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A prospective observational cohort study comparing the treatment effectiveness and safety of ciclosporin, dupilumab and methotrexate in adult and paediatric patients with atopic dermatitis: results from the UK–Irish A-STAR register

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Full details of the A-STAR Study Group are provided in Appendix 2.

Abstract

Background The main conventional systemic treatments for atopic dermatitis (AD) are methotrexate (MTX) and ciclosporin (CyA). Dupilumab was the first novel systemic agent to enter routine clinical practice. There are no head-to-head randomized controlled trials or real-world studies comparing these agents directly. Network meta-analyses provide indirect comparative efficacy and safety data and have shown strong evidence for dupilumab and CyA.

Objectives To compare the real-world clinical effectiveness and safety of CyA, dupilumab and MTX in AD.

Methods We compared the effectiveness and safety of these systemic agents in a prospective observational cohort study of adult and paediatric patients recruited into the UK–Irish Atopic eczema Systemic TherApy Register (A-STAR). Treatment effectiveness measures included Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure (POEM), Peak Pruritus Numerical Rating Scale (PP-NRS), Dermatology Life Quality Index (DLQI) and children's DLQI (cDLQI). The minimum duration of treatment was 28 days and follow-up was 12 months. Adjusted Cox-regression analysis was used to compare the hazard ratios of achieving EASI-50, EASI-75 and EASI-90 over time, and linear mixed-effects models were used to estimate changes in efficacy scores. Treatment safety was assessed by examining adverse events (AEs) at follow-up visits.

Results We included 488 patients (311 adults and 177 children/adolescents) on dupilumab (n=282), MTX (n=149) or CyA (n=57). CyA and MTX were primarily used as the first-line treatment, while dupilumab was mainly a second-line systemic treatment as per UK National Institute of Clinical and Care Excellence (NICE) recommendations. EASI-50, EASI-75 and EASI-90 were achieved more rapidly in the dupilumab and CyA groups compared with MTX. After adjustment for previous severity, the reduction in EASI, POEM, PP-NRS and DLQI was greater for patients treated with dupilumab compared with MTX. In patients with severe disease the reduction in EASI, POEM and PP-NRS was even greater with CyA. The incidence rates of AEs were similar across groups (734, 654 and 594 per 10 000 person-month on CyA, dupilumab and MTX, respectively).

Conclusions This real-world comparison of CyA, dupilumab and MTX in AD suggests that dupilumab is consistently more effective than MTX and that CyA is most effective in very severe disease within 1 year of follow-up.

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Lay summary

Atopic dermatitis (AD) is a common skin disease which causes dry and itchy skin. AD affects around one in five children and one in 10 adults in the UK. The main conventional systemic treatments are with drugs called methotrexate (MTX) and ciclosporin (CyA). As well as these, dupilumab was the first novel systemic agent to enter routine clinical practice. However, there are no studies that have directly compared the effectiveness or safety of these treatments. This study aimed to compare the effectiveness and safety of CyA, dupilumab and MTX. We compared these treatments in adults and children with AD who were participating in the UK–Irish Atopic eczema Systemic TherApy Register (A-STAR). Treatment effectiveness was assessed using the Eczema Area and Severity Index (EASI), and with patient-reported severity scores for itch and quality of life. Patients were treated for a minimum of 28 days and followed up for 12 months. Treatment safety was determined by patient-reported side-effects at follow-up visits. A total of 488 patients were assessed, including 282 patients on dupilumab, 149 on MTX and 57 on CyA. We found that the time taken for AD severity EASI scores to reduce by 50%, 75% and 90% was shorter for patients on dupilumab and CyA, compared with MTX. Improvements in itch and quality of life were greater for patients treated with dupilumab, compared with MTX. In patients with severe AD, improvement was even greater than with CyA. The incidence of side-effects was similar with dupilumab, CyA and MTX treatments.Overall, our findings suggest that dupilumab is consistently more effective than MTX and that CyA is most effective in very severe disease within 1 year of follow-up.

What is already known about this topic?

- The conventional systemic agents ciclosporin (CyA) and methotrexate (MTX) have been used to treat atopic dermatitis (AD) for decades.
- Dupilumab was the first novel systemic agent for AD to enter routine clinical practice, and several trials have demonstrated its efficacy and safety.
- Network meta-analyses have shown strong indirect comparative efficacy and safety profiles for dupilumab and CyA but there are no head-to-head trials comparing these agents directly.

What does this study add?

- This real-world effectiveness and safety comparison in adult and paediatric AD found that patients treated with dupilumab and CyA experience a greater reduction in Eczema Area and Severity Index, Patient Oriented Eczema Measure and itch compared with those treated with MTX.
- There was a similar incidence of adverse events with all three medications.

Atopic dermatitis (AD) affects up to 20% of children and 10% of adults and has a major impact on quality of life.[1,2] Most patients can be treated effectively with emollients and topical anti-inflammatory agents. However, around 5% require systemic immunomodulatory therapies to induce disease remission and long-term control.[3]

Conventional systemic AD treatments include methotrexate (MTX) and ciclosporin (CyA). Most clinicians find that conventional systemic immunomodulatory therapies cannot be used for many years because of adverse events (AEs) or intolerability. The development of novel agents with improved long-term safety profiles is therefore needed.

Dupilumab was the first novel systemic AD treatment to enter routine clinical practice. Several phase III randomized controlled trials (RCTs) have demonstrated its efficacy and safety profile, compared with placebo, for adults, children and young people with AD.[4] These trials included carefully selected patients who were managed under strictly controlled conditions, which limits the generalizability of the findings to real-world dermatology practice.

In real-world practice these treatments tend to be used for slightly different clinical presentations of AD. CyA is often used as a short-term and fast-acting rescue treatment in more severe AD when rapid disease control is needed; it is often stopped within a year to avoid AEs. In contrast, MTX and dupilumab are typically used for more long-term disease control.

Recent AD registry-based studies have shown clinical effectiveness outcomes and safety profiles of dupilumab to be consistent with RCT results in adults.[5–10] Ocular symptoms, including conjunctivitis, are the most significant side-effects of dupilumab. However, to the best of our knowledge, the real-world effectiveness and safety of dupilumab have not yet been shown in comparison to CyA and MTX. Apart from small studies comparing MTX with CyA and azathioprine, which showed comparable effectiveness,[11–13] there are very few head-to-head comparisons of systemic AD therapies. Recent RCTs comparing dupilumab and the Janus kinase (JAK) inhibitors in adult AD found abrocitinib[14] to have comparable efficacy to dupilumab while upadacitinib[15] showed superior efficacy after 16 weeks of treatment.

An indirect analysis comparing adult dupilumab registry data with historical real-world conventional systemic data showed dupilumab has a longer drug survival than MTX and CyA.[16] Network meta-analyses (NMAs) provide further indirect comparative efficacy and safety data for systemic therapies in AD, and have shown dupilumab and high-dose CyA were similarly effective and superior to MTX and azathioprine.[17–19] However, the data for NMAs are extracted from

published RCTs, and the findings are therefore also limited by the constraints of the RCT setting and patient selection criteria. Comparative studies of systemic AD therapies are lacking.

The UK–Irish Atopic eczema Systemic TherApy Register (A-STAR) is a prospective, multicentre register of paediatric and adult patients with AD treated with systemic immunomodulatory drugs. The study provides real-world data on the use of systemic therapies in AD, enabling the evaluation of drug effectiveness and safety beyond the confines of short-term RCTs.

The aim of this study was to compare the real-world clinical effectiveness and safety profile of CyA, dupilumab and MTX in paediatric and adult AD.

Patients and methods

Study design

A prospective observational cohort study was performed to compare CyA, dupilumab and MTX treatment outcomes, using data from the UK–Irish A-STAR register. All patients who started CyA, dupilumab or MTX treatment between 1 October 2018 and 30 October 2023 were examined, but only treatment courses lasting 28 days or more were used for the effectiveness analysis. Patients were aged 3–82 years and fulfilled the UK Working Party's AD diagnostic criteria. Patients on more than one systemic treatment at the same time were not included. Patients also used concomitant topical therapy including corticosteroids, calcineurin inhibitors and emollients in the context of routine clinical care, as prescribed by their local physician.

Patients were assessed at baseline, 4 and 12 weeks after starting treatment, and at 12-weekly intervals thereafter. Patient characteristics assessed at baseline included demographics, comorbidities (including delayed and immediate allergies), prior AD treatments and concomitant medications. This study was carried out in accordance with the latest World Medical Association Declaration of Helsinki (2013 amendment). Participants, or in the case of children and adolescents, their parents/carer, provided written informed consent at study enrolment. The study is covered by research ethics committee reference no. 18/WA/0200, ISRCTN 11210918.

Outcome measures

Treatment effectiveness was assessed using validated physician-assessed and patient-reported outcome measures at baseline and all follow-up visits. Physician-assessed severity was measured by the Eczema Area and Severity Index (EASI, 0–72). Patient-reported outcome measures included the Patient-Oriented Eczema Measure (POEM, 0–28), Peak Pruritus Numerical Rating Scale (PP-NRS, 0–10), Dermatology Life Quality Index (DLQI, 0–30) for those aged 16 years and older, and the children's DLQI (cDLQI, 0–31) for younger patients. EASI-50 (≥ 50% improvement in EASI score from baseline), EASI-75 (≥ 75% improvement in EASI score from baseline) and EASI-90 (≥ 90% improvement in EASI score from baseline) were calculated for each group. Treatment safety was assessed by examining AEs at all follow-up visits. The relatedness to the drug of the AEs was assessed by the treating physician using MedDRA pharmacovigilance coding, as is standard practice in treatment registers and clinical trials. AEs occurring during the treatment course only were recorded and risk windows were not implemented.

Statistical analysis

Baseline patient characteristics, treatment duration and safety data were summarized using descriptive statistics. Fisher's exact test was used to compare the baseline distributions of categorical variables.

Patients with treatment courses of more than 28 days were included in the effectiveness analysis and patients were followed up for a maximum of 12 months. The baseline value for each outcome measure (EASI, POEM, PP-NRS and DLQI) was the latest score recorded within a 28-day window *before* treatment initiation. If there was no measurement within 28 days prior to treatment initiation, the first score measured within 28 days after starting treatment was used. From the survival analysis below we excluded 132 treatment runs for which the baseline EASI was not available within the specified windows.

Survival analysis

To compare the speed at which each treatment group achieved EASI-50, EASI-75 and EASI-90 over time we used three separate Cox-regression models. The outcome event was whether at each visit the EASI score had reached a reduction from baseline of 50%, 75% or 90%, for each model, respectively. All models were adjusted for age, sex, ethnicity (White/non-White), number of previous systemic treatments received and baseline EASI.

Predictive change analysis

To account for the effect of disease severity on treatment effectiveness, we modelled the predicted change in disease severity scores between consecutive visits where outcome = (following score – current score)/(months between visits). We used linear mixed-effects models with the interaction between mean-centred current score and the treatment as key explanatory variables, and adjusted for age, sex, ethnicity (White/non-White), treatment duration, number of previous treatments and a random-effect term by individual to account for repeated measures.

To compare the treatment effectiveness in paediatric AD, a subgroup analysis, using the same survival and consecutive change analysis, was performed on participants under the age of 18 years. A complete case analysis was conducted and missing data were not imputed. All analyses were conducted using R 3.4.1 computational software.[20]

Results

Baseline patient characteristics

We included 488 patients [mean (SD) age 27.4 (15.6) years] and their baseline characteristics are summarized in Table 1. Of these 488 patients, 217 (44.5%) were female; 282 (mean age 28.8 years, 44% female) were treated with dupilumab,

Table 1 Baseline patient characteristics

Variable	Ciclosporin *N* = 57	Dupilumab *N* = 282	Methotrexate *N* = 149
Sex, *n* (%)			
Female	28 (49.1)	124 (44.0)	65 (43.6)
Male	29 (50.9)	155 (55.0)	84 (56.4)
Unknown	0 (0)	3 (1.0)	0 (0)
Ethnicity, *n* (%)			
White	45 (78.9)	203 (72.0)	110 (73.8)
Asian	6 (10.5)	38 (13.5)	23 (15.4)
Black	1 (1.8)	16 (5.7)	6 (4.0)
Other	4 (7.0)	21 (7.4)	6 (4.0)
Mixed	0 (0)	1 (0.4)	3 (2.0)
Unknown	1 (1.8)	3 (1.1)	1 (0.7)
Age in years, mean (SD)	28.1 (15.8)	28.8 (15.2)	24.5 (15.9)
Age categories, *n* (%)			
0–10	9 (15.8)	14 (5.0)	32 (21.5)
11–15	6 (10.5)	56 (19.9)	28 (18.8)
16–18	2 (3.5)	32 (11.3)	8 (5.4)
19–25	9 (15.8)	44 (15.6)	25 (16.8)
26–35	13 (22.8)	56 (19.9)	21 (14.1)
36–45	11 (19.3)	31 (11.0)	19 (12.8)
> 45	7 (12.3)	49 (17.4)	16 (10.7)
Treatment duration in months, mean (SD)	8.0 (7.98)	17.9 (14.2)	13.7 (12.6)
Past treatments, *n* (%)			
0	22 (38.6)	17 (6.0)	78 (52.3)
1	18 (31.6)	121 (42.9)	47 (31.5)
2	7 (12.3)	71 (25.2)	16 (10.7)
+3	10 (17.5)	73 (25.9)	8 (5.4)
EASI, mean (SD)	22.3 (12.5)	19.1 (13.6)	18.0 (11.4)
PP-NRS, mean (SD)	7.3 (1.95)	6.1 (2.6)	6.7 (2.4)
POEM, mean (SD)	19.3 (7.3)	17.8 (7.9)	19.2 (6.8)
DLQI, mean (SD)	14.7 (7.6)	13.8 (8.6)	14.7 (7.97)
cDLQI, (mean (SD)	11.7 (7.5)	12.0 (7.7)	14.0 (7.4)
Follow-up time (person-month)	458.0	5052.4	2045.3

cDLQI, Children's DLQI; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale.

149 (mean age 24.5 years, 44% female) received MTX, and 57 (mean age 28.1 years, 49% female) were treated with CyA.

While most baseline characteristics were similar across study groups, there were some differences between the treatment groups. The mean age of patients treated with dupilumab was higher than those treated with MTX ($P < 0.009$). More patients receiving dupilumab had received treatment with a prior systemic agent than those treated with CyA (94% vs. 61% $P < 0.0001$) or MTX (94% vs. 48% $P < 0.0001$). The baseline mean PP-NRS score was lower in the dupilumab group than in the CyA group (6.1 vs. 7.3 $P < 0.001$) and the MTX group (6.1 vs. 6.7 $P < 0.032$). Patients were on CyA treatment for a significantly shorter mean duration (8.0 months) than those on MTX (13.7 months) and dupilumab (17.9 months).

The systemic treatment dosing regimens followed clinical practice and ranged from 1.4 to 5 mg kg^{-1} daily of CyA and 5–25 mg weekly of MTX. The most common dose for adults on dupilumab was 300 mg every 2 weeks. The most common dose for children on dupilumab was 200 mg every 2 weeks, with some patients on 200 mg every 3 weeks, 200 mg every 4 weeks and 200 mg every 8 weeks.

Treatment effectiveness

Survival analysis

Raw and adjusted survival curves can be seen in Figure 1 and the hazard ratios (HRs) from Cox models in Table 2. In summary, CyA achieves EASI-50, EASI-75 and EASI-90 more rapidly than dupilumab, which in turn achieves these three outcomes more rapidly than MTX (all point estimates of HRs are positive). The statistically significant differences are between CyA and MTX in EASI-50, EASI-75 and EASI-90 ($P < 0.0005$, $P < 0.021$ and $P < 0.0007$, respectively); between CyA and dupilumab in EASI-50 ($P < 0.014$); and between dupilumab and MTX in EASI-75 and EASI-90 ($P < 0.04$ and $P < 0.0016$, respectively). The unadjusted HRs between treatment groups of achieving EASI-50, EASI-75 and EASI-90 are shown in Table S1 (see Supporting Information).

Effectiveness adjusting for disease severity

To guide clinical decision-making between physicians and patients, linear models were additionally used to predict changes in severity score with each treatment after a visit. The regression lines in Figure 2 show that the higher the disease severity at a visit, the greater the expected reduction in severity is at the next visit. This holds for all four severity outcomes and the three treatments and is partly explained by the well-known regression-to-the-mean effect. There is significant evidence that the strength of this effect (the slope of the line) differs by treatment in the models for EASI ($P < 0.0006$, Figure 2a), showing that the lines are closer together at lower EASI scores but deviate from each other as the EASI increases. The POEM (Figure 2b) and PP-NRS (Figure 2c) model lines for dupilumab and MTX are more or less parallel with dupilumab always below (i.e. more

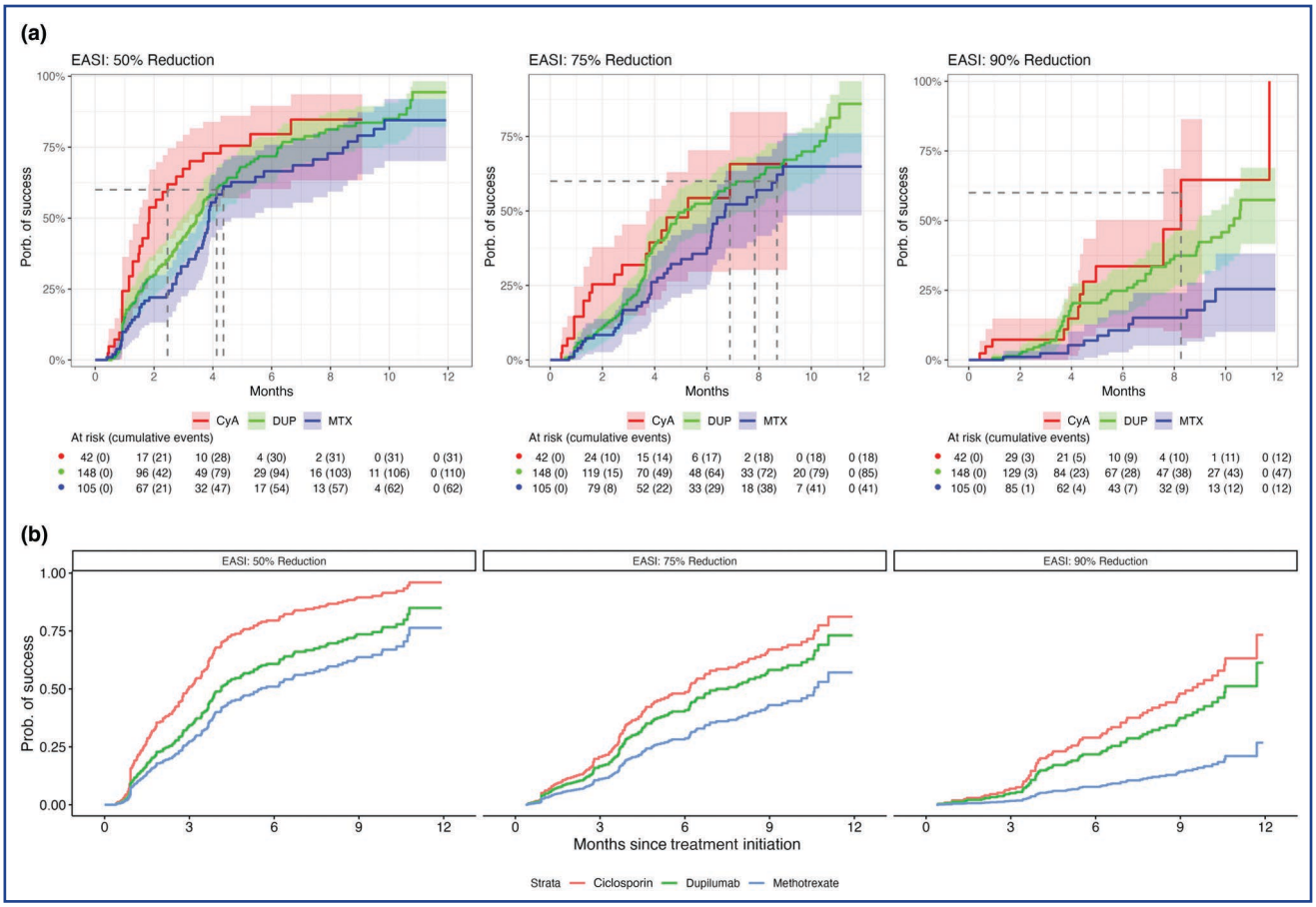


Figure 1 The proportion of patients on ciclosporin (CyA), dupilumab (DUP) and methotrexate (MTX) achieving EASI-50, EASI-75 and EASI-90 over time. Kaplan–Meier analysis: (a) unadjusted and (b) adjusted for age, sex, ethnicity, number of previous treatments and baseline EASI.

effective) than MTX, while CyA has a stronger slope cutting through the other two. This suggests that at high POEM and PP-NRS scores CyA might be more effective than dupilumab, while at low scores it might be less effective than MTX. In DLQI the pattern is similar but the slope of the CyA line is less pronounced and the difference between slopes is not significant ($P<0.08$, Figure 2d).

The tables below each panel in Figure 2 illustrate the estimated difference in effectiveness between treatments at different disease severities. Low, middle and high example values for (a) EASI, (b) POEM, (c) PP-NRS and (d) DLQI scores, which represent the severity range of patients requiring systemic treatment, are shown. The black dashed lines in the figures correspond to these values. The differences between treatments in the estimated score reduction per month, as estimated by the model, are shown with 95% confidence intervals (CIs).

Table 2 Adjusted hazard ratios between treatment groups of achieving EASI-50, EASI-75 and EASI-90; mean (95% confidence interval)

Comparison	EASI-50	EASI-75	EASI-90
Dupilumab – Methotrexate	1.31 (0.93–1.85) $P=0.1215$	1.55 (1.02–2.36) $P=0.0399$	3.04 (1.53–6.04) $P=0.0015$
Ciclosporin – Methotrexate	2.22 (1.42–3.47) $P=0.0004$	1.97 (1.11–3.50) $P=0.0204$	4.24 (1.86–9.62) $P=0.0006$
Ciclosporin – Dupilumab	1.69 (1.12–2.57) $P=0.0130$	1.27 (0.75–2.17) $P=0.3787$	1.39 (0.71–2.73) $P=0.3332$

Models adjusted for age, sex, ethnicity, number of previous treatments and baseline Eczema Area and Severity Index (EASI)

Eczema Area and Severity Index

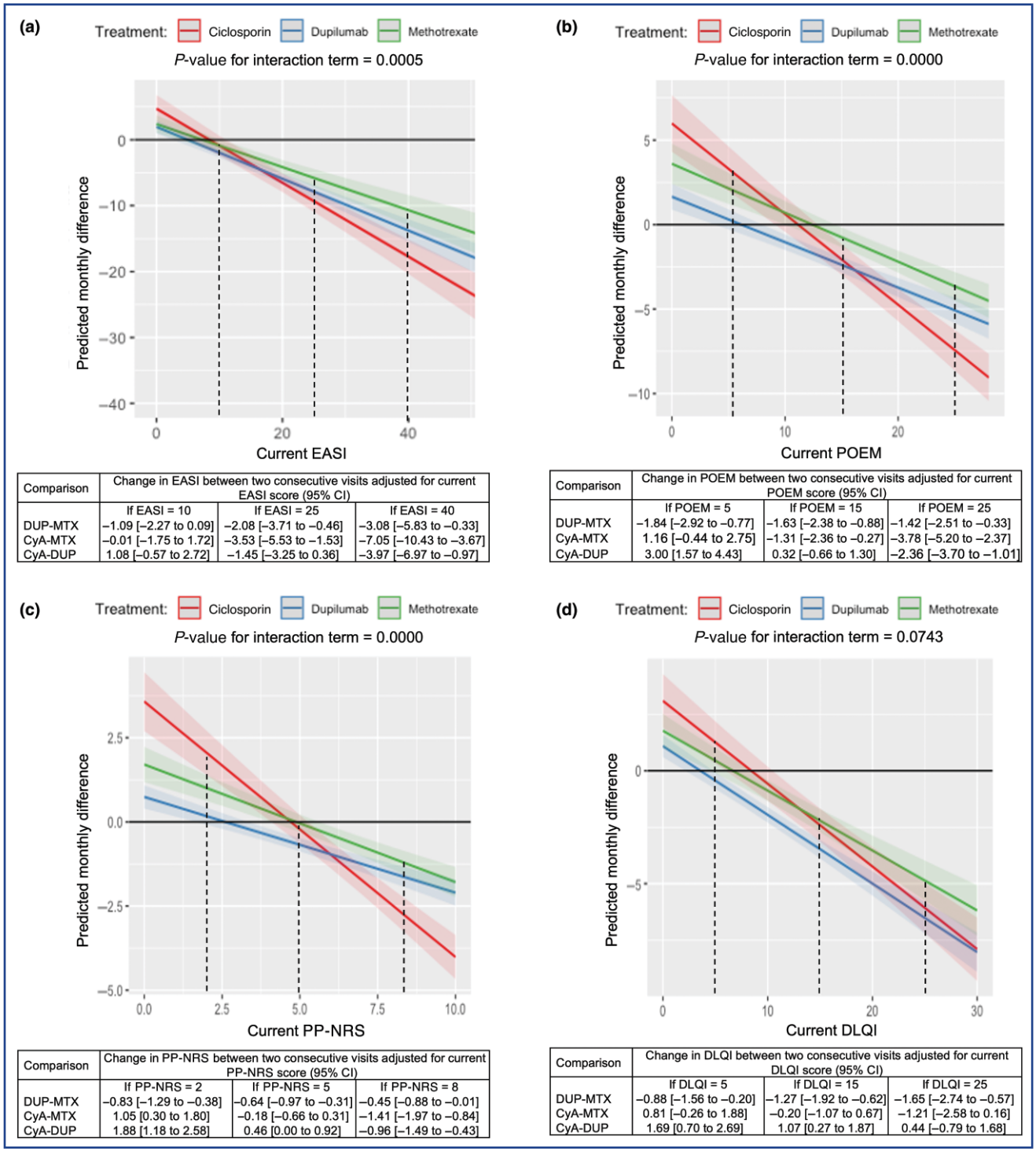
The differences between treatments in reducing EASI, POEM and PP-NRS scores depend significantly on the current score (Figure 2a–c). For example, in patients with an EASI score of 40, those on CyA are expected to benefit from an EASI reduction in the next month 3.97 points larger than in those on dupilumab (95% CI −6.97 to −0.97) and 7.05 points larger than in those on MTX (95% CI −10.43 to −3.67) given the same age, sex, ethnicity, treatment duration and number of previous treatments (Figure 2a). The EASI reduction in patients with an EASI of 40 on dupilumab is also significantly greater than in those on MTX (3.08 points; the 95% CI −5.83 to −0.33 excludes 0). At EASI = 25, dupilumab and CyA are significantly more effective than MTX (comparison 95% CI excludes 0) but the difference between CyA and dupilumab is not significant. In patients with EASI = 10, there are no significant differences between any treatment comparisons. This corresponds with the three lines converging on the left-hand side of Figure 2a.

Patient Oriented Eczema Measure, Peak Pruritus Numeric Rating Scale and Dermatology Life Quality Index

Dupilumab performs consistently better than MTX at all levels of severity in all three outcomes as all 95% CIs

comparing dupilumab and MTX have their upper limit below 1.

However, CyA compares with the other two differently depending on the score level. At the highest POEM and PP-NRS scores, CyA achieves greater reductions than MTX and dupilumab. At mid-level scores, CyA performs somewhere between the other two, and at lower scores CyA performs worse than MTX and dupilumab with statistically significant



Comparison	Change in EASI between two consecutive visits adjusted for current EASI score (95% CI)		
	If EASI = 10	If EASI = 25	If EASI = 40
DUP-MTX	−1.09 [−2.27 to 0.09]	−2.08 [−3.71 to −0.46]	−3.08 [−5.83 to −0.33]
CyA-MTX	−0.01 [−1.75 to 1.72]	−3.53 [−5.53 to −1.53]	−7.05 [−10.43 to −3.67]
CyA-DUP	1.08 [−0.57 to 2.72]	−1.45 [−3.25 to 0.36]	−3.97 [−6.97 to −0.97]

Comparison	Change in POEM between two consecutive visits adjusted for current POEM score (95% CI)		
	If POEM = 5	If POEM = 15	If POEM = 25
DUP-MTX	−1.84 [−2.92 to −0.77]	−1.63 [−2.38 to −0.88]	−1.42 [−2.51 to −0.33]
CyA-MTX	1.16 [−0.44 to 2.75]	−1.31 [−2.36 to −0.27]	−3.78 [−5.20 to −2.37]
CyA-DUP	3.00 [1.57 to 4.43]	0.32 [−0.66 to 1.30]	−2.36 [−3.70 to −1.01]

Comparison	Change in PP-NRS between two consecutive visits adjusted for current PP-NRS score (95% CI)		
	If PP-NRS = 2	If PP-NRS = 5	If PP-NRS = 8
DUP-MTX	−0.83 [−1.29 to −0.38]	−0.64 [−0.97 to −0.31]	−0.45 [−0.88 to −0.01]
CyA-MTX	1.05 [0.30 to 1.80]	−0.18 [−0.66 to 0.31]	−1.41 [−1.97 to −0.84]
CyA-DUP	1.88 [1.18 to 2.58]	0.46 [0.00 to 0.92]	−0.96 [−1.49 to −0.43]

Comparison	Change in DLQI between two consecutive visits adjusted for current DLQI score (95% CI)		
	If DLQI = 5	If DLQI = 15	If DLQI = 25
DUP-MTX	−0.88 [−1.56 to −0.20]	−1.27 [−1.92 to −0.62]	−1.65 [−2.74 to −0.57]
CyA-MTX	0.81 [−0.26 to 1.88]	−0.20 [−1.07 to 0.67]	−1.21 [−2.58 to 0.16]
CyA-DUP	1.69 [0.70 to 2.69]	1.07 [0.27 to 1.87]	0.44 [−0.79 to 1.68]

Figure 2 Predicted change in (a) EASI, (b) POEM, (c) PP-NRS and (d) DLQI per month between two consecutive visits in each treatment group. Monthly change in outcome score between consecutive visits [(score in following visit – score in current visit)/(months between visits)] are modelled with a linear mixed-effects model adjusting for the outcome measure at the current visit, age, sex, ethnicity, time on the current treatment and number of previous treatments. The tables below each figure show the estimated difference in effectiveness between treatments at low, middle and high (a) EASI, (b) POEM, (c) PP-NRS and (d) DLQI scores (black dashed lines) at the current visit. 'Current' score = outcome measure at the first of two consecutive visits.CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numeric Rating Scale

differences. The DLQI pattern is similar to those for POEM and PP-NRS, although CyA is not more effective than dupilumab at improving quality of life at higher DLQI scores. Dupilumab is more effective at reducing DLQI than MTX at any level.

Paediatric subgroup analysis

The results of the paediatric subgroup analysis are provided in Tables S2 and S3 and Figures S1 and S2 (see Supporting Information).

Treatment safety

There were a total of 605 AEs reported throughout the study (Table 3). There were no differences in the overall incidence of AEs between treatment groups. In the CyA group, there were 57 AEs in 27 (47.4%) treatment courses (incidence rate 734 per 10 000 person-months). In the dupilumab group there were 395 AEs in 174 (61.7%) treatment courses (incidence rate 654 per 10 000 person-months), compared with 153 AEs in 73 (48.99%) treatment courses (incidence rate 594 per 10 000 person-months) in the MTX arm. Gastrointestinal disorders, including nausea and vomiting, were more common with MTX (incidence rate 244 compared with 136 and 79 per 10 000 person-months for CyA and dupilumab respectively). Eye disorders were more common with dupilumab (incidence rate 274 vs. 82 and 49 per 10 000 person-months for CyA and MTX repsectively). Nervous system disorders, mainly headaches, were more common with CyA (incidence rate 190 and reported in 75 and 41 per 10 000 person-months for dupilumab and MTX repsectively).

Fifteen serious AEs (SAEs) were reported which led to hospitalization in 11 cases, three life-threatening events and one death (Table 4). Seven of the 15 SAEs occurred in seven of 282 (2%) patients on dupilumab, and all were considered unlikely to be related to the treatment apart from one case of herpes simplex infection. Eight of the 15 SAEs were reported in eight of 149 (5%) patients on MTX, including two events which were considered related to the treatment: one herpes simplex infection and one varicella infection. There were no SAEs reported in the 57 patients on CyA.

Discussion

The time to achieve EASI-50, EASI-75 and EASI-90 was shorter with dupilumab and CyA than with MTX. When taking into consideration the effect of disease severity on treatment effectiveness, dupilumab was consistently more effective than MTX at all severities and across all four outcomes measures (EASI, POEM, PP-NRS and DLQI). CyA effectiveness was more complex. In very severe disease, CyA tended to achieve greater reductions in outcome scores than dupilumab and MTX (except possibly for DLQI). In less severe disease the effectiveness of CyA was between that of MTX and dupilumab respectively, except with EASI reduction where CyA was still more effective than dupilumab. In more moderate disease, CyA was less effective than dupilumab in all outcomes and not more (sometimes less) effective than MTX. This pattern is consistent with clinical practice in which CyA is often used as an effective rescue treatment to rapidly control very severe disease.

Dupilumab has been shown in real-world monotherapy studies to have a comparable effectiveness to RCT findings in adults and children.[21–23] Real-world studies from the USA[21] and Europe[22] comparing dupilumab with conventional systemics, including CyA and MTX, found increased dupilumab drug survival compared with conventional systemics. However, comparisons of treatment effectiveness and safety were not reported. The recently updated European and American guidelines for the management of atopic dermatitis in adults make strong recommendations for the use of dupilumab and other novel therapies while the conventional systemics including MTX and CyA are only cautiously recommended.[23–25] However, many regulatory bodies, such as the UK National Institute for Clinical and Care Excellence (NICE), stipulate that a conventional systemic agent needs to be tried first, before a novel one can be entertained. This guidance is unlikely to change in the future. In addition, MTX is an affordable systemic treatment option for middle- and low-resource settings.[26]

We found that the differences between treatments in reducing EASI, POEM and PP-NRS between consecutive study visits were dependent on AD severity. The increased effectiveness of CyA compared with MTX and dupilumab in very severe disease reached levels above the minimal clinically important differences (MCIDs) for these measures. For instance, at a high POEM of 25, the expected score reduction with CyA was 3.78 points greater than that with MTX (MCID 3.4 points). Similarly, at a high EASI of 40, the EASI reduction with CyA was 7.05 points greater than that with MTX (MCID 6.6 points).

When comparing treatment effectiveness exclusively in paediatric patients we observed similar trends to those found in the combined adult and paediatric study population. All EASI reductions were more rapidly achieved with dupilumab and CyA than with MTX treatment and we observed similar patterns in EASI changes between consecutive visits after adjustment for severity. Many of these differences between treatments did not reach statistical significance. This is likely to be because of the smaller sample size in the paediatric cohort. Similarly, differences between treatments in PP-NRS reduction were not significant in the paediatric subgroup. Consistent with the combined adult and paediatric analysis, in more severe paediatric AD, CyA was the most effective treatment at reducing patient-assessed severity.

A limitation of this study was the baseline differences between treatment groups, which reflect real-world clinical practice. The CyA group had a higher baseline severity and shorter duration of treatment than the MTX and dupilumab groups. In the comparison of treatment effectiveness, all linear models were adjusted for baseline EASI as well as age, sex, ethnicity (White/non-White) and number of previous systemic treatments received. Future studies with larger populations would allow for stratified analyses according to ethnicity and sex, to further account for these potential confounders. The baseline differences reflect the clinical preference for CyA as short-term and fast-acting rescue treatment in more severe AD when rapid disease control is needed. CyA is often stopped within a year due to AEs or to prevent AEs. This is in contrast with dupilumab, which is mostly well tolerated with long-term use. We acknowledge that these treatments are used in different clinical scenarios and this needs to be considered when applying the results of this comparison study to clinical practice.

Table 3 The most frequent adverse events (AEs)[a] in the ciclosporin, dupilumab and methotrexate treatment groups

	Dupilumab ($n=282$) 395 events in 174 (61.7%) TCs IR[b] = 654/10 000 PM			Methotrexate ($n=149$) 153 events in 73 (48.99%) TCs IR[b] = 594/10 000 PM			Ciclosporin ($n=57$) 57 events in 27 (47.4%) TCs IR[b] = 734/10 000 PM		
SOC/AE	**AEs**	**TCs, *n* (%)**	**IR[b]**	**AEs**	**TCs, *n* (%)**	**IR[b]**	**AEs**	**TCs, *n* (%)**	**IR[b]**
Eye disorders									
SOC	75	73 (25.9)	274.4	6	6 (4.0)	48.8	3	3 (5.3)	81.5
Dry eye	13	13 (4.6)	48.9	0	0 (0)	0	0	0 (0)	0
Eye irritation	12	12 (4.3)	45.1	1	1 (0.7)	8.1	0	0 (0)	0
Eye pruritus	9	9 (3.2)	33.8	0	0 (0)	0	1	1 (1.8)	27.2
Noninfective conjunctivitis	18	17 (6.0)	63.9	0	0 (0)	0	1	1 (1.8)	27.2
Ocular hyperaemia	6	6 (2.1)	22.6	0	0 (0)	0	0	0 (0)	0
Ocular surface disease	3	3 (1.1)	11.3	0	0 (0)	0	0	0 (0)	0
Gastrointestinal disorders									
SOC	21	21 (7.4)	78.9	32	30 (20.1)	244.1	5	5 (8.8)	135.9
Abdominal pain	5	5 (1.8)	18.8	4	4 (2.7)	32.6	2	2 (3.5)	54.4
Diarrhoea	3	3 (1.1)	11.3	4	4 (2.7)	32.6	0	0 (0)	0
Mouth ulceration	0	0 (0)	0	3	3 (2.0)	24.4	0	0 (0)	0
Nausea	6	6 (2.1)	22.6	17	15 (10.1)	122.1	0	0 (0)	0
Vomiting	4	4 (1.4)	15.0	2	2 (1.3)	16.3	1	1 (1.8)	27.2
Immune system disorders									
SOC	12	11 (3.9)	41.4	4	4 (2.7)	32.6	1	1 (1.8)	27.2
Anaphylactic reaction	3	3 (1.1)	11.3	2	2 (1.3)	16.3	0	0 (0)	0
Hypersensitivity	3	2 (0.7)	7.5	0	0 (0)	0	1	1 (1.8)	27.2
Seasonal allergy	4	4 (1.4)	15.0	1	1 (0.7)	8.1	0	0 (0)	0
Infections and infestations									
SOC	91	88 (31.1)	330.8	59	55 (36.9)	447.6	12	12 (21.1)	326.1
Acute nasopharyngitis	18	16 (5.7)	60.1	15	14 (9.4)	113.9	2	2 (3.5)	54.4
Conjunctivitis	4	4 (1.4)	15.0	1	1 (0.7)	8.1	0	0 (0)	0
COVID-19	16	16 (5.7)	60.1	10	9 (6.0)	73.2	1	1 (1.8)	27.2
Ear infection	4	4 (1.4)	15.0	1	1 (0.7)	8.1	0	0 (0)	0
Folliculitis	0	0 (0)	0	3	3 (2.0)	24.4	1	1 (1.8)	27.2
Herpes simplex	10	9 (3.2)	33.8	3	3 (2.0)	24.4	0	0 (0)	0
Influenza	4	4 (1.4)	15.0	0	0 (0)	0	0	0 (0)	0
LRTI	7	7 (2.5)	26.3	5	4 (2.7)	32.6	1	1 (1.8)	27.2
Skin infection	8	8 (2.8)	30.1	10	9 (6.0)	73.2	4	4 (7.0)	108.7
Investigations									
SOC	16	16 (5.7)	60.1	4	4 (2.7)	32.6	4	4 (7.0)	108.7
Eosinophil count increased	4	4 (1.4)	15.0	0	0 (0)	0	1	1 (1.8)	27.2
Metabolism and nutrition disorders									
SOC	3	3 (1.1)	11.3	3	3 (2.0)	24.4	0	0 (0)	0
Decreased appetite	1	1 (0.4)	3.8	3	3 (2.0)	24.4	0	0 (0)	0
Musculoskeletal and connective tissue disorders									
SOC	16	16 (5.7)	60.1	4	4 (2.7)	32.6	3	3 (5.3)	81.5
Arthralgia	4	4 (1.4)	15.0	0	0 (0)	0	1	1 (1.8)	27.2
Pain in extremity	4	4 (1.4)	15.0	2	2 (1.3)	16.3	0	0 (0)	0
Nervous system disorders									
SOC	20	20 (7.1)	75.2	5	5 (3.4)	40.7	7	7 (12.3)	190.2
Headache	9	9 (3.2)	33.8	4	4 (2.7)	32.6	2	2 (3.5)	54.4
Psychiatric disorders									
SOC	14	14 (4.95)	52.6	3	3 (2.0)	24.4	2	2 (3.5)	54.4
Depressed mood	3	3 (1.1)	11.3	1	1 (0.7)	8.1	0	0 (0)	0
Respiratory, thoracic and mediastinal disorders									
SOC	18	18 (6.4)	67.7	3	3 (2.0)	24.4	3	3 (5.3)	81.5
Asthma	5	5 (1.8)	18.8	1	1 (0.7)	8.1	0	0 (0)	0
Cough	4	4 (1.4)	15.0	1	1 (0.7)	8.1	1	1 (1.8)	27.2
Skin and subcutaneous tissue disorders									
SOC	68	67 (23.7)	251.8	17	13 (8.7)	105.8	8	8 (14.0)	217.4
Acne	5	5 (1.8)	18.8	0	0 (0)	0	2	2 (3.5)	54.4
Alopecia	9	8 (2.8)	30.1	1	1 (0.7)	8.1	1	1 (1.8)	27.2
Eczema	31	31 (10.99)	116.5	10	7 (4.7)	56.97	3	3 (5.3)	81.5
Erythema	5	5 (1.8)	18.8	0	0 (0)	0	0	0 (0)	0

IR, incidence rate; LRTI, lower respiratory tract infection; PM, person-month; SOC, system organ class; TCs, treatment courses. [a]AEs are based on MedDRA code Preferred Terms. [b]The incidence rate is calculated as number of events over the person-months in the groups (× 10 000).

Unlike the CyA and MTX groups, almost all patients treated with dupilumab were not treatment naïve. This is consistent with other real-world studies[27] and reflects the UK NICE recommendation[28] that patients have an inadequate response or contraindication to treatment with at least one conventional systemic therapy, before dupilumab is prescribed. In practice, most patients on dupilumab will have received treatment with a first-line conventional systemic, such as CyA and MTX, prior

Table 4 Serious adverse events (SAE)[a] on dupilumab and methotrexate[b]

Treatment/System organ class	SAE	Relatedness to the drug	SAE category
Dupilumab			
Cardiac disorders	Acute myocardial infarction	Unlikely	Death
Immune system disorders	Anaphylactic reaction	Unlikely	Life threatening
	Anaphylactic reaction	Unlikely	Life threatening
Infections and infestations	Herpes simplex	Likely	H/PEH
Injury, poisoning and procedural complications	Fibula fracture	Unlikely	H/PEH
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	Unlikely	H/PEH
Skin and subcutaneous tissue disorders	Dermatitis exfoliative generalized	Unlikely	H/PEH
Methotrexate			
Immune system disorders	Anaphylactic reaction	Unlikely	H/PEH
	Anaphylactic reaction	Unlikely	Life threatening
Infections and infestations	Skin infection	Unlikely	H/PEH
	Skin infection	Unlikely	H/PEH
	Herpes simplex	Likely	H/PEH
	Varicella	Likely	H/PEH
Injury, poisoning and procedural complications	Accidental overdose	Unlikely	H/PEH
	Joint injury	Unlikely	H/PEH

H/PEH, Hospitalization or prolonged existing hospitalization. [a]SAEs are based on MedDRA code Preferred Terms. [b]No SAEs were reported in any patients on ciclosporin.

to dupilumab, and therefore have partially treated disease with less potential for improvement compared with the MTX and CyA subjects. Although we have adjusted for the number of previous treatments in the statistical analysis, the observed differences in drug effectiveness may partly reflect the more treatment-resistant disease of the dupilumab cohort. We can reason how our estimate would be affected by this potential bias. If we assume our dupilumab-treated patients have more treatment-resistant disease, we would expect that our dupilumab cohort would show an underestimation of the 'true' effect of dupilumab in a group of more treatment-naïve patients, comparable with those in our MTX cohort. Despite this underestimation, dupilumab still shows greater effectiveness than MTX in all outcomes. Therefore, the true difference in effectiveness between dupilumab and MTX is likely to be even greater in favour of dupilumab.

While there were no differences in total AE incidence between treatment groups, specific AE subtypes were associated with each treatment. Gastrointestinal disorders were more frequent in the MTX group, eye disorders were more frequent in the dupilumab group, and neurological AEs, mainly headaches, were more frequent with CyA, all AE profiles known to be associated with these systemic therapies.[27,29–32] Interestingly, we did not see increased renal impairment and dyslipidaemia in the CyA cohort. This may be due to the short duration of treatment in this group, suggesting that the treatment was stopped before the onset of these AEs. The incidence of AEs in the dupilumab group was higher than has been previously reported. This may partly be because some patients in the A-STAR register who were started on dupilumab were prescribed prophylactic eye drops and warned about the potential side-effect of eye irritation. This may have alerted patients to this possible side-effect and increased the likelihood of AE reporting in this group. The follow-up period and sample size in this study are relatively modest and not sufficiently powered to conclusively report SAEs. Future analysis of more participants, over longer time periods and with linked Hospital Episode Statistics data, is needed.

Further real-world studies are needed to validate the findings of this study, also comparing dupilumab with other novel biologics and JAK inhibitors. Recent real-world monotherapy studies of baricitinib[33] and upadacitinib[34] have found similar effectiveness to RCT data, and a small ($n=23$) real-world study found comparable effectiveness between upadacitinib and dupilumab in paediatric AD at 24 weeks.[35] However, these agents have not yet been compared with conventional systemics in large, long-term studies. Mechanistic studies are also needed to further understand the factors underlying treatment responses to systemic AD therapies. These may, for instance, reveal immune or microbiome-based biomarkers to predict treatment response and allow for a more personalized approach to treating AD.

This real-world comparison of CyA, dupilumab and MTX in AD suggests that dupilumab is consistently more effective than MTX and that CyA is most effective in very severe disease. These findings should inform clinical practice and guide treatment decisions in paediatric and adult AD.

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Conflicts of interest

The full conflicts of interest statement is provided in Appendix 3.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The study is covered by Research ethics committee reference no. 18/WA/0200, ISRCTN 11210918.

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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Michael R. Ardern-Jones, Paula Beattie, Sara Brown, Victoria Brown, Michael J. Cork, Sharmela Darné, May Fadhil, Caoimhe Fahy, Leila Ferguson, Carsten Flohr, Ross Hearn, John R. Ingram, Graham A. Johnston, Effi Ladoyanni, Alison Layton, Claire Leitch, Joanne Llewellyn, Mark Lunt, Irene Man, Louise Newell, Graham Ogg, Urvi Popli, Nick Reynolds, Ann Sergeant, Ben Thompson, Joanne Topliffe, Shyamal Wahie, Hannah Wainman, Richard B. Warren, Aaron Wernham, Richard Woolf, Zenas Z.N. Yiu.

Appendix 3 Full list of authors' conflicts of interest

J.R.I. received a stipend as Editor-in-Chief of the *British Journal of Dermatology* (at the time of submission) and an authorship honorarium from UpToDate; he is a consultant for AbbVie, Boehringer Ingelheim, ChemoCentryx, Citryll, MoonLake, Novartis, UCB Pharma and UNION Therapeutics and has served on advisory boards for Insmed, Kymera Therapeutics and Viela Bio; his department receives income from the copyright of the Dermatology Life Quality Instrument (DLQI) and related instruments; he is treasurer of the CHORD-COUSIN Collaboration (C3) dermatology outcomes consortium. A.D.I. has received honoraria for consultancy from AbbVie, Arena Pharmaceuticals, Aslan, BenevolentAI, Chugai, Dermavant,

Genentech, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Regeneron and Sanofi.

G.A.J. has received educational grants from Sanofi-Genzyme. G.O. holds patents relevant to inflammatory skin disease. Research funds are administered through his institution from Janssen and UCB. M.R.A.-J. has received speaker, adviser, honoraria, travel/research/departmental grants from AbbVie, Almirall, Amgen, Ducentis, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, UCB and Unilever. C.F. is chief investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK–Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a principal investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/); he also leads the EU Trans-Foods consortium; his department has received funding from Pfizer and Sanofi-Genzyme for skin microbiome work; he has also received compensation from the *British Journal of Dermatology* (reviewer and section editor) and EuroGuiDerm (guidelines lead). All other authors declare no conflicts of interest.