Adv Exp Med Biol - Clinical and Experimental Biomedicine (2022) 13: 63–78
https://doi.org/10.1007/5584_2020_611

Published online: 31 December 2020

Benefit of Biological Drugs for Quality of Life in Patients with Ankylosing Spondylitis: A Systematic Review and Meta-Analysis of Clinical Trials

Wojciech Tański, Natalia Świątoniowska-Lonc, Krzysztof Dudek, and Beata Jankowska-Polańska

Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease involving the axial skeleton, peripheral joints, and extra-articular manifestations like psoriasis, inflammatory bowel disease, or uveitis. A deterioration of quality of life (QoL) affects the disease management and therapeutic decision-making. This meta-analysis focused on the influence of biological drugs on the QoL in SA compared to the effects of other therapeutic modalities. We searched the databases of MedLine, Academic Search Ultimate, CINAHL Complete, and Health Source – Nursing/Academic Edition for articles related to AS treatment using the terms "ankylosing spondylitis" OR "rheumatoid spondylitis" OR "spondylitis" AND "quality of life" OR "patient-reported outcomes" OR "well-being" OR "health-related quality of life" OR "biological treatment". The search came up with 10 English-language articles published between 2010 and 2020. Patients were evaluated with the following indexes and questionnaires: Assessment of Spondyloarthritis International Society (ASAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Quality of Life (ASQoL), 36-Item Short-Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Functional (BASFI) Indexes. We found that the QoL, assessed with the ASQoL, improved significantly better in patients treated with biological drugs when compared to those treated with other standard therapies or placebo at a 4-month follow-up. However, improvements in other disease characteristics could not be differentiated based on the therapy modality. The finding that biological drugs are superior in improving the QoL should strengthen the recommendations for their use in patients with AS.

W. Tański
Department of Internal Medicine, Fourth Military Teaching Hospital, Wroclaw, Poland
e-mail: wtanski@op.pl

N. Świątoniowska-Lonc
Department of Clinical Nursing, Faculty of Health Science, Wroclaw Medical University, Wroclaw, Poland
e-mail: natalia.swiat@o2.pl

K. Dudek
Department of Transport Systems, Faculty of Mechanical Engineering, Wroclaw University of Technology, Wrocław, Poland
e-mail: krzysztof.dudek@pwr.edu.pl

B. Jankowska-Polańska (✉)
Department of Clinical Nursing, Faculty of Health Science, Wroclaw Medical University, Wroclaw, Poland
e-mail: beata.jankowska-polanska@umed.wroc.pl

Keywords

Ankylosing spondylitis · Biologic drugs · Disability · Inflammation · Patient management · Quality of life · Rheumatic disease · Rheumatic disease · Therapy

1 Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by a broad spectrum of clinical manifestations, laboratory abnormalities, and imaging features. The prevalence of AS in the general population is between 0.1% and 6%. The disease affects young people, and its incidence is highest in people in their thirties. The AS is associated with the presence of the HLA-B27 antigen, found in 90–95% of patients (Zhu et al. 2019). The underlying mechanisms are related to inflammatory, infectious, immunological, and genetic disorders. Typical symptoms include pain in the spine, chest, and peripheral joints, fatigue, stiffness, physical disability, fever, weight loss, and shortness of breath. The symptoms are hardly specific, which leads to delayed diagnosis and treatment. The AS may also involve non-articular tissues, notably the heart, lungs, eyes, or digestive tract, increasing the risk of premature death (Reveille and Weisman 2013).

AS treatment is based on non-steroidal anti-inflammatory drugs (NSAIDs). When these drugs are ineffective and high disease activity persists, clinically demonstrated by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score > 4 and the elevated erythrocyte sedimentation rate (ESR) and plasma C-reactive protein (CRP), biological drugs can be used. They offer considerable hope for effective treatment. Particularly, tumor necrosis factor-alpha (TNF-α) inhibitors appear effective. The introduction of biologicals in AS treatment has enabled the effective containment of the inflammatory process in patients with highly active and aggressive disease (Gao et al. 2012).

Rheumatic diseases are associated with an increased risk of organ pathology but also with a progressive disability and increased psychological burden. AS symptoms affect all aspects of patients' daily life. This leads to disease progression and disability which compromises fitness to work, work quality, daily activities, and, generally, health-related quality of life (QoL).

The interest in QoL dates to the 1970s and is associated with the holistic view of medicine. Therapeutic interventions are expected to prolong life and improve its quality. According to the positive concept of health, it is not the mere absence of disease but good physical and mental functioning and social adaptation. In clinical practice, QoL assessment complements objective indicators of outcome. It facilitates the selection of an optimal treatment protocol from the existing options. QoL assessment is based on patient self-reporting. It shows limitations in functioning, identifies areas where the patient experiences such limitations, and suggests priorities and preferences that may be relevant to further management planning (Megari 2013). In rheumatology, QoL has significant clinical implications but is not often addressed in practice. Studies are often limited to the assessment of correlations between basic symptoms of pain and stiffness and QoL. Concerning the impact of AS on QoL, studies show that patients suffer from impaired physical and mental health (Yang et al. 2016). However, few studies have yet addressed the influence of treatment with biological drugs on AS symptoms and QoL.

Rheumatologic patients usually associate the notion of health with functional status and quality of living with the disease. Management planning follows the alternating sequence of disease remission and exacerbation. The characteristics of rheumatic diseases make it difficult to establish long-term treatment objectives. When seeking the optimal treatment protocol, besides ways to delay the development of joint lesions and alleviate the associated symptoms, one must seek to improve the patient's daily functioning and his perceived QoL. To this end, QoL assessment should be an essential part of patient management and therapeutic decision-making. The purpose of this meta-analysis was to assess the QoL of patients with

AS, with the particular emphasis on the influence of using biological therapy on QoL as compared to the effects of other therapeutic modalities.

2 Methods

2.1 Search Strategies

This meta-analysis concerned the English-language articles published between 2010 and 2020 which addressed the features and therapy of AS. We performed a systematic searched of electronic databases such as PubMed, MedLine, Academic Search Ultimate, AHFS Consumer Medication Information, Open Dissertations, CINAHL Complete Dentistry and Oral Sciences, GreenFILE, Health Source – Consumer Edition, Health Source: Nursing/Academic Edition, International Pharmaceutical Abstracts, and MasterFILE Premier using the terms "ankylosing spondylitis" OR "rheumatoid spondylitis" OR "spondylitis" AND "quality of life" OR "patient-reported outcomes" OR "well-being" OR "health-related quality of life" OR "biological treatment". The search followed the Cochrane guidelines and was consistent with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Inclusion criteria consisted of age $\geq$18 years (7 studies), meeting the modified New York standards for ankylosing spondylitis (4 studies) or standards for axial ankylosing spondylitis in the Assessment of Spondyloarthritis International Society (ASAS) (3 studies), the need for daily treatment with NSAIDs or NSAIDs intolerance (4 studies), score $\geq$4 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), pain score $\geq$4 on the numeric rating scale (NRS 0–10) (6 studies), and written informed consent (4 studies). Out of the several hundred articles identified, the search came up with 10 relevant studies, conducted in 15 countries on 5 continents. A detailed methodological flow diagram is presented in Fig. 1. Studies that contained incomplete data, case reports, reviews, lack of QoL assessment, and studies on children were excluded.

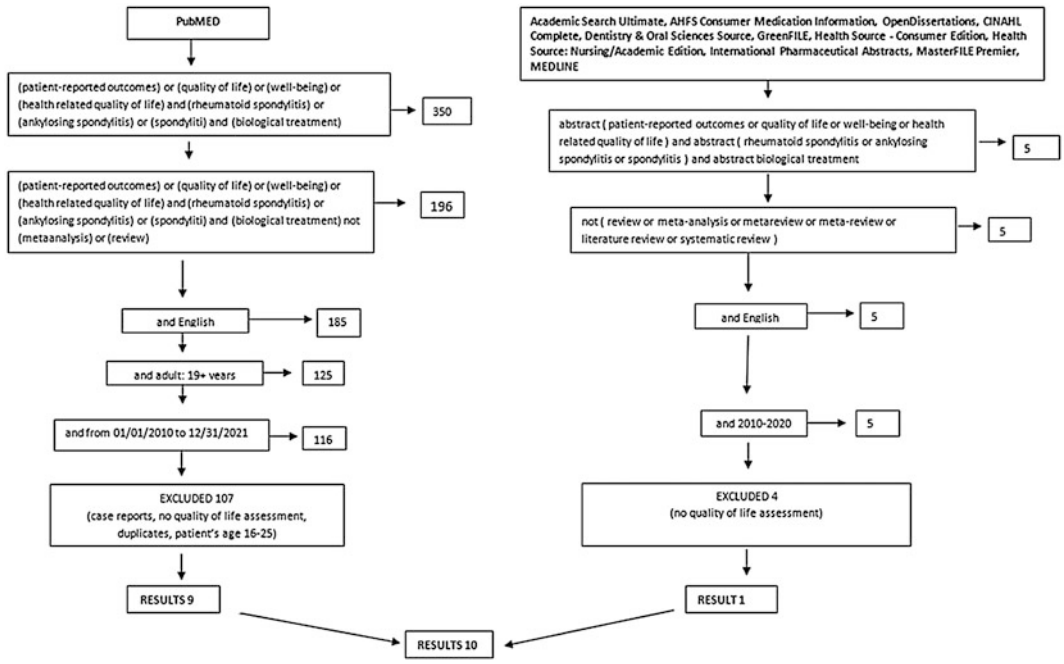

Fig. 1 Diagram showing the search-flow for the literature relevant for ankylosing spondylitis treatment

Questionnaire Structures The questionnaires used in the relevant studies were as follows: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Quality of Life (ASQoL), 36-Item Short-Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Bath Ankylosing Spondylitis Functional Index (BASFI) (Rohde et al. 2020; van der Heijde et al. 2019; Fattahi et al. 2018a, b; Jafarnezhad-Ansariha et al. 2018; van der Heijde et al. 2018a, b; Arısoy et al. 2013; Pathan et al. 2013; Ertenli et al. 2012).

The ASQoL questionnaire is a disease-specific patient-reported outcome measure, based on the needs-model of QoL. It comprises 18 items, each with a dichotomous yes/no response option scored 1 and 0, respectively. A total score ranges from 0 to 18, with higher scores indicating a poorer QoL (Doward et al. 2003). The SF-36 is a 36-item questionnaire assessing the patient's health status. The questionnaire comprises eight domains: vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning, and mental health. Physical component score (PCS) and mental component score (MCS) may be calculated separately or along with eight domains of SF-36 Responses in each domain are converted to a scale of 0 to 100, with all items having assigned the same weight. The higher the score the better is the QoL (Ware Jr and Sherbourne 1992). The FACIT-F questionnaire covers four life domains of chronically ill patients. It comprises 5 parts: physical well-being (PWB) – 7 questions; social/family well-being (SWB) – 7 questions; emotional well-being (EWB) – 6 questions; functional well-being (FWB) – 7 questions, and fatigue subscale (FS) – 13 questions. Each question is rated on a five-point Likert scale. The higher the score the better is the QoL (Cella 1997). The BASFI questionnaire assesses the degree of functional limitation, with higher scores indicating a worse condition.

Literature articles were thoroughly screened by two reviewers for consistency with the subject of this meta-analysis above outlined. They determined if the content consists of interpretable patterns that sufficiently contribute to the accumulated knowledge and evidence-based practice and could advance the process of rehabilitation and care for SA patients. Any discrepancies in the reviewers' assessments were resolved by consensus. Data were extracted and put in the standardized forms that included general information, patient characteristics, study design, risk of bias according to the Newcastle-Ottawa Scale, and intermediate-to-long term (>6 months) main outcomes.

2.2 Study Groups

The active arm of this analysis included 593 patients (85.6% male) aged 22–60, suffering from AS for 1–21 years and treated with biological drugs. The main identified biological drugs used were the following: filgotinib (58 cases), adalimumab (92 cases), ixekizumab (164 cases), β-D-mannuronic acid (60 cases), apremilast (17 cases), infliximab (23 cases), and upadacitinib (89 cases). In the remaining cases, the generic nature of a biological drug was not provided.

The control group treated with other drugs included 702 (70.4% male) patients of 22–58 years of age, who suffered from AS for 1–18 years. They were treated by variable combinations of traditional drugs like NASIDs (582 cases), disease-modifying antirheumatic drugs (561) that notably included methotrexate (284 cases), analgesics (93 cases), and steroids (80 cases). In some studies, biological drugs were mixed with non-biological ones in an unstratified manner and were thus considered together. Aside from the used medications, 191 patients in the control group also received a placebo; 152 patients received a placebo in addition to other standard treatment and 39 patients received placebo alone.

2.3 Statistical Analysis

In this meta-analysis, we examined differences in the clinical improvements between SA patients treated with biological drugs (intervention group) and traditional non-biological drugs or placebo. In some studies, the drugs used were not stratified into types and thus were considered together. The effect-size (ES) was based on the standardized mean difference in a random or fixed model, based on the Q test of homogeneity. The random-effects model was used assuming that different studies would reflect different ES due to differences in patient samples and methods. In this model, the DerSimonian and Laird estimate with 95% confidence intervals (95%CI) were used, estimating the difference between the two groups based on the number of pooled standard deviations by which the two groups differed. This part of the analysis was performed using the R-software v3.6.2 for statistical computing for Windows. For the fixed model, Hedges' *g*, a bias-free measure of standardized mean differences, was used to estimate the ES, according to the formula: *g* x (mean-1 - mean-2)/SD*; where SD* is the pooled and weighted standard deviation of both study and control groups. The results were presented as forest plots. The total was calculated by assigning relative weights to treatment effects from the evaluated publications, depending on the sample size and standard error. A p-value of <0.05 defined a statistically significant difference. Calculations were performed using a commercial package of Statistica v13.3 software (StatSoft Inc; Tulsa, OK).

3 Results

3.1 Treatment of Ankylosing Spondylitis (AS)

The ASQoL assessment showed that patients treated with biological drugs showed a significantly better QoL at 4-month follow-up when compared to those treated with classical therapy alone (Hedges' *g* analysis for heterogeneity: df = 7, Q = 124.5, I^2 = 94.4%, p < 0.001, *vs.* df = 7, Q = 3.3, I^2 = 0.0%, p = 0.854, respectively), while both groups started from a similar baseline level of QoL (Fig. 2).

Since we found a beneficial influence on QoL of biological drugs in SA patients, we posed a question of whether the self-perceived improvement could relate to a particular biological drug used. The lack of standardization in studies on the effects of biological therapy makes it hard to compare patient outcomes. There are variably incomplete data, and different follow-up periods and instruments assessing the QoL and functional performance in the relevant studies surveyed. Nonetheless, we tallied the following information about the effects of single biological drugs.

Filgotinib – selective Janus kinase 1 (JAK1) inhibitor (*n = 58*) (van der Heijde et al. 2018a) – treatment follow-up at 3 months. ASQoL score: baseline 12.8 ±3.5, follow-up 8.0 ±5.2 – improvement by 4.8 points; SF-36 PCS (physical): baseline 33.1 ±5.6, follow-up 41.6 ±7.9 – improvement by 8.5 points; SF-36 MCS (mental): baseline 43.7 ±11.1; follow-up 47.7 ±9.3 – improvement by 4.0 points.

Ixekizumab – monoclonal antibody against interleukin-17A, (van der Heijde et al. 2018b) – treatment follow-up at 4 months. Q2W (*n = 83*): SF-36 PCS (physical): baseline 34.1 ±7.6, follow-up 42.1 ±0.8 – improvement by 8.0 points; Q4W (*n = 81*): SF-36 MCS (mental): baseline 34.0 ±8.0, follow-up 41.7 ± 0.8 – improvement by 7.7 points.

β-D-mannuronic acid – marine algal polysaccharide (*n = 30*) (Fattahi et al. 2018a, b; Jafarnezhad-Ansariha et al. 2018) **–** treatment follow-up at 3 months. ASQoL score: baseline 9.8 ±4.5; follow-up 6.6 ±4.6 – improvement by 3.2 points; baseline 9.1 ±0.7; follow-up 6.0 ±0.6 - improvement by 3.1 points; and baseline 9.8 ±4.5; follow-up 6.7 ±0.6 – improvement by 3.1 points, respectively.

Apremilast – phosphodiesterase 4 (PDE4) inhibitor (*n = 17*) (Pathan et al. 2013) – treatment follow-up at 3 months. FACIT-F score:

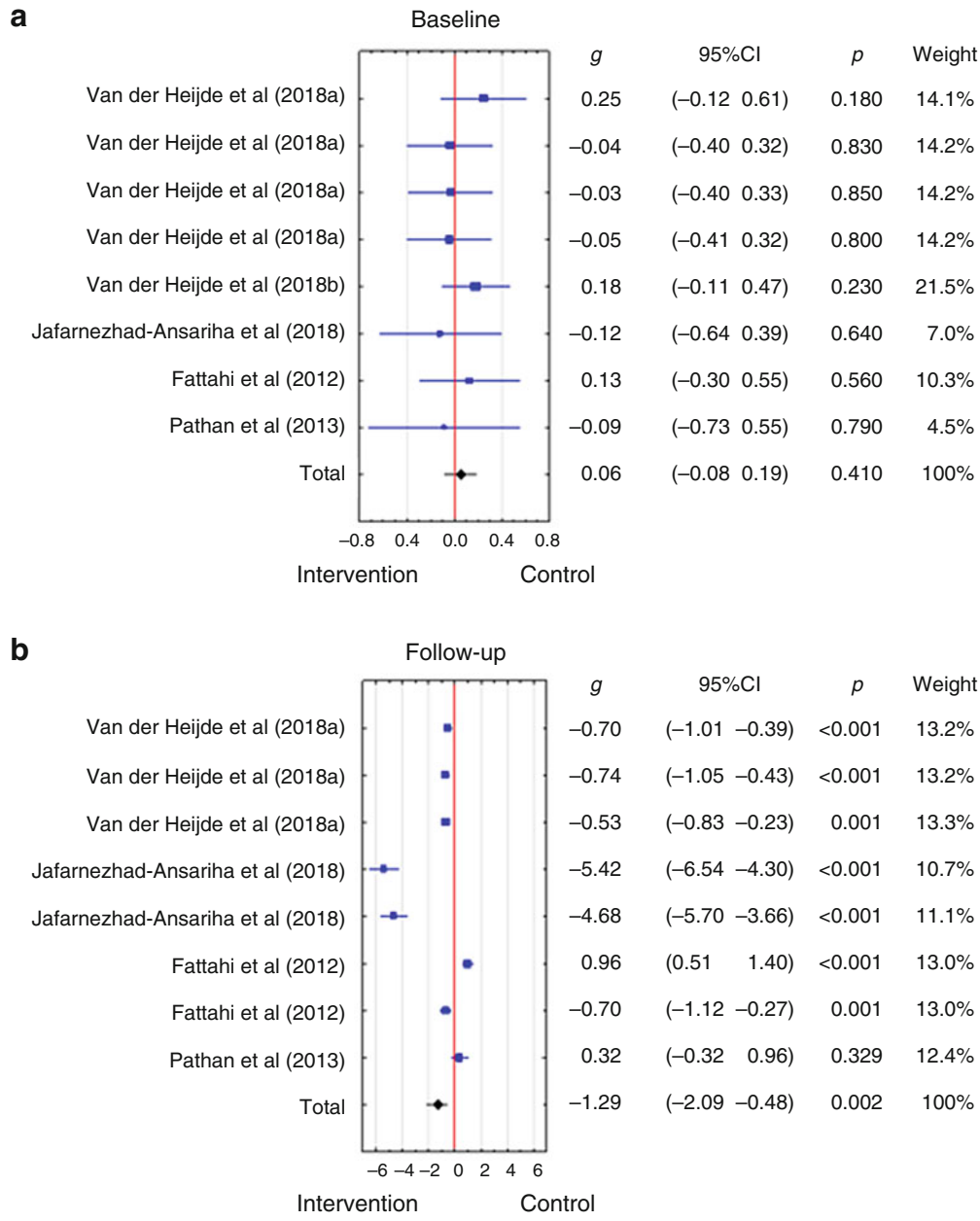

Fig. 2 Quality of life (QoL) in ankylosing spondylitis (AS) treated with biological drugs (intervention group) when compared to the control group not using biological drugs, assessed with ASQoL, except for a study of Pathan et al. (2013), where the FACIT-F questionnaire was used. Note no difference in QoL between the two groups at onset (**a**) and a distinctly better QoL at a 4-month follow-up (**b**)

baseline 107.8 ±25.7, follow-up 117.1 – improvement by 9.3 points. The improvement concerned the physical, social, and emotional domains, as well as the fatigue.

Upadacitinib – Janus kinase (JAK) inhibitor (Van der Heijde et al. 2019) – QoL improvement was verified based on the difference between the biological *versus* non-biological

treatment due to the unspecified treatment follow-up period.

The superior quality of life, assessed with the ASQoL questionnaire, was the single parameter found in this meta-analysis with benefits related to the implementation of treatment with biological drugs. All the other measurements showed improvements in response to treatment, irrespective of biological or traditional drugs used, or even placebo. Therefore, in further analysis, all the drugs were grouped. The AS disease activity, assessed on the BADSI scale, improved from baseline to follow-up while using biologicals (Fig. 3). However, a positive trend of improving the functional performance was also observed with traditional treatments as well as placebo, regardless of the treatment duration (Table 1).

Besides disease activity level, C-reactive protein (CRP) in blood plasma, a marker of inflammation in AS patients, is relevant for the monitoring of treatment effects. Figure 4 shows a significant drop in CRP levels after treatment with biological drugs ($p = 0.001$ for the entire group; Hedges' g analysis). A decline in CRP was noted while using all individual biological drugs included in the analysis except for one case when its level tended to rise after treatment with β-D-mannuronic acid (Jafarnezhad-Ansariha et al. 2018). However, CRP also declined while using other drugs, with a single exception of placebo in a study by Van der Heijde et al. (2018a). Detailed results for biological and other drugs are displayed in Table 2.

In the management of AS patients, the American College of Rheumatology (ACR) recommends the comprehensive ASAS assessment of the

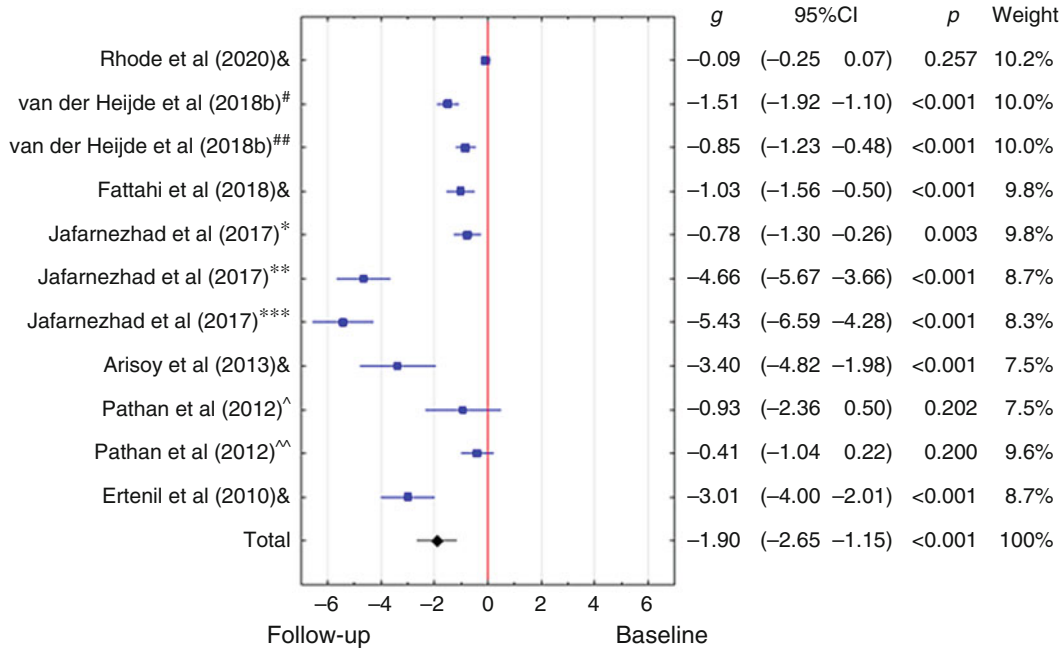

Fig. 3 Disease activity level in ankylosing spondylitis (AS) in patients treated with both biological and traditional drugs at baseline and follow-up after treatment, assessed with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The random-effects model with Hedges' g. The effect size and confidence interval for each study appear graphically on a separate row (blue). The summary effect and its confidence interval are displayed at the bottom (black). 95% CI, lower and upper 95% confidence intervals; &drugs unstratified, #filgotinib, ##placebo, *β-D-mannuronic acid, **naproxen, ***placebo, ^apremilast, ^^placebo

Table 1 Disease activity level in ankylosing spondylitis (AS) in patients treated with both biological and traditional drugs at baseline and follow-up after treatment, assessed on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at baseline and follow-up after treatment, considering all drugs

Source	Treatment	Baseline		Follow-up		
		Patients (n)	Score	Months	Patients (n)	Score
Rohde et al. (2020)	Drugs unstratified	380	3.1 ±2.1	60	240	2.9 ±2.2
Van der Heijde et al. (2018a)	Filgotinib	58	6.9 ±1.2	3	58	4.5 ±2.0
	Placebo	58	7.0 ±1.3	3	58	5.6 ±1.9
Fattahi et al. (2018a)	Drugs unstratified	30	5.8 ±1.3	4	30	4.1 ±1.9
Jafarnezhad-Ansariha et al. (2018)	β-D-mannuronic acid	30	5.8 ±0.2	4	30	5.5 ±0.5
	Naproxen	28	5.7 ±0.2	4	28	3.9 ±0.5
	Placebo	27	5.9 ±0.2	4	27	3.8 ±0.5
Arısoy et al. (2013)	Drugs unstratified	9	7.0 ±1.1	4	9	2.1 ±1.6
Pathan et al. (2013)	Apremilast	17	4.8 ±2.2	4	17	3.2 ±1.6
	Placebo	19	4.4 ±1.8	4	19	3.6 ±2.0
Ertenli et al. (2012)	Drugs unstratified	16	6.0 ±1.2	4	16	2.3 ±1.2

Scores are means ±SD

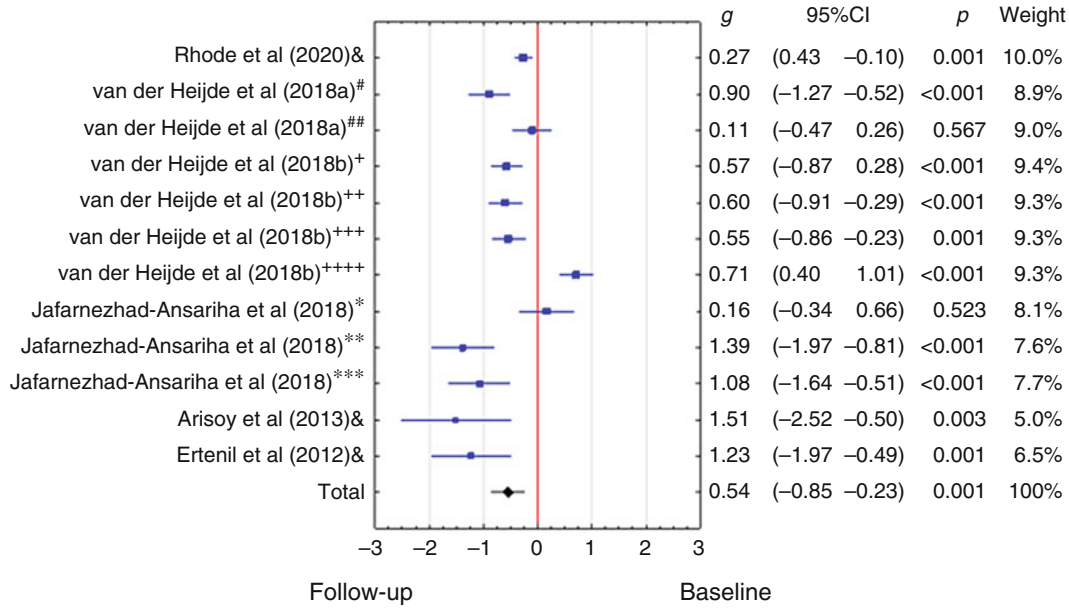

Fig. 4 C-reactive protein (CRP) in the blood plasma of ankylosing spondylitis (AS) patients treated with biological and traditional drugs at baseline and follow-up after treatment. The random-effects model with Hedges' *g*. The effect size and confidence interval for each study appear graphically on a separate row (blue). The summary effect and its confidence interval are displayed at the bottom (black). 95% CI, lower and upper 95% confidence intervals; &drugs unstratified, #filgotinib, ##placebo, +adalimumab, ++ixekizumab Q2W, +++ixekizumab Q4W, ++++placebo, *β-D-mannuronic acid, **naproxen, ***placebo

Table 2 C-reactive protein (CRP) in the blood plasma of ankylosing spondylitis (AS) patients at baseline and treatment follow-up, considering all drugs

Source	Treatment	Baseline		Follow-up		
		Patients (n)	mg/L	Months	Patients (n)	mg/L
Rohde et al. (2020)	Drugs unstratified	380	10.0 ±13.2	60	240	6.7 ±10.7
Van der Heijde et al. (2018b)	Filgotinib	58	19.6 ±13.3	3	58	8.8 ±10.5
	Placebo	58	21.2 ±23.0	3	58	18.9 ±20.2
Van der Heijde et al. (2018a)	Adalimumab	90	12.5 ±17.6	4	90	5.3 ±1.9
	Ixekizumab Q2W	83	13.4 ±15.3	4	83	6.8 ±2.0
	Ixekizumab Q4W	81	12.2 ±13.3	4	81	7.1 ±2.0
	Placebo	87	16.0 ±2.1	4	87	17.4 ±1.9
Jafarnezhad-Ansariha et al. (2018)	β-D-mannuronic acid	30	8.3 ±1.2	4	30	8.5 ±1.1
	Naproxen	28	8.0 ±0.8	4	28	6.8 ±0.9
	Placebo	27	8.1 ±0.9	4	27	7.0 ±1.1
Arzsoy et al. (2013)	Drugs unstratified	9	22.9 ±15.0	1.5	9	5.2 ±4.9
Ertenli et al. (2012)	Drugs unstratified	16	3.7 ±3.5	1.5	16	0.6 ±0.5

Scores are means ±SD

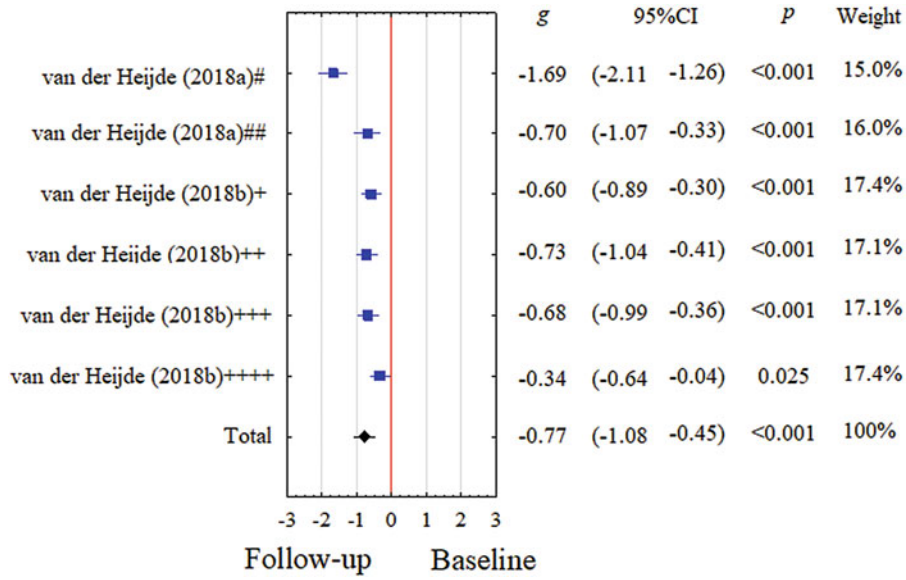

Fig. 5 Effectiveness of clinical treatment using biological drugs and placebo in ankylosing spondylitis (AS) patients, based on the SpondyloArthritis International Society (ASAS) assessment at baseline and follow-up after treatment. The random-effects model with Hedges' *g*. The effect size and confidence interval for each study appear graphically on a separate row (blue). The summary effect and its confidence interval are displayed at the bottom (black). 95% CI, lower and upper 95% confidence intervals; #filgotinib, ##placebo, +adalimumab, ++ixekizumab Q2W, +++ixekizumab Q4W, ++++placebo

patient's functioning, which is used as a criterion for initiating biological therapy (Ward et al. 2016). In our meta-analysis, a comparison of ASAS scores at baseline and follow-up after treatment showed a significant improvement in functioning in patients using biological drugs as well as in those receiving a placebo, with inappreciable differences (Fig. 5 and Table 3).

Table 3 SpondyloArthritis International Society (ASAS) scoring in ankylosing spondylitis (AS) patients at baseline and treatment follow-up, considering biological drugs and placebo

Source	Treatment	Baseline		Follow-up		
		Patients (n)	Score	(Months)	Patients (n)	Score
Van der Heijde et al. (2018b)	Filgotinib	58	4.2 ±0.6	3	58	2.8 ±1.0
	Placebo	58	4.2 ±0.8	3	58	3.6 ±0.9
Van der Heijde et al. (2018a)	Adalimumab	90	8.2 ±3.7	4	90	5.9 ±4.0
	Ixekizumab Q2W	83	8.4 ±3.6	4	83	5.7 ±3.9
	Ixekizumab Q4W	81	7.5 ±3.3	4	81	5.1 ±3.6
	Placebo	87	8.1 ±3.5	4	87	6.9 ±3.8

Scores are means ±SD

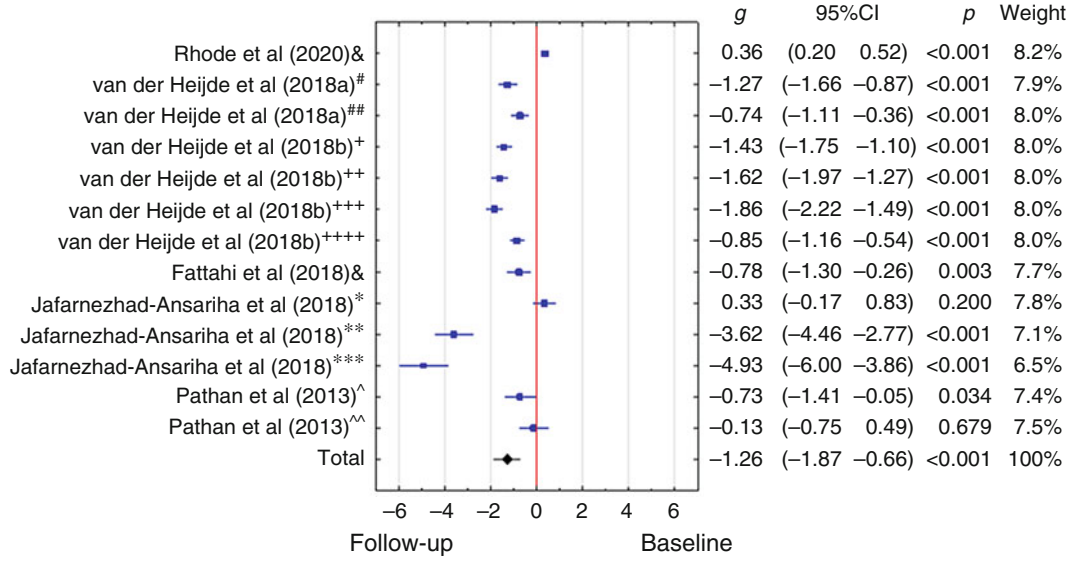

Fig. 6 Functional assessment in ankylosing spondylitis (AS) patients treated with biological and traditional drugs at baseline and treatment follow-up, based on the Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaire. The random-effects model with Hedges' *g*. The effect size and confidence interval for each study appear graphically on a separate row (blue). The summary effect and its confidence interval are displayed at the bottom (black). 95% CI, lower and upper 95% confidence intervals; *filgotinib, **placebo, $^{+}$adalimumab, $^{++}$ixekizumab Q2W, $^{+++}$ixekizumab Q4W, $^{++++}$placebo, $^{\#}$β-D-mannuronic acid, $^{\#\#}$naproxen, $^{\#\#\#}$placebo, ^apremilast, ^^placebo

The evaluation of functional performance in the AS patients using the BASFI also showed, overall, significant score decreases pointing to improvements, irrespective of the therapy mode (Fig. 6). There were, however, single exceptions to the opposite. Rohde et al. (2020) noticed no improvement in the BASFI score (2.6 *vs.* 3.4; p >0.05) in a group of patients treated with biological drugs at a 5-year follow-up. Likewise, no functional improvement was noticed while using a placebo (4.7 *vs.* 5.8; p >0.05) in a study of Jafarnezhad-Ansariha et al. (2018) (Table 4).

Table 4 Functional assessment in AS patients based on the Bath Ankylosing Spondylitis Functional Index (BASFI) at baseline and follow-up after treatment, considering all drugs

Study	Treatment	Baseline		Follow-up		
		Patients (n)	Score	Months	Patients (n)	Score
Rohde et al. (2020)	Drugs unstratified	380	2.6 ±2.2	60	240	3.4 ±2.2
Van der Heijde et al. (2018a)	Filgotinib	58	7.0 ±1.5	3	58	4. 6 ±2.2
	Placebo	58	6.9 ±1.6	3	58	5.6 ±1.9
Van der Heijde et al. (2018b)	Adalimumab	90	6.1 ±2.1	4	90	4.0 ±0.2
	Ixekizumab Q2W	83	6.3 ±2.1	4	83	3.9 ±0.2
	Ixekizumab Q4W	81	6.1 ±1.8	4	81	3.7 ±0.2
	Placebo	87	6.4 ±1.9	4	87	5.2 ±0.2
Fattahi et al. (2018a)	Drugs unstratified	30	4.4 ±2.0	3	30	2.9 ±1.8
Jafarnezhad-Ansariha et al. (2018)	β-D-mannuronic acid	30	4.4 ±0.3	3	30	3.3 ±0.3
	Naproxen	28	4.2 ±0.3	3	28	2.7 ±0.3
	Placebo	27	4.7 ±0.3	3	27	5.8 ±0.3
Pathan et al. (2013)	Apremilast	17	4.6 ±2.4	3	17	2.8 ±2.2
	Placebo	19	3.5 ±2.2	3	19	3.2 ±2.0

Scores are means ±SD

Table 5 Factors affecting the quality of life (QoL) in ankylosing spondylitis (AS) patients

Factors increasing QoL	Factors decreasing QoL
Younger age, higher education, lower disease burden, low BASDAI, high BAS-G, high CRP, no use of biological treatment at baseline, and low HAQ score (Rohde et al. 2020), upadactinib 15 mg once a day (van der Heijde et al. 2019), filgotinib (van der Heijde et al. 2018a), adalimumab and ixekizumab (van der Heijde et al. 2018b), β-D-mannuronic acid, naproxen, lower CRP, and longer time elapsing from the intervention (Arısoy et al. 2013), apremilast (Pathan et al. 2013)	Anxiety and depression, erythrocyte sedimentation rate, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score (Arısoy et al. 2013)

3.2 Positive and Negative Predictors of Quality of Life (QoL) in Patients with Ankylosing Spondylitis (AS)

Besides QoL scoring, the research on QoL often includes the search for the presaged predictors of QoL. In the relevant publications, the following factors are listed as positive predictors: age, social support, professional activity, illness acceptance, and rehabilitation. Conversely, negative predictors are the following: living alone, depression, severe symptoms, pain, frequent hospitalizations, and old age (Jankowska-Polanska et al. 2017; Polanski et al. 2016). The present meta-analysis revealed that positive predictors for QoL among patients with AS included younger age, better education, lower symptom severity, treatment with biologicals and other selected drugs, and shorter treatment duration. The adverse predictors were anxiety and depression, and greater symptom severity. These results are summarized in Table 5.

Biological drugs are recommended for SA patients who do not respond to other drugs over 6 months' treatment. These drugs, however, have adverse events that are displayed and compared against placebo in Fig. 7. The most often in decreasing frequency are the following: infections, inclusive of upper respiratory tract infections (133 patients), neutropenia grade 1 (32 patients), headache (31 patients), and injection site reactions (25 patients). Out of these

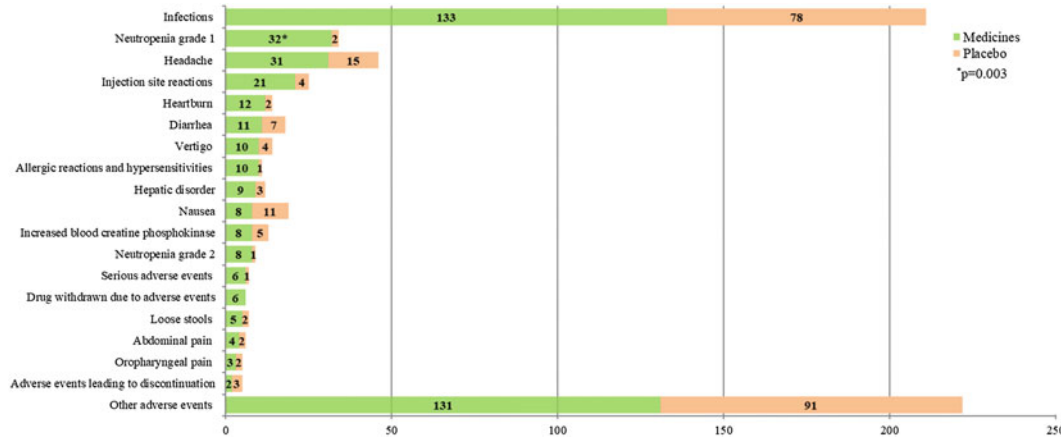

Fig. 7 Adverse effects in ankylosing spondylitis (AS) patients treated with biological drugs *versus* placebo; *significant difference between biological drugs and placebo

events, neutropenia grade 1 occurred significantly more often in patients treated with biological drugs (adaliumumab Q2W, ixekizumab Q2W, and ixekizumab Q4W) than placebo; 5.7% versus 0.6%, respectively ($p = 0.003$). The incidence of the other treatment-associated adverse events differed insignificantly between the biological drugs and placebo.

4 Discussion

According to the New York criteria, AS affects 0.007–1.7% of the global population, with an annual incidence of 0.44–7.3 *per* 100,000 individuals (Stolwijk et al. 2012). The prevalence in central Europe is estimated at 0.5% and most patients are men. It is a potentially serious disease with a variety of symptoms, typically requiring multidisciplinary treatment coordinated by a rheumatologist. Treatment for AS is complex, comprising medicines, physiotherapy, psychotherapy, and surgical interventions. The severity of chronic pain and stiffness increases gradually as the inflammation spreads to higher segments of the spine, disrupting its normal curvature. The associated ankylosis, peripheral joint deformities, and extremity contractures often lead to severe disability. As the disease often affects young people, most commonly in their thirties, it interferes with professional and social activity. About 10–30% of patients give up professional activity within 10 years of disease onset due to the progressive functional restriction. The available literature indicates that the life expectancy of AS patients is shorter than that in the general population due to disease complications (Haroon et al. 2015). This meta-analysis shows that biological drugs used in SA offer the benefit of a better patient QoL compared with the traditional non-biological treatment. Both kinds of treatments have the potential to generate a similar specter of multi-system adverse effects during a long-term follow-up. Biological drugs, noticeably, significantly more often may cause mild neutropenia than do non-biological ones. Nonetheless, the advantage of QoL with biological drugs provides a rationale to consider them as the more effective option.

The main objective of AS treatment is achieving the best possible QoL in the long term, by managing symptoms and inflammation, preventing progressive structural damage, and maintaining or restoring functional performance and ability to participate in social activities. For more than 10 years, biological drugs have been used as a pharmacological tool for AS treatment in Poland, with a lot of hope placed in these medications by physicians and patients alike. The drugs in use are monoclonal antibodies that

bind to humoral factors and cells involved in the immune response, thus inhibiting inflammation. Their application provides benefits like a rapid effect, symptom alleviation, longer periods of remission, a lower level of pain, and better QoL. Notably, QoL in terms of physical functioning is enhanced more than that of mental health (Law et al. 2018). Gorman et al. (2002) have reported that etanercept produces significant improvements in morning stiffness, spinal pain, number of swollen joints, and functional performance in AS patients. Studies on the use of TNF-α inhibitors in AS treatment also show less pain and improvements in functional activity and performance and laboratory tests, including blood CRP levels (Tłustochowicz 2011). In this meta-analysis, we also found a downward trend in CRP blood content, taken as a clinical index of treatment effectiveness. Likewise, in a study performed at the Institute of Rheumatology in Prague, Chechia, nearly one-half of AS patients treated with biological drugs had a positive and effective clinical response (Lachaine et al. 2013). In a study by van der Heijde et al. (2018b), patients treated with adalimumab showed an improvement in QoL at a 3–6-month follow-up, sustained for 5 years despite the signs of inflammation found in X-ray images. The improvement was particularly clear while using the BASFI and ASQoL questionnaires. According to those authors, the QoL is mainly determined by functional performance and disease activity. On the other side, the physical domain of QoL is affected by spine mobility and disease activity determined by the irreversible structural damage and reversible inflammation in the spine (Machado et al. 2010). Rohde et al. (2020) have found that patients with axial spondyloarthritis do not show a deterioration in health-related QoL during 5 years of treatment with biological drugs but have a significant improvement in physical health evaluated by the generic SF-36 questionnaire. In another study, the administration of 15 mg of upadacitimid once daily produced a response 2 weeks after treatment onset in SA patients, consisting of back pain reduction that lasted for 14 consecutive weeks and was confirmed by abating inflammation of the spine and sacroiliac joints in the magnetic resonance imaging (van der Heijde et al. 2019). The authors have documented that improvements in functioning and a reduction in disease activity were greater in patients treated with biological drugs than in those receiving placebo, with adverse events being of no major concern or requiring a change or discontinuation of therapy. However, patients treated with the biological drug had a higher creatinine kinase level, albeit not associated with more severe functional impairment.

In another study, the effect of filgotinib was assessed, with the primary endpoint being a change in disease activity from the baseline level (van der Heijde et al. 2018a). At a 3-month follow-up, the mean ankylosing spondylitis disease activity score (ASDAS) was higher in the filgotinib group when compared to placebo, showing the effectiveness of the drug in reducing symptoms of AS inflammation. The biological drug was well tolerated. The incidence of adverse events in the biological therapy group was akin to that in the placebo group as also was the number of patients who discontinued the treatment. In a different study by van der Heijde et al. (2018b), ixekizumab was administered every 3 or 4 weeks and its effects were compared against placebo. At a 4-month follow-up, physical function improved, and the disease activity was lower in patients treated with the biological drug, and the improvements were greater than those possibly observed with placebo. No difference was found concerning adverse events between the biological drug and placebo.

Another biological drug, proven effective in SA, is β-D-mannuronic acid (Fattahi et al. 2018a). The drug appeared effective 2 weeks after treatment onset and over 3 months of continued therapy. Likewise, improvements mainly concerned the disease activity and functional performance. This study did not compare the drug with a placebo. In another study, Jafarnezhad-Ansariha et al. (2018) have compared the therapeutic effectiveness of β-D-mannuronic acid to a combination of naproxen and placebo. The outcome measure was a mean change from baseline to therapy week 12. The authors show beneficial effects of the drug in that

it reduced pain, stiffness, and inflammation assessed by the blood CRP level, as well as improvements in physical function assessed by BASDAI and BASFI scores. Further, treatment-associated adverse events did not exceed those observed in the control treatment consisting of naproxen and placebo. Fattahi et al. (2018b) have also compared the therapeutic effectiveness of β-D-mannuronic against naproxen with placebo and confirmed good tolerance and high effectiveness of the biological drug over a 3-month follow-up. Beneficial effects included less pain, better functional performance, and lower CRP levels. In this study, the biological drug was associated with fewer adverse events compared to naproxen. On the other hand, Pathan et al. (2013) have investigated the treatment with an oral phosphodiesterase 4 inhibitor, apremilast, on the premise that it might be effective and well-tolerated in AS patients as it modulates biomarkers of bone biology. The study, however, has failed to establish the presence of appreciable benefits at a 3-month follow-up compared to placebo.

The known effects of biological drugs are not limited to the inhibition of disease progression, improvements in functional status, and reductions in stiffness, pain, and inflammation. Studies have shown the effectiveness of TNF-α inhibitors, e.g., infliximab, in the treatment of depressive symptoms accompanying the AS (Arısoy et al. 2013). In a study by Ertenli et al. (2012), infusions of infliximab were associated with a gradual reduction of depression and anxiety symptoms and QoL improvements since the very beginning of the intervention, and the drug's effectiveness increased with consecutive infusions.

Among predictors of QoL, the literature notably mentions higher education associating with a better long-term health-related QoL (Kotsis et al. 2014). The relation of patient age to the QoL remains somehow debatable. A younger age often means a shorter duration of illness, and thus, less structural damage and fewer complications (Rohde et al. 2020). On the other hand, the duration of illness is difficult to establish in patients with axial SA as symptoms may develop for up to 10 years before the diagnosis is made (Feldtkeller et al. 2000).

A major limitation of this meta-analysis is a lack of standardized data in all papers included in it, which concerns the research instruments used, intervention duration, and inclusion or not of a control group. Moreover, the scoring of instruments is not always compatible with each other in different papers, which hampers the interpretation of findings. Another limitation is the use of different active substances and different follow-up periods across the studies. Additionally, some studies included the assessment at just two-time points whereas repeated assessments at multiple equal intervals would have produced clearer results.

5 Conclusions

We conclude that patients suffering from ankylosing spondylitis, generally, benefit from regular treatment concerning QoL and functional performance. The benefits are greater with biological therapy than with using a placebo. The QoL is positively influenced by younger age, higher education, better functional status, biological therapy, and a longer of treatment, and negatively influenced by anxiety and depression. There appears no appreciable difference concerning the adverse events between biological and standard therapy, except for the propensity for neutropenia that is more common in the biologically treated patients. To achieve a well-scrutinized view on ankylosing spondylitis treatment, it is recommendable that future evaluations be based on studies that involve the controlled use of the same drug and employ the same standardized research instruments. Nonetheless, we believe that the finding that biological drugs are superior in improving the QoL should strengthen the recommendations for their use in patients with AS.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval This review article does not contain any studies with human participants or animals performed by any of the authors.

References

Arısoy O, Bes C, Cifci C, Sercan M, Soy M (2013) The effect of TNF-alpha blockers on psychometric measures in ankylosing spondylitis patients: a preliminary observation. Rheumatol Int 33:1855–1864

Cella D (1997) Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Center on Outcomes, Research and Education (CORE). Version 4. Evanston Northwestern Healthcare and Northwestern University, Evanston, IL

Doward LC, Spoorenberg A, Cook AS, Whalley D, Helliwell PS, Kay LJ, McKenna SP, Tennant A, van der Heijde D, Chamberlain MA (2003) Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 62(1):20–26

Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O, Calguneri M, Kalyoncu U (2012) Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. Rheumatol Int 32(2):323–330

Fattahi MJ, Ahmadi H, Jafarnezhad-Ansariha F, Mortazavi-Jahromi SS, Rehm BHA, Cuzzocrea S, Matsuo H, Mirshafiey A (2018a) Oral administration effects of β-d-mannuronic acid (M2000) on Th17 and regulatory T cells in patients with ankylosing spondylitis. Biomed Pharmacother 100:495–500

Fattahi MJ, Jamshidi AR, Mahmoudi M, Vojdanian M, Yekaninejad MS, Jafarnezhad-Ansariha F, Ahmadi H, Rehm BHA, Matsuo H, Cuzzocrea S, Hosseini M, Hashemi SN, Aghazadeh Z, Mirshafiey A (2018b) Evaluation of the efficacy and safety of β-D-mannuronic acid in patients with ankylosing spondylitis: a 12-week randomized, placebo-controlled, phase I/II clinical trial. Int Immunopharmacol 54:112–117

Feldtkeller E, Bruckel J, Khan MA (2000) Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol 12(4):239–247

Gao X, Wendling D, Botteman MF, Carter JA, Rao S, Cifaldi M (2012) Clinical and economic burden of extra-articular manifestations in ankylosing spondylitis patients treated with anti-tumor necrosis factor agents. J Med Econ 15(6):1054–1063

Gorman JD, Sack KE, Davis JC Jr (2002) Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 346(18):1349–1356

Haroon NN, Paterson JM, Li P, Inman RD, Haroon N (2015) Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. Ann Intern Med 163 (6):409–416

Jafarnezhad-Ansariha F, Yekaninejad MS, Jamshidi A, Mansouri R, Vojdanian M, Mahmoudi M, Fattahi MJ, Hashemi SN, Rehm BHA, Matsuo H, Esposito E, Cuzzocrea S, Mirshafiey A (2018) The effects of β-D-mannuronic acid (M2000), as a novel NASID, on COX1 and COX2 activities and gene expression in ankylosing spondylitis patients and the murine monocyte/macrophage, J774 cell line. Inflammopharmacology 26(2):375–384

Jankowska-Polanska B, Uchmanowicz I, Wysocka A, Uchmanowicz B, Lomper K, Fal AM (2017) Factors affecting the quality of life of chronic dialysis patients. Eur J Pub Health 27(2):262–267

Kotsis K, Voulgari PV, Drosos AA, Carvalho AF, Hyphantis T (2014) Health-related quality of life in patients with ankylosing spondylitis: a comprehensive review. Expert Rev Pharmacoecon Outcomes Res 14 (6):857–872

Lachaine J, Beauchemin C, Desjardins O (2013) Use of biological agents in the treatment of rheumatoid arthritis: an analysis of the Quebec provincial drug reimbursement program database. Value Health 3:230–231

Law L, Rehnman JB, Deminger A, Klingberg E, Jacobsson LTH, Forsblad-d'Elia H (2018) Factors related to health-related quality of life in ankylosing spondylitis, overall and stratified by sex. Arthritis Res Ther 20(1):284

Machado P, Landewé R, Braun J, Hermann KA, Baker D, van der Heijde D (2010) Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 69(8):1465–1470

Megari K (2013) Quality of life in chronic disease patients. Health Psychol Res 1(3):e27

Pathan E, Abraham S, Van Rossen E, Withrington R, Keat A, Charles PJ, Paterson E, Chowdhury M, McClinton C, Taylor PC (2013) Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. Ann Rheum Dis 72 (9):1475–1480

Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A (2016) Quality of life of patients with lung cancer. Onco Targets Ther 9:1023–1028

Reveille JD, Weisman MH (2013) The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. Am J Med Sci 345:431–436

Rohde G, Berg KH, Pripp AH, Přrven A, Haugeberg G (2020) No deterioration in health-related quality of life in patients with axial spondyloarthritis followed for 5 years in ordinary outpatient clinics in the biological treatment era. Qual Life Res 29:99–107

Stolwijk C, Boonen A, van Tubergen A, Reveille JD (2012) Epidemiology of spondyloarthritis. Rheum Dis Clin N Am 38(3):441–476

Tłustochowicz M (2011) Rytuksymab in treatment of rheumatoid arthritis. Reumatologia 49(1):55–61. (Article in Polish)

van der Heijde D, Baraliakos X, Gensler LS, Maksymowych WP, Tseluyko V, Nadashkevich O, Abi-Saab W, Tasset C, Meuleners L, Besuyen R, Hendrikx T, Mozaffarian N, Liu K, Greer JM, Deodhar A, Landewé R (2018a) Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. Lancet 392 (10162):2378–2387

van der Heijde D, Cheng-Chung Wei J, Dougados M, Mease P, Deodhar A, Maksymowych WP, Van den Bosch F, Sieper J, Tomita T, Landewé R, Zhao F, Krishnan E, Adams DH, Pangallo B, Carlier H, COAST-V study group (2018b) Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet 392(10163):2441–2451

van der Heijde D, Song IH, Pangan AL, Deodhar A, van den Bosch F, Maksymowych WP, Kim TH, Kishimoto M, Everding A, Sui Y, Wang X, Chu AD, Sieper J (2019) Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet 394 (10214):2108–2117

Ward MM, Deodhar A, Akl EA et al (2016) 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 68 (2):282–298

Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6):473–483

Yang X, Fan D, Xia Q, Wang M, Zhang X, Li X, Cai G, Wang L, Xin L, Xu S, Pan F (2016) The health-related quality of life of ankylosing spondylitis patients assessed by SF-36: a systematic review and meta-analysis. Qual Life Res 25(11):2711–2723

Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X, Qiu G, Cao X, Weng X (2019) Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res 7(22)