
Real-world evidence of dupilumab efficacy and risk of adverse events: A systematic review and meta-analysis



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Background: Dupilumab, the first biological drug to be approved for the treatment of moderate to severe atopic dermatitis in adolescents and adults, has shown good efficacy and safety in clinical trials.

Objective: To evaluate real-world data on the efficacy and safety of dupilumab in atopic dermatitis.

Methods: PubMed and EMBASE were searched for observational studies with data on efficacy, drug survival, and safety of dupilumab for the treatment of atopic dermatitis. Primary outcomes were mean percentage change in Eczema Area and Severity Index (EASI) score and proportion of atopic dermatitis patients achieving 50%, 75%, and 90% improvement in EASI score after dupilumab therapy.

Results: Twenty-two unique studies encompassing 3303 atopic dermatitis patients were included. After 16 weeks of dupilumab therapy, the pooled proportion of patients achieving 50%, 75%, and 90% EASI score improvement was 85.1%, 59.8%, and 26.8%, respectively, and the weighted mean reduction in EASI score was 69.6%. Conjunctivitis was the most common adverse event, reported in a pooled proportion of 26.1%.

Limitations: Limited data in terms of size and follow-up time were available.

Conclusion: Real-world data show that dupilumab is a successful and well-tolerated therapy for atopic dermatitis, but ocular adverse events commonly occur. Registries are needed to monitor for adverse events. (J Am Acad Dermatol 2021;84:139-47.)

Key words: adverse events; atopic dermatitis; dupilumab; efficacy; real-world evidence; registries.

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INTRODUCTION

Atopic dermatitis is a chronic inflammatory pruritic skin disease affecting approximately 3% to 5% of adults.¹ Most atopic dermatitis patients are managed with education, trigger avoidance, emollients, topical anti-inflammatory agents, and light therapy, but moderate to severe atopic dermatitis requires additional systemic immunosuppressive or biologic therapy.

Dupilumab is a monoclonal antibody that blocks the interleukin (IL) 4 receptor α and thereby inhibits signaling of IL-4 and IL-13.^{2,3} Clinical trials of dupilumab have shown clinically meaningful reductions in signs and symptoms of atopic dermatitis and an acceptable safety profile.⁴⁻⁶

In 2017 and 2019, the Food and Drug Administration and European Medicines Agency approved dupilumab for treatment of adult and adolescent patients, respectively, with moderate to severe atopic dermatitis. The Food and Drug Administration approved dupilumab for patients whose disease is not adequately controlled with topical therapies or for use when these therapies are not advisable, and the European Medicines Agency approved dupilumab for patients who are candidates for systemic therapy.

Clinical trials have strict eligibility criteria, which may prohibit the inclusion of patients with multiple morbidities, and certain patient profiles may not have been represented,⁶ which may further limit the generalizability of these trials. Clinicians rely on real-world data generated after launch of dupilumab to sufficiently appreciate risk and benefits of the medication.

In this systematic review and meta-analysis, we examined evidence of the efficacy and safety profile of dupilumab in atopic dermatitis after marketing.

MATERIALS AND METHODS

Before the study began, a protocol was registered on PROSPERO.

The systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.⁷ Two authors (A.-S.H. and N.L.) independently searched the databases PubMed and EMBASE from inception through October 2019, using the search term “dupilumab.”

Additionally, all abstracts from the 28th European Academy of Dermatology and Venereology Congress were screened.

Observational studies in English with a sample size of greater than or equal to 10 patients were eligible for inclusion. Primary outcomes were mean percentage reduction in Eczema Area and Severity

Index (EASI) score in atopic dermatitis patients from baseline until evaluation of the efficacy, and proportion of atopic dermatitis patients achieving 50%, 75%, and 90% improvement in EASI score. Secondary outcomes included mean percentage reduction in scores for the Dermatology Life Quality Index, Patient-Oriented Eczema Measure, Pruritus Numerical Rating Scale, Pruritus Visual Analog Scale,

and Scoring Atopic Dermatitis; proportion of patients achieving an Investigator Global Assessment score of 0 or 1; drug survival; and common adverse events and rare adverse events of interest reported after treatment with dupilumab. Common adverse events were defined as being reported in greater than 1% of patients in greater than or equal to 3 studies. Quality of included studies was rated as good, fair, or poor with the quality assessment tool for before-after (pre-post) studies with no control group.⁸

For detailed information on materials and methods, see Supplemental text available via Mendeley at <https://data.mendeley.com/datasets/ndgdbkr4br/1>.

Statistical analysis

Efficacy outcomes were grouped based on weeks of treatment with dupilumab. For efficacy outcomes and proportion of patients reporting adverse events, StatsDirect software (version 3, StatsDirect Ltd, Cheshire, United Kingdom) was used to calculate means weighted by study sample size and pooled proportions with 95% confidence interval (CI) based on random-effects model. The heterogeneity of studies was assessed with Cochran Q test and I^2 statistics.

RESULTS

The search process yielded 1236 nonduplicate studies. Twenty-four publications were included, covering 22 unique studies and 3303 atopic dermatitis patients (Supplemental Fig 1). Studies originated from Asia ($n = 1$),⁹ Europe ($n = 13$),¹⁰⁻²⁴

CAPSULE SUMMARY

- Dupilumab has shown good efficacy and safety in clinical trials for treatment of moderate to severe atopic dermatitis in adults and adolescents.
- Real-world data show that dupilumab treatment for atopic dermatitis is effective and well tolerated in the short term, but ocular adverse events commonly occur.

Abbreviations used:

CI:	confidence interval
EASI:	Eczema Area and Severity Index
IL:	interleukin

the Middle East (n = 1),²⁵ and North America (n = 7).²⁶⁻³² Twenty studies examined adults,^{9-15,17,18,20-27,29,30,32} 1 adults and children,³¹ and 1 children.²⁸ Included patients had moderate to severe atopic dermatitis in 15 studies^{9-11,13,15,18,20,23,24-30} and severe atopic dermatitis in 4,^{12,17,21,22} whereas severity was not reported in 3.^{14,31,32} In most studies, the dose of dupilumab was a 600-mg loading dose followed by a maintenance dose of 300 mg every second week (standard dose).^{9,10,15,17,19-24,29,30} Concomitant topical anti-inflammatory therapy was allowed or recommended in 10 studies^{9-11,15,18,21-24,30} and not allowed in 1,¹⁷ and no information was given in 11.^{12-14,20,25-29,31,32} All studies were of good (n = 6) or fair (n = 16) quality. For further details on each study, see Supplemental Table I.

Efficacy of dupilumab

Mean percentage reduction in EASI score. Mean percentage reduction in EASI score after treatment with dupilumab was presented in 8 studies including 659 atopic dermatitis patients (Table I, Fig 1). The weighted mean reduction was 54.1% (95% CI 41.1%-67.0%) after 4 weeks (4 studies, 303 patients),^{9,10,15,23} and 71.9% (95% CI 66.2%-77.6%) after 12 weeks (4 studies, 364 patients).^{9,10,14,23} One study with 82 patients found a median reduction in EASI score of 71% after 12 weeks.¹¹ The weighted mean reduction in EASI score was 69.6% (95% CI 60.0%-79.2%) after 16 weeks (4 studies, 357 patients),^{15,20,23,24} 79% after 24 weeks (1 study, 70 patients),¹⁸ and 95.5% after 52 weeks (1 study, 17 patients).²⁰

Proportion of atopic dermatitis patients achieving 50% improvement in EASI score. Seven studies including 557 atopic dermatitis patients presented data on the proportion of patients achieving 50% EASI score improvement (Table I, Fig 2).^{10,11,14,15,17,21,23} The pooled proportion was 73.1% (95% CI 58.2%-85.7%) of 291 patients after 4 weeks (4 studies),^{10,15,17,23} 77.2% (95% CI 72.1%-82.0%) of 424 patients after 12 weeks (4 studies),^{10,11,14,23} 85.1% (95% CI 80.3%-89.2%) of 245 patients after 16 weeks (2 studies),^{15,23} and 88.9% of 10 patients after 20 to 28 weeks (1 study).²¹

Proportion of atopic dermatitis patients achieving 75% improvement in EASI score. Seven studies including 564 atopic

dermatitis patients presented data on proportion of patients achieving 75% EASI score improvement (Table I, Fig 2). The pooled proportion was 33.6% (95% CI 17.2%-52.4%) of 281 patients after 4 weeks (3 studies),^{10,15,23} 59.0% (95% CI 48.2%-69.4%) of 434 patients after 12 weeks (5 studies),^{10,11,14,21,23} 59.8% (95% CI 53.9%-65.7%) of 262 patients after 16 weeks (3 studies),^{15,20,24} 88.9% of 10 patients after 20 to 28 weeks (1 study),²¹ and 100% of 17 patients after 52 weeks (1 study).²⁰

Proportion of atopic dermatitis patients achieving 90% improvement in EASI score. Six studies including 482 atopic dermatitis patients presented data on proportion of patients achieving 90% EASI score improvement (Table I, Fig 2). The pooled proportion was 10.0% (95% CI 2.5%-21.8%) of 281 patients after 4 weeks (3 studies),^{10,15,23} 28.5% (95% CI 20.6%-37.1%) of 352 patients after 12 weeks (4 studies),^{10,14,21,23} 26.8% (95% CI 20.2%-33.8%) of 262 patients after 16 weeks (3 studies),^{15,20,23} 55.6% of 10 patients after 20 to 28 weeks (1 study),²¹ and 75.0% of 17 patients after 52 weeks (1 study).²⁰

Investigator Global Assessment score of 0/1. Three studies including 270 atopic dermatitis patients presented data on proportion of patients achieving Investigator Global Assessment score 0/1 (Table I). Investigator Global Assessment score 0/1 was achieved by 61% of 19 patients after 16 weeks (1 study)¹³ and by 32% of 187 patients after an undefined treatment period (1 study).²⁷ One study grouped atopic dermatitis patients according to allergic contact dermatitis status and found that 48% of 33 atopic dermatitis patients with unsuspected allergic contact dermatitis, 57% of 17 atopic dermatitis patients with confirmed allergic contact dermatitis, and 73% of 14 atopic dermatitis patients with suspected allergic contact dermatitis achieved Investigator Global Assessment score 0/1 after an undefined treatment period.²⁶

For information on mean percentage reduction in scores for Scoring Atopic Dermatitis, Dermatology Life Quality Index, Patient-Oriented Eczema Measure, Pruritus Visual Analog Scale, and Pruritus Numerical Rating Scale, and for drug survival, see Table I and the Supplemental text.

Adverse events of dupilumab

The most commonly reported adverse event during dupilumab therapy was conjunctivitis (Table II, Fig 3), which was reported by a pooled proportion of 26.1% (95% CI 17.8%-35.4%) of 908 atopic dermatitis patients (14 studies).^{9-13,15,18,20-23,28-30} The pooled proportion was higher in Europe (30.8% [95% CI 20.6%-42.1%]; 650 patients; 10 studies),^{10-13,15,18,20-23}

Table I. Efficacy outcomes after dupilumab treatment in atopic dermatitis patients

Country	Publication	Time, weeks	Total no. of patients	EASI reduction, mean, %	Proportion achieving EASI-50, %	Proportion achieving EASI-75, %	Proportion achieving EASI-90, %	Proportion achieving IGA 0/1, %	SCORAD reduction, mean, %	DLQI reduction, mean, %	POEM reduction, mean, %	P-VAS reduction, mean, %	24-Hour P-NRS reduction, mean, %	7-Day P-NRS reduction, mean, %
Denmark	Olesen (2019)	4	34	72.4	82.4	58.8	23.5	—	—	—	—	70.3	—	—
		12	30	76.7	90.0	63.3	33.3	—	—	—	—	67.5	—	—
France	Faiz (2019)	12	82	71.3*	72.0	48.8	—	—	52.5 [†]	—	—	—	—	—
France	Tauber (2019)	16	19	—	—	—	—	61.0	55.0 [†]	—	—	—	—	—
Germany	Weidinger (2019)	12	174	74.2	77.1	57.1	25.7	—	—	64.7	53.0	—	—	—
Italy	Fargnoli (2019)	4	109	54.2	59.6	28.4	9.3	—	—	52.9	—	—	51.5	—
		16	109	72.5	87.2	60.6	32.4	—	—	69.1	—	—	69.5	—
	Ferrucci (2019)	4	67	—	—	—	—	—	—	—	55.0	—	—	—
		16	25	—	—	—	—	—	—	—	60.0	—	—	—
Italy	Pistone (2019)	4	10	—	100	—	—	—	—	75.0	—	—	—	—
Japan	Uchida (2019)	4	22	43.5	—	—	—	—	—	—	—	—	—	—
		12	22	69.2	—	—	—	—	—	—	—	—	—	—
Spain	Armario-Hita (2019)	24	70	79.3	—	—	—	—	69.3	62.8	—	69.9	—	—
		52	12	—	—	—	—	—	82.3	89.5	—	74.7	—	—
Spain	Fernandez (2019)	16	17	72.1	—	55.0	18	—	—	—	—	—	—	—
		52	17	95.5	—	100	75	—	—	—	—	—	—	—
Sweden	Ivert (2019)	12	10	—	—	88.9	60.0	—	—	—	—	—	—	—
		20–28	10	—	88.9	88.9	55.6	—	—	—	—	—	—	—
Netherlands	Ariens (2019)	4	138	51.1	62.7	20.1	3.0	—	—	—	—	—	—	28.3
		8	138	64.8	81.7	44.3	13.0	—	—	—	—	—	—	45.3
		12	138	68.4	82.7	55.6	23.3	—	—	—	—	—	—	48.8
		16	136	73.1	85.7	61.7	24.1	—	—	—	—	—	—	53.5
Netherlands	De Wijs (2019)	16	95	61.0	—	—	—	—	—	66.0	53.0	—	57.0	41.0
USA	Chipalkatti (2019a)	—	17 [‡]	—	—	—	—	57.0	—	—	—	—	—	—
	Chipalkatti (2019b)	—	14 [§]	—	—	—	—	73.0	—	—	—	—	—	—
	Chipalkatti (2019c)	—	33	—	—	—	—	48.0	—	—	—	—	—	—
USA	Eichenfield (2019)	—	187	—	—	—	—	32.0	—	—	—	—	—	—
Pooled outcome		4		54.1	73.1	33.6	10.0	—	—	55.0	—	—	—	—
		12		71.9	77.2	59.0	28.5	—	—	—	—	—	—	—
		16		69.6	85.1	59.8	26.8	—	—	67.7	54.5	—	63.7	48.4

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, percentage of patients achieving 50% EASI score improvement; EASI-75, percentage of patients achieving 75% EASI score improvement; EASI-90, percentage of patients achieving 90% EASI score improvement; IGA, Investigator Global Assessment; P-NRS, Pruritus Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; P-VAS, Pruritus Visual Analog Scale; SCORAD, Scoring Atopic Dermatitis; USA, United States; —, data not reported in the article.

*Median EASI score reduction.

[†]Median SCORAD score reduction.

[‡]Atopic dermatitis patients with confirmed allergic contact dermatitis.

[§]Atopic dermatitis patients with suspected allergic contact dermatitis.

^{||}AD patients with no suspicion of allergic contact dermatitis.

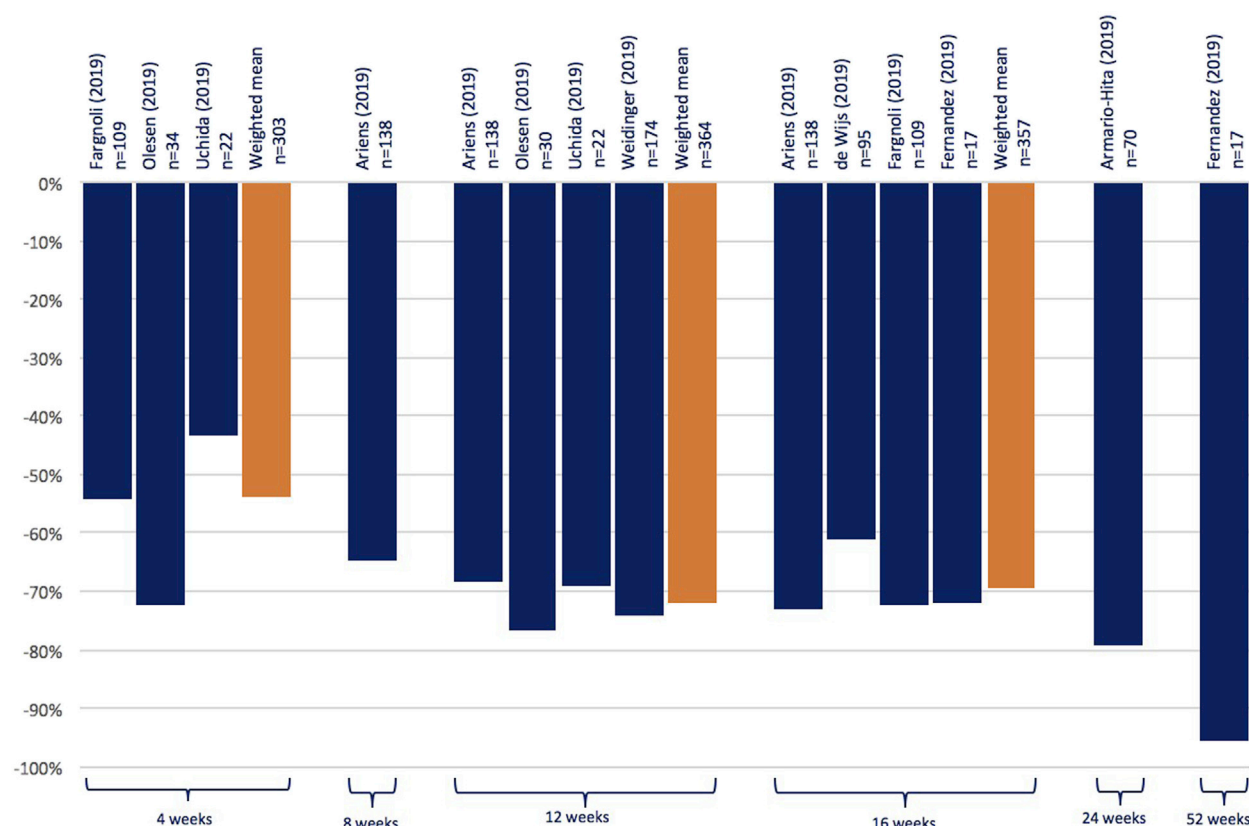


Fig 1. Mean percentage change in Eczema Area and Severity Index score after dupilumab treatment in atopic dermatitis patients.

and Asia (36.4%; 22 patients; 1 study)⁹ than in North America (11.2% [95% CI 6.3%-17.4%]; 236 patients; 3 studies).²⁸⁻³⁰ North American studies had a short (7.8 weeks)²⁹ or unknown follow-up period³⁰ or comprised a pediatric-only population.²⁸ In 4 studies, conjunctivitis was diagnosed by an ophthalmologist.^{13,21,23,29} Conjunctivitis was diagnosed by an investigator in 84 French atopic dermatitis patients (38.2%). Of these, 38 patients consulted an ophthalmologist, who confirmed conjunctivitis in 32 (82.1%).¹¹ In most studies, the type of conjunctivitis was not described in detail.^{9,10,13,15,18,20,22,23,30} Among 240 French atopic dermatitis patients, 38.1% developed unspecific noninfectious conjunctivitis and 1.9% developed infectious conjunctivitis.¹¹ Among 48 US atopic dermatitis patients, 18.8% developed allergic conjunctivitis diagnosed by an ophthalmologist.²⁹ In 138 French atopic dermatitis patients with conjunctivitis, 42.6% were considered to have mild disease and 57.4% moderate to severe disease.²³ Time until conjunctivitis occurred after initiation of dupilumab was reported in a Dutch study (138 patients), with a median time of 56 days²³; a Japanese study (22 patients), with a range of 2 to 6 weeks⁹; and a Swiss study (10 patients), with a median time of 6 weeks.²²

Several studies reported information on history of conjunctivitis before dupilumab therapy.^{9-13,18,21,23} Development of conjunctivitis was observed more often in patients with a history of allergic conjunctivitis (57.3%) than in those without one (35.7%).¹¹ Of Dutch patients who developed conjunctivitis, 76.1% had a history of it, and a history of conjunctivitis was more common in patients who developed moderate to severe conjunctivitis (84.6%) than mild conjunctivitis (65.0%).²³ Most studies reported that conjunctivitis was treatable and did not lead to discontinuation of dupilumab.^{9,10,13,15,20,21,23,28} However, among 241 patients, 4.2% discontinued dupilumab because of noninfectious ocular disease.¹¹ For more information on conjunctivitis in each study, see Supplemental Table I.

Blepharitis was reported by a pooled proportion of 9.6% (95% CI 3.4%-18.6%) of 493 atopic dermatitis patients (5 studies).^{11,21,23,29,30} Keratitis was reported by a pooled proportion of 6.2% (95% CI 3.8%-9.1%) of 307 atopic dermatitis patients (3 studies).^{11,21,30} Overall, ocular surface disease was reported by a pooled proportion of 45.2% (95% CI 31.2%-59.6%) of 387 atopic dermatitis patients (4 studies).^{11,24,25,31}

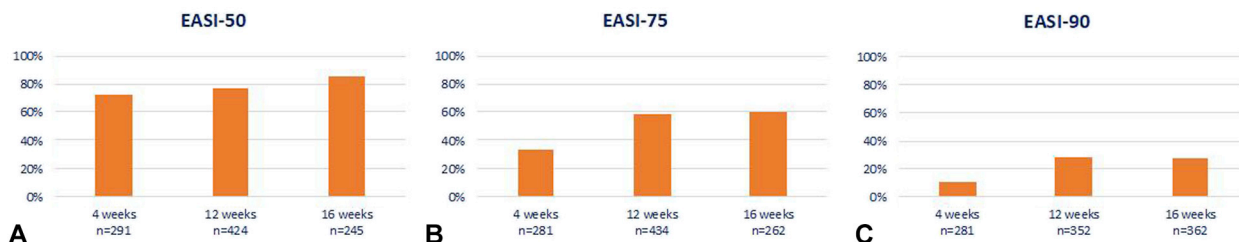


Fig 2. Pooled proportion of atopic dermatitis patients achieving 50%, 75%, and 90% improvement in the Eczema Area and Severity Index score (EASI-50, EASI-75, and EASI-90, respectively) after dupilumab treatment. **A**, Pooled proportion of atopic dermatitis patients achieving EASI-50 after 4, 12, and 16 weeks. **B**, Pooled proportion of atopic dermatitis patients achieving EASI-75 after 4, 12, and 16 weeks. **C**, Pooled proportion of atopic dermatitis patients achieving EASI-90 after 4, 12, and 16 weeks.

Herpes simplex virus was reported by a pooled proportion of 5.8% (95% CI 3.3%-9.0%) of 546 atopic dermatitis patients (6 studies).^{11,20,21,23,24,30} Three studies reported cases of nonocular herpes simplex virus,¹¹ reactivation of herpes uveitis,²¹ and reactivation of orofacial herpes simplex virus,²⁶ and 3 studies gave no information about location of herpes simplex virus.^{20,23,30} Injection site reactions were reported by a pooled proportion of 5.3% (95% CI 3.1%-8.0%) of 669 atopic dermatitis patients (7 studies),^{9,11,15,22,23,28,29} and headache was reported by a pooled proportion of 5.5% (95% CI 1.8%-11.0%) of 484 atopic dermatitis patients (4 studies).^{11,15,20,23}

Rare adverse events of interest included facial redness, alopecia, and arthralgia. Facial redness was reported in 5.4% of 111 US patients in 1 study²⁸ and in 10.6% of 85 US patients in 1 study.³¹ Alopecia was reported in 3.6% of 138 Dutch patients²³ and in less than 1% of 138 French patients.¹¹ Arthralgia was reported in 1.8% of 109 Italian patients.¹⁵

DISCUSSION

Main findings

This systematic review and meta-analysis provided real-world efficacy and safety data for dupilumab therapy in adults with atopic dermatitis. Most data were generated in Europe and the United States and had relatively short follow-up time. Dupilumab was effective and well tolerated, but ocular adverse events were commonly reported and were the main reason for discontinuation.

Interpretation

The efficacy of dupilumab treatment in atopic dermatitis patients was overall consistent with results of clinical trials.³³ The pooled proportion of patients achieving 50%, 75%, and 90% EASI score improvement was 85.1%, 59.8%, and 26.8%, respectively, after 16 weeks of treatment compared with 65% to 80%, 44% to 69%, and 30% to 40% in clinical trials.^{6,34}

A weighted mean reduction in EASI score of 69.6% was observed after 16 weeks of treatment compared with 69.1% to 72.0% in clinical trials.³³ Clinical trials of dupilumab required a washout period of topical and systemic therapies before randomization and were mostly monotherapy trials. However, in clinical practice, patients often continue other systemic and topical therapies. Furthermore, nontrial patients may have had disease of overall milder severity compared with those in clinical trials. Despite these differences, clinical trials and real-world studies have shown an overall consistency on the efficacy of dupilumab.

Time to onset of action was relatively fast, with effect after 4 weeks of treatment, but with improvement through week 16 (Fig 2). Drug survival was high, which indicates that dupilumab is well tolerated and effective, but this may also be due to the absence of other available effective treatments in partial responders or those with mild or moderate adverse events.

The safety profile of dupilumab was overall consistent with data from clinical trials.³⁵ Injection site reactions, headache, and herpes simplex virus infections were recorded, whereas more recently reported adverse events such as alopecia areata, arthritis, and facial redness only were mentioned in 2 studies or fewer.^{11,15,23,31} Although dupilumab has been shown to directly inhibit T helper cell type 2 as well as T helper cell type 17/22 axes (indirectly), it does not affect T helper cell type 1 responses.³⁶ Paradoxical T helper cell type 1 immune activation after inhibition of type 2 inflammation is possible, but expected to be uncommon.^{37,38} There is a need for better characterization of immune responses (eg, dupilumab therapy has been associated with improvement of both alopecia areata and coincidental alopecia areata cases).^{9,11,23,39} Facial redness after dupilumab therapy has been observed by clinicians, but the mechanism is currently

Table II. Adverse events reported after dupilumab treatment in atopic dermatitis patients

Country	Publication	Time, weeks	Total no. of patients	Ocular surface disease, %	Conjunctivitis, %	Blepharitis, %	Keratitis, %	Herpes simplex virus, %	Injection site reaction, %	Headache, %
Denmark	Olesen (2019)	12	30	—	18.4	—	—	—	—	—
France	Faiz (2019)	12	241	48.6	38.2	14.1	6.4	5.3	9.2	2.9
France	Maudinet (2019)	24	18	—	27.0	—	—	—	—	—
France	Tauber (2019)	16	18	—	44.4	—	—	—	—	—
Israel	Nahum (2019)	16	37	43.2	—	—	—	—	—	—
Italy	Fargnoli (2019)	16	109	—	11.0	—	—	—	1.8	1.8
Japan	Uchida (2019)	6	22	—	36.4	—	—	—	4.5	—
Spain	Amario-Hita (2019)	24	70	—	8.6	—	—	—	—	—
	Ruiz-Villaverde (2019)	52	30	—	16.6	—	—	—	—	—
Spain	Fernandez (2019)	52	17	—	41.2	—	—	11.8	—	11.8
Sweden	Ivert (2019)	20–28	10	—	70.0	30.0	10.0	20.0	—	—
Switzerland	Bersuch (2018)	6	12	—	50.0	—	—	—	8.3	—
Netherlands	Ariens (2019)	16	138	—	34.1	2.9	—	2.9	5.1	10.1
Netherlands	De Wijs (2019)	16	95	62.0	—	—	—	8.4	—	—
USA	Igelman (2019)	36	111*	—	9.0	—	—	—	2.7	—
USA	Raffi (2019)	7.8	48	—	18.8	22.9	—	—	4.2	—
USA	Waldman (2019)	—	85	27.1	—	—	—	—	—	—
USA	Wang (2019)	—	77	—	7.8	2.6	3.9	2.6	—	—
Pooled proportion				45.2	26.1	9.6	6.2	5.8	5.3	5.5

USA, United States.

*Pediatric patients.

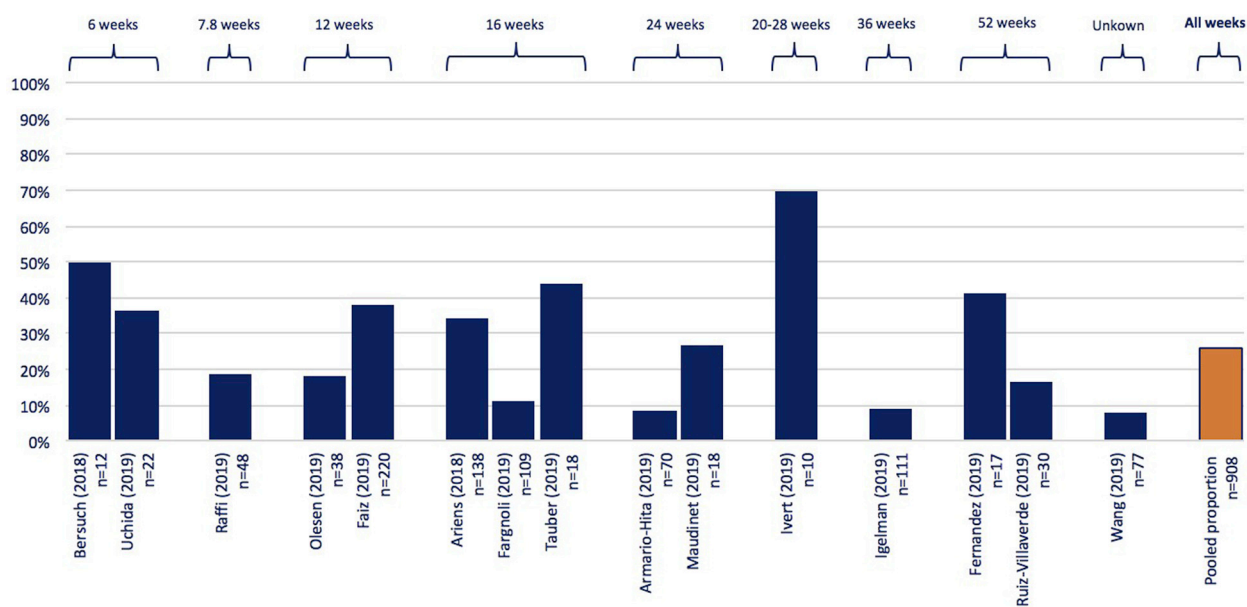


Fig 3. Proportion of atopic dermatitis patients with conjunctivitis as an adverse event after dupilumab treatment.

unknown, although several hypotheses have been suggested.^{40,41}

Conjunctivitis was generally prevalent, being recorded for 26.1% of dupilumab-treated atopic dermatitis patients compared with 8% in pooled data from clinical trials.³⁵ Although it is currently not possible to predict who will develop conjunctivitis during treatment with dupilumab, patients with a history of allergic conjunctivitis seem to have a higher risk.¹¹ There is anecdotal evidence that prophylactic use of artificial tears may reduce the risk of conjunctivitis.^{42,43} The mechanism behind dupilumab-induced conjunctivitis is currently unknown, and the increased occurrence of blepharitis needs to be better understood. Possible mechanisms involve colonization with *Demodex*, leading to IL-17–driven inflammation,⁴⁴ increased level of eosinophil counts because an increase in eosinophilic factors was observed in tears and mucus of patients with atopic keratoconjunctivitis,⁴⁵ and increased activity of ligands (eg, OX40 ligand) involved in atopic keratoconjunctivitis.⁴⁶

Uncommon events are normally not captured in clinical trials because of limited follow-up and low number of patients. Registries that systematically collect efficacy and safety measures are necessary because these may identify rare events. Treatment of Atopic Eczema (TREAT) Register Taskforce is an international network of registries that collects, in a standardized method, observational data of atopic dermatitis patients treated in routine daily practices.⁴⁷

LIMITATIONS

Limited data in terms of size and follow-up time were available, which may result in underestimations or overestimations of the efficacy of dupilumab and reporting of important adverse events. Most studies were conducted in Europe and North America, limiting generalization. Monitoring bias is a concern because investigators may have treated patients more frequently for the purpose of collecting data on dupilumab. This may improve adherence among patients. Because of the nature of real-world studies, there was no uniformity between studies regarding previous allowed therapies or concomitant therapies. Definition and assessment of adverse events varied across studies, with only a few studies reporting detailed information. Also, it is currently unclear which adverse events can be regarded as adverse effects. Uncommon adverse events may not have been detected because of the short follow-up period and number of patients included. Because dupilumab has been approved for only a few years, it is possible that only a small number of patients with multiple

morbidities have been treated. Furthermore, because of the known ocular adverse events, clinicians might be restrictive in prescribing dupilumab to atopic dermatitis patients with severe ocular diseases.

CONCLUSION

According to real-world data, the efficacy of dupilumab to treat adult atopic dermatitis was successful, with no short-term safety signals besides conjunctivitis, blepharitis, injection site reactions, and herpes simplex virus. There is a continuous need for registries to monitor common and uncommon serious adverse events.

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