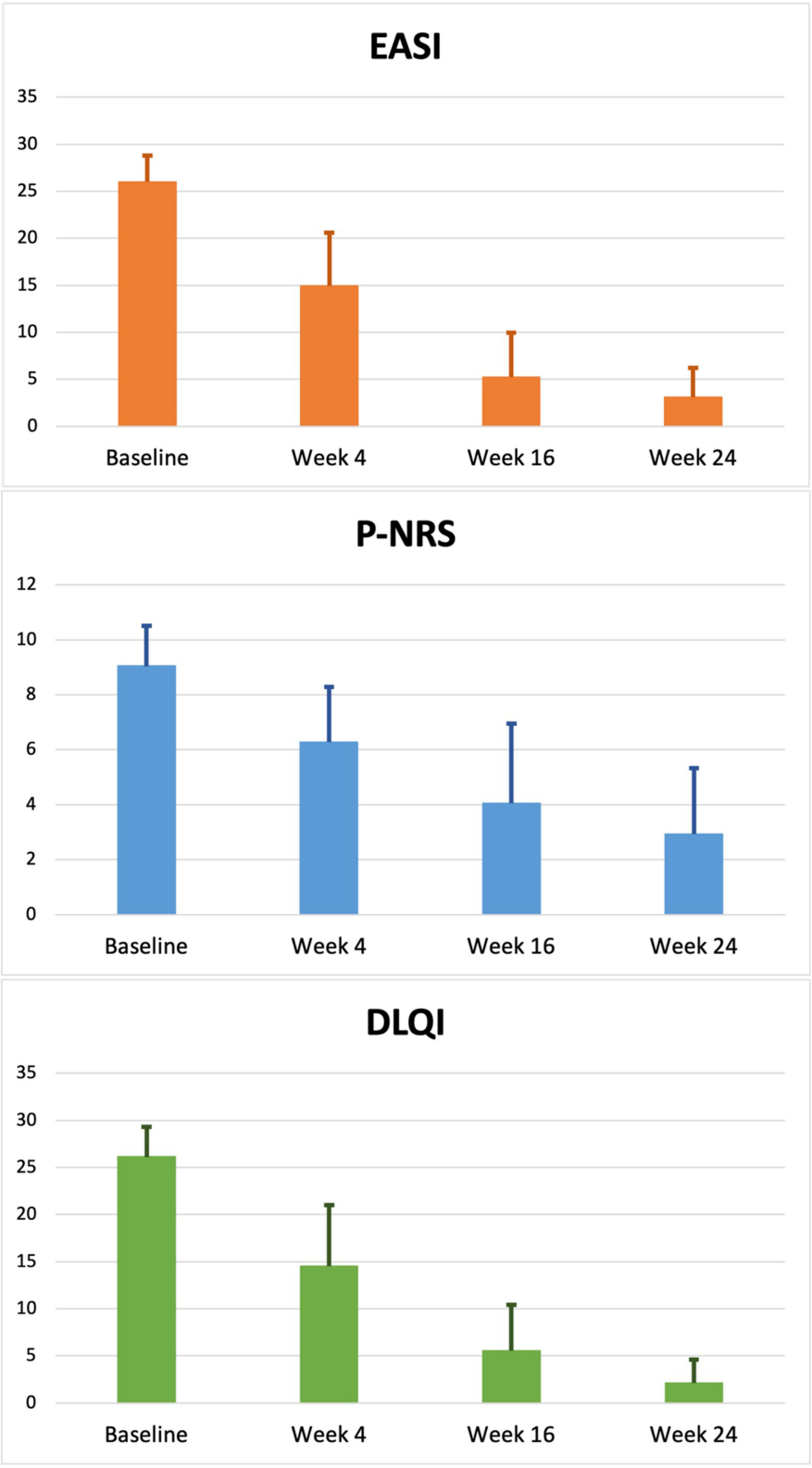

Figure 1 Improvement of EASI, P-NRS and DLQI at baseline, Week 4, Week 16, and Week 24.EASI: Eczema Area Severity Index; DLQI: Dermatology Life Quality Index; P-NRS: Pruritus – Numerical Rating Scale.

Discussion

Recent knowledge on AD pathogenesis allowed the development of selective drugs specifically targeting ILs involved in the disease.[2] Among these, tralokinumab, specifically targeting IL13, has been recently licensed, showing promising results in terms of safety.[8] Indeed, the only contraindication for its administration is hypersensitivity to the active substance or to any of the excipients.[8] However, studies regarding its use in SPs are scant. These data are essential since SPs usually require additional consideration in treatment selection as the comorbidities or concomitant drugs may interfere with the use of the investigated drug.[18] Moreover, these patients may exhibit a different response to treatment and frequency of AEs.[19] Therefore, physicians frequently exhibit reluctance to utilize certain drugs, particularly those that are newly introduced, in SPs.

In this context, differently from dupilumab, the other monoclonal antibody approved for AD,[21–24] data on SPs patients undergoing treatment with tralokinumab are scant.

Our study enrolling 27 SPs patients, showed a significant improvement of EASI and P-NRS since week 4, continuing to improve up to week 24. Similarly, DLQI significantly decrease at each timepoint as compared to baseline. Finally, no AEs were reported during the study period. Of interest, our cohort included oncologic patients, a patient with a history of severe infection, as well as subjects affected by severe neurological, psychiatric, pulmonary, and/or cardiovascular disease.

Reviewing current literature, data on tralokinumab use in SPs are limited. Indeed, as reported by drug insert package, there are limited data on tralokinumab use in elderly patients, or subjects with renal or hepatic impairment.[8]

A post hoc analysis of Phase III trials (ECZTRA 1, ECZTRA 2, ECZTRA3) enrolling 75 adults 65 years or older showed that efficacy and safety outcomes in this population were similar as compared with the younger patient cohorts after 16 weeks of treatment.[25] Moreover, the proportions of patients experiencing AEs in the tralokinumab and placebo groups were similar in elderly cohort.[25]

Currently, real-life experiences are limited to a case report, which reported a case of an 83-year-old male patient affected by AD and vitiligo, hypertension, heart rhythm abnormalities requiring pacemakers, recurrent conjunctivitis, benign prostatic hypertrophy, and idiopathic Raynaud's phenomenon successfully treated with tralokinumab, without AEs collected.[26]

Of interest, a Phase II study (ECZTRA 5) enrolling 215 patients receiving tralokinumab (n = 107) or placebo (n = 108) for 16 weeks showed that tralokinumab was not inferior to placebo for immune response to Tdap (tetanus/diphtheria/pertussis) (91.9% vs 96.1%) and meningococcal (86.0% vs 84.2%) vaccines administered at week 12.[27]

Finally, a case series enrolling AD patient who participated in the ECZTEND trial, showed that tralokinumab does not seem to be associated with more severe COVID-19 disease as well as tralokinumab does not seem to reduce the effectiveness of COVID-19 vaccines.[28]

Globally, the introduction of new drugs targeting AD pathogenesis has revolutionized the management of this disease.[29–34] However, more and more studies are required to offer patients a personalized approach.

To sum up, data on tralokinumab use in SPs are scant. Despite limited, our experience showed that tralokinumab is effective and safe in elderly patients and subjects affected by severe comorbidities.

Main strengths of our study are the data accuracy and the homogeneity of clinical evaluation. However, main limitations should be stated such as the retrospective design, the reduced follow-up period, the reduced cohort, and the lack of a control group.

Conclusion

In our study, the effectiveness and safety of tralokinumab have been evaluated in elderly AD patients or patients affected by malignancies, severe neurological, psychiatric, pulmonary, and/or cardiovascular disease, and C hepatitis. A statistically significant improvement was reported for each investigated score (EASI, P-NRS, DLQI) since week 4, continuing to improve up to week 24. Moreover, no AEs were collected. Despite promising, further observational data with more patients or longer follow-up periods are needed to confirm our results.

Data Sharing Statement

Data that support the findings of this study are available from the corresponding author, LP, upon reasonable request.

Informed Consent Statement

The patients in this manuscript have given written informed consent for the publication of their case details.

Disclosure

Cataldo Patruno reports personal fees from LeoPharma, outside the submitted work. The authors report no other conflicts of interest in this work.

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