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A randomised controlled trial protocol assessing the effectiveness, safety and cost-effectiveness of methotrexate versus ciclosporin in the treatment of severe atopic eczema in children: The TREatment of severe Atopic eczema Trial (TREAT)

Short title: The TREatment of severe Atopic eczema Trial (TREAT)

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Trial Registration:

Current Controlled Trials ISRCTN15837754 (registered 09/03/2016)

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Roles and responsibilities:

Funder:

The National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) and Research for Patient Benefit Programmes provide financial resources for the conduct of the trial, provides on-going support to the Chief Investigator (CI) to ensure that the trial progresses smoothly and monitors progress against key milestones via the submission of regular progress reports.

Trial Sponsor:

Guy's and St Thomas' (GST) NHS Foundation Trust, Guy's Hospital, Great Maze Pond, London SE1 9RT, and King's College London (KCL), Strand, London, WC2R 2 LS

The funder and sponsor both approve protocol amendments prior to submission for ethical/regulatory approval. The funder and sponsor will not have a role in the analyses and interpretation of the data or the decision to submit the results.

Role of trial sponsor:

GST and KCL have agreed to take on the joint role of Co-sponsor for the study. The Co-Sponsors act as Sponsor for the trial under the Research Governance Framework for Health and Social Care, and the Medicines for Human Use (Clinical Trial) Regulations 2004 and Amended Regulations 2006. The Co-Sponsors have delegated trial management activities to the King's Health Partners Clinical Trials Office (KHP-CTO) and the Clinical Trials Research Centre (CTRC), University of Liverpool. The sponsors will at all times maintain adequate insurance in relation to the study. KCL, through its own professional indemnity (Clinical Trials) and no fault compensation and the GST NHS Foundation Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees.

Role and responsibilities of the Trial Coordinating Centre:

TREAT is co-ordinated by the CTRC at the University of Liverpool. The Co-Sponsors have delegated the trial management activities along with trial data management, statistics and information systems to the CTRC.

Role and responsibilities of the Trial Oversight Committees:

The study has an independent Trial Steering Committee (TSC) (comprising independent members as well as the Chief Investigator as voting members) and an Independent Data & Safety Monitoring Committee (IDSMC). Day to day oversight is conducted by the Trial Management Group (TMG), chaired by the Chief Investigator. The roles and responsibilities of the committees are defined in the TSC Terms of Reference and the IDSMC Charter, available upon request.

What's already known about this topic?

- Oral systemic immuno-modulatory medication is regularly used off-licence in children with severe atopic eczema.
- Ciclosporin (CyA) is the commonest first line systemic agent used in this context, but Methotrexate (MTX) has emerged as an important therapeutic alternative.
- There is currently no adequately powered randomised controlled trial that compares both treatments in children.

What does this study add?

- TREAT addresses this gap and compares the effectiveness, safety, cost-effectiveness and impact on patient's quality of life of these two drugs.
- TREAT also examines the effects of both drugs using systemic and cutaneous markers of inflammation and the effect of filaggrin (*FLG*) genotype and T cell cytokine signatures on treatment response.

Abstract:

Background: Oral systemic immuno-modulatory medication is regularly used off-licence in children with severe atopic eczema. However, there is no firm evidence regarding the effectiveness, safety, cost-effectiveness and impact on quality of life from an adequately powered randomised controlled trial (RCT) using systemic medication in children.

Patients/Methods: Multi-centre, parallel group, assessor-blind, pragmatic RCT of 36 week duration with a 24 week follow-up period. 102 children aged 2-16 years with moderate to severe atopic eczema, unresponsive to topical treatment will be randomised (1:1) to receive methotrexate (MTX; 0.4mg/kg per week) or ciclosporin (CyA; 4mg/kg/day). The trial has co-primary outcomes: change from baseline to 12 weeks in Objective Severity Scoring of Atopic Dermatitis (o-SCORAD) and time to first significant flare following treatment cessation.

Analysis plan: The main aims of the trial are to assess whether there is a difference in the speed of onset, effectiveness, side-effect profile and reduction in flares post-treatment between CyA and MTX, and, also the cost-effectiveness of the drugs. Treatment impact on quality of life will also be examined as well as whether *FLG* genotype influences treatment response. In addition, the trial studies the immune-metabolic effects of CyA and MTX.

Conclusions: The TREAT trial addresses important therapeutic questions, highlighted in systematic reviews and treatment guidelines for atopic eczema. The trial design is pragmatic to reflect current clinical practice.

Keywords: Atopic eczema, atopic dermatitis, eczema, methotrexate, ciclosporin

Background

Atopic eczema (syn. 'atopic dermatitis, 'eczema') is a chronic, pruritic inflammatory skin disease, affecting around 20% of UK children, 16% of whom have moderate-severe disease.[1] It comes at a high cost, for patients and families as well as society.[2,3] Severe atopic eczema is often accompanied by significant sleep disturbance, poor school attendance and social withdrawal, as well as attention-deficit hyperactivity disorder, anxiety and clinical depression.[4] Skin infections are also common in poorly controlled atopic eczema and a reason for hospital admission.[4]

Although most cases of atopic eczema are adequately controlled with emollients, topical anti-inflammatory treatments and/or ultraviolet (UV) therapy, around 2% of children require oral immuno-suppressive treatment to induce and maintain disease control.[5] There are, however, only limited systemic treatment options available and there is concern about their potential short- and long-term side effects.[5] The treatment of severe atopic eczema in children taskforce survey in 765 consultant dermatologists and paediatricians from 8 European countries was conducted to establish which systemic treatment options are available.[6] This showed that the first choice systemic immuno-suppressive agent was overall ciclosporin (CyA) with 43%, compared to the UK where 39% use azathioprine (AZA) and 35% use CyA.[6] Although MTX was only the third most commonly used systemic treatment in the survey in the UK, it is increasingly being used as a first line systemic agent in children, as shown by our most recent treatment survey in the US.[7] Furthermore, while there is significant concern about the long-term prescribing of CyA (renal toxicity) and AZA (in particular lymphoma and progressive multifocal leukoencephalopathy), MTX is generally considered well-tolerated and safe in the long-term.[5,8] In addition, two RCTs and their follow up studies suggested no significant difference in efficacy between MTX and AZA in adults and MTX and CyA in children, even

if CyA appears to show its treatment effect more quickly.[8-11] However, these studies were statistically underpowered.[12]

There is therefore a clear need to compare MTX with the most established immuno-suppressive medication, CyA, which has also been highlighted in a systematic review.[13] Both drugs have demonstrated a reduction in atopic eczema severity and improve quality of life.[4,5,14]

The protocol for the trial is presented here and has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[15]

Objectives:

The primary objectives are to compare the safety and efficacy of MTX versus CyA, in recalcitrant atopic eczema in children, during 36 weeks of treatment and to compare disease control post-treatment cesssation (time to return to baseline disease severity) over the 24 weeks follow-up period. Secondary objectives are to examine i) the number of flares during the trial period as well disease severity throughout follow up, ii) the impact on quality of life, iii) the effects of both drugs using novel systemic and cutaneous markers of inflammation during treatment, iv) the effect of filaggrin (*FLG*) genotype and T cell cytokine signatures on treatment efficacy, v) the side-effect profiles of both drugs, and vi) a comparison of the cost effectiveness of both drugs in a health economic evaluation.

Patients and methods

Trial design and study setting

TREAT is a phase III multi-centre, parallel group, assessor-blind, pragmatic RCT aiming to recruit 102 children. Study sites are in 13 secondary and tertiary care Paediatric Dermatology Departments across the UK and Ireland (Supplementary Table S1).

Children are identified in the paediatric dermatology clinics at the study sites. Inclusion criteria include (see full criteria in Table 1): (i) age 2-16 years; (ii) severe recalcitrant atopic eczema, defined as an inadequate clinical response to moderate (face) to potent (body) topical CS and an o-SCORAD severity score ≥30, and (iii) residence within travelling distance of the recruiting centre**.** Exclusion criteria include (see full criteria in Table 2): (i) serious underlying medical condition; (ii) previous exposure to systemic immuno-suppressive or biologic agent(s); (iii) recent use of oral CS, phototherapy or live vaccines.

Interventions

Participants are randomised to either oral/subcutaneous MTX or oral CyA using an allocation ratio of 1:1 and will receive the trial drug for a period of 36 weeks and are followed up for a further 24 weeks following treatment cessation.

CyA and MTX are commonly used in children for other chronic inflammatory conditions. For instance, for severe paediatric psoriasis a dose of 0.4mg/kg/week MTX (max 25mg per week) is used, as in the TREAT trial (Children's British National Formulary).[16] The Children's British National

Formulary stipulates a maximum dose for CyA for severe atopic eczema of 5mg/kg/day, while a dose of 4mg/kg/day is used in the TREAT trial based on the TREAT survey results.[6]

Supplementary Table S2 (supplementary appendix) summarises the formulations of MTX and CyA used in the study. The assessor who will perform the severity assessments will be blinded to the trial allocation.

Ciclosporin (Neoral® brand)

Participants are prescribed 4mg/kg/day given in two divided doses for the treatment period of 36 weeks. After 12 weeks, dose increases (to a maximum of 5mg/kg/day) or decreases are allowed, dependent on treatment response. Dose modifications according to blood pressure and blood test results are detailed in Supplementary Table S3 (supplementary appendix). As Neoral® is the only brand with both liquid and capsule preparations, the brand Neoral® was selected for TREAT.

Methotrexate

Participants are prescribed an initial test dose of 0.1mg/kg at week 0 and then the therapeutic dose of 0.4mg/kg/week (maximum dose 25mg/week) until week 12, providing there are no significant side effects and safety blood tests results (see Supplementary Table S4 (supplementary appendix)). After week 12, dose modifications according to treatment response are allowed (maximum dose 25mg/week). Only the 2.5mg strength of MTX tablet will be prescribed and dispensed. Subcutaneous administration is available to those who suffer significant gastrointestinal intolerance. Participants on the MTX arm will also be prescribed folic acid 1mg once daily apart from on the day of MTX

administration. Dose modifications according to blood pressure and blood test results are detailed in Supplementary Table S5 (supplementary appendix).

Adherence

Participants are instructed to return unused medication, which will be counted and recorded on the accountability log prior to being disposed/destroyed according to local NHS policy. If for any reason a participant misses a treatment dose, this will be documented in the participant diary.

Potential side effects

CyA's main potential side-effect is an increase in blood pressure and nephrotoxicity. Regular blood pressure and renal function measurements are therefore mandatory in routine clinical care. To assess renal function more carefully both plasma creatinine and cystatin C levels are measured in TREAT (at baseline, 2, 8, 12, 36, and 60 weeks) as well as urinary tubular N-acetyl-beta-D-glucosaminidase (at baseline, 2, 12, 36 and 60 weeks), a sensitive marker of renal tubular function.[17]

As for MTX, gastrointestinal disturbance (e.g. nausea), liver function abnormalities and bone-marrow suppression are the main potential side effects. Based on both paediatric dermatology and rheumatology experience, however, MTX appears to be generally well-tolerated and safe in children, even in settings where higher doses are used, often for prolonged time periods and in combination with biologics.[4,5,18-21] In TREAT, safety

bloods are taken one week post MTX test dose to capture rare idiosyncratic reactions. In addition, children in both study arms have safety bloods every two weeks for the first month, then monthly until week 12 and then eight-weekly thereafter while on treatment, in keeping with the American Academy of Dermatology guidelines for the use MTX and CyA in children with severe atopic eczema.[22]

Drugs known to interact with CyA or MTX may be prescribed when considered necessary for the patient's safety and well-being. If concomitant drugs are given, careful monitoring for drug-related adverse effects is recommended, as would be the case in clinical practice. Since CyA is metabolised by cytochrome p450 (CYP3A) isoenzymes, in particular CYP3A4, drugs known to significantly alter plasma or whole blood concentrations of CyA through this route are prohibited during the study.

Concomitant medication

Participants will continue on their standard eczema care in line with National Institute for Health and Care Excellence (NICE) guidance, including regular emollients, (antiseptic) bath additives and mild-to-potent topical corticosteroids (TCS), topical calcineurin inhibitors and oral antihistamines of the patient's/local investigator's choice. Rescue oral antibiotics and oral corticosteroids are also permitted. Any medication required for any ongoing illness and any rescue medications are recorded both during the treatment and follow up period. Use of wet wraps or other occlusive dressings are prohibited throughout the study period.

Outcomes

Primary outcomes:

Two primary outcomes are assessed:

1. The change in atopic eczema severity between baseline & 12 weeks of treatment in the two treatment arms using the –o-SCORAD, and
2. Time to first flare (defined as time to return to baseline or worse o-SCORAD score) during the 24 weeks after treatment cessation in the MTX vs CyA groups.

Secondary outcomes:

1. To examine atopic eczema severity using validated severity scores: Eczema Area and Severity Index (EASI), Investigators Global Assessment (IGA), o-SCORAD and Patient Orientated Eczema Measure (POEM) scores between 0 and 12, 36, 48, 60 weeks;

2. To compare the number of flares in each study arm as well as the proportion of children who re-flared during the 24 weeks after treatment cessation;

3. To study the impact on quality of life through change in Children's Dermatology Life Quality Index (CDLQI, children age ≥4 years), Infant's Dermatology Quality of Life Index (IDQOL, children <4 years of age), Dermatitis Family Index (DFI) and Child Health Utility 9D (CHU-9D) scores between 0, 12, 36, 48 and 60 weeks;

4. To determine the proportion of participants achieving 50% improvement in the o-SCORAD and EASI index at 12, 36, 48, and 60 weeks;

5. The difference in the proportion of participants withdrawing from treatment due to adverse events;

6. To assess the cost-effectiveness of CyA vs MTX;

7. To study the immuno-metabolic effects of MTX and CyA, especially in relation to markers of glycolytic activation and T cell cytokine signature, at baseline, during treatment and up to 24 weeks after completion of treatment;

8. To compare the drug side effects/toxicity profiles of both MTX and CyA;

9. To examine the association between MTX polyglutamate and CyA trough levels and reduction in atopic eczema severity as well as drug-related side effects; and

10. To study the impact of *FLG* genotype (yes/no) on reduction in atopic eczema severity.

Sample size

Randomising a total of 102 participants, 51 into each of the study arms, satisfies both of the following sample size calculations. For the first primary outcome (o-SCORAD), the change from baseline to 12 weeks will be calculated for each participant. The study aims to detect a minimum clinically important difference (MCID) of 8 o-SCORAD points between the two treatment groups, assuming a standard deviation (SD) of 10 (based on the only other paediatric RCT with systemic immuno-suppressive medication in children which saw a SD of 6.3 (MTX arm) vs 8.9 (CyA arm) at 12 weeks)[7] a sample size of 41 per group, increasing to 49 per group to allow for an estimated 18% loss to follow up, will be required to provide 90% power using a t-test with a 0.025 two-sided significance level. The co-primary outcome of this trial is whether or not a patient re-flares following treatment, as this may be an important factor influencing potential change in prescribing behaviour. The number of patients on CyA burst treatment who went into remission after three months of treatment in the study by Harper et al was three out of 21, indicating that 86% of patients re-flared,[23] assuming a similar flare risk in our CyA group. A sample size of 43 in each group (51 in each

group with estimated loss to follow up of 18%) will have 80% power to detect a reduction in re-flare of 30% (from 86% to 56%), using a two-sided test with a 0.025 significance level.

Recruitment

Participants will be identified by the clinical team at each centre via a search of the patient database/s or clinic list review. At the routine clinic visit, the patient will be provided with verbal and written information about the study and instructions on how to proceed if they are interested in taking part. All patients will be provided with a full explanation of the trial, before informed written consent/assent is taken.

Consent

Age-appropriate participant information sheets are provided for parents/guardians and children (available upon request). The process of obtaining patient assent and parent/guardian informed consent is in accordance with the Research Ethics Committee guidance, and Good Clinical Practice (GCP). The investigator, or their nominee (medically qualified physician), and the participant and/or parent/guardian sign and date the consent form, before the participant can participate in the study. No trial-specific procedures are conducted before informed consent has been obtained, and participants are reminded that they may withdraw from the trial at any time without it affecting the quality of their care in the future. Information on the collection, storage and use of the trial samples is provided in the participant information sheets and consent form.

Confidentiality

Data that contain names or other participant identifiers, such as informed consent forms, will be stored separately from the case report forms, questionnaires and patient diaries identified by screening/randomisation numbers. The database will be secured with password-protected access systems. Individual participant medical information obtained as a result of this study is considered confidential. Participants' study information will not be released outside of the study without the written permission of the participant, except as necessary for monitoring by authorised individuals (i.e. CTRC, Sponsor, Regulatory Authorities, and NHS Trust) which is clearly stated in the consent form. The CTRC will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Screening visit

Informed consent can be taken at or prior to the screening visit, just prior to assessments. Patients are assigned a screening number for use on study documentation until randomisation takes place. At screening, a full medical history is taken, with review of concomitant medication and full assessment against the eligibility criteria as well as a pregnancy test, where indicated. An o-SCORAD is completed together with safety bloods. As a safety measure, some patients may require a chest x-ray at the screening visit if there is a risk of TB exposure, with a radiology report of clear/normal chest X-ray needed before randomisation occurs. Patients who fail screening, based on the inclusion/exclusion criteria (see Tables 1 & 2), can be invited for re-screening after 14 days, if appropriate.

Baseline visit

The baseline visit will occur within a maximum of 14 days of the screening visit. However, the screening and baseline visit can be carried out on the same day. At this visit, informed consent status is checked, as is eligibility and a review of concomitant medication. As per Table 3, the clinician conducts a physical examination and the blinded assessor completes an o-SCORAD, EASI and IGA. An additional pregnancy test will be performed where indicated. The parent and child complete QoL questionnaires, POEM, Health related QOL during the visit and are given a patient diary (including POEM) to complete at home. Blood and urine samples are collected for safety screening and *FLG* genotyping and skin tape strips for mechanistic work. (Tape strips and mechanistic bloods are not collected at all sites.) All participants who provide consent and fulfil the eligibility criteria (confirmed by a medically qualified physician) will be randomised by the Local Investigator or their nominee and either CyA or MTX are dispensed.

Randomisation method

Participants will be randomised to receive MTX or CyA in a 1:1 ratio at the baseline visit. Randomisation lists will be generated by an independent statistician using a computer generated randomisation schedule stratified by site, using a secure (24-hour) web-based randomisation programme controlled centrally by the CTRC. The block sizes will not be disclosed in order to ensure allocation concealment.

Participant timeline

Once the participant is randomised to their allocated treatment during the baseline visit (week 0), each participant will be enrolled for 60 weeks (36 weeks treatment, followed by a 24 week observational period). Details of the timeline for participants are summarised in Figure 1.

Blinding

Blinding of the local investigator, research nurse and the participant will not be possible, as CyA is given in two divided doses daily and MTX only once a week, but the severity assessors (o-SCORAD, EASI & IGA), are blinded to treatment allocation. At each visit, data are collected as to whether or not the assessment is made blinded. These data are monitored centrally and reviewed on a regular basis.

Visit schedule

The schedule for assessments during the treatment and the follow-up phase are shown in Table 3.

Participant retention

Participants may withdraw from treatment if the parent/legal representative (or the participant where applicable) withdraws consent, develops an unacceptable toxicity based on the Local Investigators judgement, development of illness preventing further treatment or any change to the participant's condition that justifies the discontinuation of treatment. If a participant withdraws from trial treatment then centres will explain the importance of remaining on trial follow up to allow complete data capture.

Safety reporting

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions of an adverse event (AE), adverse reaction (AR), serious adverse event, serious adverse reaction and suspected unexpected serious adverse reaction will be used during the course of the trial. All adverse events will be reported from randomisation until four weeks after treatment cessation. Non-serious ARs and AEs should be reported to the CTRC within seven days of the site being made aware of the event. Serious ARs/SAEs/SUSARs should be reported to the CTRC within 24 hours of the site being made aware of the event. SUSARs will be reported to the MHRA by the KHP CTO and CTRC will notify main REC of all SUSARs. All investigator will be informed of all SUSARS occurring throughout the course of the study.

Mechanistic studies

Immunological parameters will be studied to see if there are significant changes in the percentages of regulatory T cells, pro/anti-inflammatory cytokine-expressing CD4+ T

cells, or in the corresponding levels of these cytokines in serum following treatment. Comparison will be made between MTX vs CyA treated patients, and investigation as to whether there is a correlation between cytokine levels and treatment response at 12 and 36 weeks and the risk of re-flares at 60 weeks.

Systemic metabolic and local skin inflammatory parameters will be studied to see if the initial treatment response at 12 weeks to MTX (vs CyA) is already associated at that stage with differences in the systemic metabolic profiles (shift from pro-inflammatory glycolytic activation to an anti-inflammatory metabolic profile), and whether this is also seen at 36 and 60 weeks, explaining a more sustained disease remission following MTX (vs CyA) therapy. Assessment will include whether observed systemic metabolic changes are associated with corresponding inflammatory profiles in the skin. Mechanistic blood samples will only be collected from sites that can transport (via courier) samples to the KCL biobank facility by 4pm on the same day (within maximum of six hours post venesection).

Data management

Each centre will undertake training in study requirements before being allowed to open to recruitment. This will include training on taking informed consent, completion of CRFs, randomisation and safety reporting. Specific training will also be given on the severity assessment measures and quality of life questionnaires.

The case report forms (CRF) are the primary data collection instrument and are sent to CTRC with copies retained at site. A full description of the data management procedures are provided in the 'Data Management Plan' and the 'Data Entry and Cleaning Manual', which can be made available upon request. All identifiable patient data is pseudonymised and source data are collected in the patients' medical records. Templates of the data collection tools completed by the study site and/or participant, including CRFs and questionnaires, are available upon request.

Statistical analysis

A separate statistical analysis plan is available upon request, which details all analyses to be conducted for both the primary and secondary outcomes and also the methods that will be used to handle missing data and sensitivity analyses. Below is a brief summary of these analyses.

The primary analysis will be by intention-to-treat, based on all randomised participants, as far as is practically possible. The analysis of change in o-SCORAD from baseline to 12 weeks will be examined using analysis of covariance with treatment group and baseline measurements as covariates. Analysis of time to first flare post treatment cessation will be summarised by Kaplan-Meier curves for each treatment group and compared overall, using the log rank test and survival regression methods.

For the secondary outcomes, continuous data will be reported as the difference in means and will be analysed using ANCOVA where appropriate and binary data will be reported in terms of relative risk with appropriate 95% confidence intervals. Missing data will be monitored and strategies developed to minimise its occurrence. The robustness of the complete case analysis will be assessed using various imputation assumptions; however these will be informed by data collected on the reasons for missing data.

This trial will contain an internal pilot study, to check the assumptions made in the sample size calculation. After the primary outcome data are available from 25 patients (o-SCORAD index at 12 weeks) the standard deviation of the 25 scores, and the 95% confidence limits for this estimate, will be calculated without unblinding allocation. If the 95% confidence limits of the estimate of the standard deviation (SD) of the o-SCORAD index at 12 weeks overlap

10 the trial will continue unchanged. If the upper 95% confidence limit of the estimate of the SD of the o-SCORAD index at 12 weeks is less than 10 the trial will continue unchanged but the Trial Steering Committee (TSC) will be informed that the trial power is greater than planned. If the lower 95% confidence limit of the estimate of the SD is greater than 10 the study is underpowered. The funder will then decide whether to invite an extension or close the study.

Cost-effectiveness analyses

A within-trial cost-effectiveness analysis will be conducted to assess whether CyA offers value for money compared to MTX for children with moderate-to-severe AE using standard methodology[24-26] and in accordance with the NICE reference case.[27] It will seek to:

- Estimate resource use and costs in severe paediatric atopic eczema in the MTX compared to the CyA arm.
- Estimate the Quality-Adjusted Life Years (QALYs) in severe paediatric atopic eczema in both arms.
- Undertake cost-effectiveness and cost-utility analyses to assess which treatment represents best value for money for NHS provision.
- Estimate uncertainty levels surrounding the decision on which treatment to provide.

We will monitor levels of resource use associated with both interventions including drug costs, monitoring costs and adverse event costs over the 36 weeks treatment period. In addition, other potentially atopic eczema-related NHS resource items, including primary care visits, prescriptions, and other health care contacts will be recorded in participant diaries at baseline and weeks 4, 8, 12, 20, 28, 36, 48 and 60. We will attach appropriate unit costs to resource use data using published

sources for a common price year[28-30] to estimate the mean overall cost per participant per study arm. Separately, we will record the time-off work parents take because of their child's atopic eczema and cost this using the human capital approach using published average wages[31]. Children's time away from school will be recorded in units of time but not monetarised.

The economic evaluation will estimate the mean incremental cost and mean incremental effect of MTX compared to CyA (separate mean incremental effects will be estimated for: CHU-9D (QALY gain); change in o-SCORAD; and flare number). The base case analysis will be the cost-utility analysis where QALY for the trial period (based upon CHU-9D[32] instrument) captured at baseline and weeks 12, 36, 48 and 60, using the proxy version for those aged under 7 years with additional guidance notes for parents of those aged under 5 years provided by the instrument developer), using linear interpolation and area under the curve with baseline adjustment.[33]

Costs and outcomes will be discounted at recommended rates[19] in weeks 53 to 60 to reflect the timeframe greater than 12 months. A regression-based approach (for instance seemingly-unrelated regression equations if assumptions are met,[34] will be used to estimate the mean incremental cost and effects. Bootstrapping will explore uncertainty levels associated with the decision to adopt either treatment through the estimation of cost-effectiveness acceptability curves[35]. A specific health economics analysis plan will be written and finalised in advance of the trial database being locked.

Monitoring

Study data is centrally monitored by the CTRC. A number of monitoring features are in place at the CTRC to ensure reliability and validity of the trial date, these are detailed in the 'Trial Monitoring Plan', available upon request. On-site monitoring visits can be triggered if necessary and will be carried out by either representatives of the CTRC or Sponsor.

Ethics and dissemination

Initial review and approval of the trial protocol along with the participant facing documents were submitted to the East of England – Cambridge East Ethics Committee, which gave a favourable opinion (16/01/2016). Any subsequent amendments to the protocol and/or participant facing documents will require ethical approval.

Protocol Amendments

Protocol amendments are assessed by the Trial Management Group and approved by the Sponsor, Research Ethics Committees and by the Regulatory Authorities in the UK and Ireland.

Summary

TREAT addresses key clinical questions for the management of children with severe atopic eczema using systemic medication, in particular whether there is a difference in speed of onset, effectiveness, side-effect profile and reduction in flares post-treatment between CyA and MTX, and, if so, the cost-effectiveness of the drugs. Furthermore, TREAT examines mechanistically how both drugs exert their anti-inflammatory profile systemically and in the skin.

Dissemination Policy

Trial results

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TMG. Access to fully anonymised participant-level datasets and statistical codes can be made by requests to the TMG, once the final results of the trial have been published.

Author's contributions

The TREAT trial was initiated by CF and designed by CF, ADI, PB, FB, APJ, LO'N, TS, LT, MW, and PRW. CF led on the MRC-NIHR EME grant application, with ADI, PB, FB, APJ, LO'N, LT, MW, NW, and PRW acting as co-applicants. TS led the NIHR Research for Patient Benefit application that funds the health economic evaluation in TREAT, with CF as Co-Principal Investigator. FA, AR-H, CS, and CW reviewed subsequent versions of the trial protocol, together with the co-applicants. CF is Chief Investigator of the trial. CF drafted the protocol paper with SB.

All authors reviewed and approved the final version of this paper. For all future papers the TMG will form the basis of the writing committee and advise on the nature of the publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org) will be respected.

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Appendix

Trial Steering Committee:

Independent members: Alison Layton (Chair, Consultant Dermatologist & Associate Medical Director for Research); Tim Burton (Patient & Public Representative); Michael Grainge (Statistician); Michael Arden-Jones (Dermatologist); Saskia King (Patient & Public Representative); Michael Perkin (Consultant Paediatric Allergist); Alain Taieb (Paediatric Dermatologist). Non-independent member: Carsten Flohr (Chief Investigator),

Independent Data and Safety Monitoring Committee:

Anthony Ormerod (Chair, Emeritus Professor in Dermatology, University of Aberdeen and Honorary Consultant Dermatologist NHS Grampian); Robert Chalmers (Honorary Consultant Dermatologist, Co-Chair and Managing Editor, Dermatology Topic Advisory Group, WHO ICD Revision Project); Xinxue Liu (Honorary Research Fellow).

Trial Management Group: Amina Ahmed (Patient & Public Representative); Farhiya Ashoor (Trial Manager); Carsten Flohr (Chief Investigator, Chair); Anna Rosala-Hallas (Trial Statistician); Amy Holton (Sponsor Representative); Alan Irvine (Principal Investigator); Ashley Jones (Lead Statistician), Tracey Sach (Health Economist); Catherine Spowart (Supervising Trial Manager); Mandy Wan (Lead

Pharmacist); Charlotte Walker (Lead Research Nurse), Paula Williamson (Director of the Clinical Trials Research Centre)

Principal Investigators: Suzannah August (Poole Hospital); Paula Beattie (Royal Hospital for Children, Glasgow); Sara Brown (Ninewells Hospital, Dundee); Mike Cork (Sheffield Children's Hospital); Ben Esdaile (Whittington); Carsten Flohr (Guy's & St Thomas' Hospital); Joanna Gach (University Hospitals Coventry & Warwickshire); Emma Howard (Birmingham Children's Hospital); Alan Irvine (Our Lady's Children's Hospital, Dublin); Tess McPherson (Oxford University Hospitals); Donal O'Kane (Royal Victoria Hospital, Belfast); Jane Ravenscroft (Nottingham University Hospitals); Lindsay Shaw (Bristol Royal Hospital for Children).

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Laboratory investigations:

Nicholas Webb (Manchester Royal Infirmary) - provision of expertise on measurement and assessment of renal function relating to study drug administration; Leonie Taams (King's College London) – immunology work; Luke O'Neil (Trinity College Dublin) – metabolomics; Irwin Mclean (University of Dundee) – *FLG* mutation analyses.

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Table 1: TREAT trial inclusion criteria

1.	Written informed consent for study participation obtained from the patient or parents/legal guardian, with assent as appropriate by the age/understanding of the patient
2.	Aged 2-16 years at the time of the screening and randomisation visit
3.	Diagnosis of severe, recalcitrant atopic eczema
4.	History of inadequate clinical response (in the opinion of the treating clinician) to potent topical corticosteroids on the body and moderate strength topical corticosteroids on the face.
5.	An objective (o)-SCORAD severity score of at least 30
6.	Participants must live within travelling distance of the recruiting centre
7.	Females of childbearing potential and males, who are sexually active, must commit to consistent and correct use of a highly effective method of contraception (e.g. combined hormonal contraception, intrauterine device, physical barrier or abstinence) for the duration of the trial and for 6 months after the last dose of study drug.
8.	Willingness to comply with study requirements
9.	Baseline visit within maximum of 2 weeks of the screening visit

Table 2: TREAT trial exclusion criteria

1.	Serious underlying medical condition
2.	Pregnant or nursing (lactating) females
3.	Any active and/or chronic infection at screening or baseline (randomisation) visit that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study
4.	Presence of moderate-to-severe impaired renal function as indicated by clinically significantly abnormal creatinine (≥ 1.5 x upper normal limit (ULN) for age and sex) AND eGFR <60ml/min/1.73m^2 at screening visit
5.	Clinical evidence of liver disease or liver injury at screening visit as indicated by abnormal liver function tests such as AST, ALT, GGT, alkaline phosphatase, or serum bilirubin (must not exceed 1.5 x the upper limit value of the normal range for age and sex)
6.	Total WBC count <3x10^9/L, or platelets <150x10^9/L or neutrophils <1.5x10^9/L or haemoglobin <8.5 g/L at screening visit
7.	Blood pressure values > 95th percentile for age and sex at screening *and* baseline visit
8.	Received systemic corticosteroids within 14 days prior to screening visit and 28 days of baseline visit
9.	Received phototherapy within 4 weeks prior to screening visit and 6 weeks of the baseline visit
10.	Previous exposure to any biologic agents or systemic immuno-suppressive therapy,

	except for oral corticosteroids for acute flare management
11.	Concomitant use of disease-modifying and/or immunosuppressive drugs
12.	Received live vaccines within 4 weeks prior to baseline visit
13	Radiology report of abnormal chest x-ray at the screening visit (at the discretion of the PI/medically qualified physician)
14	Receiving treatment with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) for which elevated plasma concentrations are associated with serious and/or life-threatening events; this includes bosentan, dabigatran, etexilate, and aliskiren.
15	Receiving treatment with products containing *Hypericum perforatum* (St. John's wort)
16	Receiving oral treatment with tacrolimus, everolimus, sirolimus or lercandipine
17	Currently participating in a conflicting study or participation in a clinical study involving a medicinal product in the last 28 days or less than 5 half-lives of the medicinal product prior to the screening visit
18	Known hypersensitivity to methotrexate or ciclosporin products
19	Insufficient understanding of the trial by the patient and/or parent/guardian

Table 3: Schedule for assessments during the treatment and follow-up phase

Procedures	Screening Visit	Baseline/ Randomisation	Week 1 (MTX arm only)	Week 2	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 48	Week 60	Unscheduled visit
		Week 0											
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	
Informed consent	x												
Inclusion/exclusion criteria	x	x											
Medical history	x												
Concomitant drugs	x	x	x	x	x	x	x	x	x	x	x	x	x
Demographics	x												
Physical exam (including mouth/throat examination and chest auscultation)		x	x	x	x	x	x	x	x	x	x	x	
o-SCORAD	x	x			x	x	x	x	x	x	x	x	x [h]
EASI, IGA		x			x	x	x	x	x	x	x	x	x [h]
POEM (patient assessed)		x			x	x	x	x	x	x	x		
Parent and child QoL (CDLQI/IDQOL & DFI)		x					x			x	x	x	
Child HRQL (CHU-9D)		x					x			x	x	x	
Resource Use (patient diary)		x			x	x	x	x	x	x	x	x	
Height & weight		x	x	x	x	x	x	x	x	x		x	
Height	x												
Blood pressure		x		x	x	x	x	x	x	x		x	x (only if required)
Adverse events (AE & SAE) [a]			x	x	x	x	x	x	x	x			x
Safety bloods [b]	x[e]		x	x	x[e]	x	x	x	x	x		x	x (only if required)
Chest X-Ray [d]	x												
Pregnancy test (beta-HCG)	x	x											
Confirmation of appropriate contraception use, where applicable	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine sample collection (NAG)		x		x			x			x		x	
Randomisation		x											
Study drug dispensing (as needed at each visit)		x			x	x	x	x	x				
MTX metabolite level (blood)				x		x	x			x			
CyA trough level (blood) [e]				x		x	x			x			
Cystatin C level (blood)		x		x		x	x			x		x	
Creatinine level (blood)		x		x		x	x			x		x	
Tape stripping for cutaneous metabolic work [f]		x					x			x		x	
Collection of blood for mechanistic studies [g]		x					x			x		x	
Collection of blood/saliva for *FLG* genotyping		x											

[a] Collect until 4 weeks after treatment stopped.
[b] Safety bloods include assessment of liver function, renal function and full blood count.
[e] Lipids to also be assessed at these time points as part of safety bloods.
[d] Screening chest X-Ray on discretion of the local PI/medically qualified physician in those at risk of TB.
e Collection of blood for ciclosporin levels should be measured in the morning, 12 hours (+/-30 minutes) after the previous evening's dose, immediately prior to the administration of the morning dose. In younger children, where regular ciclosporin dosing occurs prior to school and in the early evening prior to bedtime (e.g. 0730 and 1930), on the evenings prior to study visits where the ciclosporin level is to be measured, the evening dose should be given later in accordance with the time of the visit appointment.
f Not collected by all participating sites
g Sites that can transport samples to King's College London by 4pm on the same day and within a maximum of 6 hours post venesection only
h Severity assessments only to be collected if an unscheduled visit occurs between week 36 and week 60

Figure 1: Patient journey through the TREAT trial