The Effectiveness of Balneotherapy in Patients with Ankylosing Spondylitis and Its Effect on Inflammation, A Pilot Study

Ankilozan Spondilitli Hastalarda Balneoterapinin Etkinliği ve İnflamasyona Etkisi, Pilot Çalışma

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ÖZET

AMAÇ: Bu çalışmada, balneoterapinin, ankilozan spondilitli hastalarda hastalık aktivitesi, ağrı, yaşam kalitesine ve inflamasyona etkisini araştırılmak amaçlanmıştır.

GERÇEK VE YÖNTEM: Bu çalışma prospektif, kontrollü, tek kör bir çalışma olarak planlandı. Toplam 60 hasta iki gruba ayrıldı. I. gruptaki hastalara balneoterapi uygulandı. Kontrol grubuna ek bir tedavi uygulanmadı. Tüm hastalar günlük rutin yaşam tarzlarına ve farmakolojik tedavilerine devam etti. Hastalar tedavinin başlangıcında ve tedavinin sonunda (21. gün) Ağrı VAS, Hasta Global VAS, BASFI, BASDAI, ASQoL, WBC, ESR ve CRP ile değerlendirildi.

BULGULAR: Her iki grupta da tedavi öncesine göre tedavi sonunda BASFI de, balneoterapi grubunda ağrı (VAS), hastanın global değerlendirmesi (VAS), ASQoL ve BASDAI de istatistiksel olarak anlamlı iyileşme tespit edildi. Gruplar arası karşılaştırmada tedavi öncesi verilerde ağrı (VAS), hastanın global değerlendirme (VAS), BASFI ve BASDAI de istatistiksel olarak anlamlı fark varken, tedavi sonrası iki grup arasında ağrı (VAS) hariç diğer verilerde istatistiksel anlamlı fark yoktu. Fark skorları karşılaştırmalarda ise ağrı (VAS), hastanın global değerlendirme (VAS), ASQoL, BASFI ve BASDAI de istatistiksel olarak anlamlı değişim fark saptanmadı.

SONUÇ: Ankilozan Spondilitli hastalarda balneoterapi iyi tolere edilebilir ve uygun hastalarda farmakolojik tedaviler ile birlikte uygulandıgı zaman tedavinin yararlı etkilerini artırabilir.

Anahtar Kelimeler: ankilozan spondilit, balneoterapi, inflamasyon, ağrı

ABSTRACT

OBJECTIVE: This study aimed to investigate whether balneotherapy triggers inflammation and improves the disease activity, pain, and quality of life in patients with ankylosing spondylitis.

MATERIALS AND METHODS: This study was planned as a prospective, controlled, single-blind study. A total of 60 patients were divided into two groups. Group I was treated with balneotherapy. No additional treatment was applied to the control group. All the patients continued their daily routine lifestyles and pharmacological treatments. Assessments were made using the Pain VAS, Patient Global VAS, BASFI, BASDAI, ASQoL, WBC, ESR, and CRP at the beginning of the treatment and at the end of treatment (day 21).

RESULTS: Compared to the pre-treatment period, there was a statistically significant improvement in both groups’ pain at the end of the treatment in BASFI, in the Balneotherapy group (VAS), in the patient’s global assessment (VAS), in ASQoL and BASDAI. A comparison between groups before treatment revealed that there was a statistically significant difference in terms of pain (VAS), patient’s global assessment (VAS), BASFI and BASDAI whereas, after treatment, there was no statistically significant difference in the data except pain (VAS). A comparison of difference scores revealed that there was a statistically significant change in pain (VAS), patient’s global assessment (VAS), ASQoL, BASFI and BASDAI whereas there was no statistically significant difference between WBC, ESR and CRP.

CONCLUSION: Balneotherapy is well tolerated and balneotherapy combined with pharmacological treatment may improve the beneficial effects of treatment in ankylosing spondylitis patients.

Keywords: ankylosing spondylitis, balneotherapy, inflammation, pain

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease of unknown etiology that usually begins in the 2nd-3rd decades (1, 2). AS usually begins with insidious chronic low back pain and stiffness. For AS patients, consulting a doctor with back pain and hip pain complaints and spinal stiffness (1, 2). AS, which is seen mostly in young age groups, leads to functional and...
physical deficiencies that negatively affect the daily activities of individuals and thus cause a significant loss of labor force.

AS treatment aims to reduce pain and inflammation, to prevent the progression of damage and to improve the quality of life. AS treatment is divided into two groups: pharmacological and non-pharmacological treatment. Non-steroidal anti-inflammatory drugs (NSAIDs), nonbiologic and biologic disease-modifying antirheumatic drugs are used in pharmacological treatment. Despite the progress in pharmacological treatment, treatment of rheumatic diseases usually requires a combination of pharmacological and non-pharmacological options appropriate to the patient’s clinical condition and needs. The Assessment of Spondylo Arthritis International Society (ASAS) / The European League Against Rheumatism (EULAR), Turkish League Against Rheumatism (TLAR) proposes the combined use of pharmacological and non-pharmacological treatment of AS (3, 4). Spa treatment, which involves many medical applications, is a non-pharmacological method commonly used in the treatment of musculoskeletal disorders. Balneotherapy and peloid therapy are the most commonly used treatment methods among them (5). Balneotherapy is used in the treatment of many rheumatic diseases such as osteoarthritis, gout, rheumatoid arthritis, AS, psoriatic arthritis, and fibromyalgia (6-12). Spa treatment in the treatment of AS is an effective non-drug treatment that is frequently applied. The mechanism of action of balneotherapy is quite complex and not fully known today. It is probable that a net benefit results from a combination of mechanical, thermal and chemical effects of balneological agents (6-7, 11-12).

Although it is used safely in particular in degenerative musculoskeletal diseases, its use in inflammatory diseases is still hesitant due to the possibility that it may increase inflammation. Finding solutions to these question marks through routine clinical and laboratory tests are significant for daily clinical practice. We designed this pilot study to investigate whether balneotherapy triggers inflammation and improves the disease activity, pain and quality of life in AS patients.

MATERIAL & METHODS 2.1 Research design This prospective, non-randomized, controlled and single-blind study was conducted in the Physical Medicine and Rehabilitation Training and Research Hospital, Spa Center, after Ethical Committee approval.

2.2 Participants The polyclinic records between April 2016 and September 2016 were examined and 81 AS patients were invited to study. Patients were examined by the physician in terms of the general and musculoskeletal system.

Inclusion criteria included: Patients who were diagnosed with AS according to the modified New York 1984 criteria, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) measurements was normal at last check, agreed to fill in the clinical assessment scales given to assess the effectiveness of treatment and agreed to the informed consent form.

Exclusion criteria included: patients with peripheral active arthritis, lymphoproliferative diseases and other neoplasms, uncontrolled arterial hypertension (HT), uncontrolled diabetes mellitus (DM), renal pathology, coronary artery disease, severe peripheral circulatory disorder, severe pulmonary diseases, pulmonary hypertension, heat-induced hot urticaria, infection, other autoimmune diseases, mental retardation, serious psychiatric problem or patients who received balneotherapy in the last six months and have not changed their medical treatment in the last three months.

21 patients (n=4 with uncontrolled DM and HT, n=5 who received balneological treatment in the last 6 months, n=3 with infection, n=3 with additional autoimmune disease, and n=6 who did not agree to participate in the study) were excluded from the study. The flow diagram of the study is presented in Figure 1.

2.3 Assignment Method and Blinding Sixty patients who met the study criteria and agreed to the patient information form were divided into two groups. After the study protocol and possible complications were explained, patients who accepted balneotherapy were included in the balneotherapy group and the other patients were included in the control group. A total of 33 people were included in the balneotherapy group and 27 people were included in the control group. Due to the nature of the treatment, patient blinding was not possible. On the other hand, the outcome evaluation process was blinded. The evaluation of the patients and the statistical analysis of the
results were made by the physician and biostatistics specialist who was not informed about the treatment and the group distribution of the patients.

2.4 Interventions

All patients were included in the study for 3 weeks. All applications were performed under physician control.

The patients in the balneotherapy group received a mineral water bath at a cure pool of 38-40°C for 20 minutes every day for 5 days each week (15 sessions in total). No additional treatment was applied to the control group. We did not intervene in any of the patients’ lifestyles or pharmacological treatments.

The output temperature of the source used was 42°C. Thermo-mineral water with a total mineralization of 1744.367 mg/L (over 1000 mg/L) and with calcium bicarbonate and sulfate, carbon dioxide, and fluoridate was used (Table 1).

2.5 Instruments

The evaluation was performed before the treatment (T0) and at the end of treatment (day 21) (T1). Pain - the Visual Analogous Scale (VAS), Patient Global VAS, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life Index (ASQoL) were used in the evaluation. Before and after the treatment, patients were followed up by White Blood Cell (WBC), ESR and CRP.

VAS is one of the widely used evaluation methods (13). The distance from the lowest VAS to the patient’s mark was measured in mm (0-100) (0 = no effect and 100 = very severe effect) and the patient’s pain severity and overall health status were determined numerically.

BASFI is an easy and fast index consisting of 10 questions measuring the functional capacity of AS patients. A high score indicates functional limitation. The reliability and validity studies of BASFI have been made in Turkey (14).

BASDAI measures disease activity index. BASDAI contains 6 questions that measure fatigue, joint pain/swelling, spinal pain, tenderness and morning stiffness. A high score indicates the severity of disease activation. The reliability and validity studies of BASDAI have been made (15).

ASQoL consists of 18 questions that measure the quality of life of AS patients. It contains questions about the quality of life and life expectancy of the patients and the effects of the disease on these expectations. Each question has yes or no answers. The sum of the yes answers gives the total ASQoL score. A high score indicates a decreased quality of life of the patient (16).

WBC, ESR (Standard Westergren method) and serum CRP levels were measured. The CRP reference range was 0-0.5 mg/dl. The CRP level was measured by the nephelometric method.

2.6 Efficacy outcome measures

The efficacy was defined as a change in outcome measures score at T1 vs. T0.

2.7 Sample size

The number of patients included in the present study was determined based on BASDAI data, according to the results of Ciprian et al. (17) The baseline mean score of BASDAI in the SPA group was 2.68 with a standard deviation of 1.22. The mean score of BASDAI was 1.83 after treatment. The sample size was based on a power of 80% (beta 0.2), and statistical significance (alpha 0.05) of 95%. Therefore, 27 patients were required in each group. We estimated a dropout rate of 10% and decide on 30 patients for each group. The study size was calculated by using the Raosoft software (© 2004 by Raosoft, Inc.).

2.8 Statistical analysis

Statistical analysis was performed with IBM SPSS 22.0 statistical package program. Descriptive statistical methods were used in the analysis of the demographic data. Shapiro-Wilk test was used to determine whether the data were normally distributed. It was determined that, except for CRP, the data were not normally distributed. For CRP, a paired sample test was used for intragroup comparisons, and Wilcoxon signed ranks test was used for other data. For comparisons between groups, the Mann-Whitney U test and independent samples t-test were used. p <0.05 was considered statistically significant.

RESULTS

All patients completed the study (Figure 1). None of the patients were excluded from the study due to the side effects of the treatment.
A statistically significant difference was found between the ages, the use of regular medications and the use of biologic therapy of the patients who participated in the study (Table 2).

Compared to the pre-treatment period, there was a statistically significant improvement in both groups’ pain at the end of the treatment in BASFI, in the balneotherapy group (VAS), in the patient’s global assessment (VAS), in ASQoL and BASDAI (Table 3).

A comparison between groups before treatment revealed that there was a statistically significant difference in terms of pain (VAS), patient’s global assessment (VAS), BASFI and BASDAI whereas, after treatment, there was no statistically significant difference in the data except pain (VAS) (Table 3).

A comparison of difference scores revealed that there was a statistically significant change in pain (VAS), patient’s global assessment (VAS), ASQoL, BASFI and BASDAI whereas there was no statistically significant difference between WBC, ESR and CRP (Table 3).

**DISCUSSION**

AS is a chronic inflammatory disease of unknown etiology that affects the axial skeleton but may also affect peripheral joints. AS usually begins in the 2nd and 3rd decades (2, 3).

The mean age of onset of the disease was found to be 34.8 ± 8.44. AS is seen 3 times more in males compared to females. Of our patients, 16 were females (26.67%) and 44 males (73.33%). The mean age and male/female ratio determined in our study were consistent with the data in the literature. According to the demographic data of the patients included in the study, as the age and pain intensity increased and the functional capacity decreased, the preference of the spa treatment increased. It was observed that patients who received biological treatment and younger patients preferred spa treatment less. This suggests that patients with less pain and better functional status do not require additional treatment. In terms of clinical data from the evaluation parameters, although the data in the balneotherapy group was worse initially; similar results were obtained with the control group after balneotherapy. Significantly less pain was observed. Pre and post-treatment WBC, ESR and CRP values were similar in both groups.

SpA treatments have been used in musculoskeletal diseases for centuries. Although there are many methods of application, the most commonly used method of treatment is balneotherapy. Balneotherapy is effective on musculoskeletal pain, such as knee, neck, back pain and
physical dysfunction and daily life activities problems (8-11,18-20).

Table 1. Water Analysis

| SOURCE NAME                  | Bolu Karacasu Thermal Spring |
|------------------------------|-------------------------------|
| **PHYSICAL PROPERTIES**     |                               |
| Temperature                  | 42 °C                         |
| **PHYSICOCHEMICAL PROPERTIES** |                               |
| Ph-value                     | 6,49                          |
| Carbonate CO$_3^{2-}$        | 0,000 mg/L                    |
| Carbon dioxide CO$_2$        | 563,2 mg/L                    |
| Hardness                     | 100,9°fH                      |
| **CATIONS**                 |                               |
| Sodium Na$^+$                | 45,980 mg/L, 2,000 mEq/L, 8,860 %
| Potassium K$^+$              | 14,467 mg/L, 0,370 mEq/L, 1,639 %
| Ammonium NH$_4^+$            | 0,000 mg/L, 0,000 mEq/L, 0,000 %
| Magnesium Mg$^{2+}$          | 27,349 mg/L, 2,251 mEq/L, 9,972 %
| Calcium Ca$^{2+}$            | 358,766 mg/L, 17,938 mEq/L, 79,469 %
| Manganese Mn$^{2+}$          | 0,242 mg/L, 0,009 mEq/L, 0,039 %
| Iron Fe$^{2+}$               | 0,130 mg/L, 0,005 mEq/L, 0,021 %
| **Total**                    | 446,934 mg/L, 22,573 mEq/L, 100,000 %
| **ANIONS**                   |                               |
| Flouride F$^-$               | 1,990 mg/L, 0,105 mEq/L, 0,471 %
| Chloride Cl$^-$              | 7,374 mg/L, 0,208 mEq/L, 0,935 %
| Bromide Br$^-$               | 0,129 mg/L, 0,002 mEq/L, 0,007 %
| Iodide I$^-$                 | 0,0147 mg/L, 0,000 mEq/L, 0,001 %
| Nitrite NO$_2^-$             | 0,3432 mg/L, 0,007 mEq/L, 0,034 %
| Nitrate NO$_3^-$             | 5,720 mg/L, 0,092 mEq/L, 0,415 %
| Sulfate SO$_4^{2-}$          | 390,000 mg/L, 8,125 mEq/L, 36,525 %
| Bicarbonate HCO$_3^-$        | 835,700 mg/L, 13,700 mEq/L, 61,587 %
| Sulfur (Sulfide) S$^{2-}$    | 0,000 mg/L, 0,000 mEq/L, 0,000 %
| Phosphate (Hidrofosfat) HPO$_4^{2-}$ | 0,280 mg/L, 0,006 mEq/L, 0,026 %
| **Total**                    | 1241,551 mg/L, 22,245 mEq/L, 100,000 %
| **INSOLUBLE SUBSTANCES**     |                               |
| Metasilicate acid H$_2$SiO$_3$ | 55,883 mg/L, 0,716 %
| Metaboric acid HBO$_2$        | 0,000 mg/L, 0,000 %
| **Total Mineralization**     | 1744,367 mg/L                  |

Forestier et al. proposed SPA treatment for chronic inflammatory diseases, chronic low back pain, OA and fibromyalgia which show sequelae but no current disease activity (12). Karagülle et al. showed that SPA treatment has an effect on pain and function in rheumatic and musculoskeletal diseases (11). The randomized controlled crossover study performed by the same study group showed the beneficial effects of spa therapy applied to
patients with rheumatoid arthritis in addition to pharmacotherapy (19). Studies on AS have shown that mud treatments and thermal baths are useful in AS and other spondyloarthritis (11, 17, 21-24). Similar to these studies, we found that balneotherapy has a positive effect on pain and functionality.

### Table 2. Characteristics of the study population

|                      | Total       | SPA (n=33)   | Control (n=27) | p     |
|----------------------|-------------|--------------|----------------|-------|
| **Age**              | 49.4±11.21  | 53.94±10.28  | 43.85±9.87     | 0.001*|
| **Gender**           |             |              |                |       |
| Female               | 16          | 7(21.2%)     | 6(22.2%)       | 0.926b|
| Male                 | 44          | 26(78.8%)    | 21(77.8%)      |       |
| **BMI(kg/m²)**       | 27.76±4.66  | 28.05±4.94   | 27.39±4.53     | 0.435a|
| **Age of Initial Symptoms** | 34.8±8.44  | 36.5±9.02    | 31.96±7.05     | 0.048 |
| **Age of First Diagnosis** | 39.17±8.72 | 41.6±8.76    | 36.07±7.68     | 0.015 |
| **Initial Symptoms (Average duration)** | 14.92±9.93 | 17.39±10.66  | 11.88±8.18     | 0.055a|
| **First Diagnosis (Average duration)** | 10.28±7.69 | 12.3±8.6     | 7.76±5.58      | 0.051a|
| **Medication use**   |             |              |                |       |
| No                   | 10(30.3%)   | 3(11.1%)     | 3(11.1%)       | 0.065b|
| Yes                  | 23(69.7%)   | 24(88.9%)    |                |       |
| **Regular medication use** |           |              |                |       |
| No                   | 14(42.4%)   | 5(18.5%)     | 5(18.5%)       | 0.044b|
| Yes                  | 19(57.6%)   | 22(81.5%)    | 22(81.5%)      |       |
| **NSAI Drugs**       |             |              |                |       |
| No                   | 13(39.4%)   | 5(18.5%)     | 5(18.5%)       | 0.075b|
| Yes                  | 20(60.6%)   | 22(81.5%)    | 22(81.5%)      |       |
| **Methotrexate**     |             |              |                |       |
| No                   | 32(97%)     | 23(85.2%)    | 23(85.2%)      | 0.130b|
| Yes                  | 1(3%)       | 4(14.8%)     | 4(14.8%)       |       |
| **Sulfasalazine**    |             |              |                |       |
| No                   | 24(72.7%)   | 18(66.7%)    | 18(66.7%)      | 0.620a|
| Yes                  | 9(27.3%)    | 9(33.3%)     | 9(33.3%)       |       |
| **Biologic treatments** |            |              |                |       |
| No                   | 28(84.8%)   | 14(51.9%)    | 14(51.9%)      | 0.007b|
| Yes                  | 5(15.2%)    | 13(48.1%)    | 13(48.1%)      |       |

*Mean±SD  *Mann-Whitney U test  *Chi-squared test

Due to the different chemical components of the water used in balneotherapy, it is difficult to determine their mechanisms of action. Although their mechanisms of action are not fully explained, thermo-mineral waters have been reported to have positive effects on pain, physical functions and quality of life through mechanical, thermal and chemical means (25). Fioravanti et al. reported that hydrostatic pressure-induced mechanical and heat effects were more dominant during balneotherapy (7). They reported that, in response to heat, the elasticity of collagen-rich tissues increases, muscle spasm decreases, and joint function is improved. In a review of randomized controlled studies conducted to investigate the effects of minerals and chemical compositions in the water used in balneotherapy on treatment, More et al. reported that, although the mechanism is not fully explained, mineral water or mud baths reduce pain more than non-mineralized water (26).

Bender et al. reported that thermo and mechanoreceptors were activated and eliminated nociception with the effect of temperature and buoyancy (27). Another study highlighting similar findings reported that warm stimuli can exert an effect by increasing the release of b-endorphins, which have an important analgesic and immunosuppressive effect (28). It has been reported that balneotherapy and mud therapy causes a reduction in circulating levels of prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin-1 β (IL-1 β) and tumor necrosis factor-a (TNF-a), which are important mediators for inflammation and pain, and also an increase in anti-inflammatory growth factor IGF-1 (6,25,29). Also, in patients with rheumatic disease, CRP levels, which increase in response to inflammation, decrease after balneotherapy administration (30).
Table 3. Comparison of the values within & between the groups and change values between the groups

|                      | T0                  | T1                  | p (T1-T0) | T1-T0 change values |
|----------------------|---------------------|---------------------|-----------|---------------------|
| **Patient global**   |                     |                     |           |                     |
| assessment (VAS) SPA | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 60(30-87)           | 20(0-82)            | 0.000*    | -30(-70-20)         |
|                      | 0.000               | 0.29                |           |                     |
| **Pain (VAS)** SPA   | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 50(38-85)           | 15(0-80)            | 0.000*    | -35(-70-0)          |
|                      | 0.002               | 0.003               |           |                     |
| **BASFI** SPA        | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 3.1(0.7-9.5)        | 2.0(0.9-9)          | 0.036*    | -1(-1.1-0.7)        |
|                      | 0.26                | 0.608               |           |                     |
| **BASDAI** SPA       | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 4.1(1-7.2)          | 2.0(0.7-7.4)        | 0.975*    | 0(-1.4-1.4)         |
|                      | 0.002               | 0.882               |           |                     |
| **ASQoL** SPA        | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 80(18-18)           | 5(0-18)             | 0.000*    | -2(-12-3)           |
|                      | 0.054               | 0.811               |           |                     |
| **WBC** SPA          | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 7600(3300-10800)    | 7300(3600-13900)    | 0.221*    | -200(-2900-3100)    |
|                      | 7340(4440-11400)    | 7530(5210-11900)    | 0.879*    | -40(-4200-2470)     |
|                      | 0.97                | 0.598               |           |                     |
| **ESR** SPA          | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 15(6-59)            | 13(4-54)            | 0.220*    | 0(-29-19)           |
|                      | 0.572               | 0.623               |           |                     |
| **CRP** SPA          | (n=33)              | Control (n=27)      |           |                     |
| p*                   | 0.43(0.03-2.19)     | 0.39(0.03-3.57)     | 0.24 b    | 0.02(-0.87-1.38)    |
|                      | 0.59±0.56           | 0.67±0.74           |           | 0.09±0.42           |
|                      | 0.33(0.09-2.8)      | 0.3(0.02-1.7)       | 0.67 b    | -0.03(-1.35-1.32)   |
|                      | 0.60±0.63           | 0.55±0.50           |           | -0.05±0.56          |
|                      | 0.949               | 0.434               |           | 0.268 b             |

Median (min-max), mean±SD  a Wilcoxon signed ranks test (within the groups)  bPaired sample test (within the groups) c change values

**Mann-Whitney U test (between the groups)  **Independent samples t-test (between the groups) T0: first day of study, T1 twenty-first day of study

Significant improvements were detected in our study in the balneotherapy group in terms of the BASDAI scores showing disease activity of AS patients. Furthermore, there was no significant difference between pre-treatment and post-treatment WBC, ESR, and CRP measurements, which are used routinely in the follow-up. Though we cannot explain the mechanism of action, this supports the fact that it has an immunomodulatory effect.

4.1 Limitations

Our study includes some methodological shortcomings. Firstly, the study did not randomize. Some patients did not have pain and did not want balneotherapy, so a randomized controlled trial was not feasible. To prevent bias, the study protocol was first determined and explained to the patients and then patients were included in the study groups. All patients underwent similar control. And the
others the small sample size, the lack of a long follow-up period and a placebo-control group are the main limitations of the present study. In our study, blinding of the patients to the treatment allocation was not possible due to the nature of the balneotherapy.

CONCLUSION
In conclusion, in our study, thermal treatment was well tolerated. According to our results, there was no effect on disease activity. Our data suggest that balneotherapy combined with pharmacological treatment may improve the beneficial effects of treatment in selected AS patients. We recommend that the data we have obtained should be supported by more randomized controlled trials.

ACKNOWLEDGMENTS
All procedures performed in studies involving human participants were by the ethical standards of the Institutional Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all participants before being included in the study.

All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

This research was not supported by any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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