The effects of ciclosporin and methotrexate on kidney function in the treatment of severe atopic dermatitis in children: results from the TREAT trial

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Dear Editor, The TREatment of severe ATopic eczema (TREAT) trial evaluated the impact of ciclosporin (CyA) vs. methotrexate (MTX) on severe atopic dermatitis in children and young people, with 103 participants randomized between May 2016 and February 2019, 52 to CyA and 51 to MTX.[1,2] Primary outcomes were changes in the Objective Severity Scoring of Atopic Dermatitis (o-SCORAD) at 12 weeks and the time to first significant flare following treatment cessation at 36 weeks. The trial reported that CyA at a dose of 4 mg kg^{-1} daily demonstrated a greater improvement in severity scoring at 12 weeks, but this was reversed in favour of MTX at a dose of 0.4 mg kg^{-1} weekly by weeks 48 and 60.

While MTX is not regarded as being nephrotoxic in low doses, CyA and MTX can both affect kidney function and frequent renal profile measurements are routinely undertaken as part of safety monitoring.[3,4] However, such standard tests are not very sensitive, as serum creatinine may change late in the evolution of acute kidney injury (AKI).

Cystatin C (CysC) may identify AKI earlier in children,[5] and a combination strategy incorporating serum creatinine, CysC and urinary N-acetyl-β-D-glucosaminidase (uNAG) measurement has also been shown to identify AKI earlier.[6] uNAG is an enzyme found in the lysosomes of proximal tubule epithelial cells, and therefore a raised level is likely to reflect proximal tubular damage.[7] Symmetric dimethylarginine (SDMA) has also been identified as a clinically useful biomarker for chronic kidney disease (CKD) and can be raised in CKD irrespective of the creatinine level.[8]

To comprehensively assess the impact of CyA vs. MTX on renal function, our initial study protocol included an evaluation of both functional (serum creatinine, SDMA, CysC) and kidney injury (uNAG) markers at baseline, and at weeks 2, 12, 36 (9 months on treatment from baseline) and 60 (6 months off treatment). Two outcomes were newly defined. The first was the change in markers across timepoints and between treatment arms, using linear mixed models, including a random intercept to allow for within-participant correlations at different visits. The covariates in the models were the baseline value and an interaction between treatment group and visit in order to estimate the treatment effect at each timepoint. The second was the total number and percentage of potentially clinically relevant treatment-emergent decreases in estimated glomerular filtration rate (eGFR). This was defined in the study protocol as a drop in eGFR > 20% from baseline, with eGFR calculated using the formula eGFR = height (in cm) × 40/plasma creatinine.

At baseline, demographics, clinical characteristics and baseline markers were well balanced between the two groups.[2] The mean values for serum creatinine, CysC, log uNAG and SDMA remained stable within normal ranges in each trial arm and were comparable between the treatment groups across timepoints (Figure 1). Using the estimated

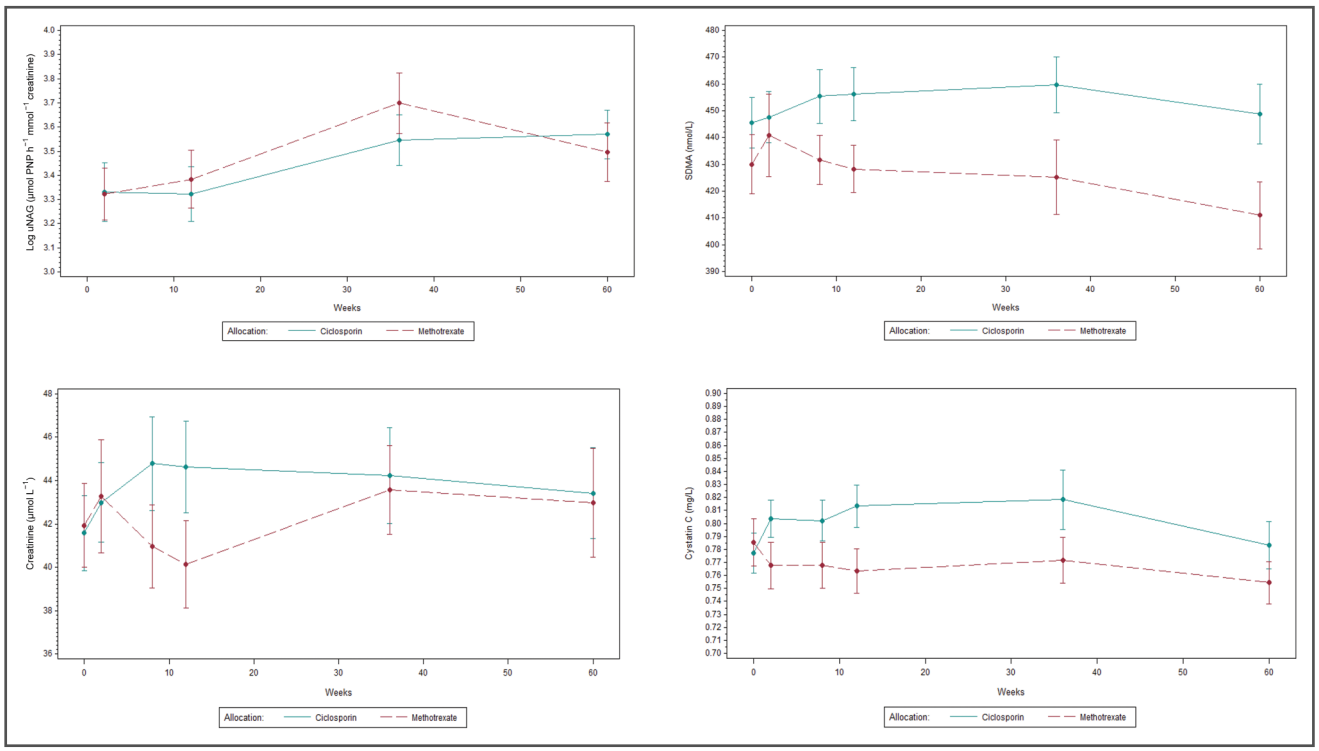

Figure 1 Mean (standard error bars) profile plots for log uNAG, SDMA, creatinine and cystatin C measurements. Normal ranges: uNAG: ≤56.0 PNP-NAG h^{-1} $mmol^{-1}$; SDMA: < 533 nmol L^{-1}; creatinine: 1 month to 4 years, 13–39 µmol L^{-1}; 5–11 years, 29–53 µmol L^{-1}; ≥12 years, 40–90 µmol L^{-1}; cystatin C: 0.5–1.27 mg L^{-1}. PNP, *p*-Nitrophenyl; NAG, N-acetyl-β-D-glucosaminidase; SDMA, symmetric dimethylarginine; uNAG, urinary NAG.

difference in means between treatment groups at each timepoint demonstrated no statistically significant differences. The total number of samples available, respectively, at each timepoint (2, 12, 36 and 60 weeks) varied between the CyA (n=47, 50, 41 and 39) and MTX (n=44, 47, 34 and 31) arms.

Across all timepoints, 17 events affecting 14 (26.9%) participants in the CyA arm and 14 events affecting eight (15.7%) participants in the MTX arm demonstrated a 20% decrease in eGFR. In all cases, the eGFR reverted to baseline values when participants were encouraged to hydrate prior to a repeat test, which suggests that these were not treatment related. No patients were required to stop treatment due to renal impairment during the study (the full analysis details are available online at: https://figshare.com/articles/journal_contribution/TREAT_trial_renal_biomarker_analysis_report/25904470).

Our study findings provide trial data in children showing that CyA was not associated with decreased renal function compared with baseline or with worse renal outcomes than MTX over a 36-week treatment period. Both MTX and CyA are efficacious, with the cheaper drug option, MTX, inducing better disease control following cessation of treatment.

More frequent monitoring to detect kidney dysfunction adds little benefit, and reducing the number of blood tests would make the drugs more acceptable to children and young people who may be put off by the treatment due to the frequency of blood tests. Moreover, fewer blood tests would reduce the overall cost of treatment to healthcare providers, and we suggest monitoring 6-monthly once on a stable treatment regimen. To avoid potentially spurious drops in eGFR, children should be encouraged to maintain hydration when MTX or CyA is prescribed.

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Conflicts of interest: The full list of authors' conflicts of interest is provided in Appendix S2 in the Supporting Information.

Data availability: Data collected for the study, including de-identified 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. All related documents are available on request at any point.

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.

Supporting Information

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

Appendix S1 Full list of authors and affiliations.

Appendix S2 Full list of conflicts of interest.

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