Exposure–response of ciclosporin and methotrexate in children and young people with severe atopic dermatitis: A secondary analysis of the TREatment of severe Atopic dermatitis Trial (TREAT)

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Conflicts of interest: CF 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 Principle 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 investigator-led funding from Sanofi-Genzyme and Pfizer for microbiome work. DOK has received funding for advisory board participation with Sanofi-Genzyme. MW is a steering committee member of the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918). TM has received funding for advisory boards and teaching from Sanofi-Genzyme, Abbvie and Pfizer. MJC has received investigator-led funding from Hyphens Pharma, Johnson & Johnson, Sanofi, L'Oréal, Leo Pharma, ACO Nordic, Pfizer, Regeneron, and Sanofi Genzyme, as well as funding for advisory board participation with Menlo. He has also received consultant fees from Boots, Eli Lilly, and Procter & Gamble. SJB is a medical advisor to the Ichthyosis Support Group and Eczema Outreach Support and has received funding from the Wellcome Trust. ADI has received consulting fees from Area, Almirall, Abbvie, Pfizer, Eli Lilly, and Sanofi-Regeneron and is the Director of the International Eczema Council. PB has received funding for advisory board participation with Abbvie and speaker fees from Pfizer. She is a steering committee member of the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a medical advisor for the National Eczema Society. SJB has received research funding (but no personal financial benefits) from the Wellcome Trust (220875/Z/20/Z), UKRI, Medical Research Council, Rosetrees Trust, Stoneygates Trust, British Skin Foundation, Charles Wolfson Charitable Trust, anonymous donations from people with eczema, Unilever, Pfizer, Abbvie, Sosei-Heptares, Janssen, European Lead Factory (multiple industry partners) and the BIOMAP

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Data availability: Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, can be made available to researchers who provide a methodologically sound proposal to the corresponding author with a signed data-access agreement.

Ethics statement: The study was approved by the Cambridge Research Ethics Committee group (15/EE/0328). Written informed consent was received from each participant.

Patient consent: Not applicable.

Learning points

- This is the first longitudinal study to investigate the exposure–response relationship of ciclosporin and methotrexate in atopic dermatitis.
- Ciclosporin and methotrexate demonstrate marked interindividual pharmacokinetic variability in children and young people with severe atopic dermatitis.
- Higher trough ciclosporin concentrations were associated with lower disease activity, suggesting a potential role for therapeutic drug monitoring in guiding individualised treatment management.
- The role of steady state erythrocyte methotrexate polyglutamates concentrations as potential biomarker for clinical response in atopic dermatitis remains unclear.

Abstract

This is a secondary analysis of a multicentre randomised controlled trial of ciclosporin and methotrexate in children and young people (CYP) with severe atopic dermatitis (AD). Longitudinal trough ciclosporin and erythrocyte methotrexate polyglutamates (MTX-PG) concentrations were measured to evaluate their associations with treatment response and adverse events. Both ciclosporin (4 mg/kg/day) and methotrexate (0.4 mg/kg/week) led to a significant reduction in disease severity scores over the 36-week treatment period. Higher trough ciclosporin concentrations were associated with lower disease severity scores and may serve as a useful tool for therapeutic drug monitoring of ciclosporin in CYP with AD. However, in contrast to a previously published study, steady-state erythrocyte-MTX-PG concentrations showed no significant association with treatment response. Drug concentrations were comparable between patients with and without drug-related adverse events.

Introduction

Ciclosporin and methotrexate, though off-label, are among the most commonly prescribed systemic treatments for children and young people (CYP) with severe atopic dermatitis (AD).[1–3] While newer monoclonal antibodies and novel immunomodulatory molecules are now available, their use is often limited by cost, making ciclosporin and methotrexate important systemic treatment options. However, both drugs exhibit significant intraindividual and interindividual pharmacokinetic variability, resulting in variations in drug exposure. Despite this, the exposure–response relationship in AD remains poorly understood, which limits individualised treatment strategies for optimal outcomes.

In clinical practice, ciclosporin (2–5 mg/kg/day) and methotrexate (200–400 micrograms/kg/week) are commonly used.[2, 3] For patients with an inadequate response, a dose increase is sometimes considered, primarily guided by adverse effects and the accepted maximum dose. However, clinicians' concerns about the potential for severe adverse effects, including nephrotoxicity, hepatotoxicity, and myelosuppression, may lead to suboptimal dosing or premature treatment discontinuation.[2–4]

Therapeutic drug monitoring (TDM) is well established for ciclosporin in organ transplantation to balance immunosuppression and toxicity, while erythrocyte methotrexate polyglutamates (erythrocyte-MTX-PG) have been explored for methotrexate dose optimisation in immune-mediated inflammatory diseases. However, data on TDM in AD remain limited, highlighting the need for further research.

Report

The TREatment of severe Atopic Eczema Trial (TREAT) is a multicentre, parallel group, assessor-blinded randomised controlled trial (RCT) comparing ciclosporin and methotrexate in CYP with severe AD.[5, 6] The trial randomised 103 participants to ciclosporin (n=52) and methotrexate (n=51) over a 36-week treatment period, collecting longitudinal clinical outcome measures of AD disease severity (including objective SCORing for Atopic Dermatitis (o-SCORAD) and the Eczema Area and Severity Index (EASI)), adverse events, along with repeated measurements of drug concentrations.

This secondary analysis of TREAT assessed the association between trough ciclosporin and steady-state erythrocyte-MTX-PG concentrations with disease severity scores and drug-related adverse events. A total of 129 ciclosporin (n=48) and 132 erythrocyte-MTX-PG (n=50) concentrations were available, measured using liquid chromatography-tandem mass spectrometry and high-performance liquid chromatography with on-line post-column derivatization and fluorescence detection, respectively.

For analysis, 110 ciclosporin (n=44) and 59 methotrexate (n=40) concentrations were included. Ciclosporin samples collected within 10 hours of the last dose were excluded as they would not reflect trough levels, and week 2 data were omitted due to the absence of clinical outcomes. For methotrexate, total erythrocyte-MTX-PG concentrations at weeks 12 and 36 were used, as literature suggests steady-state levels are reached by 12 weeks post-initiation. Missing drug concentration data were not estimated or imputed. Analyses were performed using R (version 4.2.1, R Core Team, 2020) and SAS (version 9.0, SAS Inc).

Baseline demographics and clinical characteristics are shown in Table 1. Drug concentrations, o-SCORAD, and EASI scores at each study visit are summarised in Table 2.

In the linear mixed model analyses (adjusted for baseline o-SCORAD or EASI score, visit week, an interaction between drug concentration and visit week as fixed effects, and participant as the random effect), higher trough ciclosporin concentrations was associated with a decrease in EASI scores (β = -0.586, 95% CI = -1.095 to -0.084; p = 0.027), and a trend of negative association was observed in o-SCORAD scores (β = -4.495, 95% CI = -9.146 to 0.091; p = 0.062) over the treatment period. There was a significant interaction between trough ciclosporin concentrations and visit week in both the EASI model (β = 0.022, 95% CI = 0.004 to 0.04; p = 0.019) and the o-SCORAD model (β = 0.174, 95% CI = 0.011 to 0.341; p = 0.043) scores, suggesting higher drug concentrations have a greater impact on the

outcome as time progresses. For methotrexate, the total erythrocyte-MTX-PG concentrations increased over time (Figure 1). In the adjusted linear mixed model analysis, erythrocyte-MTX-PG concentrations measured at weeks 12 and 36 showed no association with o-SCORAD (β = 1.017, 95% CI = -4.456 to 6.34; p = 0.718) or EASI (β = 0.077, 95% CI = -0.477 to 0.625; p = 0.789) scores.

Both ciclosporin and methotrexate were found to be safe and well tolerated in the trial. The incidence of serious adverse events was relatively low in both treatment groups. Trough ciclosporin and steady-state erythrocyte-MTX-PG concentrations were comparable between individuals with and without drug-related adverse events (Supplementary Figure 1 and 2).

Discussion

The use of ciclosporin is complicated by pharmacokinetic variability, which is influenced by factors such as body size, food intake, gastrointestinal status, renal function, and hepatic function. Consequently, TDM is used to guide dose adjustments in organ transplantation, aiming to optimise therapeutic efficacy and minimise toxicity. However, its role in lower-dose regimens for autoimmune and inflammatory diseases, such as psoriasis, chronic spontaneous urticaria, and AD, remains unclear. A systematic review (n = 38 studies) on ciclosporin-associated nephrotoxicity in AD found that only 10 studies included trough concentration monitoring, without assessing its association with toxicity or disease activity.[7]

To our knowledge, this is the first study to assess the association between trough ciclosporin concentrations and treatment response in CYP with AD using data from an assessor-blinded RCT. Our findings show that higher trough ciclosporin concentrations were significantly associated with improved EASI scores, with a non-significant trend toward lower o-SCORAD scores. This supports an exposure response relationship and highlights the potential role of trough concentration monitoring for guiding dose adjustments in CYP with suboptimal treatment response. However, the optimal timing for ciclosporin monitoring remains controversial. In psoriasis, Herrero-Moyano et al. found that higher 2-

hour post-dose concentrations (C2) were associated with better disease control, while the presence of pathological concentrations of serum creatinine was associated with trough concentrations, but not C2.[8] Further research in AD is needed to explore the predictive value of different monitoring time points.

Methotrexate serum concentrations are unreliable biomarker for treatment response due to rapid clearance and intracellular transport. Instead, erythrocyte-MTX-PG concentrations have been explored as biomarkers in immune-mediated inflammatory diseases, though findings remain conflicting. A meta-analysis (n=25 studies) reported higher erythrocyte-MTX-PG concentrations were associated with lower disease activity in rheumatoid arthritis, juvenile idiopathic arthritis, and psoriasis.[9] Data in inflammatory skin disease is limited, with only one cross-sectional study by Rahman et al., who found higher erythrocyte-MTX-PG concentrations in responders (31.5 nmol/L) vs. non-responders (18.1 nmol/L, P = 0.035), with a significant difference observed in the AD subgroup (n=30).[4]

Our results show erythrocyte-MTX-PG accumulation over time, reaching a mean concentration of 130 nmol/L at week 12, which remained stable at week 36. Interestingly, erythrocyte-MTX-PG concentrations in TREAT participants were much higher than those reported by Rahman et al., despite similar methotrexate doses (0.33–0.48 mg/kg/week).[4] This discrepancy likely reflects wide interindividual pharmacokinetic variability, as evidenced by the 10-fold difference in erythrocyte-MTX-PG concentrations within TREAT participants at both time points. Although methotrexate significantly improved disease severity scores in CYP, we found no significant association between erythrocyte-MTX-PG concentrations and improvement in o-SCORAD or EASI, contrasting with Rahman et al.'s findings.[4] The disparity could be due to differences in outcome measures (continuous vs. dichotomous data) and higher steady-state concentrations in TREAT patients.

The TREAT trial confirmed that ciclosporin and methotrexate are effective for CYP with AD; however, both exhibit considerable pharmacokinetic variability. Our findings suggest that TDM may play a role in

optimising treatment response. Future prospective studies incorporating comprehensive pharmacokinetic and pharmacogenetic data are needed to better characterise the exposure–response relationship of ciclosporin and methotrexate in AD.

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Figure legend

Figure 1: Erythrocyte methotrexate polyglutamates concentrations over time

Table 1. Demographic and baseline characteristics

	Ciclosporin n = 44	**Methotrexate** n = 40
Sex, n (%)		
Female	17 (39%)	22 (55%)
Male	27 (61%)	18 (45%)
Ethnicity, n (%)		
White British	23 (52%)	18 (45%)
Black British	6 (14%)	4 (10%)
Asian	1 (2%)	2 (5%)
Other	14 (32%)	16 (40%)
Age (years)	10.96 (4.03)	9.90 (4.14)
BMI (kg/m^2)	19.09 (4.43)	19.13 (3.92)
o-SCORAD	48.73 (11.37)	44.51 (9.42)
EASI	29.88 (12.59)	25.06 (10.42)
v-IGA, n (%)		
Mild	0 (0%)	0(0%)
Moderate	14 (32%)	15 (38%)
Severe	26 (59%)	23 (58%)
Very severe	4 (9%)	2 (5%)
POEM	19.63 (5.42)	20.39 (5.86)

Data presented as mean (standard deviation) unless otherwise stated. Abbreviation: BMI = Body mass index; o-SCORAD = objective SCORing for Atopic Dermatitis; EASI = Eczema Area and Severity Index; v-IGA = validated investigator global assessment; POEM = Patient-Oriented Eczema Measure.

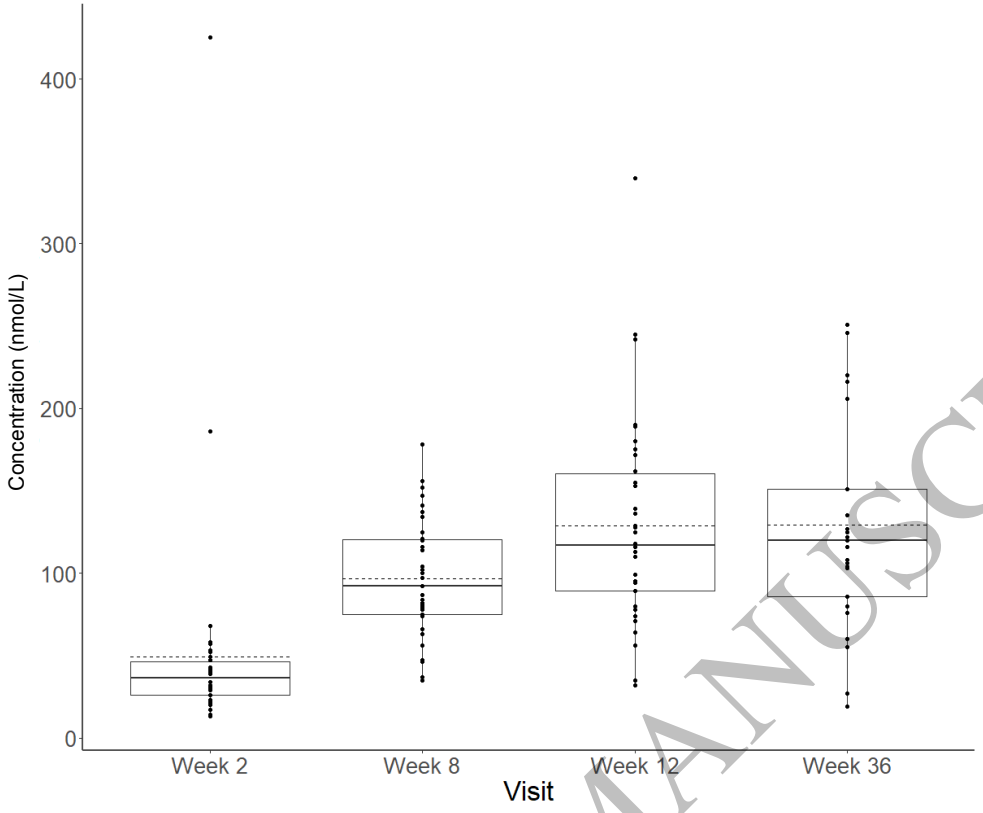
Table 2: Drug concentrations and clinical outcome measures of atopic dermatitis disease severity.

Ciclosporin group				
	Baseline n = 44	**Week 8 n = 32**	**Week 12 n = 34**	**Week 36 n = 30**
o-SCORAD	48.73 (11.37)	28.23 (12.74)	27.84 (10.53)	26.14 (12.31)
EASI	29.88 (12.59)	13.38 (11.73)	11.73 (9.02)	11.4 (10.27)
Trough ciclosporin concentration (micrograms/L)	NA	73.47 (89.49)	95.09 (161.56)	98.8 (207.35)

Methotrexate group				
	Baseline n = 40	**Week 8**	**Week 12 n = 33**	**Week 36 n = 24**
o-SCORAD	44.51 (9.42)	NA	28.13 (10.71)	19.59 (8.61)
EASI	25.06 (10.42)	Na	11.48 (8.31)	5.00 (3.25)
Steady state erythrocyte-MTX-PG concentrations (nmol/L)	NA	NA	129.48 (64.64)	131.00 (67.57)

Data presented as mean (standard deviation). Abbreviation: o-SCORAD = objective SCORing for Atopic Dermatitis; EASI = Eczema Area and Severity Index; MTX-PG_{1-5} = methotrexate polyglutamates species 1 to 5; NA = non-applicable

Figure 1: Erythrocyte methotrexate polyglutamates concentrations over time



Note: Week 8 data do not reflect steady-state concentrations and thus not included in the linear mixed model analysis.