Comparison of efficacy of methotrexate and azathioprine in patients with chronic actinic dermatitis: A randomized controlled trial

(Trial no: NCT06476366)

Date: 14/06/2024

SYNOPSIS &TRIAL PROTOCOL

For

Ethical Review Committee

By

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Supervisor

Brig. Aisha Akhtar

Associate Professor and head of dermatology department

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NON-DUPLICATION CERTIFICATE

It is to certify that Dr. Ahsan Tameez Ud Din is doing her FCPS training in Dermatology at Pak-Emirates Military Hospital, Rawalpindi under my supervision. The topic ***"Comparison of efficacy of methotrexate and azathioprine in patients with chronic actinic dermatitis: A randomized controlled trial"*** *which he has selected for his synopsis has not been done previously within the last 5 years at Pak-Emirates Military Hospital, Rawalpindi. The synopsis study design has no ethical concerns.*

Supervisor

Brig. Aisha Akhtar

Professor and head of dermatology department

Pak-Emirates Military Hospital, Rawalpindi.

SUPERVISOR CERTIFICATE

I hereby certify that Dr. Ahsan Tameez Ud Din, Postgraduate Trainee Dermatology, RTMC # DER-2024-124-19481 has been working under my direct supervision from 18-01-2024 to date in Pak-Emirates Military Hospital, Rawalpindi. The enclosed synopsis titled:

"Comparison of efficacy of methotrexate and azathioprine in patients with chronic actinic dermatitis: A randomized controlled trial"

will be prepared according to "FCPS Research Synopsis Guidelines" under my direct supervision. I have read the synopsis and have found it satisfactory.

Supervisor

Brig. Aisha Akhtar

Professor and head of dermatology department

Pak-Emirates Military Hospital, Rawalpindi.

Comparison of efficacy of methotrexate and azathioprine in patients with chronic actinic dermatitis: A randomized controlled trial

Introduction:

Chronic actinic dermatitis (CAD) is a recurrent hypersensitivity dermatitis of photo-exposed areas, predominantly affecting the elderly population [1-3]. It is a relatively common photodermatitis and is clinically characterized by vesiculation and erythema in acute phase while the chronic lesions present with a more characteristic, infiltrated and lichenified appearance. There is a sharp cut-off at the non-exposed areas of the body along with the sparing of facial skin creases and folds [1,4]. CAD is associated with a lower age of onset and in a higher proportion of females as compared to male in skin of color which highlights the need to be cognizant of such subtle differences while treating the local populations with a diverse range of skin tones [4,5].

Photoprotection is the cornerstone of treatment but potent topical corticosteroids are frequently required [1,6]. Courses of systemic corticosteroids may be required to treat or prevent acute flares, but considering the side effects of this modality in elderly population, there is a palpable need for a safer alternative [7]. Azathioprine (AZP) is an immunosuppressant which has been used successfully as a steroid sparing agent in the treatment of CAD [1,2,8]. Methotrexate (MTX) is a folic acid analogue which exerts its action through the inhibition of DNA synthesis. It is used in a variety of inflammatory dermatoses ranging from psoriasis to eczema and it is logical to assume that the efficacy of this drug extends to CAD which has similar underlying pathological bases [2,9-11].

There is a scarcity of evidence regarding MTX efficacy in patients with CAD and very few head to head comparisons between MTX and AZT have been published. The aim of this study

is to evaluate the efficacy of AZT and MTX in patients with CAD. These drugs have been used successfully as steroid-sparing alternatives in a variety of related dermatoses and this trial may help in paving the path towards the ubiquitous use of these cost-effective and relatively safer drugs in CAD patients of our population.

OBJECTIVE:

To compare the safety and efficacy of AZT and MTX in the treatment of CAD by using Eczema Area and Severity Index (EASI) and Investigator Global Assessment (IGA) scores (Annexures B and C).

Outcome measures

Primary: A reduction of 50% in the EASI score as compared to baseline score (EASI-50)

Secondary: An IGA score of 0-2 will be considered as a secondary outcome measure.

OPERATIONAL DEFINITIONS:

Severity of eczema:

Severity of CAD will be defined with regards to the Eczema Area and Severity Index (EASI) score. In clinical trials, the EASI is a scale used to evaluate the degree and severity of eczema. The investigator rates the severity of the four disease features of eczema (erythema, infiltration and/or papulation, excoriations, and lichenification) on the EASI using a scale from "0" (absent) to "3" (severe). Each of the four body regions, the head, arms, trunk, and legs, has its scores tallied together. Additionally, each body region's percentage of the afflicted area is

converted to a score ranging from 0 to 6, and the affected area is multiplied by each body area score. The total EASI score is between 0 and 72 .

Mild disease: Patients with a score of 1.1-7.0 on the EASI scale will be classified as having mild disease.

Moderate disease: Patients with a score of 7.1 to 21.0 on the EASI scale will be classified as having moderate disease.

Severe disease: Patients with a score of 21.1-50.0 on the EASI scale will be classified as having severe disease.

Very Severe disease: Patients with a score of 50.1-72.0 on the EASI scale will be classified as having very severe disease.

Disease flare:

Disease flare will be defined as the worsening of the existing lesions or the appearance of new lesions with symptoms that result in a hospital visit or increase in the frequency of topical/systemic medications used for eczema control.

Disease Remission:

Disease remission will be defined as the resolution of all the lesions of CAD and appearance of no new lesions for at least 4 weeks.

NULL HYPOTHESIS:

There is no difference in the efficacy of AZT and MTX in the treatment of CAD.

MATERIAL AND METHODS

Setting

Department of Dermatology, Pak Emirates Military Hospital (PEMH)

Duration

One year after the approval of research proposal (or until the completion of sample size)

Study Design

Non-blinded, parallel group, Randomized Controlled Trial

Sample Size

Sample size (n) was calculated to be **33** by using WHO sample size calculator by using following formula and parameters as per study outcomes reported by Verma et al [12]

$$n = \frac{\{Z_{1-\alpha/2}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P1\,(1-P1) + (P2(1-P2)}\}^2}{(P_1-P_2)^2}$$

Power of test (α): 95%

Level of significance (1-β): 5%

Proportion of population achieving primary outcome with azathioprine (P1): 47.5%

Proportion of population achieving primary outcome with methotrexate (P2): 85%

Trial Registration

The study will be registered with the international clinical trials registry of United states National library of Medicine at clinicaltrials,gov. CONSORT guidelines will be followed while conducting the study.

Patient selection and Funding

Only the patients entitled for treatment in PEMH will be enrolled in the study. The availability of the drugs will be ensured through coordination with the hospital pharmacist. No external funding is planned for conducting the trial.

Sampling Technique

Consecutive sampling technique will be employed.

Inclusion Criteria

All newly as well as already diagnosed patients with CAD (male or female), aged 30-80 years, presenting to the outpatient department or the emergency department of PEMH or CMH will be included in the study.

Exclusion Criteria

Following patients will be excluded:

- Patients with coexisting conditions requiring immunosuppressants, preexisting liver disease, dementia, any other neuropsychiatric disorder.
- Patients with known hypersensitivity to AZT or MTX.
- Patients with active infections

Consent:

Written informed consent will be taken by the patients on a printed form of their preferred language (Urdu/English). Patients will be made fully aware of all their rights, possible benefits and risks of participation and will be explained regarding the right to withdraw from treatment at any point during the trial. English and Urdu versions of the consent form are attached as Annexure-D.

Randomization and Allocation

After the enrolment of patients and taking informed consent, participants will be randomly allocated in a 1:1 ratio in two treatment groups via lottery method. The allocation will be concealed using sequentially numbered, opaque envelopes. Owing to the nature of the treatment groups, the blinding of neither the investigators nor the participants will be feasible.

Intervention protocol

After confirming the results of the baseline blood tests, treatment will be initiated as per following protocol:

- Group A will be administered tablet azathioprine at a dose of 0.3mg/kg daily after testing for thiopurine methyltransferase (TPMT) levels.
- Group B will be administered oral methotrexate starting from 5mg/week and increasing the dose by 2.5mg/week to the final dose of 10mg/week. Daily 0.5mg folic acid tablets (excluding the day of the MTX) will be administered.

Both treatments will be continued for 24 weeks and monitoring and dose adjustment will be done according to clinical protocol.

Follow-up and Outcome assessment

Weekly complete blood picture (CBC) will be done until the last dose escalation for group B patients. Both group of patients will be advised regarding strict sun protection measures (sunblock, hats, sunglasses). The baseline investigations for both groups included CBC, liver function tests (LFTs), renal function tests (RFTs), electrocardiogram, chest X-ray and urine analysis while TPMT levels will be assessed specifically for group B patients. The patients will be followed up at week 4, 12 and 24. CBC, RFTs and LFTs will be done at each follow-up. EASI score will be calculated at baseline and at subsequently at each follow-up visit.

A comparison from the EASI score from the last visit will be made at each follow-up to assess whether any patient achieved the primary outcome of EASI-50 (50% improvement in EASI score from baseline). Investigator global assessment (IGA) score will be used as a secondary outcome measure. It is a subjective measure of disease severity which is assessed by the physician on patient's every visit. It ranges from 0 to 4 (0-clear, 1-almost clear, 2-mild, 3-moderate, 4-severe). An IGA score of 0-2 will be considered as the outcome measure. Patients will be also asked for any specific side-effects of the treatment at every follow-up. The data including the demographic profile of the participants will be recorded on a printed form. The data will be kept under lock and key and will be available only to the treating physician and the research team.

Monitoring of side-effects during the trial period:

The patients will be kept under close surveillance and will be contacted by phone in case of failure to follow at the given dates. Any reported side-effects will be carefully documented and if required, patients will be admitted and and alternate treatment will be started after stopping the culprit drug. The patients will have a freedom to choose to withdraw from the trial even in the absence of any side-effect.

Post-trial care:

The patients will be kept under regular, 3 monthly follow-ups and any side-effects will be reported. In case of adverse events, patient would be admitted and alternate treatment will be started after stopping the culprit drug.

Data Analysis

Statistical analysis will be performed using SPSS version 23.0. Mean and standard deviation or median will be calculated for age and duration of symptoms. Frequency and percentage will be calculated for gender (male/female), marital status (yes/no), place of living (rural/urban), and achievement of EASI-50 score (yes/no). Comparison of efficacy between both groups will be compared by chi square test and p-value ≤ 0.05 will be taken as significant. Effect modifiers like age, gender, marital status, duration of symptoms, place of living (rural/urban) will be controlled through stratifications. Post-stratification chi square test will be applied to see their effects on efficacy and p value ≤ 0.05 will be considered as significant.

Dissemination of findings

The findings of the study will be shared with the medical community through presentation in research conferences and through publication in national/international medical journal. The participants of the study will be entitled to ask for the study findings at any time and will be provided with a written/printed form on demand.

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ANNEXURE A

Comparison of efficacy of methotrexate and azathioprine in patients with chronic actinic dermatitis

Name Age Sex Occupation

Marital status Group A/B Residence: Urban/Rural

Education Co-morbid (HTN, DM, Smoking)

Duration of disease EASI SCORE: IGA score

Baseline investigations:

Hb platelet count TLC BIL ALT AST

ALP Urea creatinine Chest Xray

ECG urine RE

Followup visits:

week	Hb	PLT	TLC	BIL	ALT	AST	UREA	CREAT	EASI	IGA
4										
12										
24										

EASI-50 achieved yes/no (if yes, achieved at week:)

IGA score 0-2 yes/no (if yes, achieved at week)

ANNEXURE B

Eczema Area and Severity Index (EASI) score

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	X	X 0.1	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.4	
						The final EASI score is the sum of the 4 region scores:	_____ (0-72)

ANNEXURE-C

Investigator Global Assessment scale (IGA score)

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate

between scores. For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

ANNEXURE-D

Informed Consent Form

Title of Study: A Non-Blinded, Parallel-Group Randomized Controlled Trial Comparing Azathioprine and Methotrexate in **Chronic Actinic Dermatitis** Patients

Principal Investigator: Dr. Ahsan Tameez Ud Din

Affiliation: Pak Emirates Military Hospital

Contact Information: ahsantameezuddinmalik@gmail.com

Introduction

You are being invited to participate in a research study. Please read this form carefully and ask any questions you may have before agreeing to take part in the study.

Purpose of the Study

The purpose of this study is to compare the effectiveness and safety of two medications, Azathioprine and Methotrexate, in the treatment of [Disease/Condition].

Procedures

If you agree to participate, you will be randomly assigned to receive either Azathioprine or Methotrexate. You will be monitored regularly through clinical visits and laboratory tests for a period of [Duration].

Risks and Benefits

Both medications may cause side effects. These will be explained to you. The benefit of participating is that you may receive improved care and contribute to medical knowledge.

Confidentiality

All information collected in this study will be kept confidential. Your identity will not be revealed in any reports or publications resulting from this study.

Voluntary Participation

Your participation is voluntary. You may choose not to participate or to withdraw at any time without any penalty or loss of benefits.

Consent

I have read and understood the information provided above. I have had the opportunity to ask questions and my questions have been answered to my satisfaction. I voluntarily agree to participate in this study.

Participant Name: _____ Signature: _____ Date: _____

Witness Name: _____ Signature: _____ Date: _____

Investigator Name: _____ Signature: _____ Date: _____

فارم کا رضامندی

RCT گروپ متوازی ،اندھا غیر ایک - موازنہ درمیان کے ٹریکسیٹ میتھو اور ازاتھائیوپرین :عنوان کا مطالعہ

تمیزالدین احسن ڈاکٹر :محقق مرکزی

ہسپتال ملٹری امارات پاک :ادارہ

معلومات رابطہ : ahsantameezuddinmalik@gmail.com

تعارف

کے آپ اگر اور پڑھیں سے غور کو فارم اس مہربانی برائے ہے۔ رہی جا دی دعوت کی ہونے شامل میں تحقیق اس کو آپ

پوچھیں۔ ضرور تو ہوں سوالات کوئی

مقصد کا مطالعے

ہے۔ کرنا موازنہ کا حفاظت اور مؤثریت کی ٹریکسیٹ میتھو اور ازاتھائیوپرین مقصد کا مطالعے اس

کار طریقہ

کے (ٹریکسیٹ میتھو یا ازاتھائیوپرین) دوا ایک کسی سے طریقے ترتیب بے کو آپ تو ہوں رضامند پر ہونے شامل آپ اگر

گی۔ جائے کی جانچ سے باقاعدگی کی آپ گا۔ جائے رکھا میں گروپ

فوائد اور خطرات

طبی اور ملنے علاج بہتر کو آپ سے مطالعے اس گے۔ جائیں بتائے کو آپ جو ہیں سکتے ہو اثرات مضر کے دواؤں دونوں

ہے۔ سکتا مل موقع کا کرنے اضافہ میں علم

رازداری

گی۔ جائے کی نہیں ظاہر شناخت کی آپ گا۔ جائے رکھا خفیہ کو معلومات تمام کی آپ میں مطالعے اس

شمولیت رضاکارانہ

سکتے کر اختیار علیحدگی یا انکار سے شمولیت وقت بھی کسی آپ ہے۔ رضاکارانہ پر طور مکمل شمولیت میں مطالعے اس

ہیں۔

رضامندی

مرضی اپنی میں ہیں۔ گئے دیے جوابات بخش تسلی کے سوالات میرے ہے۔ سمجھا اور پڑھا کو معلومات گئی دی اوپر نے میں ہوں۔ رضامند پر ہونے شامل میں مطالعے اس سے

نام کا کنندہ شرکت: _____ دستخط: _____ تاریخ: _____

نام کا گواہ: _____ دستخط: _____ تاریخ: _____

نام کا محقق: _____ دستخط: _____ تاریخ: _____