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Efficacy and safety of BSZY cream for mild-to-moderate atopic facial dermatitis: protocol of a randomised, double-blind, controlled trial

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ABSTRACT

Introduction Limited by the specific location of atopic facial dermatitis, treatment options for atopic dermatitis are limited. Our previous research confirms that BiShengZhiYan cream (BSZY cream) can reconstruct the damaged skin barrier and strengthen the repair ability of skin. However, little evidence of its efficacy and safety for the treatment of atopic facial dermatitis is available.

Methods and analysis A protocol for a randomised, double-blind, controlled trial of BSZY cream is designed for patients with mild-to-moderate atopic facial dermatitis. We will recruit 130 patients with mild-to-moderate atopic facial dermatitis from the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. The participants will be assigned to the BSZY cream group (treatment group) or the emulsion matrix group (control group) randomly. The intervention period will be 4 weeks, once daily in the morning and once in the evening. The primary outcome is the Scoring Atopic Dermatitis Scale. The Clinical Dermatologist Evaluation Form, Patient Self-Assessment Questionnaire and Safety Indicators will be evaluated as secondary outcomes. The follow-up will be conducted at week 8±3 days. The skin condition is assessed by a clinical dermatologist at week 0±3 days, week 2±3 days and week 4±3 days.

Ethics and dissemination The protocol has been approved by Shanghai University of Traditional Chinese Medicine's Yueyang Hospital ethics committee (No. 2023-024). All participants will be asked to sign an informed consent in compliance with the Declaration of Helsinki. On completion of the trial, we plan to disseminate the results through peer-reviewed publications and present the findings at relevant scientific conferences. Data will be provided on reasonable request under participant confidentiality and data privacy regulations.

Trial registration number NCT05792826.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Novelty of research focus: this is the first trial protocol specifically designed to evaluate the treatment of atopic facial dermatitis with BiShengZhiYan cream, addressing a gap in the current treatment of atopic facial dermatitis.
⇒ Randomised controlled trial design: the trial protocol employs a rigorous randomised, double-blind, controlled trial design, which enhances the reliability of the results by minimising bias.
⇒ Single-centre study with short-term findings: a single-centre design and short follow-up period may limit the generalisability and the long-term implications of the findings to other populations and settings.
⇒ Limited patient population: only focuses on individuals with mild-to-moderate atopic facial dermatitis, which restricts the applicability of the results to more severe cases or other areas of atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease that manifests clinically with varying degrees of pruritus, dry skin and eczema-like rash. AD affects 10–20% of children and 5–10% of adults, with approximately 89% of cases being diagnosed as mild to moderate.[1 2]

Severe pruritus and the chronic, recurrent nature of AD contribute significantly to the disease burden of sufferers, especially in atopic facial dermatitis patients. The exact pathogenesis of AD remains unclear, and effective therapies are lacking. Current drugs only focus on symptom control and quality of life improvement such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) etc.[3–5] However, those agents have side effects, especially in sensitive skin areas, leading to low patient compliance and poor treatment outcomes.[6] TCSs have even been shown to reduce stratum corneum hydration and increase transdermal water loss, thereby significantly

reducing skin barrier function in patients with AD.[7] Moreover, due to the specific location of atopic facial dermatitis, common drugs greatly increase the risk of adverse reactions (such as atrophy, striae, rosacea and telangiectasia).[8 9] There is an urgent need for safe and effective interventions for the treatment of mild and moderate atopic facial dermatitis.

In our clinical practice, we have found that BiSheng-ZhiYan cream (BSZY cream) is effective in treating patients with an impaired skin barrier and may be helpful and safe for AD control.[10] The main effective ingredients of BSZY face cream include 2% MossCellTec, PL-Ceramide and PL-PhytoSLC etc. Our previous research data showed that the BSZY face cream can rebuild the damaged skin barrier, enhance its self-healing ability and improve its adaptability to the environment.[11 12] BSZY cream has passed 46 allergen tests and zebrafish irritation tests as well as human patch tests, with few adverse reactions and good tolerability (online supplemental file 1). Moreover, BSZY cream has been approved for marketing use as a safe moisturising emollient for skin care in China for several years. BSZY cream was in China in June 2022 for the purpose of repairing the facial skin barrier (Shanghai G Cosmetics Formulation 2022005471) (online supplemental file 2, https://hzpba.nmpa.gov.cn/gccx/).

However, little clinical evidence of the efficacy and safety of BSZY cream for the treatment of atopic facial dermatitis is available. Therefore, we designed a randomised, double-blind, controlled trial to evaluate the efficacy and safety of BSZY cream for the treatment of mild-to-moderate atopic facial dermatitis.

METHODS AND DESIGN

Study design

This ongoing trial adopts a single-centre, randomised, double-blind design. Patient enrolment starts in late June 2023 and is expected to end in March 2025. The protocol has been approved by Shanghai University of Traditional Chinese Medicine's Yueyang Hospital ethics committee (No. 2023-024).

An estimated 130 participants from the outpatient department of dermatology at Yueyang Hospital will be recruited and randomly assigned to receive the BSZY cream or emulsion matrix group at a 1:1 ratio.

This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials 2013 guidelines.[13] Figure 1 shows the study flowchart, and table 1 presents the schedule of enrolment, interventions and assessments. The entire study period lasts 8 weeks, and subjects receive either BSZY cream or placebo two times per day for 4 weeks with return visits at week 0±3 days, week 2±3 days, week 4±3 days or week 8±3 days where a clinical dermatologist assesses their skin condition. Subjects are not allowed to engage in activities such as prolonged sun exposure, outdoor sports or travel during the entire study period.

Participation and recruitment

Participants will recruit from Yueyang Hospital. Patients with AD with a verified diagnosis are evaluated. The clinical research coordinator will interview potential patients in the outpatient to determine whether they satisfy the inclusion and exclusion criteria. Before participants voluntarily sign their written informed consents willingly at the outset of the study, we meticulously explain the details of the trial to them. Before proceeding to randomisation, the qualified subjects have been fully informed and have met the eligibility criteria. See the online supplemental file 3 for an example of the patient consent form.

Diagnostic criteria

The diagnostic criteria are based on the Hanifin-Rajka criteria, which require the presence of three or more of the following basic features and three or more of the secondary features from the Chinese Atopic Dermatitis Treatment Guidelines (2020 Edition)[14]:

1. Fulfil the classic diagnostic criteria for AD, such as the Hanifin-Rajka criteria.
2. Characteristic AD lesions on the facial area.
3. Other analogous conditions, including rosacea, seborrheic dermatitis and acne, are excluded.

Eligibility criteria

The broad inclusion criteria for the research are as follows:

1. Meet the diagnostic criteria of AD in the China Atopic Dermatitis Treatment Guidelines (2020 Edition).[14]
2. Age≥18 years.
3. The ability to cooperate with receiving topical cream treatment.
4. Voluntary participants will sign a paper informed consent.
5. Willingness to replace the test product with a cream-based product currently in use; it is not recommended to use personal skin care products in that dosage form throughout the testing period.
6. Facial manifestations of AD.

Exclusion criteria

1. Scoring Atopic Dermatitis (SCORAD) Score>50 (AD SCORAD Score: mild 0–24, moderate 25–50, severe>50).
2. Previous allergies to ingredients such as skin care products, soaps, alcohol, fragrances or medications.
3. Insulin-dependent diabetic patients.
4. Received anticancer chemotherapy within the last 6 months.
5. Patients with immune deficiencies or autoimmune diseases.
6. Lactating or pregnant women.
7. Bilateral mastectomy and bilateral axillary lymph node dissection.
8. Subjects with observed facial wounds, abrasions, tattoos or other conditions affecting the determination of test results.

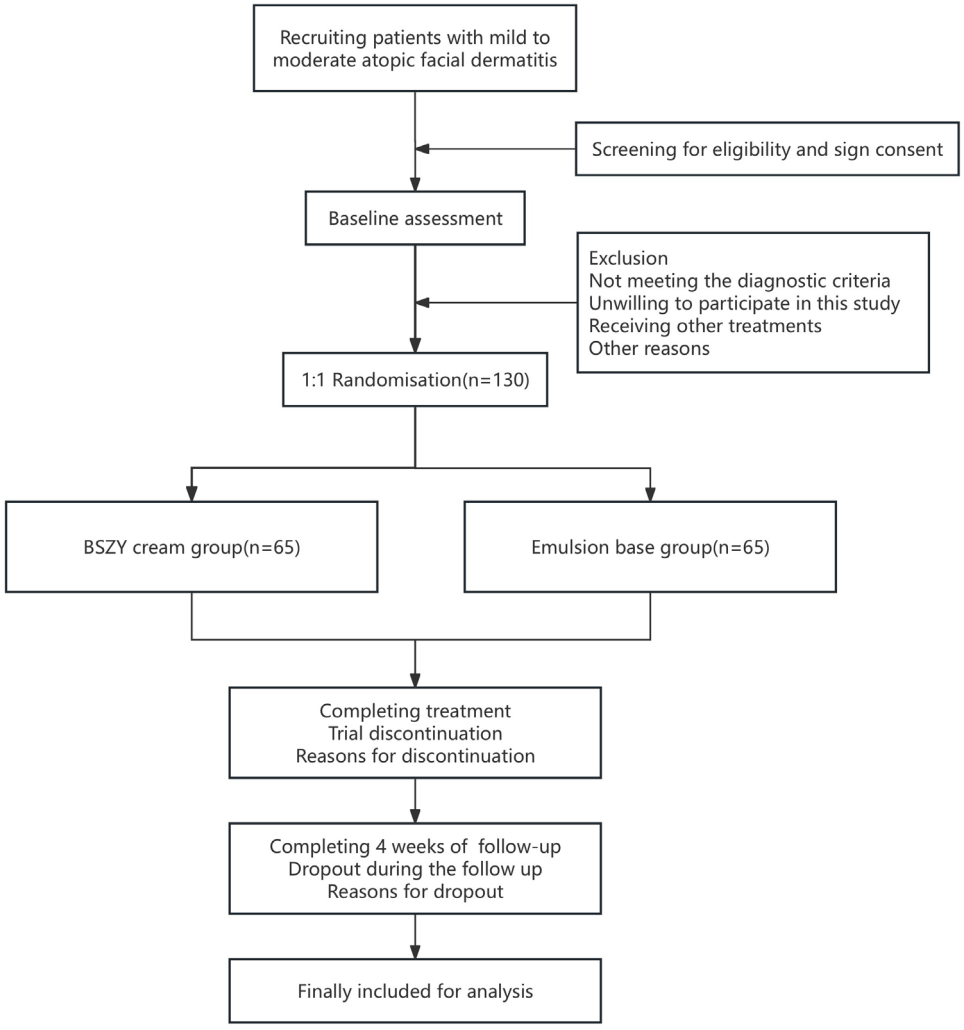

Figure 1 Flow chart of the trial. BSZY, BiShengZhiYan.

9. Have participated in outdoor, travel and other high-intensity sun exposure activities that may cause skin damage in the month prior to the test.
10. Those who are also participating in another clinical test or have participated in a facial clinical test within the last 3 months.
11. The use of vitamin A, hydroxy acid, salicylic acid or hydroquinone applied within the last 3 months; prescription drugs (antibiotics, vitamin A, hydroxy acid and steroids) within the last 6 months; or oral contraceptives (if you have been taking the same type of contraceptive for the last 6 months, you can continue to take them).
12. Clinical dermatologists or professionals believe that there are other medical reasons that could affect the test results.

Rejection, suspension and dropout criteria

1. Serious allergic reactions or adverse reactions to drugs.
2. Patients who voluntarily discontinue and refuse to continue their medication.

Randomisation and blinding

The software (Graphpad Prism 10) is used to create the randomised numbers. A private envelope with a random sequence for group categorisation is sealed. Patients are divided into emulsion matrix or BSZY cream groups at random at a 1:1 ratio. Only one investigator opens the sealed envelope containing the group assignment. Individual patient care is implemented to avoid communication. The efficacy evaluators and statisticians are separated and blinded. The design of this study is double blind. The group assignment is hidden from the patients. Both the treatment group (BSZY cream) and the control group (emulsion base) are provided by the manufacturer and distributed once every 2 weeks by the designated research nurse. Except for the first dispensing, the unused lotion will be collected and counted every time after dispensing.

Interventions

Included participants will be assigned to either the treatment group (receiving BSZY cream) or the control group (receiving the emulsion base) randomly. They will receive interventions for a duration of 4 weeks with

Table 1 Timeline of data collection

Subjects	Research period	Screening	Treatment			Follow-up
		Week 0	Week 0 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 8 (±3 days)
Enrolment and baseline information	Inclusion/exclusion criteria	x				
	Informed agreement	x				
	Random allocation	x				
	Demographic features	x				
	History of disease	x				
	Registration	x				
	Visia photo		x	x	x	x
Intervention	BSZY cream group		x	x	x	x
	Emulsion matrix group		x	x	x	x
Efficacy evaluation	SCORAD Score*		x	x	x	x
	Clinical dermatologist assessment		x	x	x	x
	Patient self-assessment forms		x	x	x	x
Safety evaluation	Adverse effects	x	x	x	x	x

*Severity Scoring of Atopic Dermatitis Score.
BSZY cream, BiShengZhiYan cream; SCORAD, Scoring Atopic Dermatitis.

a frequency of two times per day. Adult man: 1 fingertip unit provides 0.5 g cream. Adult woman: 1 fingertip unit provides 0.4 g cream. The control group and treatment group use creams manufactured by the same producer, which display no variations in colour, odour, shape or observable appearance. It is not recommended to add or replace any previously unused skin care products during the trial. One point five fingertip units for each application[14] (fingertip units) represents a convenient way to ensure the amount of cream applied is consistent.

Outcome measurement

Primary outcomes

Scoring Atopic Dermatitis (SCORAD)

In this study, the SCORAD Scale[15] will be used for the primary efficacy assessment. The SCORAD Score will be calculated based on the types of lesions and body areas and is assessed separately for the head, neck, arms, legs, anterior trunk, back and genitalia based on the area of skin involved and the severity of erythema, exudation, crusting, lichenification and dryness. The scores report the severity of the patients' symptoms, with a total score ranging from 0 to 103. Scores of 25 or lower indicate mild severity, scores of 26–50 indicate moderate severity and scores of 51–103 indicate severe severity. Patients are monitored for changes in SCORAD during treatment and for improvements in AD, and changes in points are calculated and compared before and after treatment.

Secondary outcomes

Clinical dermatologist evaluation form

At weeks 0, 2, 4 and 8 after the patient's admission, the clinician will assess the skin condition of the patient's entire face on a scale of 0–4 for each of the four indicators: erythema, papules, oedema and desquamation. This evaluation form is shown in table 2.

Patient Self-Assessment Questionnaire

Patients will complete the skin sensory Self-Assessment Questionnaire at week 0, week 2, week 4 and week 8 after admission to the group to assess improvements in their subjective symptoms.

Safety indicators

The timing, duration, severity, management and consequences of adverse events (AEs) associated with the study drug are documented, and their relationship to the use of the study drug is identified.

AEs occurring during this trial are recorded and reported to the investigator. In the case of acute allergic symptoms, such as contact dermatitis, the drug is discontinued and remedial measures are taken if necessary. Mild patients are given topical or oral antihistamines, while severe cases are treated with systemic therapy. Unblinding can occur in emergency situations if necessary.

Sample size estimation

Based on our previous study and related literature (a randomised trial of Lactobacillus rhamnosus IDCC 3201 tyndallization (RHT3201) for treating AD),[16] the estimated changes in the SCORAD Score after 4 weeks are −13.89±10.05 (SD=10) and −8.37±9.95 (SD=10) in the intervention group and control group, respectively. The ratio of both groups is 1:1, the two-sided significance level is set as 0.05, and the power is 0.8. According to the sample size estimation Formula $n = \frac{(Z_\alpha + Z_\beta) \times 2\sigma^2}{\delta^2}$, 52 patients in

Table 2 Clinical dermatologist evaluation form (based on Investigator's Global Assessment)

Score level	Reddening	Erythema	Pimples	Oedema	Debridement
0 points	No symptoms	No symptoms	No symptoms	No symptoms	No symptoms
1 point	Slight localised redness (barely visible)	Slight erythema (barely visible)	Mild papules (barely visible)	Slight oedema (barely visible)	Vaguely appearing dry, can be distinguished by a closer look
2 points	Significant localised redness	Visible erythema	Visible papules	Mild oedema (skin elevation in profile)	Mildly dry, fine scales
3 points	Extensive redness	Moderate-to-severe erythema	Moderate-to-severe papules	Moderate oedema (skin elevation of approximately 1 mm)	Moderately dry, large and visible scales
4 points	Severe redness over a large area	Severe erythema (purplish red) to slight scorching	Severe patchy papules	Severe oedema (skin bulge of more than 1 mm)	Heavy dryness, extensive scaling and raised periphery

each group are calculated. The expected drop-out rate is 20%, with a total of 130 patients in the two groups.

Statistical analysis

Data processing

Clinical study data are privacy oriented, all data are entered in pairs using an electronic CRF (Case Report Form), and the database is locked at the end of the trial. The last observation carryover method is used for randomised missing data.

Data analysis

The full analysis set is used for the intention-to-treat analysis of the data, and Graphpad Prism 10 is used for the statistical analysis of the data. Differences are deemed statistically significant at $p<0.05$. The measurement data conform to a normal distribution and χ^2 test and are statistically described as $\overline{X}\pm S$. Pretreatment and post-treatment comparisons within the group itself are performed by paired t-tests, and comparisons between groups are performed by two independent samples t-tests; if the data do not conform to a normal distribution, the median and quartiles are used for statistical description, and comparisons are performed by the Wilcoxon rank-sum test.

Patient and public involvement

Patients and the public are not formally involved in the setup of the trial. The study's protocol includes all procedures related to subject safety and personal data protection and is developed mainly in a public hospital but without specific patient consultation.

DISCUSSION

The treatment of AD is a research hotspot in the field of dermatology.[17] However, most attention is currently focused on the treatment of moderate-to-severe AD, while the treatment of mild-to-moderate AD is neglected, especially in atopic facial dermatitis, the treatment of which is often limited by its location. Although the pathogenesis of AD remains unclear, it is generally accepted to involve a complex interaction between skin barrier dysfunction, abnormal skin microbiota, and predominantly type 2 immune dysregulation.[18–20]

Nevertheless, managing mild-to-moderate AD remains limited to the utilisation of TCSs, TCIs, PDE-4 (Phosphodiesterase-4) inhibitors and topical Janus kinase inhibitors (JAK).[18 21 22] The prolonged use of those agents has its own drawbacks in atopic facial dermatitis patients, including transient sensations of burning, stinging, erythema and pruritus, etc. Given these challenges, treatment priorities for atopic facial dermatitis focus on restoring barrier function, minimising triggers and alleviating symptoms.[19] A clinical study has demonstrated that barrier repair products significantly prolong eczema-free periods and reduce recurrence risk.[23] Therefore, restoring and preserving the skin barrier emerges as a critical strategy in managing mild-to-moderate AD, particularly atopic facial dermatitis.[24] Despite guidelines on AD increasingly emphasise the foundational role of moisturisers in maintaining skin integrity,[25 26] there is a notable lack of clinical studies specifically evaluating the efficacy of skin barrier repair products for atopic facial dermatitis.

Stepwise therapy is currently advised by the medical profession for the clinical treatment of AD.[14] While patients with mild-to-moderate atopic facial dermatitis frequently use topical treatments, individuals with severe atopic facial dermatitis are prioritised for systemic treatment, which includes immunosuppressants, biologics and JAK.[27–29]

As a non-hormonal skin barrier dysfunction repair solution, BSZY cream is less likely to induce negative reactions when it is used in sensitive regions of the body, such as the face. Our previous experiments showed that BSZY cream can increase the thickness of the epidermal layer and the water content of the stratum corneum, reduce epidermal sensitivity, regulate epidermal pH and cause a significant decrease in skin haemoglobin content and the Visia red zone in subjects.[30] Therefore, we designed this randomised controlled clinical trial to determine

the clinical efficacy of BSZY cream in mild-to-moderate atopic facial dermatitis.

At present, multiple guidelines for the treatment of AD recommend moisturisers as a foundational therapeutic approach for patients with mild-to-moderate symptoms.[25 26 31] Consequently, we chose a cream-based emollient with sole moisturising effects as the control group. This design allows for a comparative assessment to ascertain whether BSZY cream exhibits superior therapeutic efficacy beyond mere moisturisation; additionally, it ensures adequate protection for all participants to receive appropriate treatment. In terms of outcome indicators, we used the SCORAD Index as the primary outcome indicator and assessed the clinical benefit of the BSZY cream from both physician and subject perspectives. Therefore, the results of the proposed randomised controlled trial on the efficacy and safety of BSZY cream for the treatment of mild-to-moderate atopic facial dermatitis are expected to provide high-level evidence.

The rigorous methodology employed in this protocol, including the randomisation process, double-blind design and specific outcome measures, provides a robust framework that can be adapted for future studies investigating treatments for atopic facial dermatitis and other skin conditions. By sharing our detailed protocol, we aim to contribute to the standardisation of trial design in dermatological research, facilitating comparisons across studies and enhancing the overall quality of evidence in the field.

Strengths and limitations

To the best of our knowledge, this is the first trial of BSZY cream for the treatment of atopic facial dermatitis. The results of the trial not only support the efficacy and safety of BSZY cream for the treatment of atopic facial dermatitis but also provide supporting data for other dermatological patients with impaired facial skin barrier function.

The limitations of this study are that it is a single-centre study and is conducted only in patients with mild-to-moderate atopic facial dermatitis. Challenges with patient adherence to topical medications are also faced. The size of the study sample and the short follow-up period limit the power of the observations.

ETHICS AND DISSEMINATION

The study protocol (NCT05792826) and applied informed consent forms were approved for their content and compliance with ethical regulations by the ethics committee of the Yueyang Hospital. Before the study is officially launched, all participants will be asked for written informed consent. The findings will be published in peer-reviewed journals.

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Contributors PYW and XW authored the study design. LC, RX and GY prepared supplementary documents. DG, HL and TD revised the paper. WG, XL, LH and YW were in charge of passing the ethical review. FL, JZ, WG and DG also contributed to the study design. After reading the final text, each author gave their approval. FL is the guarantor.

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Competing interests None declared.

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