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Ineffectiveness in head-and-neck dermatitis

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ORIGINAL ARTICLE

A nationwide 104 weeks real-world study of dupilumab in adults with atopic dermatitis: Ineffectiveness in head-and-neck dermatitis

Ida Vittrup[1,2] | Niels Steen Krogh[3] | Henrik Hedegaard Pliess Larsen[1,2] | Jesper Elberling[2] | Lone Skov[2] | Kristina Sophie Ibler[4] | Gregor B. E. Jemec[4] | Charlotte G. Mortz[5] | Rasmus Overgaard Bach[5] | Carsten Bindslev-Jensen[5] | Maiken Glud Dalager[6] | Alexander Egeberg[1] | Tove Agner[1] | Mette Deleuran[7] | Christian Vestergaard[7] | Jacob Pontoppidan Thyssen[1]

[1]Department of Dermatology, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Copenhagen, Denmark

[2]Department of Dermatology and Allergy, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark

[3]ZiteLab ApS, Frederiksberg, Denmark

[4]Department of Dermatology, Zealand University Hospital, University of Copenhagen, Roskilde, Denmark

[5]Department of Dermatology and Allergy Center, Odense University Hospital, Odense, Denmark

[6]Department of Dermatology, Aalborg University Hospital, Aalborg, Denmark

[7]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

Correspondence
Jacob P. Thyssen, Department of Dermatology and Venereology, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Copenhagen, Denmark.
Email: jacob.pontoppidan.thyssen@regionh.dk

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Abstract

Background: Evaluation of effectiveness and safety of new systemic treatments for atopic dermatitis (AD) after approval is important. There are few published data exceeding 52-week therapy with dupilumab.

Objectives: To examine the safety, effectiveness and drug survival of dupilumab in a Danish nationwide cohort with moderate-to-severe AD up to 104 weeks exposure.

Methods: We included 347 adult patients with AD who were treated with dupilumab and registered in the SCRATCH registry during 2017–2022.

Results: At all visits, we observed improvement in AD severity measured by Eczema Area and Severity Index (EASI) [median (IQR)]. EASI score at baseline was 18.0 (10.6–25.2), at week 4: 6.5 (3.5–11.6), at week 16: 3.7 (1.2–6.2), at week 52: 2.0 (0.8–3.6), at week 104: 1.7 (0.8–3.8). While drug survival was high (week 52: 90%; week 104: 86%), AD in the head-and-neck area remained present in most patients at high levels; proportion with head-and-neck AD at baseline was 76% and 68% at week 104. 35% of patients reported any AE. Conjunctivitis was the most frequent (25% of all patients) and median time to first registration of conjunctivitis was 201 days.

Conclusions: While 2-year drug survival was 86%, dupilumab was unable to effectively treat AD in the head-and-neck area, and conjunctivitis was found in 25% of patients.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease that is common in adults.[1] Most patients obtain disease control with trigger avoidance, and frequent use of emollients and anti-inflammatory topical treatments. However, some patients need systemic therapy to reduce AD activity and severity. A few systemic immunomodulating drugs have traditionally been used for the treatment of AD including methotrexate and azathioprine, although only cyclosporine is approved in Europe.

Dupilumab, a monoclonal antibody targeting the IL-4Rα-subunit of the IL4 and IL13-receptor, reduces type 2 inflammation. In January 2018, dupilumab was approved in Denmark for treatment of adults with moderate-to-severe AD. Real-world evidence studies have confirmed the

short-term effectiveness and safety of dupilumab in adults with AD.[2–5] However, few studies have so far investigated the same daily-practice parameters and drug survival beyond 52-weeks' follow-up, and none have been based on nationwide complete datasets.[6–9]

We examined the short- and long-term safety, effectiveness and drug survival of dupilumab treatment in a Danish nationwide cohort of patients with moderate-to-severe AD. The cohort is embedded in the prospective, multicentre Severe and ChRonic Atopic dermatitis Treatment CoHort (SCRATCH) registry, including virtually all Danish patients treated with dupilumab for AD.[10] The register complies with TREatment of ATopic eczema (TREAT) Registry Taskforce recommendations.[11]

MATERIALS AND METHODS

Study design and population

Baseline characteristics of adult patients in the SCRATCH registry have previously been described.[10] For the present study, we included all dupilumab-treated adult patients registered in the SCRATCH registry between October 2017 (with special approval from the Danish Medicines Agency, three patients started early access treatment in October 2017) and March 2022 in Danish dermatology departments. Participants who went directly from a clinical trial of dupilumab and into regular treatment were excluded. Informed consent was obtained from all patients.

Patients with AD were enrolled at treatment initiation by the treating physician (dermatologists or residents in dermatology) and followed over time. At all clinical visits, physicians and patients completed detailed information on AD severity (Eczema Area and Severity Index [EASI]), AD localization, Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Numerical Rating Scale (NRS) 72 h mean pruritus, and NRS 72 h mean degree of sleep loss, and adverse events (AE). Clinical visit frequency would vary between centres and patients, especially during COVID-19 pandemic. Visits were categorized according to time since medication initiation: baseline: day 0 (±2 w); 4 weeks: day 28 (±2 w); 16 weeks: day 112 (±6 w); 52 weeks: day 364 (±6 w); 104 weeks: day 728 (±6 w). If a patient had several visits during a specific time interval, the visit with the shortest date deviation was chosen. Only first treatment series with dupilumab were included in this study (20 later series excluded).[12] Treatment series with <90 days pause, were considered as one series. If a patient changed hospital department, then a 120 days-registration pause was allowed.

Statistics

Summary statistics were generated and expressed as median and interquartile range, or numbers and frequencies. Effectiveness outcomes were evaluated at baseline, weeks 4, 16, 52 and 104 and included absolute EASI, POEM, DLQI, NRS 72 h mean pruritus, and 72 h mean degree of sleep loss scores. Effectiveness was further evaluated according to AD localization, as proportion of patients reporting eczema in different body parts at baseline and follow-up. We also studied the proportion achieving EASI 50, EASI 75, EASI 90, EASI 100, an absolute EASI ≤7, a DLQI score ≤1, an NRS 72 h mean pruritus and degree of sleep loss score ≤1 and a minimum 4-point improvement in NRS 72 h mean pruritus and degree of sleep loss score. Results were stratified according to sex, age and comorbid asthma. Wilcoxon Signed-Rank test was performed to compare differences in continuous non-normally distributed variables between study visits. The Wilcoxon rank sum test was used to compare differences in continuous non-normally distributed variables between the groups. For the four-point improvement frequencies, only patients with a baseline score ≥4 were included. The risk of and time to discontinuation of dupilumab was estimated using unadjusted Kaplan–Meier survival analysis. Patients were censored from the analyses ($n = 28$) if they did not have a study visit registered in the database in 365 days. Kaplan–Meier curves for (1) all-cause discontinuation, (2) discontinuation due to lack of effectiveness and (3) discontinuation due to AEs were generated. If the reason to discontinue dupilumab treatment was unrelated to insufficient treatment response or AEs the patients were censored at time of discontinuation in that specific analysis.

The research project was approved by the Danish Data Protection Agency (Approval number P-2019-746). Approval by the National Committee on Health Research Ethics was not required as the study does not include research on biological material.

All data management and analysis were performed using SAS Studio 3.8 (Enterprise Edition) and R version 4.1.3.

RESULTS

The study included 347 adult AD patients (60% males) in their first dupilumab treatment series (Table 1). The median (IQR) age at baseline was 42 (29–55) years. Median EASI score at baseline was 18.0 (10.6–25.2). Most (81%) patients had been treated with at least two traditional systemic medications before initiating dupilumab. At baseline, 92% of patients were treated with concomitant topical treatment, mostly moderately potent and/or potent topical corticosteroid. The most commonly reported anatomical area affected by AD at baseline was head-and-neck (76%) and truncal area (72%).

Safety

196 AEs were registered in 121 patients (121/347, 35%) (Table 2). Most (141/196, 72%) were considered related to dupilumab treatment. Median time from treatment initiation to registration of an AE was 243 (112–477) days. The

TABLE 1 Baseline characteristics of 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment

	Dupilumab (n = 347)
Age, median (IQR)	42 (29–55)
Male sex, n (%)	209 (60.2)
BMI, median (IQR)[a]	25.4 (22.7–29.1)
Age at AD onset, median (IQR)[b]	1.0 (0.0–6.0)
Current asthma, n (%)[c]	136 (53.1)
Current rhinitis, n (%)[b]	160 (63.8)
Current allergic conjunctivitis, n (%)[d]	32 (17.9)
Previous systemic treatments, n (%)[e]	
Azathioprine	193 (73.1)
Methotrexate	201 (76.1)
Prednisolone	138 (52.3)
Cyclosporine	78 (29.5)
Mycophenolate mofetil	47 (17.8)
Two or more	213 (80.7)
Concomitant topical treatment, n (%)[f]	137 (91.9)
EASI, median (IQR)[g]	18.0 (10.6–25.2)
POEM, median (IQR)[h]	21.0 (16.0–25.0)
DLQI, median (IQR)[i]	13.0 (7.0–19.0)
72 h mean pruritus (NRS 0–10), median (IQR)[j]	8.0 (6.0–9.0)
72 h mean degree of sleep loss (NRS 0–10), median (IQR)[g]	6.0 (4.0–8.0)

Abbreviations: BMI, body mass index (kg/m^2); DLQI; dermatology life quality index; EASI, eczema area and severity index; IQR, interquartile range; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure.

Results are based on patients with non-missing data: [a]N = 246, [b]N = 251, [c]N = 256, [d]N = 179, [e]N = 264, [f]N = 149, [g]N = 274, [h]N = 267, [i]N = 253, [j]N = 275.

most frequently reported AE was eye problems (132/196, 67%), with conjunctivitis as the most common diagnosis (119/196, 61%). Conjunctivitis affected a total of 25% (88/347) and with the first recording in the registry after a median of 201 days. Seven per cent (14/196) of recorded AEs related to skin problems including e.g. facial eczema, rosacea, injection site reactions and urticaria. Twelve AEs (12/196, 6%) were infections, most frequently staphylococcal and herpes simplex infections. Five per cent (9/196) of AE reports were related to headache or migraine. Nausea/vomiting, fatigue and muscle pain were infrequently (2%) reported.

Effectiveness

A significant improvement in median EASI score was observed at all follow-up study visits (baseline: 18.0 [n = 274]; W4: 6.5 [n = 72]; W16: 3.7 [n = 201]; W52: 2.0 [n = 124]; W104: 1.7 [n = 60]; p < 0.0001 for all) compared to baseline (Table 3 and Figure 1). A steep decrease in severity was seen over the first 4 to 16 weeks hereafter the severity plateaued. Similar observations were made for median POEM, DLQI, NRS 72 h itch, and 72 h sleep scores. Thirteen per cent had achieved a complete remission of their AD after 104 weeks of dupilumab treatment, while 44% and 32% had achieved a DLQI score ≤1 and 72 h mean pruritus score ≤1, respectively (Table 3 and Figure 1). The proportion of patients that achieved an absolute EASI≤7 increased over time reaching about 90% after 52 and 104 weeks (Table 3 and Figure 1). Patients who had tried at least two systemic medications before initiating dupilumab had a slightly better effectiveness response at week 16 (3.0 [n = 144] and 6.0 [n = 19], p = 0.024) and week 52 (1.6 [n = 82] and 3.2 [n = 10], p = 0.028; Figure S1). The proportion using concomitant topical treatment decreased to 74% of patients at 104 weeks follow-up (data not shown). Over the study period, much lower proportions of patients reported AD in most body regions, for example, 55% reporting hand dermatitis at baseline and only 24% at 104 weeks follow-up (Figure 2). However, eczema in the head-and-neck area seemed to persist and more than 2/3 of patients still had AD in this area after 2 years of dupilumab treatment (Figure 2).

A higher proportion of women reached EASI improvement measures at most study visits (Table S1 and Figure S2). Women had a strong initial response in relation to itch and sleep loss scores, with almost 80% achieving a 4-point improvement after 4 weeks, but the effect decreased afterwards.

Patients older than 60 years seemed to have a slightly delayed EASI response after 4 weeks, but at 16 weeks it was similar to patients under 60 years of age (Table S2 and Figure 1). Patients in the youngest age group had significantly higher DLQI, POEM and itch scores at week 16 compared to the middle-aged group, and for POEM and itch scores also at week 52 (Table S2).

Patients with current asthma had significantly higher baseline and week 4 EASI scores compared to patients without asthma (W4: current: 7.1; never/previously: 3.4, p = 0.012) (Table S3 and Figure S3). Patients with comorbid asthma had less improvement in EASI scores at all visits, except at week 104 where similar effects were observed.

Discontinuation and drug survival

Forty-one patients (12%) discontinued dupilumab treatment during the study period (Table S4). Of these, 39% discontinued due to AEs, while 20%, and 17% discontinued due to insufficient effect and pregnancy, respectively. The reasons for the remaining 10 discontinuations were, respectively, AD improvement, patient demand, other or missing. Median treatment duration of those who discontinued was 229 days, while it was shorter if the discontinuation was due to AEs (215 days) or insufficient effect (137 days). Dupilumab therapy was retained in 90% and 86% after 52 and 104 weeks, respectively (Figure 3).

Drug adjustments

We observed 31 dose switches in 28 patients after a median of 473 days (IQR 213–659). Of the 28 first-adjustments, 17

TABLE 2 Adverse events registered during 104 weeks follow-up in Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment stratified on registration in weeks 0–52 and weeks 52–104

	Dupilumab (n = 347)			
	All	Weeks 0–52	Weeks 52–104	Treatment duration, median (IQR)
Number of AEs registered, n (%)	196 (100.0)	126 (64.3)	70 (35.7)	243 (112–477)
Patients with AE registered, n (%)	121 (34.9)	89 (25.6)	55 (15.9)	
Relation to treatment, physician-judged, n (%)				
Related to dupilumab	141 (71.9)	92 (73.0)	49 (70.0)	
Related to standard treatment	4 (2.0)	NA	NA	
Unknown	18 (9.2)	7 (5.6)	11 (15.7)	
Missing	33 (16.8)			
AE types, n (%)				
Eye problems	132 (67.3)	84 (66.7)	48 (68.6)	265 (119–467)
Conjunctivitis	119 (60.7)	74 (58.7)	45 (64.3)	283 (122–469)
Skin problems	14 (7.1)	6 (4.8)	8 (11.4)	403 (150–570)
All infections	12 (6.1)	9 (7.1)	3 (4.3)	222 (136–365)
Headache/migraine	9 (4.6)	NA	NA	150 (112–227)
Nausea, vomiting	4 (2.0)	NA	NA	287 (238–431)
Fatigue	3 (1.5)	NA	NA	126 (112–567)
Muscle pain	3 (1.5)	NA	NA	511 (57–700)
Other (unspecified)	6 (3.1)	NA	NA	78 (72–111)
NA (each <3 observations)[a]	6 (3.1)	NA	NA	211 (112–532)
Missing		7 (3.6)		248 (112–623)

Abbreviation: NA, not applicable.

aCovers joint pain, dryness of mouth, pulmonary symptoms and influenza feeling.

patients had their dose increased or their treatment interval reduced, mostly to 300 mg every week or injection every 10th day. The adjustments were made after a median of 434 days (IQR 224–680). One later discontinued treatment due to insufficient effect. Eleven patients had their dose reduced or their dosing interval increased after a median of 497 days. Most to 300 mg every third week, but 3 of these patients later had the dosing switched back to standard dosing. One discontinued treatment after being decreased in dose due to pregnancy/wish for pregnancy. In both groups, the median baseline EASI score was 18.7, but at 16 weeks follow-up the score was 5.6 (n = 13) vs 3.0 (n = 6, p = 0.044) for later increased and decreased, respectively.

Dupilumab restarters

In the study period, 18 patients restarted dupilumab (second series) and 2 later started a third series. The baseline EASI score decreased from 18.0 in the first series to 11.9 in the restart series. The absolute EASI response in the restarted series mimicked the initial dupilumab response, while there seemed to be some effectiveness loss in the itch response in the restart series (Figure S4).

DISCUSSION

Main findings

In this 104 weeks real-world study of 347 patients with AD initiating dupilumab treatment, 35% reported an AE with conjunctivitis being far the most frequent. Dupilumab treatment led to maintained reductions in clinical and patient-reported outcome measures, but proportion of patients with AD in the head-and-neck area remained very high. Most had long-term treatment persistence, with 86% of patients persisting with dupilumab treatment at 104 weeks follow-up.

Safety

Thirty-five per cent of our patients reported AEs in the 2-year follow-up, which is similar to 32–35% in three studies with 1 year follow-up from Italy and Portugal,[13–15] but lower than 61% observed in a Czech study with 2-year follow-up.[7] One in four patients reported conjunctivitis, which is comparable to other studies with long follow-up,[5,6,13,15,16] while also markedly higher than selected studies with up to 2-year follow-up.[9,14,17] Differences in reporting patterns and specific focus on conjunctivitis and preventive initiatives with

TABLE 3 Effectiveness outcomes in 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment

	Dupilumab ($N = 347$)				
	Baseline	**Week 4**	**Week 16**	**Week 52**	**Week 104**
EASI					
Median (IQR)	18.0 (10.6–25.2)	6.5 (3.5–11.6)*	3.7 (1.2–6.2)*	2.0 (0.8–3.6)*	1.7 (0.8–3.8)*
EASI 50, *n* (%)		46 (71.9)	156 (88.6)	89 (92.7)	40 (87.0)
EASI 75, *n* (%)		20 (31.3)	107 (60.8)	76 (79.2)	36 (78.3)
EASI 90, *n* (%)		7 (10.9)	47 (26.7)	43 (44.8)	27 (58.7)
EASI 100, *n* (%)		0 (0.0)	6 (3.4)	11 (11.5)	6 (13.0)
Absolute EASI ≤ 7, *n* (%)	37 (13.5)	40 (55.6)	154 (76.6)	112 (90.3)	54 (90.0)
POEM					
Median (IQR)	21.0 (16.0–25.0)	9.0 (5.0–13.0)*	7.0 (3.0–12.5)*	6.0 (3.0–11.0)*	7.0 (4.0–11.5)*
DLQI					
Median	13.0 (7.0–19.0)	5.0 (2.0–8.0)*	3.0 (1.0–8.0)*	2.0 (1.0–5.0)*	2.0 (1.0–6.0)*
Absolute DLQI ≤ 1, *n* (%)	7 (2.8)	13 (21.0)	64 (32.2)	42 (36.2)	28 (44.4)
72 h mean pruritus, NRS					
Median (IQR)	8.0 (6.0–9.0)	3.0 (2.0–5.0)*	2.0 (1.0–4.0)*	2.0 (1.0–5.0)*	2.0 (1.0–5.0)*
Absolute 72 h mean pruritus ≤ 1, *n* (%)	3 (1.1)	11 (18.3)	64 (32.0)	45 (37.8)	20 (31.7)
≥4 points improvement, *n* (%)		35 (71.4)	115 (71.9)	63 (68.5)	35 (66.0)
72 h mean degree of sleep loss, NRS					
Median (IQR)	6.0 (4.0–8.0)	2.0 (0.0–4.0)*	1.0 (0.0–3.0)*	1.0 (0.0–3.0)*	1.0 (0.0–3.0)*
Absolute 72 h mean degree of sleep loss ≤ 1, *n* (%)	40 (14.6)	29 (49.2)	111 (57.2)	70 (59.8)	39 (61.9)
≥4 points improvement, *n* (%)		27 (67.5)	92 (69.2)	50 (65.8)	26 (60.5)

Results are based on patients with non-missing data: EASI: W0 $N = 274$; W4 $N = 72$; W16 $N = 201$; W52 $N = 124$; W104 $N = 60$; POEM: W0 $N = 267$; W4 $N = 64$; W16 $N = 212$; W52 $N = 119$; W104 $N = 64$; DLQI: W0 $N = 253$; W4 $N = 62$; W16 $N = 199$; W52 $N = 116$; W104 $N = 63$; 72 h mean pruritus: W0 $N = 275$; W4 $N = 60$; W16 $N = 200$; W52 $N = 119$; W104 $N = 63$; 72 h mean degree of sleep loss: W0 $N = 274$; W4 $N = 59$; W16 $N = 194$; W52 $N = 117$; W104 $N = 63$.Number of patients with data from a specific visit and baseline: EASI: W4 $N = 64$; W16 $N = 176$; W52 $N = 96$; W104 $N = 46$.

Number of patients with data from a specific visit and baseline and a baseline score of at least 4: 72 h mean pruritus: W4 $N = 49$; W16 $N = 160$; W52 $N = 92$; W104 $N = 53$; 72 h mean degree of sleep loss: W4 $N = 40$; W16 $N = 133$; W52 $N = 76$; W104 $N = 43$.

Abbreviations: DLQI; dermatology life quality index; EASI, eczema area and severity index; IQR, interquartile range; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure.

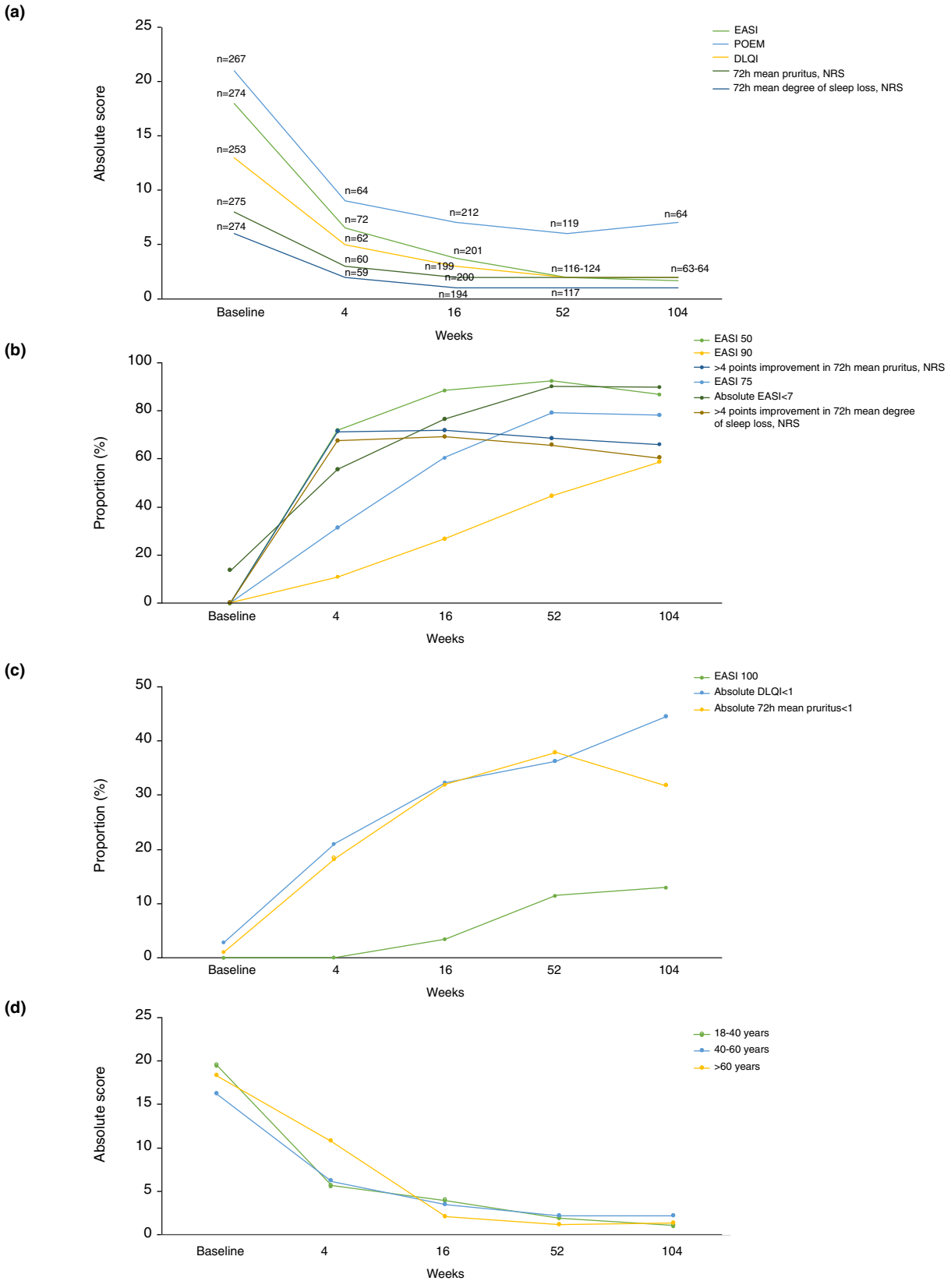
*$p < 0.0001$ compared to baseline.

artificial tears might explain the differences. Consistent with previous results[13] most (66.7%) cases of conjunctivitis were considered mild-to-moderate. The median time to report an ocular AE was much longer in our study, contrasting findings from other studies.[6,13,18,19] In Danish AD treatment guidelines, clinical monitoring is recommended after no later than 16 weeks with dupilumab,[20] which would explain some, but not all, of the delay. Further, Nordic recommendation to promote use of artificial tears when starting dupilumab is likely followed in most centres and is part of the patient information.[21] Importantly, conjunctivitis is also very common in Danish patients who are not treated with dupilumab.[22]

Effectiveness

Other long-term studies support that absolute median EASI scores decrease to approximately 2.0–3.0[5,13,18] after 1-year of treatment with dupilumab and that around 60% of

FIGURE 1 (a) Median EASI, POEM, DLQI, 72 h mean NRS pruritus, and 72 h mean NRS sleep loss at baseline, weeks 4, 16, 52 and 104 in 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment. (b) Proportion achieving EASI 50, EASI 75, EASI 90, EASI < 7, a > 4 points improvement in 72 h mean NRS pruritus and 72 h mean NRS degree of sleep loss, an absolute 72 h mean pruritus and sleep loss score < 1 at baseline, weeks 4, 16, 52 and 104 in 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment. (c) Proportion achieving a deep response (EASI 100, DLQI < 1, itch < 1) at weeks 4, 16, 52 and 104 in 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment. (d) Median EASI at baseline, weeks 4, 16, 52 and 104 in 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment stratified by age group. DLQI; dermatology life quality index; EASI, eczema area and severity index; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure.



patients has achieved EASI 90 after 104 weeks of therapy.[9] Importantly, while we only identified few patients with AEs related to facial redness or rosacea-like inflammation, we observed that the proportion of patients reporting persistent AD in the head-and-neck area remained very high at week 104. Though the patients with 104 weeks follow-up

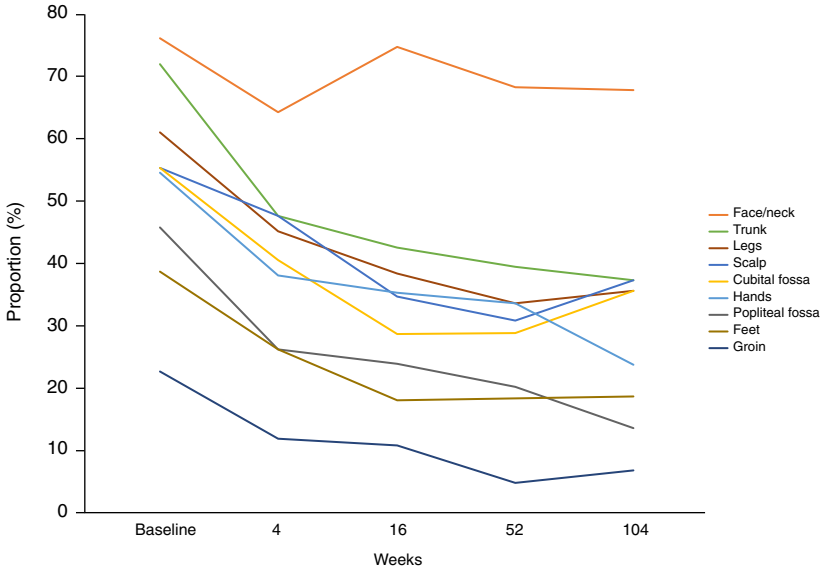


FIGURE 2 Proportion of Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment reporting atopic dermatitis in specific body areas at baseline and after 4, 16, 52 and 104 weeks of dupilumab treatment.

are limited to those with sufficient follow-up time and still receiving dupilumab treatment, these findings highlight an important limitation of dupilumab treatment in AD patients. Thus, head-and-neck dermatitis is associated with reduced quality of life and increased demand for resolution of AD.[23,24] Other treatments that do not share this limitation may be considered in these patients. Improvement with dupilumab in the head-and-neck area has been reported in trials and in real-world studies.[25–27] Importantly, we present patient-reported eczema localization, which is essentially different from evaluating Investigator's Global Assessment (IGA) scores or EASI improvements in the region. Surely, eczema in the head-and-neck region can improve, but for two-third of our patients, lesions were still present at 104-week follow-up. Also, the fact that skin clearance of AD in the face or neck is especially important to the patients,[24] which might cause them to report even small lesion, could explain the differences between results. Several case series have reported exacerbation or new-onset of head-and-neck dermatitis with dupilumab in both adolescents and adults.[28–30] The persisting lesions in the head-and-neck area reported by our patients could also be a result of AEs of facial redness described with dupilumab misinterpreted as eczema by the patient, which would also explain the low occurrence of facial side effect in this study.

Similar to Bosma et al.[6] we found women to have lower baseline EASI scores than men. Women further tended to achieve EASI 75 and EASI 90 more often than men in our study, confirming previous findings.[17,31]

We observed that patients over 60 years of age had slightly delayed treatment response at week 4. However, better treatment response at week 16 support the results from Patruno et al.[32]

Patients with current asthma had a delayed and lower effectiveness response than those without comorbid asthma, probably explained by asthmatic AD patients having worse baseline AD.

Discontinuation and drug survival

12% of the study population discontinued dupilumab treatment during the two-year follow-up period. This is slightly higher than in other long-term studies, where dropouts were 4–8%.[6,9,15,33,34] Of the 16 discontinuations due to AEs, only one reported eye problems as the cause. Fourteen reports used the more general term 'side effects' and four of them had a previous AE report of eye inflammation. Some of these patients restarted dupilumab treatment again at a later time point. Most patients discontinued treatment due to AEs (16/347, 4.6%) or inadequate treatment response (8/347, 2.3%), similar to other studies.[5,6,13,35] Among those who discontinued treatment, the median treatment duration was 7.6 months, supporting finds from Kojanova et al.[9] (7.3 months). Treatment duration was shorter if discontinuation was due to an AE (7.2 months) or insufficient effect (4.6 months), which is in line with Danish AD treatment guidelines, stating that treatment effect should be evaluated after 16 weeks and only good or partial responders can continue treatment.[20]

We found a high two-year drug survival rate (86%). Earlier studies have reported similar rates.[7,9,35,36] In the first 3 years of the study period, no alternative treatment option was available for these patients, which might have increased the drug survival.

Strengths and limitations

The SCRATCH registry is nationwide and includes virtually all Danish patients initiating dupilumab treatment.

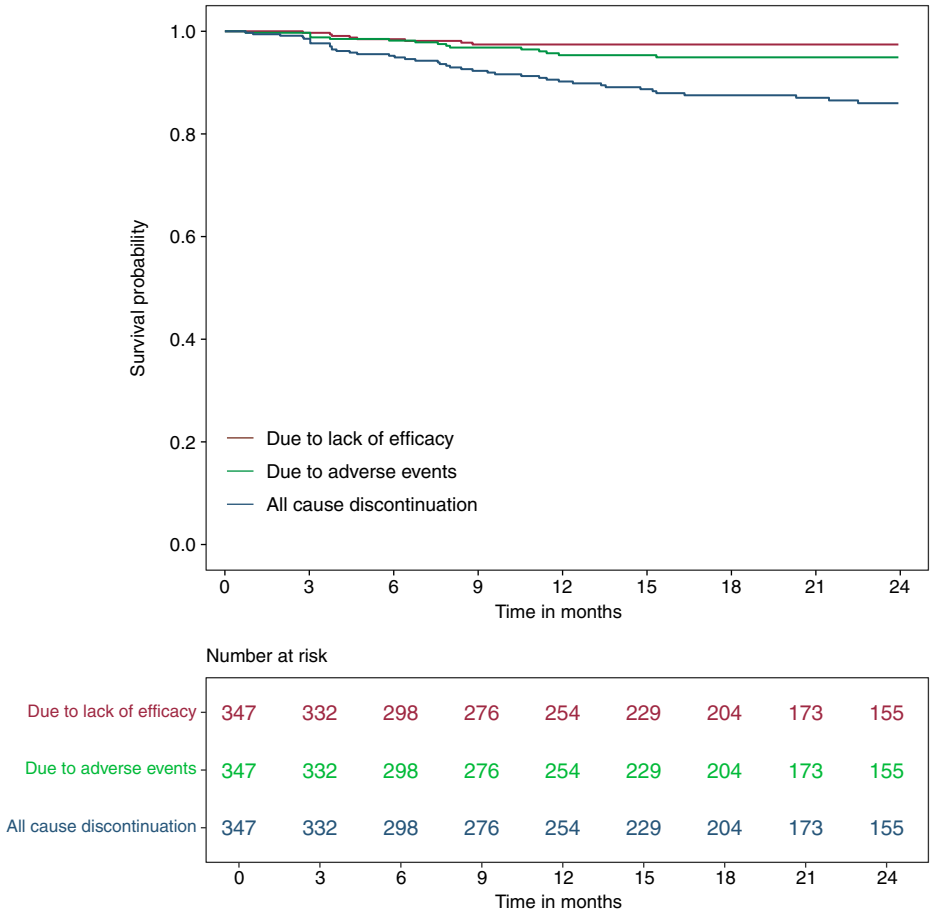


FIGURE 3 Drug survival during 104 weeks of follow-up in 347 Danish patients with moderate-to-severe atopic dermatitis in dupilumab treatment. Kaplan–Meier curves are presented for (1) All cause discontinuation, (2) Due to lack of effectiveness and (3) Due to adverse events.

Due to the nature of a real-life clinical practice setting, we are subject to missing and incomplete data, and few individuals had complete data from all visits. We had no other treatment group for comparison. The COVID-19 pandemic and a national nurse strike caused many physical appointments to be converted to telephone calls, which limited the collection of data to the registry. As a result, drug survival censoring time was set to 365 days, which is quite long and might have prolonged drug survival. Danish treatment recommendations changed during the study period.[10] Thus, in the beginning patients had to fail two traditional systemic drugs before initiating dupilumab therapy, but this was changed in 2021 to one drug only. This potentially affected characteristics of the study population. According to Danish AD guidelines, it is mandatory to use the register, but there is no financial incentive for neither the patient nor the physician, which might affect the number of patients included.

CONCLUSION

We report no new safety signals with prolonged dupilumab therapy and observed maintained treatment persistence over 104 weeks. Importantly, however, dupilumab was unable to effectively treat AD in the head-and-neck.

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CONFLICT OF INTEREST

IV: has received salary from research funding from Sanofi/Regeneron Pharmaceuticals, and honoraria for lecturing from Pfizer. NSK: has no conflicts of interest to declare. HHPL: has no conflicts of interest to declare. JE: has received research, speaking, and/or consulting support from a variety of companies including Pfizer, Leo Pharma, Sanofi, Galderma, Novartis, Eli Lilly, AbbVie, AstraZeneca, Saniona, Boehringer Ingelheim, La Roche-Posay and Pierre Fabre Laboratories. LS: has been an advisor, investigator and speaker for Abbvie, Eli Lilly, Novatis,

Sanofi, Celgene, Leo Pharma, Pfizer, BMS, UCB, Boehringer Ingelheim and Almirall. LS received research funding from Abbvie, Novartis, Janssen, BMS, Sanofi LEO pharma and LEO Foundation. KI: has received personal fees from Astra Zeneca, Leo Pharma, Sanofi Genzyme and Eli Lilly. GBEJ: reports grants and/or personal fees from Abbvie, Coloplast, Chemocentryx, LEO pharma, LEO Foundation, Afyx, Incyte, InflaRx, Janssen-Cilag, Novartis, UCB, CSL Behring, Regeneron, Sanofi, Kymera and VielaBio outside the submitted work. CGM: has no conflicts of interest to declare. ROB: has no conflicts of interest to declare. CB-J: has no conflicts of interest to declare. MGD: has served on advisory boards with Abbvie, Leo Pharma and Eli Lilly. Has received honoraria as a consultant from Eli Lilly. AE: has received research funding from Pfizer, Eli Lilly, Novartis, Bristol-Myers Squibb, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Zuellig Pharma Ltd., Galápagos NV, Sun Pharmaceuticals, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly and Company, Novartis, Union Therapeutics, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb and Janssen Pharmaceuticals. TA: Advisory board, consultancy, lectures or clinical trials for Sanofi, Eli Lilly, Abbvie and Leo Pharma. MD: AbbVie, Eli Lilly, LEO Pharma, La Roche Posay, Incyte, ASLAN Pharmaceuticals, Arena Pharmaceuticals, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – has received research support and/or honoraria for lecturing, and consulting/advisory board agreements. CV: has received honoraria for lectures and add boards from Sanofi Genzyme, Eli Lilly, Pfizer, LEO Pharma, Novartis and Abbvie. He has received research grants from Sanofi Genzyme, Leo Pharma, Novartis and Pfizer. JPT: is an advisor for AbbVie, Almirall, Arena Pharmaceuticals, OM Pharma, Aslan Pharmaceuticals, Union Therapeutics, Eli Lilly & Co, LEO Pharma, Pfizer, Regeneron and Sanofi-Genzyme, a speaker for AbbVie, Almirall, Eli Lilly & Co, LEO Pharma, Pfizer, Regeneron and Sanofi-Genzyme, and received research grants from Pfizer, Regeneron and Sanofi-Genzyme.

DATA AVAILABILITY STATEMENT

Due to patient anonymity and local research regulations, data cannot be made openly available. Further information about the data and conditions for access are available via contact to the corresponding author.

ORCID

Ida Vittrup https://orcid.org/0000-0002-3192-6135
Niels Steen Krogh https://orcid.org/0000-0002-8520-1674
Jesper Elberling https://orcid.org/0000-0002-8925-4722
Lone Skov https://orcid.org/0000-0002-4784-9680
Kristina Sophie Ibler https://orcid.org/0000-0002-5324-1591
Gregor B. E. Jemec https://orcid.org/0000-0002-0712-2540
Charlotte G. Mortz https://orcid.org/0000-0001-8710-0829
Rasmus Overgaard Bach https://orcid.org/0000-0003-2502-3551
Carsten Bindslev-Jensen https://orcid.org/0000-0002-8940-038X
Alexander Egeberg https://orcid.org/0000-0001-8257-1816
Tove Agner https://orcid.org/0000-0002-7543-8299
Mette Deleuran https://orcid.org/0000-0003-0593-9925
Christian Vestergaard https://orcid.org/0000-0001-6485-3158
Jacob Pontoppidan Thyssen https://orcid.org/0000-0003-3770-1743

REFERENCES

1. Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy. 2015;70:836–45. https://doi.org/10.1111/ALL.12619
2. Nettis E, Ferrucci S, Ortoncelli M, Pellacani G, Foti C, Di Leo E, et al. Use of dupilumab for 543 adult patients with moderate-to-severe atopic dermatitis: a multicenter, retrospective study. J Investig Allergol Clin Immunol. 2020;32:1–28.
3. Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz JD, Reguiai Z, 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;81:143–51.
4. Kreeshan FC, Al-Janabi A, Warren RB, Hunter HJA. Real-world experience and laboratory monitoring of Dupilumab in patients with moderate to severe atopic dermatitis in a tertiary Centre. Dermatol Ther (Heidelb). 2021;11:149–60. https://doi.org/10.1007/s13555-020-00469-6
5. Ariëns LFM, van der Schaft J, Spekhorst LS, Bakker DS, Romeijn GLE, Kouwenhoven TA, et al. Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-Week results from the Dutch BioDay registry. J Am Acad Dermatol. 2021;84:1000–9.
6. Bosma AL, de Wijs LEM, Hof MH, van Nieuwenhuizen BR, Gerbens LAA, Middelkamp-Hup MA, et al. Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: results of the TREAT NL (TREatment of ATopic eczema, The Netherlands) registry. J Am Acad Dermatol. 2020;83:1375–84.
7. Georgakopoulos JR, Felfeli T, Drucker AM, Jo CE, Piguet V, Yeung J. Two-year efficacy, safety, and drug survival of dupilumab for atopic dermatitis: a real-world Canadian multicenter retrospective study. JAAD Int. 2021;4:67–9. https://doi.org/10.1016/j.jdin.2021.06.001
8. Pereyra-Rodriguez JJ, Dominguez-Cruz J, Armario-Hita JC, Ruiz-Villaverde R. 104-week safety and effectiveness of dupilumab in the treatment of severe atopic dermatitis. The experience of 5 reference dermatology units in Spain. An Bras Dermatol. 2021;96:787–90.
9. Kojanova M, Tanczosova M, Strosova D, Cetkovska P, Fialova J, Dolezal T, et al. Dupilumab for the treatment of atopic dermatitis: real-world data from The Czech Republic BIOREP registry. J Dermatolog Treat. 2022;33:1–9. https://doi.org/10.1080/09546634.2022.2043545
10. Hedegaard Pliess Larsen H, Vittrup I, Frier Ruge I, Elberling J, Skov L, Ibler K, et al. Severe and ChRonic atopic dermatitis treatment CoHort (SCRATCH): a Danish real-world evidence atopic dermatitis treatment registry. Acta Derm Venereol. 2022;102:adv00760.
11. Vermeulen FM, Gerbens LAA, Bosma AL, Apfelbacher CJ, Irvine AD, Arents BWM, et al. TREatment of ATopic eczema (TREAT) registry taskforce: consensus on how and when to measure the core dataset for atopic eczema treatment research registries. Br J Dermatol. 2019;181:492–504.
12. Egeberg A, Rosenø NAL, Aagaard D, Lørup EH, Nielsen ML, Nymand L, et al. Drug survival of biologics and novel immunomodulators

for rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and psoriasis – a nationwide cohort study from the DANBIO and DERMBIO registries. Semin Arthritis Rheum. 2022;53:151979. https://doi.org/10.1016/j.semarthrit.2022.151979
13. Nettis E, Fabbrocini G, Ortoncelli M, Pellacani G, Argenziano G, di Leo E, et al. Long-term effectiveness of dupilumab up to 52 weeks in atopic dermatitis in 253 adult patients. Br J Dermatol. 2021;184:561–3.
14. Napolitano M, Ferrillo M, Patruno C, Scalvenzi M, D'Andrea M, Fabbrocini G. Efficacy and safety of Dupilumab in clinical practice: one year of experience on 165 adult patients from a tertiary referral Centre. Dermatol Ther (Heidelb). 2021;11:355–61. https://doi.org/10.1007/s13555-021-00505-z
15. Torres T, Paiva-Lopes MJ, Gonçalo M, Claro C, Oliveira M, Gomes J, et al. Dupilumab for atopic dermatitis: a real-world Portuguese multicenter retrospective study. J Dermatolog Treat. 2022;33:1–6. https://doi.org/10.1080/09546634.2022.2035309
16. Uchida H, Kamata M, Kato A, Mizukawa I, Watanabe A, Agematsu A, et al. One-year real-world clinical effectiveness, safety, and laboratory safety of dupilumab in Japanese adult patients with atopic dermatitis: a single-center retrospective study. J Am Acad Dermatol. 2021;84:547–50.
17. Jang DH, Heo SJ, Kook HD, Lee DH, Jung HJ, Park MY, et al. A 52 weeks dupilumab treatment for moderate to severe atopic dermatitis in Korea: long-term efficacy and safety in real world. Sci Rep. 2021;11:1–10. https://doi.org/10.1038/s41598-021-02950-4
18. Sears AV, Woolf RT, Gribaleva E, Abdelrahman W, Robbie S, Menon B, et al. Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: a single-Centre, prospective 1-year observational cohort study of the first 100 patients treated. Br J Dermatol. 2021;184:755–7. https://doi.org/10.1111/bjd.19631
19. Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. J Am Acad Dermatol. 2021;84:139–47. https://doi.org/10.1016/j.jaad.2020.08.051
20. Deleuran M, Carlsen B, Thomsen SF, Holm E, Mørtz C, Vestergaard C. Udredning og behandling af patienter med atopisk dermatitis [Diagnosis and treatment of patients with atopic dermatitis, In Danish]. Available from: https://dds.nu/wp-content/uploads/2020/11/AD-guideline-oktober-2020.pdf.
21. Thyssen JP, Heegaard S, Ivert L, Remitz A, Agner T, De Bruin-Weller M, et al. Management of ocular manifestations of atopic dermatitis: a consensus meeting using a modified delphi process. Acta Derm Venereol. 2020;100:1–6.
22. Rønnstad ATM, Hansen PM, Halling AS, Egeberg A, Kolko M, Heegaard S, et al. Factors associated with ocular surface disease and severity in adults with atopic dermatitis: a nationwide survey. J Eur Acad Dermatol Venereol. 2022;36:592–601.
23. Lio P, Wollenberg A, Thyssen JP, Pierce E, Rueda M, DeLozier A, et al. Impact of atopic dermatitis lesion location on quality of life in adult patients in a real-world study. J Drugs Dermatol. 2020;19:943–8.
24. Egeberg A, Thyssen JP. Factors associated with patient-reported importance of skin clearance among adults with psoriasis and atopic dermatitis. J Am Acad Dermatol. 2019;81:943–9. https://doi.org/10.1016/j.jaad.2019.06.018
25. Lee H, Kim BR, Kim KH, Lee DH, Na JI. One-year effectiveness and safety of Dupilumab treatment for moderate-to-severe atopic dermatitis in Korean patients: a real-world retrospective analysis. Allergy Asthma Immunol Res. 2022;14:117–22.
26. Stingeni L, Bianchi L, Antonelli E, Caroppo ES, Ferrucci SM, Ortoncelli M, et al. Moderate-to-severe atopic dermatitis in adolescents treated with dupilumab: a multicentre Italian real-world experience. J Eur Acad Dermatol Venereol. 2022;36:1292–9.
27. Blauvelt A, Rosmarin D, Bieber T, Simpson EL, Bagel J, Worm M, et al. Improvement of atopic dermatitis with dupilumab occurs equally well across different anatomical regions: data from phase III clinical trials. Br J Dermatol. 2019;181:196–7.
28. Zhu GA, Chen JK, Chiou A, Ko J, Honari G. Assessment of the development of new regional dermatoses in patients treated for atopic dermatitis with Dupilumab. JAMA Dermatol. 2019;155:850–2.
29. Soria A, Du-Thanh A, Seneschal J, Jachiet M, Staumont-Sallé D, Barbarot S. Development or exacerbation of head and neck dermatitis in patients treated for atopic dermatitis with Dupilumab. JAMA Dermatol. 2019;155:1312–5.
30. Bax CE, Khurana MC, Treat JR, Castelo-Soccio L, Rubin AI, McMahon PJ. New-onset head and neck dermatitis in adolescent patients after dupilumab therapy for atopic dermatitis. Pediatr Dermatol. 2021;38:390–4.
31. Olesen CM, Holm JG, Nørreslet LB, Serup JV, Thomsen SF, Agner T. Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral Centre. J Eur Acad Dermatol Venereol. 2019;33:1562–8. https://doi.org/10.1111/jdv.15609
32. Patruno C, Napolitano M, Argenziano G, Peris K, Ortoncelli M, Girolomoni G, et al. Dupilumab therapy of atopic dermatitis of the elderly: a multicentre, real-life study. J Eur Acad Dermatol Venereol. 2021;35:958–64.
33. Ariëns LFM, van der Schaft J, Bakker DS, Balak D, Romeijn MLE, Kouwenhoven T, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry. Allergy. 2020;75:116–26.
34. Quint T, Brunner PM, Sinz C, Steiner I, Ristl R, Vigl K, et al. Dupilumab for the treatment of atopic dermatitis in an Austrian cohort-real-life data shows rosacea-like folliculitis. J Clin Med. 2020;9:1241. https://doi.org/10.3390/jcm9041241
35. Spekhorst LS, Ariëns LFM, van der Schaft J, Bakker DS, Kamsteeg M, Oosting AJ, et al. Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: results from the BioDay registry. Allergy. 2020;75:2376–9.
36. Khosravi H, Zhang S, Anderson AM, Ferris LK, Choudhary S, Patton T. Dupilumab drug survival, treatment failures, and insurance approval at a tertiary care center in the United States. J Am Acad Dermatol. 2020;82:1023–4. https://doi.org/10.1016/j.jaad.2019.12.034

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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