J Prev Epidemiol. 2022;7(2):e23162 Original Article

doi 10.34172/jpe.2022.23162 Journal of Preventive Epidemiology http jprevepi.com

Spondyloarthritis; clinical manifestations and evaluation of response to treatment in Iran

Seyed Mohammad Hashem Montazeri[1], Seyed Mojtaba Alavi[1], Fatemeh Radmard[1], Maryam Masoumi[1*], Mostafa Vahedian[2]

[1]Clinical Research and Development Center, Qom University of Medical Sciences, Qom, Iran
[2]Department of Biostatistics and Epidemiology, Neuroscience Research Center, School of Medicine, Qom University of Medical Sciences, Qom, Iran

Correspondence to:
Maryam Masoumi, Email: M.masoumiy@gmail.com, research@mail.muq.ac.ir

Received: 8 Aug. 2021
Accepted: 10 Nov. 2021
ePublished: 1 Dec. 2021

Keywords: Spondyloarthropathy, Sacroiliitis, Treatment, Indomethacin

Abstract

Introduction: Spondyloarthropathies (SpAs) are inflammatory diseases with symptoms such as spinal pain, sacroiliac, and peripheral involvement. The prevalence of SpAs is reported from 0.2% to 1.6%. SpAs can cause significant disabilities for patients. Its medical treatment is mainly with non-steroidal anti-inflammatory (NSAIDs) and anti-TNF drugs.
Objectives: The primary purpose of this study is to carefully detect the clinical manifestations of patients, demographic characteristics, and the effectiveness of common medications in this disease.
Patients and Methods: The present study is a retrospective descriptive study. The statistical population is 101 patients with SpA who have demographic information and items related to clinical conditions, radiographic findings and response to treatment.
Results: One hundred one patients with SpA [46 (45.5%) female] with the age of 36.83± 10.45 years were studied. Around 66 patients (64.7%) had ankylosing spondylitis (AS), with the highest prevalence of AS. The most common clinical symptoms in patients were axial and peripheral/ extra-articular symptoms. The response to patients' treatment were 61 patients (60.4%) had responded to the first stage of treatment, since only one patient needed to change the treatment steps in five times.
Conclusion: We found, most patients with SpA were young patients. The most common radiological finding was Sacroiliitis. The most common clinical finding was extra-articular manifestations. Peripheral manifestations of the disease in women and axial images in men were common. The highest response to treatment was observed with the combination of indomethacin, sulfasalazine (SSZ) and indomethacin (alone).

Citation: Montazeri AMH, Alavi SM, Radmard F, Masoumi M, Vahedian M. Spondyloarthritis; clinical manifestations and evaluation of response to treatment in Iran. J Prev Epidemiol. 2022;7(2):e23162. doi: 10.34172/jpe.2022.23162.

Introduction

Spondyloarthritis (SpA) represents a group of HLAB 27 related diseases with inflammation of the spine, sacroiliac, and less frequently peripheral joints. This group includes ankylosing spondylitis (AS) and peripheral SpAs, psoriatic arthritis (PsA), reactive arthritis (ReA), SpA related to inflammatory bowel disease (IBD) and juvenile SpA. Inflammatory back pain, articular (arthritis, enthesitis, dactylitis), and extra-articular (IBD, psoriasis and HLA related uveitis) are common symptoms (1).

There is enormous variation in reported prevalence, but it is estimated that Spa is ranged from 0.20% in South-East Asia to 1.61% in Northern Arctic communities. Each sub-group of Spa has a different prevalence (2). There is not a detailed study about the prevalence of Spa in different Asian races like Iranian people. The different prevalence of HLA B27 is one of the causes of the different prevalence of Spa between nations (3). Some studies said that SpA is a more common disease in men than women (male to female ratio is 2–3:1), but this ratio in the radiologic disease of Spa is equal between genders (4). Most patients with ankylosing spondylitis can experience normal life, while most patients with this disease may suffer from severe dryness in the spine and limited mobility, thereby, the disease intensifies and

Key point

The strength of our study is that we examined the prevalence of spondyloarthropathies and its subtypes for the first time in Iran. In addition, this study helps to understand the clinical manifestations and thus the faster diagnosis. Due to the economic issues, physicians need to pay attention to regular treatments such as indomethacin and sulfasalazine because of their excellent response and low price, which could help increasing medication adherence. According to our results, it is not essential to treat most patients with biological agents.

makes them disabled (5). Medical treatment of Spa is based on non-steroidal anti-inflammatory drugs (NSAIDs), and the use of tumor necrosis factor inhibitors (TNFi) despite NSAID treatment is not efficient (6).

Objectives

In this study, we try to detect clear manifestations of Spa, the prevalence of each subtype, reveal demographic features and probable relations to better diagnosis and management. We also evaluate response to treatment with common drugs to help therapists choose the best medicine in patients.

Patients and Methods

Study design

This study was a descriptive-analytical cross-sectional study to determine clinical presentation, the prevalence of each sub-type of SpAs, and the efficiency of indomethacin in the treatment of SpA patients. This study is retrospective and all patients received the standard treatments according to their clinical conditions, and no clinical intervention and invasive testing were performed in their treatment process. In our study, data were provided from patients' medical records, including responses to treatment and results of tests and examinations.

Data source

One hundred-one cases who were diagnosed with SpA from 2016 to 2019 were included. All participants were enrolled in the study through a census. All patients underwent complete physical examination and detailed para-clinical evaluations such as laboratory tests and imaging to diagnose SpA. All subjects had entry criteria; ESSG (European Spondyloarthropathy Study Group) criteria for diagnosis of SpA, New York Modified Criteria for the Diagnosis of Ankylosing Spondylitis, CASPAR (Classification Criteria for Psoriatic Arthritis (CASPAR)) criteria for diagnosis of psoriatic arthritis, patients with IBD and arthritis considered IBD-SpA, patients who got arthritis after urinary tract infection (UTI) or gastrointestinal infections considered as reactive arthritis, and patients with positive ESSG criteria without other criteria considered as undifferentiated SpA.

Data collection and study design

In this study, patients' medical records were observed, and required variables including demographic, clinical, para-clinical, and imaging data were recorded. Demographic data includes gender, age, age of onset of clinical presentation, age of diagnosis of disease, and delayed time of diagnosis. Clinical presentations were categorized as anterior uveitis (AU), extra-articular, root, and peripheral involvement. Plasma hemoglobin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were laboratory data. Each type of treatment and its response were recorded too.

Response to treatment assessed with Assessment of SpondyloArthritis international Society (ASAS) -ESR criteria. Back pain, peripheral pain/swelling, duration of morning stiffness, patient global (patients assessment in measuring disease activity), and ESR are items of ASDAS-ESR criteria (7). Its spectrum is from inactive disease to very high disease activity, since <1.3 is categorized as inactive disease, <2.1 is defined as low disease activity, <3.5 is described as high disease activity, and >3.5 represents very high disease activity (8). According to results we got from ASDAS-ESR differences, the current situation's response to treatment was evaluated. In response to treatment, less than 1.1 (<1.1) was defined as clinically important improvement, and response to treatment more than 2 (>2) represents major improvement.

Statistical analysis

Data entered to statistical software SPSS version 22 and analyzed using descriptive and analytical statistics. The quantitative data is described with mean and standard deviation. The qualitative data were expressed as frequency and frequency percentage. Chi-square and Fisher's exact test were used to determine the relationship between qualitative variables, and for quantitative data, the independent-T test was used. The significance level in this study was considered less than 0.05.

Results

In the present study, 101 patients with SpA were studied, of which 46 (45.5%) were female, and 55 (54.5%) were male. The mean and age deviation of patients was 36.83± 10.45, and the highest number of patients was in the age range of 21-35 years (Table 1). In this study,35 (34.6%) of the patients had symptoms of the disease in the age range of 21 to 30 years,1 (0.9%) was less than 10 years, and 2 patients (1.9%) were more than 50 years in the first clinical symptoms of the disease (Table 2).

Among the 101 study patients, 66 (64.7%) of the patients were diagnosed with AS, with the highest prevalence being related to AS, since one (1%) of the patients were diagnosed with HLA-related uveitis (Table 3).

The prevalence of the disease among women and men

Table 1. Demographic features include age and sex distribution of patients

		Number of patients	Percent
Gender	Female	46	45.5
	Male	55	54.5
Age (y)	< 20	7	6.9
	21–30	24	23.7
	31–40	33	32.6
	41–50	27	26.7
	51–60	8	7.9
	>70	2	1.9
Total		101	100

Table 2. Age of patients (by years) at the onset of clinical manifestations

		N	Percent
Age (year)	< 10	2	1.9
	11–20	17	16.8
	21–30	35	34.6
	31–40	29	28.7
	41–50	17	16.8
	>50	1	0.9
Total		101	100.0

by age has a similar pattern, and only at the age of 27 men were more affected. Radiographs of patients were examined.

According to the results, the most radiological findings were related to sacroiliac. Around 61% of the total population have sacroiliac manifestations on radiography (Table 4). According to the results, most of the clinical signs were related to axial and peripheral-extra-articular involvement. About 22 patients (21.8%) had axial

Table 3. Frequency and percentage of patients with different subtypes of spondyloarthropathy in the study

Diagnosis					
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	AS	66	64.7	65.3	65.3
	ReA	12	11.8	11.9	77.2
	PsA	17	16.7	16.8	94.1
	IBD	5	4.9	5.0	99.0
	HLA-B27 related Uveitis	1	1.0	1.0	100.0
	Total	101	99.0	100.0	
Missing		1	1.0		
Total		102	100.0		

Table 4. Frequency of various radiological manifestations of the disease among patients

Radiological findings		**Frequency**	**Percent**	**Cumulative Percent**
Radiology	Arthritis	1	1.0	1.0
	Bilateral effusion in hip, spine	1	1.0	2.0
	BME	1	1.0	3.0
	BME, sclerosis	1	1.0	4.0
	Calcaneal fasciitis and periostitis	1	1.0	5.0
	Enthesopathy	1	1.0	5.9
	Erosion	7	6.9	12.9
	Erosion, BME	6	5.9	18.8
	Erosion, bone proliferation	1	1.0	19.8
	Increased uptake in sternum and sternal rib end bone scan	1	1.0	20.8
	left arthritis	1	1.0	21.8
	Nl	9	8.9	30.7
	Sacroiliitis	39	38.6	69.3
	Sacroiliitis, bamboo spine	2	2.0	71.3
	sacroiliitis, Barrel-shaped vertebrae	2	2.0	73.3
	Sacroiliitis, BME	1	1.0	74.3
	Sacroiliitis, erosion	1	1.0	75.2
	Sacroiliitis, erosion, BME	2	2.0	77.2
	Sacroiliitis, spine	2	2.0	79.2
	Sacroiliitis grade I-II	3	3.0	82.2
	Sacroiliitis grade I, II, erosion, BME	1	1.0	83.2
	Sacroiliitis grade II	3	3.0	86.1
	Sacroiliitis grade II, bamboo spine	1	1.0	87.1
	Sacroiliitis grade II, erosion	1	1.0	88.1
	Sacroiliitis grade II, fasciitis, periostitis	1	1.0	89.1
	Sacroiliitis grade II-III	4	4.0	93.1
	Sacroiliitis grade II-III, erosion	1	1.0	94.1
	Sacroiliitis grade IV	1	1.0	95.0
	Sacroiliitis grade IV, bamboo spine	2	2.0	97.0
	Sacroiliitis grade IV, lumbar syndesmophytes	1	1.0	98.0
	Sacroiliitis grade IV, spine	1	1.0	99.0
	Sacroiliitis	1	1.0	100.0
	Total	101	100.0	

BME, bone marrow edema

involvement, and 12 patients (11.9%) had peripheral joint involvement (Table 5). The presence of concurrent peripheral involvement in women was four times more than men and simultaneous axial and root involvement in men was five times more than women (Table 6).

Patients' disease status was assessed at the time of referral using ASDAS-ESR scoring system, 57 (56.4%) of patients in very high condition, 40 (39.6%) of patients in high condition, 3 (3%) were in low-condition. Only one patient (1%) could not be evaluated with ASDAS-ESR due to having AU without joint involvement and was reported as an inactive condition (Table 7).

In this study, the ASDAS-ESR test was used to evaluate the outcome of patients' response to treatment; based on the results of the ASDAS-ESR difference, the response phase of patients' treatment was measured and compared to the current situation. After treatment was divided based on the numbers obtained, greater than equal to 1/1, the clinical condition of patients was considered as clinically important improvement, and greater than equal to two was considered a major improvement. In this study, 85 cases in the group of major improvement and 15 cases were included in the clinically important improvement group. Only one case of AU was observed that due to lack of joint involvement, and it was not possible to assess his clinical condition based on the ASDAS-ESR test, thus estimating the patient based on clinical condition and diagnosis and was considered as wholly (Table 8).

According to the results of treatment response of the patients and their need to change the drug, 61 (60.4%) of the patients had responded to the first stage of treatment, and only one patient needed to change the treatment steps five times. The highest response to treatment in the first stage was the response to indomethacin and sulfasalazine (SSZ) drugs in combination or indomethacin (alone), while the response to treatment of other drugs in the first stage such as adalimumab, celecoxib and etanercept was not the same as others. Based on the study results, the drug combination of SSZ, Enbrel, and indomethacin was also an effective drug used in treating the fifth stage only in the present study (Tables 9 to 13).

Table 5. Frequency of each clinical manifestation of the disease

Presentation	N	Percent	Cumulative Percent
AU	1	1.0	1.0
Axis	22	21.8	22.8
Axis, extra-articular	10	9.9	32.7
Axis, root	6	5.9	38.6
Axis, root, extra-articular	3	3.1	41.6
Extra-articular	4	4.0	45.5
Peripheral	7	6.9	52.5
Peripheral, axis	10	9.9	62.4
Peripheral, axis, root	5	5.0	67.3
Peripheral, axis, root, extra-articular	2	2.0	69.3
Peripheral, extra-articular	12	11.9	81.2
Peripheral, extra-articular, axis	9	8.9	90.1
Peripheral, extra-articular, root	4	4.0	94.1
Peripheral, root	3	3.1	97.0
Root	3	3.0	100.0
Total	101	100.0	

Table 6. Sexual distribution of each clinical manifestation

		Gender		Total
		Female	Male	
Presentation	AU	1	0	1
	Axis	12	10	22
	Axis, extra articular	3	7	10
	Axis, root	1	5	6
	Axis, root, extra articular	2	1	3
	Extra articular	2	2	4
	Peripheral	2	5	7
	Peripheral, axis	8	2	10
	Peripheral, axis, root	3	2	5
	Peripheral, axis, root, extra articular	0	2	2
	Peripheral, extra articular	6	6	12
	Peripheral, extra articular, axis	2	7	9
	Peripheral, extra articular, root	2	2	4
	Peripheral, root	1	2	3
	Root	1	2	3
Total		46	55	101

Discussion

This study aimed to identify SpAs manifestations accurately, identify the most common findings, and evaluate the effectiveness of existing therapies in treating patients, especially among Iranians. Therefore, physicians can identify and treat patients more easily and quickly.

We found that the most common disease among SpAs is ankylosing spondylitis.

According to our study, most of the clinical signs were related to axial and peripheral or extra-articular

Table 7. Classification of patients based on ASDAS-ESR scoring system

State	Frequency	Percent	Cumulative Percent
Very high	57	56.4	56.4
High	40	39.6	96.0
Low	3	3.0	99.0
Inactive	1	1.0	100.0
Total	101	100.0	

Table 8. Frequency of patients at each stage of treatment (note that only patients who needed re-treatment and other drugs entered the next stages of treatment)

Treatment steps	Frequency	Percent	Cumulative Percent
1	61	60.4	60.4
2	28	27.7	88.1
3	6	5.9	94.1
4	5	5.0	99.0
5	1	1.0	100.0
Total	101	100.0	

Table 9. Treatment response status (complete or partial) of drugs used in the first stage of treatment

Treatment 1	Response (No. of patients)		Total
	Complete	Partial	
Adalimumab	1	0	1
Celecoxib	1	0	1
Etanercept	1	0	1
Indomethacin	20	0	20
Indomethacin, MTX	1	0	1
Indomethacin, SSZ	44	2	46
Indomethacin, SSZ, MTX	4	0	4
Indomethacin, SSZ, PDN	3	0	3
Meloxicam, SSZ	1	0	1
MTX, PDN, SSZ	3	0	3
MTX, SSZ, PDN	1	0	1
MTX, SSZ, Indomethacin, PDN	3	0	3
MTX, SSZ, Diclofenac	1	0	1
Naproxen	1	0	1
Naproxen, SSZ	4	0	4
Naproxen, SSZ, MTX	1	0	1
Naproxen, SSZ	1	0	1
PDN, Meloxicam, MTX	1	0	1
PDN, MTX	3	0	3
PDN, MTX, Leflunomide	1	0	1
PDN, SSZ	1	0	1
PDN, SSZ, Naproxen	1	0	1
SSZ, MTX	1	0	1

MTX: Methotrexate, SSZ: Sulfasalazine, PDN: Prednisolone.

involvement. Peripheral manifestations of the disease are more common among women, but axial manifestations are more common among men. Likewise, the prevalence of the disease among women and men by age has a similar pattern. In a study done in London (9), female/male ratio was 2:1, which women were twice more than men, and peripheral manifestation of SpAs was more common in men. Another study (10) showed that men experience more peripheral symptoms compared to women. They reported that 63% (2/3) peripheral arthritis in men and 20% in women.

We found that the most common disease among SpAs is ankylosing spondylitis. SpAs prevalence is different in every region; it was from 0.01% (11) in Japan to 2.5% in Northern Arctic natives (12, 13). Saraux et al found a 0.30% prevalence of SpAs in France with almost equal prevalence in men (0.31%) and women (0.29%). They showed, ankylosing spondylitis and psoriatic arthritis were the most common sub-types in this study (14). Collantes et al (15) discovered that the prevalence of SpAs in Spain is 68% in men and 32% in women. Moreover, ankylosing spondylitis was the most common type of SpAs, as same to our study. The prevalence of the disease among women and men by age has a similar pattern.

According to our research, simple and accessible drugs such as indomethacin can still be good choices with a significant impact on the treatment of patients. NSAIDs and non-pharmacological therapy are the first line of SpAs

Table 10. Treatment response status (complete or partial) of drugs used in the second treatment of the disease

Treatment 2	Response (No. of patients)		Total
	Complete	Partial	
Adalimumab	3	0	3
Adalimumab, MTX	1	0	1
Celecoxib	1	0	1
Celecoxib, SSZ	1	0	1
Celecoxib, SSZ,PDN, MTX	1	0	1
Diclofenac, SSZ	1	0	1
Etanercept	2	0	2
Indomethacin, infliximab	2	0	2
Indomethacin, SSZ, infliximab	2	0	2
Indomethacin, SSZ, adalimumab	3	0	3
Infliximab	7	0	7
Meloxicam, SSZ	1	0	1
MTX, PDN, SSZ	1	0	1
MTX, PDN, SSZ, CSA	1	0	1
MTX, SSZ	1	0	1
Naproxen	3	0	3
Naproxen, MTX	1	0	1
Naproxen, SSZ	3	1	4
Naproxen, SSZ, MTX	1	0	1
Naproxen, SSZ, PDN	1	0	1
SSZ, Etanercept	1	0	1
SSZ, MTX, Naproxen	1	0	1

MTX: Methotrexate, SSZ: Sulfasalazine, PDN: Prednisolone.

Table 11. Treatment response status (complete or partial) of drugs used in the third treatment of the disease

Treatment 3	Response (No. of patients)		Total
	Complete	Partial	
Adalimumab	2	0	2
Celecoxib	1	0	1
Etanercept	2	0	2
Indomethacin, SSZ, Adalimumab	1	0	1
Infliximab	2	0	2
Infliximab, MTX, SSZ	1	0	1
MTX, PDN, Adalimumab	1	0	1
Naproxen, SSZ, MTX, PDN	1	0	1
SSZ, Meloxicam	1	0	1
SSZ, MTX, Naproxen	1	0	1

MTX: Methotrexate, SSZ: Sulfasalazine, PDN: Prednisolone.

Table 12. Treatment response status (complete or partial) of drugs used in the fourth treatment of the disease

Treatment 4	Response (No. of patients)		Total
	Complete	Partial	
Adalimumab	1	0	1
Infliximab	2	0	2
MTX, Diclofenac, SSZ, PDN	1	0	1
Naproxen, SSZ, Adalimumab	1	0	1
PDN, SSZ	1	0	1

MTX: Methotrexate, SSZ: Sulfasalazine, PDN: Prednisolone.

Table 13. Status of response to treatment (complete or partial) of drugs used in the patient who needed the fifth course of treatment

Treatment 4	Response (No. of patients)		Total
	Complete	Partial	
Enbrel, SSZ, Indomethacin	1	0	1

SSZ: Sulfasalazine.

therapy (16, 17). A study showed that all NSAIDs have similar efficacy for controlling axial SpAs, and they are not associated with more adverse effects than placebos (18).

Wang et al (19) reviewed 26 trials of 20 NSAIDs to compare their efficacy in ankylosing spondylitis. All 20 NSAIDs were more effective than placebos for reducing pain, and 15 of them were significantly better than placebo, and they did not have a significant difference in decreasing morning stiffness and side effects. Overall, they revealed that etoricoxib and oxaprozin were better than other NSAIDs in controlling pain and were safer than naproxen.

Poddubnyy et al(20) followed SpA patients for two years on NSAIDs intake. They found that high-dose NSAIDs were associated with lessen radiographic spinal progression in AS patients. They discovered that diclofenac, ibuprofen, indomethacin, and piroxicam were most frequently NSAIDs used in SpAs. There is not enough studies that examined the efficacy of Indomethacin on SpAs patients.

Van der Horst-Bruinsma et al (21) suggested that SSZ with typical therapy of axial spondyloarthropathies (NASID+ physical exercise) could be a proper regime for peripheral SpAs. In contrast, Braun et al, (22) discovered SSZ was effective for patients wit h IBD and patients without peripheral arthritis. Moreover, Braun et al discovered that SSZ does not have a remarkable improvement in the clinical course of undifferentiated SpAs.

Sieper et al (23) identified that combination therapy with infliximab+naproxen is more efficient than Naproxen alone. They figured outpatients with early active axial SpA who had infliximab + naproxen had more significant clinical remission than patients who used naproxen alone. In our study, patients how used SSZ+ indomethacin had better disease control. The strengths of our study were to identify the most common manifestations of SpA by comparing gender, radiologically and clinically among Iranians and evaluating the effect of common treatments.
Our study's limitations are as follows: a retrospective study, lack of attention and study of the impact of factors such as patients' occupation and profession, underlying diseases such as diabetes and autoimmune diseases, smoking, family history, nutritional status and limited statistical population of patients.
Further longitudinal studies with more detailed laboratory and clinical examinations among a larger number of patients, especially of different races, can be helpful in generalization the results of our study.

Conclusion

According to the present study results, the largest group of patients with SpA were young, and the most common radiological finding was related to sacroiliitis, although the most common manifestations of the disease were extra-articular. Peripheral manifestations are more common among women than men and axial types among men. After referral and receiving the first stage of treatment, which was often a combination of indomethacin and SSZ or indomethacin alone, they had the highest response to treatment, and their clinical status has significantly improved compared to the time of referral.

Limitations of the study

This study is retrospective. Lack of comparison groups to more accurately assess the effectiveness of different types of drugs, limited statistical population of patients, non-consideration of racial differences. We hope that these limitations will be addressed through future longitudinal studies.

Authors' contribution

MM and FR conceptualized and planned the research. FR extracted all patient's data. MV, FR, SM contributed to the analysis of the results. SM and MV contributed to the interpretation of the results. SM and SA took the lead in writing the manuscript. SM wrote the abstract. MM and SA edited the manuscript. MM supervised all steps of the study.

Conflicts of interest

Authors declare they have no conflict of interest.

Ethical issues

The research followed the tenets of the declaration of Helsinki. The ethics committee of Qom University of Medical Sciences approved this study (ethical code # IR.MUQ.REC.1399.119). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Fatemeh Radmard at this university. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

No funding or sponsorship was received for this study or publication of this article.

References

1. Giovannini L, Orlandi M, Lodato C, Cioffi E, Tenti S, Bardelli M, et al. One year in review 2015: spondyloarthritis. Clin Exp Rheumatol. 2015;33:769-78.
2. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. Arthritis Care Res (Hoboken). 2016;68:1320-31. doi: 10.1002/acr.22831.
3. Khan MA. Race-related differences in HLA association with ankylosing spondylitis and Reiter's disease in American blacks and whites. J Natl Med Assoc. 1978;70:41-2.
4. van Tubergen A. The changing clinical picture and epidemiology of spondyloarthritis. Nat Rev Rheumatol. 2015;11:110-8. doi: 10.1038/nrrheum.2014.181. doi:10.1038/nrrheum.2014.181.
5. Garshasbi M, Mahmoudi M, Razmara E, et al. Identification of RELN variant p.(Ser2486Gly) in an Iranian family with ankylosing spondylitis; the first association of RELN and AS. Eur J Hum Genet. 2020;28:754-762. doi: 10.1038/s41431-020-0573-4.
6. Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2016;68:282-98. doi: 10.1002/art.39298.
7. Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Assessment of SpondyloArthritis international Society.

Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24. doi: 10.1136/ard.2008.094870.
8. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. Assessment of SpondyloArthritis international Society (ASAS). ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:1811-8. doi: 10.1136/ard.2008.100826.
9. Roussou E, Sultana S. Spondyloarthritis in women: differences in disease onset, clinical presentation, and Bath Ankylosing Spondylitis Disease Activity and Functional indices (BASDAI and BASFI) between men and women with spondyloarthritides. Clin Rheumatol. 2011;30:121-7. doi: 10.1007/s10067-010-1581-5.
10. Jiménez-Balderas FJ, Mintz G. Ankylosing spondylitis: clinical course in women and men. J Rheumatol. 1993;20:2069-72.
11. Hukuda S, Minami M, Saito T, Mitsui H, Matsui N, Komatsubara Y, et al. Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. J Rheumatol. 2001;28:554-9.
12. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis. 2002;61 Suppl 3:iii8-18. doi: 10.1136/ard.61.suppl_3.iii8.
13. Alexeeva L, Krylov M, Vturin V, Mylov N, Erdesz S, Benevolenskaya L. Prevalence of spondyloarthropathies and HLA-B27 in the native population of Chukotka, Russia. J Rheumatol. 1994;21:2298-300.
14. Saraux A, Guillemin F, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis. 2005;64:1431-5. doi: 10.1136/ard.2004.029207.
15. Collantes E, Zarco P, Muñoz E, Juanola X, Mulero J, Fernández-Sueiro JL, et al. Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER) extended report. Rheumatology (Oxford). 2007;46:1309-15. doi: 10.1093/rheumatology/kem084.
16. Wendling D, Lukas C, Paccou J, Claudepierre P, Carton L, Combe B, et al. French Society for Rheumatology (SFR). Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. Joint Bone Spine. 2014;81:6-14. doi: 10.1016/j.jbspin.2013.12.002.
17. Zochling J, van der Heijde D, Burgos-Vargas R, Collantes E, Davis JC Jr, Dijkmans B,et al. 'ASsessment in AS' international working group; European League Against Rheumatism. ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2006;65:442-52. doi: 10.1136/ard.2005.041137.
18. Kroon FP, van der Burg LR, Ramiro S, Landewé RB, Buchbinder R, Falzon L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database Syst Rev. 2015;(7):CD010952. doi: 10.1002/14651858.CD010952.
19. Wang R, Dasgupta A, Ward MM. Comparative efficacy of non-steroidal anti-inflammatory drugs in ankylosing spondylitis: a Bayesian network meta-analysis of clinical trials. Ann Rheum Dis. 2016;75:1152-60. doi: 10.1136/annrheumdis-2015-207677.
20. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012;71:1616-22. doi: 10.1136/annrheumdis-2011-201252.
21. van der Horst-Bruinsma IE, Nurmohamed MT. Management and evaluation of extra-articular manifestations in spondyloarthritis. Ther Adv Musculoskelet Dis. 2012;4:413-22. doi: 10.1177/1759720X12458372.
22. Braun J, Zochling J, Baraliakos X, Alten R, Burmester G, Grasedyck K, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. Ann Rheum Dis. 2006;65:1147-53. doi: 10.1136/ard.2006.052878.
23. Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, et al. All INFAST Investigators. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. Ann Rheum Dis. 2014;73:101-7. doi: 10.1136/annrheumdis-2012-203201.