Acupuncture and osteopathic medicine for atopic dermatitis: a three-armed, randomized controlled explorative clinical trial

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Abstract

Background. Patients with atopic dermatitis (AD) frequently use acupuncture (ACU) and osteopathic medicine (OM), although their therapeutic benefits are unclear.

Aim. To investigate the effectiveness of ACU and OM in patients with AD.

Methods. In a three-armed, single-centre, randomized controlled open explorative clinical trial, adult patients with AD received ACU, OM or no study intervention (control group; CG) plus routine care. Outcomes included disease severity (SCORing Atopic Dermatitis; SCORAD), itching intensity (visual analogue scale; VAS), frequency of topical corticosteroid (TCS) use over 7 days and cost-effectiveness. Endpoints were analysed by analysis of covariance adjusted for the respective baseline value and TCS use.

Results. Overall, 121 patients (92 women, 29 men) with a mean ± SD age of 31.4 ± 10.5 years were randomized. After 12 weeks, the adjusted means (95% CI) for ACU, OM and control were, respectively, 22.3 (18.3–26.3), 26.4 (22.6–30.2) and 23.7 (19.9–27.5) for SCORAD (P = 0.32); 27.9 (19.5–36.4), 35.0 (26.9–43.0) and 42.3 (34.7–50.0) for VAS itching (P < 0.05); and 2.3 (0.8–3.9), 1.9 (0.4–3.5) and 4.3 (2.6–6.0), for TCS use (P = 0.10). ACU and OM were not cost-effective compared with the CG.

Conclusion. Although no differences in disease severity were found, our findings indicate that ACU might reduce itching in patients with AD. Furthermore, ACU and OM showed a trend towards reducing TCS use.

Introduction

Atopic dermatitis (AD) has a high lifetime prevalence and is associated with personal, social and economic burdens. 1 AD symptoms can lead to impairments in quality of life (QoL) and work performance. 2 Symptomatic treatment with topical corticosteroids (TCSs) entails a risk of adverse events (AEs), including adrenal insufficiency and glaucoma. 3 More than half of patients with AD use complementary medicine, 4 including acupuncture (ACU) and osteopathic medicine (OM). ACU is a Chinese medicine treatment in which the skin is punctured with small needles at defined points. Experimental and clinical studies suggest the effectiveness of ACU for reducing itch and improving disease severity in AD. 5,6 OM is a diagnostic and therapeutic medical practice that applies manual treatment techniques. OM might influence the neurovegetative system, 7 and there is limited evidence for possible benefits of OM in adults with AD. 8,9

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The aim of this study was to determine the feasibility, exploratory effectiveness and cost-effectiveness of semistandardized ACU and OM treatments in adult patients with AD compared with a control group (CG), and to gather experience and data for planning future confirmatory trials.

Methods

Study design and setting

In this three-armed, single-centre, randomized controlled open explorative clinical trial, adult patients with AD were randomized to receive ACU, OM or no study intervention (CG). Randomization (1 : 1 : 1 ratio) was performed in the study centre, using computer-generated block randomization (variable block length), stratified by TCS use within the previous 4 weeks (yes/no). Treatment allocation was concealed. The study was performed at the University Outpatient Clinic for Complementary Medicine (Charité-Universitätsmedizin Berlin, Germany).

Patients

Patients were recruited in Berlin by public transport advertisements, newspapers and digital media.

Inclusion criteria were age 18–65 years, AD diagnosis with symptoms for at least 6 months, at least three of the four AD criteria of Williams et al.,10 Three-Item Severity Score (TIS)11 of 2–7 and mean perceived itching intensity of the skin of 40–80 mm on a visual analogue scale (VAS) (scale is 0–100 mm: 0 = no itching, 100 = maximum imaginable itching) over the previous 7 days.

Exclusion criteria were: other types of dermatosis; use of systemic corticosteroids (previous 3 months); TCS class IV; systemic AD medication (e.g. immunomodulators); AD treatment with ACU, OM or psychotherapy (previous 3 months); therapies with an assumed positive effect on AD symptoms (e.g. hyposensitization, phototherapy); present malignant tumours; rheumatic diseases; body mass index \( \geq 30.0 \) kg/m\(^2\); pregnancy/breastfeeding; serious organic or mental illness; and drug and/or alcohol abuse.

Study interventions

Using a modified Delphi method, semistandards were developed by OM and ACU experts, clinicians and trial specialists. The study interventions were applied within 12 weeks after randomization by certified physicians and therapists.

Patients randomized to ACU received eight semistandardized treatments in 30-min sessions at intervals of 1–2 weeks. The obligatory ACU points large intestine channels 4 and 11 (bilaterally) and spleen channels 6 and 10 (unilateral or bilateral) were supplemented by optional points, including ear ACU.

Patients randomized to OM received five 45-min semistandardized OM treatments at approximately 2-week intervals. Obligatory treatment locations were the cervical column, thoracic column, ribs, diaphragm, lungs, intestines, cranial bones and cranial fascia.

Patients in the CG received no study intervention; after 12 weeks, they could choose to receive either eight ACU treatments or five OM treatments.

Patients in all groups were allowed to use routine care, including TCS and emollients.

Outcome parameters

Owing to the exploratory nature of this trial, no primary outcome parameter was defined. The most relevant timepoint for group comparisons was 12 weeks (after completion of the study intervention phase, and before the optional ACU or OM treatment for the CG patients).

At baseline and after 12 and 26 weeks, independent raters (physicians and nurses who are also dermatitis trainers and specialized in SCORing Atopic Dermatitis (SCORAD) rating) performed a group allocation-blinded assessment of the severity of AD using SCORAD; responders were defined as those who showed an improvement of 8.7 points (minimal clinically important difference; MCID) from baseline to 12 weeks12 and the Eczema Area and Severity Index (EASI).12

At baseline and after 6, 12 and 26 weeks, standardized patient questionnaires measured the following parameters. Average itching intensity within the previous 7 days was measured by VAS,13 and responders were defined by \( \geq 50\% \) improvement from baseline to Week 12. TCS use within the previous 7 days was measured as number of applications of TC, with halving of TCS use considered clinically relevant. Disease-specific QoL was assessed by the Dermatology Life Quality Index (DLQI),14 and general QoL by the 12-item Short Form Health Survey (SF-12).15 For therapeutic safety, AEs (specifically related to ACU and OM) were also assessed. During the first 12 weeks, all patients kept diaries in which they recorded their perceived sleep disturbances16 and skin condition (VAS), and reported all medications used (TCS, emollients, other medicaments) and AEs on a daily basis. For
details (range, MCID) concerning outcomes, see Tables 1 and 2.

**Statistical analysis**

For this explorative clinical trial, no sample size calculation was performed. In total, 120 patients were considered logistically manageable and sufficient to achieve the study's exploratory objectives. The data analysis strategies were defined beforehand in a statistical analysis plan. Baseline and safety data were analysed descriptively. Using the intention-to-treat (ITT) principle, patients were analysed according to the treatment to which they were randomized (without imputation of missing values). VAS itching and SCORAD scores were additionally analysed for the per-protocol (PP), population excluding patients who attended < 70% of their treatment sessions (ACU/OM) or controls who received ACU or OM (CG); and participants who used unpermitted medication or interventions, became pregnant or were not stratified by TCS use at baseline. Continuous outcomes,

**Table 1** Baseline characteristics of the participants.

| Parameter\(^a\) | \(n\) | ACU (n = 39) | OM (n = 40) | Control (n = 42) | Total (n = 121) |
|-----------------|------|-------------|-------------|-----------------|----------------|
| Age, years      | 121  | 31.4 ± 10.9 | 31.6 ± 10.0 | 31.1 ± 10.8     | 31.4 ± 10.5    |
| Sex, n (%)      |      |             |             |                 |                |
| F               | 121  | 28 (71.8)   | 33 (82.5)   | 31 (73.8)       | 92 (76.0)      |
| M               |      | 11 (28.2)   | 7 (17.5)    | 11 (26.2)       | 29 (24.0)      |
| BMI, kg/m\(^2\) | 121  | 22.1 ± 2.8  | 22.2 ± 2.6  | 22.2 ± 2.5      | 22.2 ± 2.6     |
| Educational/employment status, n (%) | | | | | |
| Abitur\(^b\)    | 121  | 38 (97.4)   | 34 (85.0)   | 38 (90.5)       | 110 (90.9)     |
| University student |   | 11 (28.2)   | 13 (32.5)   | 14 (33.3)       | 38 (31.4)      |
| Employed (not student) | 83  | 23 (92.0)   | 25 (100.0)  | 22 (91.7)       | 70 (94.6)      |
| Duration of AD, years | 120 | 26.3 ± 13.2 | 27.4 ± 10.8 | 27.2 ± 13.2     | 27.0 ± 12.4    |
| Concomitant disease, n (%) | 121 | 19 (48.7)   | 25 (62.5)   | 26 (61.9)       | 70 (57.9)      |
| Allergic asthma | 121  | 4 (10.3)    | 11 (27.5)   | 20 (47.6)       | 35 (28.9)      |
| History of allergy | 121 | 32 (82.1)   | 33 (82.5)   | 35 (83.3)       | 100 (82.6)     |
| Previous psychotheraphy | 121 | 12 (30.8)   | 8 (20.0)    | 13 (31.0)       | 33 (27.3)      |
| AD medication in previous 3 months, n (%) | 121 | 30 (76.9)   | 28 (70.0)   | 27 (64.3)       | 85 (70.2)      |
| Previous treatment with ACU, n (%) | 121 | 13 (33.3)   | 18 (45.0)   | 14 (33.3)       | 45 (37.2)      |
| For AD          | 4 (30.8) | 10 (55.6) | 10 (71.4) | 24 (53.3) | |
| And/or for other diagnosis | 9 (69.2) | 9 (50.0) | 4 (28.6) | 22 (48.9) | |
| Previous treatment with OM, n (%) | 121 | 11 (28.2) | 8 (20.0) | 15 (35.7) | 34 (28.1) |
| For AD          | 1 (9.1) | 1 (12.5) | 2 (13.3) | 4 (11.8) | |
| And/or for other diagnosis | 10 (90.9) | 7 (87.5) | 13 (86.7) | 30 (88.2) | |
| SCORAD (range 0–103)\(^c\), n (%) | 121 | 32.2 ± 18.7 | 29.6 ± 12.1 | 36.3 ± 15.4     | 32.8 ± 15.7    |
| EASI (range 0–72)\(^c\), n (%) | 121 | 6.9 ± 9.1 | 3.7 ± 4.0 | 6.6 ± 8.0 | 5.7 ± 7.4 |
| VAS itching (range 0–100 mm)\(^d\), n (%) | 121 | 62.6 ± 16.2 | 58.3 ± 16.3 | 57.4 ± 15.1     | 59.4 ± 15.9    |
| Patients applying TCS\(^e\), n (%) | 121 | 33 (84.6) | 27 (67.5) | 29 (69.0) | 89 (73.6) |
| TCS use, frequency over 7 days, n (%) | 89 | 4.7 ± 8.5 | 4.7 ± 6.3 | 5.6 ± 8.8 | 5.0 ± 7.9 |
| DLQI (range 0–30)\(^c\) | 120 | 10.2 ± 5.0 | 9.3 ± 5.5 | 9.0 ± 5.3 | 9.5 ± 5.2 |
| SF-12 Physical component (range 9.9–70.1)\(^e\) | 120 | 49.7 ± 8.0 | 49.1 ± 7.7 | 49.9 ± 6.7 | 49.6 ± 7.4 |
| Mental component (range 5.9–72.3)\(^e\) | 120 | 45.5 ± 9.9 | 44.3 ± 8.7 | 48.2 ± 8.2 | 46.0 ± 9.0 |
| VAS sleep disturbances (range 0–100 mm)\(^f\) | 67 | 46.6 ± 23.0 | 33.5 ± 21.9 | 43.4 ± 24.2 | 40.7 ± 23.4 |
| VAS skin condition (range 0–100 mm)\(^g\) | 121 | 50.3 ± 21.9 | 52.9 ± 20.8 | 53.1 ± 17.9 | 52.1 ± 20.1 |
| Three Item Severity Score (0–9)\(^h\) | 121 | 3.7 ± 1.5 | 3.6 ± 1.3 | 4.6 ± 1.5 | 4.0 ± 1.5 |
| Unable to work due to AD past 3 months, n (%) | 93 | 5 (16.7) | 4 (13.8) | 3 (8.8) | 12 (12.9) |
| Days unable to work due to AD past 3 months | 12 | 3.2 ± 2.2 | 4.0 ± 4.7 | 4.3 ± 4.9 | 3.75 ± 3.5 |
| Costs of AD in past 12 weeks, EUR | | | | | |
| Direct          | 121  | 171.71 ± 210.46 | 241.12 ± 707.35 | 143.23 ± 156.72 | 184.77 ± 432.14 |
| Indirect        | 119  | 117.56 ± 365.08 | 111.68 ± 497.04 | 88.53 ± 443.39 | 105.58 ± 346.17 |
| Total           | 121  | 286.25 ± 411.45 | 352.80 ± 849.13 | 229.65 ± 486.25 | 288.61 ± 609.35 |

ACU, acupuncture; AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; OM, otopathic medicine; SCORAD, SCORing Atopic Dermatitis; SF-12, 12-item Short Form Health Survey; TCS, topical corticosteroids class I–III; VAS, visual analogue scale. \(^a\)Data are mean ± SD unless otherwise stated; \(^b\)German qualification required for university entrance; \(^c\)lower values indicate better status; \(^d\)itching: 0 = none, 100 = extreme; \(^e\)higher values indicate better status; \(^f\)sleep disturbance: 0 = none, 100 = extreme; \(^g\)skin disturbance: 0 = none, 100 = extreme.
Table 2 Endpoints at 6, 12 and 26 weeks after randomization (means adjusted for the respective baseline value and topical corticosteroid use) and responders at 12 weeks for selected outcomes.

| Outcome                  | n  | OR, mean (95% CI) | Mean difference (95% CI) |
|--------------------------|----|-------------------|--------------------------|
|                          |    | ACU               | OM                       | CG           | P    | Control vs. ACU | Control vs. OM | OM vs. ACU |
| **SCORAD (range 0–103)** |    |                   |                          |              |      |                 |                |            |
| Week 12                  | 117| 22.3 (18.3–26.3)  | 26.4 (22.6–30.2)         | 23.7 (19.9–27.5) | 0.32 | 1.4 (–4.2 to 6.9) | –2.7 (–8.1 to 2.7) | 4.1 (–1.4 to 9.6) |
| Responder                |    | 1.5 (0.6–4.4)     | 0.5 (0.2–1.3)            | –             | –   | –                | –               | –          |
| Week 26                  | 69 | 19.6 (14.9–24.4)  | 19.8 (15.4–24.2)         | –             | 0.96 | –                | –               | –          |
| **EASI (0–72)**          |    |                   |                          |              |      |                 |                |            |
| Week 12                  | 116| 3.4 (1.7–5.2)     | 5.4 (3.7–7.0)            | 4.3 (2.6–5.9) | 0.28 | 0.8 (–1.5 to 3.2) | –1.1 (–3.4 to 1.3) | 1.9 (–0.5 to 4.3) |
| Week 26                  | 69 | 3.1 (1.1–5.0)     | 3.4 (1.6–5.2)            | –             | 0.79 | –                | –               | –          |
| **VAS itching (0–100 mm)**|    |                   |                          |              |      |                 |                |            |
| Week 6                   | 112| 42.0 (35.1–48.9)  | 45.9 (39.3–52.5)         | 49.7 (43.4–55.9) | 0.27 | 7.7 (–1.7 to 17.0)| 3.7 (–5.3 to 12.8) | 3.9 (–5.6 to 13.5) |
| Week 12                  | 109| 27.9 (19.5–36.4)  | 35.0 (26.9–43.0)         | 42.3 (34.7–50.0) | <0.05| 14.4 (3.0 to 25.8) | 7.3 (–3.8 to 18.4) | 7.1 (–4.6 to 18.7) |
| Responder                |    | 2.4 (0.9–6.5)     | 1.6 (0.6–4.2)            | –             | –   | –                | –               | –          |
| Week 26                  | 69 | 32.7 (23.4–41.9)  | 28.5 (19.6–37.3)         | –             | 0.51 | –                | –               | –4.2 (–17.0 to 8.6) |
| **TCS use**              |    |                   |                          |              |      |                 |                |            |
| Week 6                   | 66 | 4.4 (2.4–6.4)     | 4.2 (2.2–6.3)            | 5.8 (3.7–7.9) | 0.47 | 1.4 (–1.4 to 4.3)| 1.6 (–1.2 to 4.4) | –0.2 (–3.0 to 2.6) |
| Week 12                  | 68 | 2.3 (0.8–3.9)     | 1.9 (0.4–3.5)            | 4.3 (2.6–6.0) | 0.10 | 1.9 (–0.3 to 4.2)| 2.4 (–0.1 to 4.6) | –0.4 (–2.6 to 1.8) |
| Week 26                  | 43 | 2.0 (0.5–3.4)     | 2.3 (0.9–3.8)            | –             | 0.73 | –                | –               | 0.3 (–1.7 to 2.4) |
| **DLQI (0–30)**          |    |                   |                          |              |      |                 |                |            |
| Week 6                   | 112| 6.9 (5.5–8.2)     | 7.6 (6.3–8.9)            | 8.6 (7.4–9.8) | 0.17 | 1.7 (–0.1 to 3.6)| 1.0 (–0.8 to 2.8) | 0.7 (–1.2 to 2.6) |
| Week 12                  | 109| 4.7 (3.2–6.2)     | 6.0 (4.6–7.4)            | 6.9 (5.5–8.2) | 0.11 | 2.2 (0.2 to 4.2)| 0.9 (–1.0 to 2.9) | 1.2 (–0.8 to 3.3) |
| Week 26                  | 68 | 5.6 (3.9–7.4)     | 5.7 (4.1–7.3)            | –             | 0.94 | –                | –               | 0.1 (–2.3 to 2.4) |
| **SF-12 PCS (9.9–70.1)** |    |                   |                          |              |      |                 |                |            |
| Week 6                   | 108| 50.4 (48.1–52.6)  | 51.0 (48.9–53.2)         | 50.1 (48.1–52.2) | 0.83 | –0.2 (–3.3 to 2.8)| –0.9 (–3.8 to 2.1)| 0.7 (–2.4 to 3.6) |
| Week 12                  | 107| 53.0 (50.8–55.2)  | 52.0 (49.9–54.1)         | 50.0 (48.0–51.9) | 0.11 | –3.0 (–6.0 to 0.1) | –2.1 (–4.9 to 0.8) | –0.9 (–4.0 to 2.1) |
| Week 26                  | 66 | 52.9 (50.9–54.9)  | 53.2 (51.4–55.1)         | –             | 0.81 | –                | –               | 0.3–2.4 to 3.0  |
| Outcome | n   | ACU (OR, mean (95% CI)) | OM (OR, mean (95% CI)) | CG (OR, mean (95% CI)) | P  | Mean difference (95% CI) |
|---------|-----|-------------------------|------------------------|------------------------|----|-------------------------|
| SF-12 MCS (5.9; 72.3);<sup>c</sup> MCID 5 | Week 6 | 108 | 44.7 (41.7–47.8) | 46.1 (43.2–49.1) | 45.3 (42.4–48.1) | 0.81 | 0.5 (–3.7 to 4.7) | –0.9 (–5.0 to 3.3) | 1.4 (–2.8 to 5.6) |
|         | Week 12 | 107 | 45.4 (42.2–48.6) | 46.9 (43.7–50.0) | 48.1 (45.2–51.0) | 0.46 | 2.7 (–1.6 to 7.1) | 1.3 (–3.1 to 5.6) | 1.5 (–3.0 to 5.9) |
|         | Week 26 | 66  | 48.6 (44.8–52.4) | 46.6 (43.2–50.1) | – | – | – | – | – |
| VAS sleep disturbance (0–100 mm);<sup>d</sup> MCID 10 | Week 6 | 61  | 23.4 (11.8–35.1) | 25.2 (15.3–35.1) | 31.0 (21.4–40.5) | 0.54 | 7.5 (–7.3 to 22.4) | 5.7 (–8.1 to 19.5) | 1.8 (–13.7 to 17.3) |
|         | Week 12 | 58  | 9.2 (–2.2–20.7) | 19.2 (9.5–28.9) | 15.2 (5.8–24.7) | 0.43 | 6.0 (–8.7 to 20.7) | –4.0 (–17.7 to 9.7) | 10.0 (–5.2 to 25.2) |
| VAS skin condition (0–100 mm);<sup>e</sup> no MCID | Week 6 | 111 | 42.4 (34.9–49.9) | 44.6 (37.6–51.7) | 48.5 (41.8–55.2) | 0.47 | 6.1 (–3.9 to 16.1) | 3.9 (–5.8 to 13.6) | 2.2 (–8.0 to 12.5) |
|         | Week 12 | 109 | 34.0 (25.4–42.5) | 30.4 (22.3–38.6) | 40.2 (32.4–47.9) | 0.22 | 6.2 (–5.4 to 17.7) | 9.8 (–1.5 to 21.0) | –3.6 (–15.4 to 8.2) |
| QALYs, Week 12 | 102 | 0.174 (0.17–0.18) | 0.175 (0.17–0.18) | 0.174 (0.169–0.178) | – | – | – | – | – |
| Total costs, EUR; Week 12 | 105 | 734.39 (429.35–954.30) | 658.34 (365.37–626.54) | 345.31 (68.08–954.30) | – | – | – | – | – |

ACU, acupuncture; AD, atopic dermatitis; CG, control group; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; MCS, mental component scale; MCID, minimal clinically important difference; OM, osteopathic medicine; OR, odds ratio; PCS, physical component scale; QALYs, quality-adjusted life years; SCORAD, SCORing Atopic Dermatitis; SF-12, 12-item Short Form Health Survey; TCS, topical corticosteroids class I–III; VAS, visual analogue scale. *Lower values indicate better status, itching: 0 = none 100 = extreme; †higher values indicate better status; ‡sleep disturbance: 0 = none, 100 = extreme; §skin disturbance: 0 = none, 100 = extreme.
including costs and quality-adjusted life years (QALYs), were analysed by analysis of covariance, including treatment (ACU, OM, CG), stratification factor (TCS use) and the respective baseline value as covariate. Post hoc sensitivity analyses included adjusting for relevant intergroup baseline differences (educational status, concomitant diseases, allergic asthma) and including the treatment group-by-baseline disease severity interaction (for the endpoints SCORAD, VAS itching and TCS use). Responders were analysed by logistic regression, adjusted for the respective baseline value and stratification factor. All P values were considered explorative, without adjustment for multiple testing. The statistical analysis was performed using R software (V3.6.3: https://www.R-project.org/).

Health economics analysis

For the 12 weeks after baseline, an explorative cost-effectiveness analysis was carried out. AD-related total costs from a societal perspective (including direct and indirect costs) were linked to the achieved QALYs. Patient questionnaires were used to systematically collect data on number of sick days, reductions in working hour and utilization of medical resources related to AD for the 12 weeks prior to and after baseline. ACU treatment was valued at €46.92/session and OM treatment at €76.14/session. The SF-12 data were converted into SF-6D health state utility values by applying an algorithm developed by Brazier and Roberts. Assuming linear changes between these longitudinal utility values, QALYs were measured by calculating the area under the curve based on these values.

Results

Patients, study interventions and baseline data

In total, 574 eligible patients were identified between October 2017 and October 2018. Of these, 121 patients [92 (76.0%) women, 29 men (24%)]; mean ± SD 31.4 ± 10.5 years] were randomized (ACU n = 39, OM n = 40, control n = 42). Three patients randomized to ACU dropped out before the first treatment (Fig. 1); all other patients received all study interventions as assigned, resulting in 288 ACU treatments and 200 OM treatments. We found small intergroup baseline differences in sex, but relevant intergroup baseline differences in educational status (German university entrance qualification), concomitant diseases and allergic asthma (Table 1).

Outcomes

The adjusted mean SCORAD was similar in all groups (Table 2). Response measure by SCORAD analysis favoured ACU but not OM over CG.

We found a clinically relevant difference in VAS itching between ACU and CG [adjusted means: ACU 27.9 (95% CI 19.5–36.4), OM 35.0 (26.9–43.0), control 42.3 (95% CI 34.7–50.0); P < 0.05] (Fig. 2a). Response measured by VAS itching analysis favoured ACU and OM over CG.

TCS use was reduced in patients receiving ACU or OM [adjusted means 2.3 (95% CI 0.8–3.9), 1.9 (95% CI 0.4–3.5), 4.3 (95% CI 2.6–6.0); P = 0.10] (Fig. 2b).

We found no other relevant differences between ACU or OM compared with CG. The sensitivity analyses (adjusting for baseline differences) or PP analysis results for SCORAD (n = 98) and VAS itching (n = 93) did not change the main findings.

No serious AEs occurred. AEs were reported by 17 patients (48.6%) in the ACU group, with a total of 30 incidents (most often aggravation of disease, haematoma and small bleeds, pain) and by 25 (64.1%) in the OM group, with a total of 83 incidents (most often tiredness, aggravation of disease, headache, muscle tension, muscle soreness).

Over the 12 weeks after baseline, adjusted QALYs were comparable for the three groups but at higher costs for ACU and OM (Table 2). The PP analysis results for adjusted QALYs (n = 87) and costs (n = 90) after 12 weeks were comparable to the ITT analysis results and confirmed the lack of cost-effectiveness of ACU and OM.

Discussion

In this trial in patients with AD, no differences in AD severity according to SCORAD or EASI were found after ACU, OM or no study intervention (CG) in addition to routine care. However, the results suggest that ACU might be associated with a clinically relevant improvement in itching, and ACU and OM might reduce TCS use. The semistandardized study interventions were feasible and overall, patients showed high adherence to the study intervention. The health economics analysis did not support cost-effectiveness for either ACU or OM.

In contrast to the literature, we did not find relevant intergroup differences for ACU or OM in SCORAD or EASI scores. A recent review found that ACU reduced AD disease severity. In 20 patients (no control), pre- and post-improvements in EASI, VAS itching, DLQI and TCS use were described after treatment with combined
ACU and Chinese herbal medicine. However, our comparison between groups reduces the study effects bias. We found a clinically relevant intergroup difference for itching that favoured ACU over the control. However, previous reports of such differences are controversial. Patients receiving ACU also used less TCS in our study, as described previously. Regarding OM in adult patients with AD, a non-peer-reviewed, single-arm, pre–post study reported SCORAD improvements in five of six patients, but these were rated by the therapist. The blinded outcome ratings of SCORAD and EASI performed in our study revealed no

Figure 1 Recruitment, treatment and follow-up of patients.

* VAS itching values and/or SCORAD-value available
Patients, which returned either questionnaires or participated in the ratings of the severity of their atopic dermatitis are not counted as lost to follow-up.
This study is the first, to our knowledge, to provide indications that OM might halve TCS use despite stable SCORAD values, and is also the first to find that patients receiving OM and ACU rated their skin condition better than the CG. Overall, both study interventions were relatively safe without serious AEs. The observed AEs are known and partly inherent to the methods. However, the number of patients reporting AEs exceeded those of earlier trials using ACU\(^20\) or OM\(^21\) to treat diagnoses other than AD.

This is the first randomized controlled trial (RCT) investigating ACU and OM in patients with AD. The strengths of this study include the relatively large sample size for a single-centre trial, the semistandardized treatments, the implementation of blinded rated outcomes and the high patient adherence rate. Furthermore, the study population was fairly homogeneous for disease severity, which augments the internal validity. The study limitations include the single-centre setting, the female preponderance and

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**Figure 2** (a,b) Follow-up time was 6, 12 and 26 weeks (all adjusted for respective baseline values and topical corticosteroid use) for the treatment groups. After 26 weeks, the control group could receive acupuncture or osteopathic medicine (not shown). (a) Visual analogue scale (VAS) for itching intensity; (b) number of topical corticosteroids used within 7 days.
the lack of patients with severe AD, which limits the generalizability of the results. Possible treatment effects in patients with severe AD should be investigated in future trials. A further limitation is that the treatment semistandards were not evaluated in advance. However, although standardized treatments for ACU and OM have been reported, we are the first to provide ACU and OM semistandards for patients with AD. The study design had potential sources of bias: patients receiving ACU or OM received more physician time and attention than control patients, and binding of patients and therapists was not possible. Consequently, the study’s intervention effects may have been overestimated. Moreover, the two assessor-blinded outcomes did not indicate any treatment effects. However, questions have recently been raised about the relevance of binding in RCTs, based on a meta-epidemiological study. Although no relevant TCS product/potency changes were observed pre–post in individual patients, we did not evaluate differences between groups. Our exploratory study had no primary outcome, thus emerging trends should be verified by confirmatory studies. To facilitate patient recruitment and ensure compliance in the CG, we offered eight ACU treatments or five OM treatments. We estimate that more ACU treatments, such as the 12 sessions used for allergic rhinitis, might have provided stronger effects. From a health economics point of view, if the intergroup comparison period had been longer than 12 weeks, more robust results might have been obtained in the cost-effectiveness analyses.

### Conclusion

Although the study showed no clinically relevant differences in disease severity by SCORAD or EASI after eight ACU treatments, five OM treatments or no intervention (control) plus routine care, we found some indication that ACU may reduce itching and that ACU and OM may reduce TCS use in patients with AD.

### What’s already known about this topic?

- More than half of patients with AD use complementary medicine, including ACU and OM.
- There is limited scientific evidence about the therapeutic benefits of ACU and OM in AD.
- Despite therapeutic improvements, not all AD symptoms are alleviated by treatment.

### What does this study add?

- Symptomatic treatment with TCSs entails a risk of AEs, including adrenal insufficiency and glaucoma.

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#### Conflict of interest

GR receives lecture fees for teaching osteopathic medicine and is a board member on a voluntary basis of the European Register for Osteopathic Physicians. The other authors declare that they have no conflict of interest.

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#### Ethics statement

The study was approved by the ethics committee of Charité–Universitätsmedizin Berlin (EA1/111/17). The trial was registered on the German Clinical Trials Register (https://www.clinicaltrialsregister.de/ctr_search?query=U1111-1169-9945; ref. no DRKS00012915; UTN: U1111-1169-9945. All patients gave oral and written informed consent before inclusion in the study, and for publication of their case details.

#### Data availability

Not shared.

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