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Clinical science

Does symptom duration impact on treatment response in axial spondyloarthritis? A meta-analysis of randomized controlled trials

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Abstract

Objectives: The ASAS consensus defines ‘early axial spondyloarthritis (axSpA)’ as symptom duration ≤ 2 years, a definition derived from expert opinion due to limited evidence. We performed a meta-analysis of randomized placebo-controlled trials (RCTs) of biologic and targeted synthetic DMARDs (bDMARDs/tsDMARDs) in axSpA to assess the impact of symptom duration on treatment response.

Methods: RCTs in adult axSpA patients comparing b/tsDMARDs to placebo were identified through systematic literature reviews supporting the ASAS-EULAR management recommendations. Primary outcome was ASAS40 response, with secondary outcomes including disease activity, function and quality of life at each trial’s primary end point. Relative risks (RRs) comparing two groups (shorter vs longer symptom duration) were calculated for efficacy outcomes for each arm and for several thresholds of symptom duration (1–5 years). RR ratios (RRRs) were calculated as the ratio of RR of the b/tsDMARD and placebo arms. Pooled effects were obtained with random-effects meta-analysis.

Results: Eleven bDMARD RCTs, comprising 3272 axSpA patients, were included. No studies involving tsDMARDs met the eligibility criteria. At the 2-year threshold, pooled RR for ASAS40 response was 2.04 (95% CI, 1.48–2.84) in early axSpA and 2.28 (95% CI, 1.65–3.15) in established disease, yielding an RRR of 0.89 (95% CI, 0.63–1.26), with no statistical significance. There were no significant differences between efficacy in shorter and longer symptom duration for other outcomes or across other symptom duration thresholds (3–5 years).

Conclusions: Based on a meta-analysis of 11 trials, no significant differences were found in the efficacy of bDMARDs compared with placebo in patients with axSpA with shorter vs longer symptom duration, across thresholds from 2 to 5 years.

Keywords: axial spondyloarthritis, symptom duration, biologic DMARDs, treatment response, meta-analysis.

Rheumatology key messages

- Short-term efficacy of bDMARDs in axSpA is independent of symptom duration at treatment initiation.
- No significant treatment effect differences were observed between early and established axSpA across endpoints.
- Although bDMARD efficacy is not impacted by symptom duration, early treatment may reduce symptom burden sooner.

Introduction

The field of spondyloarthritis (SpA) has experienced significant advancements in recent years, particularly in the identification and management of axial spondyloarthritis (axSpA) [1]. One of the latest developments has been the emerging research on the initial stage of the disease [2]. In this regard, a lack of consensus on the concept of early SpA resulted in heterogeneous populations across studies, hindering research methodologies and hampering the interpretation of the results [3]. Recognizing this challenge, the Assessment of

SpondyloArthritis international Society (ASAS) initiated the ASAS-SPEAR (SPondyloarthritis EARly definition) project to develop a consensus definition for ‘early axSpA’ to be used in research settings [4]. Through a multi-step process involving systematic literature reviews (SLRs), a Delphi survey, discussions and voting, a consensus definition was reached for ‘early axSpA’ [3–5]. The ASAS community endorsed a definition based on symptom duration, specifically referring to patients with a diagnosis of axSpA with ≤ 2 years of axial symptoms—including spinal or buttock pain or morning

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stiffness—considered by a rheumatologist as related to axSpA. Of note, the symptom duration threshold used in this definition was based on expert opinion due to limited evidence on the treatment effectiveness with different thresholds [4, 5].

Indeed, the impact of symptom duration on treatment outcomes remains uncertain [6]. While biologic and targeted synthetic DMARDs (bDMARDs and tsDMARDs) have consistently shown efficacy in clinical outcomes, there is scarce robust evidence addressing whether earlier treatment initiation leads to improved outcomes in axSpA [5]. Most randomized controlled trials (RCTs) have not assessed the impact of symptom duration on response to treatment. Some *post hoc* analyses and observational studies suggest that patients receiving treatment earlier may experience better outcomes compared with those treated later in the disease course [7–9]. However, these findings must be interpreted with caution due to the heterogeneous definitions of early treatment used in existing studies; besides, most of these conclusions have been withdrawn based on numeric comparisons in patients in the shorter vs longer symptom duration groups taking only one intervention group into account and not accounting for the potential effect of the other intervention arm, i.e. active drug and placebo [5].

Given this lack of evidence, there is a need for a systematic analysis to clarify whether symptom duration influences treatment response in axSpA. Therefore, we conducted a meta-analysis of placebo-controlled clinical trials involving bDMARDs and tsDMARDs in adult patients with axSpA, aiming to assess whether symptom duration impacts treatment response. Our primary objective was to determine whether shorter symptom duration, including the ASAS ‘early axSpA’ definition, is associated with different treatment outcomes compared with longer symptom durations. Furthermore, we sought to identify the optimal threshold that best differentiates between shorter and longer symptom duration in treatment response.

Methods

Study design

We conducted an SLR and meta-analysis to investigate the impact of symptom duration on treatment outcomes in patients with axSpA. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

Study selection and risk of bias

To identify the eligible studies, we made use of previous SLRs performed for the ASAS-European Alliance of Associations for Rheumatology (EULAR) management recommendations, including the 2022 update, of approved bDMARDs and tsDMARDs [11–13]. The search of the included SLRs included studies until February 2022 retrieved from MEDLINE, EMBASE and Cochrane CENTRAL databases. From these, the eligible studies were selected by DB and DC, following predefined eligibility criteria. Risk of bias (RoB) was assessed by the reviewers from the SLR of the ASAS/EULAR recommendations using V.2 of the Cochrane RoB tool (RoB 2) [14]. Overall RoB for each study was expressed as ‘low’, ‘unclear’ or ‘high’.

Eligibility criteria

Eligible studies included RCTs involving adult patients (aged ≥ 18 years) diagnosed with axSpA, treated with bDMARDs or tsDMARDs compared with placebo, and reporting symptom duration from the onset of axial symptoms. Interventions included treatment with approved bDMARDs at that point—adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, secukinumab or ixekizumab—and tsDMARDs—tocilizumab, or upadacitinib.

Patients were categorized as having shorter vs longer symptom duration, including thresholds of 1, 2, 3, 4 and 5 years. Patients with recorded symptom duration were classified into shorter or longer duration groups according to the predefined thresholds. The terms ‘early disease’ and ‘established disease’ were used for the 2-year cut-off. A patient could be included in multiple analyses corresponding to different thresholds. To ensure meaningful subgroup analyses, studies were required to have at least 20% of patients within each subgroup specified by the symptom duration threshold. When the proportion of patients below each symptom duration threshold was not mentioned in the potentially eligible studies, the authors or trial sponsors were contacted to assess the eligibility of the trial.

Data sources

De-identified individual patient data (IPD) were obtained from sponsors of industry-funded RCTs. Data were received after approval by data-sharing committees of the respective companies through platforms such as Vivli, the Yale University Open Data Access (YODA) Project, ClinicalStudyDataRequest.com (CSDR) and individual company websites [15–17]. For investigator-initiated trials not sponsored by industry, we contacted the principal investigators to obtain the necessary data. Data were obtained by analysing IPD and, at the trial level, compiling aggregated information based on a standardized data extraction sheet.

Data extraction and outcomes

Data on study characteristics, patient demographics (age, sex), disease characteristics (symptom duration, disease subtype—radiographic axSpA [r-axSpA] or non-radiographic axSpA [nr-axSpA]), HLA-B27 status, treatments (intervention and comparator) and outcomes were collected. Outcomes were collected for the subgroups defined based on each symptom duration threshold.

The primary outcome was the proportion of patients achieving ASAS40 response at the timing of the primary outcome assessment of each study, namely 12–16 weeks. This outcome was selected as it is nowadays the most common primary end point of RCTs. Secondary outcomes included ASAS20, ASAS5/6 response, ASAS partial remission, changes in the Axial Spondyloarthritis Disease Activity Score (ASDAS), ASDAS clinically important improvement (improvement ≥ 1.1), ASDAS major improvement (improvement ≥ 2.0), achievement of ASDAS low disease activity (< 2.1), achievement of ASDAS inactive disease (< 1.3), change in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), BASDAI50 response, change in CRP serum levels, functional assessment (change in the Bath Ankylosing Spondylitis Functional Index [BASFI]), spinal mobility (change in the Bath Ankylosing Spondylitis Metrology Index [BASMI]) and quality of life measures (change in the ASAS Health Index [ASAS HI], Ankylosing Spondylitis Quality of

Life [ASQoL], European Quality of Life-5 Dimensions [EQ-5D] and the 36-Item Short Form Health Survey physical and mental component scores [SF-36]).

Statistical analysis

The analysis involved two steps: individual study-level analysis and meta-analysis of all included studies. Relative risks (RRs) were calculated as the ratio of outcomes between patients with shorter vs longer symptom duration thresholds. Following this, relative risk ratios (RRRs), together with their CIs, were computed to compare the RR of the b/tsDMARD-treated group with that of the placebo group. This allowed to assess whether shorter symptom duration (vs longer symptom duration) influenced the response to b/tsDMARD therapy relative to placebo, indicating whether symptom duration affected treatment response to b/tsDMARD therapy vs placebo. For continuous outcomes, mean differences and their S.D. were calculated for each treatment group. Subsequently, differences in differences (DiD) were calculated to represent the difference in treatment effects between shorter vs longer symptom duration thresholds. An Intention-to-Treat approach was applied, and missing data were managed through imputation methods following the imputation for the trial main analysis. For dichotomous outcomes, missing values were imputed using non-responder imputation, assuming that missing responses equate to non-response. For continuous outcomes, missing data were handled using multiple imputation. Pooled analyses were performed using random-effects models to account for variability across studies.

In order to assess the impact of the axSpA subtype on outcomes, trials were classified as r-axSpA or nr-axSpA according to inclusion criteria; studies enrolling both subtypes were excluded of this sub-analysis. For each symptom-duration cut-off, study-specific RRRs were pooled within each subtype with inverse-variance fixed-effect models to assess the impact on the primary outcome; 95% CIs were derived from the pooled log-RRR, and heterogeneity was quantified with Cochran's Q and I^2 . Subtype differences were tested with the Q interaction statistic, interpreting a P -value of the interaction >0.05 as no evidence of differential treatment effect.

Statistical heterogeneity across studies was assessed in all meta-regression models using the I^2 statistic. The data were analysed with R statistical software (version 4.1.1; <https://www.r-project.org/>).

Patient consent for publication

Not applicable, as this study used anonymized, de-identified data from clinical trial repositories.

Ethics approval

This study is based on secondary data analysis from anonymized clinical trials obtained through Vivli, YODA, ClinicalStudyDataRequest and Engagezone platforms. Institutional review board (IRB) approval was not required as no direct patient contact or identifiable information was involved.

Results

Studies and population

Overall, 355 references of RCTs on b/tsDMARDs were retrieved from the SLRs informing the ASAS-EULAR

recommendations for the management of axSpA [1], identifying 11 RCTs that met the inclusion criteria [9, 18–27]. All the included studies presented low RoB. The characteristics of the included studies are detailed in Table 1. These studies evaluated various bDMARDs, including placebo as the comparator in all of them. No studies involving tsDMARDs met the eligibility criteria. Among the included trials, four investigated golimumab, two each evaluated certolizumab pegol and secukinumab, and one study each assessed adalimumab, etanercept and ixekizumab (Supplementary Table S1). Most of them included different disease activity outcomes, with BASDAI response and CRP included in all studies; functional ability or quality of life outcomes were assessed less frequently, and particularly the latter with different outcomes (Supplementary Table S2).

These studies involved a total of 3272 patients with axSpA (see Fig. 1). The mean age of patients across studies was 37.9 years (S.D. 11.6), with a mean symptom duration of 9.3 years (S.D. 9.2). The majority of patients were male (59%).

Outcomes

Among the included studies, seven RCTs were eligible for the analysis of the primary end point (Supplementary Tables S1 and S3). At the 2-year symptom duration threshold, the RRRs for early vs established disease in achieving ASAS40 across the included studies ranged from 0.47 to 2.59, with all CIs crossing 1 (Supplementary Table S4). The pooled RR for achieving ASAS40 was 2.04 (95% CI, 1.48–2.84) in patients with early disease and 2.28 (95% CI, 1.65–3.15) in those with established disease when comparing bDMARDs to placebo. The RRR of ASAS40 at the 2-year cut-off comparing the treatment effect between early and established disease was 0.89 (95% CI, 0.63–1.26), indicating no statistically significant difference between the two groups (Fig. 2).

Similarly, for the other symptom duration thresholds (3–5 years), no significant differences were observed for ASAS40 in the pooled analysis (Table 2, Supplementary Table S4). Only two studies included $>20\%$ of patients within the 1-year symptom duration threshold, precluding pooled analysis of this cut-off. At the 3-year symptom duration threshold, the pooled RRR for ASAS40 was 1.14 (95% CI, 0.79–1.66), at 4 years was 1.11 (95% CI, 0.80–1.54) and at 5 years was 1.08 (95% CI, 0.78–1.49). These results indicate that the efficacy of bDMARDs compared with placebo in achieving ASAS40 did not differ significantly between patients with axSpA with shorter vs longer symptom duration across these symptom duration thresholds in the analysed trials.

The analysis of secondary disease activity outcomes yielded consistent results with the primary outcome, without any outcome or study showing a consistently significant difference between shorter and longer symptom duration. The pooled RRRs for secondary efficacy categoric endpoints—including achievement of ASAS20 response (Supplementary Table S5), ASAS5/6 response (Supplementary Table S6), ASAS partial remission (ASAS PR; measures in four domains, including patient global assessment, back pain, function and inflammation, are ≤ 2 on a 0–10 visual analogue scale) (Supplementary Table S7), ASDAS low disease activity (ASDAS LDA; ASDAS < 2.1) (Supplementary Table S8), ASDAS inactive disease (ASDAS ID; ASDAS < 1.3) (Supplementary Table S9), ASDAS clinical important improvement (ASDAS CII; improvement ≥ 1.1) (Supplementary

Table 1. Characteristics of the studies

Study name (first author, year)	<i>n</i>	axSpA subgroup	Patient population	Interventions	Comparator	Timing of assessment (weeks)	RoB	Age	Male	HLA- B27+	Symptom duration (years)	≤2 Years symptom duration	≤5 Years symptom duration
GO-RAISE (Inman 2008) [20]	356	r-axSpA	TNFi-naïve	GOL 50 Q4W	PBO	14	Low	39.2 (12)	255 (72)	296 (83)	14.01 (10.7)	46 (13)	87 (24)
ABILITY-1 (Sieper 2013) [19]	192	nr-axSpA	TNFi-naïve	ADA 40 Q2W	PBO	12	Low	38.0 (11)	89 (46)	148 (77)	10.1 (8.9)	27 (14)	71 (38)
NCT01248793 (Bao 2014) [18]	213	r-axSpA	TNFi-naïve	GOL 50 Q4W	PBO	14	Low	30.5 (10)	177 (83)	200 (94)	7.1 (6.2)	52 (24)	108 (51)
EMBARC (Dougados 2014) [21]	225	nr-axSpA	TNFi-naïve	ETA 50 QW	PBO	12	Low	31.9 (8)	133 (60)	154 (68)	2.5 (1.8)	101 (46)	220 (99)
RAPID-AXSPA (Landewe 2014) [24]	325	axSpA (55% r-axSpA)	TNFi-naïve + TNFi-IR (16%)	CZP 200, CZP 400	PBO	12	Low	39.6 (12)	211 (62)	255 (79)	10.4 (9.5)	60 (18)	126 (39)
GO-AHEAD (Sieper 2015) [22]	198	nr-axSpA	TNFi-naïve	GOL 50 Q4W	PBO	16	Low	31.2 (7)	113 (57)	164 (83)	1.1 (1.3)	158 (80)	197 (99)
GO-ALIVE (Deodhar 2018) [25]	208	r-axSpA	TNFi-naïve + TNFi-IR (14%)	GOL 100 Q8W	PBO	16	Low	38.8 (10)	163 (78)	187 (90)	10.9 (9.03)	31 (15)	75 (36)
C-AXSPAND (Deodhar 2019) [9]	317	nr-axSpA	TNFi-naïve + TNFi-IR (6%)	CZP 200 Q2W	PBO	12	Low	37.6 (10)	154 (49)	261 (82)	7.9 (7.6)	68 (21)	157 (49)
COAST-X (Deodhar 2020) [23]	303	nr-axSpA	TNFi-naïve	IXE 80 Q2W, IXE 80 Q4W	PBO	16	Low	40.3 (13)	143 (47)	221 (73)	10.7 (9.7)	55 (18)	121 (40)
PREVENT (Deodhar 2021) [27]	555	nr-axSpA	TNFi-naïve + TNFi-IR (10%)	SEC 150	PBO	16	Low	39.8 (112)	255 (46)	382 (69)	8.6 (8.7)	133 (24)	249 (45)
SKIPPAIN (Poddubnyy 2021) [26]	380	axSpA (71% r-axSpA)	TNFi-naïve + TNFi-IR (12%)	SEC 150	PBO	8	Low	42.0 (12)	235 (62)	309 (81)	12.9 (9.9)	33 (9)	87 (23)

Results are expressed in *n* (%) for categorical variables and mean (S.D.) for continuous variables. Early axSpA refers to ≤2 years symptom duration.

axSpA: axial spondyloarthritis; r-axSpA: radiographic axSpA; nr-axSpA: non-radiographic axSpA; RoB: risk of bias; GOL: golimumab; Q4W: every 4 weeks; PBO: placebo; TNFi: tumour necrosis factor inhibitor; ADA: adalimumab; Q2W: every 2 weeks; ETA: etanercept; QW: every week; CZP: certolizumab pegol; TNFi-IR: tumour necrosis factor inhibitor inadequate responder; Q8W: every 8 weeks; IXE: ixekizumab; Q4W: every 4 weeks; SEC: secukinumab.

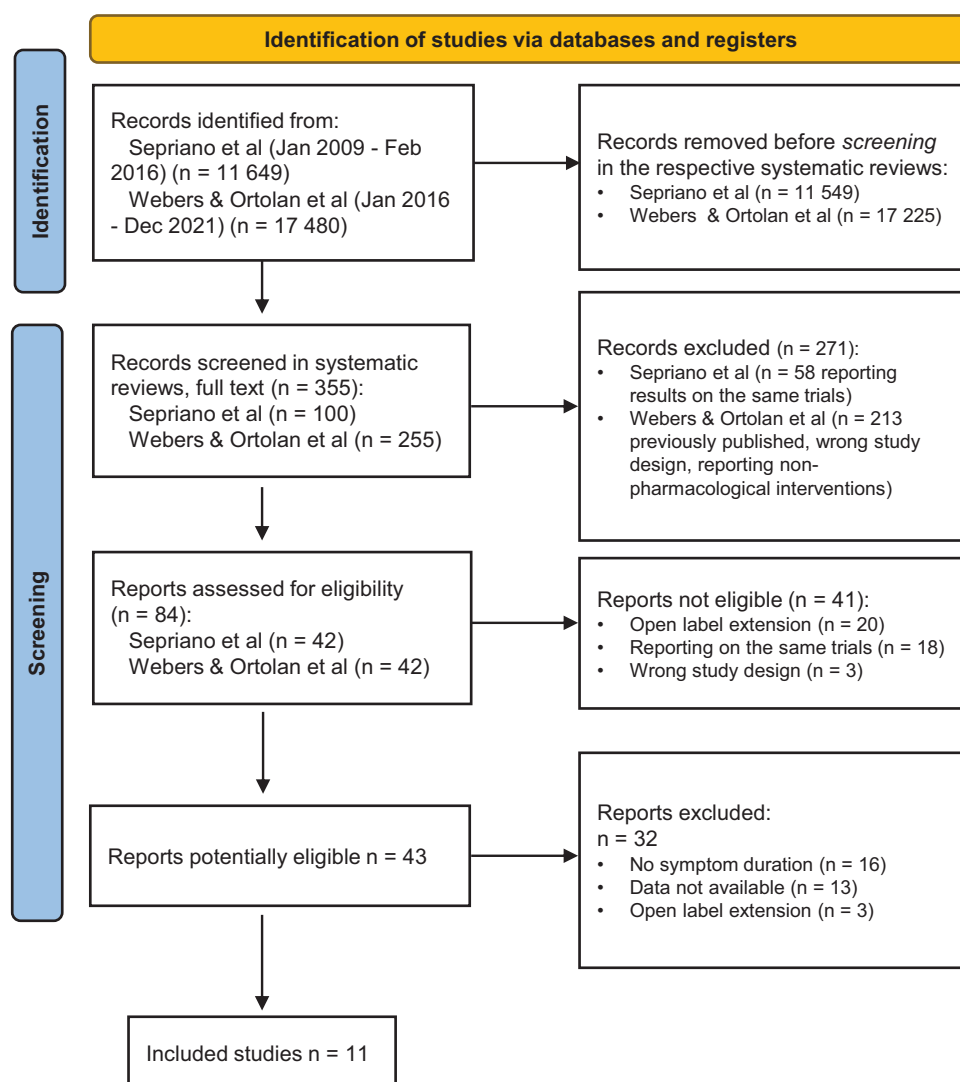


Figure 1. Flowchart of studies search and selection

Table S10), ASDAS major improvement (ASDAS MI; improvement ≥ 2.0) (Supplementary Table S11) and BASDAI50 (Supplementary Table S12)—did not show significant differences between shorter vs longer symptom duration thresholds (Table 2). As an example, at the 2-year threshold, the pooled RRR for achieving an ASAS20 response was 0.96 (95% CI, 0.77–1.20), and for achieving ASDAS <2.1 , the RRR was 0.96 (95% CI, 0.67–1.37). Similarly, the pooled DiD for continuous disease activity outcomes, such as mean ASDAS (Supplementary Table S13) or BASDAI (Supplementary Table S14), did not demonstrate a significant DiD favouring either early or established disease groups. At the 2-year threshold, the pooled DiD (95% CI) for ASDAS was 0.09 (−0.27, 0.45), while for BASDAI was −0.05 (0.54, 0.45). Comparable results were shown for the different thresholds of symptom duration for ASDAS and BASDAI.

As presented in Table 3, analyses of other disease outcomes showed no significant differences in treatment effects between shorter vs longer symptom duration thresholds. For functional measures like BASFI (Supplementary Table S15) and BASMI (Supplementary Table S16), the CIs of the DiDs of the included studies consistently crossed 1, indicating lack of

statistical significance; the pooled DiD were therefore not statistically significant. Similarly, inflammatory markers (CRP levels) (Supplementary Table S17) and quality of life assessments such as ASAS HI (Supplementary Table S18), ASQoL (Supplementary Table S19), EQ-5D (Supplementary Table S20), SF-36 PCS (Supplementary Table S21) and SF-36 MCS (Supplementary Table S22) demonstrated no significant differences between the groups.

Despite the lack of a meta-analysis at the 1-year symptom duration threshold, none of the outcomes reached a statistically significant difference between shorter and longer symptom duration at this threshold in either of the two included studies (Supplementary Tables S23 and S24). Heterogeneity across studies was generally low, with I^2 values indicating minimal between-study variability for most outcomes.

Exploratory stratified analysis

Concerning r-axSpA vs nr-axSpA, nine studies were eligible; three enrolled only r-axSpA and six only nr-axSpA, while two mixed trials were excluded. Full details of the subtype-stratified analysis are presented in Supplementary Table S25, which summarizes the pooled interaction estimates. For the

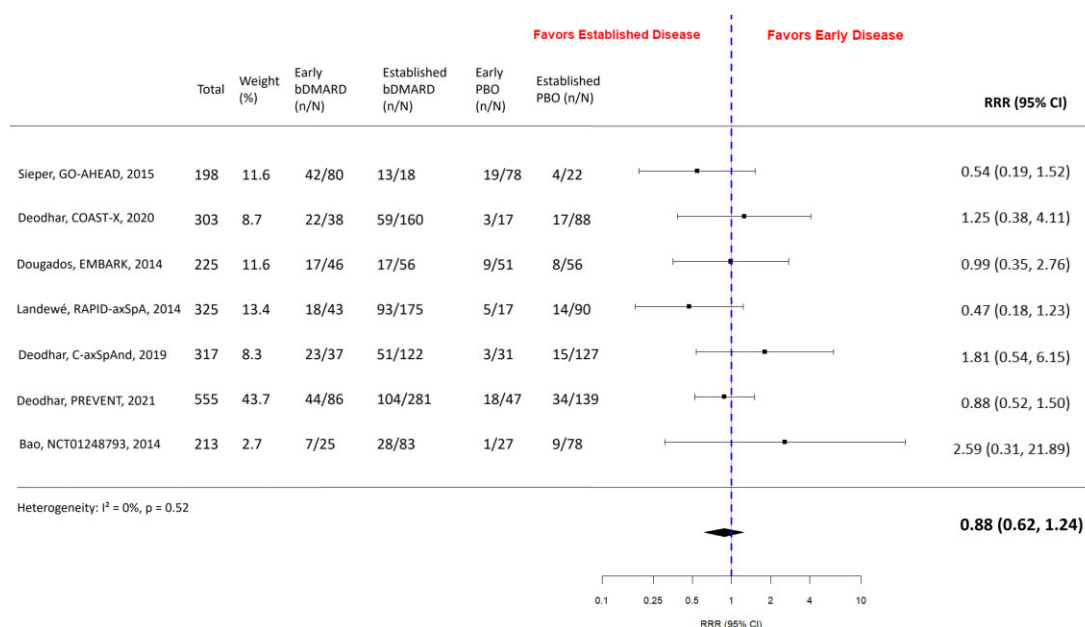


Figure 2. Pooled relative risk ratio for achieving ASAS40 response in early vs established disease (according to the 2-year symptom duration threshold) in bDMARDs vs placebo arm. bDMARD: biologic DMARD; PBO: placebo; RRR: relative risk ratio

≤ 2 -year threshold only one r-axSpA study contributed (RRR = 2.59, 95% CI 0.31–21.76). At the ≤ 3 , ≤ 4 and ≤ 5 year thresholds, pooled RRRs in r-axSpA ranged from 0.83 to 1.24 and in nr-axSpA from 1.22 to 1.29; all CIs overlapped and between stratum Q tests were non-significant.

Discussion

In this meta-analysis of RCTs involving 3272 patients with axSpA, we investigated whether symptom duration influences the efficacy of b/tsDMARDs compared with placebo. We have shown that treatment response to bDMARDs did not differ significantly between patients with shorter vs longer symptom duration thresholds ranging from 1 to 5 years—including the threshold of 2 years of the definition of ‘early axSpA’. This observation was consistent across disease activity outcomes and other outcomes, such as functional impairment, spinal mobility, inflammatory markers and quality of life assessments. These results suggest that the short-term efficacy of bDMARDs in axSpA is independent of symptom duration at the time of treatment initiation.

Our findings contribute to the ongoing discussion about the impact of symptom duration on treatment outcomes in axSpA. Some previous studies suggested potential benefits of early initiation of bDMARDs [28]. For instance, the INFAST study reported that patients with disease duration ≤ 3 years, treated with infliximab plus naproxen, showed better outcomes across various efficacy measures compared with those treated with naproxen alone [29]. Disease duration has been previously identified as a predictor of a major clinical response, as measured with BASDAI50 [30]. The ESTHER trial, which included patients with symptom duration of < 5 years, demonstrated efficacy of etanercept vs sulfasalazine in this group of patients, which was maintained after 3 years of treatment [31]. In a *post hoc* analysis of the C-axSpAnd trial, certolizumab pegol treated patients with shorter symptom duration defined by the threshold of five years were reported to show numerically higher improvements in

outcomes [9]. However, these studies including patients with short symptom duration did not directly compare the efficacy of treatment vs placebo in both shorter and longer symptom duration thresholds. One cannot exclude that the same pattern of responses as described in the bDMARD group is found in the placebo group, so before attributing the difference to the shorter symptom duration, both treatment arms need to be considered in the analysis [5].

In contrast with these studies, our meta-analysis did not find significant differences in treatment response between patients with axSpA with shorter vs longer symptom duration thresholds. This aligns with recent evidence from a large registry study of 3064 patients, which found comparable TNFi effectiveness, retention rates and ASAS40 response achievement at one year between early and established axSpA after adjusting for age, sex, HLA-B27 status and baseline disease activity [32]. In this line, the previous meta-analysis of published data on RCTs in the context of the ASAS-SPEAR project yielded limited evidence on the efficacy of early treatment in axSpA. Only when compared with longer symptom duration using RRR, patients with early nr-axSpA treated with bDMARDs had higher chance of achieving ASAS40 (almost 4-fold), according to pooled data from two studies [5]. However, these results were not shown in r-axSpA or in the broader group of axSpA.

The lack of a significant difference between patients with shorter and longer symptom thresholds challenges the commonly held assumption that earlier treatment leads to better clinical outcomes in axSpA [6]. This is of note given the accepted emphasis on early intervention in other chronic inflammatory conditions, such as RA, where earlier use of DMARDs has shown to be associated with improved outcomes and the possibility of disease remission [33]. In contrast, for axSpA, this has not been demonstrated. However, the absence of a significant difference in short-term efficacy does not imply that early initiation of b/tsDMARDs does not offer additional benefits. Starting treatment sooner can certainly lead to an earlier reduction in symptoms and disease

Table 2. Pooled relative risk ratio (categorical variables) and differences in differences (continuous variables) for achieving disease activity outcomes in shorter vs longer symptom duration (according to different thresholds) in bDMARDs vs placebo arm

Outcome	Threshold of symptom duration (years)	Trials	Patients	Pooled RRR/differences in differences (95% CI)*	I ²
ASAS40	2	7	2136	0.88 (0.62–1.24)	0
	3	8	2338	1.14 (0.75–1.75)	26.1%
	4	8	2261	1.11 (0.80–1.54)	0
	5	8	2261	1.08 (0.78–1.49)	0
ASAS20	2	7	2136	0.96 (0.77–1.20)	0
	3	8	2338	1.09 (0.83–1.44)	36.6%
	4	8	2261	1.14 (0.92–1.40)	0
	5	8	2261	1.15 (0.94–1.41)	0.4%
ASAS PR	2	7	2136	1.10 (0.58–2.09)	0
	3	8	2338	1.30 (0.67–2.54)	0
	4	8	2261	1.15 (0.58–2.30)	0
	5	8	2261	1.32 (0.66–2.64)	0
ASAS 5/6	2	7	2136	0.87 (0.61–1.24)	0
	3	8	2338	0.86 (0.47–1.58)	53.5%
	4	8	2261	0.95 (0.67–1.35)	0
	5	8	2261	0.93 (0.66–1.31)	0
ASDAS <2.1	2	6	1923	0.96 (0.67–1.37)	16.8%
	3	7	2125	0.98 (0.72–1.33)	0
	4	7	2280	0.96 (0.68–1.36)	0
	5	7	2280	0.92 (0.66–1.29)	0
ASDAS <1.3	2	6	1923	1.21 (0.70–2.07)	0
	3	7	2125	1.13 (0.60–2.56)	0
	4	7	2280	0.93 (0.43–2.02)	0
	5	7	2280	0.90 (0.33–2.51)	24.5%
ASDAS CII	2	6	1923	1.03 (0.76–1.39)	0
	3	7	2125	0.90 (0.64–1.24)	19.2%
	4	7	2280	0.83 (0.64–1.10)	0
	5	7	2280	0.84 (0.64–1.11)	0
ASDAS MI	2	6	1923	0.84 (0.43–1.64)	8.5%
	3	7	2125	0.92 (0.49–1.72)	0
	4	7	2280	0.57 (0.29–1.13)	0
	5	7	2280	0.65 (0.32–1.30)	0
ASDAS*	2	6	1923	0.09 (–0.27, 0.45)	54.2%
	3	7	2125	–0.05 (–0.30, 0.19)	35.1%
	4	7	2280	–0.07 (–0.26, 0.12)	0
	5	7	2280	–0.13 (–0.33, 0.06)	0
BASDAI50	2	6	1923	0.97 (0.67, 1.39)	0
	3	7	2125	1.17 (0.69, 0.01)	43.8%
	4	7	2280	1.85 (0.97, 0.54)	62.7%
	5	7	2280	1.26 (0.87, 1.83)	0.8%
BASDAI*	2	7	2136	–0.03 (0.49, 0.44)	0
	3	9	2694	–0.28 (–0.67, 0.12)	2.4%
	4	9	2849	–0.31 (–0.68, 0.06)	0
	5	9	2849	–0.39 (–0.76, –0.03)	0

* When the RRR is 1 (or the differences in differences is 0), the efficacy is equal between early and established disease patients. A value of RRR >1 (or differences in differences >0) indicates a higher efficacy in patients with early disease.
 RRR: relative risk ratio; ASAS: Axial SpondyloArthritis international Society; PR: Partial Remission; ASDAS: Axial Spondyloarthritis Disease Activity Score Response; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index. ASDAS CII: ASDAS clinically important improvement (improvement ≥ 1.1); ASDAS MI: ASDAS major improvement (improvement ≥ 2.0); ASAS PR: ASAS partial remission (measures in four domains, including patient global assessment, back pain, function and inflammation, are ≤ 2 on a 0–10 visual analogue scale).

manifestations compared with delaying or forgoing intervention, thereby sparing patients from prolonged discomfort and improving their quality of life sooner. Evaluating the impact

of early and sustained treatment on long-term outcomes, such as sustained disease activity, flare rates and radiographic progression, is critical yet methodologically challenging.

Table 3. Pooled differences in differences for achieving function, mobility and HRQoL outcomes in shorter vs longer symptom duration (according to different thresholds) in bDMARDs and PBO arm

Outcome	Threshold (years)	Trials	Patients	Differences in differences (95% CI)*	I ²
BASFI	2	7	2136	-0.2 (-0.7, 0.29)	5.2%
	3	9	2694	-0.15 (-0.71, 0.41)	52.6%
	4	8	2469	-0.19 (-0.61, 0.23)	17.9%
	5	8	2469	-0.32 (-0.78, 0.13)	0
BASMI	2	7	2136	-0.18 (-0.38, 0.01)	11.9%
	3	9	2694	-0.15 (-0.3, 0.01)	0
	4	8	2469	-0.11 (-0.29, 0.06)	0
	5	8	2469	-0.03 (-0.17, 0.11)	0
CRP	2	9	2694	-0.22 (-0.71, 0.27)	0
	3	8	2469	-0.11 (-0.57, 0.35)	0
	4	9	2849	0.11 (-0.78, 1.0)	0
	5	9	2849	0.14 (-0.65, 0.94)	0
ASAS HI	4	2	683	-0.89 (-2.58, 0.8)	0
	5	2	683	2.39 (0.27, 4.51)	0
ASQOL	2	6	1620	-0.14 (-0.34, 0.07)	0
	3	5	1630	0.19 (-1.03, 1.4)	63.6%
	4	4	1405	0.1 (-0.92, 1.12)	50.0%
	5	4	1405	-0.09 (-0.23, 0.04)	0
EuroQol	2	5	1698	-0.01 (-0.15, 0.13)	0
	3	6	1900	0.04 (-0.11, 0.19)	13.7%
	4	6	1900	0.14 (-0.1, 0.39)	39.6%
	5	6	1900	0.01 (-0.13, 0.15)	0
SF-36 PCS	2	7	2136	0.08 (-1.55, 1.7)	0
	3	8	2536	0.38 (-1, 1.75)	0
	4	8	2469	0.63 (-0.71, 1.97)	0
	5	8	2469	1.08 (-0.24, 2.41)	0
SF-36 MCS	2	7	2136	-0.37 (-3.12, 2.38)	37.0%
	3	8	2536	-0.43 (-2.31, 1.45)	0
	4	8	2469	0.43 (-1.35, 2.21)	0
	5	8	2469	0.99 (-0.78, 2.75)	0

* When the differences in differences is 0, the efficacy is equal between early and established disease patients. A value of differences in differences > 0 indicates a higher efficacy in patients with early disease. RRR: relative risk ratio; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASAS HI: Axial Spondyloarthritis Assessment Score Health Index; ASQOL: Ankylosing Spondylitis Quality of Life; EQ-5D: EuroQol-5 Dimensions; SF-36: Short Form-36; PCS: Physical Component Summary; MCS: Mental Component Summary.

Setting up long-term studies in axSpA with appropriate comparators is difficult, and maintaining unbiased comparisons over time introduces additional complexities. In the absence of these trials, indirect evidence may be considered. Recent studies indicate that newer axSpA cohorts with shorter symptom duration (e.g. DESIR inception cohort, showing mean progression of 0.2 mSASSS-units at 2 years) show reduced structural damage compared with older cohorts (e.g. OASIS, with a mean symptom duration of 20 years, showing mean progression of 2 mSASSS-units at 2 years), suggesting that early diagnosis and treatment initiation could be potentially disease-modifying [34–36]. Thus, comparable short-term responses do not preclude clinically meaningful long-term divergence; while our findings suggest that short-term clinical

response to bDMARDs is not associated with symptom duration, the potential long-term benefits of early intervention need further dedicated investigation to fully understand the implications of treatment timing in axSpA management.

Several factors may explain why symptom duration does not appear to influence treatment response in axSpA. First, the research challenge that this question poses. The studies included in our meta-analysis were primarily designed to compare the efficacy of active treatment vs placebo in the overall population, without specifically assessing the interaction between symptom duration and treatment response. Any *post hoc* subgroup analysis based on symptom duration could be biased, as the absence of randomization stratified by duration may lead to an imbalance in prognostic factors between shorter and longer symptom duration groups, potentially distorting the results. Besides, the inherent short-term nature of the endpoints assessed in most RCTs—typically ranging from 12 to 16 weeks—may not be sufficient to detect differences in treatment response based on symptom duration; the reliance on short-term endpoints means that any divergence in radiographic progression, flares or sustained functional improvement between shorter and longer symptom duration remains untested. AxSpA is a chronic condition, and the effects of early vs late treatment initiation may become more apparent over longer periods. Although our findings suggest that short-term clinical efficacy of bDMARDs is independent of symptom duration, a harmonized definition of ‘early axSpA’ retains substantial research value. A shared benchmark enables prospectively stratified RCTs in which symptom duration is balanced at baseline, overcoming the methodological constraints inherent to *post hoc* subgroup analyses. This facilitates the design of duration-stratified trials that allow powered assessments of long-term structural, functional, flare dynamic or patient-reported outcomes.

The choice of the 2-year symptom-duration threshold as primary outcome of this study follows the ASAS-SPEAR consensus definition of early axSpA, which reconciled expert opinion with the limited empirical evidence available [4]. Notably, in our additional analyses employing thresholds at 3, 4 and 5 years, the pooled RRRs varied by less than 10% and all CIs overlapped the estimate derived from the 2-year cut-off. These concordant results indicate that the absence of an exposure–response gradient cannot be attributed to a too restrictive definition of ‘early’ disease, stressing the robustness of our conclusions across a spectrum of symptom-duration definitions. Across four symptom-duration thresholds, radiographic status did not modify the relative effectiveness of early vs late treatment, supporting the robustness of our main findings.

It is important to consider the potential limitations of our study. First, the shortest threshold that was available to be evaluated here was considerably longer than the ‘window of opportunity’ often used in other inflammatory diseases, such as RA and PsA, where thresholds are set at ~3 months. Second, the definition of ‘early’ vs ‘established’ disease was based on symptom duration thresholds aligned with the ASAS consensus. As a result of symptom duration not having always been collected, only a limited number of RCTs could be included, which may affect the statistical power and generalizability of our findings. In this regard, the present meta-analysis inherits the heterogeneity of symptom-duration cut-offs used by the original investigators, limiting the level of detail with which different thresholds of symptom

durations can be explored. However, a multi-threshold approach including 1, 2, 3, 4 and 5 years was undertaken to mitigate this limitation. Besides, our analysis was restricted to data from RCTs involving b/tsDMARDs; no studies involving tsDMARDs, or newer agents like interleukin-17 dual inhibitors, could be included. Besides, trials of NSAIDs and conventional synthetic DMARDs were largely omitted: such studies are seldom available to analyse complete datasets including efficacy outcomes and symptom duration, while frequently employ open-label designs. These methodological differences limit our ability to generalize findings across the full spectrum of therapeutic classes. Moreover, to enable meaningful comparisons within each study, we included only RCTs where each symptom duration threshold constituted at least 20% of the total study population. While this cut-off is arbitrary, it was chosen to ensure minimal representation in both shorter and longer symptom duration thresholds disease groups. Concerning potential sub-analysis, only radiographic subtypes could be explored at the study level, as subgroups defined by HLA-B27 or MRI inflammation across individual studies were too small for reliable analyses. Future IPD meta-analyses will be necessary to determine whether these biological factors modify the impact of symptom duration on treatment response.

On the other hand, a major strength of our study is the access to individual studies, which allowed us to assess the impact of interventions for different thresholds of symptom duration. This was made possible through data-secured platforms (which shield trial participants from reidentification). In RCTs, comparing treatment effects between shorter and longer symptom duration groups requires considering both intervention arms, as analysing outcomes without adjusting for placebo effects does not fully capture whether symptom duration influences the efficacy of bDMARDs. To accurately assess this interaction, it is important to consider the relative treatment effects between shorter vs longer symptom duration disease groups while adjusting for placebo responses; this method accounts for variations in placebo responses and baseline characteristics, providing an accurate assessment of whether symptom duration modifies bDMARD efficacy.

Future research should make use of large observational registries that record symptom onset and treatment initiation to validate our findings in real-world settings, implement duration-stratified randomization in long-term RCTs powered to detect differences in radiographic progression, and integrate imaging, biomarker and genomic data within these cohorts to refine the biological window in which therapeutic intervention might modify the disease course.

In conclusion, our meta-analysis reveals that the short-term efficacy of bDMARDs in axSpA does not appear to be influenced by symptom duration, challenging the conventional notion that early intervention yields better outcomes in this disease. However, early treatment still offers undeniable benefits by providing faster symptom relief and potentially improving patients' quality of life sooner. The impact of early treatment on long-term outcomes, including disease progression and functional impairment, remains open for future investigation. Ultimately, our findings add a nuance to optimal timing for bDMARD initiation in axSpA, suggesting that when it comes to the race against time, axSpA might just be running at its own pace. To help on this race, future studies should focus on identifying predictors of treatment response

and optimizing therapeutic strategies to improve outcomes for patients with axSpA.

Supplementary material

[Supplementary material](#) is available at *Rheumatology* online.

Data availability

The data used in this study were accessed through Vivli, the Yale University Open Data Access (YODA) Project, ClinicalStudyDataRequest and Engagezone platforms, with permission from data contributors, including Eli Lilly, Janssen, Pfizer, UCB, Novartis and MSD. Data access is subject to approval by the respective platforms and data contributors.

Author contributions

D.B. was responsible for formal analysis, discussion and interpretation of findings, and drafting the original article. D. C. contributed to the study design, discussion and interpretation of findings, and revision of the article. S.R. and V.N. conceived the study, study design and setup, provided methodological review, discussion and interpretation of findings, and supervision.

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