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Efficacy And Safety Of Ciclosporin Versus Methotrexate In The Treatment Of Severe Atopic Dermatitis In Children And Young People A Multicentre Parallel Group Assessor-Blinded Clinical Trial.

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ABSTRACT

Conventional systemic drugs are used to treat children and young people (CYP) with severe atopic dermatitis (AD) worldwide, but no robust randomized controlled trial (RCT) evidence exists regarding their efficacy and safety in this population. While novel therapies have expanded therapeutic options, their high cost means traditional agents remain important, especially in lower-resource settings.To compare the safety and efficacy of ciclosporin (CyA) with methotrexate (MTX) in CYP with severe AD in the Treatment of Severe Atopic Eczema Trial (TREAT) trial. This Multicentre Parallel Group Assessor-Blinded Clinical Trial Was Conducted In Department Of Dermatology & Venerology, Nandha Medical College and Hospital Perundurai Road, Erode, Tamil Nadu, India In the year 2024.103 Eligible participants aged 2–16 years and unresponsive to potent topical treatment were randomized to either oral CyA (4 mg kg^{-1} daily) or MTX (0.4 mg kg^{-1} weekly) for 36 weeks and followed-up for 24 weeks. Co-primary outcomes were changed from baseline to 12 weeks in Objective Severity Scoring of Atopic Dermatitis (o-SCORAD) and time to first significant flare (relapse) after treatment cessation. 52 to CyA and 51 to MTX. CyA showed greater improvement in disease severity by 12 weeks [mean difference in o-SCORAD −5.69, 97.5% confidence interval (CI) −10.81 to −0.57 (P = 0.01). More participants achieved ≥ 50% improvement in o-SCORAD (o-SCORAD 50) at 12 weeks in the CyA arm vs. the MTX arm [odds ratio (OR) 2.60, 95% CI 1.23–5.49; P = 0.01]. By 60 weeks MTX was superior (OR 0.33, 95% CI 0.13–0.85; P = 0.02), a trend also seen for ≥ 75% improvement in o-SCORAD (o-SCORAD 75), EASI 50, and EASI 75. Participant-reported flares post-treatment were higher in the CyA arm (OR 3.22, 95% CI 0.42–6.01; P = 0.02). QoL improved with both treatments and was sustained after treatment cessation. Filaggrin status did not affect outcomes. The frequency of adverse events (AEs) was comparable between both treatments. Five (10%) participants on CyA and seven (14%) on MTX experienced a serious AE. Both CyA and MTX proved effective in CYP with severe AD over 36 weeks. Participants who received CyA showed a more rapid response to treatment, while MTX induced more sustained disease control after discontinuation.

Keyw ords: Ciclosporin, Methotrexate, Atopic Dermatitis**,** Filaggrin status.

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INTRODUCTION

Atopic dermatitis (AD; also called 'atopic eczema') is a chronic inflammatory skin disease characterized by intense pruritus, affecting one in five children in the UK and other high-income settings.[1] Prevalence varies, with a rising incidence in developing countries [1]. AD is associated with a high-cost burden on patients and families, and on healthcare systems [2, 3]. Children and young people (CYP) with moderate-to-severe AD often suffer significant sleep disturbance and poor mental health, poor attendance at school, and social withdrawal. Most cases of AD are adequately controlled with emollients, topical corticosteroids (TCS), or topical calcineurin inhibitors (TCIs) [4]. Treatment options for CYP who do not respond to these topical therapies remain limited [5]. Around 5% of pediatric patients with AD require systemic drugs to induce and maintain disease control [6, 7]. While several monoclonal antibodies and novel small molecules have recently been approved for AD, only dupilumab and upadacitinib are widely approved for CYP older than 12 years, and only dupilumab for those aged ≥ 6 months. Many third-party payers and health technology assessment agencies, such as the UK's National Institute for Health and Care Excellence, restrict the prescribing of newer drugs to those failing to respond to conventional systemic treatment. With increasing interest in AD globally, cost-effective treatments are in focus for payers. Ciclosporin (CyA) is the most used conventional systemic medication in pediatric patients with moderate-to-se- vere AD, with methotrexate (MTX) emerging as a potential alternative [7 8]. A recent network meta-analysis of AD treatments in adults showed that high-dose CyA generally resulted in better improvement than MTX in clinical AD signs, with the therapeutic results comparable to dupilumab up to 16 weeks [9]. These results correspond to an early systematic review published before the introduction of biologic therapies, which recommended CyA over MTX as a treatment for moderate-to-severe AD in adults [10].

MATERIALS AND METHODS

This Multicentre Parallel Group Assessor-Blinded Clinical Trial Was Conducted In the Department Of Dermatology & Venerology, Nandha Medical College and Hospital Perundurai Road, Erode, Tamil Nadu, India In the year 2024.103 Eligible participants aged 2–16 years and unresponsive to potent topical treatment were randomized to either oral CyA (4 mg kg–1 daily) or MTX (0.4 mg kg–1 weekly) for 36 weeks and followed-up for 24 weeks. Exclusion criteria: Patients who had previous exposure to any biological agents or systemic immunosuppressive therapy were excluded. Any patients who had received systemic corticosteroids within 14 days before the screening visit and 28 days of the baseline visit or received phototherapy within 4 weeks before the screening visit and 6 weeks of the baseline visit were also excluded, as were patients considered to have a serious underlying medical condition that could have compromised their safety in the study. Patients were randomly assigned CyA or MTX in a 1:1 ratio at the baseline visit using an online randomization program, which concealed allocation and was controlled cen- trally by the Liverpool Clinical Trials Centre. Owing to the nature of the trial interventions, blinding the local investigator, research nurse, and participants was not possible. Once all baseline assessments had been performed, participants were randomized to the study drug, which was then dispensed by the local hospital pharmacy. Participants randomized to the CyA arm were prescribed 4 mg kg^{-1} daily in two divided oral doses for the treatment period of 36 weeks. After 12 weeks, dose increases (up to a maximum of 5 mg kg^{-1} daily) or decreases were allowed, depending on individual treatment response. Participants randomized to the MTX arm [any brands with UK/European Union (EU) marketing authorization] were prescribed a single oral test dose of 0.1 mg kg^{-1} at week 0 and then 0.4 mg kg^{-1} weekly (maximum dose 25 mg PO weekly) until week 36. Only the MTX 2.5 mg tablets were dispensed. Participants in the MTX arm were also prescribed oral folic acid 1 mg once daily apart from on the day of MTX administration. Participants randomized to the MTX arm were followed up at week 1, to monitor for potential myelosuppression. All participants were seen at weeks 2, 4, 8, 12, 20, 28, 36, 48 and 60 for efficacy and safety parameters. Quality of life (QoL) questionnaires were collected at weeks 12, 36, 48 and 60. All participants were given diaries to complete weekly throughout the study.

Statistical analysis

The first co-primary outcome was analyzed using an ANCOVA model and 97.5% confidence intervals (CIs). A sensitivity analysis was conducted that included the study site as a random effect in a

linear mixed model. The second co-pri- mary outcome assessment was analyzed using the Cox proportional hazards model and 97.5% CIs. The assumption of proportional hazards was investigated by the inclusion of an interaction term between time and treatment allocation in the model.

RESULTS

Table 1: Demographic And Baseline Characteristics Of 103 Patients Included In The Treatment Of Severe Atopic Eczema

	Ciclosporin (*n* = 52)	Methotrexate (*n* = 51)
Sex		
Female	21 (40)	28 (55)
Male	31 (60)	23 (45)
Age (years), mean (SD)	10.34 (4.21)	9.82 (4.01)
BMI (kg m^{-2})[a]	18.80 (4.16)	19.30 (4.15)
o-SCORAD, mean (SD)	48.34 (11.35)	45.25 (9.60)
EASI, mean (SD)	28.97 (12.53)	27.12 (11.62)
v-IGA		
Mild	0 (0)	1 (2)
Moderate	16 (31)	18 (35)
Severe	31 (60)	29 (57)
Very severe	5 (10)	3 (6)
POEM, mean (SD)[b]	20.40 (5.26)	20.84 (5.47)
DFI, mean (SD)[a]	15.24 (7.89)	15.59 (7.67)
CDLQI, mean (SD)[c]	14.67 (6.96)	15.26 (6.57)

Table:1Post-hoc analysis indicated that the proportions of participants achieving EASI 50, EASI 75, and EASI 90 at week 12 in the CyA group was significantly higher compared with those in the MTX group, although by week 60 this effect had reversed. The proportion of participants achieving v-IGA 0 or 1 was higher in the CyA group at week 12 (*n* = 6/52; 11%) than in the MTX group (*n* = 1/51; 2.0%), similar at week 36 and higher in the MTX group at weeks 48 and 60. In both treatment groups, QoL (estimated by CDLQI, DFI, and IDQOL) improved postbaseline to a level of the MCID for these scores There were no significant differences in these scores between the treatment groups at any time point. Overall, participants in the CyA group reported a higher number of days on topical anti-inflammatory treatments than those in the MTX group over the entire course of the trial. The mean (SD) total number of days on TCS was 94.50 (37.36) in the CyA group vs. 78.72 (56.46) in the MTX group. The mean (SD) total number of days on TCIs was 51.16 (56.60) in the CyA group vs.26.09 (35.46) in the MTX group. A higher number of the mean (SD) total days on emollients 159.52 (67.86) was reported in the MTX group vs. the CyA group 142.00 (35.25).

Table 2: Most common nonserious adverse events (AEs) occurring in at least 10% of participants in the treatment of severe Atopic Eczema Trial (TREAT) trial

	Ciclosporin (*n* = 51)		Methotrexate (*n* = 52)		Total (*n* = 103)	
	Events	Participants	Events	Participants	Events	Participants
Any nonserious AE	369	48 (94)	407	47 (92)	776	95 (93.1)
Most common nonserious AEs						
Skin and subcutaneous tissue disorders						
Eczema	45	22 (43)	19	15 (29)	64	37 (36.3)
Nervous system disorders						
Headache	24	14 (27)	27	11 (22)	51	25 (24.5)
Gastrointestinal disorders						
Abdominal pain upper	18	9 (18)	11	3 (6)	29	12 (11.8)
Vomiting	13	9 (18)	11	9 (18)	24	18 (17.6)
Nausea	12	9 (18)	35	22 (43)	47	31 (30.4)

Abdominal pain	10	7 (14)		14	2 (4)		24	9 (8.8)
Diarrhea	10	8 (16)		8	7 (14)		18	15 (14.7)
Mouth ulceration	0	0 (0)		12	6 (12)		12	6 (5.9)
Investigations								
The glomerular filtration rate abnormal	17	14 (27)		14	8 (15.7)		31	22 (21.6)
Infections and infestations								
Nasopharyngitis	8	7 (14)		9	9 (18)		17	16 (15.7)
Eczema infected	8	6 (12)		8	6 (12)		16	12 (11.8)
General disorders and administration site conditions								
Fatigue	4	3 (6)		35	12 (23)		39	15 (14.7)
Metabolism and nutrition disorders								
Decreased appetite	4	3 (6)		11	8 (16)		15	11 (10.8)
Data are presented as *n* (%).								

Table 3: Serious adverse events in the treatment of severe Atopic Eczema Trial (TREAT) trial.

	Ciclosporin (*n*= 51)			**Methotrexate (*n*=51)**			**Total (*n*=102)**	
	Events	**Participants**		**Events**	**Participants**		**Events**	**Participants**
Skin and subcutaneous tissue disorders	1	1 (2)		0	0 (0)		1	1 (1.0)
Infections and infestations	3	3 (6)		4	4 (8)		7	7 (6.9)
Ear and labyrinth disorders	1	1 (2)		1	1 (2)		2	2 (2.0)
Respiratory, thoracic, and mediastinal disorders	0	0 (0)		2	2 (4)		2	2 (2.0)
Data are presented as *n* (%).								

DISCUSSION

We conducted a multicentre assessor-blinded RCT comparing CyA and MTX in pediatric patients with AD recalcitrant to potent topical therapy. Those treated with CyA had a greater improvement in o-SCORAD between baseline and 12 weeks than those given MTX. By 36 weeks there was no difference between treatment groups, measured by o-SCORAD. After treatment discontinuation (weeks 48 and 60), the o-SCORAD of participants in the MTX group was significantly lower compared with those treated with CyA [11]. These results were mirrored by the mean reduction in EASI,o-SCORAD, and POEM scores, as well as the categorical severity measure scores (EASI and o-SCORAD 50, 75, and 90, and IGA 0/1) across the study time points. There was no difference between treatment groups in the number of participants needing to restart systemic therapy or returning to baseline o-SCORAD following treatment cessation – a very high bar as a definition of significant disease reflare (relapse) [12]. However, there was a higher number of participant-reported flares in the CyA vs. the MTX group. There were no statistically significant differences noted in CDLQI/IDQoL or DFI scores across treatment groups, although both showed a clear decrease in scores from baseline to week 12 above the MCID; this effect was largely sustained during follow-up off therapy [13]. The number of participants in the CyA group using either TCS or TCI in the 24 weeks post-treatment discontinuation was consistently higher than in the MTX group. Although marginally fewer participants in the CyA group were diagnosed with a skin infection or were prescribed antibiotics post-treatment discontinuation vs. the MTX group, the mean number of participant-reported flares post-treatment cessation was higher in the CyA group than in the MTX group [14]. Taken together, this suggests that flares were more common in the CyA group, once treatment was discontinued.The incidence of SAEs was relatively low in both treatment groups but slightly higher than in two other mother- apy novel systemic trials recently conducted in adolescents, one with subcutaneous dupilumab (interleukin-4 receptor α-antagonist) and another with oral abrocitinib (JAK1 inhibitor) [15]. The number of participants who discontinued treatment due to treatment-related AEs was low in both groups in the TREAT trial, as was the incidence of severe infections. Only two participants in the MTX arm discontinued treatment due to nausea. The majority of AEs were mild and there were no significant abnormalities on blood-safety testing.Both CyA and MTX resulted in similar disease improve- ment above the MCID for all severity scores after week 36, indicating that both are effective options for CYP with severe AD. Owing to its slightly faster action [16].

CONCLUSION

In conclusion, the TREAT trial demonstrated that both CyA and MTX are effective, well-tolerated treatments for CYP with severe AD. CyA acts more quickly, while MTX induces better disease control after treatment discontinuation. Where first-line novel systemic biologics and small-molecule prescribing are restricted by regulatory and/or funding bodies, MTX provides an efficacious and low-cost alternative to CyA. This is particularly relevant for healthcare settings with limited financial resources. The optimum duration for MTX therapy and the possibility of MTX-inducing disease modification merit additional investigation.

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