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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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Abstract

This is a secondary analysis of a multicentre randomized controlled trial of ciclosporin and methotrexate in children and young people (CYP) with severe atopic dermatitis (AD). Longitudinal trough ciclosporin and erythrocyte methotrexate polyglutamate (MTX-PG) concentrations were measured to evaluate their associations with treatment response and adverse events. Both ciclosporin (4 mg kg^{-1} daily) and methotrexate (0.4 mg kg^{-1} weekly) 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.

Ciclosporin and methotrexate, although 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 considerable intraindividual and interindividual pharmacokinetic variability, resulting in variations in drug exposure. Despite this, the exposure–response relationship in AD remains poorly understood, which limits individualized treatment strategies for optimal outcomes.

In clinical practice, ciclosporin (2–5 mg kg^{-1} daily) and methotrexate (200–400 µg kg^{-1} weekly) are commonly used.[2,3] For patients who exhibit an inadequate response, an increased dose is sometimes considered, primarily guided by clinical judgement regarding the accepted maximum dose and the absence of adverse effects. However, clinicians' concerns about the potential for severe adverse events, including nephrotoxicity, hepatotoxicity and myelosuppression, may lead to suboptimal dosing or premature discontinuation of treatment.[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-PGs) have been explored for methotrexate dose optimization 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) was a multicentre, parallel group, assessor-blinded randomized controlled trial (RCT) to compare ciclosporin and methotrexate treatment in CYP with severe AD.[5,6] The trial randomized 103 participants to ciclosporin ($n=52$) or methotrexate ($n=51$) groups over a 36-week treatment period, collecting longitudinal clinical outcome measures of AD disease

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severity, including objective SCORing for Atopic Dermatitis (o-SCORAD) and the Eczema Area and Severity Index (EASI). Adverse events were monitored, and drug concentrations were measured regularly.

In this secondary analysis of TREAT data, we 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 online post-column derivatization and fluorescence detection, respectively.

For our analysis, 110 ciclosporin ($n=44$) and 59 methotrexate ($n=40$) concentrations were included. Ciclosporin samples collected within 10 h of the most recent dose were excluded as they would not reflect trough levels, and week 2 data were omitted due to an absence of clinical outcomes. For methotrexate, total erythrocyte-MTX-PG concentrations at weeks 12 and 36 were used, as the 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.).

Participants' baseline demographics and clinical characteristics are shown in Table 1. Drug concentrations and o-SCORAD and EASI scores at each study visit are summarized in Table 2.

In the linear mixed model analyses (adjusted for visit week, baseline o-SCORAD or EASI score, and with an interaction between drug concentration and visit week as fixed effects and participant as the random effect), over the treatment period, higher trough ciclosporin concentrations were associated with a decrease in EASI scores ($\beta=-0.586$, 95% confidence interval (CI) −1.095 to −0.084; $P=0.027$), and a trend toward a negative association was observed in o-SCORAD scores ($\beta=-4.495$, 95% CI −9.146 to 0.091; $P=0.062$). There was a significant interaction between trough ciclosporin concentrations and visit week in both the EASI model ($\beta=0.022$, 95% CI 0.004–0.04; $P=0.019$) and the o-SCORAD model ($\beta=0.174$, 95% CI 0.011–0.341; $P=0.043$) scores, suggesting higher drug concentrations have a greater impact on clinical outcomes 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 ($\beta=1.017$, 95% CI −4.456 to 6.34; $P=0.718$) or EASI ($\beta=0.077$, 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 participants.[6] The incidence of serious adverse events was relatively low in both treatment groups.[6,10] Trough ciclosporin and steady-state erythrocyte-MTX-PG concentrations were comparable between individuals with and without drug-related adverse events (Figures S1 and S2; see Supporting Information).

The use of ciclosporin is complicated by pharmacokinetic variability, which is influenced by factors such as body size, food intake, gastrointestinal status, and renal and hepatic function. Consequently, TDM is used to guide dose adjustments of ciclosporin when used in patients who have undergone organ transplantation, aiming to optimize therapeutic efficacy and minimize 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) of ciclosporin-associated nephrotoxicity in patients with AD found that only 10 studies included trough concentration monitoring, with no assessment of its association with toxicity or disease activity.[7]

To the best of 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 showed that higher trough ciclosporin concentrations were significantly associated with improved EASI scores, with a nonsignificant trend toward lower o-SCORAD scores. This supports the existence of 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 patients with psoriasis, Herrero-Moyano *et al.* found that higher 2-h 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 into ciclosporin treatment for AD is needed to explore the predictive value of different monitoring timepoints.

Methotrexate serum concentration is an unreliable biomarker for treatment response due to the rapid clearance and intracellular transport of methotrexate. Instead, erythrocyte-MTX-PG concentrations have been explored as potential biomarkers in immune-mediated inflammatory diseases, although the findings to date remain conflicting. A meta-analysis ($n=25$ studies) found that higher erythrocyte-MTX-PG concentrations were associated with lower disease activity

Table 1 Demographic and baseline characteristics of children and young people who participated in the TREatment of severe Atopic Eczema Trial (TREAT) and whose sample measurements were included in our analysis

Characteristics	Ciclosporin $n=44$	Methotrexate $n=40$
Sex, *n* (%)		
Girls	17 (39)	22 (55)
Boys	27 (61)	18 (45)
Ethnicity, *n* (%)		
White British	23 (52)	18 (45)
Black British	6 (14)	4 (10)
Asian	1 (2)	2 (5)
Other ethnic groups	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 score	48.73 (11.37)	44.51 (9.42)
EASI score	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 score	19.63 (5.42)	20.39 (5.86)

Data presented as mean (standard deviation) unless otherwise stated. BMI, body mass index; EASI, Eczema Area and Severity Index; o-SCORAD, objective SCORing for Atopic Dermatitis; POEM, Patient-Oriented Eczema Measure; v-IGA, validated Investigator's Global Assessment.

Table 2 Drug concentrations and clinical outcome measures of atopic dermatitis disease severity by treatment group in children and young people who participated in the TREatment of severe Atopic Eczema Trial (TREAT) and whose sample measurements were included in our analysis

	Ciclosporin group			
	Baseline *n*=44	**Week 8 *n*=32**	**Week 12 *n*=34**	**Week 36 *n*=30**
o-SCORAD score	48.73 (11.37)	28.23 (12.74)	27.84 (10.53)	26.14 (12.31)
EASI score	29.88 (12.59)	13.38 (11.73)	11.73 (9.02)	11.4 (10.27)
Trough ciclosporin concentration (μg L^{-1})	NA	73.47 (89.49)	95.09 (161.56)	98.8 (207.35)
	Methotrexate group			
	Baseline *n*=40	**Week 8 *n*=0**	**Week 12 *n*=33**	**Week 36 *n*=24**
o-SCORAD score	44.51 (9.42)	N/A	28.13 (10.71)	19.59 (8.61)
EASI score	25.06 (10.42)	N/A	11.48 (8.31)	5.00 (3.25)
Steady-state erythrocyte-MTX-PG concentration (nmol L^{-1})	N/A	N/A	129.48 (64.64)	131.00 (67.57)

Data presented as mean (standard deviation). EASI, Eczema Area and Severity Index; o-SCORAD, objective SCORing for Atopic Dermatitis; MTX-PG_{1-5}, methotrexate polyglutamate species 1–5; N/A, not applicable.

in rheumatoid arthritis, juvenile idiopathic arthritis, and psoriasis.[9] Data in inflammatory skin disease are limited, with just one cross-sectional study by Rahman *et al.*, who found higher erythrocyte-MTX-PG concentrations in responders (31.5 nmol L^{-1}) vs. nonresponders (18.1 nmol L^{-1}, $P=0.035$), with a significant difference also observed in the AD subgroup ($n=30$).[4]

Our results showed erythrocyte-MTX-PG accumulation over time, reaching a mean concentration of 130 nmol L^{-1} 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^{-1} weekly).[4] This discrepancy probably reflects wide interindividual pharmacokinetic variability, as evidenced by the 10-fold difference in erythrocyte-MTX-PG concentrations within TREAT participants at the two timepoints. Although methotrexate significantly improved disease severity scores in CYP with AD, we found no significant association between erythrocyte-MTX-PG concentrations and improvement in

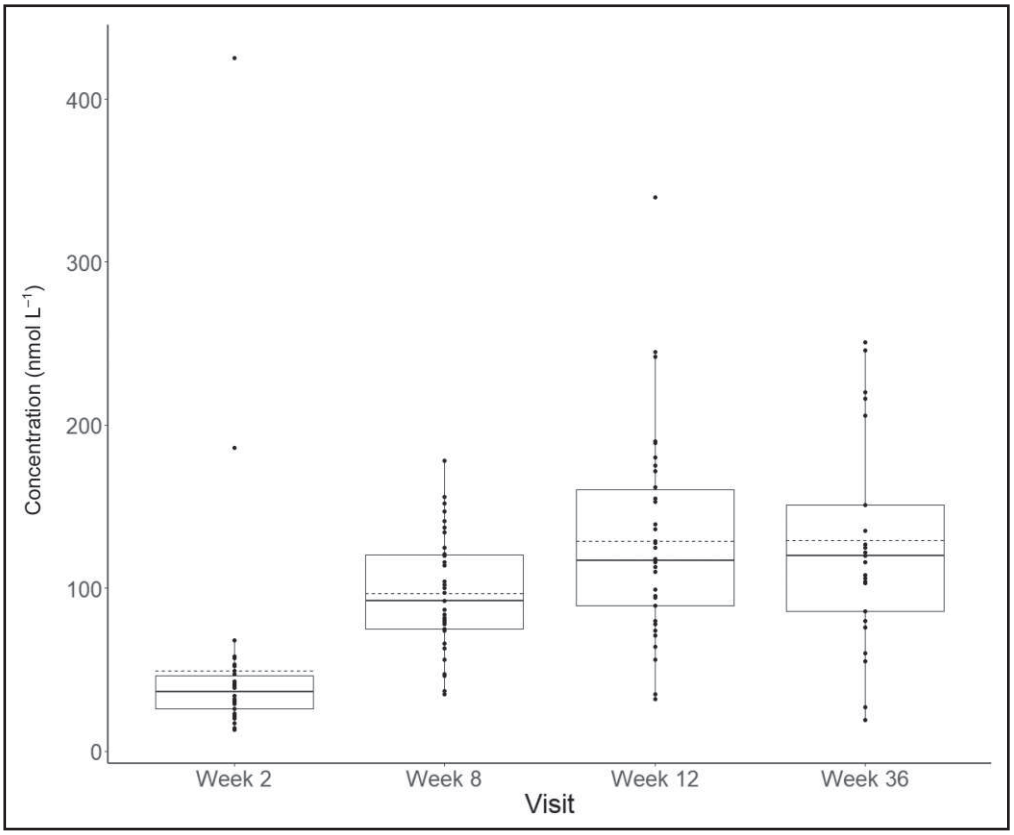

Figure 1 Erythrocyte methotrexate polyglutamate concentrations over time in children and young people who participated in the TREatment of severe Atopic Eczema Trial (TREAT) ($n=40$).

o-SCORAD or EASI scores, contrasting with Rahman *et al.*'s findings.[4] This disparity could be due to differences in outcome measures (continuous vs. dichotomous data) and higher steady-state concentrations in TREAT participants.

The TREAT trial confirmed that ciclosporin and methotrexate are effective treatments for CYP with AD; however, both exhibit considerable pharmacokinetic variability. Our findings suggest that TDM may play a role in optimizing treatment response. Future prospective studies incorporating comprehensive pharmacokinetic and pharmacogenetic data are needed to better characterize the exposure–response relationship of ciclosporin and methotrexate in patients with AD.

Learning points

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

Funding sources

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Conflicts of interest

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 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. D.O.K. has received funding for advisory board participation with Sanofi Genzyme. M.W. is a steering committee member of the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918). T.M. has received funding for advisory boards and teaching from Sanofi Genzyme, AbbVie and Pfizer. M.J.C. 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. S.J.B. is a medical adviser to the Ichthyosis Support Group and Eczema Outreach Support and has received funding from Wellcome. A.D.I. has received consulting fees from Area, Almirall, AbbVie, Pfizer, Eli Lilly and Sanofi Regeneron and is the Director of the International Eczema Council. P.B. 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 adviser for the National Eczema Society. S.J.B. has received research funding (but no personal financial benefits) from Wellcome (220875/Z/20/Z), UK Research and Innovation, Medical Research Council, Rosetrees Trust, Stoneygates Trust, British Skin Foundation, Charles Wolfson Charitable Trust, anonymous donations from individuals with eczema, Unilever, Pfizer, AbbVie, Sosei-Heptares, Janssen, European Lead Factory (multiple industry partners) and the BIOMAP Consortium (EC-IMI project ref. no. 821511). T.H.S. was part-funded through an NIHR Career Development Fellowship (CDF-2014-07-006) at the start of the study. T.H.S. is a member of the UK Dermatology Clinical Trials Network Steering Committee and was chair of the NIHR Research for Patient Benefit East of England Research Advisory Committee between 1 January 2020 and 31 December 2023. T.H.S. was also a member of the following NIHR funding committees: HTA Additional Capacity Funding Board (no dates given); HTA Antimicrobial Resistance Themed Call Board, 10 December 2013 to 3 June 2014; HTA Efficient Study Designs – 2, 1 November 2015 to 31 July 2016; HTA Efficient Study Designs Board, 13 October 2014 to 17 December 2014; HTA End of Life Care and Add-on Studies, 1 September 2015 to 9 February 2016; HTA Primary Care Themed Call board, 17 September 2013 to 18 February 2014; HTA General Committee, 1 August 2016 to 31 July 2017; and HTA Commissioning Committee, 19 June 2017 to 31 December 2019. The other authors declare no conflicts of interest.

Data availability

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

Ethics statement

This study was approved by the Cambridge Research Ethics Committee group (15/EE/0328).

Patient consent

Written informed consent was provided by the parent or legal guardian of each participant. Assent was obtained from participants where appropriate.

Supporting Information

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

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