Dermatol Ther (Heidelb) (2022) 12:2383–2395
https://doi.org/10.1007/s13555-022-00814-x

BRIEF REPORT

# Release of Cervical Muscle Tension Improves Psychological Stress and Symptoms of Moderate-to-Severe Atopic Dermatitis: a Case Series with 20 Patients

Shusaku Hosono · Koji Fujita · Akimoto Nimura · Keiichi Akita

Received: July 21, 2022 / Accepted: September 8, 2022 / Published online: September 21, 2022
© The Author(s) 2022

## ABSTRACT

***Introduction***: Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that is triggered by intense pruritus, impaired skin barrier function, and immune responses to allergenic substances. Break-through therapies for AD include molecular-targeted drugs and the effective management of severe symptoms of AD. However, patients with clinical improvements may continue scratching owing to the influence of psychological stress, which might lead to quick relapses of stressors and subsequent intensive scratching. New drugs may be ineffective because of such scratching behavior caused by stressors. Therefore, it may be useful to consider adjunctive treatment options that focus on external stressors as triggers of deterioration of AD. We hypothesized that improvement of psychological stress by relieving cervical muscle tension would reduce pruritus and atopic symptoms.

***Methods***: Overall, 21 patients with moderate-to-severe AD were treated to relieve cervical muscular tension using Spineliner SA201, which assists in osteopathic manipulative treatment. We assessed the subjective and objective symptoms of AD, cervical muscle tension, which was evaluated using cervical range of motion (ROM), and psychological burden. Only moisturizers were applied topically during the study period, and no topical corticosteroid therapy was used.

***Results***: Twenty patients who completed the treatment demonstrated improvement in the symptoms of AD: changes on the visual analog scale (VAS) for pruritus were −44.2%, Eczema Area and Severity Index (EASI) was −67.9%, thymus and activation-regulated chemokine (TARC) was −56.2%, Hospital Anxiety and Depression Scale (HADS) was −27.2%, sleep disturbance was −49.7%, and Dermatology Life Quality Index (DLQI) was −46.7%. Additionally, the cervical muscle tension improved significantly: changes in cervical ROM were 14.7%.

***Conclusions***: Release of cervical muscle tension may improve psychological stress and have an effect on moderate-to-severe AD.

The manuscript was prepared according to the guidelines provided in the CONSORT guidelines.

S. Hosono · K. Akita
Department of Clinical Anatomy, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

S. Hosono
Department of Dermatology, Hosono Clinic, Tokyo, Japan

K. Fujita (✉) · A. Nimura
Department of Functional Joint Anatomy, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-Ku, Tokyo 113-8519, Japan
e-mail: fujiorth@tmd.ac.jp

## PLAIN LANGUAGE SUMMARY

Atopic dermatitis is a chronic relapsing inflammatory skin disease triggered by intense pruritus, impaired skin barrier function, and immune responses. Standard dermatological therapies for patients with atopic dermatitis include topical glucocorticoid treatments. In some cases, scratching and inflammation could not be adequately controlled, a relapse could not be prevented after remission, and their efficacy is limited. Break-through therapies for atopic dermatitis include new molecular biological drugs, which have demonstrated significantly improved and effective management of severe atopic symptoms. However, patients with clinical improvements may continue scratching owing to psychological stress, which might lead to quick relapses of stressors and subsequent intensive scratching. New drugs may be ineffective owing to such scratching behavior caused by stressors. Therefore, it may be useful to consider adjunctive treatment options focusing on external stressors as triggers for worsening atopic dermatitis. We hypothesized that improvement of psychological stress by relieving cervical muscle tension would reduce pruritus and atopic symptoms. Overall, 21 patients with moderate-to-severe atopic dermatitis were treated to relieve cervical muscular tension using Spineliner SA201, which assists in osteopathic manipulative treatment. We assessed the subjective and objective atopic symptoms, cervical muscle tension, and psychological burden. Only moisturizers were applied topically during the study period, and no topical corticosteroid therapy was used. Twenty patients completed the treatment, atopic symptoms improved significantly, cervical muscular tension improved, and the psychological burden decreased with the treatment. Release of cervical muscle tension may improve psychological stress and affect moderate-to-severe atopic dermatitis.

**Keywords:** Atopic dermatitis; Cervical muscular tension; Itch–scratch cycle; Psychological stress

**Key Summary Points**

***Why carry out this study?***

Psychological stress may cause repeated scratching, which may lead to pruritus, and may perpetuate the itch–scratch cycle and aggravate atopic dermatitis (AD)

We suggest a new approach for treating psychological stress that causes acute exacerbation of AD and scratching habits

***What was learned from the study?***

The release of cervical muscle tension may improve psychological stress and affect moderate-to-severe AD

The release of muscle tension as a specific countermeasure to psychological stress can enhance the effectiveness of dermatological treatment for AD

## INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease triggered by intense pruritus, impaired skin barrier function, and type 2 helper T-cell immune responses to allergenic substances [1]. Standard dermatological therapies for patients with moderate-to-severe AD include topical treatments, such as topical glucocorticoids and calcineurin inhibitors to reduce cutaneous inflammation; however, scratching and inflammation could not be adequately controlled and relapse could not be prevented after remission in some cases, and their efficacy is limited [2]. Break-through therapies for AD include new drugs, such as dupilumab and upadacitinib, that have demonstrated significantly improved and effective management of severe symptoms of AD in the short term [3].

Despite good short-term outcomes, there is a lack of clinical research on the long-term effects of new AD drugs [4]. Furthermore, the same

mechanism might occur in patients with clinical improvements with molecular targeted drugs, thus resulting in a rapid relapse of stressors and subsequent intensive scratching [5]. A risk exists that drugs may no longer be effective because of the scratching behavior caused by stressors [5]. Therefore, it may be useful to consider adjunctive treatment options focusing on external stressors as triggers that worsen AD.

The management of AD with a focus on psychological stress includes autogenic training (AT) and progressive muscle relaxation (PMR) as relaxation methods; additionally, acupuncture has been reported to be effective as well [6] 7. Studies of the musculoskeletal system have also demonstrated that high levels of psychological stress can modulate the autonomic nervous system and induce increased muscle tension, especially neck stiffness [8]. Recently, Hosono et al. reported that the release of cervical muscular tension in three cases of moderate-to-severe AD improved neck stiffness, severe pruritus, sleep disturbances, and atopic symptoms [9]. However, they evaluated only three cases, and psychological factors were not fully considered in the evaluations. The study of psychological factors may provide additional clues to solve the potential future problems that may occur with molecular-targeted drugs.

We hypothesized that the improvement of psychological stress by relieving cervical muscle tension would reduce pruritus and atopic symptoms. This study analyzed the relationship between reduction in atopic subjective and objective symptoms, improvements in the cervical range of motion (ROM), and a decrease in the psychological burden in 20 patients with moderate-to-severe AD.

# METHODS

## Patients and Treatment

This study included 21 consecutive patients with moderate-to-severe AD examined at the Hosono Clinic, Tokyo, Japan, from July 2019 to December 2020. Patients were eligible to enroll in this study according to the following inclusion criteria: age $\geq$ 18 years; visual analog scale (VAS) score for pruritis of 50 mm, which has a range of 0–100 mm, with higher scores indicating worse itching [10]; a score of 3 (moderate) or 4 (severe) on the Investigator's Global Assessment (IGA), which ranges from 0 to 4, with higher scores indicating worse disease severity [11]; and a score of more than 10 on the Eczema Area and Severity Index (EASI; scores range from 0 to 72, with higher scores indicating more severe disease) [12]. Patients were excluded if they had received any of the following: systemic treatment for AD within 4 weeks before participating in this study; topical calcineurin inhibitors or very potent or potent topical glucocorticoids within 2 weeks prior to the study; or moderately potent or mild topical glucocorticoids or antihistamines (systemic or topical) within 1 week before the study. None of the patients received ultraviolet radiation therapy during this period.

The patients were treated to release cervical muscular tension using Spineliner SA201 (Sigma Inc., Cranberry Township, PA, USA) [13], which can be used as an adjunct to osteopathic manipulative treatment [14]. The treatment was executed by the stimulation of resonance oscillation of the muscles at all contact points, which could be practiced in a single visit to the clinic. Each treatment session took approximately 10–15 min and was practiced once to twice a week for 3 months. Each patient received a total of 15 treatments. All patients discontinued topical corticosteroid treatments before this study. When rescue therapy was needed, we were prepared to use topical corticosteroids, but it was not required.

## Assessment of Clinical Efficacy

The outcome measures and time schedules of this study are presented in Table 1. All the outcome measurements were evaluated before initiating the treatment. Patient-reported outcomes in this study included the VAS for pruritis, and the Patient-Oriented Eczema Measure (POEM), ranging from 0 to 28, with higher scores indicating worse severity [15]. Additionally, the minimal clinically important difference (MCID) in the POEM score has been

**Table 1** Timetable of outcome measurements

| | Pre | Tx1 | Tx2 | Tx3 | Tx4 | Tx5 | Tx6 | Tx7 | Tx8 | Tx9 | Tx10 | Tx11 | Tx12 | Tx13 | Tx14 | Tx15 | Post |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient-reported outcome** | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| VAS for pruritis | | | | | | | | | | | | | | | | | |
| POEM score | | | | | | | | | | | | | | | | | |
| VAS for sleep disturbance | | | | | | | | | | | | | | | | | |
| 5-D pruritis scale | ○ | | | | | | ○ | | | | | ○ | | | | | ○ |
| HADS score | | | | | | | | | | | | | | | | | |
| PSQI score | | | | | | | | | | | | | | | | | |
| DLQI score | | | | | | | | | | | | | | | | | |
| SF36 | | | | | | | | | | | | | | | | | |
| **Dermatological findings** | ○ | | | | | | ○ | | | | | ○ | | | | | ○ |
| EASI score | | | | | | | | | | | | | | | | | |
| IGA score | | | | | | | | | | | | | | | | | |
| BSA score | | | | | | | | | | | | | | | | | |
| **Laboratory testing** | ○ | | | | | | ○ | | | | | ○ | | | | | ○ |
| TARC, LDH, | | | | | | | | | | | | | | | | | |
| eosinophil counts, IgE | | | | | | | | | | | | | | | | | |
| **Cervical ROM** | ○ | | | | | | ○ | | | | | ○ | | | | | ○ |

*BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area Severity Index, *HADS* Hospital Anxiety and Depression Scale, *IGA* Investigator's Global Assessment, *IgE* immunoglobulin E, *LDH* lactate dehydrogenase, *POEM* Patient-Oriented Eczema Measure, *PSQI* Pittsburgh Sleep Quality Index, *ROM* range of motion, *SF36* Short Form-36 Health Survey, *TARC* thymus and activation-regulated chemokine, *Tx* treatment, *VAS* visual analog scale

estimated as a change of 3.4 points [15]. The 5-D itch scale ranges from 5 to 25, with higher scores indicating a greater itching effect [16]. AD severity was assessed using EASI; a change of 6.6 points in the EASI score is the estimated MCID [15]. Additionally, IGA, which is scored from 0 (clear) to 4 (severe), and body surface area (BSA) affected by AD were also used. Hematological parameters were assessed, which included serum levels of thymus and activation-regulated chemokine (TARC), peripheral eosinophil counts, lactate dehydrogenase serum levels (LDH), and total immunoglobulin E serum levels (IgE). TARC serum levels (normal, < 450 pg/mL for adults) are related to AD severity [17]. The eosinophils in the peripheral blood (normal, 70–450/μL) are useful in estimating AD severity [18]. LDH serum levels (normal, 105–245 IU/L) are a useful parameter of AD severity in the short term [18]. Total IgE levels in serum (normal, < 170 IU/mL) are an indicator of the long-term response to the AD treatment [19–21]. Tension in the cervical muscle was assessed by measuring the cervical ROM using radiography, with higher scores indicating more flexibility and mobility and less stiffness [22].

Patient-reported outcomes regarding the psychological burden included the Hospital Anxiety and Depression Scale (HADS), VAS for sleep disturbance, Pittsburgh Sleep Quality Index (PSQI), Dermatology Life Quality Index (DLQI), and Short Form-36 Health Survey (SF-36v2). HADS screens for symptoms of anxiety and depression. It is scored on a scale of 0–21 for each subscale; a score ≤ 7 is normal, a score of 8–10 is considered borderline, and a score ≥ 11 indicates clinically significant anxiety or depression [23]. The VAS score for sleep disturbance ranges from 0 to 100, with higher scores indicating no sleep at all [24]. PSQI sets a range from 0 to 21, with higher scores indicating more sleep disturbance [25]. The DLQI has a range of 0–30, and higher scores are associated with a lower quality of life (QoL) [26, 27] and an MCID change of 4 points [27]. The SF-36v2 score ranges from 0 to 100, with higher scores indicating a greater health-related QoL (HRQoL) [28].

Only nonmedicated emollients were applied topically during the study period, and emollients with antioxidant or anti-inflammatory substances were not used. Topical medicated treatments [topical corticosteroids, calcineurin inhibitors, Janus kinase (JAK) inhibitors, antihistamines, antibiotic ointments, tars] and systemic treatments (oral corticosteroids, molecular-targeted drugs, or antiallergic medications) were not used.

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and reviewed and approved by the local ethics review board in Tokyo (no. 635023-20181214). Documented informed consent was obtained from all patients.

### Statistical Analysis

The Wilcoxon signed-rank test was conducted to examine the statistical significance of the differences pre- and post-treatment. Statistical analyses were processed with Excel 2019 (Microsoft, USA). The differences were considered to be statistically significant at $p < 0.05$.

## RESULTS

### Patient Characteristics

Overall, 21 patients participated in this study, and 20 completed the treatment (Table 2). One patient experienced an exacerbation, was

**Table 2** Patient characteristics

| *N* | **20** |
|---|---|
| Male sex, *N* (%) | 8 (40) |
| Age (range), years | 40 (20–58) |
| BMI (range), kg/m$^2$ | 20.1 (14.9–31.3) |
| Duration of disease (range), years | 29.5 (14–45) |
| Comorbidity | |
| Bronchial asthma, *N* (%) | 6 (30) |
| Allergic conjunctivitis, *N* (%) | 3 (15) |
| Allergic rhinitis, *N* (%) | 9 (45) |

*BMI* body mass index, *N* number

**Table 3** Outcome comparison between pre- and post-treatment

| | Pre | Post | *p* |
|---|---|---|---|
| **Itch and other cutaneous symptoms** | | | |
| VAS for pruritis (SD) | 87.2 (9.0) | 48.6 (24.7) | < 0.01* |
| POEM score (SD) | 24.1 (4.1) | 20.6 (7.3) | < 0.01* |
| 5-D pruritis scale (SD) | 19.9 (2.1) | 14.0 (2.7) | < 0.01* |
| EASI score (SD) | 36.3 (10.2) | 11.6 (6.0) | < 0.01* |
| BSA score (SD) | 74.7 (10.2) | 37.5 (15.2) | < 0.01* |
| IGA score of 4, *N* (%) | 17 (85) | 0 (0) | |
| **Laboratory testing** | | | |
| TARC (SD) | 6988.4 (5480.7) | 3057.5 (3886.8) | 0.010* |
| LDH (SD) | 340.1 (91.1) | 287.0 (78.8) | < 0.01* |
| Eosinophil counts (SD) | 1505.2 (777.3) | 1056.9 (634.3) | 0.011 * |
| IgE (SD) | 6256.1 (5480.7) | 6589.4 (5741.6) | 0.596 |
| **Cervical ROM (SD)** | 95.9 (15.4) | 110.2 (10.1) | < 0.01* |
| **Psychological burden** | | | |
| HADS score (SD) | 18.1 (6.0) | 13.1 (7.5) | 0.024 * |
| VAS for sleep disturbance (SD) | 82.8 (13.7) | 41.6 (23.7) | < 0.01* |
| PSQI score (SD) | 13.9 (2.1) | 9.2 (3.7) | < 0.01* |
| DLQI score (SD) | 21.6 (3.7) | 11.5 (6.6) | < 0.01* |

*BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area Severity Index, *HADS* Hospital Anxiety and Depression Scale, *IGA* Investigator's Global Assessment, *IgE* immunoglobulin E, *LDH* lactate dehydrogenase, *N* number, *POEM* Patient-Oriented Eczema Measure, *PSQI* Pittsburgh Sleep Quality Index, *ROM* range of motion, *SD* standard deviation, *TARC* thymus and activation-regulated chemokine, *Tx* treatment, *VAS* visual analog scale

*$p < 0.05$ by Wilcoxon signed-rank test

hospitalized, and withdrew from the study owing to psychological stress caused by a natural disaster. The mean overall duration of treatment was 76 (42–133) days.

### Clinical Efficacy of Itch and Other Cutaneous Symptoms

The VAS score for pruritus decreased significantly after the treatment (Table 3 and Fig. 1a). The total POEM and 5-D itch scores improved significantly compared with the respective pre-treatment scores (Table 3). Regarding itch frequency on POEM, all patients experienced pruritus daily during the week before the treatment, and 80% (16/20) of them described experiencing pruritus every day of the week after the treatment (Table 4). Regarding the duration of itch on the 5-D pruritus scale, 70% (14/20) of the patients experienced pruritus for at least 12 h per day before the treatment, and 15% (3/20) of patients reported pruritus for at least 12 h per day after the treatment. The degree of itch was graded as unbearable and severe on the 5-D pruritus scale by 30% (6/20) and 60% (12/20) of patients before the treatment, respectively; after the treatment, 0% and 30% (6/20) of patients reported their itch as unbearable and severe, respectively. Concerning improvement or worsening, 35% (7/20) and

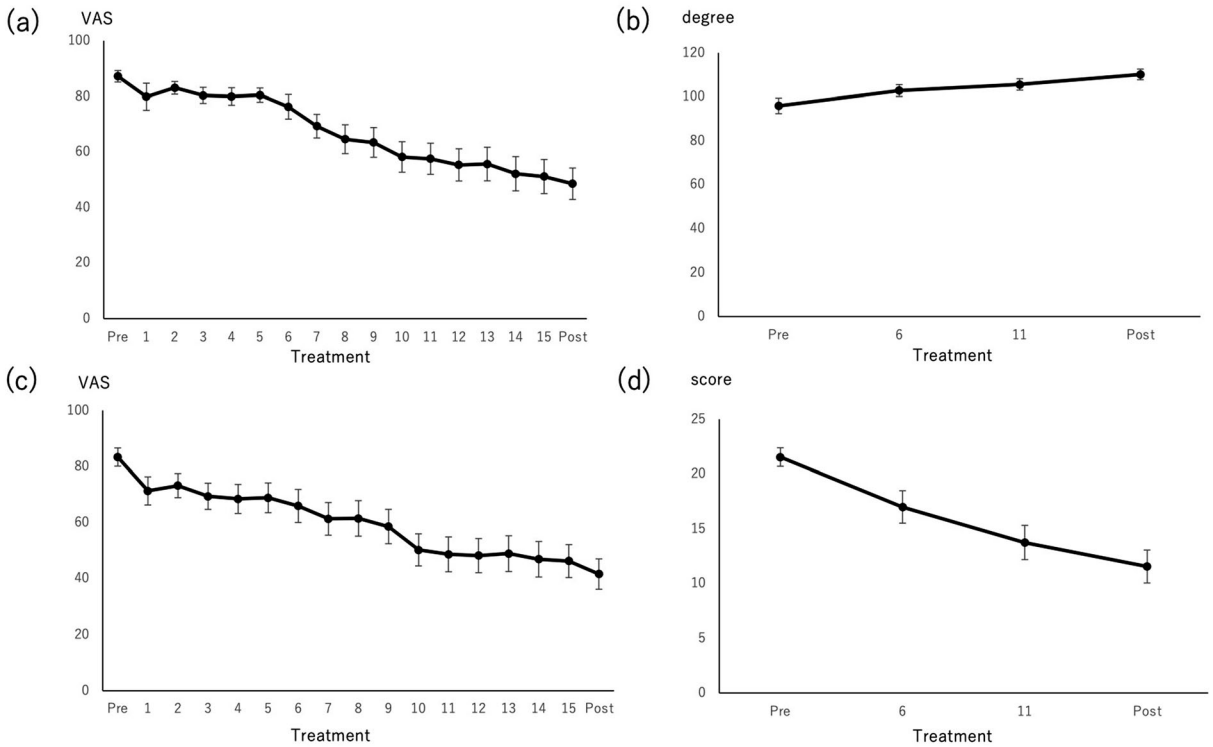


**Fig. 1** Effects of Spineliner SA201 (Sigma Inc., Cranberry Township, PA, USA) treatment on patient-reported outcomes and cervical muscle tension. (**a**) VAS score for pruritus after the treatment. The VAS score for pruritus decreased significantly after the treatment. (**b**) Cervical ROM after the treatment. The cervical ROM improved significantly after the treatment. (**c**) VAS for sleep disturbance after the treatment. VAS score for sleep disturbance decreased significantly after the treatment. (**d**) DLQI after the treatment. DLQI decreased significantly after the treatment. *DLQI* Dermatological Life Quality Index, *ROM* range of motion, *VAS* visual analog scale

50% (10/20) of patients reported that their symptoms worsened and remained unchanged before the treatment, respectively; after the treatment, 5% (1/20) each reported their symptoms were worsened and unchanged, respectively. Before the treatment, 15% (3/20) and 0% of patients reported that itching was slightly better but still present and much better but still present, respectively; after the treatment, 45% (9/20) of patients reported that itching was slightly better or much better but still present.

EASI, IGA, and BSA scores were significantly improved after the treatment (Table 3). In the EASI score, 95% (19/20) of patients reached EASI-50, 45% (9/20) reached EASI-75, and none reached EASI-90 (Table 5). A two-grade reduction of IGA score from the baseline was achieved by 40% (8/20) of the patients, and 5% (1/20) of patients had IGA scores of 0 (clear) or 1 (almost clear) after the treatment (data not shown).

## Clinical Efficacy Based on Laboratory Results

The serum TARC and LDH levels, as well as the eosinophil count in the peripheral blood, were significantly improved after the treatment. However, the change in the serum total IgE levels did not achieve statistical significance (Table 3 and Fig. 2).

**Table 4** Comparison of patient-reported itch between pre- and post-treatment

| | Pre | Post |
|---|---|---|
| **Itch frequency per week from POEM** | | |
| Every day, *N* (%) | 20 (100) | 16 (80) |
| 5–6 days | 0 (0) | 3 (15) |
| 3–4 days | 0 (0) | 1 (5) |
| 1–2 days | 0 (0) | 0 (0) |
| No days | 0 (0) | 0 (0) |
| **Duration of itch from 5-D pruritus scale** | | |
| All day, *N* (%) | 3 (15) | 0 (0) |
| 18–24 h per day | 4 (20) | 1 (5) |
| 12 to < 12 h per day | 7 (35) | 2 (10) |
| 6 to < 12 h per day | 5 (25) | 11 (55) |
| < 6 h per day | 1 (5) | 6 (30) |
| **Degree of itch from 5-D pruritus scale** | | |
| Unbearable, *N* (%) | 6 (30) | 0 (0) |
| Severe | 12 (60) | 6 (30) |
| Moderate | 2 (10) | 10 (50) |
| Mild | 0 (0) | 4 (20) |
| Not present | 0 (0) | 0 (0) |
| **Direction of itch gotten better or worse from 5-D pruritus scale** | | |
| Getting worse, *N* (%) | 7 (35) | 1 (5) |
| Unchanged | 10 (50) | 1 (5) |
| Little bit better but still present | 3 (15) | 9 (45) |
| Much better but still present | 0 (0) | 9 (45) |
| Completely resolved | 0 (0) | 0 (0) |

*N* number, *POEM* Patient-Oriented Eczema Measure

## Clinical Efficacy of Release of Cervical Stiffness

Cervical ROM, which is related to neck stiffness, was significantly improved. The average cervical ROM was 95.9° before the treatment and improved to 110.2° after the treatment (Table 3 and Fig. 1b).

**Table 5** Change of EASI score

| | *N* (%) |
|---|---|
| EASI-50 | 19 (95) |
| EASI-75 | 9 (45) |
| EASI-90 | 0 (0) |

*EASI* Eczema Area Severity Index, *N* number

## Clinical Efficacy of Psychological Burden

The total HADS score decreased significantly after the treatment (Table 3). Before the treatment, 45% (9/20) of the patients had subscale scores of at least 11 for anxiety or depression, which is regarded as the threshold value in anxiety or depression clinical cases. The percentage of patients with anxiety or depression subscale scores of 11 or higher decreased to 30% (6/20) after the treatment (Table 6). The VAS score for sleep disturbance and the PSQI score, which strongly suggests sleep disturbance, significantly decreased after the treatment (Table 3 and Fig. 1c). The total DLQI score, which coincides with a significant impact on the patients' daily lives, decreased significantly after the treatment (Table 3 and Fig. 1d).

Additionally, SF36v2 is a self-administered generic HRQoL questionnaire composed of 36 items related to eight domains and three summaries. It demonstrated significant improvements in the domains of role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH), and a mild change in physical functioning (PF) after the treatment (Table 7). The physical component summary (PCS) did not change, while the mental component summary (MCS) and role-social component summary (RCS) significantly improved (data not shown).

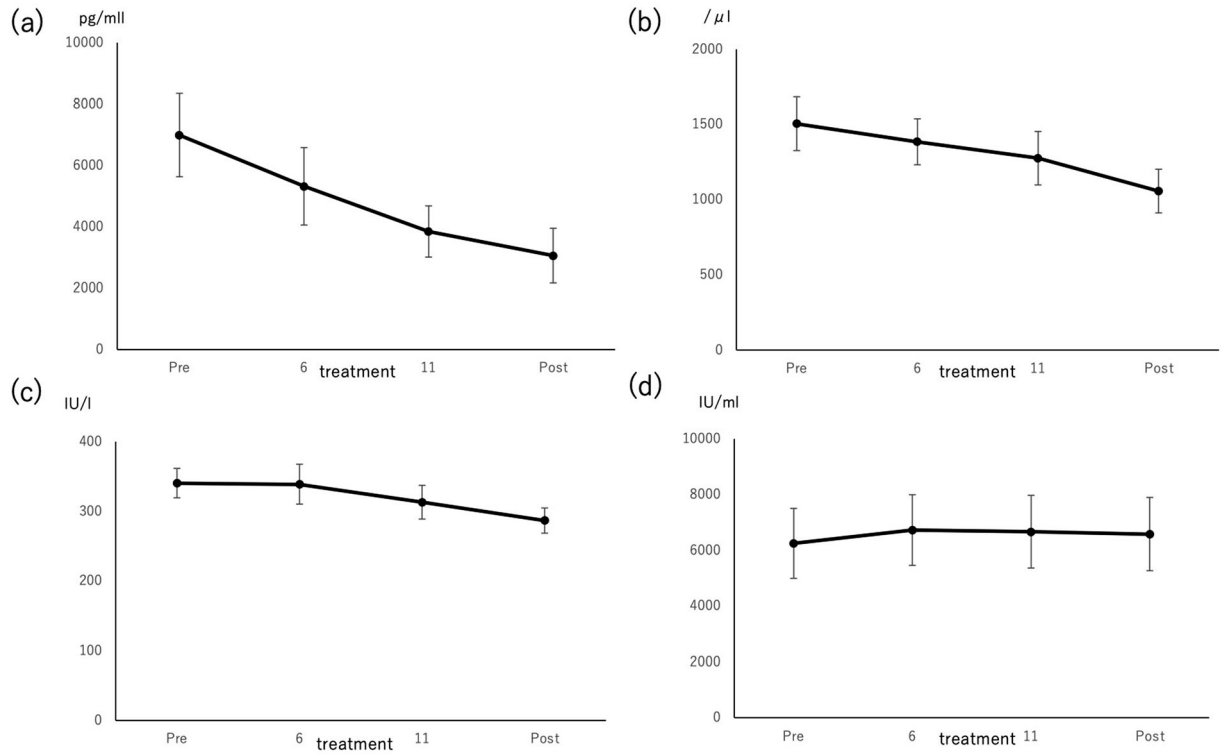


**Fig. 2** Effects of Spineliner SA201 (Sigma Inc., Cranberry Township, PA, USA) treatment on different markers of atopic dermatitis. (**a**) Serum levels of TARC reduced remarkably after the treatment. (**b**) Peripheral blood eosinophil count reduced after the treatment. (**c**) Serum levels of LDH reduced after the treatment. (**d**) Serum levels of total immunoglobulin (Ig)E did not change significantly after the treatment. *LDH* lactate dehydrogenase, *TARC* thymus and activation-regulated chemokine

## DISCUSSION

In this study, our treatment in 20 patients demonstrated improvement in the symptoms of AD: changes on the VAS for pruritus were −44.2%, EASI was −67.9%, TARC was −56.2%, HADS was −27.2%, sleep disturbance was −49.7%, and DLQI was −46.7%. The improved POEM, EASI, and DLQI scores exceeded the respective MCID values. Additionally, cervical muscle tension improved significantly: changes in the cervical ROM were 14.7%.

Forty patients with AD were treated with dupilumab in a single-center study on molecular-targeted drugs in Japan [29]. The study reported that EASI and IGA scores were significantly improved, and serum levels of TARC and LDH were markedly reduced by the treatment. Approximately 90% of participants reached EASI-50, 72.5% reached EASI-75, and 22.5% reached EASI-90. Although the effectiveness of the present treatment is considered inferior in terms of EASI achievement rate, it is considered similar to that of molecular-targeted drugs. Additionally, we evaluated psychological stress, which was not examined in that study.

Pruritus triggered by psychological stress causes scratching and forms a vicious cycle that worsens AD [30]. Therefore, countermeasures against stress are considered important [31]. It has been highlighted that stress-induced scratching may worsen atopic symptoms even after treatment with molecular-targeted drugs [5]. Scratching worsens pruritus, causes sleep disturbance, and lowers HRQoL, which in turn worsens AD [30]. Stress has been evaluated in the past [32] and is believed to be correlated with depression and anxiety symptoms [33]. It

**Table 6** Comparison of HADS score between pre- and post-treatment

| | Pre | Post | *p* |
|---|---|---|---|
| **HADS total score** | 18.1 | 13.1 | 0.024 * |
| **HADS-A score** | 10.0 | 7.7 | 0.061 |
| HADS-A ≧ 11, *N* (%) | 8 (40) | 6 (30) | |
| HADS-A ≧ 8, *N* (%) | 12 (60) | 10 (50) | |
| **HADS-D score** | 8.2 | 5.4 | 0.021* |
| HADS-D ≧ 11, *N* (%) | 4 (20) | 1 (5) | |
| HADS-D ≧ 8, *N* (%) | 11 (55) | 3 (15) | |

*HADS* Hospital Anxiety and Depression Scale, *HADS-A* Hospital Anxiety and Depression Scale anxiety, *HADS-D* Hospital Anxiety and Depression Scale depression, *N* number

*$p < 0.05$ by Wilcoxon signed-rank test

**Table 7** Comparison of SF36 between pre- and post-treatment

| | Pre | Post | *p* |
|---|---|---|---|
| Physical functioning | 71.3 (22.4) | 80.8 (20.8) | 0.172 |
| Role physical | 31.9 (27.9) | 59.1 (31.0) | < 0.01* |
| Bodily pain | 38.1 (29.2) | 59.4 (28.2) | 0.024* |
| General health | 38.5 (19.2) | 51.8 (19.8) | 0.037* |
| Vitality | 31.9 (18.2) | 52.8 (18.7) | < 0.01* |
| Social functioning | 31.9 (24.5) | 66.3 (22.3) | < 0.01* |
| Role emotional | 32.9 (35.8) | 68.3 (29.7) | < 0.01* |
| Mental health | 36.0 (19.6) | 64.3 (19.9) | < 0.01* |

*SF36* Short Form-36 Health Survey

*$p < 0.05$ by Wilcoxon signed-rank test

worsens the symptoms of depression and anxiety, causes sleep disturbances, and lowers HRQoL [34]. Anxiety stimulates a type 2 helper T-cell immune response that promotes IgE synthesis [35]. It is also known that stress increases muscle tension in the neck [8].

Reduction of stress improves the atopic symptoms, and mind–body therapies, such as PMR and acupuncture, have been highlighted as adjunctive therapies [36]. In a study of PMR in AD, EASI scores and stress markers were reported to improve [37]. In another study on acupuncture, improvements in EASI scores were reported [38], and psychological interventions were also effective in treating atopic pruritus [7].

Exercise is also important in regulating skin metabolism [39]. In the relationship between exercise and AD, sweating is believed to be a worsening factor in AD; however, exercise may positively affect AD [40]. Exercise improves blood circulation and relieves muscle tension; however, no study has directly targeted cervical muscle tension in AD.

In this study, the release of cervical muscle tension using Spineliner SA201 for moderate-to-severe AD showed improvement in itching and other atopic symptoms and allergy-related markers without standard dermatological treatments, such as topical corticosteroids and molecular-targeted drugs. This treatment also reduced HADS, which correlates with psychological stress, and significantly improved VAS scores for sleep disturbances. DLQI and SF36v2 scores, which are associated with HRQoL, also improved. These results reflect a reduction in psychological stress, which improved pruritus, atopic symptoms, and immune response by releasing cervical stiffness (Fig. 3).

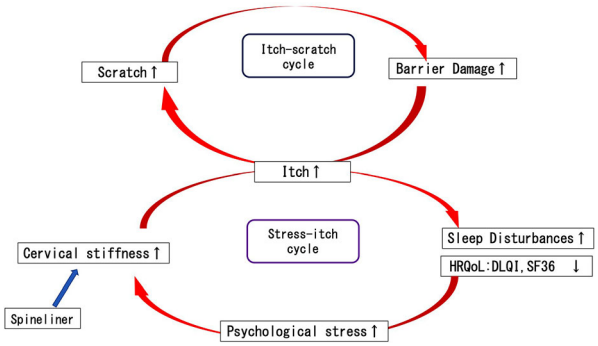


**Fig. 3** Relationship between psychological stress, cervical stiffness, and itch–scratch cycle. Psychological stress can provoke or exacerbate pruritus and increase cervical stiffness. Psychological stress and itching form a vicious cycle, which exacerbates itching, scratching, impaired barrier function, and further stress. The release of cervical stiffness can break the cycle

A mismatch is observed between the improvement of pruritus and skin lesion reductions. The Spineliner SA201 treatment in this study reduces atopic pruritus and psychological stress but may not be potent enough to suppress skin inflammation directly. In addition, the lack of topical corticosteroids to reduce skin inflammation might be the reason for the mismatch between improvement of pruritus and skin lesion reduction.

This treatment has no side effects, unlike drugs such as corticosteroids and molecular-targeted drugs, although the appropriate treatment duration and termination still needs to be studied. In addition to the effects of this treatment on AD, it is expected to enhance the therapeutic effects of corticosteroids and molecular-targeted drugs, which may contribute to increasing the treatment options for AD. Psychological conditions, and atopic symptoms, need to be the targeted focus of treatment, even with molecular-targeted drugs.

This study has several limitations. This study included a small group of patients, which may have resulted in sample bias, a short duration of Spineliner SA201 treatment, and a short follow-up period. Additionally, our results may not be applicable to any other population groups, such as older patients and children. Finally, establishing a causal relationship between improvements in psychological stress and atopic symptoms was not possible in this study. Further clinical trials with larger study populations are required, and case–control studies are planned.

## CONCLUSION

The release of cervical muscle tension may improve psychological stress and affect the symptoms of moderate-to-severe AD.

## ACKNOWLEDGEMENTS

We would like to thank the participants of the study.

***Funding.*** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

***Medical Writing assistance.*** We would like to thank Editage (www.editage.com) for English language editing.

***Author contributions.*** All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Shusaku Hosono, Koji Fujita, and Akimoto Nimura. Shusaku Hosono wrote the first draft of the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript.

***Disclosure statement.*** Shusaku Hosono, Koji Fujita, Akimoto Nimura, and Keiichi Akita declare they have no conflicting interests.

***Compliance with Ethics Guidelines.*** This study was reviewed and approved by the local Ethics Review Board in Tokyo (no.635023–20,181,214) and performed in accordance with the Helsinki convention on human rights. The documented informed consent was obtained from all patients.

***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Open Access.*** This article is licensed under a Creative Commons Attribution-Non-Commercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated

otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

## REFERENCES

1. Otsuka A, Nomura T, Rerknimitr P, Seidel JA, Honda T, Kabashima K. The interplay between genetic and environmental factors in the pathogenesis of atopic dermatitis. Immunol Rev. 2017;278:246–62.

2. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375:2335–48.

3. Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol. 2021;157:1047–55.

4. Abuabara K, Margolis DJ, Langan SM. The long-term course of atopic dermatitis. Dermatol Clin. 2017;35:291–7.

5. Ständer S. How acute stress impacts the itch–scratch cycle in atopic dermatitis: a clinical lesson. Br J Dermatol. 2019;180:689–90.

6. Lipman ZM, Labib A, Yosipovitch G. Current clinical options for the management of itch in atopic dermatitis. Clin Cosmet Investig Dermatol. 2021;14:959–69.

7. Schut C, Mollanazar NK, Kupfer J, Gieler U, Yosipovitch G. Psychological interventions in the treatment of chronic itch. Acta Derm Venereol. 2016;96:157–61.

8. Lundberg U, Kadefors R, Melin B, et al. Psychophysiological stress and EMG activity of the trapezius muscle. Int J Behav Med. 1994;1:354–70.

9. Hosono S, Fujita K, Nimura A, Akita K. Release of cervical muscular tension improved severe pruritus in moderate-to-severe atopic dermatitis: a case series. JAAD Case Rep. 2020;6:510–3.

10. Reich A, Heisig M, Phan NQ, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol. 2012;92:497–501.

11. Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: many options, no standards. J Am Acad Dermatol. 2016;74:288–94.

12. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group Exp Dermatol. 2001;10:11–8.

13. R R. Conservative management of biceps brachii spasticity and pain with vibration at the proper frequency range produced by oscillating percussion: case report. J Pain Relief. 2014;3:2.

14. Barnes PL, Laboy F 3rd, Noto-Bell L, Ferencz V, Nelson J, Kuchera ML. A comparative study of cervical hysteresis characteristics after various osteopathic manipulative treatment (OMT) modalities. J Bodyw Mov Ther. 2013;17:89–94.

15. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67:99–106.

16. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010;162:587–93.

17. Kakinuma T, Nakamura K, Wakugawa M, et al. Thymus and activation-regulated chemokine in atopic dermatitis: serum thymus and activation-regulated chemokine level is closely related with disease activity. J Allergy Clin Immunol. 2001;107:535–41.

18. Kou K, Aihara M, Matsunaga T, et al. Association of serum interleukin-18 and other biomarkers with disease severity in adults with atopic dermatitis. Arch Dermatol Res. 2012;304:305–12.

19. Thijs J, Krastev T, Weidinger S, et al. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. Curr Opin Allergy Clin Immunol. 2015;15:453–60.

20. Kiiski V, Karlsson O, Remitz A, Reitamo S. High serum total IgE predicts poor long-term outcome in atopic dermatitis. Acta Derm Venereol. 2015;95:943–7.

21. Hu Y, Liu S, Liu P, Mu Z, Zhang J. Clinical relevance of eosinophils, basophils, serum total IgE level, allergen-specific IgE, and clinical features in atopic dermatitis. J Clin Lab Anal. 2020;34: e23214.

22. Puglisi F, Ridi R, Cecchi F, Bonelli A, Ferrari R. Segmental vertebral motion in the assessment of neck range of motion in whiplash patients. Int J Legal Med. 2004;118:235–9.

23. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. An updated literature review. J Psychosom Res. 2002;52:69–77.

24. Bender BG, Leung SB, Leung DY. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. J Allergy Clin Immunol. 2003;111:598–602.

25. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.

26. Badia X, Mascaró JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. The Cavide Research Group. Br J Dermatol. 1999;141:698–702.

27. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230:27–33.

28. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health. 1999;53:46–50.

29. Yamauchi T, Sasaki S, Lee ES, et al. Dupilumab treatment ameliorates clinical and hematological symptoms, including blood eosinophilia, in patients with atopic dermatitis. Int J Dermatol. 2021;60:190–5.

30. Sanders KM, Akiyama T. The vicious cycle of itch and anxiety. Neurosci Biobehav Rev. 2018;87: 17–26.

31. Chida Y, Steptoe A, Hirakawa N, Sudo N, Kubo C. The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis. Int Arch Allergy Immunol. 2007;144:1–9.

32. Chrostowska-Plak D, Reich A, Szepietowski JC. Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol. 2013;27:e239–42.

33. Oh SH, Bae BG, Park CO, et al. Association of stress with symptoms of atopic dermatitis. Acta Derm Venereol. 2010;90:582–8.

34. Talamonti M, Galluzzo M, Silvaggio D, Lombardo P, Tartaglia C, Bianchi L. Quality of life and psychological impact in patients with atopic dermatitis. J Clin Med. 2021;10:2.

35. Hashizume H, Horibe T, Ohshima A, Ito T, Yagi H, Takigawa M. Anxiety accelerates T-helper 2-tilted immune responses in patients with atopic dermatitis. Br J Dermatol. 2005;152:1161–4.

36. Graubard R, Perez-Sanchez A, Katta R. Stress and skin: an overview of mind body therapies as a treatment strategy in dermatology. Dermatol Pract Concept. 2021;11: e2021091.

37. Bae BG, Oh SH, Park CO, et al. Progressive muscle relaxation therapy for atopic dermatitis: objective assessment of efficacy. Acta Derm Venereol. 2012;92:57–61.

38. Park JG, Park HJ, Chae Y, Kim YK, Lee H, Kim K. Acupuncture treatment for symptom management in atopic dermatitis: a study protocol for a randomized, participant- and assessor-blind, sham-controlled trial. Evid Based Complement Alternat Med. 2019;2019:1907578.

39. Crane JD, MacNeil LG, Lally JS, et al. Exercise-stimulated interleukin-15 is controlled by AMPK and regulates skin metabolism and aging. Aging Cell. 2015;14:625–34.

40. Son WK, Yoon W, Kim S, et al. Can moderate-intensity aerobic exercise ameliorate atopic dermatitis? Exp Dermatol. 2020;29:699–702.