Water-Filtered Infrared A Irradiation in Axial Spondyloarthritis: Heat for Lower Back Pain

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Abbreviations

ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing spondylitis disease activity score
axSpA	axial Spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functionality index
BAS-G	Bath ankylosing spondylitis global score
bDMARD(s)	Biological disease modifying anti-rheumatic drug(s)
CG	Control group
DMARD(s)	Disease modifying anti-rheumatic drug(s)
EULAR	European league against rheumatism
IG	Intervention group
IL	Interleukin
MRCT	Multimodal rheumatologic complex treatment
NGF	Nerve growth factor
NRS	Numeric rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
nr-axSpA	non-radiographic axSpA
r-axSpA	radiographic axSpA
sl-wIRA	serial locally applied wIRA
TNF-α	Tumor necrosis factor α

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20.1 Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease mainly affecting the axial skeleton [1] with a prevalence of 9–30 per 10,000 in the general population, and an incidence of about 3.1 per 100,000/year [2, 3]. Although patients with axSpA typically present with chronic back pain and stiffness of the pelvis and lower back, any part of the spine and even the peripheral joints can be affected [1]. AxSpA leads to an increased morbidity and mortality, and affected patients often experience a loss of function as most patients develop structural changes of the axial skeleton at some point in their lives [1, 2]. The term "axSpA" thereby includes patients who have already developed structural and radiologically assessable damage (radiographic axSpA, r-axSpA, formerly called ankylosing spondylitis) and patients without such damage (non-radiographic axSpA, nr-axSpA) [1]. Since axSpA is a chronic, non-curable disease with potential for a severe disease progression, lifelong pharmacological therapy is common [1, 4]. Treatments aim to maximize health-related quality of life by controlling symptoms and inflammation, preventing progressive structural damage, preserving/normalizing function and social life [4]. Regarding pharmacological treatment, patients with active axSpA are initially treated with non-steroidal anti-inflammatory drugs (NSAIDs). For patients with inadequate responses to NSAIDs, biological disease modifying anti-rheumatic drug (bDMARD) therapy can be started [1, 4]. Innovations and advances in disease modifying anti-rheumatic drugs (DMARDs) over the last two decades have led to the so-called "biologic era" which has delivered effective pharmacological therapy for rheumatic diseases, and especially for axSpA [5]. Nonetheless, current data from the German Collaborative Arthritis Centers show that a significant proportion of patients with axSpA continue to have moderate to high disease activity despite these pharmacological treatments [6]. Concerning trends in outcomes for axSpA, two aspects can be considered. For one, the proportion of patients with good functional status has increased from 36% in 2000 to 49% in 2012 in Germany. On the other side, more than 50% of patients with axSpA continue to experience at least a limited functional status [7]. In addition, periods of flares (clinical worsening) and remission are common for inflammatory rheumatic diseases, in general, and are frequent in axSpA [8]. The term "flare" is poorly defined and often interpreted differently by rheumatologists and patients and has not been well investigated [9]. However, a definition for a clinically relevant exacerbation in axSpA which has recently been established for use in clinical trials based on the Ankylosing Spondylitis Disease Activity Score (ASDAS) [8] may encourage further research and promote reproducibility. Nevertheless, flares seem to occur quite frequently. About 74% of patients primarily treated with NSAIDs [10] and 25% of patients primarily treated with bDMARDs report at least one flare [11], both within a 3-month-period. Although not always long-lasting (>3 days), flares are related to a decrease in physical activity and well-being [11]. In addition, as flares remain quite common even under (stable) bDMARD-therapy [11], not every flare can lead to a change in pharmacological treatment. Therefore,

recommendations by the Assessment of SpondyloArthritis International Society (ASAS)/European League Against Rheumatism (EULAR) for the management of axSpA clearly recommend a combination of non-pharmacological and pharmacological treatment for optimal management [4]. In non-pharmacological treatment, physical therapy (PT) interventions play a central role in the treatment algorithm of axSpA [12, 13].

The use of hyperthermia in physical medicine, in particular in axSpA in the form of whole-body hyperthermia (WBH) applications, such as mud baths, low-dose radon exposure in combination with WHB, overheating baths, and water-filtered infrared A irradiation (wIRA-WBH), have been shown to reduce pain and disease activity [14–18]. Additionally, the use of WBH in treating axSpA has an effect on pro- and anti-inflammatory cytokines [17–19].

wIRA is a special form of infrared irradiation in the range of 780–1400 nm with high tissue penetration and low thermal load on the skin surface, which is easy to apply and contact-free [20]. wIRA has both temperature-dependent and non-thermal effects, the latter not associated with relevant thermal energy transfer and/or relevant temperature changes [20].

Based on the positive effects of wIRA-WBH in axSpA [16], we have used locoregional wIRA (serial locally applied wIRA, or sl-wIRA) on the back to achieve positive effects in axSpA. Therefore, we investigated the effects of sl-wIRA on (1) pain levels, (2) disease activity and functionality, (3) levels of molecular markers of disease activity, and (4) dosage of non-steroidal anti-inflammatory drug (NSAID) [21].

20.2 Trial Design

To evaluate the effects of sl-wIRA on the back of patients with axSpA, we conducted a prospective monocentric randomized controlled trial with an assessor-blinded parallel group design. Participants were randomly assigned in a 1:1 ratio to one of two treatment groups using simple randomization procedures (computerized random numbers). All patients aged 18–80 with axSpA fulfilling the ASAS classification criteria [22] receiving stable NSAID therapy or stable non-pharmacological therapy for at least 4 weeks prior to treatment with moderate disease activity defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of four to seven receiving an inpatient 7-day multimodal rheumatologic complex treatment (MRCT) were eligible [21].

Both the intervention group (IG) as well as the control group (CG) received a 7-day MRCT in an inpatient setting. MRCT is a specific concept of German inpatient care which focuses on physical therapy in addition to occupational therapy, behavioral therapy, and patient education for patients with rheumatic diseases suffering from exacerbated pain and functional impairment [23, 24]. The 7-day MRCT delivered 11 h of different MRCT modalities to each patient, with every modality being applied for a duration of 30 min. In total, 22 applications

(7× physiotherapy, 3× pain processing strategies, 7× classic massage, 3× electrotherapy, 2× patient disease training program) were delivered to each patient. In addition, the IG received standardized sl-wIRA treatment of the back (2 applications daily [morning/afternoon] for 30 min for 6 days totaling in 12 applications) using a Hydrosun®750 radiator. Irradiation was applied vertically in an irradiation field of 25 cm encompassing the lower thoracic and lumbar area in prone position.

20.3 Trial Outcomes

A total of 71 patients were recruited and completed the trial; all of them could be analyzed (35 patients in the IC and 36 patients in the CG) [21]. The mean age was 51 years with a mean disease duration of 5.9 years. Disease activity, disease-related functional capacity, and disability between the groups were comparable (Table 20.1).

20.3.1 Effects of wIRA on Lower Back Pain

wIRA treatment led to a significant between-group difference in pain after the intervention (95% confidence interval (CI), −2.8 to −0.8, $p = 0.006$). The IG experienced a significant improvement of −1.6 ± 0.3 (mean ± standard error [SE]) from baseline to after the intervention (95% CI, −2.2 to −0.9, $p < 0.001$), whereas the control group experienced a nominal improvement of −0.3 ± 0.2 (95% CI, −0.8 to 0.1, $p = 0.088$) (Table 20.2). Furthermore, an onset of a significant analgesic effect of sl-wIRA treatment could be seen immediately after two applications, on the evening of day 1 in the IG, with a significant between-group difference. Subsequently, significant differences in the IG (before and after treatment) and between groups were found in each comparison. Analgesic effects did not vanish after night rest at day 2 and cumulatively increased as pain values progressively decreased at each reading (Table 20.3).

Table 20.1 Patient and disease characteristics at baseline (values are means ± SD)

	Intervention group ($n = 36$)	Control group ($n = 35$)
Age (years)	51.7 ± 10.8	51.1 ± 10.2
Disease duration (years)	5.8 ± 4.2	6.1 ± 4.5
Sex (female/male)	24 (66%) / 12 (34%)	24 (68%) / 11 (32%)
HLA-B27 positivity	30 (83%)	32 (91%)
BASDAI	4.8 ± 1.8	4.6 ± 2.1
BASFI	4.1 ± 2.2	4.5 ± 2.6
NSAIDs	34 (94%)	32 (91%)

BASDAI bath ankylosing spondylitis disease activity index, *BASFI* bath ankylosing spondylitis functional index, *NSAIDs* non-steroidal anti-inflammatory drugs.

Table 20.2 Change in pain levels (Numeric Rating Scala, or NRS) between baseline and after-trial completion. Mean ± standard deviation and [min; max] are displayed for values at certain time points. Differences are displayed using mean ± standard error

	Baseline	After intervention	Difference	*p*-value (95% CI)
IG ($n = 36$)	4.1 ± 2.4 [0;8]	2.6 ± 2.0 [0;7]	−1.6 ± 0.3	< 0.001 (−2.2 to −0.9)
CG ($n = 35$)	4.8 ± 2.5 [1;9]	4.4 ± 2.2 [1;8]	−0.3 ± 0.2	0.088 (−0.8 to 0.1)
p-value (95% CI)		0.006 (−2.8 to −0.8)		

IG intervention group, *CG* control group, *CI* confidence interval.

Table 20.3 Onset and development of sl-wIRA effects on pain levels. Pain levels (NRS) were assessed at days 1, 2, 5 and 6 before and after treatment (2 applications of wIRA on the lower back per day, 12 applications in total). Mean ± standard deviation and [min;max] are displayed

	Intervention group ($n = 36$)	Control group ($n = 35$)	*p*-value**
Baseline (day 1 before treatment)	4.1 ± 2.4 [0;8]	4.8 ± 2.5 [1;9]	
Day 1 after treatment	3.5 ± 2.2 [0;8]	4.7 ± 2.3 [1;9]	
Difference (*p*-value*)	−0.7 ± 1.2 [−3;4] ($p < 0.001$)	−0.1 ± 0.6 [−1;1] ($p < 0.405$)	$p < 0.001$
Day 2 before treatment	3.9 ± 2.2 [0;8]	4.8 ± 2.2 [1;8]	
Day 2 after treatment	3.3 ± 2.2 [0;7]	4.8 ± 2.2 [1;9]	
Difference (*p*-value*)	−0.6 ± 1.1 [−3;2] ($p < 0.005$)	−0.0 ± 0.7 [−1;1] (n.s.)	$p < 0.007$
Day 5 before treatment	3.6 ± 2.3 [0;8]	4.8 ± 2.1 [1;8]	
Day after treatment	3.1 ± 2.2 [0;7]	4.5 ± 2.1 [1;8]	
Difference (*p*-value*)	−0.5 ± 0.9 [−3;1] ($p = 0.003$)	−0.3 ± 0.9 [−2;2] ($p = 0.032$)	(n.s.)
Day 6 before treatment	3.3 ± 2.4 [0;8]	4.6 ± 2.3 [1;9]	
Day 6 after treatment (trial completion)	2.6 ± 2.0 [0;7]	4.4 ± 2.2 [1;8]	
Difference (*p*-value*)	−0.7 ± 1.0 [−3;1] ($p < 0.0005$)	−0.2 ± 0.6 [−1;1] (n.s.)	$p < 0.023$

**p*-values of the Wilcoxon test for intra-group differences to compare two related samples.
***p*-values of the Mann–Whitney test for between-group differences in differences between both treatment arms.

20.3.2 Effects of wIRA on Disease Activity and Functional Impairment in axSpA Patients

Both the IG and the CG experienced a significant reduction of disease activity, as measured by BASDAI, whereas only patients in the IG experienced a significant improvement in functionality, as measured by BASFI. There was no significant difference between the IG and the CG in BASFI nor BASDAI after trial completion. BAS-G, which reflects the effect of axSpA on the patient's well-being, was significantly changed in the IG with a mean difference (±SD) of −0.5 ± 1.1 ($p = 0.006$), whereas a significant difference was just missed in the CG ($p = 0.051$) (Tables 20.4 and 20.5).

Table 20.4 Change in functionality and disease activity between baseline and after-trial completion

		T0 (baseline)	T1 (after trial completion)	Difference	*p*-value (Wilcoxon test)
BASFI	IG (n = 36)	4.1 ± 2.2	3.7 ± 2.2	−0.4 ± 0.9	0.004
	CG (*n* = 35)	4.5 ± 2.6	4.1 ± 2.5	−0.4 ± 1.3	0.055
BASDAI	IG (*n* = 36)	4.8 ± 1.8	4.2 ± 1.8	−0.6 ± 1.1	0.004
	CG (*n* = 35)	4.6 ± 2.1	4.1 ± 2.3	−0.5 ± 1.0	0.007

BASDAI bath ankylosing spondylitis disease activity index, *BASFI* bath ankylosing spondylitis functionality index, *IG* intervention group, *CG* control group, *axSpA* axial spondyloarthritis.
Functionality was measured using BASFI, disease activity was measured using BASDAI. Mean ± standard deviation and [min; max] is displayed. BASDAI is a validated tool for assessing disease activity of axSpA and contains six questions determining fatigue, back and joint pain, pain at the tendons and morning stiffness. The BASDAI ranges from 0 = no disease activity to 10 = maximal disease activity with a score of >4 indicating active disease. BASFI is a validated tool to determine functional restrictions due to axSpA using 10 questions related to everyday activities with a BASFI score of 0 indicating no restriction and a score of 10 indicating poorest functionality.

Table 20.5 Course of BAS-G. Mean ± standard deviation and [min;max] are displayed for values at certain time points. Differences are displayed using mean ± standard error

	T0 (baseline)	T1 (after trial completion)	Difference	p-value (Wilcoxon test)
IG (*n* = 36)	5.8 ± 2.1 [0.0; 10.0]	5.3 ± 2.0 [0.0; 8.5]	−0.5 ± 0.18 [−3.0; 2.0]	0.006 (−0.89 to −0.16)
CG (*n* = 35)	5.3 ± 2.7 [2.0; 12.0]	4.4 ± 1.8 [1.0; 8.0]	−1.0 ± 0.56 [−9.0; 3.0]	0.051 (−2.4 to −0.12)
p-value			(n.s.) (−0.02 to 1.8)	

20.3.3 Effects of wIRA on Pro- and Anti-Inflammatory Cytokines

TNF-α levels were only significantly reduced between baseline and trial completion in the IG, and there was a significant difference in measured TNF-α levels between the IG and CG. There were no physiologically relevant or statistically significant changes in serum levels of pro-inflammatory (IL-1 and IL-6) and anti-inflammatory cytokines (IL-10) either within or between the two groups.

20.3.4 Effects of wIRA on Concomitant Use of Analgesics

Twenty-six (76%) of patients in the IG decreased their NSAID intake after trial completion (at day 7). Out of these 26, 10 (29.4%) opted to completely stop NSAID usage at day 7. In contrast, only one patient of the CG decreased NSAID intake.

20.3.5 Adverse Effects

No adverse or severe adverse events were recorded in both groups.

20.4 Discussion

To the best of our knowledge, this is the first randomized controlled trial to investigate the effects of sl-wIRA on the progressive onset and development of pain and a range of other clinical parameters and cytokine levels as molecular markers of inflammatory processes in patients with axSpA [21].

20.4.1 Discussion of Study Data

sl-wIRA as part of a 7-day MRCT significantly reduced pain levels and disease activity and improved functionality. TNF-α levels significantly decreased. Compared to the control group, auxiliary sl-wIRA led to significant benefits in terms of pain reduction ($p = 0.006$). Whereas the control group showed a non-significant pain reduction of −0.3 (mean), the intervention group experienced a change in pain levels of −1.6 (mean) ($p < 0.0005$) in this 6-day-trial.

wIRA application is a rapid acting and effective method to significantly reduce pain in axSpA. The significant analgesic effect is already measurable after only two applications and increases with further treatment. The treatment group showed a significant improvement in pain and BAS-G in comparison to the non-treatment group with only six treatment days involving two applications per day. Baseline BASDAI (mean: 4.8 IG and 4.6 CG), BASFI (mean: 4.1 IG and 4.5 CG), and pain levels (mean: 4.1 IG and 4.8 CG) were elevated as only patients with active axSpA were eligible for this trial. Since flares, although poorly defined outside of clinical trials [9], are common in axSpA patients treated primarily with bDMARDs [11] and in patients treated with NSAIDs [10], sl-wIRA treatment seems to be a good alternative to changing pharmacological therapy. A complementary and easy-to-apply wIRA treatment that can be performed in an outpatient setting seems to be suitable for initial treatment with a focus on a quick pain reduction, especially when flare duration is variable. In addition, wIRA can be easily "dosed" by varying (1) the irradiation distance and thus the irradiance and treatment field as well as (2) the duration of the irradiation. Pain reduction leads to improved physiotherapeutic mobilization, ultimately resulting in an improvement in quality of life. In addition, 76% of patients in the IG decreased their dosages of NSAIDs after completion of the trial to varying extent, with some even stopping NSAID therapy. Although it cannot be stated how long patients continued with the reduced dosage, potential side effects of NSAID could be minimized for at least 1 day.

20.4.2 Additional Pathophysiological Aspects

The rapid onset of pain relief lasting for up to 6 days is based on thermal and non-thermal effects. The *thermal effect* results from increased blood flow and improved elimination of accumulated metabolites, such as pain mediators, as well as an increased metabolic rate due to the increased tissue temperature. The *non-thermal effect* results from a direct effect on cellular structures and cells as well as an altered

skeletal muscle tension with consecutive pain reduction [20]. The pro-inflammatory cytokines IL-1ß, IL-6, and TNF-α play a central role in both the inflammatory process and the inflammation induced pain [25]. Local nociceptive reactions involve peripheral polymodal nociceptors expressing glycoprotein 130 (gp 130) which plays a role in cytokine signaling [26, 27]. Proinflammatory cytokines also induce systemic effects. For example, IL-6 and PGE_2 are regulators of the hepatic synthesis of C-reactive protein (CRP) [25]. A distinction between hyperalgesic mediators, e.g., prostaglandins, IL-1, -6, -8, TNF-α, and analgesic mediators, such as IL-1, -4, -10, -13, needs to be made. Cytokine interactions are prominent during inflammatory pain. In the early stage, hyperalgesic mediators dominate, whereas at the same time analgesically active cytokines are induced by the immune system [26, 27]. A drop of these mediators may reduce depolarization of the peripheral nociceptors due to reduced input from ascending neurons in the cortical pain matrix, and therefore enhance a consecutive decrease in pain sensation.

During inflammation, the nociceptors of the joints are sensitized to mechanical stimuli and usually mute sensory C-fibers become mechanosensitive [28]. A decrease in inflammatory mediators could thus influence this process.

Proinflammatory cytokines induce the production of nerve growth factor (NGF) [28] which activates and sensitizes tropomysin receptor kinase (TrkA)-positive sensitive neurons to mechanical, chemical, and thermal stimuli and changes the properties of Aδ fibers (sensitization). A blockade of NGF-TrkA causes a reduction of skeletal pain [28]. It is possible that a decrease of the proinflammatory cytokines reduces the NGF production with consecutive desensitization of TrkA-positive-sensitive neurons. It might therefore be that the significant reduction ($p = 0.001$) of TNF-α in the intervention group from (mean) 8.8 pg/mL (baseline) to 5.8 pg/mL (after-trial completion) with a significant difference between the IG and the CG ($p = 0.01$) is of importance, even though no significant changes in the cytokines IL-1, -6, and -10 after sl-wIRA treatments for 6 days were detected.

The change in TNF-α levels in the intervention group could possibly explain the profound effect of the intervention on pain in this study. In a model of knee inflammation for example, reduced TNF-α levels have been shown to have antinociceptive effects [26]. These effects resulted from a neuronal site of action rather than from a reduction of inflammation. As the effects on TNF-α appeared only in the intervention group, they are probably related to sl-wIRA treatment. In the context of this study, we consider the temperature-dependent effects of wIRA to be particularly important. In addition, previous studies have shown whole-body hyperthermia [14, 15, 17] and whole-body wIRA hyperthermia [16, 19] to influence levels of pro- and anti-inflammatory cytokines, whereas whole-body wIRA-HT also induced changes in TNF-α levels [16, 19].

In this study, there was a significant reduction in disease activity, as measured by BASDAI, in both the IG and CG, whereas only the IG showed a significant increase in functionality capacity, as measured by BASFI. However, there were no significant differences between both groups. Since only patients with axSpA on NSAID therapy with a BASDAI between 4 and 7 correlating to active disease (moderate to high disease activity) were eligible to participate, we considered it unethical to test

against placebo without any additional active treatment in addition to baseline NSAID therapy. Therefore, all patients received a 7-day MRCT, which provided each patient with a high volume (22 units) of physical therapy modalities and were shown to be effective in treating axSpA in a 14-day program [24]. While this choice was for the benefit of the patient and may have led to no dropouts in this trial, it may have influenced outcomes in these secondary parameters of disease activity (BASDAI) and functionality (BASFI). The more so as the trial period only lasted 7 days, and BASDAI and BASFI were designed as disease-specific outcome measures to assess differences over a longer period of time and are normally assessed in routine care once every 12 weeks.

Regarding non-pharmacological treatment in axSpA, although physical therapy interventions play a central role [4], its potential is often not exploited in everyday practice [6]. In this study, eligibility criteria similar to those used in randomized controlled trials for pharmacological treatments were used (BASDAI >4 under NSAID therapy and DMARD naïve) [29]. It could be shown that an enhanced additive physical therapy reduced pain and disease activity and improved physical function. Therefore, additive and or enhanced physical therapy should be considered for every patient with axSpA who has responded poorly pharmacological treatment and can, in some cases at least, be preferred to pharmacological therapy escalation.

20.5 Summary

This sl-wIRA trial shows that locoregional applied hyperthermia in patients with axSpA is an effective treatment option to reduce pain in axSpA with rapid onset and a cumulative beneficial effect with each use as shown over 6 days. Moreover, the pain reduction thus achieved leads to reduced pain medication, beneficial effects on inflammation, disease activity, and functional capacity. Therefore, it could be a valid option to effectively treat patients with axSpA in addition to pharmacological therapy.

References

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017;390:73–84.
2. Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. Nat Rev Dis Primers. 2015;1:15013.
3. Wang R, Ward MM. Epidemiology of axial spondyloarthritis: an update. Curr Opin Rheumatol. 2018;30:137–43.
4. Van Der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978–91.
5. Godfrin-Valnet M, Prati C, Puyraveau M, et al. Evaluation of spondylarthritis activity by patients and physicians: ASDAS, BASDAI, PASS, and flares in 200 patients. J Bone Spine. 2013;80:393–8.
6. Albrecht K, Huscher D. Verordnen wir ausreichend Physikalische Medizin? Aktuelle Daten aus der Kerndokumentation der Arbeitsgemeinschaft Regionaler Kooperativer Rheumazentren. Akt Rheumatol. 2017;42:118–21.

7. Huscher D, Thiele K, Rudwaleit M, et al. Trends in treatment and outcomes of ankylosing spondylitis in outpatient rheumatological care in Germany between 2000 and 2012. RMD Open. 2015;1:e000033.
8. Molto A, Gossec L, Meghnathi B, et al. An assessment in SpondyloArthritis International Society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. Ann Rheum Dis. 2018;77:124–7.
9. Keat ACS. Axial spondyloarthritis flares - whatever they are. J Rheumatol. 2017;44:401–3.
10. Jacquemin C, Maksymowych WP, Boonen A, Gossec L. Patient-reported flares in ankylosing spondylitis: a cross-sectional analysis of 234 patients. J Rheumatol. 2017;44:425–30.
11. Jacquemin C, Molto A, Servy H, et al. Flares assessed weekly in patients with rheumatoid arthritis or axial spondyloarthritis and relationship with physical activity measured using a connected activity tracker: a 3-month study. RMD Open. 2017;3:e000434.
12. Dagfinrud H, Hagen KB, Kvien TK. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev. 2008;1:CD002822. https://doi.org/10.1002/14651858.CD002822.pub3.
13. Perrotta FM, Musto A, Lubrano E. New insights in physical therapy and rehabilitation in axial Spondyloarthritis: a review. Rheumatol Ther. 2019;6:479–86.
14. Dischereit G, Goronzy JE, Müller-Ladner U, et al. Effects of serial mud baths on inflammatory rheumatic and degenerative diseases. Z Rheumatol. 2019;78:143–54.
15. Dischereit G, Neumann N, Müller-Ladner U, et al. The impact of serial low-dose radon hyperthermia exposure on pain, disease activity and pivotal cytokines of bone metabolism in ankylosing spondylitis – a prospective study. Akt Rheumatol. 2014;39:304–9.
16. Lange U, Müller-Ladner U, Dischereit G. Effectiveness of whole-body hyperthermia by mild water-filtered infrared A radiation in ankylosing spondylitis – a controlled, randomised. Prospective Study Akt Rheumatol. 2017;42:122–8.
17. Moder A, Hufnagl C, Lind-Albrecht G, et al. Effect of combined low-dose radon-and hyperthermia treatment (LDRnHT) of patients with ankylosing spondylitis on serum levels of cytokines and bone metabolism markers: a pilot study. Int J Low Radiat. 2010;7:423–35.
18. Lange U, Dischereit G. Effects of different iterative whole-body hyperthermia on pain and cytokines in rheumatic diseases: a current review. Akt Rheumatol. 2018;43:479–83.
19. Tarner IH, Müller-Ladner U, Uhlemann C, Lange U. The effect of mild whole-body hyperthermia on systemic levels of TNF-alpha, IL-1beta, and IL-6 in patients with ankylosing spondylitis. Clin Rheumatol. 2009;28:397–402.
20. Vaupel P, Krüger W, editors. Wärmetherapie mit wassergefilterter Infrarot-A-Strahlung. Stuttgart: Hippokrates; 1992.
21. Klemm P, Eichelmann M, Aykara I, et al. Serial locally applied water-filtered infrared A radiation in axial spondyloarthritis – a randomized controlled trial. Int J Hyperthermia. 2020;37:965–70.
22. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of assessment of SpondyloArthritis international society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777–83.
23. Klemm P, Hudowenz O, Asendorf T, et al. Multimodale rheumatologische Komplexbehandlung bei rheumatoider Arthritis – eine monozentrische Retrospektivanalyse. Z Rheumatol. 2019;78:136–42.
24. Klemm P, Hudowenz O, Asendorf T, et al. Evaluation of a special concept of physical therapy in spondyloarthritis: German multimodal rheumatologic complex treatment for spondyloarthritis. Clin Rheumatol. 2020;39:1513–20.
25. Rittner HL, Brack A, Stein C. Pain and the immune system: friend or foe? Anaesthesist. 2002;51:351–8.
26. Boettger MK, Hensellek S, Richter F, et al. Antinociceptive effects of tumor necrosis factor α neutralization in a rat model of antigen-induced arthritis: evidence of a neuronal target. Arthritis Rheum. 2008;58:2368–78.
27. Kulkarni B, Bentley DE, Elliott R, et al. Arthritic pain is processed in brain areas concerned with emotions and fear. Arthritis Rheum. 2007;56:1345–54.

28. Peuker E. Neuroanatomische Grundlagen des Gelenkschmerzes. Akt. Rheumatology. 2016;41:300–5.
29. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;72:815–22.