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Clinical Paper

Treatment outcomes of patients with Atopic Dermatitis (AD) treated with dupilumab through the Early Access to Medicines Scheme (EAMS) in the UK

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SUMMARY

BACKGROUND

Dupilumab, a monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling is indicated in dermatology for the treatment of moderate-to-severe atopic dermatitis (AD) in adult and adolescent patients 12 years and older and severe AD in children 6-11 years, who are candidates for systemic therapy. Dupilumab received Early Access to Medicines Scheme (EAMS) approval for adults in March 2017.

OBJECTIVES

The purpose of this study was to assess the efficacy outcomes of treatment with dupilumab in EAMS.

METHODS

A retrospective analysis of adult patients enrolled in the dupilumab EAMS in the UK. Scores were assessed at baseline and follow up, including the Eczema Area and Severity Index (EASI), Investigator's Global Assessment Score (IGA) and Dermatology Life Quality Index (DLQI).

RESULTS

Data were available for 57 adult patients treated with dupilumab for at least 12 weeks; 73.6% of patients had received prior treatment with 3 or 4 immunosuppressants. Baseline scores for the EASI and DLQI were 27.93 (standard deviation, SD 13.09) and 18.26 (SD 6.18) respectively. AD severity scores showed statistically significant improvement at week 16±4 weeks ($p < 0.001$ for all). The mean change in EASI was 14.13 points with 66.7% and 36.7% achieving a 50% (EASI-50) and 75% (EASI-75) improvement in EASI, respectively at $16^{+/-}$ 4 weeks. IGA scores improved by at least two categories for 75% patients. DLQI scores decreased by a mean of 9.0 points, with 80% patients demonstrating a MCID 4-point improvement. For 85% patients, clinicians rated the treatment response as being either 'better' (19%) or 'much better' (65%).

CONCLUSIONS

Dupilumab is associated with a significant and clinically relevant improvements in AD as measured by patient- and physician-reported outcome measures. Importantly, the clinical efficacy, despite the refractory disease of this EAMS cohort, is comparable to that previously reported in clinical trials.

INTRODUCTION

Systemic therapy is typically considered in atopic dermatitis (AD) resistant to topical therapy and where phototherapy is ineffective or contraindicated[1,2]. Traditionally used systemic agents include azathioprine, methotrexate and ciclosporin. Of these, only ciclosporin is licensed in AD and the EMA licence limits use up to 12 months.

Dupilumab, a monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling is indicated in dermatology for the treatment of moderate-to-severe atopic dermatitis (AD) in adult and adolescent patients 12 years and older and severe AD in children 6-11 years, who are candidates for systemic therapy.

In the United Kingdom (UK) the Early Access to Medicines Scheme (EAMS) aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. Promising Innovative Medicine (PIM) status was granted to dupilumab in December 2015 and EAMS positive scientific opinion in March 2017. Dupilumab was made available to adult patients with severe AD who had failed to respond, or who are intolerant of, or ineligible for all approved therapies with or without corticosteroids.

The efficacy and safety of dupilumab has been evaluated in pivotal randomised, double-blind, placebo-controlled studies (SOLO 1, SOLO 2, CAFÉ and CHRONOS)[4,7]. It is

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hypothesised that treatment of AD via EAMS would match that shown previously in large RCTs. Therefore, the aim of this analysis was to assess the efficacy in EAMS a pre-license access scheme in the UK.

PATIENTS AND METHODS

Patients

Patient inclusion and exclusion criteria have been listed in Table 1.

Inclusion criteria:

-Signed written informed consent
-Adult patients >18 years with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all approved therapies (ciclosporin)
-Patient has received treatment with dupilumab for ≥3 months before the date of data collection as part of the Early Access to Medicines Scheme
-Patient has returned for at least one follow-up visit since initiation of treatment

Exclusion criteria:

-Patient has been on dupilumab <3 months before the date of data collection
-Patient has not attended any follow-up visits
-Patient has received treatment with dupilumab prior to EAMS e.g. previous enrolment in a dupilumab clinical trial
-The patient has active chronic or acute infection requiring systemic treatment with antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 1 week before the first anticipated date for dupilumab administration
-The patient has known or suspected immunodeficiency, including a history of invasive opportunistic infections (e.g. tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the treating physician
-The patient has used any of the following treatments within 5 half-lives (if known) or 12 weeks before the first anticipated date for dupilumab administration (if half-life is not known or not applicable)
-Immunosuppressive/immunomodulating drugs [e.g., systemic corticosteroids (more than physiological replacement doses), ciclosporin, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.]
-Investigational drugs
-The patient has severe or recent (within 12 weeks) endoparasitic (e.g. helminth) infections, suspected infection, or is at high risk for such infections
-The patient has severe concomitant illness(es), new conditions, or insufficiency understood conditions that, in the treating physician's judgment, might result in unreasonable risk to the patient
-The patient is a pregnant or breastfeeding woman, or is planning to become pregnant or breastfeed
-The patient is female and of childbearing potential and is unwilling to use adequate methods of contraception to avoid pregnancy
-The patient has a potential allergy or hypersensitivity to the excipients of the dupilumab product (L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, water for injection, acetic acid

*Italicised text are criteria that were part of EAMS enrolment

Table 1. In-/exclusion criteria

Dupilumab was made available to adult patients in the UK with severe atopic dermatitis who had failed to respond, or who were intolerant of or ineligible for all approved therapies. Dupilumab could be used with or without topical corticosteroids.

The study was a retrospective review of the hospital medical notes, databases and electronic systems of eligible patients (those who had received treatment with dupilumab through the EAMS for more than 3 months) with AD recruited to EAMS at 8 dermatology sites throughout the UK. All data was collected by the clinical teams and overseen by the lead dermatologist for EAMS at each site.

Baseline patient data was available from EAMS entry forms held by the sponsor (Sanofi Genzyme). Patients were independently selected by their hospital physician in line with the EAMS indication; applications were reviewed and accepted by the sponsor's medical lead (RR). Applications were received electronically from sites in a pseudo-anonymised format (initials and date of birth collected), once accepted, patients were assigned an EAMS reference number and applications were held by the medical team.

Follow-up data collection and analysis was conducted by an independent healthcare research consultancy (York Health Economics Consortium, YHEC). Sites were contacted directly and provided with paper/electronic clinical report forms (CRF). Data were collected in an anonymised format by members of the direct care team. Data were only collected for patients who had consented at the start of EAMS. The collected data were sent in an anonymised format (EAMS reference number) to YHEC for data management, analysis and report generation.

All data were entered onto data collection forms from electronic health records by study site contacts at each site.

Instruments, clinician rating and data collection

Severity of atopic dermatitis (AD) was rated by the clinician using the Eczema Area and Severity Index (EASI) [5] which ranges from 0 to 72, as well as the Investigator's Global Assessment Score (IGA) with scores ranging from 0 to 4[1].

EASI scores were categorised as follows: 0 =clear; 0.1 to 1 = almost clear; 1.1 to 7 = mild disease; 7.1 to 21 = moderate disease; 21.1 to 50 = severe disease; ≥51 = very severe disease[6].

Patients completed the Dermatology Life Quality Index (DLQI)[7] with scores ranging from 0 to 30.

The DLQI scores were categorised as follows: 0 to 1 = no effect on patient's life; 2 to 5 = small effect; 6 to 10 = moderate effect; 11 to 20 = very large effect; 21 to 30 = extremely large effect[8].

Absolute and percentage change were recorded for both the EASI and DLQI scores. Also reported was EASI-50 and EASI-75 (50% and 75% improvement in EASI score, respectively). An EASI reduction of 6.6 points indicates a minimally clinically important difference (MCID)[9]; a 4-point reduction is the MCID for the DLQI scores[10].

Clinicians also recorded a response to treatment rated on a 5-point Likert scale: "Much worse", "Worse", "About the same", "Somewhat better" and "Much better".

The timing of follow-up visits varied between patients, therefore time since the previous clinic visit was categorised as follows: 2 to 4 weeks (14 to 27 days); 4 to 8 weeks (28 to 55 days); 8 to 12 weeks (56 to 83 days); 12 to 20 weeks (84 to 139 days; also referred to as 16±4 weeks) and 20 weeks or more (≥140 days).

Data management and Statistical analysis

A total of 8 EAMS sites based in England and Northern Ireland provided data for inclusion in this study. The analysis mainly comprised descriptive statistics. Continuous variables were summarised using mean and standard deviation, with minimum and maximum values reported to provide the

1 http://www.eczemacouncil.org/research/investigator-global-assessment-scale/

range. Categorical variables were summarised as frequency and proportion.

Inferential statistics were used to assess the statistical significance of observed differences for the 16±4 weeks' timeframe. For continuous scale variables a paired samples *t*-test was performed. For ordinal variables a Wilcoxon Signed Rank test was performed.

Pearson's correlations were performed to assess the relationships between different measures of severity.

No imputation was performed for missing data. Missing values were excluded from relevant analyses. Precise sample sizes are reported for each analysis. Quality control was undertaken on the data as follows: each clinical site was contacted and the anonymised data for 10% of the total patients held at the clinical site were checked against the data recorded in the study database.

The analysis was conducted using IBM SPSS Statistics software (version 24).

Ethics

This was a retrospective analysis of data. Patient consent was obtained prior to enrolment on the EAMS. Anonymised data were obtained directly from the patients' care team. This study was approved by the NHS Health Research Authority (Reference: 19/HRA/0017, 10th April 2018) and all necessary local NHS Trust approvals were obtained.

RESULTS

Patients

The quality control checks revealed no differences between data recorded at clinical sites and within the study database. Figure 1 depicts the number of patients for whom data were available, exclusions and reasons for exclusions. Of the 65 patients treated with dupilumab via the EAMS scheme, 8 were excluded due to insufficient data. The remaining 57 patients comprised 20 (35.1%) females and 36 males (63.2 %) with a mean age of 41.2 years (SD: 14.21 years; range: 20 to 76 years); Gender and age were not available in one and two patients, respectively.

Past immunosuppressant use was reported for 91.2% (52 patients), the majority of which (73.6%; 42 patients) had been prescribed three or four different immunosuppressants. The most common immunosuppressants prescribed were ciclosporin (86.2%; 50 patients), azathioprine (81.0%; 47 patients) and methotrexate (70.7%; 41 patients).

Thirty patients (52.6%) were on one immunosuppressant at time of enrolment and one patient (1.8%) was on two. In these patients, ciclosporin was most common (19.0%; 11 patients), followed by methotrexate (15.5%; 9 patients).

EASI Scores

Baseline EASI scores were available in 55 of 57 patients and ranged from 4.3 (mild disease) to 72.0 (very severe disease)[6] with the most common category being severe disease, and

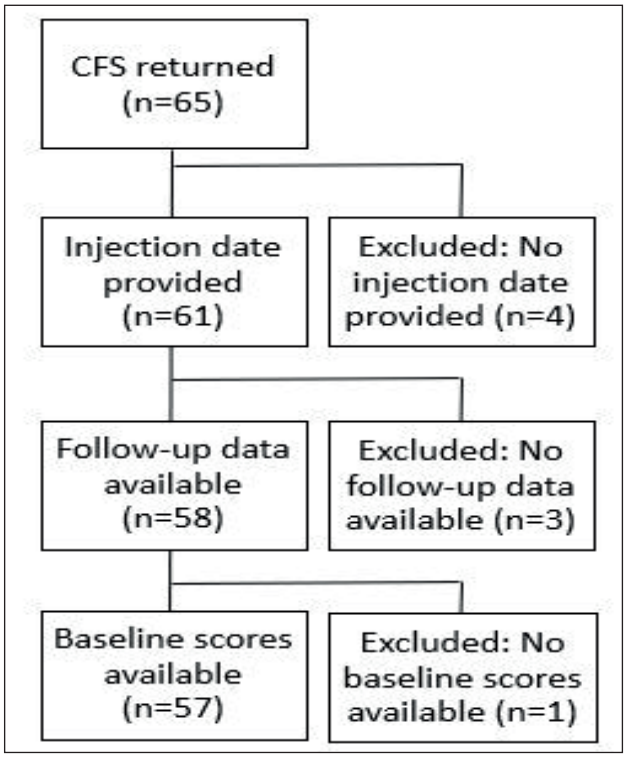

Figure 1.
Diagram demonstrating flow of excluded and included patient data.

Statistic	Measure	All (*n*=55)	Immunosuppressant use at enrolment		Gender	
			No (*n*=26)	Yes (*n*=29)	Female (*n*=19)	Male (*n*=36)
Mean (SD)	EASI score at baseline	27.93 (13.09)	29.99 (14.62)	26.09 (11.50)	24.41 (12.65)	29.79 (13.11)
Frequency (n, % within stratification group)	EASI scores 'clear' at baseline	0	0	0	0	0
	EASI scores 'almost clear' at baseline	0	0	0	0	0
	EASI scores 'mild' at baseline (<7)	2 (3.7%)	0	2 (6.9%)	0	2 (5.6%)
	EASI scores 'moderate' at baseline (7.1-21)	13 (24.1%)	7 (26.9%)	6 (20.7%)	7 (36.8%)	6 (16.7%)
	EASI scores 'severe' at baseline (21.1-50)	38 (69.1%)	17 (65.4%)	21 (72.4%)	11 (57.9%)	27 (75.0%)
	EASI scores 'very severe' at baseline (>50.1)	2 (3.7%)	2 (7.7%)	0	1 (5.3%)	1 (2.8%)

Table 2. EASI Scores at baseline

			Stratification			
		All (*n*=32)	Immunosuppressant use at enrolment		Gender	
			No (*n*=11)	Yes (*n*=21)	Female (*n*=13)	Male (*n*=18)
	EASI rating at the 16+/-4 week follow-up					
Mean (SD)	EASI score	7.62 (6.26)	6.09 (6.73)	8.42 (6.02)	7.59 (6.16)	7.59 (6.69)
Frequency (n, % within stratification group)	Clear	5 (15.6%)	3 (27.3%)	2 (9.5%)	3 (23.1%)	2 (11.1%)
	Almost clear	1 (3.1%)	1 (9.1%)	0	0	1 (5.6%)
	Mild (<7)	9 (28.1%)	3 (27.3%)	6 (28.6%)	3 (23.1%)	6 (33.3%)
	Moderate (7.1-21)	16 (50.0%)	4 (36.4%)	12 (57.1%)	7 (53.8%)	4 (44.4%)
	Severe (21.1-50)	1 (3.1%)	0	1 (4.8%)	0	1 (5.6%)
	Very severe (>50.1)	0	0	0	0	0
	Change in EASI severity between baseline and the 16+/-4 week follow-up					
		All (*n*=30)	No (*n*=11)	Yes (*n*=19)	Female (*n*=12)	Male (*n*=18)
Mean (SD)	Absolute change in EASI score	14.13 (10.71)	16.04 (12.08)	13.03 (10.01)	11.36 (9.90)	15.98 (11.10)
	Percentage change in EASI score	55.84% (43.01%)	62.46% (53.16%)	52.00% (36.98%)	51.69% (40.63%)	58.60% (45.46%)
Frequency (n, % within stratification group)	MCID reduction	22 (73.3%)	8 (72.7%)	14 (73.7%)	8 (66.7%)	14 (77.8%)
	50% reduction or greater	20 (66.7%)	9 (81.8%)	11 (57.9%)	8 (66.7%)	12 (66.7%)
	75% reduction or greater	11 (36.7%)	6 (54.5%)	5 (26.3%)	3 (25.0%)	8 (44.4%)

Table 3. EASI scores at follow-up

the sample mean values for the full cohort (27.93, SD = 13.09) corresponding to a rating of severe disease (Table 2).

Follow-up EASI scores were available for 32 patients at 16+/-4 weeks (Table 3) with a mean score of 7.62 (SD = 6.26; range = 0.0 to 21.6). No patients had 'very severe' disease at follow-up and only one had 'severe disease' based on EASI score (Figure 2).

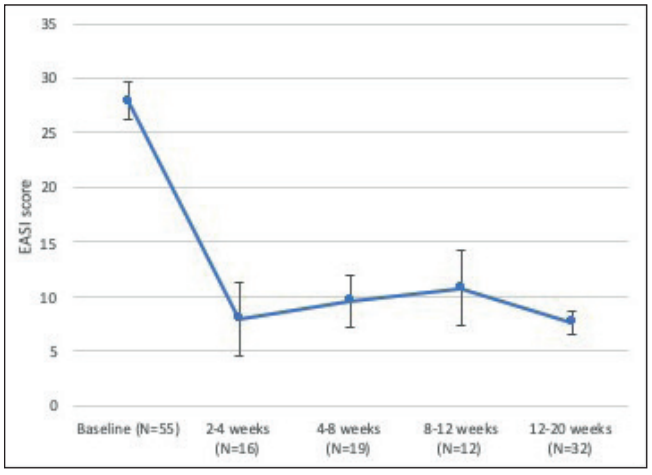

Figure 2. Mean EASI scores at baseline and 16+/-4 weeks

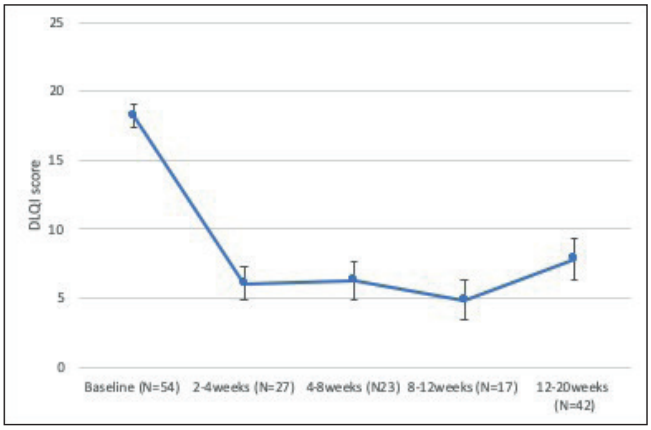

Figure 3. Mean DLQI scores at baseline and 16+/-4 weeks

In 30 patients a baseline and 16+/-4 week follow-up EASI score was available. The mean change in EASI score was an improvement of 14.13 points (SD= 10.71; range of +9 to -33). Mean percentage improvement was 55.84% (SD= 43.01%) between baseline and follow-up at 16+/-4 weeks. EASI-50 was observed in 20 patients (66.7%) and EASI-75 in 11 (36.7%); 22 patients (73.3%) reported a reduction of at least 6.6 points, indicative of a MCID.

A paired-samples t-test indicated that the EASI scores at the 16+/-4 week follow-up were significantly lower than at baseline (p<0.001).

IGA Scores

			Immunosuppressant use at enrolment		Gender	
Statistic	Measure	All (*n*=51)	No (*n*=25)	Yes (*n*=26)	Female (*n*=17)	Male (*n*=34)
Frequency (n, % within stratification group)	IGA scores 'clear' at baseline	0	0	0	0	0
	IGA scores 'almost clear' at baseline	0	0	0	0	0
	IGA scores 'mild' at baseline	2 (3.9%)	1 (4.0%)	1 (3.8%)	1 (5.9%)	1 (2.9%)
	IGA scores 'moderate' at baseline	13 (25.5%)	6 (24.0%)	7 (26.9%)	5 (29.4%)	8 (23.5%)
	IGA scores 'severe' at baseline	36 (70.6%)	18 (72.0%)	18 (69.2%)	11 (64.7%)	25 (73.5%)

Table 4. IGA scores at baseline

Baseline IGA scores were available in 51 of 57 patients. IGA scores ranged from 2 (mild) - 4 (severe) with a median score of 4 (70.8%, see Table 4). Both baseline and 16+/-4 week follow-up IGA scores were available for a total of 28 patients (Table 5). In 21 (75%) patients the IGA ratings improved by ≥

		All (*n*=34)	Immunosuppressant use at enrolment		Gender	
			No (*n*=14)	Yes (*n*=20)	Female (*n*=11)	Male (*n*=22)
Frequency (n, % within stratification group)	IGA rating at the 16+/-4 week follow-up					
	Clear	6 (17.6%)	4 (28.6%)	2 (10.0%)	3 (27.3%)	3 (13.6%)
	Almost clear	14 (41.2%)	6 (42.9%)	8 (40.0%)	2 (18.2%)	12 (54.5%)
	Mild disease	9 (26.5%)	2 (14.3%)	7 (35.0%)	4 (36.4%)	4 (18.2%)
	Moderate disease	4 (11.8%)	1 (7.1%)	3 (15.0%)	2 (18.2%)	2 (9.1%)
	Severe disease	1 (2.9%)	1 (7.1%)	0	0	1 (4.5%)
	Change in IGA severity between baseline and the 16+/-4 week follow-up					
		All (*n*=28)	No (*n*=13)	Yes (*n*=15)	Female (*n*=8)	Male (*n*=20)
	Increase in severity	1 (3.6%)	0	1 (6.7%)	1 (12.5%)	0
	No change in severity	1 (3.6%)	1 (7.7%)	0	0	1 (5.0%)
	Improvement by one category	5 (17.9%)	2 (15.4%)	3 (20.0%)	2 (25.0%)	3 (15.0%)
	Improvement by two or more categories	21 (75.0%)	10 (76.9%)	11 (73.3%)	5 (62.5%)	16 (80.0%)

Table 5. IGA scores at follow-up

Statistic	Measure	All (*n*=54)	Immunosuppressant use at enrolment		Gender	
			No (*n*=25)	Yes (*n*=29)	Female (*n*=19)	Male (*n*=35)
Mean (SD)	DLQI score at baseline	18.26 (6.18)	19.48 (7.50)	17.21 (4.64)	20.11 (5.13)	17.26 (6.53)
Frequency (n, % within stratification group)	DLQI scores 'no impact' at baseline (0-1)	0	0	0	0	0
	DLQI scores 'small impact' at baseline (2-5)	1 (1.9%)	1 (4.0%)	0	0	1 (2.9%)
	DLQI scores 'moderate impact' at baseline (6-10)	4 (7.4%)	3 (12.0%)	1 (3.4%)	0	4 (11.4%)
	DLQI scores 'very large impact' at baseline (11-20)	29 (53.7%)	9 (36.0%)	20 (69.0%)	9 (47.4%)	20 (57.1%)
	DLQI scores 'extremely large impact' at baseline (21-30)	20 (37.0%)	12 (48.0%)	8 (27.6%)	10 (52.6%)	10 (28.6%)

Table 6. DLQI scores at baseline

		Stratification				
		All (*n*=42)	Immunosuppressant use at enrolment		Gender	
			No (*n*=16)	Yes (*n*=26)	Female (*n*=14)	Male (*n*=27)
	DLQI rating the 16+/-4 week follow-up					
Mean (SD)	DLQI score	7.86 (9.49)	4.44 (7.08)	9.96 (10.27)	8.57 (9.25)	7.52 (9.94)
Frequency (n, % within stratification group)	No impact (0-1)	14 (33.3%)	8 (50.0%)	6 (32.1%)	5 (35.7%)	9 (33.3%)
	Small impact (2-5)	9 (21.4%)	4 (25.0%)	5 (19.2%)	1 (7.1%)	8 (29.6%)
	Moderate impact (6-10)	7 (16.7%)	2 (12.5%)	5 (19.2%)	3 (21.4%)	3 (11.1%)
	Very large impact (11-20)	6 (14.3%)	0	6 (23.1%)	3 (21.4%)	3 (11.1%)
	Extremely large impact (21-30)	6 (14.3%)	2 (12.5%)	4 (15.4%)	2 (14.3%)	4 (14.8%)
	Change in DLQI severity between baseline and the 16+/-4 week follow-up					
		All (*n*=40)	No (*n*=16)	Yes (*n*=24)	Female (*n*=13)	Male (*n*=27)
Mean (SD)	Absolute change in DLQI score	8.98 (7.91)	12.13 (7.97)	6.88 (7.30)	10.54 (9.23)	8.22 (7.26)
	Percentage change in DLQI score	58.85% (42.11%)	75.90% (34.34%)	47.48% (43.60%)	54.64% (44.31%)	60.88% (41.73%)
		All (*n*=30)	No (*n*=11)	Yes (*n*=19)	Female (*n*=12)	Male (*n*=18)
Frequency (n, % within stratification group)	MCID reduction	32 (80.0%)	14 (87.5%)	18 (75.0%)	10 (76.9%)	22 (81.5%)
	DLQI MCID and EASI 50% reduction or greater	16 (53.3%)	8 (72.7%)	8 (42.1%)	7 (58.3%)	9 (50.0%)

Table 7. DLQI scores at follow-up

2 categories, and in an additional 5 (17.9%) an improvement of one category was observed. For one patient there was no change and for another and increase in IGA was observed.

A Wilcoxon Signed Rank test indicated that the IGA scores at the 16+/-4 weeks follow-up (median = 1) were significantly lower than at baseline (p<0.001).

DLQI Scores

Baseline DLQI scores were available in 54 of 57 patients (mean 18.26; SD 6.18, corresponding to 'very large' impact) (Table 6). DLQI scores were available at baseline and week 16+/-4 in 40 patients. The mean change in DLQI score was an improvement of 8.98 points (SD= 7.91; range = 14 to 29 points). A MCID was observed in 32 patients (80.0%). Of the 30 patients for whom both EASI and DLQI change scores were available at the 16+/-4 weeks follow-up, 16 (53.3%) achieved an EASI-50 and MCID in DLQI scores.

		Stratification				
		All (*n*=26)	Immunosuppressant use at enrolment		Gender	
			No (*n*=9)	Yes (*n*=17)	Female (*n*=7)	Male (*n*=19)
Clinician rated response to treatment at the 16$^{+/-4}$ week follow-up						
Frequency (n, % within stratification group)	Much worse	0	0	0	0	0
	Worse	2 (7.7%)	0	2 (11.8%)	1 (14.3%)	1 (5.3%)
	About the same	2 (7.7%)	0	2 (11.8%)	2 (28.6%)	0
	Somewhat better	5 (19.2%)	0	5 (29.4%)	1 (14.3%)	4 (21.1%)
	Much better	17 (65.4%)	9 (100%)	8 (47.1%)	3 (42.9%)	14 (73.7%)

Table 8.
Clinician-rated response to treatment at follow-up

Measure	EASI at the 16$^{+/-4}$ week follow-up	IGA at the 16$^{+/-4}$ week follow-up	DLQI at the 16$^{+/-4}$ week follow-up	Clinician-rated response at the 16$^{+/-4}$ week follow-up
EASI at the 16$^{+/-4}$ week follow-up				
IGA at the 16$^{+/-4}$ week follow-up	0.89 (p<0.001; n=24)			
DLQI at the 16$^{+/-4}$ week follow-up	0.67 (p<0.001; n=32)	0.75 (p<0.001; n=34)		
Clinician-rated response at the 16$^{+/-4}$ week follow-up	0.47 (p=0.51; n=18)	0.66 (p=0.003; n=18)	0.64 (p=0.001; n=25)	

Table 9. Correlations between endpoints at follow-up

A paired-samples t-test indicated that the DLQI scores at the 16$^{+/-4}$ week follow-up (mean 8.09) were significantly lower than at baseline (mean 17.05; t(39)=7.175, p<0.001).

Clinician-rated response to treatment at follow-up

The most common clinician-rated treatment response for the 26 patients for whom data were available at the 16$^{+/-4}$ weeks follow-up was 'much better' (65.4%). Two patients (7.7%) were graded as worse (105 and 125 days since first injection), while a further two were rated as showing no change (Table 8).

Relationship between endpoints at follow-up

Table 9 shows the relationship between endpoints at follow-up. Positive relationships between severity scales were significant and considered moderate to strong, particularly between the EASI and the IGA (r=0.89, p<0.001).

DISCUSSION

The aim of this study was to investigate the treatment efficacy of dupilumab in adult patients with AD treated in EAMS a pre-license access scheme in the UK.

The results demonstrated a significant improvement in AD severity between baseline and 16 $^{+/-4}$ week follow-up, as measured by EASI and IGA. EASI-50 and EASI-75 improvements were observed in 67% and 37% respectively and importantly a minimally clinically important difference of 6.6 points or more was observed in 73%. IGA scores improved by at least two categories for 75% patients, and by one category for 17.9%. This corresponded with improvements in DLQI scores with a minimally clinically important improvement observed in 80%. Furthermore, a clinician-rated treatment response was reported as either "better" or "much better" in 19% and 65% of patients, respectively.

The efficacy of dupilumab in AD has previously been demonstrated in several randomised controlled trials[3,4]. Due to the potential of selection bias within clinical trials it is important that efficacy of new drugs is also evaluated outside the clinical trial setting. In one recently published real-world study of 19 AD patients treated with dupilumab, a median SCORAD decrease of 55% and increase in patients with IGA of 0/1 from 5% to 61% was observed after 16 weeks[11]. Limitations of that study suggested by the authors included the small number of patients and the fact it was based in a single-centre. Importantly, our larger multi-centre real-world study mirrors these results and the efficacy demonstrated within the clinical trial programme despite the fact patients treated within EAMS had more refractory disease (75% having failed 3-4 prior immunosuppressant drugs, reflecting a more severe cohort that those who access in the real-world setting either by licence, "candidates for systemic therapy", or by NICE criteria "failure on 1 immnuosupressant"[12,13,14]). Of the pivotal studies, the CAFÉ trial most closely represents the EAMS patient population, i.e. failure to respond / intolerant/inadvisable for ciclosporin. In CAFÉ, an EASI-50 and DLQI improvement of ≥ 4 was observed in 85% and 88% of patients, respectively. In the present study, we observed a 67% EASI-50 and 80% DLQI ≥ 4 improvement.

As with any retrospective study based on secondary use of data, interpretation of study endpoints depended on the completeness and quality of the source medical records and the reliability of the abstraction of data from the medical records, meaning potential confounders could not be accurately assessed. Full datasets were not available for all patients enrolled in EAMS due to missing baseline or incomplete follow-up data. Quality control was undertaken on a small subset of patients (10%) to minimise disruption at the clinical site. Another potential limitation is that no safety or adverse events data were recorded as part of this aspect of the study. Further data are required from other real-world cohorts and registries to further understand the efficacy and safety of dupilumab on a wider scale.

In conclusion, dupilumab is associated with significant and clinically-relevant improvements in AD as measured by patient- and physician-reported outcome measures. Importantly, the clinical efficacy, despite the highly immunosuppressant refractory population in this EAMS cohort, is comparable to that previously reported in large randomised clinical trials.

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Conflicts of interest

LD, RR and RH are employees of and hold stock options in Sanofi Genzyme.
DOK has received honoraria as a speaker and /or advisory board member for Abbvie, Novartis, Lilly, UCB and Janssen. MAJ has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Amgen, Lilly, Sanofi, Leo Pharma and Pfizer. PL has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for AbbVie, Almirall, Actelion, Celgene, Janssen, Lilly, Sanofi, Leo, UCB and Novartis. LS has no conflicts of interest. MC has received honoraria and/or grants as an investigator, speaker, and/or advisory board member for Eli Lily, Leo Pharma, Novartis, L'Oreal, Procter and Gamble, Oxagen, Johnson & Johnson, Pfizer, Regeneron, Sanofi, UCB and Hyphens Pharma. SV has received an educational grant from Abbvie. HC has received honoraria for advisory board participation from Sanofi, Abbvie, Novartis and Janssen.

Contributions

Data collection DOK, MA-J, PL, LS, MC, SV, HLC
Data analysis RH ABS, RR, LD, DOK
Manuscript preparation DOK, LD, RR, ABS, RH
Manuscript review MA-J, DOK, PL, LS, MC, SC, HLC

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