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Is it Feasible to Achieve the Recommended Therapeutical Target in Patients with Axial Spondyloarthritis who Remain on Biological Therapy?

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Is it Feasible to Achieve the Recommended Therapeutical Target in Patients with Axial Spondyloarthritis who Remain on Biological Therapy?

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Contributorship

VNC, and CP conceived the study, participated in its design and coordination, and critically revised the manuscript. DB and KF performed the data collection, statistical analysis, interpretation and drafted the manuscript. PB, IM, RN, DP, LN, AV, MN and AB participated in the design, data interpretation and critically revised the Manuscript.

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Ethics approval

The study is attached to the project approved by the ethics committee from La Paz University Hospital with approval code PI-1479.

Patient and Public Involvement statement

Patients were not involved in the design of the study.

Data sharing statement

Extra data is available by emailing Diego Benavent (d_benavent@hotmail.com)

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ABSTRACT

Objectives: To determine the frequency of sustained remission (R) or low disease activity (LDA) in patients with axial spondyloarthritis (axSpA) undergoing long-term biological therapy and to analyze predictive factors for achieving these outcomes.

Methods: An observational study of a prospective cohort (SpA-Paz) including patients with axSpA who initiated biological treatment between 2003-2017. Collected data included demographic and clinical characteristics at the beginning of treatment and disease activity (measured by ASDAS and BASDAI&CRP) every 6 months up to a maximum of 2 years. Sustained R was defined as ASDAS<1.3 and/or BASDAI<2 & normal CRP and sustained LDA ASDAS<2.1 and/or BASDAI<4 & normal CRP on at least 3 consecutive visits.

Results: In total 186 patients (66.1% men and 75.3% with radiographic sacroiliitis) were included. Overall, 76.8% of patients achieved ASDAS R/LDA (R53.2%/LDA23.6%) in at least one visit. Forty percent (R17.6%/LDA22.4%) of the patients fulfilled the sustained ASDAS R/LDA state, whereas only 30.8% maintained this status (R14.8%/LDA15.9%) according to BASDAI&CRP. In the multivariate analysis, male sex (OR=4.01), younger age at the beginning of biological therapy (OR=0.96) and an HLA*B27 positive status (OR=4.30) were associated with achieving sustained ASDAS R/LDA.

Conclusions: In clinical practice, around one third of patients on bDMARDs achieve a sustained R/LDA status, but these rates drop to one sixth when targeting remission, preventing the use of the latter as a feasible target. Male sex, HLA*B27 positivity, and younger age at the beginning of biological therapy are the main predictors for achieving sustained R/LDA.

Keywords: axial spondyloarthritis, remission, low-disease activity, bDMARDs

Article summary

- Disease activity control (preferably sustained remission and alternatively sustained low disease activity) is the recommended target to achieve on the management of axial spondyloarthritis.
- Two composite indices (ASDAS and BASDAI) are available for this purpose. However, whether the achievement of the recommended target is feasible in clinical practice remains unknown.

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- Our study showed that sustained remission in axSpA in a real-world setting, measured both by ASDAS and BASDAI&CRP, might be too ambitious as a target, since it seems unachievable for the majority of patients.
- However, sustained LDA seem acceptable for making a good target for clinical practice, since it is ambitious, but achievable for approximately one in three patients.
- The fact that remission is not currently a realistic target does not mean that this remains unfeasible in a near future if efforts focus on such unmet needs.

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BACKGROUND

The term axial spondyloarthritis (axSpA) comprises radiographic axSpA (r-axSpA), traditionally denominated as ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA), the two types mainly differing in the presence or absence of radiographic sacroiliitis (1). Management recommendations for axSpA have been developed in recent years, providing guidance for the diagnosis and treatment of individual patients in clinical practice. The Assessment of SpondyloArthritis international Society (ASAS) and the European Alliance of Associations for Rheumatology (EULAR) published the most recent update to the recommendations for the management of patients with axSpA in 2016 (2). Following this, the American College of Rheumatology (ACR), in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN), published an update to their recommendations for r-axSpA and nr-axSpA (3). Whereas the 2016 update to the ASAS-EULAR management recommendations for axSpA asserted that treatment should be guided in accordance with a predefined target, this is not supported by the ACR/SAA/SPARTAN recommendations. Indeed, the American recommendations do not include disease activity scores and conditionally recommend against using a treat-to-target strategy, alleging a lack of substantial evidence that might otherwise prove the potential to slow radiographic progression and the risk of rapid change in treatments. Despite these differences, both recommendations have substantial overlap, reflecting the consistent management of axSpA across the world. These recommendation sets are the cornerstone on axSpA management for the rheumatology community.

In addition, an international task force recently updated a set of recommendations for axSpA treatment to target (4). There are currently two main indices for the assessment of disease activity in axSpA, namely the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) (5). The BASDAI is a self-reported questionnaire that includes 6 items assessing back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and duration and severity of morning stiffness (6). The ASDAS is a composite index that includes four self-reported items, namely spinal pain, peripheral joint pain/swelling, duration of morning stiffness and patient global level of disease activity, and one value for acute phase reactant, namely C-reactive protein (CRP) or, alternatively, the erythrocyte sedimentation rate (ESR) (7). The ASDAS has shown equivalent or superior psychometric performance compared to

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the BASDAI, and therefore is the recommended index to monitor disease activity in patients with axSpA. As an alternative, the BASDAI can also be used (8).

The ASAS/EULAR recommendations for managing patients with axSpA state that the therapeutic goal for clinical practice is to maximize long-term health-related quality of life. While goals are useful for establishing the right direction, a specific target is critical to promote progress and achieve the desired results. Weighing this in the context of managing patients with axSpA, despite the stated recommendation to predefine a specific target, this was never clearly defined, either for specific thresholds or for time boundaries. In general, it is accepted that the absence of disease activity reflects the disease activity status of remission. According to the treat-to-target expert recommendations, the treatment target should be clinical remission/inactive disease, which can be defined by an ASDAS <1.3; however, low disease activity might also be considered as an alternative target (9). Worth noting is the fact that the management recommendations underscored the need to sustain remission over time. Although the exact time frame was not specified, this led to the realization that a single measurement of remission is not sufficient to determine whether or not the therapeutic target has been achieved. Therefore, although it is not explicitly stated, it can be inferred that the target is sustained absence of disease activity over several consecutive visits. However, whether this is feasible in clinical practice remains unknown. Furthermore, it is unknown how many of the patients who remain on long-term biological treatment reach the therapeutic objective recommended by these scientific societies.

The main objective of this study is to determine the frequency of sustained remission or low disease activity (LDA) in patients with axSpA undergoing long-term biological therapy, and to assess whether the scope of this objective varies according to the used index. Additionally, we also aimed to determine predictive factors of sustained remission / LDA in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

METHODS

This is a longitudinal study using the prospective cohort SpA-Paz, which is an ongoing, observational cohort including all patients with axSpA who initiate treatment with bDMARDs at the University Hospital La Paz, Madrid, Spain. For this study, patients initiating bDMARDs between January 2003 and the December 2017 were included.

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The inclusion criteria were as follows: a) adult patients diagnosed with axSpA according to their prescribing rheumatologist; b) initiation of first biological therapy (Tumor Necrosis Factor inhibitors [TNFi] or interleukin [IL]-17 inhibitors); c) at least two years of follow-up with assessment visits every 6 months; d) at least two assessments of ASDAS-CRP or BASDAI&CRP during follow-up. A 2-year follow-up cut-off was established to homogenize the definition of "long-term therapy" from the start of bDMARDs.

Data collection

Demographic information, disease characteristics, bDMARDs type, concomitant treatment and laboratory tests before starting biological therapy were collected from the electronic health records at baseline. The presence of radiographic sacroiliitis, according to the modified New York (mNY) criteria, was assessed by the consensus of at least two out of three expert rheumatologists. Clinical disease activity was measured by ASDAS-CRP and BASDAI&CRP at baseline and at 6-month intervals after initiating bDMARDs for a period of two years.

According to ASDAS, disease activity was defined as follows: inactive disease (ASDAS <1.3), LDA (ASDAS ≥ 1.3 and < 2.1), high disease activity (ASDAS ≥ 2.1 and < 3.5) and very high disease activity (ASDAS ≥3.5) (10).

According to BASDAI, remission was considered present with a BASDAI <2 & normal CRP, whereas LDA was considered present with a BASDAI <4 & normal CRP. Both sustained remission and sustained LDA required a sustained outcome for at least 3 consecutive follow-up visits during the study period. If any visit was missing, but a BASDAI and /or ASDAS assessment was still conducted at 3 successive visits, patients remained eligible and accounted as consecutive visits.

Statistical analysis:

Descriptive analyses for the demographic, clinical and complimentary test information were performed. Categorical variables were described as absolute frequencies and percentages. Continuous variables were described using means and standard deviations (S.D.). The frequency of patients that achieved R/LDA, according to both ASDAS and BASDAI&CRP from at least one of the visits (momentary R/LDA), was calculated. Additionally, the frequency of patients whose clinical activity status remained unchanged over at least 3 consecutive follow-up visits (sustained R/LDA) were calculated. Only

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patients with a valid value for the calculated outcomes over these 3 consecutive visits, separated by 6 months between them, were assessed for their sustained treatment response.

Baseline predictive factors for achieving sustained R/LDA were identified using univariable and multivariable binary logistic regression models, inserting the possible predictors as independent variables and the R/LDA response achievement (by ASDAS or BASDAI&CRP, in two separate models) as the outcome. All of those variables with a p-value lower than 0.1 in the univariable were included in the multivariable analysis. Odds ratios (ORs) with p-value <0.05 were used as measures of association. All data were analyzed using SPSS software version 24.

RESULTS:

Demographic and Clinical Characteristics

Out of the 267 patients who initiated a bDMARD during the study period, 81 were excluded for discontinuation of the drug during follow-up or due to incomplete information. Therefore, 186 patients with axSpA fulfilled the inclusion criteria and were included in the analysis (**Figure 1**). Mean age was 54 ± 14.1 years and 123 (66.1%) were men. One hundred forty patients (75.3%) were classified as r-axSpA, whereas 46 (24.7%) were nr-axSpA; 139 (74.7%) were HLA*B27 positive. Other socio-demographic and disease characteristics of the patients at baseline are shown in Table 1.

Overall, 143 patients (76.8%) achieved ASDAS remission (R)/LDA (99 [53.2%] R/ 44 [23.6%] LDA) in at least one of the visits after 2 years of follow-up (momentary R/LDA) (**Figure 2**). However, only 66 patients (40% of those assessed) sustained an ASDAS R/LDA status over three consecutive visits (29 [17.6%] R/ 37 [22.4%] LDA). Regarding BASDAI, 138 patients (74.2%) were classified as BASDAI&CRP R/LDA (82 [44.1%] R/ 56 [30.1%] LDA) in at least one of the visits, but only 56 patients (30.8% of those assessed) sustained BASDAI&CRP R/LDA status over at least three consecutive visits (27 [14.8%] R/ 29 [15.9%] LDA).

Among the 165 patients that had a valid ASDAS-CRP for at least 3 visits, 66 (40%) achieved sustained ASDAS-CRP R/LDA. No statistically significant differences were observed for most of the baseline characteristics between the patients who sustained ASDAS-CRP R/LDA and those who did not fulfill these criteria; this was particularly notable in the rates of radiographic sacroiliitis (83.3 vs 73.7%, p=0.18) (**Table 1**).

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However, patients who achieved sustained ASDAS R/LDA were more frequently male (81.8 vs 54.5%, p<0.001), were younger at diagnosis (31.1 vs 38.8 years, p<0.001), younger age at biologic initiation (41.6 vs 46.7, p=0.02), and were more HLA*B27 positive (89.1 vs 69.1%, p=0.04). Interestingly, both momentary and sustained ASDAS-CRP outcomes showed significant differences when stratified by gender (**Figure 3**).

Among the 182 patients who had a valid BASDAI&CRP assessment during at least 3 visits, 56 (30.8%) achieved sustained BASDAI&CRP R/LDA. Patients who achieved sustained BASDAI&CRP R/LDA were more frequently male 54 (78.3 vs 59.5%, p=0.01), were younger at diagnosis (30.1 vs 37.9 years, p=0.02), younger at biologic initiation (40.6 vs 46.1, p=0.02), and had higher baseline levels of methotrexate (33.9 vs 17.5, p=0.01). No significant differences were observed for the remaining characteristics.

In the multivariate analysis, an independent association with male sex (OR=4.01; 95% CI=1.83-8.77), younger age at the beginning of biological therapy (OR=0.96; 95% CI=0.94-0.99) and HLA*B27 positivity (OR=4.30; 95% CI=1.68-11.01) in those patients who achieved sustained ASDAS R/LDA were identified. Additionally, male sex (OR=3.19; 95% CI=1.46-6.99), younger age at the beginning of biological treatment (OR= 0.97; 95% CI=0.95-0.99) and the use of methotrexate (OR=3.07; 95% CI =1.39-6.78) were associated with patients who achieved sustained BASDAI&CRP R/LDA.

DISCUSSION

The present study explored the rates of patients who achieved momentary and sustained R/LDA, as measured by ASDAS and BASDAI, after receiving biological treatment for at least 2 years, in order to assess whether achieving and maintaining these outcomes is a realistic target in clinical practice. In addition, it also evaluated predictive factors of sustained R/LDA in patients receiving bDMARDs. Considerable controversy surrounds the specific treatment target for axSpA. While remission or inactive disease by ASDAS or BASDAI is probably the preferred outcome, the feasibility of achieving this in clinical practice remains uncertain, and it is furthermore unclear whether this target is consistent with clinical decisions to maintain such therapy.

In our cohort, 3 out of 4 patients achieved momentary R/LDA in at least 1 of the visits after 2 years of follow-up, as measured both by ASDAS and BASDAI&CRP. Compared with previous research, a recent analysis by the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) showed that two-thirds of axSpA patients achieved an ASDAS LDA at 1 year (11). A study that drew from 12

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European registries and that included 24,195 European axSpA patients initiating a first TNFi demonstrated that 27% of patients achieved ASDAS remission after 6 months, while 59% achieved BASDAI LDA. Crude response rates for both indices progressively increased at 12 and 24 months (12). It is worth noting that these studies assessed outcomes at a given time point, whereas rates in our study involved achieving the outcome at any given visit during the follow-up. Therefore, the slight differences among studies, and the plausibility that almost three quarters of patients achieved this outcome at some point in our study were confirmed.

Concerning sustained outcomes, of all the included patients classified as responders based on medical criteria and who were undergoing long-term biological therapy, 40% fulfilled a sustained ASDAS R/LDA status during three consecutive visits, whereas 30.8% sustained a BASDAI&CRP R/LDA status. More specifically, only 17.6% and 14.8% of patients achieved sustained remission status as measured by ASDAS and BASDAI&CRP during the same period, respectively. Unlike studies that assess whether patients achieve a specific outcome status at a given moment, those that have investigated whether this outcome is sustained over time remain scarce. *Landewé et al* investigated sustained remission in patients with early axSpA during the first 48 weeks of certolizumab treatment within a clinical trial. Their results showed that more than 40% of them achieved sustained remission; this was defined as an ASDAS < 1.3 at week 32 and < 2.1 at week 36 (or vice versa), and < 1.3 at week 48 (13). Differences in study designs and in definitions of remission indicate that these rates are not comparable to those recorded in our study. Whereas in the aforementioned clinical trial a LDA measurement was permissible during follow-up, a more stringent definition was used in our clinical practice study; i.e., documentation of sustained remission over three consecutive visits was required. Interestingly, when sustained LDA status was assessed in our study, 40% of patients did achieve this outcome. This is similar to the rates shown in the clinical trial, where the definition of remission was more inclusive, counting as well those patients who presented brief LDA.

Several studies have recently shown that the presence of both local and systemic inflammation leads to structural damage. Data from the Outcome in Ankylosing Spondylitis International Study (OASIS) revealed that higher disease activity, as measured by the ASDAS, leads to further radiographic progression, which has similarly been confirmed in other studies (14,15). Hence, the importance of suppressing inflammation and, therefore, disease activity in order to decelerate radiographic

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progression. While the goal seems clear, the need to set a specific target to achieve that desired goal remains pressing. As recommended by an international task force, a treat-to-target approach could improve outcomes in axSpA (4). However, the only available treat-to-target trial in axSpA, the TICOSPA trial, was only recently published (16). The primary endpoint, which was the percentage of patients with a significant improvement in the ASAS-Health Index (ASAS-HI) score (≥30%) over one-year's follow-up, was not met. However, secondary disease activity endpoints were met, yielding a general trend in favor of tight control. The primary endpoint was probably too ambitious given the difficulty of improving the overall health and functioning within such a short time frame. However, TICOSPA has arguably been a stepping-stone for treatment target strategies in clinical practice. It thus appears reasonable to focus on disease activity outcome measures as a means for optimizing treat-to-target strategies.

In this sense, our study showed that sustained remission of the disease, measured both by ASDAS and BASDAI&CRP, might be too ambitious at this time, since it seems unachievable for the majority of patients. Examination of sustained LDA yielded results that seem acceptable for making a good target: it is ambitious, but achievable for approximately one in three patients. However, this indicates that two-thirds of the patients who continue bDMARDs- and are therefore in a presumably satisfactory clinical status according to medical criteria- are not achieving this sustained target. Thus, there is a still pending task in this respect, one that could be improved by adjusting the outcomes to the patient's baseline status, setting clinical improvement as a more pragmatic measurement to assess the current status of each patient. In any case, the fact that remission is not currently a realistic target does not mean that this remains unfeasible in a near future if efforts focus on such unmet needs.

Therefore, it seems rational to assess factors that would potentially facilitate a better clinical response, and to work in that direction. Worth noting is the fact that patients who achieved sustained ASDAS R/LDA were more frequently male, were younger at diagnosis, younger age at biologic initiation, and were more HLA*B27 positive in our study. Most of these features remained similar when BASDAI&CRP was established as the outcome variable. Remarkably, some of these characteristics are non-modifiable and static, namely gender and HLA*B27 status. When assessing modifiable factors, it seems clear that clinicians should advocate for any modifications in quest of the targeted outcomes; in this sense, earlier diagnosis and treatment might prove to be the single-most important factors clinicians can influence. However, this cannot be done for non-

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modifiable factors. This begs the question of whether it is the target itself that should be adapted for different groups, particularly in light of gender-related differential clinical responses.

Our study has some limitations. First, the observational design demands caution when interpreting the results, since they are prone to both selection and information bias, as well as to loss of follow-up. Indeed, not all patients present all outcome assessment parameters at every visit. However, as only those patients with at least three assessments were included, the consistency of the results was maintained, while yielding information from a representative sample of a typical patient population in clinical practice. Second, the absence of established definitions for momentary and sustained outcomes has led to various proposed definitions that may be judged arbitrary. Nevertheless, the fact that established cut-offs were examined facilitated the interpretation of sustained outcomes, while also providing evidence that might serve as the basis for a future consensus definition.

In conclusion, remission does not currently appear to be a realistic target in those axSpA patients treated with long-term bDMARDs therapy. On the other hand, low disease activity status seems a measurable, achievable and reasonable target for axSpA patients in clinical practice. Male patients and those of younger age at biologic initiation have shown to be predictive factors of good outcomes, when assessed by either ASDAS or BASDAI&CRP. In this regard, earlier diagnosis and treatment of the disease holds great promise in terms of targeting the desired outcome of remission. Future steps will involve the identification of a target adaptable to different populations or even specific patients, according to non-modifiable clinical factors.

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Table 1. Clinical characteristics stratified by momentary and sustained outcomes

	Full Analysis Set	Momentary outcome achievement		Sustained outcome achievement		p-value	
	Total (n=186)	Momentary R/LDA ASDAS (n=143)	Never R/LDA ASDAS (n=43)	Sustained R/LDA ASDAS (n=66)	Non-Sustained R/LDA ASDAS (n=99)	p-value 1 (Momentary)	p-value 2 (Sustained)
Demographic and clinical features							
Sex (male)	123 (66.1)	104 (72.7)	19 (44.2)	54 (81.8)	54 (54.5)	<0.001	<0.001
Age(years)							
At diagnosis	35.7 ±13.5	35.2±13.4	37.6±13.9	31.1 ±11.5	38.8±13.7	0.25	<0.001
At the beginning of first biologic	44.3 ±13.7	44.5±13.6	43.5±13.9	41.6 ±13.4	46.7±12.9	0.82	0.02
Smoking habit	86 (46.2)	68 (47.6)	18 (41.9)	32 (48.5)	46 (46.5)	0.60	0.87
Radiographic mNY criteria	140 (75.3)	109 (76.2)	31(72.1)	55 (83.3)	73 (73.7)	0.69	0.18
HLA*B27 positive	139 (74.7)	112 (80.0)	27 (64.3)	57 (89.1)	67 (69.1)	0.04	0.004
Dactylitis	5 (2.7)	5 (3.5)	0	2 (3.0)	2 (2.0)	0.59	0.68
Enthesitis	46 (24.7)	35 (24.5)	11 (25.6)	17 (25.8)	25 (25.3)	0.88	0.94
Psoriasis	8 (4.3)	7 (4.9)	1 (2.3)	3 (4.5)	4 (4.0)	0.46	0.87
Uveitis	36 (19.4)	28 (19.6)	8 (18.6)	12 (18.2)	21 (21.2%)	0.88	0.69
IBD	4 (2.2)	4 (2.8)	0	1 (1.5)	3 (3.0)	0.27	0.65
Baseline measurements							
CRP (mg/L)	14.5±21.3	14.4±21.4	14.7±21.1	15.9±22.9	15.0±21.5	0.93	0.81
BASDAI	5.6±1.9	5.5±1.8	6.0±1.9	5.4 ±1.9	5.9±1.8	0.11	0.08
ASDAS	3.3±1.0	3.2± 1.0	3.8±0.8	3.2 ±0.9	3.4 ±1.0	0.005	0.27
PhyGA	36.3± 21.0	36.5±20.9	35.6±21.7	38.6 ±21.9	35.7±20.3	0.84	0.47
PtGA	61.3± 21.6	59.6±21.7	67.2±20.5	60.0 ±21.3	63.8 ±20.3	0.046	0.25

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Concomitant treatment							
csDMARDs	97 (52.2)	74 (51.7)	23 (53.5)	34 (51.5)	53 (53.5)	0.86	0.87
Methotrexate	42 (22.6)	34 (23.8)	8 (18.6)	16 (24.2)	20 (20.2)	0.54	0.57
Sulfasalazine	67(36.0)	52(36.4)	15 (34.9)	22 (33.3)	38 (38.4)	0.86	0.62
Prednisone	21 (11.3)	16 (11.2)	5 (11.6)	7 (10.6)	13 (13.1)	0.93	0.80
NSAIDs	186 (100)	38 (100)	19 (100)	66 (100)	99 (100)	-	-

R: remission; LDA: Low disease activity; IBD: Inflammatory Bowel Disease; mNY: modified New York; CRP: C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; PhyGA: physician global assessment; PtGA: patient global assessment; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; NSAID: Non-steroidal anti-inflammatory drugs. Patients with sustained outcomes are those who presented outcomes on at least 3 consecutive visits; thus, the number of patients decreased with respect of the full analysis

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Figure 1. Patient disposition during the 2-year follow-up

Figure 2. Momentary and sustained outcomes (remission and low disease activity).

REM: remission; LDA: Low disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-Reactive Protein; ASDAS: Ankylosing Spondylitis Disease Activity Score

Figure 3. Momentary and sustained outcomes (remission or low disease activity, as measured by ASDAS-CRP) stratified by gender.

REM: remission; LDA: Low disease activity; *p<0.001; # p<0.05

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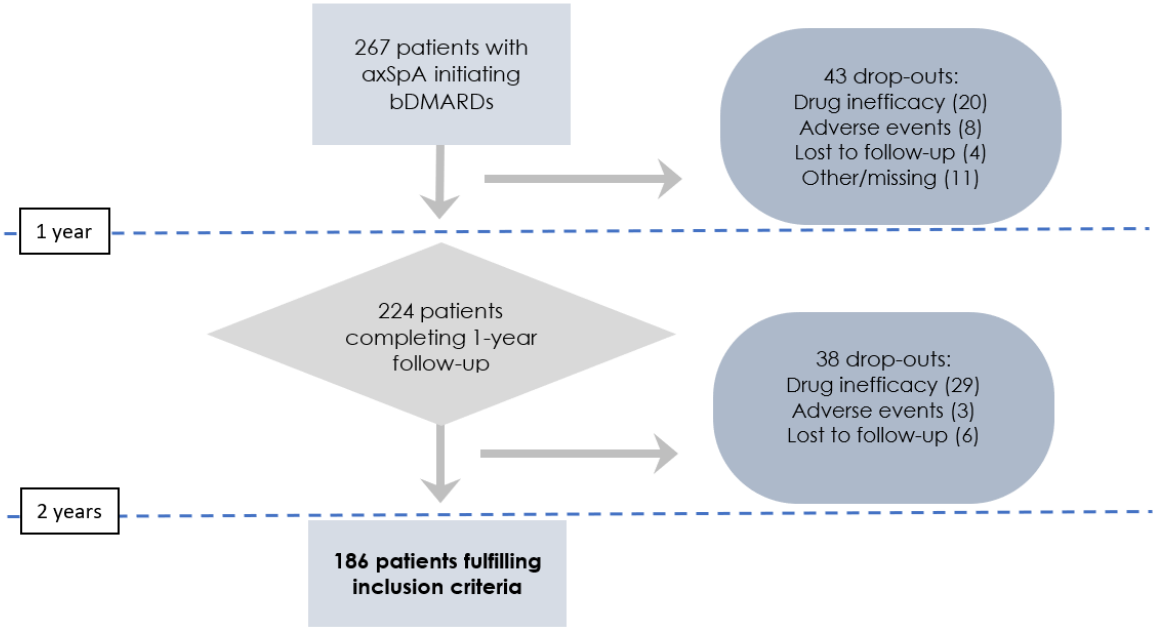

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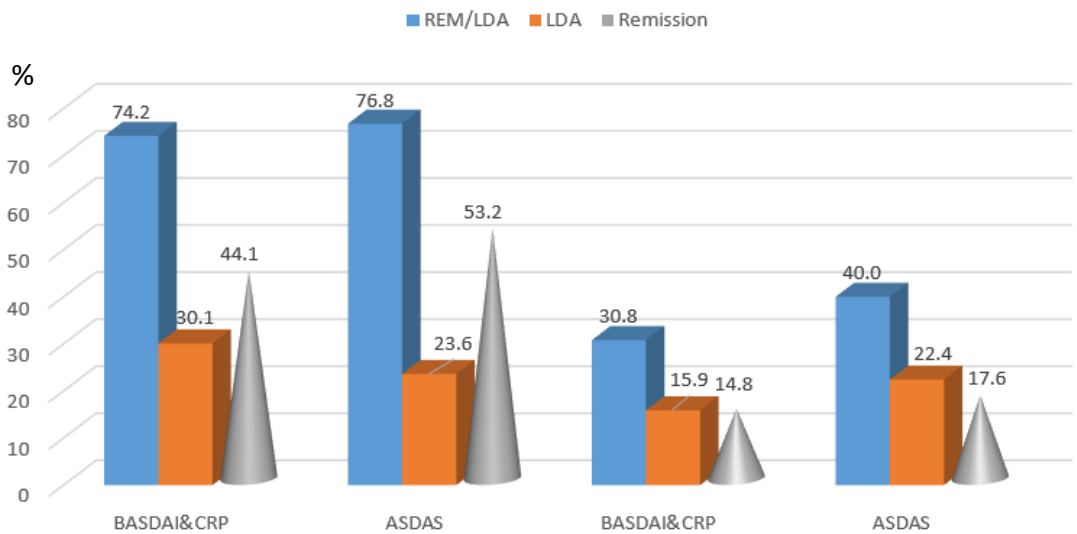

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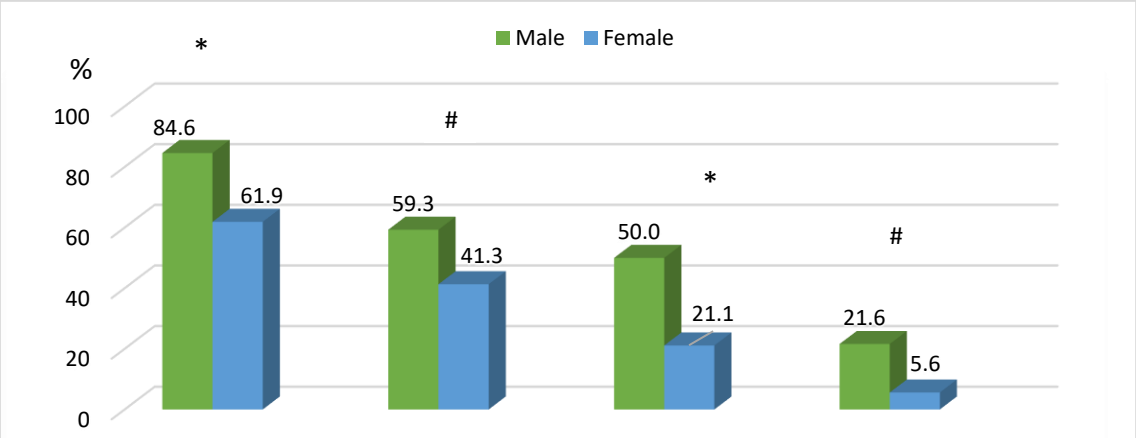

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Achievement Rate and Predictive Factors of the Recommended Therapeutical Target in Patients with Axial Spondyloarthritis who Remain on Biological Therapy: A Prospective Study

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Achievement Rate and Predictive Factors of the Recommended Therapeutical Target in Patients with Axial Spondyloarthritis who Remain on Biological Therapy: A Prospective Study

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Contributorship

VNC, and CP conceived the study, participated in its design and coordination, and critically revised the manuscript. DB and KF performed the data collection, statistical analysis, interpretation and drafted the manuscript. PB, IM, RN, DP, LN, AV, MN and AB participated in the design, data interpretation and critically revised the Manuscript.

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Ethics approval

The study is attached to the project approved by the ethics committee from La Paz University Hospital with approval code PI-1479.

Patient and Public Involvement statement

Patients were not involved in the design of the study.

Data sharing statement

Extra data is available by emailing Diego Benavent (d_benavent@hotmail.com)

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ABSTRACT

Objectives: To determine the frequency of sustained remission (R) or low disease activity (LDA) in patients with axial spondyloarthritis (axSpA) undergoing long-term biological therapy and to analyze predictive factors for achieving these outcomes.

Methods: An observational study of a prospective cohort (SpA-Paz) including patients with axSpA who initiated biological treatment between 2003-2017. Collected data included demographic and clinical characteristics at the beginning of treatment and disease activity (measured by ASDAS and BASDAI&CRP) every 6 months up to a maximum of 2 years. Sustained R was defined as ASDAS<1.3 and/or BASDAI<2 & normal CRP and sustained LDA ASDAS<2.1 and/or BASDAI<4 & normal CRP on at least 3 consecutive visits.

Results: In total 186 patients (66.1% men and 75.3% with radiographic sacroiliitis) were included. Overall, 76.8% of patients achieved ASDAS R/LDA (R53.2%/LDA23.6%) in at least one visit. Forty percent (R17.6%/LDA22.4%) of the patients fulfilled the sustained ASDAS R/LDA state, whereas only 30.8% maintained this status (R14.8%/LDA15.9%) according to BASDAI&CRP. In the multivariate analysis, male sex (OR=4.01), younger age at the beginning of biological therapy (OR=0.96) and an HLA*B27 positive status (OR=4.30) were associated with achieving sustained ASDAS R/LDA.

Conclusions: In clinical practice, around one third of patients on bDMARDs achieve a sustained R/LDA status, but these rates drop to less than one in five when targeting remission, preventing the use of the latter as a feasible target. Male sex, HLA*B27 positivity, and younger age at the beginning of biological therapy are the main predictors for achieving sustained R/LDA.

Keywords: axial spondyloarthritis, remission, low-disease activity, bDMARDs

Article summary

- Disease activity control (preferably sustained remission and alternatively sustained low disease activity) is the recommended target to achieve on the management of axial spondyloarthritis.
- Whether the achievement of the recommended target using the main composite indices (ASDAS and BASDAI) is feasible in clinical practice remains unknown.
- Predictive factors for achieving sustained remission or low disease activity are yet to be elucidated.

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- Our study aims to determine the frequency of sustained remission or low disease activity in patients with axSpA undergoing long-term biological therapy in clinical practice.
- Additionally, we aimed to determine predictive factors of sustained remission / low disease activity in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs)."

- **BACKGROUND**

The term axial spondyloarthritis (axSpA) comprises radiographic axSpA (r-axSpA), traditionally denominated as ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA), the two types mainly differing in the presence or absence of radiographic sacroiliitis (1). Management recommendations for axSpA have been developed in recent years, providing guidance for the diagnosis and treatment of individual patients in clinical practice. The Assessment of SpondyloArthritis international Society (ASAS) and the European Alliance of Associations for Rheumatology (EULAR) published the most recent update to the recommendations for the management of patients with axSpA in 2016 (2). Following this, the American College of Rheumatology (ACR), in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN), published an update to their recommendations for r-axSpA and nr-axSpA (3). Whereas the 2016 update to the ASAS-EULAR management recommendations for axSpA asserted that treatment should be guided in accordance with a predefined target, this is not supported by the ACR/SAA/SPARTAN recommendations. Indeed, the American recommendations do not include disease activity scores and conditionally recommend against using a treat-to-target strategy, alleging a lack of substantial evidence that might otherwise prove the potential to slow radiographic progression and the risk of rapid change in treatments. Despite these differences, both recommendations have substantial overlap, reflecting the consistent management of axSpA across the world. These recommendation sets are the cornerstone on axSpA management for the rheumatology community.

In addition, an international task force recently updated a set of recommendations for axSpA treatment to target (4). There are currently two main indices for the assessment of disease activity in axSpA, namely the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) (5). The BASDAI is a self-reported questionnaire that includes 6 items assessing back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and duration and severity

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of morning stiffness (6). The ASDAS is a composite index that includes four self-reported items, namely spinal pain, peripheral joint pain/swelling, duration of morning stiffness and patient global level of disease activity, and one value for acute phase reactant, namely C-reactive protein (CRP) or, alternatively, the erythrocyte sedimentation rate (ESR) (7). The ASDAS has shown equivalent or superior psychometric performance compared to the BASDAI, and therefore is the recommended index to monitor disease activity in patients with axSpA. As an alternative, the BASDAI can also be used (8).

The ASAS/EULAR recommendations for managing patients with axSpA state that the therapeutic goal for clinical practice is to maximize long-term health-related quality of life. While goals are useful for establishing the right direction, a specific target is critical to promote progress and achieve the desired results. Weighing this in the context of managing patients with axSpA, despite the stated recommendation to predefine a specific target, this was never clearly defined, either for specific thresholds or for time boundaries. In general, it is accepted that the absence of disease activity reflects the disease activity status of remission. According to the treat-to-target expert recommendations, the treatment target should be clinical remission/inactive disease, which can be defined by an ASDAS <1.3; however, low disease activity might also be considered as an alternative target (9). Worth noting is the fact that the management recommendations underscored the need to sustain remission over time. Although the exact time frame was not specified, this led to the realization that a single measurement of remission is not sufficient to determine whether or not the therapeutic target has been achieved. Therefore, although it is not explicitly stated, it can be inferred that the target is sustained absence of disease activity over several consecutive visits. However, whether this is feasible in clinical practice remains unknown. Furthermore, it is unknown how many of the patients who remain on long-term biological treatment reach the therapeutic objective recommended by these scientific societies.

The main objective of this study is to determine the frequency of sustained remission or low disease activity (LDA) in patients with axSpA undergoing long-term biological therapy, and to assess whether the scope of this objective varies according to the used index. Additionally, we also aimed to determine predictive factors of sustained remission / LDA in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

METHODS

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This is a longitudinal study using the prospective cohort SpA-Paz, which is an ongoing, observational cohort including all patients with axSpA who initiate their first treatment with bDMARDs at the University Hospital La Paz, Madrid, Spain. For this study, patients initiating bDMARDs between January 2003 and the December 2017 were included.

The inclusion criteria were as follows: a) adult patients diagnosed with axSpA according to their prescribing rheumatologist; b) initiation of first biological therapy (Tumor Necrosis Factor inhibitors [TNFi] or interleukin [IL]-17 inhibitors); c) at least two years of follow-up with assessment visits every 6 months; d) at least two assessments of ASDAS-CRP or BASDAI&CRP during follow-up. A 2-year follow-up cut-off was established to homogenize the definition of "long-term therapy" from the start of bDMARDs. All patients signed written informed consent.

Data collection

Demographic information, disease characteristics, bDMARDs type, concomitant treatment and laboratory tests before starting biological therapy were collected from the electronic health records at baseline. Baseline patients' characteristics were collected retrospectively at biologic initiation. Time windows for concomitant medication and laboratory tests extended three months prior biological initiation until the date of start of biologic. The presence of radiographic sacroiliitis, according to the modified New York (mNY) criteria, was assessed by the consensus of at least two out of three expert rheumatologists. Clinical disease activity was measured by ASDAS-CRP and BASDAI&CRP at baseline and at 6-month intervals after initiating bDMARDs for a period of two years.

According to ASDAS, disease activity was defined as follows: inactive disease (ASDAS <1.3), LDA (ASDAS ≥ 1.3 and < 2.1), high disease activity (ASDAS ≥ 2.1 and < 3.5) and very high disease activity (ASDAS ≥3.5) (10).

According to BASDAI, remission (R) was considered present with a BASDAI <2 & normal CRP, whereas LDA was considered present with a BASDAI <4 & normal CRP. Both sustained remission and sustained LDA required a sustained outcome for at least 3 consecutive follow-up visits during the study period. If any visit was missing, but a BASDAI and /or ASDAS assessment was still conducted at 3 successive visits, patients remained eligible and accounted as consecutive visits. Since patients in remission or inactive disease also fulfil LDA criteria, a category including all patients that achieved at least LDA was created, under the name of R/LDA.

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Sample size was not based on data from previous publications because there are few reliable estimates in the literature regarding the sustained outcomes. Due to the exploratory character of the study, no formal sample size calculation was performed.

Statistical analysis:

Descriptive analyses for the demographic, clinical and complimentary test information were performed. Categorical variables were described as absolute frequencies and percentages. Continuous variables were described using means and standard deviations (S.D.). The frequency of patients that achieved R/LDA, according to both ASDAS and BASDAI&CRP from at least one of the visits (momentary R/LDA), was calculated. Additionally, the frequency of patients whose clinical activity status remained unchanged over at least 3 consecutive follow-up visits (sustained R/LDA) were calculated. Only patients with a valid value for the calculated outcomes over these 3 consecutive visits, separated by 6 months between them, were assessed for their sustained treatment response.

Baseline predictive factors for achieving sustained R/LDA were identified using univariable and multivariable binary logistic regression models, inserting the possible predictors as independent variables and the R/LDA response achievement (by ASDAS or BASDAI&CRP, in two separate models) as the outcome. All of those variables with a p-value lower than 0.1 in the univariable were included in the multivariable analysis. Odds ratios (ORs) with p-value <0.05 were used as measures of association. All data were analyzed using SPSS software version 24.

RESULTS:

Demographic and Clinical Characteristics

Out of the 267 patients who initiated a bDMARD during the study period, 81 were excluded for discontinuation of the drug during follow-up or due to incomplete information. Therefore, 186 patients with axSpA fulfilled the inclusion criteria and were included in the analysis (**Figure 1**). Mean age was 54 ± 14.1 years and 123 (66.1%) were men. One hundred forty patients (75.3%) were classified as r-axSpA, whereas 46 (24.7%) were nr-axSpA; 139 (74.7%) were HLA*B27 positive. Other socio-demographic and disease characteristics of the patients at baseline are shown in Table 1.

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Out of 186 patients, 155 (83%) completed 5 follow-up visits, 25 (14%) 4 visits and 6 (3%) 3 visits. Overall, 143 patients (76.8%) achieved ASDAS remission R/LDA (99 [53.2%] R/ 44 [23.6%] LDA) in at least one of the visits within the 2 years of follow-up (momentary R/LDA) (**Figure 2**). However, only 66 patients (40% of those assessed) sustained an ASDAS R/LDA status over three consecutive visits (29 [17.6%] R/ 37 [22.4%] LDA). Regarding BASDAI, 138 patients (74.2%) were classified as BASDAI&CRP R/LDA (82 [44.1%] R/ 56 [30.1%] LDA) in at least one of the visits, but only 56 patients (30.8% of those assessed) sustained BASDAI&CRP R/LDA status over at least three consecutive visits (27 [14.8%] R/ 29 [15.9%] LDA).

Among the 165 patients that had a valid ASDAS-CRP for at least 3 visits, 66 (40%) achieved sustained ASDAS-CRP R/LDA. No statistically significant differences were observed for most of the baseline characteristics between the patients who sustained ASDAS-CRP R/LDA and those who did not fulfill these criteria (**Table 1**). This was particularly notable in the rates of radiographic sacroiliitis (83.3 vs 73.7%, p=0.18). Indeed, a stratified analysis by sacroiliac radiographic damage, showed no statistically significant differences (p=0.18) in the achievement of sustained ASDAS R/LDA in patients with r-axSpA (n=55, 43%) as compared with patients with nr-axSpA (n=11, 29.7%). However, patients who achieved sustained ASDAS R/LDA were more frequently male (81.8 vs 54.5%, p<0.001), were younger at diagnosis (31.1 vs 38.8 years, p<0.001), younger age at biologic initiation (41.6 vs 46.7, p=0.02), and HLA*B27 positive (89.1 vs 69.1%, p=0.04). Interestingly, both momentary and sustained ASDAS-CRP outcomes showed significant differences when stratified by gender (**Figure 3**).

Regarding BASDAI&CRP, among the 182 patients who had a valid assessment during at least 3 visits, 56 (30.8%) achieved sustained BASDAI&CRP R/LDA. Patients who achieved sustained BASDAI&CRP R/LDA were more frequently male (78.3 vs 59.5%, p=0.01), were younger at diagnosis (30.1 vs 37.9 years, p=0.02), younger at biologic initiation (40.6 vs 46.1, p=0.02), and had higher baseline levels of methotrexate (33.9 vs 17.5, p=0.01). No significant differences were observed for the remaining characteristics. In the multivariate analysis, an independent association with male sex (OR=4.01; 95% CI=1.83-8.77), younger age at the beginning of biological therapy (OR=0.96; 95% CI=0.94-0.99) and HLA*B27 positivity (OR=4.30; 95% CI=1.68-11.01) in those patients who achieved sustained ASDAS R/LDA were identified. Additionally, male sex (OR=3.19; 95% CI=1.46-6.99), younger age at the beginning of biological treatment

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(OR= 0.97; 95% CI=0.95-0.99) and the use of methotrexate (OR=3.07; 95% CI =1.39-6.78) were associated with patients who achieved sustained BASDAI&CRP R/LDA.

DISCUSSION

The present study explored the rates of patients who achieved momentary and sustained R/LDA, as measured by ASDAS and BASDAI, after receiving biological treatment for at least 2 years, in order to assess whether achieving and maintaining these outcomes is a realistic target in clinical practice. In addition, it also evaluated predictive factors of sustained R/LDA in patients receiving bDMARDs. Considerable controversy surrounds the specific treatment target for axSpA. While remission or inactive disease by ASDAS or BASDAI is probably the preferred outcome, the feasibility of achieving this in clinical practice remains uncertain, and it is furthermore unclear whether this target is consistent with clinical decisions to maintain such therapy.

In our cohort, 3 out of 4 patients achieved momentary R/LDA in at least 1 of the visits after 2 years of follow-up, as measured both by ASDAS and BASDAI&CRP. Compared with previous research, a recent analysis by the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) showed that two-thirds of axSpA patients achieved an ASDAS LDA at 1 year (11). A study that drew from 12 European registries and that included 24,195 European axSpA patients initiating a first TNFi demonstrated that 27% of patients achieved ASDAS remission after 6 months, while 59% achieved BASDAI LDA. Crude response rates for both indices progressively increased at 12 and 24 months (12). It is worth noting that these studies assessed outcomes at a given time point, whereas rates in our study involved achieving the outcome at any given visit during the follow-up. Therefore, the slight differences among studies, and the plausibility that almost three quarters of patients achieved this outcome at some point in our study were confirmed.

Concerning sustained outcomes, of all the included patients classified as responders based on medical criteria and who were undergoing long-term biological therapy, 40% fulfilled a sustained ASDAS R/LDA status during three consecutive visits, whereas 30.8% sustained a BASDAI&CRP R/LDA status. More specifically, only 17.6% and 14.8% of patients achieved sustained remission status as measured by ASDAS and BASDAI&CRP during the same period, respectively. Unlike studies that assess whether patients achieve a specific outcome status at a given moment, those that have investigated whether this outcome is sustained over time remain scarce. *Landewé et al* investigated sustained

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remission in patients with early axSpA during the first 48 weeks of certolizumab treatment within a clinical trial. Their results showed that more than 40% of them achieved sustained remission; this was defined as an ASDAS < 1.3 at week 32 and < 2.1 at week 36 (or vice versa), and < 1.3 at week 48 (13). Differences in study designs and in definitions of remission indicate that these rates are not comparable to those recorded in our study. Whereas in the aforementioned clinical trial a LDA measurement was permissible during follow-up, a more stringent definition was used in our clinical practice study; i.e., documentation of sustained remission over three consecutive visits was required. Interestingly, when sustained LDA status was assessed in our study, 40% of patients did achieve this outcome. This is similar to the rates shown in the clinical trial, where the definition of remission was more inclusive, counting as well those patients who presented brief LDA.

Several studies have recently shown that the presence of both local and systemic inflammation leads to structural damage. Data from the Outcome in Ankylosing Spondylitis International Study (OASIS) revealed that higher disease activity, as measured by the ASDAS, leads to further radiographic progression, which has similarly been confirmed in other studies (14,15). Hence, the importance of suppressing inflammation and, therefore, disease activity in order to decelerate radiographic progression. While the goal seems clear, the need to set a specific target to achieve that desired goal remains pressing. As recommended by an international task force, a treat-to-target approach could improve outcomes in axSpA (4). However, the only available treat-to-target trial in axSpA, the TICOSPA trial, was only recently published (16). The primary endpoint, which was the percentage of patients with a significant improvement in the ASAS-Health Index (ASAS-HI) score (≥30%) over one-year's follow-up, was not met. However, secondary disease activity endpoints were met, yielding a general trend in favor of tight control. The primary endpoint was probably too ambitious given the difficulty of improving the overall health and functioning within such a short time frame. However, TICOSPA has arguably been a stepping-stone for treatment target strategies in clinical practice. It thus appears reasonable to focus on disease activity outcome measures as a means for optimizing treat-to-target strategies.

In this sense, our study raised some evidence that sustained remission of the disease, measured both by ASDAS and BASDAI&CRP, might be too ambitious at this time, since it seems unachievable for the majority of patients in our sample. Examination of sustained LDA yielded results that seem acceptable for making a good target: it is ambitious, but

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achievable for approximately one in three patients. However, this indicates that two-thirds of the patients who continue bDMARDs in our study- and are therefore in a presumably satisfactory clinical status according to medical criteria- are not achieving this sustained target. These results need to be assessed by further studies in a broader population and in different settings to confirm their external validity. In case that these exploratory results are confirmed, there will still be a pending task in this respect, one that could be improved by adjusting the outcomes to the patient's baseline status, setting clinical improvement as a more pragmatic measurement to assess the current status of each patient. In any case, the fact that remission is not currently a realistic target does not mean that this remains unfeasible in a near future if efforts focus on such unmet needs.

Therefore, it seems rational to assess factors that would potentially facilitate a better clinical response, and to work in that direction. Worth noting is the fact that patients who achieved sustained ASDAS R/LDA were more frequently male, were younger at diagnosis, younger age at biologic initiation, and HLA*B27 positive in our study. Most of these features remained similar when BASDAI&CRP was established as the outcome variable. Remarkably, some of these characteristics are non-modifiable and static, namely gender and HLA*B27 status. When assessing modifiable factors, it seems clear that clinicians should advocate for any modifications in quest of the targeted outcomes; in this sense, earlier diagnosis and treatment might prove to be the single-most important factors clinicians can influence. However, this cannot be done for non-modifiable factors. This begs the question of whether it is the target itself that should be adapted for different groups, particularly in light of gender-related differential clinical responses.

Our study has some limitations. First, the observational design demands caution when interpreting the results, since they are prone to both selection and information bias, as well as to loss of follow-up. Indeed, not all patients present all outcome assessment parameters at every visit. However, as only those patients with at least three assessments were included, the consistency of the results was maintained, while yielding information from a representative sample of a typical patient population in clinical practice. Second, the absence of established definitions for momentary and sustained outcomes has led to various proposed definitions that may be judged arbitrary. Nevertheless, the fact that established cut-offs were examined facilitated the interpretation of sustained outcomes, while also providing evidence that might serve as the basis for a future consensus definition. Besides, some of the demographic and clinical data was only collected at

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baseline and not during follow-up, which hinders the comparison among groups regarding the characteristics of interest during the study period. Due to the scarcity of previous reliable data in the literature regarding sustained outcomes, no formal sample size calculation was performed. In addition, we did not include any radiologic outcomes to assess clinical response of patients, as they were not available in clinical practice. This is related to the lack of standardized recommendations to assess radiographic progression routinely over a period of less than two years and to use magnetic resonance imaging for monitorization of disease activity (17).

In conclusion, remission does not currently appear to be a realistic target in those axSpA patients treated with long-term bDMARDs therapy. On the other hand, low disease activity status seems a measurable, achievable and reasonable target for axSpA patients in clinical practice. Male patients and those of younger age at biologic initiation have shown to be predictive factors of good outcomes, when assessed by either ASDAS or BASDAI&CRP. In this regard, earlier diagnosis and treatment of the disease holds great promise in terms of targeting the desired outcome of remission. Future steps will involve the identification of a target adaptable to different populations or even specific patients, according to non-modifiable clinical factors.

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Table 1. Clinical characteristics stratified by momentary and sustained outcomes

	Full Analysis Set	Momentary outcome achievement		Sustained outcome achievement		p-value	
	Total (n=186)	Momentary R/LDA ASDAS (n=143)	Never R/LDA ASDAS (n=43)	Sustained R/LDA ASDAS (n=66)	Non-Sustained R/LDA ASDAS (n=99)	p-value 1 (Momentary)	p-value 2 (Sustained)
Demographic and clinical features							
Sex (male)	123 (66.1)	104 (72.7)	19 (44.2)	54 (81.8)	54 (54.5)	<0.001	<0.001
Age(years)							
At diagnosis	35.7 ±13.5	35.2±13.4	37.6±13.9	31.1 ±11.5	38.8±13.7	0.25	<0.001
At the beginning of first biologic	44.3 ±13.7	44.5±13.6	43.5±13.9	41.6 ±13.4	46.7±12.9	0.82	0.02
Smoking habit	86 (46.2)	68 (47.6)	18 (41.9)	32 (48.5)	46 (46.5)	0.60	0.87
Radiographic mNY criteria	140 (75.3)	109 (76.2)	31(72.1)	55 (83.3)	73 (73.7)	0.69	0.18
HLA*B27 positive	139 (74.7)	112 (80.0)	27 (64.3)	57 (89.1)	67 (69.1)	0.04	0.004
Dactylitis	5 (2.7)	5 (3.5)	0	2 (3.0)	2 (2.0)	0.59	0.68
Enthesitis	46 (24.7)	35 (24.5)	11 (25.6)	17 (25.8)	25 (25.3)	0.88	0.94
Psoriasis	8 (4.3)	7 (4.9)	1 (2.3)	3 (4.5)	4 (4.0)	0.46	0.87
Uveitis	36 (19.4)	28 (19.6)	8 (18.6)	12 (18.2)	21 (21.2%)	0.88	0.69
IBD	4 (2.2)	4 (2.8)	0	1 (1.5)	3 (3.0)	0.27	0.65
Baseline measurements							
CRP (mg/L)	5.3 (2.5-19.8)	5.3 (2.4-20.8)	14.4 (2.5-18.0)	5.3 (3.0-22.5)	5.9 (2.9-24.2)	0.93	0.81
BASDAI	5.6±1.9	5.5±1.8	6.0±1.9	5.4 ±1.9	5.9±1.8	0.11	0.08
ASDAS	3.3±1.0	3.2± 1.0	3.8±0.8	3.2 ±0.9	3.4 ±1.0	0.005	0.27
PhyGA	40 (20-50)	40 (20-50)	35.6 (20-50)	40 (20-60)	30 (20-50)	0.84	0.47
PtGA	60 (50-80)	60 (50-76.2)	70 (54-80)	60 (50-70.5)	66.5 (50-80)	0.046	0.25

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Concomitant treatment							
csDMARDs	97 (52.2)	74 (51.7)	23 (53.5)	34 (51.5)	53 (53.5)	0.86	0.87
Adalimumab	39 (21.0)	33 (23.1)	6 (14)	16 (24.2)	19 (19.2)	0.43	0.44
Etanercept	45 (24.2)	15 (34.9)	15 (34.9)	15 (22.7)	22 (22.2)		
Infliximab	69 (37.1)	53 (37.1)	17 (39.5)	20 (30.3)	41 (41.4)		
Certolizumab	2 (1.1)	1 (0.7)	1 (2.3)	0	2 (2.0)		
Golimumab	28 (15.1)	24 (16.8)	4 (9.3)	14 (21.2)	14 (14.1)		
Secukinumab	1 (0.5)	1 (0.7)	0	0	1 (1.0)		
Methotrexate	42 (22.6)	34 (23.8)	8 (18.6)	16 (24.2)	20 (20.2)	0.54	0.57
Sulfasalazine	67(36.0)	52(36.4)	15 (34.9)	22 (33.3)	38 (38.4)	0.86	0.62
Prednisone	21 (11.3)	16 (11.2)	5 (11.6)	7 (10.6)	13 (13.1)	0.93	0.80
Current/previous NSAIDs	186 (100)	38 (100)	19 (100)	66 (100)	99 (100)	-	-

Results are shown as absolute numbers (percentages) or expressed as the mean ± standard deviation or median (Q1-Q3). R: remission; LDA: Low disease activity; IBD: Inflammatory Bowel Disease; mNY: modified New York; CRP: C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; PhyGA: physician global assessment; PtGA: patient global assessment; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; NSAID: Non-steroidal anti-inflammatory drugs. Patients with sustained outcomes are those who presented outcomes on at least 3 consecutive visits; thus, the number of patients decreased with respect of the full analysis

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Figure 1. Patient disposition during the 2-year follow-up

Figure 2. Momentary and sustained outcomes (remission and low disease activity).

REM: remission; LDA: Low disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-Reactive Protein; ASDAS: Ankylosing Spondylitis Disease Activity Score.

Figure 3. Momentary and sustained outcomes (remission or low disease activity, as measured by ASDAS-CRP) stratified by gender.

REM: remission only; REM/LDA: remission or low disease activity; *p<0.001; # p<0.05

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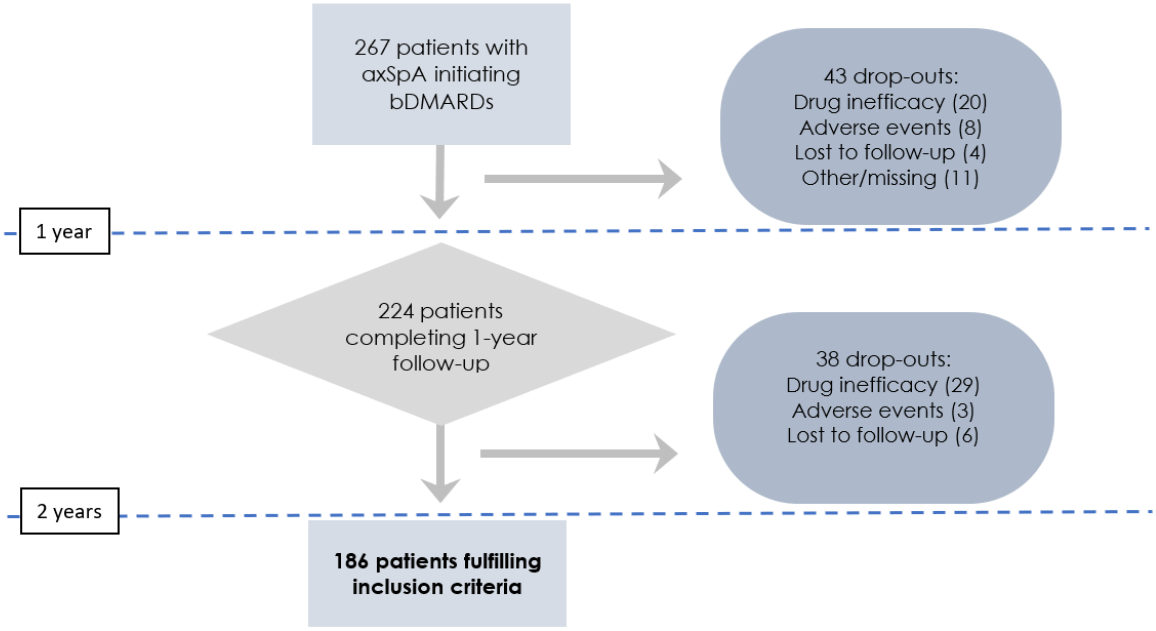

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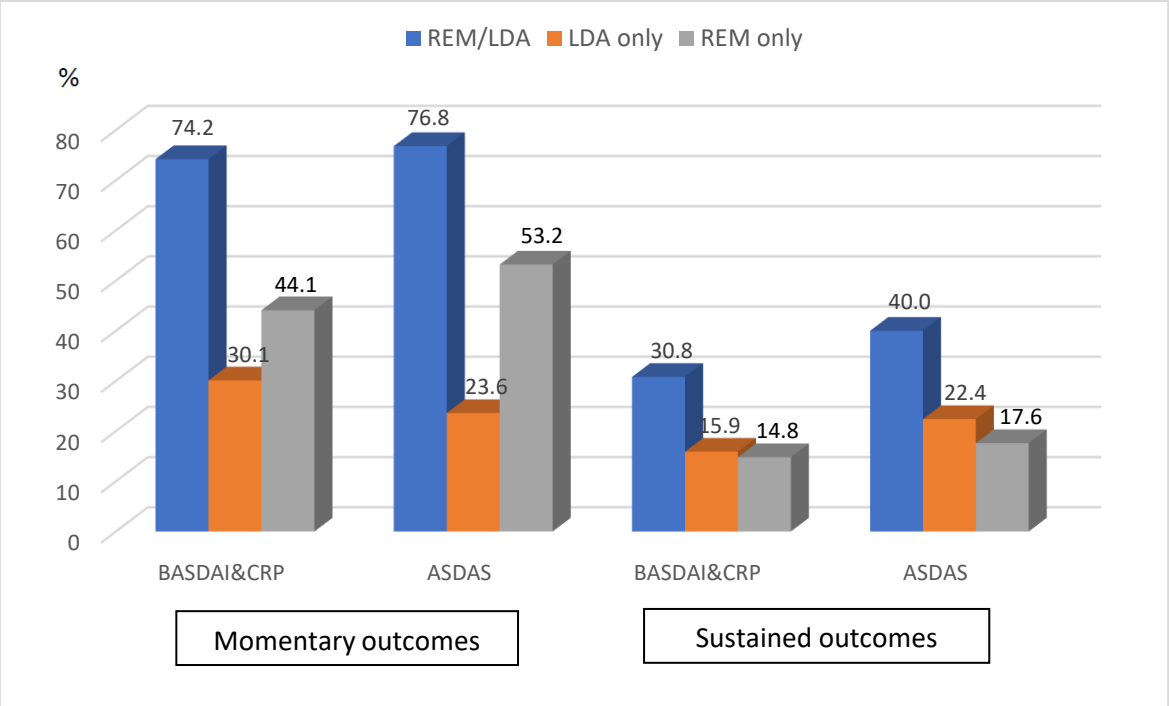

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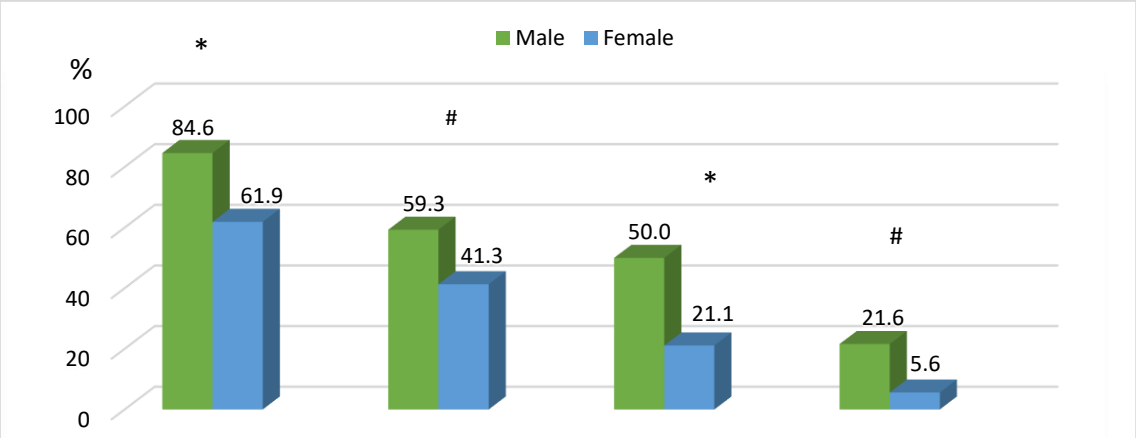

Figure 3. Momentary and sustained outcomes (remission or low disease activity, as measured by ASDAS-CRP) stratified by gender.

REM: remission only; REM/LDA: remission or low disease activity; *p<0.001; # p<0.05

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Achievement Rate and Predictive Factors of the Recommended Therapeutical Target in Patients with Axial Spondyloarthritis who Remain on Biological Therapy: A Prospective Cohort Study in Spain

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Achievement Rate and Predictive Factors of the Recommended Therapeutical Target in Patients with Axial Spondyloarthritis who Remain on Biological Therapy: A Prospective Cohort Study in Spain

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Contributorship

VNC, and CP conceived the study, participated in its design and coordination, and critically revised the manuscript. DB and KF performed the data collection, statistical analysis, interpretation and drafted the manuscript. PB, IM, RN, DP, LN, AV, MN and AB participated in the design, data interpretation and critically revised the Manuscript.

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Ethics approval

The study is attached to the project approved by the ethics committee from La Paz University Hospital with approval code PI-1479.

Patient and Public Involvement statement

Patients were not involved in the design of the study.

Data sharing statement

Extra data is available by emailing Diego Benavent (d_benavent@hotmail.com)

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ABSTRACT

Objectives: To determine the frequency of sustained remission (R) or low disease activity (LDA) in patients with axial spondyloarthritis (axSpA) undergoing long-term biological therapy and to analyze predictive factors for achieving these outcomes.

Design: Prospective, observational cohort study.

Setting: Spanish hospital.

Participants: Patients with axSpA who initiated biological treatment between 2003-2017.

Intervention: Assessment of demographic and clinical characteristics at the beginning of treatment and disease activity every 6 months up to a maximum of 2 years.

Main outcome measures: Disease activity was measured by ASDAS and BASDAI&CRP. Sustained R was defined as ASDAS<1.3 and/or BASDAI<2 & normal CRP and sustained LDA ASDAS<2.1 and/or BASDAI<4 & normal CRP on at least 3 consecutive visits.

Results: In total 186 patients (66.1% men and 75.3% with radiographic sacroiliitis) were included. Overall, 76.8% of patients achieved ASDAS R/LDA (R53.2%/LDA23.6%) in at least one visit. Forty percent (R17.6%/LDA22.4%) of the patients fulfilled the sustained ASDAS R/LDA state, whereas only 30.8% maintained this status (R14.8%/LDA15.9%) according to BASDAI&CRP. In the multivariate analysis, male sex (OR=4.01), younger age at the beginning of biological therapy (OR=0.96) and an HLA*B27 positive status (OR=4.30) were associated with achieving sustained ASDAS R/LDA.

Conclusions: In clinical practice, around one third of patients on bDMARDs achieve a sustained R/LDA status, but these rates drop to less than one in five when targeting remission, preventing the use of the latter as a feasible target. Male sex, HLA*B27 positivity, and younger age at the beginning of biological therapy are the main predictors for achieving sustained R/LDA.

Keywords: axial spondyloarthritis, remission, low-disease activity, bDMARDs

Strengths and limitations

- This analysis determines the frequency of sustained remission or low disease activity by the current recommended measures in axSpA (ASDAS or

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BASDAI&CRP), yielding a snapshot of the actual status of patients in clinical practice.

- Our study provides data to support sustained low disease activity over remission as the most desirable target to achieve in the management of patients with axSpA.
- Predictive factors of sustained remission / low disease activity in patients with biologic drugs are determined, which further studies may explore.
- The main limitation of this study arises from the observational design, which demands caution when interpreting the results.
- Since data was collected from clinical practice, there is some degree of missing data.

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BACKGROUND

The term axial spondyloarthritis (axSpA) comprises radiographic axSpA (r-axSpA), traditionally denominated as ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA), the two types mainly differing in the presence or absence of radiographic sacroiliitis (1). Management recommendations for axSpA have been developed in recent years, providing guidance for the diagnosis and treatment of individual patients in clinical practice. The Assessment of SpondyloArthritis international Society (ASAS) and the European Alliance of Associations for Rheumatology (EULAR) published the most recent update to the recommendations for the management of patients with axSpA in 2016 (2). Following this, the American College of Rheumatology (ACR), in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN), published an update to their recommendations for r-axSpA and nr-axSpA (3). Whereas the 2016 update to the ASAS-EULAR management recommendations for axSpA asserted that treatment should be guided in accordance with a predefined target, this is not supported by the ACR/SAA/SPARTAN recommendations. Indeed, the American recommendations do not include disease activity scores and conditionally recommend against using a treat-to-target strategy, alleging a lack of substantial evidence that might otherwise prove the potential to slow radiographic progression and the risk of rapid change in treatments. Despite these differences, both recommendations have substantial overlap, reflecting the consistent management of axSpA across the world. These recommendation sets are the cornerstone on axSpA management for the rheumatology community.

In addition, an international task force recently updated a set of recommendations for axSpA treatment to target (4). There are currently two main indices for the assessment of disease activity in axSpA, namely the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) (5). The BASDAI is a self-reported questionnaire that includes 6 items assessing back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and duration and severity of morning stiffness (6). The ASDAS is a composite index that includes four self-reported items, namely spinal pain, peripheral joint pain/swelling, duration of morning stiffness and patient global level of disease activity, and one value for acute phase reactant, namely C-reactive protein (CRP) or, alternatively, the erythrocyte sedimentation rate (ESR) (7). The ASDAS has shown equivalent or superior psychometric performance compared to

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the BASDAI, and therefore is the recommended index to monitor disease activity in patients with axSpA. As an alternative, the BASDAI can also be used (8).

The ASAS/EULAR recommendations for managing patients with axSpA state that the therapeutic goal for clinical practice is to maximize long-term health-related quality of life. While goals are useful for establishing the right direction, a specific target is critical to promote progress and achieve the desired results. Weighing this in the context of managing patients with axSpA, despite the stated recommendation to predefine a specific target, this was never clearly defined, either for specific thresholds or for time boundaries. In general, it is accepted that the absence of disease activity reflects the disease activity status of remission. According to the treat-to-target expert recommendations, the treatment target should be clinical remission/inactive disease, which can be defined by an ASDAS <1.3; however, low disease activity might also be considered as an alternative target (9). Worth noting is the fact that the management recommendations underscored the need to sustain remission over time. Although the exact time frame was not specified, this led to the realization that a single measurement of remission is not sufficient to determine whether or not the therapeutic target has been achieved. Therefore, although it is not explicitly stated, it can be inferred that the target is sustained absence of disease activity over several consecutive visits. However, whether this is feasible in clinical practice remains unknown. Furthermore, it is unknown how many of the patients who remain on long-term biological treatment reach the therapeutic objective recommended by these scientific societies.

The main objective of this study is to determine the frequency of sustained remission or low disease activity (LDA) in patients with axSpA undergoing long-term biological therapy, and to assess whether the scope of this objective varies according to the used index. Additionally, we also aimed to determine predictive factors of sustained remission / LDA in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

METHODS

This is a longitudinal study using the prospective cohort SpA-Paz, which is an ongoing, observational cohort including all patients with axSpA who initiate their first treatment with bDMARDs at the University Hospital La Paz, Madrid, Spain. For this study, patients initiating bDMARDs between January 2003 and the December 2017 were included.

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The inclusion criteria were as follows: a) adult patients diagnosed with axSpA according to their prescribing rheumatologist; b) initiation of first biological therapy (Tumor Necrosis Factor inhibitors [TNFi] or interleukin [IL]-17 inhibitors); c) at least two years of follow-up with assessment visits every 6 months; d) at least two assessments of ASDAS-CRP or BASDAI&CRP during follow-up. A 2-year follow-up cut-off was established to homogenize the definition of "long-term therapy" from the start of bDMARDs. Exclusion criteria were patients in clinical trials. All patients signed written informed consent.

Data collection

Demographic information, disease characteristics, bDMARDs type, concomitant treatment and laboratory tests before starting biological therapy were collected from the electronic health records at baseline. Baseline patients' characteristics were collected retrospectively at biologic initiation. Time windows for concomitant medication and laboratory tests extended three months prior biological initiation until the date of start of biologic. The presence of radiographic sacroiliitis, according to the modified New York (mNY) criteria, was assessed by the consensus of at least two out of three expert rheumatologists. Clinical disease activity was measured by ASDAS-CRP and BASDAI&CRP at baseline and at 6-month intervals after initiating bDMARDs for a period of two years.

According to ASDAS, disease activity was defined as follows: inactive disease (ASDAS <1.3), LDA (ASDAS ≥ 1.3 and < 2.1), high disease activity (ASDAS ≥ 2.1 and < 3.5) and very high disease activity (ASDAS ≥3.5) (10).

According to BASDAI, remission (R) was considered present with a BASDAI <2 & normal CRP, whereas LDA was considered present with a BASDAI <4 & normal CRP. Both sustained remission and sustained LDA required a sustained outcome for at least 3 consecutive follow-up visits during the study period. If any visit was missing, but a BASDAI and /or ASDAS assessment was still conducted at 3 successive visits, patients remained eligible and accounted as consecutive visits. Since patients in remission or inactive disease also fulfil LDA criteria, a category including all patients that achieved at least LDA was created, under the name of R/LDA.

Sample size was not based on data from previous publications because there are few reliable estimates in the literature regarding the sustained outcomes. Due to the exploratory character of the study, no formal sample size calculation was performed.

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Statistical analysis:

Descriptive analyses for the demographic, clinical and complimentary test information were performed. Categorical variables were described as absolute frequencies and percentages. Continuous variables were described using means and standard deviations (S.D.). The frequency of patients that achieved R/LDA, according to both ASDAS and BASDAI&CRP from at least one of the visits (momentary R/LDA), was calculated. Additionally, the frequency of patients whose clinical activity status remained unchanged over at least 3 consecutive follow-up visits (sustained R/LDA) were calculated. Only patients with a valid value for the calculated outcomes over these 3 consecutive visits, separated by 6 months between them, were assessed for their sustained treatment response.

Baseline predictive factors for achieving sustained R/LDA were identified using univariable and multivariable binary logistic regression models, inserting the possible predictors as independent variables and the R/LDA response achievement (by ASDAS or BASDAI&CRP, in two separate models) as the outcome. All of those variables with a p-value lower than 0.1 in the univariable were included in the multivariable analysis. Odds ratios (ORs) with p-value <0.05 were used as measures of association. All data were analyzed using SPSS software version 24.

RESULTS:

Demographic and Clinical Characteristics

Out of the 267 patients who initiated a bDMARD during the study period, 81 were excluded for discontinuation of the drug during follow-up or due to incomplete information. Therefore, 186 patients with axSpA fulfilled the inclusion criteria and were included in the analysis (**Figure 1**). Mean age was 54 ± 14.1 years and 123 (66.1%) were men. One hundred forty patients (75.3%) were classified as r-axSpA, whereas 46 (24.7%) were nr-axSpA; 139 (74.7%) were HLA*B27 positive. Other socio-demographic and disease characteristics of the patients at baseline are shown in Table 1.

Out of 186 patients, 155 (83%) completed 5 follow-up visits, 25 (14%) 4 visits and 6 (3%) 3 visits. Overall, 143 patients (76.8%) achieved ASDAS remission R/LDA (99 [53.2%] R/ 44 [23.6%] LDA) in at least one of the visits within the 2 years of follow-up (momentary R/LDA) (**Figure 2**). However, only 66 patients (40% of those assessed)

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sustained an ASDAS R/LDA status over three consecutive visits (29 [17.6%] R/ 37 [22.4%] LDA). Regarding BASDAI, 138 patients (74.2%) were classified as BASDAI&CRP R/LDA (82 [44.1%] R/ 56 [30.1%] LDA) in at least one of the visits, but only 56 patients (30.8% of those assessed) sustained BASDAI&CRP R/LDA status over at least three consecutive visits (27 [14.8%] R/ 29 [15.9%] LDA).

Among the 165 patients that had a valid ASDAS-CRP for at least 3 visits, 66 (40%) achieved sustained ASDAS-CRP R/LDA. No statistically significant differences were observed for most of the baseline characteristics between the patients who sustained ASDAS-CRP R/LDA and those who did not fulfill these criteria (**Table 1**). This was particularly notable in the rates of radiographic sacroiliitis (83.3 vs 73.7%, p=0.18). Indeed, a stratified analysis by sacroiliac radiographic damage, showed no statistically significant differences (p=0.18) in the achievement of sustained ASDAS R/LDA in patients with r-axSpA (n=55, 43%) as compared with patients with nr-axSpA (n=11, 29.7%). However, patients who achieved sustained ASDAS R/LDA were more frequently male (81.8 vs 54.5%, p<0.001), were younger at diagnosis (31.1 vs 38.8 years, p<0.001), younger age at biologic initiation (41.6 vs 46.7, p=0.02), and HLA*B27 positive (89.1 vs 69.1%, p=0.04). Interestingly, both momentary and sustained ASDAS-CRP outcomes showed significant differences when stratified by gender (**Figure 3**).

Regarding BASDAI&CRP, among the 182 patients who had a valid assessment during at least 3 visits, 56 (30.8%) achieved sustained BASDAI&CRP R/LDA. Patients who achieved sustained BASDAI&CRP R/LDA were more frequently male (78.3 vs 59.5%, p=0.01), were younger at diagnosis (30.1 vs 37.9 years, p=0.02), younger at biologic initiation (40.6 vs 46.1, p=0.02), and had higher baseline levels of methotrexate (33.9 vs 17.5, p=0.01). No significant differences were observed for the remaining characteristics.

In the multivariate analysis, an independent association with male sex (OR=4.01; 95% CI=1.83-8.77), younger age at the beginning of biological therapy (OR=0.96; 95% CI=0.94-0.99) and HLA*B27 positivity (OR=4.30; 95% CI=1.68-11.01) in those patients who achieved sustained ASDAS R/LDA were identified. Additionally, male sex (OR=3.19; 95% CI=1.46-6.99), younger age at the beginning of biological treatment (OR= 0.97; 95% CI=0.95-0.99) and the use of methotrexate (OR=3.07; 95% CI =1.39-6.78) were associated with patients who achieved sustained BASDAI&CRP R/LDA.

DISCUSSION

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The present study explored the rates of patients who achieved momentary and sustained R/LDA, as measured by ASDAS and BASDAI, after receiving biological treatment for at least 2 years, in order to assess whether achieving and maintaining these outcomes is a realistic target in clinical practice. In addition, it also evaluated predictive factors of sustained R/LDA in patients receiving bDMARDs. Considerable controversy surrounds the specific treatment target for axSpA. While remission or inactive disease by ASDAS or BASDAI is probably the preferred outcome, the feasibility of achieving this in clinical practice remains uncertain, and it is furthermore unclear whether this target is consistent with clinical decisions to maintain such therapy.

In our cohort, 3 out of 4 patients achieved momentary R/LDA in at least 1 of the visits after 2 years of follow-up, as measured both by ASDAS and BASDAI&CRP. Compared with previous research, a recent analysis by the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) showed that two-thirds of axSpA patients achieved an ASDAS LDA at 1 year (11). A study that drew from 12 European registries and that included 24,195 European axSpA patients initiating a first TNFi demonstrated that 27% of patients achieved ASDAS remission after 6 months, while 59% achieved BASDAI LDA. Crude response rates for both indices progressively increased at 12 and 24 months (12). It is worth noting that these studies assessed outcomes at a given time point, whereas rates in our study involved achieving the outcome at any given visit during the follow-up. Therefore, the slight differences among studies, and the plausibility that almost three quarters of patients achieved this outcome at some point in our study were confirmed.

Concerning sustained outcomes, of all the included patients classified as responders based on medical criteria and who were undergoing long-term biological therapy, 40% fulfilled a sustained ASDAS R/LDA status during three consecutive visits, whereas 30.8% sustained a BASDAI&CRP R/LDA status. More specifically, only 17.6% and 14.8% of patients achieved sustained remission status as measured by ASDAS and BASDAI&CRP during the same period, respectively. Unlike studies that assess whether patients achieve a specific outcome status at a given moment, those that have investigated whether this outcome is sustained over time remain scarce. *Landewé et al* investigated sustained remission in patients with early axSpA during the first 48 weeks of certolizumab treatment within a clinical trial. Their results showed that more than 40% of them achieved sustained remission; this was defined as an ASDAS < 1.3 at week 32 and < 2.1 at week 36 (or vice versa), and < 1.3 at week 48 (13). Differences in study designs and in

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definitions of remission indicate that these rates are not comparable to those recorded in our study. Whereas in the aforementioned clinical trial a LDA measurement was permissible during follow-up, a more stringent definition was used in our clinical practice study; i.e., documentation of sustained remission over three consecutive visits was required. Interestingly, when sustained LDA status was assessed in our study, 40% of patients did achieve this outcome. This is similar to the rates shown in the clinical trial, where the definition of remission was more inclusive, counting as well those patients who presented brief LDA.

Several studies have recently shown that the presence of both local and systemic inflammation leads to structural damage. Data from the Outcome in Ankylosing Spondylitis International Study (OASIS) revealed that higher disease activity, as measured by the ASDAS, leads to further radiographic progression, which has similarly been confirmed in other studies (14,15). Hence, the importance of suppressing inflammation and, therefore, disease activity in order to decelerate radiographic progression. While the goal seems clear, the need to set a specific target to achieve that desired goal remains pressing. As recommended by an international task force, a treat-to-target approach could improve outcomes in axSpA (4). However, the only available treat-to-target trial in axSpA, the TICOSPA trial, was only recently published (16). The primary endpoint, which was the percentage of patients with a significant improvement in the ASAS-Health Index (ASAS-HI) score (≥30%) over one-year's follow-up, was not met. However, secondary disease activity endpoints were met, yielding a general trend in favor of tight control. The primary endpoint was probably too ambitious given the difficulty of improving the overall health and functioning within such a short time frame. However, TICOSPA has arguably been a stepping-stone for treatment target strategies in clinical practice. It thus appears reasonable to focus on disease activity outcome measures as a means for optimizing treat-to-target strategies.

In this sense, our study raised some evidence that sustained remission of the disease, measured both by ASDAS and BASDAI&CRP, might be too ambitious at this time, since it seems unachievable for the majority of patients in our sample. Examination of sustained LDA yielded results that seem acceptable for making a good target: it is ambitious, but achievable for approximately one in three patients. However, this indicates that two-thirds of the patients who continue bDMARDs in our study- and are therefore in a presumably satisfactory clinical status according to medical criteria- are not achieving this sustained target. These results need to be assessed by further studies in a broader population and in

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different settings to confirm their external validity. In case that these exploratory results are confirmed, there will still be a pending task in this respect, one that could be improved by adjusting the outcomes to the patient's baseline status, setting clinical improvement as a more pragmatic measurement to assess the current status of each patient. In any case, the fact that remission is not currently a realistic target does not mean that this remains unfeasible in a near future if efforts focus on such unmet needs.

Therefore, it seems rational to assess factors that would potentially facilitate a better clinical response, and to work in that direction. Worth noting is the fact that patients who achieved sustained ASDAS R/LDA were more frequently male, were younger at diagnosis, younger age at biologic initiation, and HLA*B27 positive in our study. Most of these features remained similar when BASDAI&CRP was established as the outcome variable. Remarkably, some of these characteristics are non-modifiable and static, namely gender and HLA*B27 status. When assessing modifiable factors, it seems clear that clinicians should advocate for any modifications in quest of the targeted outcomes; in this sense, earlier diagnosis and treatment might prove to be the single-most important factors clinicians can influence. However, this cannot be done for non-modifiable factors. This begs the question of whether it is the target itself that should be adapted for different groups, particularly in light of gender-related differential clinical responses.

Our study has some limitations. First, the observational design demands caution when interpreting the results, since they are prone to both selection and information bias, as well as to loss of follow-up. Indeed, not all patients who initiated treatment with a bDMARD fulfilled the inclusion criteria after two years; 81 patients did not complete the required period of follow-up for inclusion. Although we acknowledge a potential bias in the final included patients towards a better treatment response, the requirement of a certain number of visits is necessary to have a homogeneous set of patients in which sustained outcomes could be assessed. Besides, not all patients present all outcome assessment parameters at every visit. However, as only those patients with at least three assessments were included, the consistency of the results was maintained, while yielding information from a representative sample of a typical patient population in clinical practice. Second, the absence of established definitions for momentary and sustained outcomes has led to various proposed definitions that may be judged arbitrary. Nevertheless, the fact that established cut-offs were examined facilitated the interpretation of sustained outcomes, while also providing evidence that might serve as

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the basis for a future consensus definition. Besides, some of the demographic and clinical data was only collected at baseline and not during follow-up, which hinders the comparison among groups regarding the characteristics of interest during the study period. Due to the scarcity of previous reliable data in the literature regarding sustained outcomes, no formal sample size calculation was performed. In addition, we did not include any radiologic outcomes to assess clinical response of patients, as they were not available in clinical practice. This is related to the lack of standardized recommendations to assess radiographic progression routinely over a period of less than two years and to use magnetic resonance imaging for monitorization of disease activity (17).

In conclusion, remission does not currently appear to be a realistic target in those axSpA patients treated with long-term bDMARDs therapy. On the other hand, low disease activity status seems a measurable, achievable and reasonable target for axSpA patients in clinical practice. Male patients and those of younger age at biologic initiation have shown to be predictive factors of good outcomes, when assessed by either ASDAS or BASDAI&CRP. In this regard, earlier diagnosis and treatment of the disease holds great promise in terms of targeting the desired outcome of remission. Future steps will involve the identification of a target adaptable to different populations or even specific patients, according to non-modifiable clinical factors.

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Table 1. Clinical characteristics stratified by momentary and sustained outcomes

	Full Analysis Set	Momentary outcome achievement		Sustained outcome achievement		p-value	
	Total (n=186)	Momentary R/LDA ASDAS (n=143)	Never R/LDA ASDAS (n=43)	Sustained R/LDA ASDAS (n=66)	Non-Sustained R/LDA ASDAS (n=99)	p-value 1 (Momentary)	p-value 2 (Sustained)
Demographic and clinical features							
Sex (male)	123 (66.1)	104 (72.7)	19 (44.2)	54 (81.8)	54 (54.5)	<0.001	<0.001
Age(years)							
At diagnosis, mean ± SD	35.7 ±13.5	35.2±13.4	37.6±13.9	31.1 ±11.5	38.8±13.7	0.25	<0.001
At the beginning of first biologic, mean ± SD	44.3 ±13.7	44.5±13.6	43.5±13.9	41.6 ±13.4	46.7±12.9	0.82	0.02
Smoking habit	86 (46.2)	68 (47.6)	18 (41.9)	32 (48.5)	46 (46.5)	0.60	0.87
Radiographic mNY criteria	140 (75.3)	109 (76.2)	31(72.1)	55 (83.3)	73 (73.7)	0.69	0.18
HLA*B27 positive	139 (74.7)	112 (80.0)	27 (64.3)	57 (89.1)	67 (69.1)	0.04	0.004
Dactylitis	5 (2.7)	5 (3.5)	0	2 (3.0)	2 (2.0)	0.59	0.68
Enthesitis	46 (24.7)	35 (24.5)	11 (25.6)	17 (25.8)	25 (25.3)	0.88	0.94
Psoriasis	8 (4.3)	7 (4.9)	1 (2.3)	3 (4.5)	4 (4.0)	0.46	0.87
Uveitis	36 (19.4)	28 (19.6)	8 (18.6)	12 (18.2)	21 (21.2%)	0.88	0.69
IBD	4 (2.2)	4 (2.8)	0	1 (1.5)	3 (3.0)	0.27	0.65
Baseline measurements							
CRP (mg/L), median (Q1-Q3)	5.3 (2.5-19.8)	5.3 (2.4-20.8)	14.4 (2.5-18.0)	5.3 (3.0-22.5)	5.9 (2.9-24.2)	0.93	0.81
BASDAI, mean ± SD	5.6±1.9	5.5±1.8	6.0±1.9	5.4 ±1.9	5.9±1.8	0.11	0.08
ASDAS, mean ± SD	3.3±1.0	3.2± 1.0	3.8±0.8	3.2 ±0.9	3.4 ±1.0	0.005	0.27
PhyGA, median (Q1-Q3)	40 (20-50)	40 (20-50)	35.6 (20-50)	40 (20-60)	30 (20-50)	0.84	0.47
PtGA, median (Q1-Q3)	60 (50-80)	60 (50-76.2)	70 (54-80)	60 (50-70.5)	66.5 (50-80)	0.044	0.25
Concomitant treatment							

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csDMARDs	97 (52.2)	74 (51.7)	23 (53.5)	34 (51.5)	53 (53.5)	0.86	0.87
Adalimumab	39 (21.0)	33 (23.1)	6 (14)	16 (24.2)	19 (19.2)	0.43	0.44
Etanercept	45 (24.2)	15 (34.9)	15 (34.9)	15 (22.7)	22 (22.2)		
Infliximab	69 (37.1)	53 (37.1)	17 (39.5)	20 (30.3)	41 (41.4)		
Certolizumab	2 (1.1)	1 (0.7)	1 (2.3)	0	2 (2.0)		
Golimumab	28 (15.1)	24 (16.8)	4 (9.3)	14 (21.2)	14 (14.1)		
Secukinumab	1 (0.5)	1 (0.7)	0	0	1 (1.0)		
Methotrexate	42 (22.6)	34 (23.8)	8 (18.6)	16 (24.2)	20 (20.2)	0.54	0.57
Sulfasalazine	67(36.0)	52(36.4)	15 (34.9)	22 (33.3)	38 (38.4)	0.86	0.62
Prednisone	21 (11.3)	16 (11.2)	5 (11.6)	7 (10.6)	13 (13.1)	0.93	0.80
Current/previous NSAIDs	186 (100)	38 (100)	19 (100)	66 (100)	99 (100)	-	-

Measures are stated for continuous variables. For the remaining variables results are shown as n (%). R: remission; LDA: Low disease activity; IBD: Inflammatory Bowel Disease; mNY: modified New York; CRP: C-Reactive Protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; PhyGA: physician global assessment; PtGA: patient global assessment; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; NSAID: Non-steroidal anti-inflammatory drugs. Patients with sustained outcomes are those who presented outcomes on at least 3 consecutive visits; thus, the number of patients decreased with respect of the full analysis

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Figure 1. Patient disposition during the 2-year follow-up

Figure 2. Momentary and sustained outcomes (remission and low disease activity).

REM: remission; LDA: Low disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-Reactive Protein; ASDAS: Ankylosing Spondylitis Disease Activity Score.

Figure 3. Momentary and sustained outcomes (remission or low disease activity, as measured by ASDAS-CRP) stratified by gender.

REM: remission only; REM/LDA: remission or low disease activity; *p<0.001; # p<0.05

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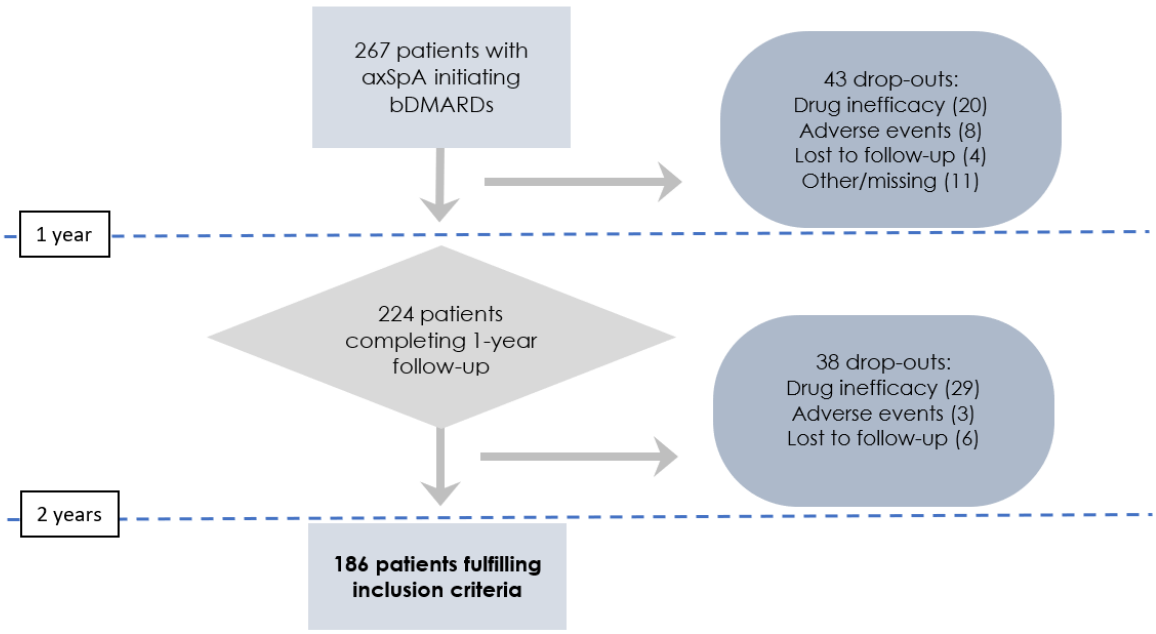

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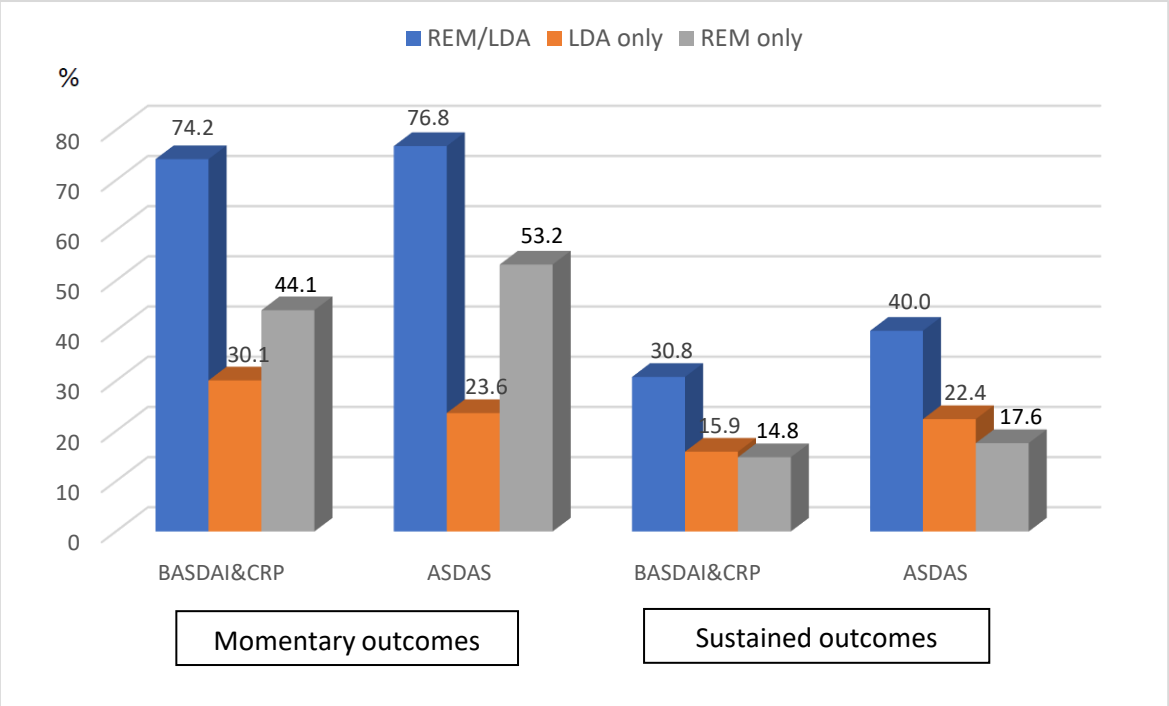

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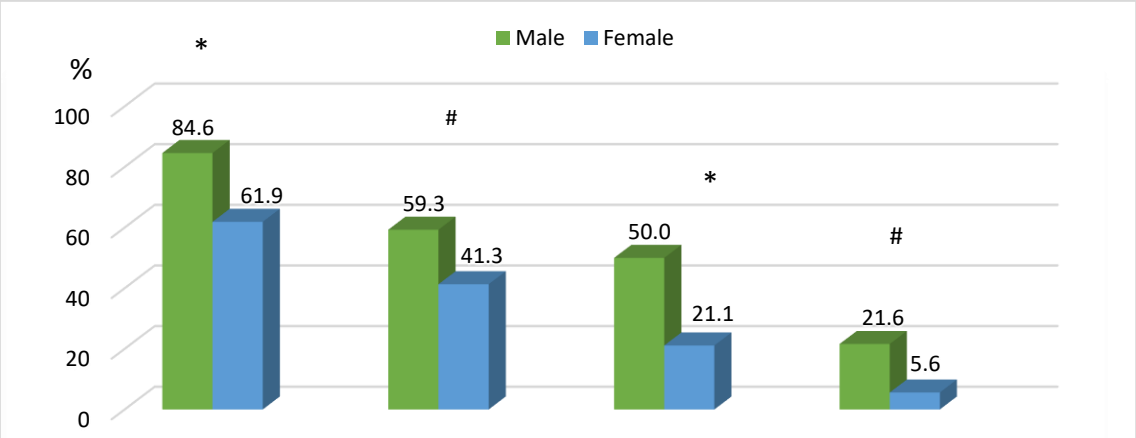

Figure 3. Momentary and sustained outcomes (remission or low disease activity, as measured by ASDAS-CRP) stratified by gender.

REM: remission only; REM/LDA: remission or low disease activity; *p<0.001; # p<0.05

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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