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Prediction of relapse in a French cohort of outpatients with schizophrenia (FACE-SZ): prediction, not association

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SYSTEMATIC REVIEW

Real-World Evidence of Tralokinumab Effectiveness and Safety: A Systematic Review and Meta-analysis

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Abstract

Background Tralokinumab, a first-in-class and second biologic approved for treating moderate-to-severe atopic dermatitis in adolescents and adults, has demonstrated consistent efficacy and safety across multiple clinical trials.

Objective We aimed to assess the real-world effectiveness and safety of tralokinumab by performing a systematic review and meta-analysis on the real-world evidence of tralokinumab.

Methods We systematically searched PubMed and EMBASE from inception until 28 July, 2024 for observational studies describing the effectiveness and safety of tralokinumab for the treatment of atopic dermatitis. The primary outcome was the proportion of patients achieving a ≥75% improvement in the Eczema Area and Severity Index (EASI-75) after 16 weeks and secondary outcomes included the proportion of patients achieving EASI-50 and EASI-90 and the proportion of patients experiencing adverse events.

Results Nineteen unique studies encompassing 911 bio-naïve and bio-experienced patients with atopic dermatitis treated with tralokinumab were included. After 16 weeks of treatment, 82%, 59% and 26% of patients achieved EASI-50, EASI-75 and EASI-90, respectively, and the proportion of patients developing conjunctivitis was 3.2%.

Conclusions Tralokinumab demonstrates strong effectiveness and good tolerability in real-world settings, with a high proportion of patients achieving a clinical response and adverse events being observed only infrequently.

Key Points

Tralokinumab has a strong effectiveness and good tolerability profile shown in an everyday clinical setting.

Importantly, conjunctivitis was uncommonly observed in patients treated with tralokinumab in a real-world setting.

1 Introduction

Atopic dermatitis (AD) is a common chronic inflammatory and pruritic skin disease affecting approximately 5% of adults in high-income countries [1]. Mild AD can effectively be managed by therapeutic patient education, trigger avoidance, optimised bathing and use of emollients, and/or topical anti-inflammatory agents, but will in moderate-to-severe cases often require the use of systemic therapies [2, 3]. Atopic dermatitis is predominately an interleukin (IL)-13 driven skin disease, [4, 5], but IL-4, IL-22, IL-31 and OX-40 play important roles, and several biologics and Janus kinase inhibitors are currently approved or in clinical development [6, 7]. Dupilumab, the first approved biologic for AD, blocks IL-4 receptor alpha and thereby inhibits IL-4 and IL-13 signalling via type I and II receptor complexes [8]. Previously, we systematically reviewed the effectiveness of dupilumab when used in a real-world setting to treat patients with moderate-to-severe AD and found it to be effective and tolerable [9]. However, not all patients respond adequately to dupilumab therapy, especially in the head-and-neck area [10], and a notable proportion of patients develop conjunctivitis or arthritis during treatment, highlighting the need for additional treatment options [9, 11, 12].

Extended author information available on the last page of the article

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Tralokinumab, a selective inhibitor of free IL-13, was approved as the first-in-class and second-ever biologic for moderate-to-severe AD in adults. The phase III clinical trials results showed slightly reduced efficacy indirectly compared with dupilumab at week 16, but with better tolerability (e.g. no or very low incidence rates) [3, 13–15]. Differences in trial populations, trial designs, intercurrent events and statistical analysis plans are known to affect trial results, limiting the possibilities of indirect comparisons of results from these different studies [16]. While network meta-analyses can be informative and used to guide indirect comparisons, they do not account for trial design differences and may therefore provide misleading results if limitations are not clear. Only head-to-head clinical trials can truly be used to evaluate differences in efficacy and tolerability, but so far only a few have been performed, i.e. upadacitinib versus dupilumab and abrocitinib versus dupilumab [17–19]. Studies on real-world experience are an important addition to randomised controlled trials and illustrate the real-world effectiveness, tolerability and experience that have accumulated with tralokinumab use in clinical practice [20–22]. We conducted a systematic review and meta-analysis collecting real-world data from patients with AD treated with tralokinumab, utilising the same methodological approach as our group's previous meta-analyses of real-world evidence of dupilumab [9].

2 Materials and Methods

A protocol was developed and registered at PROSPERO (CRD42024572801). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed.

2.1 Literature Search

Two authors (ATMR and DI) independently searched the databases PubMed and EMBASE from inception until 28 July, 2024. The following search terms were used "(atopic dermatitis OR atopic eczema) AND (tralokinumab OR adtralza OR adbry)". All titles and abstracts available from the search were screened. A full-text version was retrieved of eligible studies and studies where there was any ambiguity of eligibility.

2.2 Inclusion and Exclusion Criteria

All observational studies investigating either the effectiveness or tolerability of tralokinumab in adults and adolescents (aged ≥ 12 years) with AD were eligible for inclusion. No restriction on sex or geography was set. Controlled clinical trials were excluded and articles in languages other than English or with fewer than four patients were excluded. Studies investigating highly selected groups (e.g. studies only assessing specific subtypes of AD) were excluded. When more than one publication presented the same study population, the publication with the most comprehensive data was included. Any disagreement between the reviewers was resolved through discussion with a third author (NL).

2.3 Data Extraction

Data were extracted and reviewed by two authors (ATMR and DI). The following data were extracted; first author, publication year, country, number of patients, number of patients previously exposed to other biologics or JAK inhibitors, baseline data on disease severity, dosage of tralokinumab, effectiveness outcomes and adverse events (AEs) reported after treatment initiation.

2.4 Outcomes

The primary outcome was the proportion of patients achieving a ≥ 75% reduction in the Eczema Area and Severity Index (EASI-75) following treatment with tralokinumab after 16 weeks. Secondary outcomes included the mean percentage reduction in EASI from baseline until an evaluation of effectiveness, the proportion of patients achieving EASI-50 and EASI-90, the proportion of patients achieving EASI-75 at other evaluation times and the proportion of experiencing AEs after treatment. Tertiary outcomes included the percentage of patients achieving an Investigator Global Assessment (IGA) score of 0/1, the mean percentage reduction in the Dermatology Life Quality Index (DLQI), the Patient-Oriented Eczema Measure (POEM), the Sleep Numerical Rating Scale (Sleep-NRS), the Pruritus Numerical Rating Scale (P-NRS) and the Peak-Pruritus Numerical Rating Scale (PP-NRS) after treatment. The study quality was evaluated and rated as good, fair or poor according to the National Institute of Health 12-question quality assessment tool for pre-post studies without a control group [23].

2.5 Statistical Analysis

Weighted means by study sample size and pooled proportions with a 95% confidence interval (CI) were calculated for effectiveness outcomes and the proportion of patients reporting AEs. All analyses were conducted using R version 4.2.0 and Python version 3.9.2.

3 Results

The search resulted in 558 non-duplicated studies (Fig. 1). After screening and full-text reading, 19 publications encompassing 911 patients with AD were included (Tables 1, 2). The study quality was assessed as being fair (eight studies [24–31]) or good (11 studies [20, 22, 32–40]) (Table 1 of the Electronic Supplementary Material (ESM)). Of the included studies, 11 studies [20, 22, 24, 28, 30, 31, 33, 35, 36, 38, 40] ($n = 738$ patients) examined adults, one study [29] ($n = 14$ patients) examined adolescents, one study [37] ($n = 37$ patients) reported on both adults and adolescents, and six studies [25–27, 32, 34, 39] ($n = 122$ patients) did not give information about the age of the population. Dosing of tralokinumab was in most studies with an initial dose of 600 mg followed by 300 mg every other week.

3.1 Effectiveness of Tralokinumab

Effectiveness of tralokinumab was investigated in 17 studies [20, 22, 24–30, 33–40] ($n = 839$ patients). Most studies included patients with moderate-to-severe AD (11 studies [20, 22, 26, 28, 30, 31, 33–35, 37, 38], $n = 768$ patients), five studies [25, 28, 29, 39, 40] ($n = 122$ patients) included patients with severe AD and one study [27] ($n = 122$ patients) did not report baseline severity (Table 1). The primary endpoint, EASI-75 after 16 weeks, was achieved by 59% (95% CI 54–65) based on eight studies [20, 25, 26, 33–35, 38, 40] and 309 patients (Fig. 2).

3.1.1 Mean Percentage Reduction in EASI

Four studies [25, 34, 36, 40] including 223 patients presented data on the mean percentage reduction in EASI (Table 1). The mean percentage reduction in EASI across

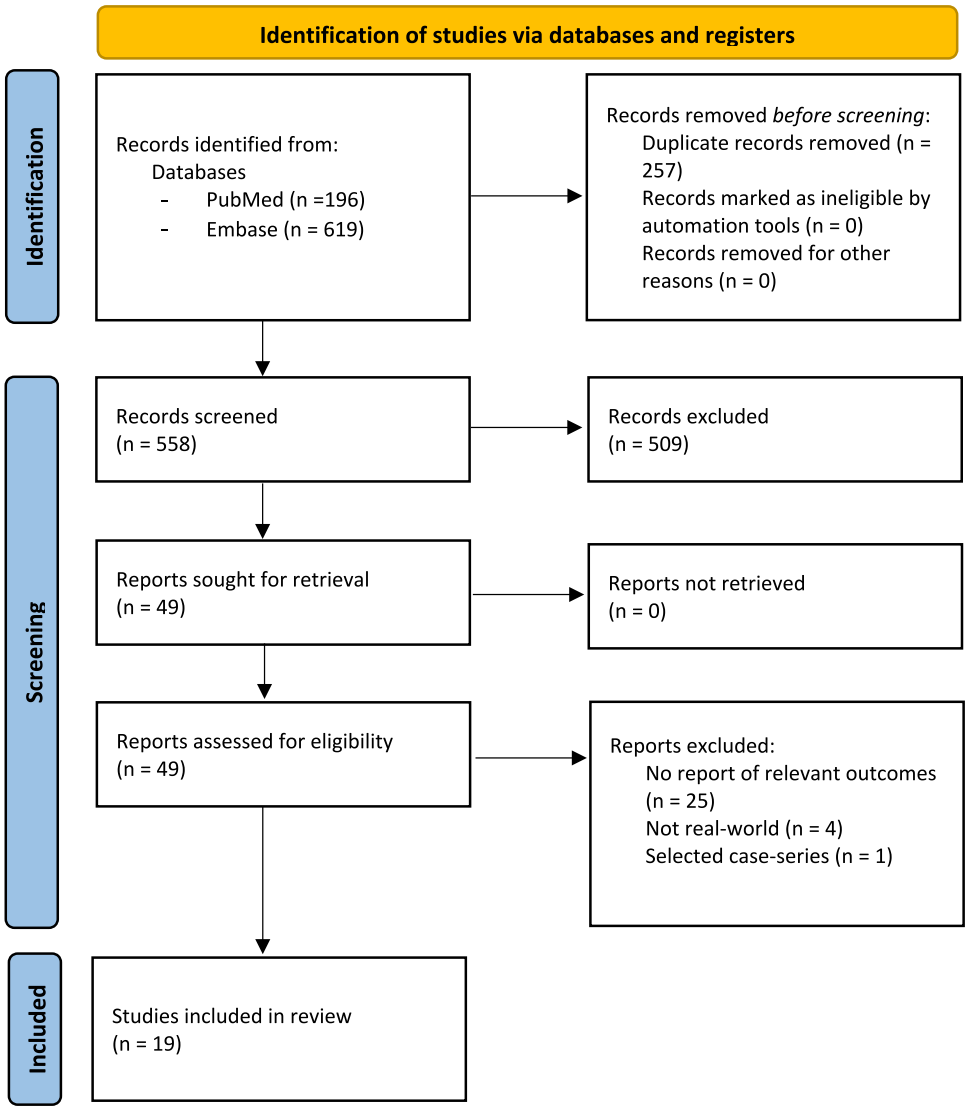

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Table 1 Effectiveness outcomes after tralokinumab treatment in patients with atopic dermatitis

Publication[c]	Country	Concomitant topicals	Time, weeks	Total patients, *n*	EASI, mean (SD)	EASI reduction, mean, %	Proportion achieving EASI-50, %	Proportion achieving EASI-75, %	Proportion achieving EASI-90, %	Proportion achieving IGA 0/1, %	DLQI reduction, mean, %	≥4-point reduction P-NRS, %	≥4-point reduction PP-NRS, %
Caroppo (2023) [24]	Italy	No information	20	5	–	–	100.0	100.0	–	–	–	–	–
Chiricozzi (2023) [20]	Europe	Yes	0	194	21.6 (9.2)	–	–	–	–	–	–	–	–
			4	150	8.7 (7.8)	–	–	42.0	21.3	–	–	–	–
			16	95	6.2 (7.3)	–	–	62.8	34.0	–	–	–	–
			32	29	3.8 (4.7)	–	–	75.9	44.8	–	–	–	–
De Greef (2023) [29]	Belgium	Yes	6	21	–	–	76.2	38.1	14.3	–	–	–	–
			16	21	–	85.2 (19.2)[a]	76.2	66.7	28.6	–	75.0 (73.3)[a]	–	–
Ferrucci (2023) [39][d]	Italy	Yes	4	60	–	–	–	–	–	–	–	–	–
			16	60	–	–	–	–	–	–	–	–	–
			24	60	–	–	–	43.4	23.3	–	–	–	–
García Castro (2023) [25][d]	Spain	Yes	16	15	–	62.1	73.3	60.0	26.7	53.0	–	53.0	–
Gargiulo (2023) [26]	Italy	Yes	16	10	3.1 (3.4)[a]	–	100.0	70.0	–	30.0	–	–	70.0
Licata (2023) [27]	Italy	No information	16	14	4.7 (0–14)[b]	–	–	–	–	–	–	–	–
Lio (2023) [22][d]	USA	No information	24	102	–	–	–	–	–	–	52.0	–	–
Pereyra–Rodríguez (2023) [38]	Spain	Yes	0	85	25.4 (8.1)	–	–	–	–	–	–	–	–
			4	85	–	–	–	–	–	–	–	–	–
			16	85	7.5 (6.9)	–	82.0	58.0	21.0	19.0	–	–	–
Pezzolo (2023) [28][d]	Italy	No information	0	12	27.6 (20–35)[b]	–	–	–	–	–	–	–	–
			8	12	–	–	–	100.0	–	–	–	–	–
			12	12	4.7 (0–13)	–	–		–	–	–		–
Schlösser (2023) [37]	The Netherlands	Yes	4, 8, 12–16	37	–	–	–	–	–	27.0	–	–	–
De Greef (2024) [29]	Belgium	No information	12–16	14	–	–	71.4	28.6	–	–	–	–	42.8

Table 1 (continued)

Publication[c]	Country	Concomitant topicals	Time, weeks	Total patients, *n*	EASI, mean (SD)	EASI reduction, mean, %	Proportion achieving EASI-50, %	Proportion achieving EASI-75, %	Proportion achieving EASI-90, %	Proportion achieving IGA 0/1, %	DLQI reduction, mean, %	≥4-point reduction P-NRS, %	≥4-point reduction PP-NRS, %
Herman (2024) [30]	USA	Yes	8–32	9	–	–	–	–	–	77.8	–	–	–
Pezzolo (2024) [21][d]	Italy	Yes	0	171	–	–	–	–	–	–	–	–	–
			32	61	–	93.4	100.0	95.1	73.8	–	81.8	–	–
			52	22	–	95.5	100.0	95.4	95.4	–	88.6	–	–
Potestio (2024) [35]	Italy	No information	0	57	27.3 (3.8)	–	–	–	–	–	–	–	–
			4	57	19.6 (3.4)	–	–	–	–	–	–	–	–
			16	57	7.4 (2.2)	–	–	54.4	–	–	–	–	–
			24	57	4.1 (2.3)	–	–	77.2	–	–	–	–	–
Sander (2024) [41][d]	Germany	No information	0	16	22.1 (6.8)	–	–	–	–	–	–	–	–
			2	16	16.6 (9.2)	28.7	26.7	0.0	0.0	0.0	–	–	33.3
			4	16	12.3 (7.6)	46.1	56.3	6.3	0.0	0.0	–	–	50.0
			6	16	8.9 (6.0)	61.1	75.0	31.3	6.3	12	–	–	62.5
			8	16	8.5 (5.9)	61.4	75.0	31.3	6.3	12	–	–	43.8
			10	16	8.9 (5.6)	59.4	56.3	31.3	6.3	0.0	–	–	68.8
			12	16	6.5 (5.0)	71.2	87.5	50.0	6.3	12	–	–	68.8
			14	16	6.4 (4.1)	71.1	87.5	43.8	12.5	6.3	–	–	62.5
			16	16	5.9 (4.0)	74.9	93.8	56.3	12.5	6.3	–	–	56.3
Gori (2024) [33]	Italy	No information	0	17	23.1 (11.8)	–	–	–	–	–	–	–	–
			4	17	9.8 (9.6)	–	65	35.3	5.8	–	–	–	–
			16	10	7.2 (10.0)	–	80	50	20	–	–	–	–
			32	4	4.8 (4.9)	–	75	50	50	–	–	–	–

Table 1 (continued)

Publication[c]	Country	Concomitant topicals	Time, weeks	Total patients, *n*	EASI, mean (SD)	EASI reduction, mean, %	Proportion achieving EASI-50, %	Proportion achieving EASI-75, %	Proportion achieving EASI-90, %	Proportion achieving IGA 0/1, %	DLQI reduction, mean, %	≥4-point reduction P-NRS, %	≥4-point reduction PP-NRS, %
Pooled outcome Prevalence/pooled mean [95% CI]			4	–	12.8 [7.7–17.8]	–	–	28.3 [12.4–52.5]	8.3 [1.4–35.7]	–	–	–	
			6	–	–	–	75.7 [59.5–86.8]	35.1 [21.6–51.5]	10.8 [4.1–25.5]	–	–	–	–
			8	–	–	–	–	89.3 [2.8–99.9]	–	–	–	–	–
			12		5.5 [3.8–7.3]	–	–	–	–	–	–	–	–
			16		6.7 [5.8–7.6]	72.0 [67.3–76.6]	82.8 [76.1–87.9]	59.2 [53.6–64.6]	26.1 [20.1–33.1]	22.3 [8.0–48.4]	–	–	60.8 [42.1–78.1]
			24		–	–	–	61.4 [35.9–81.9]	–	–	–	–	–
			32		–	–	–	83.6 [57.4–95.1]	60.1 [40.7–76.9]	–	–	–	–

CI confidence interval, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EASI-50* improvement of ≥ 50% in EASI, *EASI-75* improvement of ≥ 75% in EASI, *EASI-90* improvement of ≥ 90% in EASI, *IGA* Investigator Global Assessment, *P-NRS* Pruritus Numeric Rating Scale, *PP-NRS* Peak P-NRS, *POEM* Patient-Oriented Eczema Measure, *SD* standard deviation

[a]Median (interquartile range)

[b]Mean (range)

[c]Standard dose of 300 mg and 300 mg every other week after, if nothing else is denoted

[d]Dose not reported

Table 2 Adverse events reported after tralokinumab treatment in patients with AD

Publication	Country	Time, weeks	Total patients, *n*	Conjunctivitis, %	Dry eye, %	AD flare, %	Red face, %	Psoriasis, %	Injection-site reaction, %	Arthritis
Caroppo (2023) [24]	Italy	20	5	0.0	0.0	0.0	0.0	0.0	0.0	–
Chiricozzi (2023) [20]	Europe	32	194	1.5	0.5	–	0.5	0.5	2.1	–
De Greef (2023) [40]	Belgium	16	21	0.0	–	23.8	–	–	19.0	–
Ferrucci (2023) [39]	Italy	24	60	6.7	–	–	3.3	5.0	–	–
Garcia Castro (2023) [25]	Spain	16	15	7.0[a]	7.0	–	–	–	–	
Gargiulo (2023) [26]	Italy	16	10	0.0	–	–	0.0	–	–	–
Pereyra–Rodríguez (2023) [38]	Spain	16	85	6.0	–	4.0	6.0	–	2.4	–
Pezzolo (2023) [28]	Italy	12	12	0.0	–	–	–	–	–	–
Schlösser (2023) [37]	The Netherlands	24	37	24.0	–	2.7[b]	–	–	–	2.7
De Greef (2024) [29]	Belgium	16	14	0.0	–	50.0	–	–	14.3	–
Musters (2024) [32]	The Netherlands	12	7	–	28.6[c]	–	–	–	–	–
Pezzolo (2024) [21]	Italy	52	171	1.7	–	–	–	1.2	2.9	–
Sander (2024) [41]	Germany	16	16	–	12.5[d]	6.3	–	–	–	–
Martora (2024) [31]	Italy	NA	65	–	–	–	–	–	60.0	–
Pooled outcomes Proportion [95% CI]				3.2 [1.3–7.7]	0.93 [0.23–3.6]	10.4 [3.2–27.4]	2.0 [0.63–6.2]	1.3 [0.49–3.9]	7.1 [5.1–9.3]	–

AD atopic dermatitis, *CI* confidence interval, *NA* not available, – no mention of the specific adverse event in the paper

[a]Blepharoconjunctivitis

[b]Mild head-and-neck dermatitis

[c]Eye disorder

[d]Eye disorder (conjunctivitis, dry eye, other unspecified complaints)

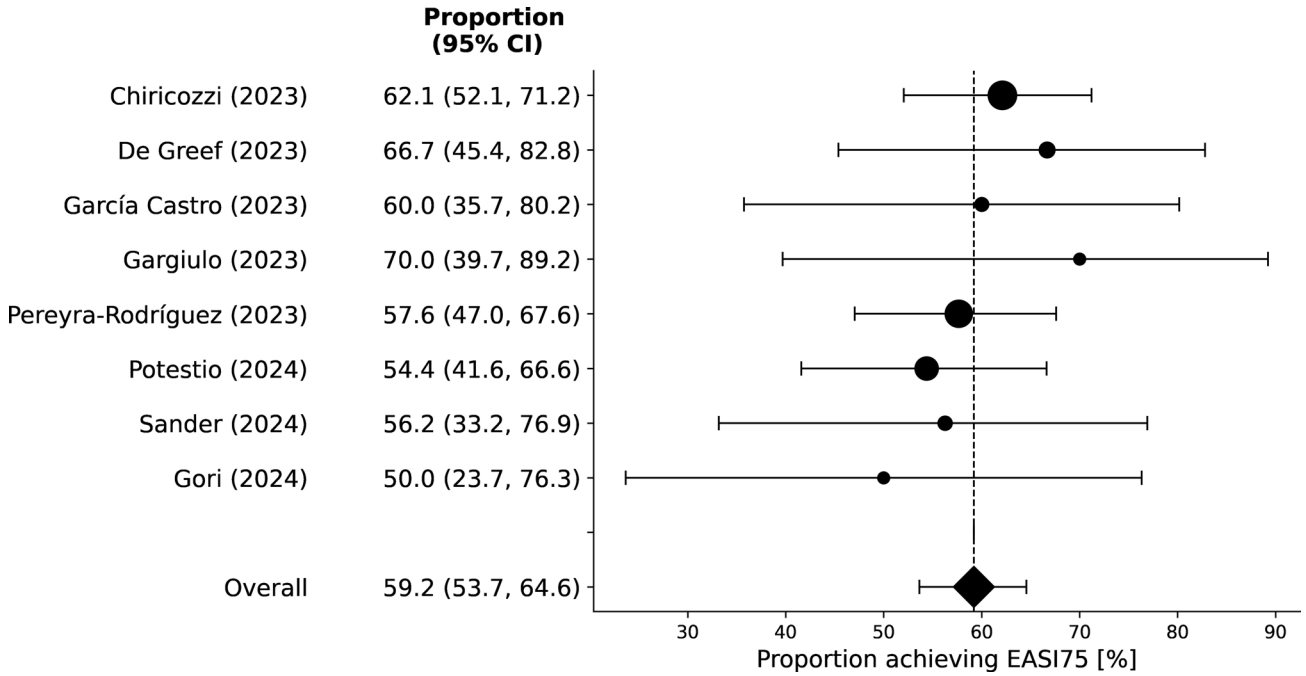

Fig. 2 Forest plot of the proportion of patients achieving Eczema Area and Severity Index-75 (EASI-75) after 16 weeks. *CI* confidence interval

studies was 72% (95% CI 67–77) after 16 weeks based on three studies [25, 34, 40] and 116 patients.

3.1.2 Proportion of Patients Achieving EASI-50

Nine studies [24–26, 29, 33, 34, 36, 38, 40] including 354 patients presented data on the proportion of patients achieving EASI-50 (Table 1, Fig. 3). The pooled proportion of patients achieving EASI-50 was 82% (95% CI 76–88) after 16 weeks (six studies [25, 26, 33, 34, 38, 40], $n = 147$ patients, Fig. 1 of the ESM).

3.1.3 Proportion of Patients Achieving EASI-75 at Other Timepoints

Thirteen studies [20, 24–26, 28, 29, 33–36, 38–40] including 677 patients presented data on the proportion of patients achieving EASI-75 (Table 1, Fig. 3). The pooled proportion of patients achieving EASI-75 was 28% (95% CI 12–53) after 4 weeks (three studies [20, 33, 34], $n = 183$ patients), 61% (95% CI 36–82) after 24 weeks (two studies [35, 39], $n = 117$ patients) and 84% (95% CI 57–95) after 32 weeks (three studies [20, 33, 36], $n = 94$ patients) (Fig. 3).

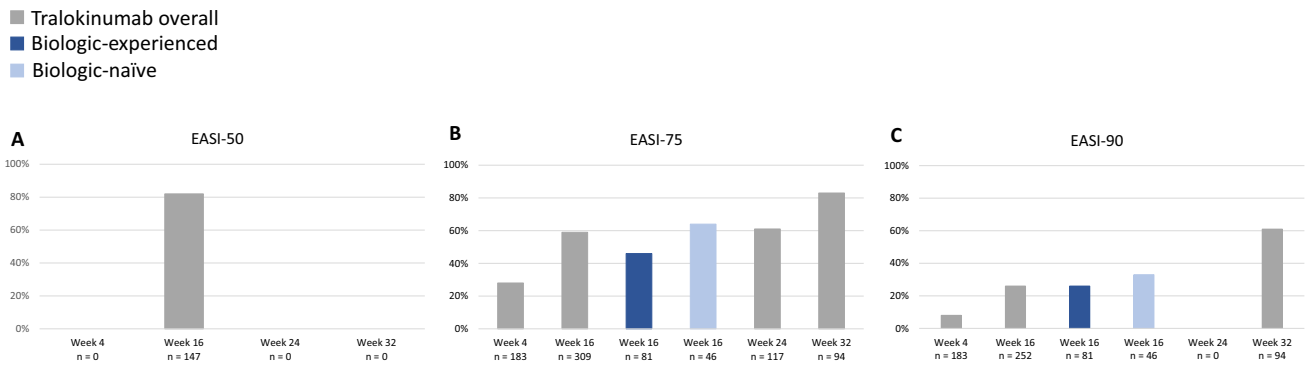

Fig. 3 Proportion of patients with atopic dermatitis achieving (**A**) Eczema Area and Severity Index (EASI)-50, (**B**) EASI-75 and (**C**) EASI-90 after treatment with tralokinumab

3.1.4 Proportion of Patients Achieving EASI-90

Eight studies [20, 25, 33, 34, 36, 38–40] including 579 patients presented data on the proportion of patients achieving EASI-90 (Table 1, Fig. 3). The pooled proportion of patients achieving EASI-90 was 8% (95% CI 0–61) after 4 weeks (two studies [20, 34], $n = 183$ patients), 26% (95% CI 20–33%) after 16 weeks (six studies [20, 25, 33, 34, 38, 40], $n = 252$ patients, Fig. 2 of the ESM) and 61% (95% CI 41–77) after 32 weeks (three studies [20, 33, 36], $n = 94$ patients).

3.1.5 Proportion of Patients Achieving IGA 0/1

Three studies [25, 26, 34] ($n = 116$ patients) reported data on IGA 0/1 after 16 weeks with 22% (95% CI 8–48) of patients achieving IGA 0/1.

3.1.6 Effectiveness According to Biologic Exposure

Two studies [20, 38] ($n = 81$ patients) specifically reported data on patients who were biologic naïve. Here, 64% (95% CI 53–74) achieved EASI-75 and 33% (95% CI 25–41) achieved EASI-90 after 16 weeks, respectively (Fig. 3 and Table 2 of the ESM). Three studies [20, 33, 38] ($n = 46$ patients) specifically reported data on patients who were biologic exposed. Here, 46% (95% CI 33–59) achieved EASI-75 and 27% (95% CI 12–44) achieved EASI-90 after 16 weeks, respectively (Fig. 3 and Table 2 of the ESM).

3.2 Patient-Reported Outcomes

Three studies reported data on a reduction in DLQI, one study ($n = 21$ patients) showed a median relative reduction in DLQI of 75% after 16 weeks [29], the second study ($n = 102$ patients) showed a mean relative reduction in DLQI of 52% after 24 weeks, [22] and the third study ($n = 171$ patients) found a mean relative reduction in DLQI of 89% and 87% after 32 and 52 weeks, [21] respectively. Three studies reported data on the proportion of patients achieving a clinical meaningful reduction in pruritus (≥ 4-point reduction). One study ($n = 15$ patients) found 53% of patients achieved ≥ 4-point reduction in the Pruritus Numerical Rating Scale (P-NRS) after 16 weeks, [25] two studies ($n = 26$ patients) found, respectively 70% and 56%, with a ≥ 4-point reduction in peak P-NRS after 16 weeks [26, 34], and one study ($n = 14$ patients) found 43% with a ≥4-point reduction in peak P-NRS after 12–16 weeks [29].

3.3 Adverse Events of Tralokinumab

Adverse events were reported in 14 studies [20, 24–26, 28, 29, 31, 32, 34, 36–40] ($n = 712$ patients) after treatment with tralokinumab (Table 2). Most studies reported prevalence data on conjunctivitis (11 studies, [20, 24–26, 28, 29, 36–40] 625 patients) between 0 and 24% with a pooled proportion of 3.2% (95% CI 1.3–7.7) (Fig. 4 and Fig. 3 of the ESM). Most cases of conjunctivitis were mild and could be controlled with lubricating and antihistamine eye drops [37, 38]. Other AEs included injection-site reactions, which was reported by seven studies [20, 24, 29, 31, 36, 38, 40] ($n = 555$ patients) with a pooled proportion of 7.1% (95% CI 5.1–9.3), dry eyes (0.9% [95% CI 0.2–3.6], five studies [20, 24, 25, 32, 34], 237 patients), red face (2% [95% CI 0.6–6.2], five studies [20, 24, 26, 38, 39], 354 patients) and AD flares (10.4% [95% CI 3.2–27.4], six studies [24, 29, 34, 37, 38, 40], 178 patients). Across all 14 studies [20, 24–26, 28, 29, 31, 32, 34, 36–40] ($n = 712$ patients), only one study ($n = 37$ patients) mentioned one patient developing monoarthritis following treatment with tralokinumab [37].

4 Discussion

In this systematic review and meta-analysis of 19 real-world studies, a mix of 911 bio-naive and bio-experienced patients with AD were treated with tralokinumab. After 16 weeks of treatment, 82%, 59% and 26% of patients had achieved EASI-50, EASI-75 and EASI-90, respectively, and the proportion of patients developing conjunctivitis was 3.2%.

Our effectiveness findings are very similar to those identified in our previous systematic review and meta-analysis on the real-world use of dupilumab where the proportions of patients achieving EASI-50, EASI-75 and EASI-90 after 16 weeks were 85.1%, 59.8% and 26.8%, respectively [9]. Notably, our study showed a higher response rate with tralokinumab compared with that observed in the clinical trial program (both monotherapy and combination therapy) of tralokinumab where the proportion of patients achieving EASI-75 was 22–56% after 16 weeks [42, 43]. The observed discrepancies between efficacy data from the clinical trial program and real-world experience are likely a result of differences in responder imputation but may also in part be due to the clinical trial program for tralokinumab [42–45]. Importantly, these real-world data for tralokinumab may be an under-estimation of true effectiveness, as both dupilumab-naïve and dupilumab-experienced patients were included. Accordingly, dupilumab-naïve patients included in our study had a higher response rate. Intriguingly, a considerable proportion of patients achieved EASI-75 among those who were dupilumab experienced, underscoring the viability of tralokinumab in patients who have not responded to dupilumab in a real-world clinical setting [33, 46, 47]. Even though the IL-13 signalling pathway is inhibited both by dupilumab and tralokinumab, albeit by different molecular mechanisms of action, these data suggest that changing

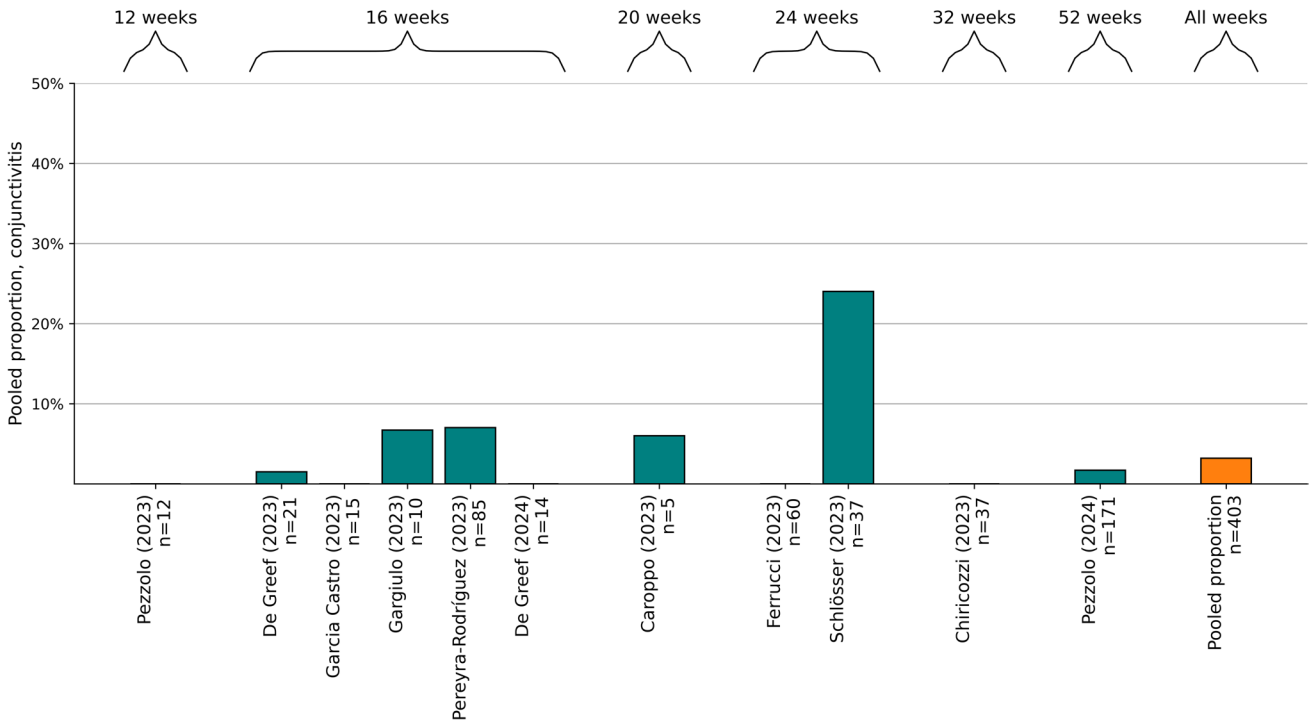

Fig. 4 Proportion of patients with conjunctivitis

to another target is not necessary among non-responders, similar to what has been observed in psoriasis [48, 49].

In the phase III clinical trial program of tralokinumab, the proportion of patients who experienced conjunctivitis was 3–11% compared with 2–3% in the placebo arm [50, 51], which is similar to the pooled proportion of 3.2% from our study. While this proportion is markedly lower than the 26.1% we found in the systematic review on real-world studies using dupilumab [9], we expect that the physician and patient reporting of conjunctivitis has declined along with dermatologists becoming more used to witnessing the ocular side-effect risk [52]. Importantly, most cases of conjunctivitis following treatment with tralokinumab were mild and could be handled with local treatment and did not lead to discontinuation of tralokinumab [37, 38]. Further, in two studies assessing the effectiveness and safety of tralokinumab in respectively 14 and 4 patients with AD with resolved dupilumab-associated conjunctivitis, no reactivation of conjunctivitis was observed in any patients following treatment with tralokinumab [27, 28]. The reason for conjunctivitis in tralokinumab-treated patients remains unclear but has in dupilumab-treated patients been hypothesised to be due to the IL-4 and IL-13 blockade, leading to (1) a decreased number of conjunctival goblet cells and thereby a lower mucus production [53, 54], (2) skewing of Th2 dominance towards a Th1/Th17 response [55, 56], or (3) overgrowth of *Demodex* mites [57] either alone or in a combination of the three [14]. The lower frequency and generally milder cases of conjunctivitis during tralokinumab treatment could be speculated to be due to the specific inhibition of only IL-13, which may reduce skewing towards a Th1/Th17 response [14]. This is supported by the fact that paradoxical reactions observed in patients treated with dupilumab including head-and-neck dermatitis, arthritis, psoriasis, and red face [11, 12, 58–61] were not or only rarely reported among patients treated with tralokinumab. Further, no new safety signals and only a few AEs were reported in patients treated with tralokinumab. However, one study focusing on only injection-site reactions did find a higher proportion of patients treated with tralokinumab experiencing injection-site reactions compared with that observed in dupilumab [31]. Importantly, all cases were mild and did not lead to treatment discontinuation. With the tralokinumab prefilled auto-injectable pen replacing syringes in most markets, which will reduce the number of necessary injections by half, the proportion of injection-site reactions is expected to decrease.

This study presents data from the real world, which constitute an important supplement to randomised clinical trials and reflects routine clinical practice. However, several limitations should be considered when interpreting the results. First, the real-world nature of the included studies prevents an unbiased control group. Consequently, it is not possible to directly compare the effectiveness and tolerability of tralokinumab with that of other drugs, and the frequency of dosing could not be addressed. Secondly, differences in the

reporting of effectiveness and safety outcomes and the time for evaluation complicates the ability to conduct a meta-analysis across all studies. In addition, few studies reported data on key patient-reported outcomes such as DLQI, POEM and pruritus. Only one study reported effectiveness data after 52 weeks, limiting the interpretation of long-term effectiveness. For AEs, only studies reporting on that specific outcome were pooled in the meta-analysis, which might inflate the number of certain AEs, but surveillance and reporting in everyday clinical practice are not as rigorous as those in randomised controlled trials, potentially underestimating occurrences of milder AEs. However, this approach was similar to our previous meta-analysis on real-world data for dupilumab. Finally, for all real-world evidence programs, there is a risk of bias as some real-world protocols require patients to follow a certain visit and reporting schedule that may mimic an intervention study and affect outcomes.

5 Conclusions

Tralokinumab demonstrates a high degree of effectiveness and tolerability in real-world settings, with a substantial proportion of patients achieving a clinical response and AEs observed infrequently.

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Declarations

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