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Long-term efficacy of spa therapy in patients with rheumatoid arthritis

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Abstract
Our previous crossover randomized trial suggested that spa therapy added to usual pharmacotherapy provides benefits that lasted 6 months over pharmacotherapy alone in rheumatoid arthritis patients. We now extend, and report the long-term results of that study. In the crossover trial, patients were randomized to spa therapy first group or control first group (first assignment, period 1, 6 months); after this period and washout phase (9 months), they crossed over to the other arm (second assignment, period 2, 6 months). In this long-term study, we now analyze the 15-month results of the first assignment, and 12-month results of the second assignment in the opposite side with a 6-month extension of the follow-up period. The clinical outcome measures were pain, patient and physician global assessment, Health Assessment Questionnaire, and Disease Activity Score-28. The 15-month results of first assignment revealed no statistically significant differences between the groups in any of the efficacy outcomes ($p > 0.05$ for all). The 12-month results for the second assignment after crossover revealed a statistically significant decrease between the groups regarding the patient global assessment scores ($p = 0.016$), physician global assessment scores ($p = 0.003$) and swollen joints counts ($p = 0.030$); however, no statistically significant difference was found between the groups in any of the other efficacy outcomes ($p > 0.05$ for all). The short- and medium-term beneficial effects of the 2-week spa therapy added to the usual pharmacotherapy observed through the initial 6-month evaluation period may be maintained mildly to moderately to the 12-month mark in rheumatoid arthritis patients receiving conventional disease-modifying antirheumatic drugs. Further studies with a larger sample size are needed for the confirmation of the study results.

Keywords Spa therapy · Balneotherapy · Salt water · Rheumatoid arthritis

Introduction

Non-pharmacological treatment interventions as an adjunct to pharmacological therapies have frequently been used, and have a supporting role in the treatment of rheumatoid arthritis (RA), despite the great advances in pharmacological therapies and their favorable effectiveness [1]. Spa therapy, which involves all the medical activities that are originated and employed in spa resorts and is aimed at health promotion, prevention, therapy, and rehabilitation, is among the non-pharmacological treatment options for RA [2]. As the central treatment modality, balneotherapy, which is the immersion in a thermal (with a temperature of 36–38 °C) and/or mineral (with high mineral content) water, is included in spa therapy regimens [3]. In addition, spa therapy employs the other balneological interventions such as mud applications, drinking or inhalation of the mineral water [3]. Some forms of hydrotherapeutic applications (e.g., showers, underwater pressure jets, and exercise in thermal water pools) as well as other non-pharmacological therapies (physical therapy modalities, massage, exercise, etc.) can also be combined within the spa therapy programs [3]. These programs may vary substantially from one spa to another, or from one country to the other country [2, 3]. Spa therapy has widely been used as a relevant part of the health care systems—at least is partly reimbursed by the health insurance systems—in the treatment and rehabilitation of rheumatic and musculoskeletal diseases including RA in many European countries including Turkey [2–9].

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The clinical studies of researchers testing the efficacy of spa therapy in RA in different countries such as Israel [10–13], Germany [14–16], Austria [16], Italy [17], Portugal [18], Eastern European countries [19–26], and Turkey [22, 27] have been published. Researchers generally reported the beneficial clinical effects after different spa therapy courses applied in different spa resorts, which might basically involve saline, radon, or sulfur balneotherapy, or mud therapy occasionally combined with the other spa treatments depending upon the experience of each center [10–27]. However, recent systematic reviews/meta-analyses evaluating the efficacy of spa therapy in RA generally conclude that although the nearly all studies reported positive results on the efficacy of spa therapy, the available existing evidence is insufficient for drawing a solid conclusion [8, 9]. Hence, we had previously designed a randomized controlled crossover trial to examine whether spa therapy had any beneficial effects in patients with RA [28]. Spa therapy, when added to usual pharmacotherapy for RA patients, provided therapeutic benefits more than the pharmacotherapy alone that lasted 6 months [28]. We now extend, and report the long-term results of that study.

Methods

Trial design and participants

In our previous randomized controlled crossover study, eligible patients were 18 years of age or older, had a diagnosis of RA according to the American College of Rheumatology (ACR) 1987 revised criteria [29], and had already been treated with stable pharmacotherapy (conventional disease-modifying antirheumatic drugs {DMARDs}; ± low-dose corticosteroids; ± non-steroidal antiinflammatory drugs {NSAIDs}) for at least 3 months [28]. Key exclusion criteria were, having been treated by any biologic DMARD, the changes in the conventional DMARD or glucocorticoids during the previous 3 months, spa therapy within the preceding 1 year, and a general contraindication to spa therapy [28]. Patients were randomly assigned to spa therapy first group or control first group (period 1, 6 months); after this period and washout phase (9 months), they crossed over to the other arm for the period 2, 6 months [28]. In this long-term study, we now report the 15-month results of the first assignment, and 12-month results of the second assignment in the opposite side with the 6-month extension of the previous crossover study (Fig. 1).

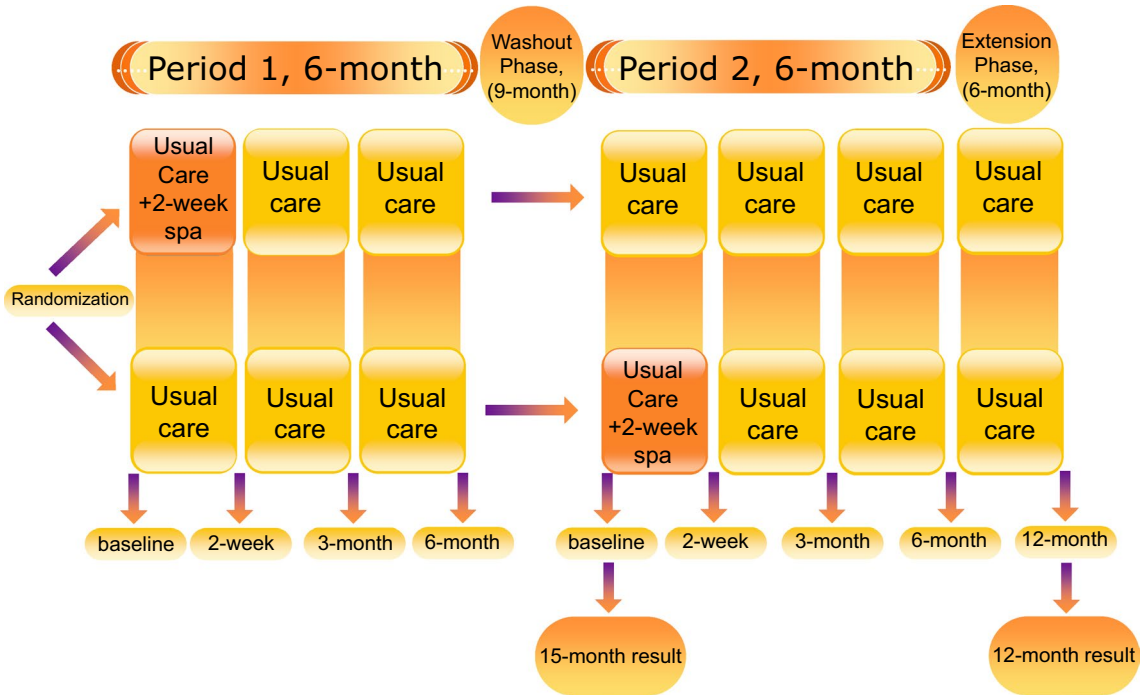

Fig. 1 Study design

Interventions

Spa therapy

Spa therapy was administered in Tuzla spa. Patients traveled to and stayed at the thermal spa facility for 2 weeks. The spa therapy regimen consisted of balneotherapy intervention alone: a daily balneotherapy session in a thermal water pool at 36–37 °C for 20 min except Sundays. Patients were advised to stay passive, and were not allowed to exercise, or swim during balneotherapy sessions. The patients rested and relaxed, or participated in the free outdoor activities such as walking, enjoying the convenient spa environment with temperate climate after balneotherapy sessions. These factors were uncontrolled due to the vacational atmosphere of the spa therapy. Tuzla spa-water used for balneotherapy has a total mineralization of 3367 mg/L, and is saline water with a high concentration of sodium chloride (1900 mg/L). Its physicochemical analysis was previously presented [28].

Usual pharmacotherapy

All patients continued their usual pharmacotherapy (conventional DMARDs; corticosteroids; and NSAIDs when needed).

Outcome measures

We followed the ACR core set of the disease activity measures for RA clinical trials. This core set includes a total of seven measures as the tender joint count, swollen joint count, patient's assessment of pain, patient global assessment, physician global assessment, patient's assessment of physical function, and the laboratory evaluation of 1 acute-phase reactant (either an erythrocyte sedimentation rate {ESR} or C-reactive protein {CRP}) [30]. This core set of outcomes was recommended to be included in all the current trials [30]. The core set of outcome measures, which were at least moderately sensitive to change (discriminant validity), sampled the broad range of improvement in RA (content validity) [30].

Tender and swollen joints were assessed by an experienced physician based on 68, and 66 joints, respectively [31]. Patient's assessment of pain, patient global assessment, and physician global assessment were evaluated using a horizontal, continuous 100-mm visual analog scale (VAS) with two end-points: left end, where 0 indicated no pain, or the best and the right end, where 100 indicated the most intense pain imaginable, or the worst. Patient's assessment of physical function was assessed using the Health Assessment Questionnaire (HAQ) which evaluates the functional disability in eight categories as in dressing, rising, eating, walking, hygiene, reaching, gripping, and in the usual activities [32]. The Turkish translation of HAQ was found to show good validity [33]. The objective RA disease activity measure, ESR was used for the laboratory evaluation of the acute-phase reactants [34]. The composite index for the disease activity assessment (i.e., Disease Activity Score {DAS28}) was used in addition to those individual variables of the disease activity [35]. DAS28 includes four variables as tender joint count; swollen joint count; patient global assessment; and ESR [35].

Statistical methods

The normality of data was checked with the Shapiro Wilk test. The results showed non-normal distribution. The outcomes, and the variables of the change (follow-up value minus baseline value) were presented as median (25th percentile–75th percentile). The data did not satisfy the assumptions of the parametric tests; therefore, the data were assessed with the use of the non-parametric tests. The efficacy analysis was conducted by the Wilcoxon signed-rank test for comparing the changes within each group and Mann–Whitney *U* test for comparing the differences between groups in the modified intention-to-treat (mITT) population (all randomized patients who received an assigned intervention and had a baseline and at least one follow-up assessment). All statistical analyses were performed with the use of Statistical Package for the Social Sciences (SPSS) software for Macintosh version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Significance level was $p < 0.005$. Benjamini Hochberg method was used in controlling the type 1 error.

Results

Of the 50 randomized patients, 37 patients completed the period 1 and washout phase (15-month result of the first assignment), and after the crossover 29 patients completed the period 2 and extension phase (12-month result of the second opposite assignment); and 37 patients constituted the mITT population for the 15-month analysis, and 29 patients constituted the mITT population for the 12-month analysis (Fig. 2). The baseline characteristics of these patients were previously reported [28]. The majority of patients were women (94.6%); the mean age was 52.7 years and the mean duration of RA was 12.9 years.

The efficacy outcomes are detailed in Tables 1 and 2. The 15-month results of the first assignment revealed no statistically significant differences between the groups in any of the efficacy outcomes ($p > 0.05$ for all) (Table 1). The 12-month results for the second assignment after crossover revealed statistically significant decrease between the groups in patient global assessment scores

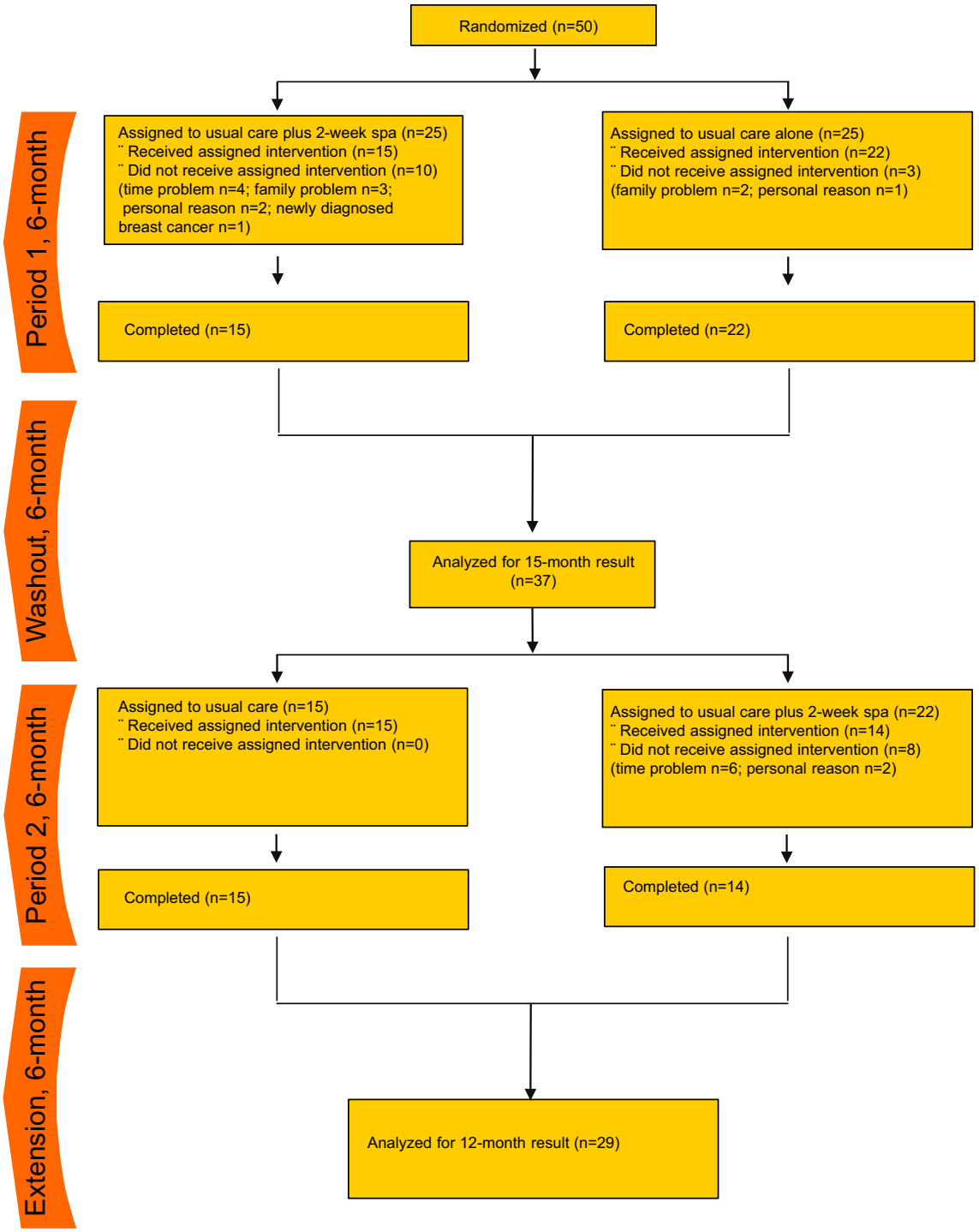

Fig. 2 Flow diagram of the study population

($p = 0.016$), physician global assessment scores ($p = 0.003$) and swollen joints counts ($p = 0.030$); however, no statistically significant difference was found between the groups in any other efficacy outcomes ($p > 0.05$ for all) (Table 2).

Discussion

To our knowledge, the present study was the first study testing the long-term efficacy of saline spa therapy in patients

Table 1 The 15-month efficacy outcomes of first assignment

Outcome	Spa first (spa group) ($n=15$)	Control first (control group) ($n=22$)	p value[a]
Pain VAS			0.446
Baseline	75.00 (50.00–86.00)	54.50 (44.50–81.25)	
15 months	44.50 (23.50–56.25)	51.50 (22.00–73.50)	
Change	− 7.00 (− 42.50 to 4.25)	− 5.00 (− 40.50 to 13.75)	
p value[b]	0.084	0.188	
PtGA VAS			0.098
Baseline	67.00 (58.00–80.00)	58.00 (49.50–79.25)	
15 months	38.50 (16.00–52.75)	51.50 (27.50–66.75)	
Change	− 28.50 (− 46.75 to − 9.75)	− 9.00 (− 30.00 to 10.50)	
p value[b]	0.007*	0.062	
PhGA VAS			0.101
Baseline	65.00 (49.00–80.00)	61.50 (46.25–80.00)	
15 months	32.00 (17.75–45.50)	47.00 (23.75–57.25)	
Change	− 27.50(− 39.75 to − 19.75)	− 17.50 (− 34.75 to 6.75)	
p value[b]	0.002*	0.004*	
Tender joints[c]			0.782
Baseline	33.00 (19.00–56.00)	53.00 (19.75–61.25)	
15 months	20.50 (9.75–28.75)	18.50 (4.75–39.50)	
Change	− 15.00 (− 24.25 to − 4.00)	− 15.50 (− 32.50 to − 4.00)	
p value[b]	< 0.001*	0.001*	
Swollen joints[c]			
Baseline	16.00 (11.00–28.00)	14.00 (8.25–23.75)	0.380
15 months	4.00 (2.50–10.25)	4.50 (1.00–9.00)	
Change	− 11.00 (− 18.50 to − 7.00)	− 7.50 (− 16.25 to − 2.75)	
p value[b]	<0.001*	0.002*	
HAQ			
Baseline	1.35 (0.80–1.90)	1.45 (0.85–2.08)	0.371
15 months	0.78 (0.60–0.91)	1.15 (0.33–1.73)	
Change	− 0.43 (− 0.71 to − 0.28)	− 0.28 (− 0.58 to − 0.03)	
p value[b]	0.005*	0.011*	
DAS28			
Baseline	6.20 (5.70–7.30)	6.50 (4.95–7.13)	0.281
15 months	5.39 (4.61–5.82)	4.98 (3.70–6.06)	
Change	− 1.00 (− 2.17 to − 0.28)	− .62 (− 1.73 to 0.16)	
p value[b]	0.001*	0.021*	
ESR			
Baseline	35.00 (22.00–57.00)	18.00 (14.00–29.25)	0.059
15 months	36.50 (20.50–48.00)	22.00 (13.00–31.50)	
Change	− 4.00 (− 11.00 to 3.50)	4.00 (− 3.50 to 7.50)	
p value[b]	0.162	0.251	

The outcome and change (follow-up value minus baseline value) variables are median (25th–75th percentile)

VAS visual analog scale, *PtGA* patient global assessment, *PhGA* physician global assessment, *HAQ* Health Assessment Questionnaire, *DAS28* Disease Activity Score for 28 joints, *ESR* erythrocyte sedimentation rate

*Statistically significant with Benjamini–Hochberg method with a false discovery rate of 0.08

[a]Mann–Whitney U test was used to compare the differences between the groups

[b]Wilcoxon signed-rank test was used to compare the changes within each group

[c]A total of 68 joints were evaluated for tenderness, and 66 joints were evaluated for swelling

Table 2 The 12-month efficacy outcomes of second assignment after crossover

Outcome	Control first (spa group) ($n=14$)	Spa first (control group) ($n=15$)	p value[a]
Pain VAS			0.141
Baseline	58.50 (43.25–75.75)	44.50 (23.50–56.25)	
12 months	40.00 (19.75–58.75)	47.00 (21.00–62.00)	
Change	− 12.50 (− 36.25 to 3.75)	− 2.50 (− 23.25 to 13.00)	
p value[b]	0.068	0.802	
PtGA VAS			0.016*
Baseline	58.50 (46.75–73.25)	38.50 (16.00–52.75)	
12 months	37.50 (21.50–51.50)	45.00 (25.00–68.00)	
Change	− 27.00 (− 46.25 to 3.75)	5.50 (− 8.50 to 23.75)	
p value[b]	0.016[d]	0.294	
PhGA VAS			0.003*
Baseline	51.50 (43.50–64.00)	32.00 (17.75–45.50)	
12 months	28.00 (20.50–48.00)	49.00 (26.50–59.50)	
Change	− 17.50 (− 37.00 to − 6.75)	8.00 (20.50)	
p value[b]	0.003[d]	0.196	
Tender joints[c]			0.098
Baseline	26.50 (8.25–50.25)	20.50 (9.75–28.75)	
12 months	30.50 (17.25–44.75)	27.00 (20.00–54.00)	
Change	− 2.50 (− 11.25 to 17.50)	12.50 (− 1.25 to 20.00)	
p value[b]	1.000	0.032	
Swollen joints[c]			
Baseline	6.50 (1.75–10.00)	4.00 (2.50–10.25)	0.030*
12 months	1.00 (0.00-6.50)	3.00 (3.00–13.00)	
Change	− 5.50 (− 8.00 to − 1.50)	2.50 (− 1.00 to 8.50)	
p value[b]	< 0.022*	0.195	
HAQ			
Baseline	1.43 (0.64–1.81)	0.78 (0.60–0.91)	0.323
12 months	0.88 (0.50–1.56)	0.85 (0.30–1.10)	
Change	− 0.35 (− 0.84 to 0.36)	0.00 (− 0.43 to 0.20)	
p value[b]	0.177	0.615	
DAS28			
Baseline	5.83 (4.48–6.72)	5.39 (4.61–5.82)	0.054
12 months	4.50 (4.03–5.67)	5.48 (4.32–6.57)	
Change	− 0.96 (− 2.44 to 0.45)	0.30 (− 0.24 to 1.19)	
p value[b]	0.093	0.311	
ESR			
Baseline	29.00 (16.50–40.00)	36.50 (20.50–48.00)	0.441
12 months	19.50 (15.75–34.50)	29.00 (22.75–39.75)	
Change	− 3.00 (− 14.50 to 2..00)	− 1.00 (− 10.00 to 9.00)	
p value[b]	0.135	0.834	

The outcome and change (follow-up value minus baseline value) variables are median (25th–75th percentile)

VAS visual analog scale, *PtGA* patient global assessment, *PhGA* physician global assessment, *HAQ* Health Assessment Questionnaire, *DAS28* Disease Activity Score for 28 joints, *ESR* erythrocyte sedimentation rate

*Statistically significant with Benjamini–Hochberg method with a false discovery rate of 0.08

[a]Mann–Whitney *U* test was used to compare the differences between the groups

[b]Wilcoxon signed-rank test was used to compare the changes within each group

[c]A total of 68 joints were evaluated for tenderness, and 66 joints were evaluated for swelling

with RA. We found that the observed improvements between groups at 6 months were maintained at 12-month mark only with regard to patient and physician global assessments and swollen joints count. In addition, the observed improvements at 6 months were not maintained in any of the efficacy outcomes between groups at 15-month mark.

We followed the ACR core set of disease activity measures that includes the patient's self-reports, physician assessments, and an objective laboratory measure [30]. Interestingly, we found improvements both in patient-reported measure (i.e., patient global assessment), and in physician assessments (i.e., physician global assessments, and swollen joints) at 12-month mark. Although no improvement was observed in the objective measure (i.e., ESR), yet this was not very surprising considering the previous suppression of inflammation by the drugs patients used. The higher ESR levels were anticipated not to be associated with the inflammation; however, the non-inflammatory factors might influence the levels [36]. On the other hand, the patient-reported measures may predict longer-term outcomes better than acute-phase reactants [37], which might be the case in our study.

During the past decades, several randomized controlled studies tested the efficacy of spa therapy in patients with RA, and in general, the beneficial clinical effects in short (up to 3 months) and medium-term (up to 6 months) have been reported [10–19, 22, 27]. Remarkably, one randomized study exists on the efficacy of spa therapy in RA beyond 6 months duration [15]. Franke et al. compared the Bad Brambach spa-water containing radon plus carbon-dioxide bath, and artificial carbon-dioxide bath within a complex multimodal spa therapy program in their study with a follow-up of 12 months [15]. They found the superiority of the radon treatment group during the entire period of 12 months follow-up regarding the main outcome [15]. Although the direct comparison of the present study with Franke et al.'s study was limited due to the differences in study design (e.g., intervention of control groups), in the duration of spa therapy course (i.e., 2 vs 3 weeks) and the chemical properties of spa waters (i.e., saline vs. radon), the observed improvements in the present study at the 12-month mark were consistent with the study of Franke et al. [15].

The results of the long-term follow-up, beyond 6 months, of the spa therapy in the other rheumatic and musculoskeletal diseases have been reported in several randomized controlled studies [38–45]. The general long-term maintenance of the beneficial effects were reported to be in the knee osteoarthritis [38–40], chronic low back pain [41], and ankylosing spondylitis [42]; however, not in hand osteoarthritis [43] or fibromyalgia [44, 45]. The present saline spa therapy study along with a previous radon spa therapy of Franke et al. [15] would provide important insights into the long-term efficacy of the spa therapy in patients with RA.

The nonspecific, and uncontrolled factors such as change of the milieu, the pleasant scenery, being in a noncompetitive atmosphere with fellow patients, resting in a holiday environment, the absence of daily duties, the changes in diet and in physical activities, and the placebo effect might have contributed to the beneficial effects of spa therapy [6, 42, 45]. Therefore, all the observed improvements could not specifically be attributable to any of the individual components of spa therapy (e.g., balneotherapy), but to spa therapy as a whole.

The clinical benefits of balneotherapy have widely been attributed to various factors, such as thermal, mechanical, and chemical effects [46]. The well-documented mechanisms of the thermal effect include pain relief, muscle relaxation, gate control theory, neuroendocrine reactions, and the immune mechanisms [46–48]. The mechanical effect, due to the hydrostatic pressure and buoyancy, may increase the joint mobility by reducing the loading on the joints [46]. Salt (NaCl), radon (Rn^{222}), and sulfur (hydrogen sulfide {H2S}) among the chemical ingredients of thermal mineral waters have recently gained interest due to the increasing evidence on their biological effects when used in balneological treatments [49–54]. Regarding the specific chemical effects of balneological agents in RA, there is initial knowledge that comes from in vitro studies, animal experiments, and in vivo human studies [55–60]. It is interesting to note that researchers in all of the published in vitro studies evaluated the sulfur as a balneotherapeutic agent [55–57]. The recent review concerning sulfur and inflammatory joint diseases concluded that the existing in vitro evidence is inconclusive in the case of RA [54]. Lange et al. demonstrated that 12 applications of radon hyperthermia exposure, in therapeutic adit of Bad Gastein-Böckstein, decreased the receptor activator of NF kappa-B ligand (RANKL), osteoprotegerin (OPG) ratio, and serum levels of tumor necrosis factor-α (TNF-α), and anti-CCP antibodies (ACPA) in patients with RA [58]. However, in our study, the water used in balneotherapy was saline. With regard to the mechanisms of the action of salt in RA, there are currently few available data from both in vivo human and animal trials [59, 60]. Cozzi et al. demonstrated that a 10-day mud bath (40–42 °C mud for 15 min and saline bath at 37–38 °C for 10 min a day) in adjuvant arthritis-induced rats significantly reduced the paw volume, and the serum levels of tumor necrosis factor (TNF)-α and interleukin (IL)-1 compared to the control [59]. As a part of the previous crossover study, we investigated the effect of spa therapy with saline balneotherapy on oxidative stress and found that it exerted antioxidant effect as reflected by the increase in non-enzymatic superoxide radical scavenger activity (NSSA) levels after spa therapy [60].

Study limitations

Our study has some limitations. First, true placebo effects caused by the belief in improvement by spa therapy, and positive attention might certainly have contributed to the observed improvements [42], particularly in the subjective outcome measures. However, it is likely that nonspecific effects including placebo effects rapidly extinguish once the specific treatment has finished, and the long-term benefit may imply that there is a specific treatment effect of the spa therapy [42, 45]. Second, we were not able to pool the results of the first assignment and second assignment, because we did not have the results of the 12-month result of the first assignment and 15-month result of the second assignment. Therefore, further studies with larger sample size are required for verification of our results. Third, there were remarkable dropouts mainly manifested as not receiving spa therapy particularly due to time problems, family problems, and personal reasons during the study period. These dropouts might cause bias for the study findings; therefore, we analyzed all randomized patients who had received a spa therapy course and who had a baseline and at least one post-baseline assessment to mitigate this problem, as similarly performed by Reginster et al. [60]. Lastly, this study included patients who received conventional DMARDs; hence, the findings cannot be extrapolated to the patients treated with biologics. Studies including patients who had been on biologics are warranted to extend our knowledge on the effects of the spa therapy in such patients group.

Conclusion

The short- and medium-term beneficial effects of the 2-week spa therapy added to usual pharmacotherapy observed through the initial 6-month evaluation period may be mildly to moderately maintained to the 12-month mark, in RA patients receiving conventional DMARDs. Further studies with larger sample size are needed for the confirmation of the study results.

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Author contributions Conception or design of the study: MK, MZK; data collection: MK, MZK; data analysis and interpretation: MK, SK, MZK; drafting the article: MK, SK, MZK; critical revision of the article: MK, SK, MZK; final approval of the version of the article to be published: MK, SK, MZK.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Trial registration The study was not registered in a clinical trials registry.

Ethical statement The formal ethics approval was not required because this work was a non-interventional extension study of the previous interventional study, and its data were obtained without any additional therapy and it was carried out without interference in standard usual care. However, it was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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