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Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

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Ivana Aleksic Milenkovic[1,♣], Sonja Stojanović[1,2], Bojana Stamenković[1,2], Tatjana Jevtović Stoimenov[3], Sandra Šarić[1], Goran Danković[4,5]

The impact of balneotherapy on IL-6 cytokine levels, disease activity, functional ability, fatigue and depression in patients with rheumatoid arthritis

Утицај балнеотерапије на ниво цитокина *IL*-6, активност болести, функционалне способности, замор и депресију код болесника са реуматоидним артритисом

[1]Niška Banja Institute for Treatment and Rehabilitation, Niš, Serbia;
[2]University of Niš, Faculty of Medicine, Department of Internal Medicine, Niš, Serbia;
[3]University of Niš, Faculty of Medicine, Department of Biochemistry, Niš, Serbia;
[4]University of Niš, Faculty of Sport and Physical Education, Niš, Serbia;
[5]Niš University Clinical Center, Clinic for Anesthesiology, Niš, Serbia

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♣**Correspondence to:**
Ivana ALEKSIĆ MILENKOVIĆ
Niška Banja Institute for Treatment and Rehabilitation, Srpskih junaka 2, 18000 Niš, Serbia
E-mail: **ivana.aleksic980@gmail.com**

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SUMMARY

Introduction/Objective The aim of this study was to determine the impact of balneotherapy on IL-6 cytokine levels, disease activity, functional capacity, fatigue and depression in patients with rheumatoid arthritis.

Methods The study included 46 patients with RA (16 with moderate, 16 with low disease activity, and 14 in remission) who underwent BT as part of a rheumatic disease treatment program, in the Niška Banja Institute, for a duration of 3 weeks. BT was administered in the form of radon mineral baths (lasting 15 to 20 minutes in the thermo-mineral waters of Niška Banja at a temperature of up to 37°C). To evaluate the effect of BT, the study utilized ELISA kits for measuring plasma cytokine IL-6 levels, DAS28 SE and CDAI for assessing and calculating disease activity indices, the HAQ questionnaire for measuring functional ability, the Beck Depression Inventory (BDI), and the FACITF questionnaire for assessing fatigue.

Results Our research results showed that the application of BT led to a statistically significant improvement ($p < 0.01$, $p < 0.001$) in the values of all examined parameters: IL-6, DAS28 SE, CDAI, HAQ, FACITF, and BDI. Comparing the improvement in these parameters among groups of patients with different disease activity levels (moderate, low, remission), the most pronounced anti-inflammatory effect of BT was observed in patients with moderate disease activity.

Conclusion BT improved almost all observed parameters. Alongside medication therapy, BT is a significant part of the comprehensive therapeutic approach for RA patients.

Keywords: balneotherapy; rheumatoid arthritis; cytokine IL-6; disease activity; functional ability; fatigue

САЖЕТАК

Увод/Циљ Циљ овог истраживања је био да се утврди утицај балнеотерапије (БТ) на ниво цитокина *IL*-6, активност болести, функционалну способност, замор и депресију код особа са реуматоидним артритисом (РА).

Методе Истраживање је обухватило 46 болесника са РА (16 са умереном, 16 са ниском активношћу болести и 14 са ремисијом) код којих је у оквиру програма лечења реуматских болесника, у Институту „Нишка Бања“ примењена БТ у трајању од 3 недеље. БТ је примењена у виду примене радонових минералних купки (трајања 15 до 20 минута у термоминералним водама Нишке Бање температуре до 37°Ц). За процену ефекта БТ у истраживању су коришћени: *ELISA* китови за мерење концентрације нивоа цитокина *IL*-6 у плазми, *DAS*28*SE* и *CDAI* за процену индекса активности болести, упитник за мерење функционалне способности – *HAQ*, Бекова скала депресивности – BDI и упитник за процену замора *FACITF*.

Резултати Резултати нашег истраживања су показали да је применом БТ дошло до статистички значајног побољшања ($p < 0.01$, $p < 0.001$) вредности свих испитиваних параметара: *IL*-6, *DAS*28*SE*, *CDAI*, *HAQ*, *FACITF* и *BDI*. Поређењем побољшања вредности ових параметара међу групама болесника са различитом активношћу болести (умерена, ниска, ремисија), најизраженије антиинфламаторно дејство БТ регистровано је код болесника са умереном активношћу болести.

Закључак БТ је побољшала скоро све посматране параметре. Поред терапије лековима, БТ је значајан део свеобухватног терапијског приступа за пацијенте са РА.

Кључне речи: балнеотерапија; реуматоидни артритис; цитокин *IL*-6; активност болести; функционална способност; замор

INTRODUCTION

Since ancient times, thermal baths and mud have been used to treat rheumatic dis-eases and other musculoskeletal disorders. Balneotherapy (BT) is a complex therape-utic discipline that utilizes natural factors for treatment. Up until the mid-20th century, BT was the primary form of treatment for individuals suffering from locomotor system diseases.

It is a modality of physical therapy whose positive effects stem from the combination of the physical properties of water (due to immersion of parts of the body or the whole body in water) and/or the transfer of temperature and absorption of mineral substances through the skin [1, 2].

Its significance is evidenced by the fact that it is still actively used today alongside modern pharmacological therapy, as it affects all aspects of the disease, especially rheumatic conditions. Rheumatoid arthritis (RA) itself is a chronic, inflammatory, autoimmune disease of unknown etiology, characterized by pain, swelling, and destruction of synovial joints. If aggressive and inadequately treated, it can lead to significant disability and premature mortality [3, 4]. Studies have shown that BT can impact various symptoms of RA, including pain reduction, improved functional abilities, and decreased inflammation [5]. However, the exact mechanism by which BT, or immersion in mineral or thermal water, improves the condition of rheumatic diseases is not fully understood. The positive effects of this process are likely the result of a combination of factors, with mechanical, thermal, and chemical effects being the most prominent. According to some theories, pain reduction may be due to the pressure and temperature of the water on the skin (heat can reduce muscle spasm and increase the pain threshold). Therapy with thermal waters is believed to have an immunomodulatory effect. Recently, it has been proven that therapy with thermal waters also induces a reduction in the levels of prostaglandin E2, leukotriene B4, interleukin-1b, and tumor necrosis factor, important mediators of inflammation [6, 7].

However, despite certain findings and the widespread use of BT in the treatment of RA, its effects have not been fully investigated and explained in various aspects of rheumatic diseases.

The aim of this study was to determine the impact of BT on IL-6 cytokine levels, disease activity, functional capacity, fatigue and depression in patients with rheumatoid arthritis.

METHODS

The study included a total of 46 patients (31 women and 15 men), with an average age of 61.32 ± 9.4 years and an average disease duration of 12.62 ± 6.42 years, diagnosed with rheumatoid arthritis based on the diagnostic criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism 2010 (EULAR). According to disease activity, the patients were divided into three groups: 16 (34.78%) with moderate disease activity, 16 (34.78%) with low disease activity, and 14 (30.44%) in remission. Prior to inclusion in the study, all patients had been on stable therapy for the past 3 months, specifically disease-

modifying antirheumatic drugs (Methotrexate at a dose of 15 to 20 mg per week), and on a stable dose of glucocorticoids for the past 6 weeks, with a maximum dose of Prednisolone 5 mg per day.

During their treatment at the Niška Banja Institute, patients received BT for a duration of 3 weeks. BT was administered as radon mineral baths (lasting 15 to 20 minutes in the thermo-mineral waters of Niška Banja (radon waters) at a temperature of up to 37°C).

For this study, IL-6 cytokine levels, specifically its concentration in plasma, were measured using commercial ELISA kits, following the manufacturer's instructions, at the Biomedical Research Center of the Medical Faculty in Niš. ELISA kits manufactured by Elabscience were used, with a detection range of 1.56 to 100 pg/mL and a sensitivity of 0.94 pg/mL. In terms of disease activity assessment, a detailed clinical examination was conducted at the initial visit and after three weeks of BT. This included counting tender and swollen joints, analyzing 28 joints in typical regions affected by rheumatoid arthritis (shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal joints of the hands, and knees). General health status was evaluated using a visual analog scale (VAS), consisting of a 10 cm line marked by the patients themselves, where 0 represents excellent health and 10 represents the worst condition. Disease activity was assessed before and after BT by calculating the Disease Activity Score DAS28 SE and the Clinical Disease Activity Index (CDAI). Functional ability was assessed using the Health Assessment Questionnaire (HAQ), which patients completed independently. Responses were scored from 0 to 3, with higher HAQ values indicating a greater degree of disability and functional impairment. The HAQ consisted of 20 questions grouped into 8 main categories related to daily activities such as rising, walking, dressing, personal care, hygiene, reaching, gripping, and other activities.

Responses for each question were graded as follows:

0 – Without difficulty;

1 – With some difficulty;

2 – With much difficulty;

3 – Unable to do.

For assessing the impact of BT on depression, the Beck Depression Inventory (BDI) was used. This scale contains 21 questions, with four possible answers for each. Each question is graded from 0 to 3, so the minimum possible total score is 0 (indicating no depression) and the maximum is 63 (indicating severe depression). BDI values indicate:

1) 1 to 9 – minimal depression;
2) 10 do 16 – mild depression;
3) 17 to 29 – moderate depression;
4) 30 to 63 – severe depression.

For assessing fatigue, the FACIT (Functional Assessment of Chronic Illness Therapy) Fatigue Scale version 4 was used. This is a short, easy-to-complete scale consisting of 13 questions measuring individual levels of fatigue during usual daily activities over the past week. Fatigue levels are measured on a Likert scale with responses: Not at all, A little bit, Somewhat, Quite a bit, Very much. The score ranges from 0 to 52, with higher values indicating less fatigue.

The obtained results were statistically processed using the SPSS 18.0 program. The statistical analysis included the arithmetic mean, standard deviation, Student's t-test, and Wilcoxon test.

The authors declare that the article was written in accordance with the ethical standards of the Serbian Archives of Medicine and the ethical standards of the institutions associated with each author (Board of Ethics of the Niška Banja Institute for Treatment and Rehabilitation, Decision dated March 23, 2019).

RESULTS

The results of our study showed a significant reduction in disease activity following the application of BT. Specifically, the DAS28 SE was statistically significantly lower ($p < 0.01$) after BT compared to before BT. The mean disease activity measured by DAS28 SE for patients in remission was 2.16 ± 0.32 before BT and 1.82 ± 0.45 after. For patients with low disease activity, the DAS28 SE was 3 ± 0.17 before BY and 2.38 ± 0.3 after. Finally, for patients with moderate disease activity, the DAS28 SE decreased from 4.43 ± 0.56 before to 3.51 ± 0.57 after BT (Table 1).

A comprasion of changes in DAS28SE values between groups showed that the greatest reduction in DAS28SE was in the group with moderate disease activity compared to the group with low activity and remission (III *vs.* I: 0.92 ± 0.28 *vs.* 0.34 ± 0.18, $p < 0.001$; III *vs.* II: 0.92 ± 0.28 *vs.* 0.62 ± 0.21, $p < 0.01$).

The results also showed that the Clinical Disease Activity Index (CDAI) was statistically significantly lower ($p < 0.01$) after BT compared to before BT across all patient groups: patients in remission (CDAI before BT 3.74 ± 1.48, after BT 2.37 ± 1.01), patients with low disease

activity (CDAI before BT 6.11 ± 1.49, after BT 3.39 ± 1.46), and patients with moderate disease activity (CDAI before BT 15.84 ± 4.47, after BT 8.94 ± 3.05) (Table 1). The greatest reduction in the CDAI index was recorded in the group with moderate disease activity (III *vs.* I: 6.9 ± 2.6 *vs.* 1.37 ± 1.23, $p < 0.001$; III *vs.* II:6.9 ± 2.6 *vs.* 2.72 ± 1.34, $p < 0.01$).

When it comes to general health status, based on the use of the visual analog scale (VAS), it was determined that there was an improvement in all observed groups of patients. The reduction in VAS parameter values was statistically significant ($p < 0.01$), (table 2). The change in VAS values was statistically significantly greater in the group of patients with moderate disease activity compared to the group with low activity and remission (III *vs.* I: 1.44 ± 0.6 *vs.* 0.45 ± 0.3, $p < 0.01$; III *vs.* II: 1.44 ± 0.6 *vs.* 0.81 ± 0.37, $p < 0.05$).

The study results also showed an improvement in functional ability after BT in all participants, regardless of the level of disease activity (moderate disease activity, low disease activity, and remission). Analysis of the data obtained from the HAQ questionnaire revealed a statistically significant reduction in HAQ scores after BT ($p < 0.01$). Specifically, the average HAQ value before BT for patients in remission was 0.59 ± 0.36, which decreased to 0.39 ± 0.25 after. For patients with low disease activity, the HAQ value before BT was 0.92 ± 0.29, which decreased to 0.55 ± 0.2 after, and there was also a reduction for patients with moderate disease activity (HAQ before BT 1.25 ± 0.33, after therapy 0.88 ± 0.27) (Table 2). By comparing the changes in HAQ questionnaire values before and after the application of BT among the groups, the results showed that the greatest change occurred in the group with moderate and low disease activity (III *vs.* I: 0.37 ± 0.21 *vs.* 0.2 ± 0.09, $p < 0.01$; III *vs.* II: 0.37 ± 0.21 *vs.* 0.37 ± 0.16, ns).

The application of BT had a favorable effect on changes in IL-6 cytokine levels. All three examined groups showed a reduction in IL-6 cytokine levels, with these changes being statistically significant only in patients with moderate disease activity ($p < 0.01$). The change in IL-6 cytokine levels in patients in remission after BT was 3.43 (before BT 17.68 ± 13.12, after BT 14.25 ± 10.88), in patients with low disease activity it was 9.99 (before BT 35.45 ± 31.17, after BT 25.46 ± 27.08), and in patients with moderate disease activity it was 14.94 (before BT 55.76 ± 43.13, after BT 40.82 ± 33.38) (Table 3). The results showed that the change in IL-6 values was statistically significantly greater in the moderate disease activity group compared to the low disease activity and remission groups (III *vs.* I: 14.94 ± 6.35 *vs.* 3.43 ± 0.2.95, $p < 0.001$, III *vs.* II: 14.94 ± 6.25 *vs.* 9.99 ± 4.38, $p < 0.01$).

The results of our study showed a positive effect of BT on depression in patients. Specifically, depression parameter values were statistically significantly lower ($p < 0.01$) after BT compared

to values before BT. The mean depression value measured by BDI was 2.89 ± 2.49 in patients in remission before BT and 1.99 ± 1.65 after. For patients with low disease activity, the BDI value was 5.33 ± 3.27 before BT and 3.02 ± 1.94 after. There was also a reduction in BDI values in patients with moderate disease activity, from 13.48 ± 6.11 before BT to 8.87 ± 3.84 after BT (Table 4). By comparing the change in BDI values among the groups, the greatest change was recorded in the moderate disease activity group (III *vs.* I: 4.61 ± 2.84 *vs.* 0.9 ± 0.65, $p < 0.001$; III *vs.* II: 4.61 ± 2.84 *vs.* 2.31 ± 1.23, $p < 0.01$).

The average fatigue value measured by the FACIT F questionnaire increased in all three examined groups after 3 weeks of BT, indicating that the application of BT had a favorable effect on the feeling of fatigue. The study results showed a statistically significant ($p < 0.01$) increase in the FACIT F parameter. The values of this parameter increased in patients in remission (FACIT F before BT 42.21 ± 6.36, after BT 46.37 ± 4.03), with low disease activity (FACIT F before BT 40 ± 6.05, after BT 45.56 ± 3.85), and in patients with moderate disease activity (FACIT F before BT 28.26 ± 5.07, after BT 36.81 ± 4.6) (Table 4). By comparing the change in FACIT-F values among the groups, the results showed that the change in FACIT-F values in the moderate disease activity group was statistically significantly greater compared to the low activity and remission groups (III *vs.* I: 8.55 ± 3.84 *vs.* 4.16 ± 2.95, $p < 0.01$; III *vs.* II: 8.55 ± 3.84 *vs.* 5.56 ± 2.93, $p < 0.01$).

DISCUSSION

BT, which includes thermal waters, mineral mud, and other natural factors such as salts and gases, is an important process in alleviating disease symptoms and improving the quality of life for patients with RA. It significantly improves the general condition of patients, including reducing pain, improving joint mobility, and decreasing inflammatory markers. Thermal waters used in BT are rich in minerals (sulfates, calcium, magnesium, sulfur, etc.), which can have anti-inflammatory effects and contribute to the reduction of RA symptoms [5, 8, 9, 10].

In a clinical sense, BT should be regarded like any other medication. It has its indications and contraindications, and besides the desired effects, it can also have side effects. Dosage is strictly individual, and its application depends on the stage and activity of the disease, previous treatment, and the general condition of the patient. Prior medication therapy is very important, as it brings the patient into the "thermal phase" which is suitable for the application of BT. The best results of this therapy can be achieved in the early stage of the disease and/or in remission,

while high disease activity is potentially a contraindication for the application of BT in RA. Additionally, when applying BT in the treatment of RA, the significance of psychotherapy and climatotherapy must also be considered as part of the complexity of treating this group of patients. The positive correlation between somatic improvement and the reduction of depression in patients with RA is well known. BT can have a positive impact on the psychological state of RA patients. The relaxing effects of thermal waters can lead to reduced stress levels and improved sleep quality, which is important given the often-present comorbid depression and insomnia in these patients [11, 12, 13].

In our study, we examined the impact of BT on the level of cytokine IL-6, disease activity, functional ability, fatigue, and depression in patients with RA who were hospitalized at the Niška Banja Institute for a 3-week rehabilitation program.

The thermomineral waters of Niška Banja are classified as homeothermal, oligomineral, earth-alkaline, and mildly radioactive radon waters, used in baths lasting from 15 to 20 minutes at temperatures up to 37°C, and applied to the body surface depending on the state of the cardiovascular system. The applied baths can lead to the normalization of synovial membrane permeability and influence the myogenic and metabolic regulation of blood flow to the synovial membrane, fibrous joint capsule, and muscles. On the other hand, similar positive effects can be expected from the radon contained in the peloid. It is prepared from radioactive bigra from the springs, having oligomineral, thermal, and radioactive effects, and is applied as compresses at temperatures from 40 to 45 degrees, with a procedure duration of 15 minutes. The application of these radon mineral baths and peloids at the Niška Banja Institute has a long-standing tradition in treating patients with RA. Experiences indicate favorable effects of BT in terms of reducing pain, subjective complaints, morning stiffness, and objective clinical and biohumoral parameters. However, it is important to note that the success of BT does not represent a cure but rather a single link in the complex treatment chain [11, 14, 15].

Based on our research, a significant improvement in the observed parameters was determined after the application of BT, which supports the thesis of the effectiveness of this therapeutic method in the treatment of RA. The results indicate a positive effect of this therapy on disease activity, functional ability, reduction of the inflammatory process, and reduction of fatigue and depression, which aligns with the findings of other studies on this topic [16–22].

Firstly, regarding the reduction of disease activity after the application of BT, as registered through the decrease in DAS28 SE and CDAI indices, it can result from several factors, as previously mentioned. Primarily, the thermal waters and minerals present in BT may have anti-

inflammatory effects, which can directly contribute to the reduction of pain and joint swelling. Secondly, the heat transferred through thermal waters can have multiple effects. On one hand, it can relax muscles, alleviate spasms, and reduce joint pain, while on the other hand, warm water can dilate blood vessels, improve blood and lymph flow, and help eliminate toxins and metabolic waste products [5, 8, 23].

All of the aforementioned factors can contribute to a greater or lesser extent to the reduction of disease activity, which in turn further enhances the quality of life.

In addition to reducing disease activity, as suggested by some authors and confirmed in our study, there is also an increase in functional ability. Specifically, there was a significant reduction in HAQ score values during a single treatment course [24, 25]. This suggests that BT is of great clinical importance as it can simultaneously reduce disease activity and increase patients' ability to perform daily activities without hindrance.

A particularly important finding from this study concerns the impact of BT on the level of cytokine IL-6, a key mediator of inflammation in RA, about which there is insufficient data in the professional literature. The study found that there was a significant reduction in IL-6 levels after BT, which was statistically significant. This may indicate that this type of therapy substantially contributes to reducing inflammatory processes at the molecular level or the reactivity of the immune system. It suggests that BT can modulate the immune response in patients with RA. Specifically, the warm water and relaxation associated with this therapy can reduce stress and anxiety levels in patients, which may indirectly affect the reduction of IL-6 production. This is very important, considering that stress is a significant factor that increases IL-6 levels through the activation of the neuroendocrine system [26, 27].

Finally, the study aimed to determine the impact of BT on feelings of fatigue and depression. The research found that BT leads to a reduction in fatigue and depression; the study results showed statistically significant changes in the values of the FACIT F and BDI parameters. This positive impact of BT on reducing fatigue and depression may primarily arise from the physiological effects of BT itself. The physical characteristics of mineral waters, such as temperature and mineral content, can contribute to muscle relaxation and pain reduction, which can indirectly improve mood and reduce stress, anxiety, and other symptoms of depression. Additionally, the mineral components of the water, such as magnesium, are known for their calming effects on the nervous system and can help regulate neurotransmitters associated with mood and fatigue [28, 29, 30].

CONCLUSION

BT, applied over three weeks in patients with RA, reduces the level of the pro-inflammatory cytokine interleukin-6, decreases disease activity, improves patients' functional ability, and reduces fatigue and depression in all RA patients, regardless of disease activity. The most pronounced anti-inflammatory effect of BT was observed in patients with moderate disease activity. Along with medication and physical therapy, BT is an important part of a comprehensive therapeutic approach for RA patients.

Conflict of interest: None declared.

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Table 1. DAS28SE and CDAI parameter values before and after balneotherapy

	Parameter	Before	After	p
Remission I	DAS28SE	2.16 ± 0.32	1.82 ± 0.45	0.002
	CDAI	3.74 ± 1.48	2.37 ± 1.01	0.002
LDA II	DAS28SE	3 ± 0.17	2.38 ± 0.3	0.002
	CDAI	6.11 ± 1.49	3.39 ± 1.46	0.002
MDA III	DAS28SE	4.43 ± 0.56	3.51 ± 0.57	0.001
	CDAI	15.84 ± 4.47	8.94 ± 3.05	0.001

LDA – low disease activity; MDA – moderate disease activity

Table 2. VAS and HAQ parameter values before and after balneotherapy

	Parameter	Before	After	p
Remission I	VAS	1.32 ± 0.48	0.87 ± 0.33	0.003
	HAQ	0.59 ± 0.36	0.39 ± 0.25	0.004
LDA II	VAS	1.89 ± 0.53	1.08 ± 0.35	0.002
	HAQ	0.92 ± 0.29	0.55 ± 0.2	0.002
MDA III	VAS	3.39 ± 0.6	1.95 ± 0.44	0.001
	HAQ	1.25 ± 0.33	0.88 ± 0.27	0.002

LDA – low disease activity; MDA – moderate disease activity; HAQ – Health Assessment Questionnaire; VAS – visual analog scale

Table 3. IL-6 parameter values before and after balneotherapy

	Before	After	p
Remission I	17.68 ± 13.12	14.25 ± 10.88	0.016
LDA II	35.45 ± 31.17	25.46 ± 27.08	0.031
MDA III	55.76 ± 43.13	40.82 ± 33.38	0.004

LDA – low disease activity; MDA – moderate disease activity

Table 4. BDI and FACITF parameter values before and after balneotherapy

	Parameter	Before	After	p
Remission I	BDI	2.89 ± 2.49	1.99 ± 1.65	0.008
	FACITF	42.21 ± 6.36	46.37 ± 4.03	0.008
LDA II	BDI	5.33 ± 3.27	3.02 ± 1.94	0.006
	FACITF	40 ± 6.05	45.56 ± 3.85	0.006
MDA III	BDI	13.48 ± 6.11	8.87 ± 3.84	0.003
	FACITF	28.26 ± 5.07	36.81 ± 4.6	0.002

LDA – low disease activity; MDA – moderate disease activity; BDI – Beck Depression Inventory; FACITF – Functional Assessment of Chronic Illness Therapy Fatigue Scale

