The effect of balneotherapy with natural mineral dissolved water on dry skin in atopic dermatitis: A phase IIa, nonrandomized, controlled study

Akihiko Uchiyama1 | Chisako Fujiwara1 | Yuta Inoue1 | Kazushi Uchida2 | Miyabi Hiyama2 | Hideyuki Itabashi2 | Sei-ichiro Motegi1

1Department of Dermatology, Gunma University Graduate School of Medicine, Maebashi, Japan
2Graduate School of Science and Technology, Gunma University, Kiryu, Japan

Correspondence
Akihiko Uchiyama, Department of Dermatology, Gunma University Graduate School of Medicine, 3-39-22, Showa, Maebashi, Gunma 371-8511, Japan. Email: akihiko1016@gunma-u.ac.jp

Funding information
Yamato Co. and donation from Graduate School of Science and Technology, Gunma University (Dr. Itabashi Lab)

Abstract

Objectives: It has been known that the use of moisturizers is useful in preventing the onset and maintaining remission of atopic dermatitis (AD). We recently focused on the moisturizing effect of natural mineral dissolved water and have conducted various studies. In this study, we investigated whether the bath treatment using natural mineral dissolved water can improve dry skin in AD patient in prospective nonblind, nonrandomized controlled study.

Methods: Thirteen adults with almost clear to moderate AD took bath therapy using tap water for 13 days, followed by bath therapy using natural mineral dissolved water for 13 days. Changes in the severity scoring, patient-oriented eczema measure, pruritus numerical rating scale, transepidermal water loss (TEWL) and hydration were evaluated at day 1, 14 and 28.

Results: Tap water using bath treatment did not change the severity scoring and itch associated score, and it partially decrease TEWL when compared with baseline condition. Bath treatment using natural mineral dissolved water slightly decrease eczema area and severity index (EASI) score and significantly decrease TEWL with respect to baseline condition. Moreover, in relatively severe AD analysis, bath treatment with mineral dissolved water significantly decreased EASI and TEWL.

Conclusions: Based on these results, bathing with natural mineral dissolved water may be effective in improving the dry skin of atopic dermatitis. Further studies are needed to evaluate its effects more clearly.

Keywords
atopic dermatitis, barrier dysfunction, bathing, dry skin, natural mineral water
1 | INTRODUCTION

Atopic dermatitis (AD) is a chronically relapsing allergic inflammatory skin with an increasing prevalence in the world. The pathogenesis of atopic dermatitis is based on epidermal barrier dysfunction and activation of type 2 helper T (Th2) lymphocytes producing cytokine, resulting in skin inflammation and pruritus. It has been well known that disease severity is closely related to poorer quality of life in adult AD, suggesting that it is very important to control the disease activity for their daily life. It has been revealed that the use of topical moisturizers improves the moisture content of the stratum corneum, that reduced in atopic dermatitis, and restores and maintains the skin barrier function, leading to the prevention of allergen penetration, prevention of dermatitis flare-ups, and suppression of itching. In the Japanese guidelines for atopic dermatitis 2020, the use of topical moisturizers all over the body including the sites that appear to be normal is highly recommended. It is reported that mutations in filagrin (FLG), a key structure of the epidermal differentiation complex which regulates homeostasis of the skin, causes various skin diseases such as ichthyosis vulgaris, AD or irritative contact dermatitis. Moreover, the increased transepidermal water loss which mirrored barrier dysfunction was found in children with mutants in FLG before development of AD. Interestingly, a randomized controlled trial study demonstrated that daily application of moisturizer during the first 32 weeks of life reduces the risk of AD/eczema in infants. These results indicate the significance to improve the barrier dysfunction of the skin by using moisturizers in AD. However, Christie et al demonstrated the difficulty of maintaining daily topical treatment by monitoring psoriasis patients. This fact led us to believe that moisturizing treatment as an alternative to topical therapy may reduce the burden on AD patients, resulting in maintenance of AD remission and improvement of quality of life.

We have recently noticed that laborers who handle natural mineral dissolved water, which used as a neutralizer for river acidification, felt improvement of their dry hands. Based on this fact, we hypothesized that natural mineral dissolved water might have a high moisturizing effect, and that topical application of natural mineral water may improve dry skin in atopic dermatitis, however, it is still unclear. The aim of this study is to investigate the effect of natural mineral dissolved water in restoration of dry skin in AD.

2 | METHOD

2.1 | Study design

This investigator-initiated clinical trial was designed as a prospective, nonblind, nonrandomized controlled study comparing natural mineral dissolved water with tap water (trial registration: UMIN Clinical Trials Registry, https://upload.umin.ac.jp/cgi-open-bin/ctr ctr_view.cgi?recptno=R000045876)(UMIN0000040220) at a single center in Japan (Gunma University), from December 2020 through March 2021. This study was approved by the Institutional Review Board (IRB) of the Gunma University in August 2020 (IRB2020-018), and all patients were provided written informed consent and ethics committees approved the protocol. This study was performed at the Department of Dermatology, Gunma University in Japan. Treatment was started at day 1 (base line) and reviewed at day 14 and 28. Participants received daily bathing treatments at home, using tap water for thirteen days (day1–13, followed by bath salts for thirteen days (day14–27). The primary end points were score on the eczema area and severity index (EASI) and pruritus numerical rating scale (NRS). Secondary end points were transepidermal water loss (TEWL) and hydration of forearm which were measured with DermaLab® (Cortex Technologies, Denmark) which allows collection of reproducible data. The treatment for atopic dermatitis, including topical steroid ointment, moisturizer, and antihistamine medicine was continued and not changed during the study period. No topical application was done on the forearm 12 hours prior to the measurement of TEWL and hydration. The use of bathwater additive was prohibited during the study period. Adverse events were reviewed at each visit.

2.2 | Patients

Inclusion criteria were patients aged 20–65 years diagnosed with AD according to the Hanifin and Rajka criteria, and the severity was almost clear to moderate (IGA<2, EASI<16). Exclusion criteria were the following patient (1) who could not take a bath during the clinical trial period, (2) who have erosion or severe dermatitis (EASI>16), and (3) who were assessed as inappropriate for any other reason by the clinical investigator or clinical trial physician. A total of 13 Japanese patients (8 males, 5 females; mean ages ± standard error (SD), 25.9 ± 5.2 years) were selected (Table 1). All patients had been diagnosed as atopic dermatitis in their childhood, and they had been receiving treatment of AD for one month prior to the start of this study.

2.3 | Treatment and evaluation protocol

All participants took baths (day1-13: 200 L tap water, 38–42°C, 5 minutes, day 14–27: Sangolite BATH SALT® 100 g dissolved in 200 L tap water) at home every day. The Sangolite BATH SALT® was made and provided by GUDi CO., Ltd, and its ingredients are shown (Table 2). The pH values of the bath water after dissolving the Sangolite BATH SALT® was designed to be mild acidic with a pH of 4–5, which is considered optimal for skin care. The changes in the severity of dermatitis were assessed using static investigator’s global assessment (sIGA) and modified EASI score, pruritus numerical rating scale (NRS) and patient-oriented eczema measure (POEM). Participants rest in the room (temperature 20–22°C,
humidity 40–60%) for 15 minutes before the physiological examination. TEWL and Hydration were measured at three locations on both forearms and the average value was calculated. The total score at baseline was set as 100% and the relative scores at each visit were quantified.

2.4 | Statistical analysis

Data were analyzed using GraphPad Prism 9 (version 1.0). p-values were calculated using the one-way analysis of variance (ANOVA), followed by Bonferroni’s multiple comparisons test. p < .05 was considered statistically significant. Error bars represent standard errors of the mean.

3 | RESULTS

3.1 | Demographic and clinical features of AD participants

A total thirteen patients with AD patients participated in the study. Baseline demographic and disease characteristics were described (Table 1). All of the participants were Japanese, and most patients were male (61.5%) with mean age 25.9 (range 21–38). One patient (7%) was classified as almost clear (EASI<1), eleven (86%) were classified as mild (EASI<7) and one (7%) was moderate (EASI<21). As for sIGA score, four participants scored 1 (almost clear) (31%) and nine scored 2 (mild disease) (69%). Overall mean of EASI total score was 4.5, mean sIGA score was 1.7, mean BSA was 15.5, mean NRS was 4.5, mean POEM was 10.4, mean TEWL was 14.9 and mean Hydration was 93.5.

3.2 | Efficacy and safety

For the primary end point analysis at day 14, each of mean value was 1.61 in sIGA (−4.5%; the least-squares mean percent change from baseline) (p > .99), 5.18% in EASI (−7.3%) (p > .99), and 4.38 in NRS (−1.7%) (p > .99), respectively. With respect to secondary end point, each of mean value was 11.7 in TEWL (−21%) (p = .63) and 99.9 in hydration (+6.9%) (p > .99). For the primary end point analysis at day 28, each of mean value was 1.61 in sIGA (−4.5%) (p > .99), 3.13 in EASI (−30.8%) (p = .18), and in 4.53 NRS (−1.7%) (p > .99), respectively. With respect to secondary end point, each of mean value was 7.23 in TEWL (−51.3%) (p = .01) and 90.7 in hydration (+6.9%) (p > .99). For the primary end point analysis at day 14, each of mean value was 1.75 in sIGA (−6.7%) (p > .99), 5.18 in EASI (−11.5%) (p > .99), and 4 in NRS (0%) (p > .99), respectively. With respect to secondary end point, each of mean value was 13.6 in TEWL (−28%) (p = .63) and 97.9 in hydration (+16.2%) (p > .99). For the primary end point analysis at day 28, each of mean value was 1.75 in sIGA (−6.7%) (p > .99), 3.56 in EASI (−39.2%) (p = .005), and 3.85 in NRS (−3.1%) (p > .99), respectively. With respect to secondary end point, each of mean value was 7.65 in TEWL (−59.3%) (p = .001) and 87.4 in hydration (+3.7%) (p > .99). There were no adverse effects during this study (Figure 2).

| TABLE 1 | Patient demographics and baseline disease characteristics |
|-----------------|------------------|-----------------|
| Characteristic  | Total patients (n = 13) |
| Age, years,     | Mean (SD) 25.9 (5.2) |
| Gender          | Male 8 (61.5%) |
|                | Female 5 (38.5%) |
| EASI total score| Mean (SD) 4.5 (2.2) |
|                | Range 0.4–7.8 |
| IGA             | Mean (SD) 1.7 (0.5) |
|                | Range 1–2 |
| BSA, %          | Mean (SD) 15.5 (8.0) |
|                | Range 3–30 |
| NRS             | Mean (SD) 4.5 (2.1) |
|                | Range 2–8 |
| POEM            | Mean (SD) 10.4 (3.7) |
|                | Range 3–15 |
| TEWL, g/m²/h    | Mean (SD) 14.9 (8.0) |
|                | Range 4.4–29.6 |
| Hydration, μ Siemens | Mean (SD) 93.5 (26.9) |
|                | Range 54.6–131.8 |

| TABLE 2 | Composition of Sangolite BATH SALT® |
|-----------------|-----------------|-----------------|
| Contents        | Sangolite BATH SALT® (wt%) | Dolomite (wt%) |
| Citric acid anhydride | 60 |  |  |
| Calcium         | 9.2 | 23.1 |  |
| Magnesium       | 4.9 | 12.2 |  |
| Silicon         | 0.3 | 0.7 |  |
| Aluminum        | 0.2 | 0.6 |  |
| Potassium       | 0.1 | 0.3 |  |
| Carbonated acid | 25.2 | 63.1 |  |
FIGURE 1  The effect of bath treatment with tap water natural mineral dissolved water on disease severity (sIGA, EASI, BSA), NRS, POEM and TEWL, hydration in AD. (A) Scheme of the experimental procedure. Physical examination was performed on day 1, 14 and 28. (B) Each panel showed the quantification of sIGA, EASI, BSA, NRS, POEM, TEWL, and hydration during experiment in all AD. n = 13. All values represent mean ± SEM. *p < .05.
In a prospective nonblind, nonrandomized controlled study, we investigated the effect of mineral dissolved water on the severity of adult AD patients. There are several reports which demonstrated the beneficial effect of balneotherapy on AD in human and mice. In our best knowledge, this is the first study which revealed the efficiency of balneotherapy using natural mineral dissolved water in AD patients.
It has been demonstrated that the elevated pH caused by barrier abnormality increases kallikrein activity, resulted in the up-regulation of thymic stromal lymphopoietin (TSLP) followed by Th2-type immune responses. \(^{25}\) Weakly acidic (pH 4.5) moisturizers have been reported to significantly improve TEWL and itch score compared to standard moisturizers. \(^{26}\) There is a possibility that the weakly acidic pH (pH 4–5) in natural mineral dissolved water might be the key factor which contributed to the improvement of dermatitis and barrier function. Another mechanistic evidence suggested that body exposure to mineral water at the spa would beneficially affect the immune system and antioxidant mechanism. \(^{27,28}\) Interestingly, most of subjects took showers but did not take baths. Actually, bath treatment using tap water (day1-day13) showed partially decreased EASI score and TEWL. This result might indicate that daily bathing may contribute to the improvement of barrier dysfunction. Since we did not conduct a crossover study at this moment, we could not exclude the effect of prolonged bath treatment itself. Moreover, the current study did not set the group with only using tap water as a control to the group with only using natural mineral dissolved water. These points are major issues in this study, and they must be accurately assessed in further examination.

Dolomite is an anhydrous carbonate mineral composed of calcium magnesium carbonate. It has long been used as a source of calcium and magnesium supplements. The ratio of calcium to magnesium in dolomite (2:1) is believed to be optimal for mineral absorption. \(^{29}\) After dissolving the Sangolite BATH SALT\(^{30}\), the calcium concentration will be about 1.14 mM and the magnesium concentration will be about 0.1 mM. This range of high calcium concentration is usually used for differentiation assay in human epithelial keratinocyte in vitro. \(^{30}\) Calcium is a central regulator of differentiation and proliferation via transcription of cornification associated gene, including profilaggrin, and involucrin. \(^{31,32}\) Elevated extracellular calcium concentration induces activation of inositol 1,4,5-trisphosphate (IP\(_3\)) and diacylglycerol (DAG). IP\(_3\) induces calcium release from endoplasmic calcium stores by the activation of IP\(_3\) receptors in ligand-dependent manner, and DAG directly activates TRPC6, one of the transient receptor potential (TRP) which regulates keratinocyte differentiation. \(^{33}\) Recent study has described the possible dysfunction of TRPC6 in atopic dermatitis, and it is also attracting attention as a new therapeutic target, \(^{34}\) suggesting that activation of TRPC6 by high calcium contained natural mineral dissolved water might be a key player which improves barrier dysfunction in AD.

It has been described that various type of pruritogens and their specific receptors activate itch signaling. \(^{35,36}\) The efficacy of emollients for treating pruritus in AD in both human and mice has been reported. \(^{37,38}\) However, NRS was not changed through this clinical trial, indicating that bath treatment, even if using natural mineral dissolved water, did not affect itch associated signaling pathway. Therefore, further study would be needed to evaluate the efficacy of natural mineral dissolved water for pruritis in AD by long-time treatment or combination of topical application of emollient and/or steroid cream/ointment.

About the safety, no adverse events were reported by the investigators during this study period. Patil et al\(^{39}\) reported the possibility of toxic effect of micro- and nano-particles of dolomite on respiratory system using lung epithelial cells A\(_{549}\) in vitro. In this study, Sangolite BATH SALT\(^{30}\) were distributed to the subjects in individual packages and they were instructed to open the packages in the bathtub. Therefore, they did not have any chance to inhale the dolomite powder, in fact, none of the subjects developed respiratory symptoms.

Since there was no Phase I clinical trial which revealed the safety of Sangolite BATH SALT\(^{30}\) in normal human, this study was designed with a small numbers of adults AD with mild severity to decrease the risk of adverse effect according to the request from IRB. Therefore, it would be required to examine randomized trial with large population, and more severe AD patient to confirm the result of this study.

Taken together, we demonstrated that balneotherapy using natural mineral dissolved water improved the severity of dermatitis and TEWL in adults with AD. Balneotherapy with natural mineral contained water might have possible therapeutic potential for disease that present with dry skin, including AD as alternative to moisturizers.

ACKNOWLEDGMENTS

This clinical trial was funded by Yamato Co. and donation from Graduate School of Science and Technology, Gunma University (Dr. Itabashi Lab).

CONFLICT OF INTEREST

This clinical trial was conducted in collaboration work among Department of Dermatology, Gunma University Graduate School of Medicine, Graduate School of Science and Technology, Gunma University, GUDi CO., Ltd, and Yamato Co., Ltd. Hideyuki Itabashi is Chairperson in GUDi CO., Ltd.

DECLARATION SECTION

Approval of the research protocol: This study was approved by the Institutional Review Board (IRB) of the Gunma University in August 2020 (IRB2020-018).

Informed Consent: All patients were provided written informed consent and ethics committees approved the protocol.

Registry and the Registration No. of the study/trial: UMIN000040220.

Animal Studies: N/A.

ORCID

Akihiko Uchiyama \(\text{https://orcid.org/0000-0002-2169-2427}\)

Sei-ichiro Motegi \(\text{https://orcid.org/0000-0001-8286-0669}\)

REFERENCES

1. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood:
ISAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733–43.

2. Avena-Woods C. Overview of atopic dermatitis. Am J Manag Care. 2017;23(8 Suppl):S115–s23.

3. Chrostowska-Plak D, Reich A, Szepiekowsk JC. Relationship between itch and psychological status of patients with atopic dermatitis. J Eur Acad Dermatol Venereol. 2013;27(2):e239–e42.

4. Klonowska J, Gleń J, Nowicki R, Trzeciak M. New cytokines in the pathogenesis of atopic dermatitis—new therapeutic targets. Int J Mol Sci. 2018;19(10):3086.

5. Birdi G, Cooke R, Knibb RC. Impact of atopic dermatitis on quality of life in adults: a systematic review and meta-analysis. Int J Dermatol. 2020;59(4):e75–e91.

6. Cowdell F, Jodette YT, Ersjer SS, Danby S, Lawton S, Roberts A, et al. Hygiene and emollient interventions for maintaining skin integrity in older people in hospital and residential care settings. Cochrane Database Syst Rev. 2020;1(1):Cd011377.

7. Lodén M, Andersson AC, Anderson C, Bergbrant IM, Frödin T, et al. Japanese guidelines for atopic dermatitis 2020. Allergol Int. 2021;70(1):160–72.

8. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Peak pruritus numerical rating scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;180(4):711–6.

9. Cabanillas B, Novak N. Atopic dermatitis and filaggrin. Curr Opin Immunol. 2016;42:1–8.

10. Palmer CNA, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee J, et al. Neural processing of itch. Neuroscience. 2013;249:1–12.

11. Carroll CL, Feldman SR, Camacho FT, Manuel JC, Balkrishnan R. The use of balneotherapy in dermatology. J Dermatol. 2011;38(6):531–5.

12. Grove GL, Grove MJ, Zerweck C, Pierce E. Comparative metrology of the evaporimeter and the DermaLab® TEWL probe. Skin Res Technol. 1999;5(1):1–8.

13. Hanifi JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermat. 1980;92:44–7.

14. Kumar A, Tominaga M, Takamori K. Itch and nerve fibers with special reference to atopic dermatitis: a phase IIa, nonrandomized, controlled study. J Cutan Med Surg. 2011;15(6):439–43.

15. Tominaga M, Takamori K. Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. J Dermatol. 2014;41(3):205–12.

16. Kamo A, Tominaga M, Negi O, Tengara S, Ogawa H, Takamori K. Topical antipruritic therapy using a pH-modified moisturizer vs. standard moisturizer in mild to moderate atopic dermatitis. An Bras Dermatol. 2020;95(3):320–5.

17. Klonowska J, Gleń J, Nowicki R, Trzeciak M. New cytokines in the pathogenesis of atopic dermatitis—new therapeutic targets. Int J Mol Sci. 2018;19(10):3086.

18. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis. J Allergy Clin Immunol. 2014;134(4):781–91.e1.

19. Schmitt J, Langan S, Williams HC. What are the best outcome measures for atopic eczema? A systematic review. J Allergy Clin Immunol. 2007;120(6):1389–98.

20. Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, scoring Atopic Dermatitis (SCORAD), objective SCORAD, atopic dermatitis severity. Br J Dermatol. 2017;177(5):1316–21.

21. Ständer S, Augustin M, Reich A, Blome C, Ebata T, Phan NQ, et al. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials. Acta Derm Venereol. 2013;93(5):509–14.

22. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure. Arch Dermatol. 2004;140(12).

23. Baigaji J, Fadriquel A, Ara J, Begum R, Ahmed MF, Kim CS, et al. Baseline therapeutic effects of high mineral spring water on the atopic dermatitis-like inflammation in hairless mice via immunomodulation and redox balance. BMC Complement Altern Med. 2017;17(1):481.

24. Huang A, Seité S, Adar T. The use of balneotherapy in dermatology. Clin Dermatol. 2018;36(3):363–8.

25. Elias PM, Wakefield JS. Mechanisms of abnormal lamellar body secretion and the dysfunctional skin barrier in patients with atopic dermatitis. J Allergy Clin Immunol. 2014;134(4):781–91.e1.

26. Goh SW, Jamil A, Safian N, Md Nor N, Muhammad N, Saradurin NL. A randomized half-body, double blind, controlled trial on the effects of a pH-modified moisturizer vs. standard moisturizer in mild to moderate atopic dermatitis. An Bras Dermatol. 2020;95(3):320–5.

27. Kubota K, Machida I, Tamura K, Take H, Kurabayashi H, Akiba T, et al. Treatment of refractory cases of atopic dermatitis with acidic hot-spring bathing. Acta Derm Venereol. 1997;77(6):452–4.

28. Oláh M, Koncz Á, Fehér J, Kálmánzchey J, Oláh C, Nagy G, et al. The effect of balneotherapy on antioxidant, inflammatory, and metabolic indices in patients with cardiovascular risk factors (hypertension and obesity)—A randomised, controlled, follow-up study. Contemporary Clinical Trials. 2011;32(6):793–801.

29. Seelig M. Cardiovascular consequences of magnesium deficiency and loss: Pathogenesis, prevalence and manifestations—Magnesium and chloride loss in refractory potassium repletion. Am J Cardiol. 1989;63(14):G4–G21.

30. Park GT, Lim SE, Jang S-I, Morasso MI. Suprabasin, a novel epidermal differentiation marker and potential cornified envelope precursor. J Biol Chem. 2002;277(47):45195–202.

31. Elsholz F, Harteneck C, Muller W, Friedland K. Calcium—a central regulator of keratinocyte differentiation in health and disease. Eur J Dermatol. 2014;24(6):650–61.

32. Lee SE, Lee SH. Skin barrier and caliber. Ann Dermatol. 2018;30(3):265.

33. Müller M, Essin K, Hill K, Beschmann H, Rubant S, Schempp CM, et al. Specific TRPC6 channel activation, a novel approach to stimulate keratinocyte differentiation*. J Biol Chem. 2008;283(49):33942–54.

34. Sun X-D, You Y, Zheng S, Hong Y, Li J, et al. The possible role of TRPC6 in atopic dermatitis. Med Hypotheses. 2012;78(1):42–4.

35. Akiyama T, Carstens E. Neural processing of itch. Neuroscience. 2013;250:697–714.

36. Tominaga M, Takamori K. Itch and nerve fibers with special reference to atopic dermatitis: therapeutic implications. J Dermatol. 2014;41(3):205–12.

37. Kamo A, Tominaga M, Negi O, Tengara S, Ogawa H, Takamori K. Topical antipruritic therapy using a pH-modified moisturizer vs. standard moisturizer in mild to moderate atopic dermatitis. An Bras Dermatol. 2020;95(3):320–5.

38. Klonowska J, Gleń J, Nowicki R, Trzeciak M. New cytokines in the pathogenesis of atopic dermatitis—new therapeutic targets. Int J Mol Sci. 2018;19(10):3086.

How to cite this article: Uchiyama A, Fujiwara C, Inoue Y, Uchida K, Hiyama M, Itabashi H, et al. The effect of balneotherapy with natural mineral dissolved water on dry skin in atopic dermatitis: A phase IIa, nonrandomized, controlled study. J Cutan Med Surg. 2021;4:159–165. https://doi.org/10.1002/cia.21295