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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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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 EASI, POEM and itch compared to those treated with MTX.
- There was a similar incidence of adverse events with all three medications.

Abstract

Background: The main conventional systemic atopic dermatitis (AD) treatments are methotrexate (MTX) and ciclosporin (CyA). Dupilumab was the first novel systemic agent to enter routine clinical practice. There are no head-to-head randomised 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: The aim of this study was to compare the real-world clinical effectiveness and safety of CyA, dupilumab and MTX in AD.

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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). Minimum duration of treatment was 28 days and follow-up was 12 months. Adjusted Cox-regression was used to compare the hazards 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: 488 patients (n=311 adults and n=177 children/adolescents) on dupilumab (n=282), methotrexate (n=149), or CyA (n=57) were included. CyA and MTX were primarily used first line, while dupilumab was mainly a second line systemic 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 to MTX. After adjustment for previous severity, the reduction in EASI, POEM, PP-NRS and DLQI was greater for patients treated with dupilumab compared to MTX. In severe patients the reduction in EASI, POEM, and PP-NRS was even greater with CyA. The incidence of AEs was 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 one follow-up year.

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Introduction

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 immuno-modulatory 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 immuno-modulatory therapies cannot be used for many years because of adverse events 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 3 randomised controlled trials (RCT) have demonstrated its efficacy and safety profile, compared to 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 generalisability 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 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 adverse events. In contrast MTX and dupilumab are typically used for more long-term disease control.

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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 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 (NMA) 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 is 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 AD patients treated with systemic immune-modulatory 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.

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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 from 1st October 2018 to 30th 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 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. Research ethics committee reference 18/WA/0200, ISRCTN 11210918.

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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 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 from 16 years of age 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 adverse events (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 summarised 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, PPNRS and DLQI) was the latest score recorded within a 28-day window *before* treatment initiation. If there

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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

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were not imputed. All analyses were conducted using R 3.4.1 computational software.[20]

Results

Baseline patient characteristics

488 patients were included (mean age 27.4 years, standard deviation (SD) 15.6 years, 217 patients (44.5%) were female and their baseline characteristics are summarised in Table 1. 282 patients (44% female, mean age 28.8 years) were treated with dupilumab. 149 patients (44% female, mean age 24.5 years) received MTX. 57 patients (49% female, mean age 28.1 years) were treated with CyA.

While most baseline characteristics were similar across study groups, there were some differences between the treatment groups (table 1). The mean age of patients treated with dupilumab was higher than those treated with MTX ($p<0.009$). More dupilumab patients 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 methotrexate group (6.1 vs 6.7 $p<0.032$). Patients were on CyA treatment for a significantly shorter mean duration (8.04 months) than those on MTX (13.7 months) and dupilumab (17.9 months).

The systemic treatment dosing regimens followed clinical practice and ranged from 1.4-5 mg/kg/day 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

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on dupilumab was 200 mg every two weeks, with some patients on 200 mg every 3 weeks, 200mg every 4 weeks and 200mg every 8 weeks.

Treatment effectiveness

Survival analysis

Raw and adjusted survival curves can be visualised in figure 1 and the hazard ratios (HR) 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 HR 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 hazard ratios between treatment groups of achieving EASI-50, EASI-75 and EASI-90 are shown in supplementary table 1.

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 ($p<0.0006$, Fig. 2A) showing that the lines are closer together at lower EASI scores but deviate from each other as the EASI increases. The POEM (Fig. 2B) and PP-NRS (Fig. 2C) model

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lines for dupilumab and MTX are more or less parallel with dupilumab always below (i.e. more 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 may 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 ($p<0.08$, Fig. 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.

EASI

The differences between treatments in reducing EASI, POEM and PP-NRS scores depend significantly on the current score (Fig. 2 A-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 those on dupilumab (95%CI -6.97 to -0.97) and 7.05 points larger than those on MTX (95%CI -10.43 to -3.67) given the same age, sex, ethnicity, treatment duration and number of previous treatments (Fig. 2A). The EASI reduction in patients with an EASI of 40 on dupilumab is also significantly greater than those on MTX (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

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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 Fig 2A.

POEM, PP-NRS and DLQI

Dupilumab performs consistently better than MTX at all levels of severity in all three outcomes as all confidence intervals comparing dupilumab and MTX have their upper limit below 1 in the three outcomes.

CyA, however, compares to 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 differences. The DLQI pattern is similar to 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 appendix S1.

Treatment safety

There were a total of 394 adverse events (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 45 AEs in 18 (40.00%) treatment courses (incidence 718 per 10,000 person-months). In the dupilumab group there were 299

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AEs in 135 (45.15%) treatment courses (incidence 664 per 10,000 person-months), compared to 111 AEs in 54 (48.64%) treatment courses (incidence 561 per 10,000 person-months) in the MTX arm. Gastrointestinal disorders, including nausea and vomiting, were more common with MTX (incidence 302) compared to 160 and 98 per 10,000 person-months for CyA and dupilumab. Eye disorders were more common with dupilumab (incidence 256) versus 120 and 42 per 10,000 person-months for CyA and MTX. Nervous system disorders, mainly headaches, were more common with CyA (incidence 239) and reported in 74 and 42 per 10,000 person-months for dupilumab and MTX.

13 serious AEs (SAEs) were reported which led to hospitalisation in 10 cases, two life threatening events and one death (Table 4). 7/13 SAEs occurred in 7 out 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. There were 6/13 SAEs reported in 6 out of 149 (4%) patients on MTX, including two events which were considered related to the treatment: one herpes simplex infection and one joint effusion. 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 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 maybe for

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DLQI). In less severe disease CyA effectiveness was between MTX and dupilumab, 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 United States[21] and Europe[22] comparing dupilumab with conventional systemics, including CyA and MTX, found increased dupilumab drug survival compared with conventional systemics. Comparisons of treatment effectiveness and safety, however, were not reported. The recently updated European and American guideline for the management of atopic dermatitis in adults makes 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, methotrexate 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 to MTX and dupilumab in very severe disease reached

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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 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 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 were 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

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is needed. CyA is often stopped within a year due to adverse events or to prevent adverse events. This is in contrast to 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.

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 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 to dupilumab, and therefore have partially treated disease with less potential for improvement compared to 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 patients have more treatment-resistant disease, we would expect that our dupilumab cohort would underestimate the "true" effect of dupilumab in a group of more treatment-naïve patients, comparable to those in our MTX cohort. Despite this underestimation, dupilumab still shows greater effectiveness than MTX in all outcomes. The true difference in effectiveness between dupilumab and MTX is therefore likely to be even greater in favour of dupilumab.

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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 ASTAR 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 Janus kinase (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.

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These may, for instance, reveal immune or microbiome-based biomarkers to predict treatment response and allow for a more personalised 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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Figure Legends

Figure 1: The proportion of patients on ciclosporin, dupilumab and methotrexate achieving EASI-50, EASI-75 and EASI-90 over time

The proportion of patients on ciclosporin, dupilumab and methotrexate achieving EASI-50, EASI-75 and EASI-90 over time (A) without adjustment and (B) with adjustment for age, sex, ethnicity, number of previous treatments and baseline EASI.

Figure 2: Predicted change in EASI, POEM, PP-NRS and DLQI per month between two consecutive visits in each treatment group.

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 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.

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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 (0.6%)	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%)
18-25	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))	8.04 (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))	7.27 (1.95)	6.12 (2.64)	6.74 (2.37)
POEM (mean (SD))	19.3 (7.29)	17.8 (7.86)	19.2 (6.83)
DLQI (mean (SD))	14.7 (7.64)	13.8 (8.60)	14.7 (7.97)
CDLQI (mean (SD))	11.7 (7.48)	12.0 (7.68)	14.0 (7.41)
Follow-up time (person-month)	458.03	5052.39	2045.31

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Table 2: Hazard ratios between treatment groups of achieving EASI-50, EASI-75 and EASI-90.

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

Models adjusted for age, sex, ethnicity, number of previous treatments and baseline EASI.

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1 **Table 3: The most frequent adverse events in the ciclosporin, dupilumab and methotrexate treatment groups**

System Organ Class	PT	Dupilumab (n=282) 395 events in 174 (61.83%) treatment courses inc rate=654 / 10,000 person-month			Methotrexate (n=149) 153 events in 73 (48.99%) treatment courses inc rate=594 / 10,000 person-month			Ciclosporin (n=57) 57 events in 27 (47.37%) treatment courses inc rate=734 / 10,000 person-month		
		Events	Treatment courses	Inc. Rate	Events	Treatment courses	Inc. Rate	Events	Treatment courses	Inc. Rate
Eye disorders	SOC	75	73 (25.89%)	274.39	6	6 (4.03%)	48.83	3	3 (5.26%)	81.52
	Dry eye	13	13 (4.61%)	48.86	0	0 (0%)	0	0	0 (0%)	0
	Eye irritation	12	12 (4.26%)	45.10	1	1 (0.67%)	8.14	0	0 (0%)	0
	Eye pruritus	9	9 (3.19%)	33.83	0	0 (0%)	0	1	1 (1.75%)	27.17
	Non-infective conjunctivitis	18	17 (6.03%)	63.90	0	0 (0%)	0	1	1 (1.75%)	27.17
	Ocular hyperaemia	6	6 (2.13%)	22.55	0	0 (0%)	0	0	0 (0%)	0
	Ocular surface disease	3	3 (1.06%)	11.28	0	0 (0%)	0	0	0 (0%)	0
Gastrointestinal disorders	SOC	21	21 (7.42%)	78.93	32	30 (20.13%)	244.14	5	5 (8.77%)	135.87
	Abdominal pain	5	5 (1.77%)	18.79	4	4 (2.68%)	32.55	2	2 (3.51%)	54.35
	Diarrhoea	3	3 (1.06%)	11.28	4	4 (2.68%)	32.55	0	0 (0%)	0
	Mouth ulceration	0	0 (0%)	0	3	3 (2.01%)	24.41	0	0 (0%)	0
	Nausea	6	6 (2.13%)	22.55	17	15 (10.07%)	122.07	0	0 (0%)	0
	Vomiting	4	4 (1.42%)	15.03	2	2 (1.34%)	16.28	1	1 (1.75%)	27.17
Immune system disorders	SOC	12	11 (3.89%)	41.35	4	4 (2.68%)	32.55	1	1 (1.75%)	27.17
	Anaphylactic reaction	3	3 (1.06%)	11.28	2	2 (1.34%)	16.28	0	0 (0%)	0
	Hypersensitivity	3	2 (0.71%)	7.52	0	0 (0%)	0	1	1 (1.75%)	27.17
	Seasonal allergy	4	4 (1.42%)	15.03	1	1 (0.67%)	8.14	0	0 (0%)	0
Infections and infestations	SOC	91	88 (31.1%)	330.77	59	55 (36.91%)	447.59	12	12 (21.05%)	326.09
	Acute nasopharyngitis	18	16 (5.67%)	60.14	15	14 (9.4%)	113.93	2	2 (3.51%)	54.35
	Conjunctivitis	4	4 (1.42%)	15.03	1	1 (0.67%)	8.14	0	0 (0%)	0

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	Covid-19	16	16 (5.67%)	60.14	10	9 (6.04%)	73.24	1	1 (1.75%)	27.17
	Ear infection	4	4 (1.42%)	15.03	1	1 (0.67%)	8.14	0	0 (0%)	0
	Folliculitis	0	0 (0%)	0	3	3 (2.01%)	24.41	1	1 (1.75%)	27.17
	Herpes simplex	10	9 (3.19%)	33.83	3	3 (2.01%)	24.41	0	0 (0%)	0
	Influenza	4	4 (1.42%)	15.03	0	0 (0%)	0	0	0 (0%)	0
	Lrti	7	7 (2.48%)	26.31	5	4 (2.68%)	32.55	1	1 (1.75%)	27.17
	Skin infection	8	8 (2.84%)	30.07	10	9 (6.04%)	73.24	4	4 (7.02%)	108.70
Investigations	SOC	16	16 (5.65%)	60.14	4	4 (2.68%)	32.55	4	4 (7.02%)	108.70
	Eosinophil count increased	4	4 (1.42%)	15.03	0	0 (0%)	0	1	1 (1.75%)	27.17
Metabolism and nutrition disorders	SOC	3	3 (1.06%)	11.28	3	3 (2.01%)	24.41	0	0 (0%)	0
	Decreased appetite	1	1 (0.35%)	3.76	3	3 (2.01%)	24.41	0	0 (0%)	0
Musculoskeletal and connective tissue disorders	SOC	16	16 (5.67%)	60.14	4	4 (2.68%)	32.55	3	3 (5.26%)	81.52
	Arthralgia	4	4 (1.42%)	15.03	0	0 (0%)	0	1	1 (1.75%)	27.17
	Pain in extremity	4	4 (1.42%)	15.03	2	2 (1.34%)	16.28	0	0 (0%)	0
Nervous system disorders	SOC	20	20 (7.07%)	75.17	5	5 (3.36%)	40.69	7	7 (12.28%)	190.22
	Headache	9	9 (3.19%)	33.83	4	4 (2.68%)	32.55	2	2 (3.51%)	54.35
Psychiatric disorders	SOC	14	14 (4.95%)	52.62	3	3 (2.01%)	24.41	2	2 (3.51%)	54.35
	Depressed mood	3	3 (1.06%)	11.28	1	1 (0.67%)	8.14	0	0 (0%)	0
Respiratory, thoracic and mediastinal disorders	SOC	18	18 (6.36%)	67.66	3	3 (2.01%)	24.41	3	3 (5.26%)	81.52
	Asthma	5	5 (1.77%)	18.79	1	1 (0.67%)	8.14	0	0 (0%)	0
	Cough	4	4 (1.42%)	15.03	1	1 (0.67%)	8.14	1	1 (1.75%)	27.17
Skin and subcutaneous tissue disorders	SOC	68	67 (23.67%)	251.84	17	13 (8.72%)	105.80	8	8 (14.04%)	217.39
	Acne	5	5 (1.77%)	18.79	0	0 (0%)	0	2	2 (3.51%)	54.35
	Alopecia	9	8 (2.84%)	30.07	1	1 (0.67%)	8.14	1	1 (1.75%)	27.17
	Eczema	31	31 (10.99%)	116.52	10	7 (4.70%)	56.97	3	3 (5.26%)	81.52
	Erythema	5	5 (1.77%)	18.79	0	0 (0%)	0	0	0 (0%)	0

1 Incident rate calculated as number of events over the person-months in the groups (x 10,000).

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1 **Table 4: Serious adverse events on ciclosporin, dupilumab and methotrexate**

Treatment	System Organ Class	PT	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	Hospitalisation or prolonged existing hospitalisation
	Injury, poisoning and procedural complications	Fibula fracture	Unlikely	Hospitalisation or prolonged existing hospitalisation
	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	Unlikely	Hospitalisation or prolonged existing hospitalisation
	Skin and subcutaneous tissue disorders	Dermatitis exfoliative generalised	Unlikely	Hospitalisation or prolonged existing hospitalisation
Methotrexate	Immune system disorders	Anaphylactic reaction	Unlikely	Hospitalisation or prolonged existing hospitalisation
		Anaphylactic reaction	Unlikely	Life Threatening
	Infections and infestations	Skin infection	Unlikely	Hospitalisation or prolonged existing hospitalisation
		Skin infection	Unlikely	Hospitalisation or prolonged existing hospitalisation
		Herpes simplex	Likely	Hospitalisation or prolonged existing hospitalisation
		Varicella	Likely	Hospitalisation or prolonged existing hospitalisation
	Injury, poisoning and procedural complications	Accidental overdose	Unlikely	Hospitalisation or prolonged existing hospitalisation
		Joint injury	Unlikely	Hospitalisation or prolonged existing hospitalisation

2

3 Incidence of the serious adverse events in each treatment group

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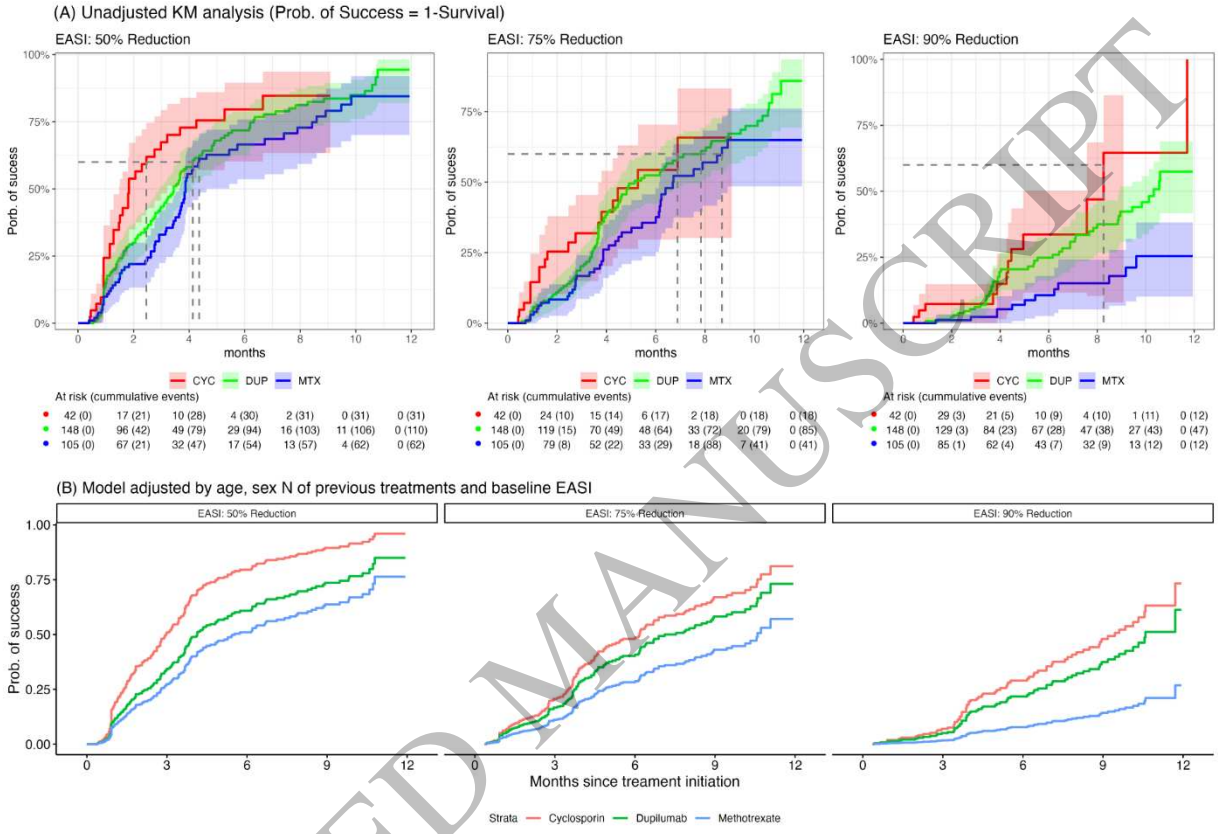

Figure 1
163x112 mm (DPI)

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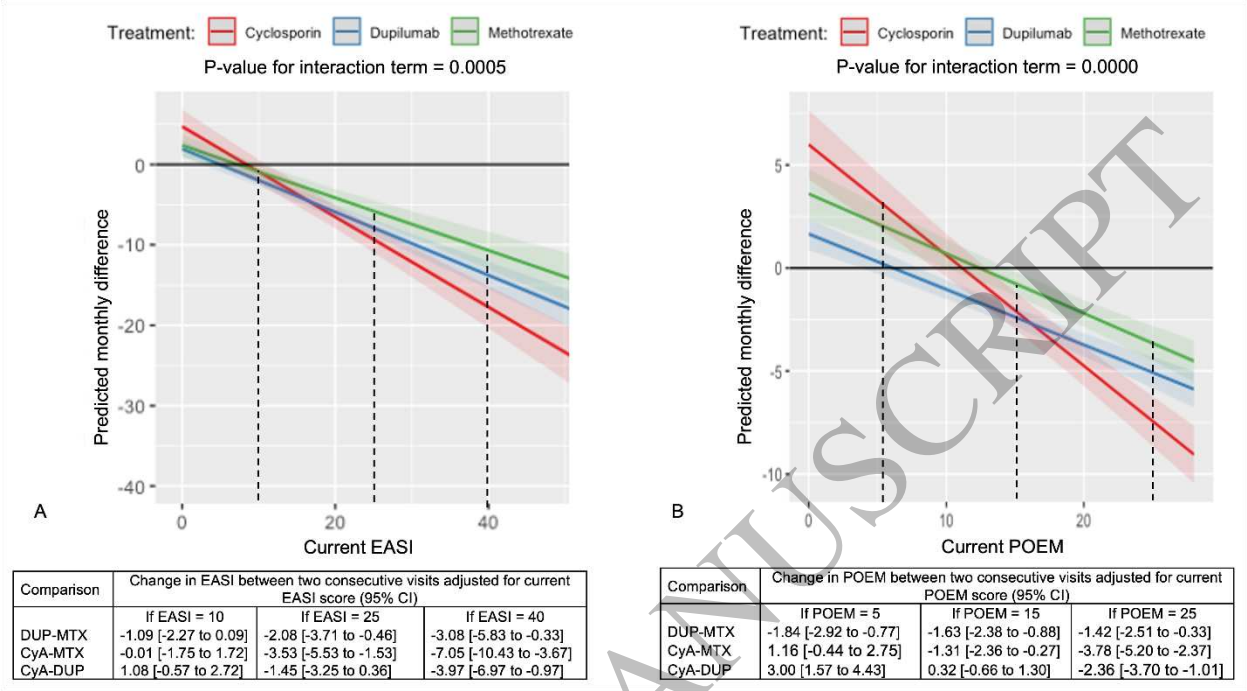
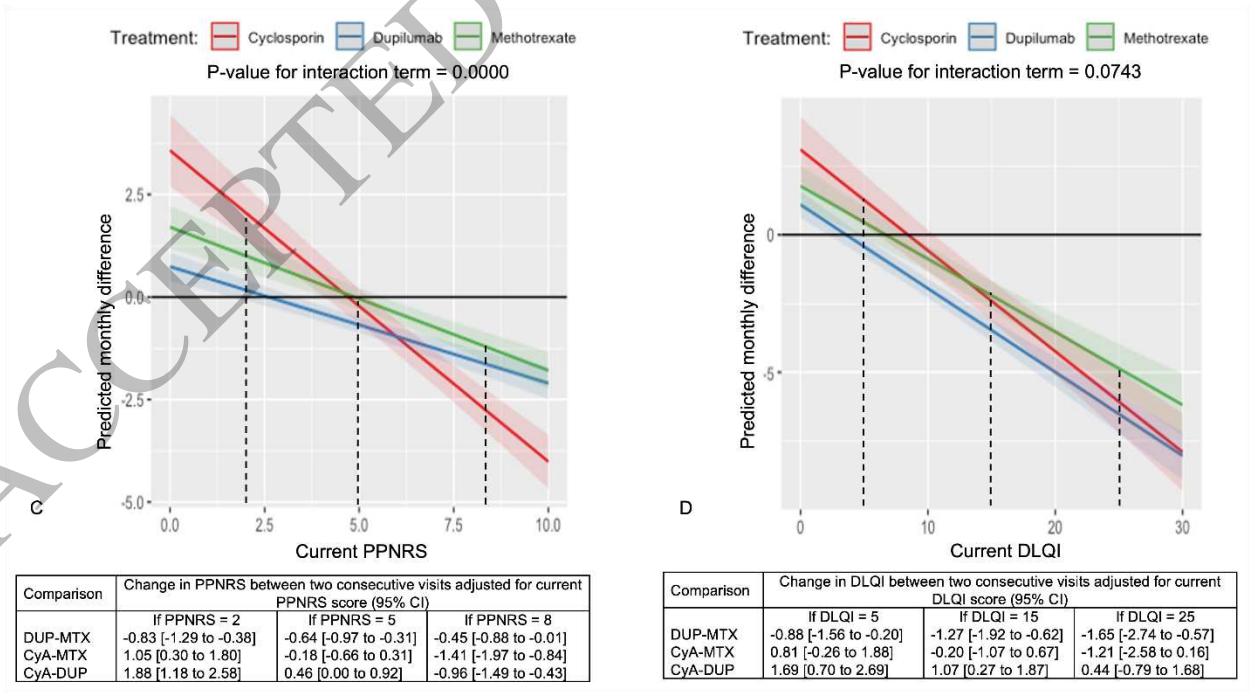


Comparison	Change in EASI between two consecutive visits adjusted for current EASI score (95% CI)		
	If EASI = 10	If EASI = 25	If EASI = 40
DUP-MTX	-1.09 [-2.27 to 0.09]	-2.08 [-3.71 to -0.46]	-3.08 [-5.83 to -0.33]
CyA-MTX	-0.01 [-1.75 to 1.72]	-3.53 [-5.53 to -1.53]	-7.05 [-10.43 to -3.67]
CyA-DUP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

Figure 2A and B
329x182 mm (DPI)



Comparison	Change in PPNRS between two consecutive visits adjusted for current PPNRS score (95% CI)		
	If PPNRS = 2	If PPNRS = 5	If PPNRS = 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 2C and D
329x182 mm (DPI)

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