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Authors: Rafał Wojciechowski, Hanna Styczyńska, Daniel Jeka

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Assessment of quality of life and clinical status in active ankylosing spondylitis patients treated with biologics and physical therapy

Short title: Quality of life in ankylosing spondylitis patients

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Rafał Wojciechowski¹, Hanna Styczyńska², Daniel Jeka³

¹*Clinical Department of Rheumatology and Connective Tissue Diseases, University Hospital No. 2, Bydgoszcz, Poland*

²*J. Biziel University Hospital No. 2 in Bydgoszcz, Bydgoszcz, Poland*

³*Clinical Innovative Therapies, Toruń, Poland*

Address for correspondence: Clinical Department of Rheumatology and Connective Tissue Diseases, University Hospital No. 2, Bydgoszcz, Poland; email: praktykalekarska@gmail.com

Abstract

Background: According to the current 2009 Assessment in SpondyloArthritis international Society (ASAS) classification criteria, ankylosing spondylitis (AS) is classified as radiographic axial inflammatory spondyloarthropathy. AS is a chronic, progressive inflammatory disease involving primarily the spine and sacroiliac joints, less commonly the peripheral joints, tendinous attachments and internal organs. According to current ASAS and European Alliance of Associations for Rheumatology (EULAR) recommendations, optimal treatment of AS patients needs a combination of pharmacotherapy and non-pharmacological treatment, based on education and rehabilitation treatment. Modern pharmacotherapy for AS, based on anticytokine therapy (biologics), significantly reduces the clinical activity of the disease, reduces active inflammation and inhibits radiographic progression. The aim of this study is to evaluate the effect of physical therapy on functional status, disease activity and quality of life in AS patients treated with biologics.

Material and methods: The study included fifty active AS patients treated with biologics, who were randomly allocated to two groups. Group I patients, in addition to treatment with a tumor necrosis factor alpha (TNF- α) inhibitor, received a course of physical therapy twice with a 6-month interval, which consisted of hydro-air massage and rehabilitation exercises. Group II patients were treated with a TNF- α inhibitor only. In both groups, the study lasted 10

months. At follow-up visits, all participants underwent a physical examination, laboratory tests and the following questionnaire-based studies: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Short Form Health Survey (SF-36) v.2.

Results: The applied physical therapy programme did not improve physical performance in the patients studied. There was no improvement in any of the physical parameters studied. Therefore, the functional status did not improve and disease activity did not decrease in the patients studied. However, some domains from the quality-of-life assessment improved.

Conclusions: Physical therapy and education should be the primary form of non-pharmacological treatment in AS patients treated with biologics.

Key words: ankylosing spondylitis; biological therapies; rehabilitation

Introduction

According to the current 2009 Assessment in Spondyloarthritis International Society (ASAS) classification criteria, ankylosing spondylitis (AS) is classified as an axial inflammatory spondyloarthropathy. This chronic, progressive inflammatory disease of the musculoskeletal system with as yet unexplained aetiology is marked by sacroiliitis, spondylarthritis and inflammation of the spinal ligaments and periarticular tissues. The leading clinical manifestation of AS is inflammatory back pain (IBP) and the inflammatory process results in progressive spinal stiffness and disability [1–5]. The diagnosis of AS is based on the 1984 modified New York criteria [6]. According to the new terminology proposed by ASAS — ankylosing spondylitis is the radiographic form of axial inflammatory spondyloarthropathy (r-axSpA, radiographic axial spondyloarthropathy). The diagnosis of AS can be made based on the 2009 ASAS classification criteria for axial spondyloarthropathy in all patients before the age of 45 with chronic back pain of an inflammatory nature, who are found to have bilateral sacroiliitis \geq grade 2 or unilateral sacroiliitis \geq grade 3 on SKB X-ray, and when at least 1 clinical criterion is simultaneously met, e.g. recurrent IBP [7-9].

According to the 2010 recommendations of ASAS and the European Alliance of Associations for Rheumatology (EULAR), optimal treatment of an AS patient needs a combination of pharmacological and non-pharmacological approaches underpinned by education and regular physical exercises [10].

Educational programmes on behaviours of daily living have a significant impact on reducing fatigue, morning stiffness, improving joint protection and scores on the Activities of Daily

Living (ADL) scale. Direct contact between the educator and the patient is more effective than conveying information through short information booklets [11]. Such a role can be played by a physiotherapist, whose individual cooperation with the patient also involves advice on how to move, how to adopt appropriate resting positions and how to choose the most appropriate sport that the patient can do recreationally [12].

Patients who know a lot about their disease, know how to manage it, can control it better, have fewer complaints and are more fit [13].

Physical therapy, with a particular focus on kinesiotherapy, is the second component of non-pharmacological treatment for AS according to ASAS/EULAR recommendations. In recent years in the scientific literature, the terms rehabilitation and physical therapy have been used by researchers interchangeably, with some simplification. It should be noted that rehabilitation is a much broader concept and is defined as a comprehensive and multidimensional activity (organisational, therapeutic, psychological, technical, educational, social) aimed at achieving the highest possible level of functioning, quality of life (QoL) and social integration of people with disabilities [14]. On the other hand, physical therapy is a therapeutic method that aims to develop, maintain or restore movement and fitness of patients to the full or best possible range [15]. The most important branches of physical therapy are kinesiotherapy, physical therapy, manual therapy, therapeutic massage, hydrotherapy, ergotherapy and balneotherapy. Patients with AS should receive an individualised rehabilitation programme that takes into account disease activity and severity [16]. In inflammatory musculoskeletal diseases, it is crucial that proper preventive measures – aimed at preventing contractures and deformities of affected joints – are implemented from the diagnosis of the disease and continued throughout its course. Later, at a more advanced stage of the disease, the aim of rehabilitation is to improve the functional performance of the musculoskeletal system, develop correct compensatory mechanisms and reduce deformities [16, 17].

Aim

This study aims to:

- evaluate the effect of applied physical therapy on disease activity;
- evaluate the effect of applied physical therapy on functional status;
- evaluate the effect of applied physical therapy on quality of life.

Material and methods

The study included fifty AS patients according to the modified New York criteria, who – due to high disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity

Index (BASDAI) ≥ 4 , despite the use of at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) at maximum or tolerated doses for the period required by the inclusion criteria for the NHF (NFZ) therapeutic programme — started treatment with TNF- α inhibitors and achieved partial improvement. Patients included in the study were randomly allocated to the treatment or control group in a 1:1 ratio. Randomisation was simple: a list of numbers ranked in random order was used, with each successive patient receiving another number from the list. Patients with allocated even numbers formed group I, while those with odd numbers formed group II. The study was a randomised, controlled and prospective clinical trial.

All patients were evaluated based on:

- Ott sign, Schober’s test, toe-to-floor distance, occiput-to-wall distance (OWD), thoracic expansion test;
- BASDAI — disease activity;
- Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaire — functional status;
- Medical Outcome Study (MOS) *Short Form Health Survey* (SF-36) v2 — quality of life.

Additional examinations were also performed and the following were determined: human leukocyte antigen B27 (HLA B-27), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, full blood count, alkaline phosphatase, gel electrophoresis of proteins and general urinalysis.

Testing scheme

The study of patients was conducted according to the design in Table 1 and lasted 41 weeks.

Table 1. Study design

Study design	Group I	Group II
Visit 0 (first week) — initial visit, qualification for study, randomisation	Initial visit Education Physical therapy session I: hydro-air massage and kinesiotherapy in the Rehabilitation Department, 10x, (2 x 5 days per week) (first and second week)	Initial visit Education Instruction and recommendation of exercises at home Exercises at home
1 st visit (third week)	Follow-up examination after completion of the first physical therapy session	Examination after 2 weeks of exercises at home

	Instruction and recommendation of exercises at home Education.	Recommendation to continue exercises at home Education.
2 nd visit (fifteenth week)	Follow-up examination Recommendation to continue exercises at home Education	Follow-up examination Recommendation to continue exercises at home Education
3 rd visit (twenty-seventh week)	Follow-up examination Education Physical therapy session II: hydro-air massage and kinesiotherapy in the Rehabilitation Department, 10x, (2 x 5 days per week) (twenty-seventh and twenty-eighth week)	Follow-up examination Recommendation to continue exercises at home Education Exercises at home
4 th visit (twenty-ninth week)	Follow-up examination after completion of the second physical therapy session Recommendation to continue exercises at home Education	Follow-up examination Recommendation to continue exercises at home Education
5 th visit (forty-first week)	Follow-up examination Education	Follow-up examination Education

Physical therapy provided in group I

Patients included in the treatment group received physical therapy twice during the study. These sessions took place after visits 0 and 3. One session of physical therapy lasted 10 days (2 x 5 working days). It included a 20-minute full-body hydro-air massage and at least one hour of kinesiotherapy.

Hydro-air massage is a very good treatment to prepare patients for exercises. It has an analgesic, relaxing effect. In addition, it relaxes and improves the mood. It was assumed that for AS patients, it would be a good introduction to planned kinesiotherapy. In a relatively short period of time, a multi-location effect can be achieved. After the massage, patients benefited from kinesiotherapy which consisted of a variety of exercises. Most of these were exercises in the full possible ranges of movement (spine, hip joints, knee joints, shoulder girdle) including weight-bearing and full suspension exercises. Active breathing exercises, breathing exercises with resistance using Thera-Band tapes were used. Exercises to strengthen the muscular strength of the gluteal, back and abdominal muscles also played an important role. During exercises led by experienced physiotherapists, special attention was paid to postural control and patients were given answers to questions they had about exercises at home and their lifestyle. Despite a general exercise regimen prepared for AS patients, each time kinesiotherapy was individual, tailored to each patient's needs and abilities.

Statistical analysis

The analysis of changes in the study groups was performed using the Wilcoxon test, while the assessment of relationships between groups was performed using the Chi² (χ^2) test. In all calculations, the level of statistical significance was $p \leq 0.05$. In the case of p-values > 0.05 , it was assumed that the changes found were not related to the treatment given.

Results

Forty-two out of fifty patients completed the study: 20 patients in Group I (undergoing physical therapy) and 22 patients in Group II. There were no significant differences in demographics or the proportion of HLA-B27 positive patients between the two groups.

The applied physical therapy programme did not improve physical performance in the patients studied. There was no improvement in any of the physical parameters studied. Ott sign, Schober's test, toe-to-floor distance, OWD and thoracic expansion test values were not significantly altered in any of the groups over the course of the study. There were also no significant differences between the two groups, due to the small size of each group and the very wide dispersion of results. At the same time, there were no statistical differences in the measured laboratory results for acute phase exponents — ESR and CRP or haemoglobin levels in the two treatment groups. No better disease control as measured by the BASDAI was achieved in the physical therapy group. Baseline and final mean BASDAI values for each group are shown in Figure 1.

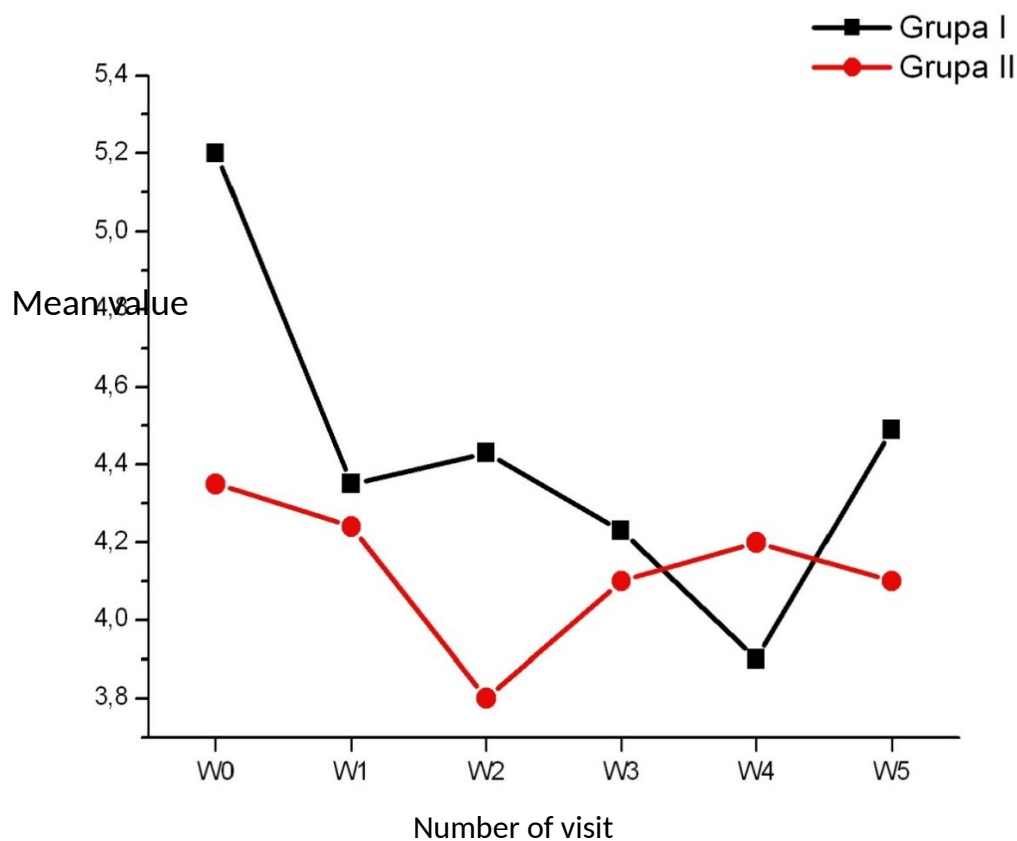


Figure 1. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) mean values for Group I and Group II during subsequent visits

The combination of biological treatment and physical therapy interventions did not improve the patients' functional status as measured by the BASFI, also referred to as the functional impairment index. The observed changes in mean BASFI values at successive visits were not significant — the scatter of results for individual patients was very large, as can be seen in standard deviation values. The results for each visit in Groups I and II are shown in Figure 2.

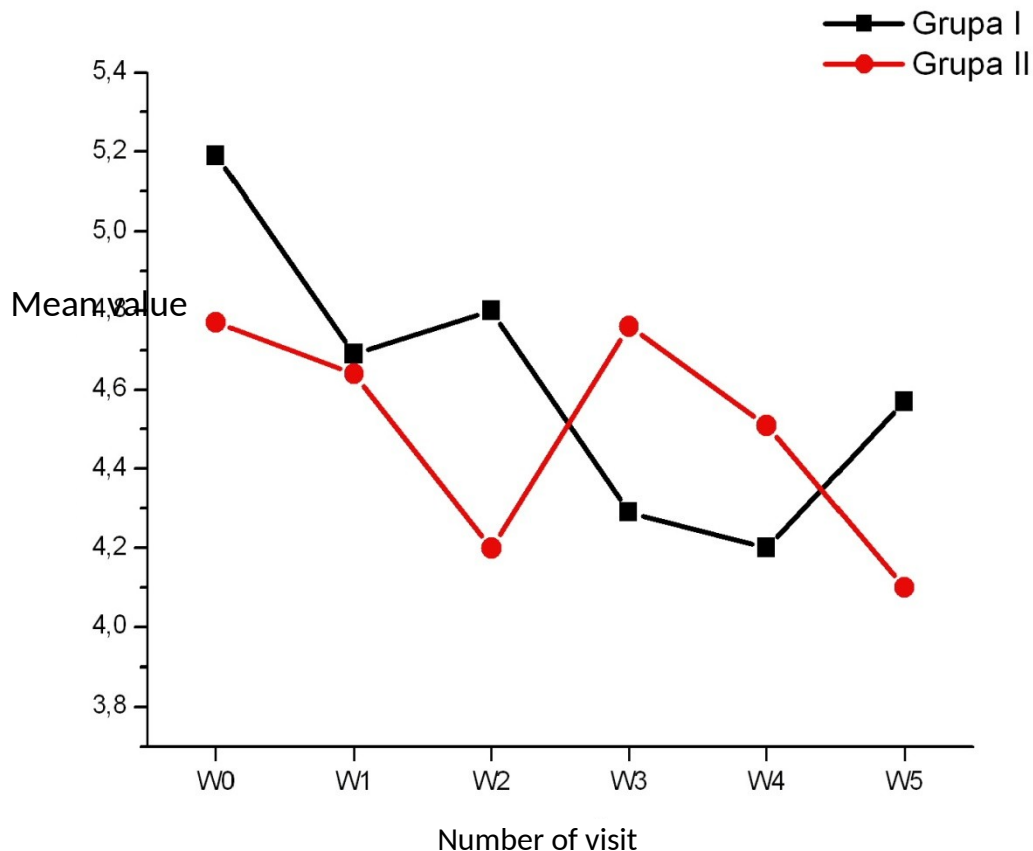


Figure 2. Bath Ankylosing Spondylitis Functional Index (BASFI) mean values for Group I and Group II during subsequent visits

The analysis of results of individual domains of the MOS SF-36v2 questionnaire for both patient groups revealed no statistically significant differences in terms of physical functioning, role limitations — physical problems, role limitations — emotional problems, general health, vitality, well-being, physical health and mental health. The mean values for individual visits did not differ significantly in the two treatment groups compared. There was a significant difference between mean values for both groups at Visit 0 for the Pain domain of the MOS SF-36v2 questionnaire ($p > 0.05$). In Group I, there was a significant difference for the mean values for Visit 0 and Visit 5 ($p > 0.05$). In Group II, there were no significant changes in mean values at subsequent visits. However, the increase in average values in Group I did not result in a significant change in the number of patients compared to the accepted norm for the general population. In Group II, there was an increase in the number of patients with below-normal results; however, this is not a significant change due to the small

patient group. At fifth visit, there were no significant differences between the mean values for Group I and Group II. Based on this, it can be concluded that the physical therapy provided in Group I contributed to the improvement of the patients' health status in terms of the Bodily Pain domain. There were no significant differences between the results for the two groups at any of the visits for the Social Functioning domain; however, group I showed a significant increase in the mean value at fifth visit compared to visit 0, while group II showed no significant changes in the mean values at subsequent visits.

Discussion

Comprehensive care for AS patients should be based on a combination of modern pharmacotherapy using biologic disease-modifying antirheumatic drugs (bDMARDs) and innovative therapies with non-pharmacological methods based on rehabilitation treatment and patient education. Attempts to determine the optimal option for rehabilitation treatment in AS patients were the subject of many research papers [19–24]. An analysis by Dagfinrud et al., who reviewed publications on the effects of different forms of physical therapy in the treatment of AS, may provide some summary information [25]. The authors concluded that individual exercises at home are better than no exercises, and group exercises under the supervision of a physiotherapist are better than exercises at home. Comprehensive spa treatment is most effective. Given the nature of the condition and the location of its lesions, kinesiotherapy should be the primary non-pharmacological treatment used for AS patients. Its role is primarily to protect against the occurrence of limitations of mobility in the spine and other joints or reduce these already existing limitations, decrease the severity of stiffness, and alleviate pain. Some authors have even changed the approach to the role of kinesiotherapy in the treatment of AS, implying that exercises should become part of patients' daily schedule, which is understood as a lifestyle [12, 26].

The problem of limited access to modern AS therapies based on biologics and innovative therapies is still a shortcoming of the current healthcare system in Poland. However, it is important to be aware that the possibility of maintaining or returning to gainful employment and thus reducing the social costs of the disease as a result of effective treatment definitely reduces the social costs of biological treatment [27, 28]. This study aims to optimise the treatment of AS patients with TNF- α inhibitors. A similar assessment of the effect of physical therapy on disease activity, functional status and QoL in AS patients treated with TNF- α inhibitors has previously been undertaken by several researchers [29-33]. Liang et al. made a collective summary of publications on the subject. The meta-analysis included five studies

and 221 patients [34]. In their conclusions, the authors highlighted that there was no statistically significant difference in terms of the improvement of patients' functional status assessment, as measured by the BASFI questionnaire, between the group treated with a TNF- α inhibitor and patients who received rehabilitation therapy in addition to biological therapy, which is consistent with the results of this study. Patients treated with a TNF- α inhibitor and physical therapy achieved better activity control as measured by improvement in the BASDAI [34].

Another systematic review of all papers published up to October 2013 on the effectiveness of different forms of rehabilitation in AS patients treated with TNF- α inhibitors was performed by Lubrano et al. [35]. After the analysis of 75 papers, it was found that for patients on biological treatment, the most effective form of rehabilitation is exercises under the supervision of a physiotherapist or a stay in a rehabilitation unit combined with patient education. The rehabilitation programme received by Group I patients in this study fully met these objectives. In addition to the hydro treatment and exercises, educational objectives were pursued during each visit to reinforce patients' motivation for health-promoting behaviour. Therefore, it should be assumed that in the patients studied, the positive effect of the rehabilitation sessions will be the maintenance of current fitness, not necessarily its improvement.

Conclusions

1. The proposed physical therapy regimen resulted in a significant improvement in QoL scores on the MOS SF-36v2 questionnaire in the domains of Bodily Pain and Social Functioning. Within the Well-being domain, there was a significant increase in the number of patients who scored above normal.
2. The proposed physical therapy regimen did not improve the BASFI in the patients studied. In the case of BASDAI, despite the lack of significant improvement, a downward trend can be observed in Group I.
3. The proposed physical therapy regimen had no effect on changing laboratory results, including acute phase indices.
4. Physical therapy in combination with biological treatment has a better effect on patients' perceived QoL than biological treatment alone.
5. Physical therapy and education should be the primary form of non-pharmacological treatment in active AS patients treated with biologics.

Data availability statement

These data are available on request.

Ethics statement

The study received the approval of the Bioethics Committee at the Nicolaus Copernicus University Ludwik Rydygier Collegium Medicum

Author contributions

RW — preparation of manuscript, interpretation of results, draft paper; HS — preparation of manuscript, data collection, interpretation of results, draft paper; DJ — interpretation of results, preparation of references data analysis.

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Conflict of interest

Authors declare no of interests.

References

1. Przepiera-Będzak H, Brzosko M. Seronegatywne zapalenia stawów kręgosłupa. In: Puszczewicz M. ed. Wielka Interna. Reumatologia. Medical Tribune Polska, Warszawa 2016: 281-288.
2. Zimmermann-Górska I. Zesztywniające zapalenie stawów kręgosłupa. In: Zimmermann-Górska I. ed. Postępy Reumatologii Klinicznej. Wydawnictwo Lekarskie PZWL, Warszawa 2014: 279-292.
3. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007; 369(9570): 1379-1390, doi: [10.1016/S0140-6736\(07\)60635-7](https://doi.org/10.1016/S0140-6736(07)60635-7), indexed in Pubmed: [17448825](https://pubmed.ncbi.nlm.nih.gov/17448825/).
4. Sieper J, Braun J. Ankylosing Spondylitis. Clinician's manual. Current Medicine Group, London 2009: 5-11.
5. Stanisławska-Biernat E, Świerkot J, Tłustołowicz W. Spondyloartropatia osiowa i zesztywniające zapalenie stawów kręgosłupa. Aktualizacja zaleceń postępowania diagnostyczno-terapeutycznego w chorobach reumatycznych na podstawie rekomendacji EULAR/ACR. Reumatologia. 2016; 54(1): 15-21.
6. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984; 27(4): 361-368, doi: [10.1002/art.1780270401](https://doi.org/10.1002/art.1780270401), indexed in Pubmed: [6231933](https://pubmed.ncbi.nlm.nih.gov/6231933/).

7. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984; 27(4): 361-368, doi: [10.1002/art.1780270401](https://doi.org/10.1002/art.1780270401), indexed in Pubmed: [6231933](https://pubmed.ncbi.nlm.nih.gov/6231933/).
8. Rudwaleit M, Heijde Dv, 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(6): 777-783, doi: [10.1136/ard.2009.108233](https://doi.org/10.1136/ard.2009.108233), indexed in Pubmed: [19297344](https://pubmed.ncbi.nlm.nih.gov/19297344/).
9. Sieper J, van der Heijde D, Landewé R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis.* 2009; 68(6): 784-788, doi: [10.1136/ard.2008.101501](https://doi.org/10.1136/ard.2008.101501), indexed in Pubmed: [19147614](https://pubmed.ncbi.nlm.nih.gov/19147614/).
10. van der Heijde D, Ramiro S, Landewé R, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2011; 70(6): 896-904, doi: [10.1136/ard.2011.151027](https://doi.org/10.1136/ard.2011.151027), indexed in Pubmed: [21540199](https://pubmed.ncbi.nlm.nih.gov/21540199/).
11. Beasley J. Osteoarthritis and rheumatoid arthritis: conservative therapeutic management. *J Hand Ther.* 2012; 25(2): 163-71; quiz 172, doi: [10.1016/j.jht.2011.11.001](https://doi.org/10.1016/j.jht.2011.11.001), indexed in Pubmed: [22326361](https://pubmed.ncbi.nlm.nih.gov/22326361/).
12. van der Linden S, van Tubergen A, Hidding A. Physiotherapy in ankylosing spondylitis: what is the evidence? *Clin Exp Rheumatol.* 2002; 20(6 Suppl 28): S60-S64, indexed in Pubmed: [12463449](https://pubmed.ncbi.nlm.nih.gov/12463449/).
13. Biernat-Stanisławska E. Poradnik dla pacjentów. Zesztywniające zapalenie stawów kręgosłupa. UCB/VEDIM, Warszawa 2015.
14. Karwat ID, Skwarcz A. Rehabilitacja medyczna — jej cele, założenia i znaczenie praktyczne. *Post Nauk Med.* 2000; 3: 61-69.
15. Mikołajewska E. Fizjoterapia a rehabilitacja medyczna — problemy semantyczne z nazewnictwem w fizjoterapii. *Fizjoterapia.* 2011; 19(4): 54-64.
16. Pacholec A, Księżopolska-Orłowska K, Jędryka-Góral A, et al. Współczesne kierunki rehabilitacji w zapalnych chorobach narządu ruchu. *Reumatologia.* 2013; 51(4): 298-303.
17. Sayfried A. Rehabilitacja osób z chorobami reumatycznymi. In: Milanowska K, Dega W. ed. *Rehabilitacja medyczna.* Wydawnictwo Lekarskie PZWL, Warszawa 2001: 402-412.
18. Passalent LA. Physiotherapy for ankylosing spondylitis: evidence and application. *Curr Opin Rheumatol.* 2011; 23(2): 142-147, doi: [10.1097/BOR.0b013e328342273a](https://doi.org/10.1097/BOR.0b013e328342273a), indexed in Pubmed: [21150624](https://pubmed.ncbi.nlm.nih.gov/21150624/).
19. Lubrano E, D'Angelo S, Parsons WJ, et al. Effectiveness of rehabilitation in active ankylosing spondylitis assessed by the ASAS response criteria. *Rheumatology (Oxford).* 2007; 46(11): 1672-1675, doi: [10.1093/rheumatology/kem247](https://doi.org/10.1093/rheumatology/kem247), indexed in Pubmed: [17893100](https://pubmed.ncbi.nlm.nih.gov/17893100/).
20. Strumse YAS, Nordvåg BY, Stanghelle JK, et al. Efficacy of rehabilitation for patients with ankylosing spondylitis: Comparison of a four-week rehabilitation programme in a Mediterranean and a Norwegian setting. *J Rehabil Med.* 2011; 43(6): 534-542, doi: [10.2340/16501977-0804](https://doi.org/10.2340/16501977-0804), indexed in Pubmed: [21491073](https://pubmed.ncbi.nlm.nih.gov/21491073/).
21. Kjekten I, Bø I, Rønningen A, et al. A three-week multidisciplinary in-patient rehabilitation programme had positive long-term effects in patients with ankylosing spondylitis: randomized controlled trial. *J Rehabil Med.* 2013; 45(3): 260-267, doi: [10.2340/16501977-1078](https://doi.org/10.2340/16501977-1078), indexed in Pubmed: [23138412](https://pubmed.ncbi.nlm.nih.gov/23138412/).

22. Anay Y, Ozcan E, Karan A, et al. The effectiveness of intensive group exercise on patients with ankylosing spondylitis. *Clinical Rehabilitation*. 2016; 17(6): 631-636, doi: [10.1191/0269215503cr658oa](https://doi.org/10.1191/0269215503cr658oa).
23. Durmus D, Alayli G, Cil E, et al. Effects of a home-based exercise program on quality of life, fatigue, and depression in patients with ankylosing spondylitis. *Rheumatol Int*. 2009; 29(6): 673-677, doi: [10.1007/s00296-008-0756-8](https://doi.org/10.1007/s00296-008-0756-8), indexed in Pubmed: [18985351](https://pubmed.ncbi.nlm.nih.gov/18985351/).
24. Van Tubergen A, Boonen A, Landewé R, et al. Cost effectiveness of combined spa-exercise therapy in ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum*. 2002; 47(5): 459-467, doi: [10.1002/art.10658](https://doi.org/10.1002/art.10658), indexed in Pubmed: [12382292](https://pubmed.ncbi.nlm.nih.gov/12382292/).
25. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. *Cochrane Database Syst Rev*. 2004(4): CD002822, doi: [10.1002/14651858.CD002822.pub2](https://doi.org/10.1002/14651858.CD002822.pub2), indexed in Pubmed: [15495035](https://pubmed.ncbi.nlm.nih.gov/15495035/).
26. Akgul O, Kiliç E, Kiliç G, et al. Physiotherapy and rehabilitation in ankylosing spondylitis: is it still the mainstay of management in the era of biologics? *Int J Clin Rheumatol*. 2013; 8(5): 579-584, doi: [10.2217/ijr.13.50](https://doi.org/10.2217/ijr.13.50).
27. Stajszczyk M. Leczenie biologiczne w chorobach reumatycznych w Polsce. Raport. , Warszawa 2013: Raport.
28. Bachanek O, Mitura J, Pawlikowski J. Availability and restrictions in the use of biologic therapy in Poland. *MONZ*. 2015; 21(3): 266-271, doi: [10.5604/20834543.1165351](https://doi.org/10.5604/20834543.1165351).
29. Colina M, Ciancio G, Govoni M. Rehabilitation treatment strategies in ankylosing spondylitis. *J Rheumatol*. 2011; 38(10): 2266; author reply 2266, doi: [10.3899/jrheum.110691](https://doi.org/10.3899/jrheum.110691), indexed in Pubmed: [21965695](https://pubmed.ncbi.nlm.nih.gov/21965695/).
30. Lubrano E, D'Angelo S, Spadaro A, et al. Rehabilitation for ankylosing spondylitis in the era of biologics: any room left for this treatment? *J Rheumatol*. 2011; 38(7): 1228-1230, doi: [10.3899/jrheum.110362](https://doi.org/10.3899/jrheum.110362), indexed in Pubmed: [21724711](https://pubmed.ncbi.nlm.nih.gov/21724711/).
31. Ciprian L, Lo Nigro A, Rizzo M, et al. The effects of combined spa therapy and rehabilitation on patients with ankylosing spondylitis being treated with TNF inhibitors. *Rheumatol Int*. 2013; 33(1): 241-245, doi: [10.1007/s00296-011-2147-9](https://doi.org/10.1007/s00296-011-2147-9), indexed in Pubmed: [21947374](https://pubmed.ncbi.nlm.nih.gov/21947374/).
32. Masiero S, Bonaldo L, Pigatto M, et al. Rehabilitation treatment in patients with ankylosing spondylitis stabilized with tumor necrosis factor inhibitor therapy: a randomized controlled trial. *J Rheumatol*. 2011; 38(7): 1335-1342, doi: [10.3899/jrheum.100987](https://doi.org/10.3899/jrheum.100987), indexed in Pubmed: [21459942](https://pubmed.ncbi.nlm.nih.gov/21459942/).
33. Masiero S, Poli P, Bonaldo L, et al. Supervised training and home-based rehabilitation in patients with stabilized ankylosing spondylitis on TNF inhibitor treatment: a controlled clinical trial with a 12-month follow-up. *Clin Rehabil*. 2014; 28(6): 562-572, doi: [10.1177/0269215513512214](https://doi.org/10.1177/0269215513512214), indexed in Pubmed: [24285801](https://pubmed.ncbi.nlm.nih.gov/24285801/).
34. Liang H, Li WR, Zhang H, et al. Concurrent Intervention With Exercises and Stabilized Tumor Necrosis Factor Inhibitor Therapy Reduced the Disease Activity in Patients With Ankylosing Spondylitis: A Meta-Analysis. *Medicine (Baltimore)*. 2015; 94(50): e2254, doi: [10.1097/MD.0000000000002254](https://doi.org/10.1097/MD.0000000000002254), indexed in Pubmed: [26683943](https://pubmed.ncbi.nlm.nih.gov/26683943/).
35. Lubrano E, Spadaro A, Amato G, et al. Tumour necrosis factor alpha inhibitor therapy and rehabilitation for the treatment of ankylosing spondylitis: a systematic review. *Semin Arthritis Rheum*. 2015; 44(5): 542-550, doi: [10.1016/j.semarthrit.2014.09.012](https://doi.org/10.1016/j.semarthrit.2014.09.012), indexed in Pubmed: [25450240](https://pubmed.ncbi.nlm.nih.gov/25450240/).

