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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057850
Article Type:	Original research
Date Submitted by the Author:	28-Sep-2021
Complete List of Authors:	Benavent, Diego; Hospital Universitario La Paz Franco-Gómez, Karen; Hospital Universitario La Paz Plasencia Rodrigues, Chamaida; Hospital Universitario La Paz Novella Navarro, Marta; Hospital Universitario La Paz Bogas, Patricia; Hospital Universitario La Paz Nieto, Romina; Hospital Provincial de Rosario Monjo, Irene; Hospital Universitario La Paz Nuño, Laura; Hospital Universitario La Paz, Villalba, Alejandro; Hospital Universitario La Paz Peiteado, D; Hospital Universitario La Paz Balsa, Alejandro; Hospital Universitario La Paz Navarro-Compan, Victoria; Hospital Universitario La Paz, Rheumatology Unit
Keywords:	RHEUMATOLOGY, EPIDEMIOLOGY, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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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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Competing interests: DB received grants/speaker/research supports from Roche and Abbvie. CP received grants/speaker/research supports from Pfizer, Sanofi, Novartis, Roche and Lilly. RN received grants/speaker/research supports from Novartis, Sanofi Genzyme, Pfizer and Montpellier. IM received grants/research supports from Novartis and speaker's fees from AbbVie, UCB, Roche and Novartis. DP received grants/research supports from Abbvie, Lilly, MSD and Roche, and had participation in company sponsored speaker's bureau from Abbvie, Novartis, Lilly, Roche, and MSD. AB received Grant/research support, fees for consultancies or as a speaker for Abbvie, Pfizer, Novartis, BMS, Nordic, Sanofi, Sandoz, Lilly, UCB, Roche. VN: consultancy/speaker/research grants from: Abbvie, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche and UCB.

### 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.

### 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)

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### Acknowledgements

The authors thank the Spanish Society of Rheumatology (SER) for the English editing service (translation funded by the SER- FERBT2021).

## 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.

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

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6 The ASAS/EULAR recommendations for managing patients with axSpA state that the  
7 therapeutic goal for clinical practice is to maximize long-term health-related quality of  
8 life. While goals are useful for establishing the right direction, a specific target is critical  
9 to promote progress and achieve the desired results. Weighing this in the context of  
10 managing patients with axSpA, despite the stated recommendation to predefine a specific  
11 target, this was never clearly defined, either for specific thresholds or for time boundaries.  
12 In general, it is accepted that the absence of disease activity reflects the disease activity  
13 status of remission. According to the treat-to-target expert recommendations, the  
14 treatment target should be clinical remission/inactive disease, which can be defined by an  
15 ASDAS <1.3; however, low disease activity might also be considered as an alternative  
16 target (9). Worth noting is the fact that the management recommendations underscored  
17 the need to sustain remission over time. Although the exact time frame was not specified,  
18 this led to the realization that a single measurement of remission is not sufficient to  
19 determine whether or not the therapeutic target has been achieved. Therefore, although it  
20 is not explicitly stated, it can be inferred that the target is sustained absence of disease  
21 activity over several consecutive visits. However, whether this is feasible in clinical  
22 practice remains unknown. Furthermore, it is unknown how many of the patients who  
23 remain on long-term biological treatment reach the therapeutic objective recommended  
24 by these scientific societies.  
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41 The main objective of this study is to determine the frequency of sustained remission or  
42 low disease activity (LDA) in patients with axSpA undergoing long-term biological  
43 therapy, and to assess whether the scope of this objective varies according to the used  
44 index. Additionally, we also aimed to determine predictive factors of sustained remission  
45 / LDA in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs).  
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## 51 **METHODS**

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53 This is a longitudinal study using the prospective cohort SpA-Paz, which is an ongoing,  
54 observational cohort including all patients with axSpA who initiate treatment with  
55 bDMARDs at the University Hospital La Paz, Madrid, Spain. For this study, patients  
56 initiating bDMARDs between January 2003 and the December 2017 were included.  
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3 The inclusion criteria were as follows: a) adult patients diagnosed with axSpA according  
4 to their prescribing rheumatologist; b) initiation of first biological therapy (Tumor  
5 Necrosis Factor inhibitors [TNFi] or interleukin [IL]-17 inhibitors); c) at least two years  
6 of follow-up with assessment visits every 6 months; d) at least two assessments of  
7 ASDAS-CRP or BASDAI&CRP during follow-up. A 2-year follow-up cut-off was  
8 established to homogenize the definition of “long-term therapy” from the start of  
9 bDMARDs.

### 17 **Data collection**

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

25 According to ASDAS, disease activity was defined as follows: inactive disease (ASDAS  
26 <1.3), LDA (ASDAS  $\geq 1.3$  and < 2.1), high disease activity (ASDAS  $\geq 2.1$  and < 3.5)  
27 and very high disease activity (ASDAS  $\geq 3.5$ ) (10).

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

### 36 **Statistical analysis:**

37 Descriptive analyses for the demographic, clinical and complimentary test information  
38 were performed. Categorical variables were described as absolute frequencies and  
39 percentages. Continuous variables were described using means and standard deviations  
40 (S.D.). The frequency of patients that achieved R/LDA, according to both ASDAS and  
41 BASDAI&CRP from at least one of the visits (momentary R/LDA), was calculated.  
42 Additionally, the frequency of patients whose clinical activity status remained unchanged  
43 over at least 3 consecutive follow-up visits (sustained R/LDA) were calculated. Only  
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3 patients with a valid value for the calculated outcomes over these 3 consecutive visits,  
4 separated by 6 months between them, were assessed for their sustained treatment  
5 response.  
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8 Baseline predictive factors for achieving sustained R/LDA were identified using  
9 univariable and multivariable binary logistic regression models, inserting the possible  
10 predictors as independent variables and the R/LDA response achievement (by ASDAS or  
11 BASDAI&CRP, in two separate models) as the outcome. All of those variables with a p-  
12 value lower than 0.1 in the univariable were included in the multivariable analysis. Odds  
13 ratios (ORs) with p-value <0.05 were used as measures of association. All data were  
14 analyzed using SPSS software version 24.  
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## 22 RESULTS:

### 23 Demographic and Clinical Characteristics

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26 Out of the 267 patients who initiated a bDMARD during the study period, 81 were  
27 excluded for discontinuation of the drug during follow-up or due to incomplete  
28 information. Therefore, 186 patients with axSpA fulfilled the inclusion criteria and were  
29 included in the analysis (**Figure 1**). Mean age was  $54 \pm 14.1$  years and 123 (66.1%) were  
30 men. One hundred forty patients (75.3%) were classified as r-axSpA, whereas 46 (24.7%)  
31 were nr-axSpA; 139 (74.7%) were HLA\*B27 positive. Other socio-demographic and  
32 disease characteristics of the patients at baseline are shown in Table 1.  
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38 Overall, 143 patients (76.8%) achieved ASDAS remission (R)/LDA (99 [53.2%] R/ 44  
39 [23.6%] LDA) in at least one of the visits after 2 years of follow-up (momentary R/LDA)  
40 (**Figure 2**). However, only 66 patients (40% of those assessed) sustained an ASDAS  
41 R/LDA status over three consecutive visits (29 [17.6%] R/ 37 [22.4%] LDA). Regarding  
42 BASDAI, 138 patients (74.2%) were classified as BASDAI&CRP R/LDA (82 [44.1%]  
43 R/ 56 [30.1%] LDA) in at least one of the visits, but only 56 patients (30.8% of those  
44 assessed) sustained BASDAI&CRP R/LDA status over at least three consecutive visits  
45 (27 [14.8%] R/ 29 [15.9%] LDA).  
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52 Among the 165 patients that had a valid ASDAS-CRP for at least 3 visits, 66 (40%)  
53 achieved sustained ASDAS-CRP R/LDA. No statistically significant differences were  
54 observed for most of the baseline characteristics between the patients who sustained  
55 ASDAS-CRP R/LDA and those who did not fulfill these criteria; this was particularly  
56 notable in the rates of radiographic sacroiliitis (83.3 vs 73.7%,  $p=0.18$ ) (**Table 1**).  
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3 However, patients who achieved sustained ASDAS R/LDA were more frequently male  
4 (81.8 vs 54.5%,  $p<0.001$ ), were younger at diagnosis (31.1 vs 38.8 years,  $p<0.001$ ),  
5 younger age at biologic initiation (41.6 vs 46.7,  $p=0.02$ ), and were more HLA\*B27  
6 positive (89.1 vs 69.1%,  $p=0.04$ ). Interestingly, both momentary and sustained ASDAS-  
7 CRP outcomes showed significant differences when stratified by gender (**Figure 3**).  
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10 Among the 182 patients who had a valid BASDAI&CRP assessment during at least 3  
11 visits, 56 (30.8%) achieved sustained BASDAI&CRP R/LDA. Patients who achieved  
12 sustained BASDAI&CRP R/LDA were more frequently male 54 (78.3 vs 59.5%,  $p=0.01$ ),  
13 were younger at diagnosis (30.1 vs 37.9 years,  $p=0.02$ ), younger at biologic initiation  
14 (40.6 vs 46.1,  $p=0.02$ ), and had higher baseline levels of methotrexate (33.9 vs 17.5,  
15  $p=0.01$ ). No significant differences were observed for the remaining characteristics.  
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17 In the multivariate analysis, an independent association with male sex (OR=4.01; 95%  
18 CI=1.83-8.77), younger age at the beginning of biological therapy (OR=0.96; 95%  
19 CI=0.94-0.99) and HLA\*B27 positivity (OR=4.30; 95% CI=1.68-11.01) in those patients  
20 who achieved sustained ASDAS R/LDA were identified. Additionally, male sex  
21 (OR=3.19; 95% CI=1.46-6.99), younger age at the beginning of biological treatment  
22 (OR= 0.97; 95% CI=0.95-0.99) and the use of methotrexate (OR=3.07; 95% CI =1.39-  
23 6.78) were associated with patients who achieved sustained BASDAI&CRP R/LDA.  
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## 35 DISCUSSION

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37 The present study explored the rates of patients who achieved momentary and sustained  
38 R/LDA, as measured by ASDAS and BASDAI, after receiving biological treatment for  
39 at least 2 years, in order to assess whether achieving and maintaining these outcomes is a  
40 realistic target in clinical practice. In addition, it also evaluated predictive factors of  
41 sustained R/LDA in patients receiving bDMARDs. Considerable controversy surrounds  
42 the specific treatment target for axSpA. While remission or inactive disease by ASDAS  
43 or BASDAI is probably the preferred outcome, the feasibility of achieving this in clinical  
44 practice remains uncertain, and it is furthermore unclear whether this target is consistent  
45 with clinical decisions to maintain such therapy.  
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53 In our cohort, 3 out of 4 patients achieved momentary R/LDA in at least 1 of the visits  
54 after 2 years of follow-up, as measured both by ASDAS and BASDAI&CRP. Compared  
55 with previous research, a recent analysis by the British Society for Rheumatology  
56 Biologics Register in Ankylosing Spondylitis (BSRBR-AS) showed that two-thirds of  
57 axSpA patients achieved an ASDAS LDA at 1 year (11). A study that drew from 12  
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3 European registries and that included 24,195 European axSpA patients initiating a first  
4 TNFi demonstrated that 27% of patients achieved ASDAS remission after 6 months,  
5 while 59% achieved BASDAI LDA. Crude response rates for both indices progressively  
6 increased at 12 and 24 months (12). It is worth noting that these studies assessed outcomes  
7 at a given time point, whereas rates in our study involved achieving the outcome at any  
8 given visit during the follow-up. Therefore, the slight differences among studies, and the  
9 plausibility that almost three quarters of patients achieved this outcome at some point in  
10 our study were confirmed.

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

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

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

28  
29 Therefore, it seems rational to assess factors that would potentially facilitate a better  
30 clinical response, and to work in that direction. Worth noting is the fact that patients who  
31 achieved sustained ASDAS R/LDA were more frequently male, were younger at  
32 diagnosis, younger age at biologic initiation, and were more HLA\*B27 positive in our  
33 study. Most of these features remained similar when BASDAI&CRP was established as  
34 the outcome variable. Remarkably, some of these characteristics are non-modifiable and  
35 static, namely gender and HLA\*B27 status. When assessing modifiable factors, it seems  
36 clear that clinicians should advocate for any modifications in quest of the targeted  
37 outcomes; in this sense, earlier diagnosis and treatment might prove to be the single-most  
38 important factors clinicians can influence. However, this cannot be done for non-  
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3 modifiable factors. This begs the question of whether it is the target itself that should be  
4 adapted for different groups, particularly in light of gender-related differential clinical  
5 responses.  
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10 Our study has some limitations. First, the observational design demands caution when  
11 interpreting the results, since they are prone to both selection and information bias, as  
12 well as to loss of follow-up. Indeed, not all patients present all outcome assessment  
13 parameters at every visit. However, as only those patients with at least three assessments  
14 were included, the consistency of the results was maintained, while yielding information  
15 from a representative sample of a typical patient population in clinical practice. Second,  
16 the absence of established definitions for momentary and sustained outcomes has led to  
17 various proposed definitions that may be judged arbitrary. Nevertheless, the fact that  
18 established cut-offs were examined facilitated the interpretation of sustained outcomes,  
19 while also providing evidence that might serve as the basis for a future consensus  
20 definition.  
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30 In conclusion, remission does not currently appear to be a realistic target in those axSpA  
31 patients treated with long-term bDMARDs therapy. On the other hand, low disease  
32 activity status seems a measurable, achievable and reasonable target for axSpA patients  
33 in clinical practice. Male patients and those of younger age at biologic initiation have  
34 shown to be predictive factors of good outcomes, when assessed by either ASDAS or  
35 BASDAI&CRP. In this regard, earlier diagnosis and treatment of the disease holds great  
36 promise in terms of targeting the desired outcome of remission. Future steps will involve  
37 the identification of a target adaptable to different populations or even specific patients,  
38 according to non-modifiable clinical factors.  
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21 open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* 2021.

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)
<b>Demographic and clinical features</b>							
<b>Sex (male)</b>	123 (66.1)	104 (72.7)	19 (44.2)	54 (81.8)	54 (54.5)	<0.001	<0.001
<b>Age(years)</b>							
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
<b>Smoking habit</b>	86 (46.2)	68 (47.6)	18 (41.9)	32 (48.5)	46 (46.5)	0.60	0.87
<b>Radiographic mNY criteria</b>	140 (75.3)	109 (76.2)	31(72.1)	55 (83.3)	73 (73.7)	0.69	0.18
<b>HLA*B27 positive</b>	139 (74.7)	112 (80.0)	27 (64.3)	57 (89.1)	67 (69.1)	0.04	0.004
<b>Dactylitis</b>	5 (2.7)	5 (3.5)	0	2 (3.0)	2 (2.0)	0.59	0.68
<b>Enthesitis</b>	46 (24.7)	35 (24.5)	11 (25.6)	17 (25.8)	25 (25.3)	0.88	0.94
<b>Psoriasis</b>	8 (4.3)	7 (4.9)	1 (2.3)	3 (4.5)	4 (4.0)	0.46	0.87
<b>Uveitis</b>	36 (19.4)	28 (19.6)	8 (18.6)	12 (18.2)	21 (21.2%)	0.88	0.69
<b>IBD</b>	4 (2.2)	4 (2.8)	0	1 (1.5)	3 (3.0)	0.27	0.65
<b>Baseline measurements</b>							
<b>CRP (mg/L)</b>	14.5±21.3	14.4±21.4	14.7±21.1	15.9±22.9	15.0±21.5	0.93	0.81
<b>BASDAI</b>	5.6±1.9	5.5±1.8	6.0±1.9	5.4 ±1.9	5.9±1.8	0.11	0.08
<b>ASDAS</b>	3.3±1.0	3.2±1.0	3.8±0.8	3.2 ±0.9	3.4 ±1.0	0.005	0.27
<b>PhyGA</b>	36.3± 21.0	36.5±20.9	35.6±21.7	38.6 ±21.9	35.7±20.3	0.84	0.47
<b>PtGA</b>	61.3± 21.6	59.6±21.7	67.2±20.5	60.0 ±21.3	63.8 ±20.3	0.046	0.25

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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3 **Figure 1. Patient disposition during the 2-year follow-up**  
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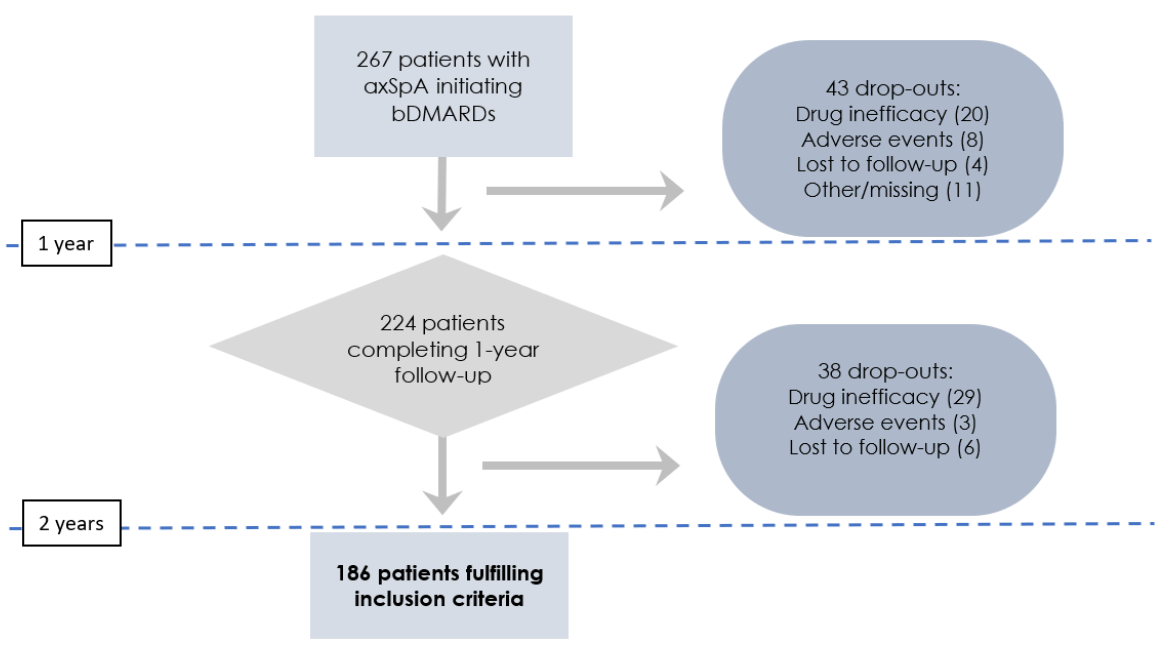
10 **Figure 2. Momentary and sustained outcomes (remission and low disease activity).**

11 REM: remission; LDA: Low disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-Reactive  
12 Protein; ASDAS: Ankylosing Spondylitis Disease Activity Score  
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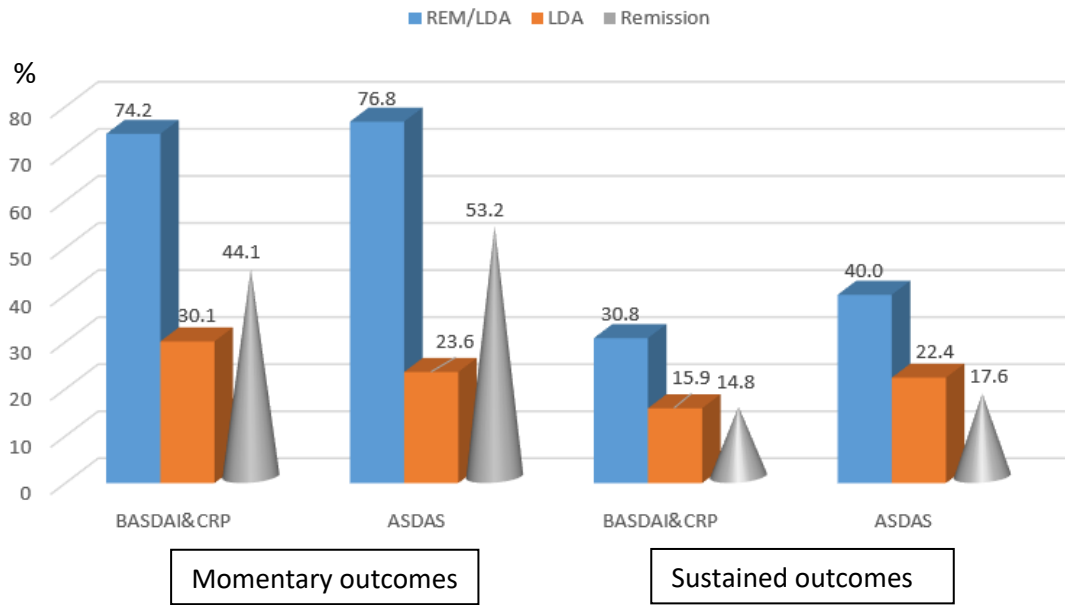
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17 **Figure 3. Momentary and sustained outcomes (remission or low disease activity, as  
18 measured by ASDAS-CRP) stratified by gender.**

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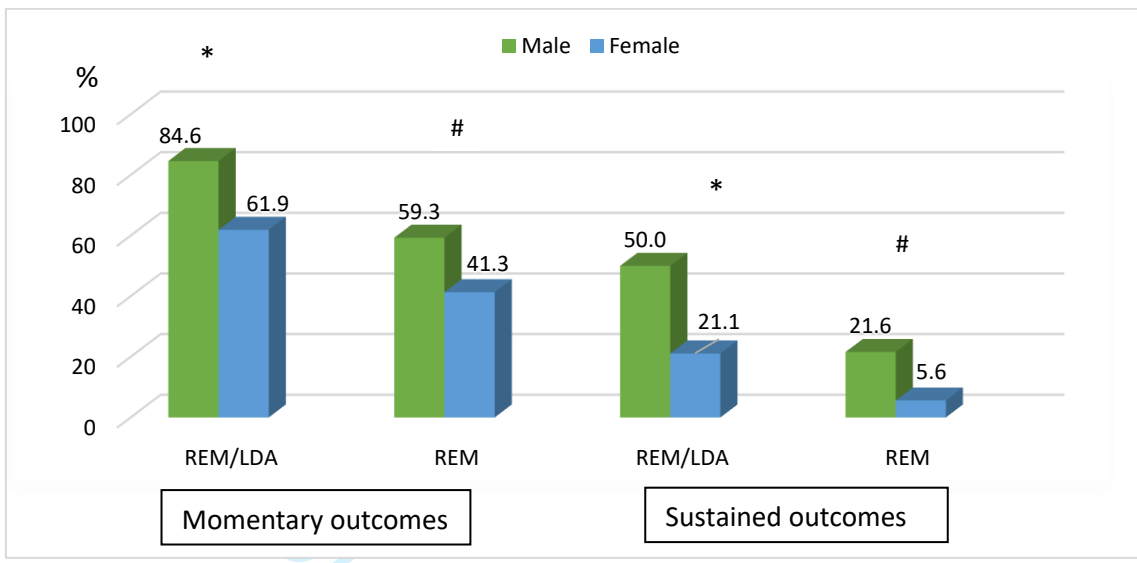


Peer review only



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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
	(e) Describe any sensitivity analyses		

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60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
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\*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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057850.R1
Article Type:	Original research
Date Submitted by the Author:	28-Jan-2022
Complete List of Authors:	Benavent, Diego; Hospital Universitario La Paz Franco-Gómez, Karen; Hospital Universitario La Paz Plasencia-Rodriguez, Chamaida; Hospital Universitario La Paz Novella Navarro, Marta; Hospital Universitario La Paz Bogas, Patricia; Hospital Universitario La Paz Nieto, Romina; Hospital Provincial de Rosario Monjo, Irene; Hospital Universitario La Paz Nuño, Laura; Hospital Universitario La Paz, Villalba, Alejandro; Hospital Universitario La Paz Peiteado, D; Hospital Universitario La Paz Balsa, Alejandro; Hospital Universitario La Paz Navarro-Compan, Victoria; Hospital Universitario La Paz, Rheumatology Unit
<b>Primary Subject Heading</b>:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	RHEUMATOLOGY, EPIDEMIOLOGY, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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3 Achievement Rate and Predictive Factors of the Recommended Therapeutical Target in  
4 Patients with Axial Spondyloarthritis who Remain on Biological Therapy: A Prospective  
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8 *D. Benavent<sup>1</sup>, K. Franco-Gómez<sup>1</sup>; C. Plasencia-Rodríguez<sup>1</sup>; M. Novella-Navarro<sup>1</sup>; P.*  
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27 Competing interests: DB received grants/speaker/research supports from Roche and  
28 Abbvie. CP received grants/speaker/research supports from Pfizer, Sanofi, Novartis,  
29 Roche and Lilly. RN received grants/speaker/research supports from Novartis, Sanofi  
30 Genzyme, Pfizer and Montpellier. IM received grants/research supports from Novartis  
31 and speaker's fees from AbbVie, UCB, Roche and Novartis. DP received grants/research  
32 supports from Abbvie, Lilly, MSD and Roche, and had participation in company  
33 sponsored speaker's bureau from Abbvie, Novartis, Lilly, Roche, and MSD. AB received  
34 Grant/research support, fees for consultancies or as a speaker for Abbvie, Pfizer,  
35 Novartis, BMS, Nordic, Sanofi, Sandoz, Lilly, UCB, Roche. VN:  
36 consultancy/speaker/research grants from: Abbvie, BMS, Janssen, Lilly, MSD, Novartis,  
37 Pfizer, Roche and UCB.  
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49 **Contributorship**

50 VNC, and CP conceived the study, participated in its design and coordination, and  
51 critically revised the manuscript. DB and KF performed the data collection, statistical  
52 analysis, interpretation and drafted the manuscript. PB, IM, RN, DP, LN, AV, MN and AB  
53 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)

#### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

#### Acknowledgements

The authors thank the Spanish Society of Rheumatology (SER) for the English editing service (translation funded by the SER- FERBT2021).

## 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.

- 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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3 of morning stiffness (6). The ASDAS is a composite index that includes four self-reported  
4 items, namely spinal pain, peripheral joint pain/swelling, duration of morning stiffness  
5 and patient global level of disease activity, and one value for acute phase reactant, namely  
6 C-reactive protein (CRP) or, alternatively, the erythrocyte sedimentation rate (ESR) (7).  
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8 The ASDAS has shown equivalent or superior psychometric performance compared to  
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10 the BASDAI, and therefore is the recommended index to monitor disease activity in  
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12 patients with axSpA. As an alternative, the BASDAI can also be used (8).  
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15 The ASAS/EULAR recommendations for managing patients with axSpA state that the  
16 therapeutic goal for clinical practice is to maximize long-term health-related quality of  
17 life. While goals are useful for establishing the right direction, a specific target is critical  
18 to promote progress and achieve the desired results. Weighing this in the context of  
19 managing patients with axSpA, despite the stated recommendation to predefine a specific  
20 target, this was never clearly defined, either for specific thresholds or for time boundaries.  
21 In general, it is accepted that the absence of disease activity reflects the disease activity  
22 status of remission. According to the treat-to-target expert recommendations, the  
23 treatment target should be clinical remission/inactive disease, which can be defined by an  
24 ASDAS <1.3; however, low disease activity might also be considered as an alternative  
25 target (9). Worth noting is the fact that the management recommendations underscored  
26 the need to sustain remission over time. Although the exact time frame was not specified,  
27 this led to the realization that a single measurement of remission is not sufficient to  
28 determine whether or not the therapeutic target has been achieved. Therefore, although it  
29 is not explicitly stated, it can be inferred that the target is sustained absence of disease  
30 activity over several consecutive visits. However, whether this is feasible in clinical  
31 practice remains unknown. Furthermore, it is unknown how many of the patients who  
32 remain on long-term biological treatment reach the therapeutic objective recommended  
33 by these scientific societies.  
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50 The main objective of this study is to determine the frequency of sustained remission or  
51 low disease activity (LDA) in patients with axSpA undergoing long-term biological  
52 therapy, and to assess whether the scope of this objective varies according to the used  
53 index. Additionally, we also aimed to determine predictive factors of sustained remission  
54 / LDA in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs).  
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## 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.

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  $\geq$  1.3 and < 2.1), high disease activity (ASDAS  $\geq$  2.1 and < 3.5) and very high disease activity (ASDAS  $\geq$ 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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3 Sample size was not based on data from previous publications because there are few  
4 reliable estimates in the literature regarding the sustained outcomes. Due to the  
5 exploratory character of the study, no formal sample size calculation was performed.  
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### 10 **Statistical analysis:**

11 Descriptive analyses for the demographic, clinical and complimentary test information  
12 were performed. Categorical variables were described as absolute frequencies and  
13 percentages. Continuous variables were described using means and standard deviations  
14 (S.D.). The frequency of patients that achieved R/LDA, according to both ASDAS and  
15 BASDAI&CRP from at least one of the visits (momentary R/LDA), was calculated.  
16 Additionally, the frequency of patients whose clinical activity status remained unchanged  
17 over at least 3 consecutive follow-up visits (sustained R/LDA) were calculated. Only  
18 patients with a valid value for the calculated outcomes over these 3 consecutive visits,  
19 separated by 6 months between them, were assessed for their sustained treatment  
20 response.  
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22 Baseline predictive factors for achieving sustained R/LDA were identified using  
23 univariable and multivariable binary logistic regression models, inserting the possible  
24 predictors as independent variables and the R/LDA response achievement (by ASDAS or  
25 BASDAI&CRP, in two separate models) as the outcome. All of those variables with a p-  
26 value lower than 0.1 in the univariable were included in the multivariable analysis. Odds  
27 ratios (ORs) with p-value <0.05 were used as measures of association. All data were  
28 analyzed using SPSS software version 24.  
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## 43 **RESULTS:**

### 44 **Demographic and Clinical Characteristics**

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46 Out of the 267 patients who initiated a bDMARD during the study period, 81 were  
47 excluded for discontinuation of the drug during follow-up or due to incomplete  
48 information. Therefore, 186 patients with axSpA fulfilled the inclusion criteria and were  
49 included in the analysis (**Figure 1**). Mean age was  $54 \pm 14.1$  years and 123 (66.1%) were  
50 men. One hundred forty patients (75.3%) were classified as r-axSpA, whereas 46 (24.7%)  
51 were nr-axSpA; 139 (74.7%) were HLA\*B27 positive. Other socio-demographic and  
52 disease characteristics of the patients at baseline are shown in Table 1.  
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3 Out of 186 patients, 155 (83%) completed 5 follow-up visits, 25 (14%) 4 visits and 6  
4 (3%) 3 visits. Overall, 143 patients (76.8%) achieved ASDAS remission R/LDA (99  
5 [53.2%] R/ 44 [23.6%] LDA) in at least one of the visits within the 2 years of follow-up  
6 (momentary R/LDA) (**Figure 2**). However, only 66 patients (40% of those assessed)  
7 sustained an ASDAS R/LDA status over three consecutive visits (29 [17.6%] R/ 37  
8 [22.4%] LDA). Regarding BASDAI, 138 patients (74.2%) were classified as  
9 BASDAI&CRP R/LDA (82 [44.1%] R/ 56 [30.1%] LDA) in at least one of the visits, but  
10 only 56 patients (30.8% of those assessed) sustained BASDAI&CRP R/LDA status over  
11 at least three consecutive visits (27 [14.8%] R/ 29 [15.9%] LDA).

12 Among the 165 patients that had a valid ASDAS-CRP for at least 3 visits, 66 (40%)  
13 achieved sustained ASDAS-CRP R/LDA. No statistically significant differences were  
14 observed for most of the baseline characteristics between the patients who sustained  
15 ASDAS-CRP R/LDA and those who did not fulfill these criteria (**Table 1**). This was  
16 particularly notable in the rates of radiographic sacroiliitis (83.3 vs 73.7%,  $p=0.18$ ).  
17 Indeed, a stratified analysis by sacroiliac radiographic damage, showed no statistically  
18 significant differences ( $p=0.18$ ) in the achievement of sustained ASDAS R/LDA in  
19 patients with r-axSpA ( $n=55$ , 43%) as compared with patients with nr-axSpA ( $n=11$ ,  
20 29.7%). However, patients who achieved sustained ASDAS R/LDA were more  
21 frequently male (81.8 vs 54.5%,  $p<0.001$ ), were younger at diagnosis (31.1 vs 38.8 years,  
22  $p<0.001$ ), younger age at biologic initiation (41.6 vs 46.7,  $p=0.02$ ), and HLA\*B27  
23 positive (89.1 vs 69.1%,  $p=0.04$ ). Interestingly, both momentary and sustained ASDAS-  
24 CRP outcomes showed significant differences when stratified by gender (**Figure 3**).

25 Regarding BASDAI&CRP, among the 182 patients who had a valid assessment during at  
26 least 3 visits, 56 (30.8%) achieved sustained BASDAI&CRP R/LDA. Patients who  
27 achieved sustained BASDAI&CRP R/LDA were more frequently male (78.3 vs 59.5%,  
28  $p=0.01$ ), were younger at diagnosis (30.1 vs 37.9 years,  $p=0.02$ ), younger at biologic  
29 initiation (40.6 vs 46.1,  $p=0.02$ ), and had higher baseline levels of methotrexate (33.9 vs  
30 17.5,  $p=0.01$ ). No significant differences were observed for the remaining characteristics.  
31 In the multivariate analysis, an independent association with male sex (OR=4.01; 95%  
32 CI=1.83-8.77), younger age at the beginning of biological therapy (OR=0.96; 95%  
33 CI=0.94-0.99) and HLA\*B27 positivity (OR=4.30; 95% CI=1.68-11.01) in those patients  
34 who achieved sustained ASDAS R/LDA were identified. Additionally, male sex  
35 (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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3 remission in patients with early axSpA during the first 48 weeks of certolizumab  
4 treatment within a clinical trial. Their results showed that more than 40% of them  
5 achieved sustained remission; this was defined as an ASDAS < 1.3 at week 32 and < 2.1  
6 at week 36 (or vice versa), and < 1.3 at week 48 (13). Differences in study designs and in  
7 definitions of remission indicate that these rates are not comparable to those recorded in  
8 our study. Whereas in the aforementioned clinical trial a LDA measurement was  
9 permissible during follow-up, a more stringent definition was used in our clinical practice  
10 study; i.e., documentation of sustained remission over three consecutive visits was  
11 required. Interestingly, when sustained LDA status was assessed in our study, 40% of  
12 patients did achieve this outcome. This is similar to the rates shown in the clinical trial,  
13 where the definition of remission was more inclusive, counting as well those patients who  
14 presented brief LDA.

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

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

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

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29 Our study has some limitations. First, the observational design demands caution when  
30 interpreting the results, since they are prone to both selection and information bias, as  
31 well as to loss of follow-up. Indeed, not all patients present all outcome assessment  
32 parameters at every visit. However, as only those patients with at least three assessments  
33 were included, the consistency of the results was maintained, while yielding information  
34 from a representative sample of a typical patient population in clinical practice. Second,  
35 the absence of established definitions for momentary and sustained outcomes has led to  
36 various proposed definitions that may be judged arbitrary. Nevertheless, the fact that  
37 established cut-offs were examined facilitated the interpretation of sustained outcomes,  
38 while also providing evidence that might serve as the basis for a future consensus  
39 definition. Besides, some of the demographic and clinical data was only collected at  
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3 baseline and not during follow-up, which hinders the comparison among groups regarding  
4 the characteristics of interest during the study period. Due to the scarcity of previous  
5 reliable data in the literature regarding sustained outcomes, no formal sample size  
6 calculation was performed. In addition, we did not include any radiologic outcomes to  
7 assess clinical response of patients, as they were not available in clinical practice. This is  
8 related to the lack of standardized recommendations to assess radiographic progression  
9 routinely over a period of less than two years and to use magnetic resonance imaging for  
10 monitorization of disease activity (17).  
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17 In conclusion, remission does not currently appear to be a realistic target in those axSpA  
18 patients treated with long-term bDMARDs therapy. On the other hand, low disease  
19 activity status seems a measurable, achievable and reasonable target for axSpA patients  
20 in clinical practice. Male patients and those of younger age at biologic initiation have  
21 shown to be predictive factors of good outcomes, when assessed by either ASDAS or  
22 BASDAI&CRP. In this regard, earlier diagnosis and treatment of the disease holds great  
23 promise in terms of targeting the desired outcome of remission. Future steps will involve  
24 the identification of a target adaptable to different populations or even specific patients,  
25 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)
<b>Demographic and clinical features</b>							
<b>Sex (male)</b>	123 (66.1)	104 (72.7)	19 (44.2)	54 (81.8)	54 (54.5)	<0.001	<0.001
<b>Age(years)</b>							
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
<b>Smoking habit</b>	86 (46.2)	68 (47.6)	18 (41.9)	32 (48.5)	46 (46.5)	0.60	0.87
<b>Radiographic mNY criteria</b>	140 (75.3)	109 (76.2)	31(72.1)	55 (83.3)	73 (73.7)	0.69	0.18
<b>HLA*B27 positive</b>	139 (74.7)	112 (80.0)	27 (64.3)	57 (89.1)	67 (69.1)	0.04	0.004
<b>Dactylitis</b>	5 (2.7)	5 (3.5)	0	2 (3.0)	2 (2.0)	0.59	0.68
<b>Enthesitis</b>	46 (24.7)	35 (24.5)	11 (25.6)	17 (25.8)	25 (25.3)	0.88	0.94
<b>Psoriasis</b>	8 (4.3)	7 (4.9)	1 (2.3)	3 (4.5)	4 (4.0)	0.46	0.87
<b>Uveitis</b>	36 (19.4)	28 (19.6)	8 (18.6)	12 (18.2)	21 (21.2%)	0.88	0.69
<b>IBD</b>	4 (2.2)	4 (2.8)	0	1 (1.5)	3 (3.0)	0.27	0.65
<b>Baseline measurements</b>							
<b>CRP (mg/L)</b>	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
<b>BASDAI</b>	5.6±1.9	5.5±1.8	6.0±1.9	5.4 ±1.9	5.9±1.8	0.11	0.08
<b>ASDAS</b>	3.3±1.0	3.2±1.0	3.8±0.8	3.2 ±0.9	3.4 ±1.0	0.005	0.27
<b>PhyGA</b>	40 (20-50)	40 (20-50)	35.6 (20-50)	40 (20-60)	30 (20-50)	0.84	0.47
<b>PtGA</b>	60 (50-80)	60 (50-76.2)	70 (54-80)	60 (50-70.5)	66.5 (50-80)	0.046	0.25

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)	0.54	0.57
Methotrexate	42 (22.6)	34 (23.8)	8 (18.6)	16 (24.2)	20 (20.2)	0.86	0.62
Sulfasalazine	67(36.0)	52(36.4)	15 (34.9)	22 (33.3)	38 (38.4)	0.93	0.80
Prednisone	21 (11.3)	16 (11.2)	5 (11.6)	7 (10.6)	13 (13.1)	-	-
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  $\pm$  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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3 **Figure 1. Patient disposition during the 2-year follow-up**  
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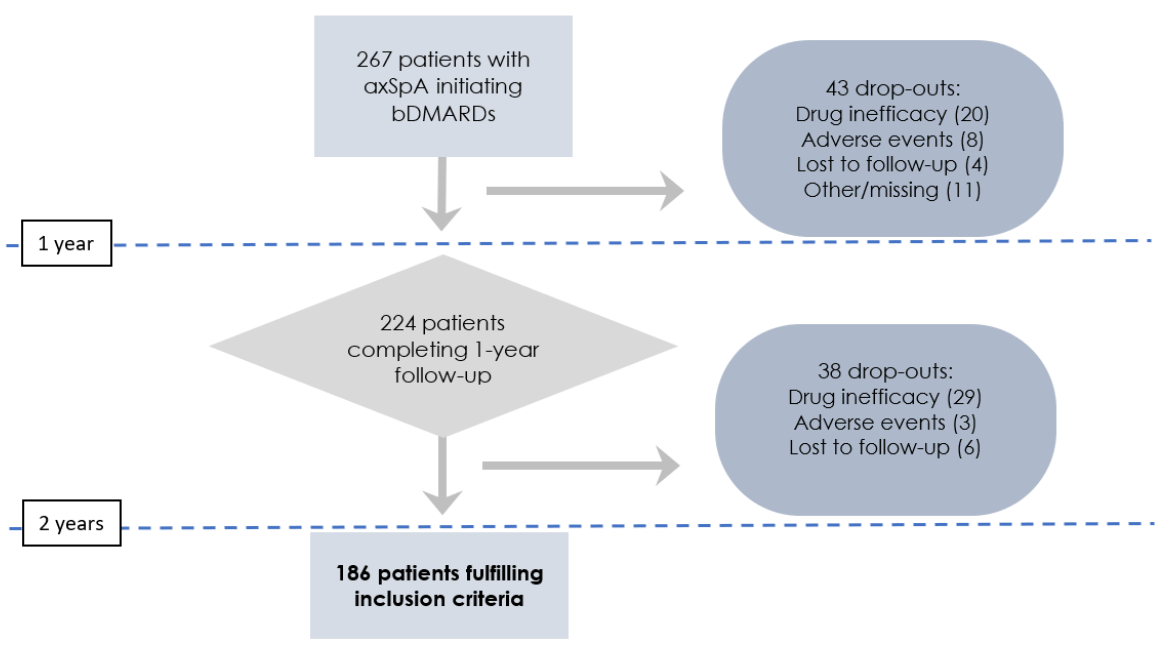
10 **Figure 2. Momentary and sustained outcomes (remission and low disease activity).**

11 REM: remission; LDA: Low disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-Reactive  
12 Protein; ASDAS: Ankylosing Spondylitis Disease Activity Score.  
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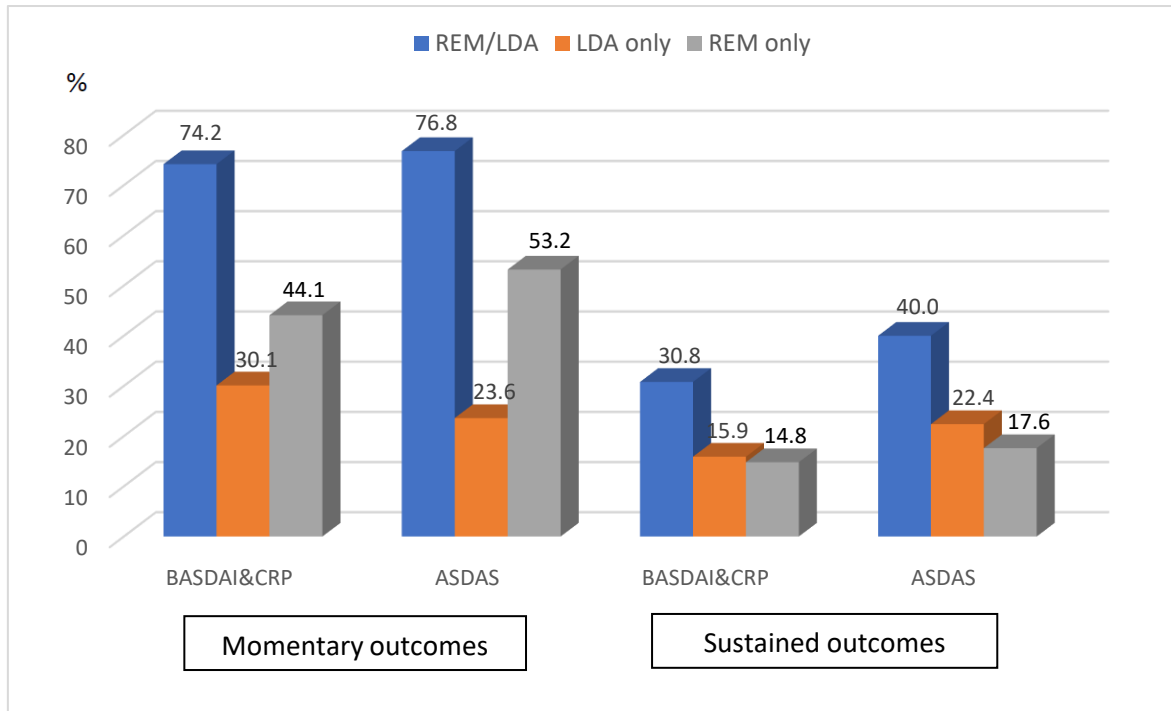
17 **Figure 3. Momentary and sustained outcomes (remission or low disease activity, as**  
18 **measured by ASDAS-CRP) stratified by gender.**

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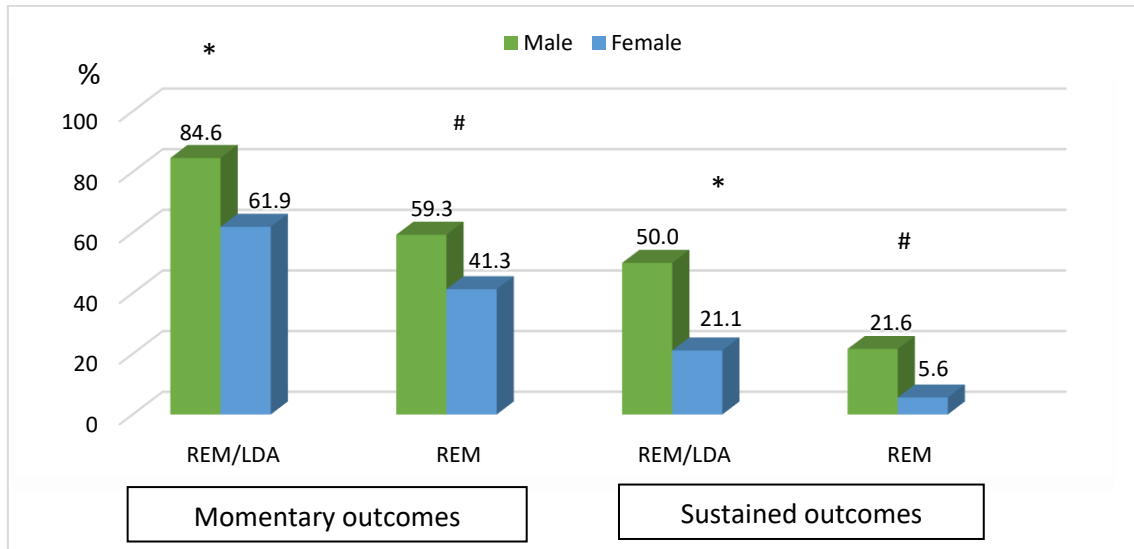
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Peer review only



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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; \* $p < 0.001$ ; #  $p < 0.05$

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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60**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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
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\*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](http://www.strobe-statement.org).

# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057850.R2
Article Type:	Original research
Date Submitted by the Author:	10-Mar-2022
Complete List of Authors:	Benavent, Diego; Hospital Universitario La Paz Franco-Gómez, Karen; Hospital Universitario La Paz Plasencia-Rodriguez, Chamaida; Hospital Universitario La Paz Novella Navarro, Marta; Hospital Universitario La Paz Bogas, Patricia; Hospital Universitario La Paz Nieto, Romina; Hospital Provincial de Rosario Monjo, Irene; Hospital Universitario La Paz Nuño, Laura; Hospital Universitario La Paz, Villalba, Alejandro; Hospital Universitario La Paz Peiteado, D; Hospital Universitario La Paz Balsa, Alejandro; Hospital Universitario La Paz Navarro-Compan, Victoria; Hospital Universitario La Paz, Rheumatology Unit
<b>Primary Subject Heading</b>:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	RHEUMATOLOGY, EPIDEMIOLOGY, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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3 Achievement Rate and Predictive Factors of the Recommended Therapeutical Target in  
4 Patients with Axial Spondyloarthritis who Remain on Biological Therapy: A Prospective  
5 Cohort Study in Spain  
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27 Competing interests: DB received grants/speaker/research supports from Roche and  
28 Abbvie. CP received grants/speaker/research supports from Pfizer, Sanofi, Novartis,  
29 Roche and Lilly. RN received grants/speaker/research supports from Novartis, Sanofi  
30 Genzyme, Pfizer and Montpellier. IM received grants/research supports from Novartis  
31 and speaker's fees from AbbVie, UCB, Roche and Novartis. DP received grants/research  
32 supports from Abbvie, Lilly, MSD and Roche, and had participation in company  
33 sponsored speaker's bureau from Abbvie, Novartis, Lilly, Roche, and MSD. AB received  
34 Grant/research support, fees for consultancies or as a speaker for Abbvie, Pfizer,  
35 Novartis, BMS, Nordic, Sanofi, Sandoz, Lilly, UCB, Roche. VN:  
36 consultancy/speaker/research grants from: Abbvie, BMS, Janssen, Lilly, MSD, Novartis,  
37 Pfizer, Roche and UCB.  
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49 **Contributorship**

50  
51 VNC, and CP conceived the study, participated in its design and coordination, and  
52 critically revised the manuscript. DB and KF performed the data collection, statistical  
53 analysis, interpretation and drafted the manuscript. PB, IM, RN, DP, LN, AV, MN and AB  
54 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)

#### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

#### Acknowledgements

The authors thank the Spanish Society of Rheumatology (SER) for the English editing service (translation funded by the SER- FERBT2021).

## 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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2  
3 BASDAI&CRP), yielding a snapshot of the actual status of patients in clinical  
4 practice.  
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- 6 • Our study provides data to support sustained low disease activity over remission  
7 as the most desirable target to achieve in the management of patients with axSpA.  
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- 9 • Predictive factors of sustained remission / low disease activity in patients with  
10 biologic drugs are determined, which further studies may explore.  
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- 12 • The main limitation of this study arises from the observational design, which  
13 demands caution when interpreting the results.  
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- 15 • Since data was collected from clinical practice, there is some degree of missing  
16 data.  
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For peer review only

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

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6 The ASAS/EULAR recommendations for managing patients with axSpA state that the  
7 therapeutic goal for clinical practice is to maximize long-term health-related quality of  
8 life. While goals are useful for establishing the right direction, a specific target is critical  
9 to promote progress and achieve the desired results. Weighing this in the context of  
10 managing patients with axSpA, despite the stated recommendation to predefine a specific  
11 target, this was never clearly defined, either for specific thresholds or for time boundaries.  
12 In general, it is accepted that the absence of disease activity reflects the disease activity  
13 status of remission. According to the treat-to-target expert recommendations, the  
14 treatment target should be clinical remission/inactive disease, which can be defined by an  
15 ASDAS <1.3; however, low disease activity might also be considered as an alternative  
16 target (9). Worth noting is the fact that the management recommendations underscored  
17 the need to sustain remission over time. Although the exact time frame was not specified,  
18 this led to the realization that a single measurement of remission is not sufficient to  
19 determine whether or not the therapeutic target has been achieved. Therefore, although it  
20 is not explicitly stated, it can be inferred that the target is sustained absence of disease  
21 activity over several consecutive visits. However, whether this is feasible in clinical  
22 practice remains unknown. Furthermore, it is unknown how many of the patients who  
23 remain on long-term biological treatment reach the therapeutic objective recommended  
24 by these scientific societies.  
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41 The main objective of this study is to determine the frequency of sustained remission or  
42 low disease activity (LDA) in patients with axSpA undergoing long-term biological  
43 therapy, and to assess whether the scope of this objective varies according to the used  
44 index. Additionally, we also aimed to determine predictive factors of sustained remission  
45 / LDA in patients with biologic disease-modifying anti-rheumatic drugs (bDMARDs).  
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## 51 **METHODS**

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53 This is a longitudinal study using the prospective cohort SpA-Paz, which is an ongoing,  
54 observational cohort including all patients with axSpA who initiate their first treatment  
55 with bDMARDs at the University Hospital La Paz, Madrid, Spain. For this study, patients  
56 initiating bDMARDs between January 2003 and the December 2017 were included.  
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3 The inclusion criteria were as follows: a) adult patients diagnosed with axSpA according  
4 to their prescribing rheumatologist; b) initiation of first biological therapy (Tumor  
5 Necrosis Factor inhibitors [TNFi] or interleukin [IL]-17 inhibitors); c) at least two years  
6 of follow-up with assessment visits every 6 months; d) at least two assessments of  
7 ASDAS-CRP or BASDAI&CRP during follow-up. A 2-year follow-up cut-off was  
8 established to homogenize the definition of “long-term therapy” from the start of  
9 bDMARDs. Exclusion criteria were patients in clinical trials. All patients signed written  
10 informed consent.  
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### 19 **Data collection**

20 Demographic information, disease characteristics, bDMARDs type, concomitant  
21 treatment and laboratory tests before starting biological therapy were collected from the  
22 electronic health records at baseline. Baseline patients' characteristics were collected  
23 retrospectively at biologic initiation. Time windows for concomitant medication and  
24 laboratory tests extended three months prior biological initiation until the date of start of  
25 biologic. The presence of radiographic sacroiliitis, according to the modified New York  
26 (mNY) criteria, was assessed by the consensus of at least two out of three expert  
27 rheumatologists. Clinical disease activity was measured by ASDAS-CRP and  
28 BASDAI&CRP at baseline and at 6-month intervals after initiating bDMARDs for a  
29 period of two years.  
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37 According to ASDAS, disease activity was defined as follows: inactive disease (ASDAS  
38 <1.3), LDA (ASDAS  $\geq 1.3$  and < 2.1), high disease activity (ASDAS  $\geq 2.1$  and < 3.5)  
39 and very high disease activity (ASDAS  $\geq 3.5$ ) (10).  
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43 According to BASDAI, remission (R) was considered present with a BASDAI <2 &  
44 normal CRP, whereas LDA was considered present with a BASDAI <4 & normal CRP.  
45 Both sustained remission and sustained LDA required a sustained outcome for at least 3  
46 consecutive follow-up visits during the study period. If any visit was missing, but a  
47 BASDAI and /or ASDAS assessment was still conducted at 3 successive visits, patients  
48 remained eligible and accounted as consecutive visits. Since patients in remission or  
49 inactive disease also fulfil LDA criteria, a category including all patients that achieved at  
50 least LDA was created, under the name of R/LDA.  
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56 Sample size was not based on data from previous publications because there are few  
57 reliable estimates in the literature regarding the sustained outcomes. Due to the  
58 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  $54 \pm 14.1$  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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3 sustained an ASDAS R/LDA status over three consecutive visits (29 [17.6%] R/ 37  
4 [22.4%] LDA). Regarding BASDAI, 138 patients (74.2%) were classified as  
5 BASDAI&CRP R/LDA (82 [44.1%] R/ 56 [30.1%] LDA) in at least one of the visits, but  
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7 only 56 patients (30.8% of those assessed) sustained BASDAI&CRP R/LDA status over  
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9 at least three consecutive visits (27 [14.8%] R/ 29 [15.9%] LDA).

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11 Among the 165 patients that had a valid ASDAS-CRP for at least 3 visits, 66 (40%)  
12 achieved sustained ASDAS-CRP R/LDA. No statistically significant differences were  
13 observed for most of the baseline characteristics between the patients who sustained  
14 ASDAS-CRP R/LDA and those who did not fulfill these criteria (**Table 1**). This was  
15 particularly notable in the rates of radiographic sacroiliitis (83.3 vs 73.7%,  $p=0.18$ ).  
16 Indeed, a stratified analysis by sacroiliac radiographic damage, showed no statistically  
17 significant differences ( $p=0.18$ ) in the achievement of sustained ASDAS R/LDA in  
18 patients with r-axSpA ( $n=55$ , 43%) as compared with patients with nr-axSpA ( $n=11$ ,  
19 29.7%). However, patients who achieved sustained ASDAS R/LDA were more  
20 frequently male (81.8 vs 54.5%,  $p<0.001$ ), were younger at diagnosis (31.1 vs 38.8 years,  
21  $p<0.001$ ), younger age at biologic initiation (41.6 vs 46.7,  $p=0.02$ ), and HLA\*B27  
22 positive (89.1 vs 69.1%,  $p=0.04$ ). Interestingly, both momentary and sustained ASDAS-  
23 CRP outcomes showed significant differences when stratified by gender (**Figure 3**).

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25 Regarding BASDAI&CRP, among the 182 patients who had a valid assessment during at  
26 least 3 visits, 56 (30.8%) achieved sustained BASDAI&CRP R/LDA. Patients who  
27 achieved sustained BASDAI&CRP R/LDA were more frequently male (78.3 vs 59.5%,  
28  $p=0.01$ ), were younger at diagnosis (30.1 vs 37.9 years,  $p=0.02$ ), younger at biologic  
29 initiation (40.6 vs 46.1,  $p=0.02$ ), and had higher baseline levels of methotrexate (33.9 vs  
30 17.5,  $p=0.01$ ). No significant differences were observed for the remaining characteristics.  
31 In the multivariate analysis, an independent association with male sex (OR=4.01; 95%  
32 CI=1.83-8.77), younger age at the beginning of biological therapy (OR=0.96; 95%  
33 CI=0.94-0.99) and HLA\*B27 positivity (OR=4.30; 95% CI=1.68-11.01) in those patients  
34 who achieved sustained ASDAS R/LDA were identified. Additionally, male sex  
35 (OR=3.19; 95% CI=1.46-6.99), younger age at the beginning of biological treatment  
36 (OR= 0.97; 95% CI=0.95-0.99) and the use of methotrexate (OR=3.07; 95% CI =1.39-  
37 6.78) were associated with patients who achieved sustained BASDAI&CRP R/LDA.  
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## 58 DISCUSSION

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

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

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

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

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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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3 different settings to confirm their external validity. In case that these exploratory results  
4 are confirmed, there will still be a pending task in this respect, one that could be improved  
5 by adjusting the outcomes to the patient's baseline status, setting clinical improvement as  
6 a more pragmatic measurement to assess the current status of each patient. In any case,  
7 the fact that remission is not currently a realistic target does not mean that this remains  
8 unfeasible in a near future if efforts focus on such unmet needs.  
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11 Therefore, it seems rational to assess factors that would potentially facilitate a better  
12 clinical response, and to work in that direction. Worth noting is the fact that patients who  
13 achieved sustained ASDAS R/LDA were more frequently male, were younger at  
14 diagnosis, younger age at biologic initiation, and HLA\*B27 positive in our study. Most  
15 of these features remained similar when BASDAI&CRP was established as the outcome  
16 variable. Remarkably, some of these characteristics are non-modifiable and static, namely  
17 gender and HLA\*B27 status. When assessing modifiable factors, it seems clear that  
18 clinicians should advocate for any modifications in quest of the targeted outcomes; in this  
19 sense, earlier diagnosis and treatment might prove to be the single-most important factors  
20 clinicians can influence. However, this cannot be done for non-modifiable factors. This  
21 begs the question of whether it is the target itself that should be adapted for different  
22 groups, particularly in light of gender-related differential clinical responses.  
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36 Our study has some limitations. First, the observational design demands caution when  
37 interpreting the results, since they are prone to both selection and information bias, as  
38 well as to loss of follow-up. Indeed, not all patients who initiated treatment with a  
39 bDMARD fulfilled the inclusion criteria after two years; 81 patients did not complete the  
40 required period of follow-up for inclusion. Although we acknowledge a potential bias in  
41 the final included patients towards a better treatment response, the requirement of a  
42 certain number of visits is necessary to have a homogeneous set of patients in which  
43 sustained outcomes could be assessed. Besides, not all patients present all outcome  
44 assessment parameters at every visit. However, as only those patients with at least three  
45 assessments were included, the consistency of the results was maintained, while yielding  
46 information from a representative sample of a typical patient population in clinical  
47 practice. Second, the absence of established definitions for momentary and sustained  
48 outcomes has led to various proposed definitions that may be judged arbitrary.  
49 Nevertheless, the fact that established cut-offs were examined facilitated the  
50 interpretation of sustained outcomes, while also providing evidence that might serve as  
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3 the basis for a future consensus definition. Besides, some of the demographic and clinical  
4 data was only collected at baseline and not during follow-up, which hinders the  
5 comparison among groups regarding the characteristics of interest during the study  
6 period. Due to the scarcity of previous reliable data in the literature regarding sustained  
7 outcomes, no formal sample size calculation was performed. In addition, we did not  
8 include any radiologic outcomes to assess clinical response of patients, as they were not  
9 available in clinical practice. This is related to the lack of standardized recommendations  
10 to assess radiographic progression routinely over a period of less than two years and to  
11 use magnetic resonance imaging for monitorization of disease activity (17).

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13 In conclusion, remission does not currently appear to be a realistic target in those axSpA  
14 patients treated with long-term bDMARDs therapy. On the other hand, low disease  
15 activity status seems a measurable, achievable and reasonable target for axSpA patients  
16 in clinical practice. Male patients and those of younger age at biologic initiation have  
17 shown to be predictive factors of good outcomes, when assessed by either ASDAS or  
18 BASDAI&CRP. In this regard, earlier diagnosis and treatment of the disease holds great  
19 promise in terms of targeting the desired outcome of remission. Future steps will involve  
20 the identification of a target adaptable to different populations or even specific patients,  
21 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)
<b>Demographic and clinical features</b>							
<b>Sex (male)</b>	123 (66.1)	104 (72.7)	19 (44.2)	54 (81.8)	54 (54.5)	<0.001	<0.001
<b>Age(years)</b>							
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
<b>Smoking habit</b>	86 (46.2)	68 (47.6)	18 (41.9)	32 (48.5)	46 (46.5)	0.60	0.87
<b>Radiographic mNY criteria</b>	140 (75.3)	109 (76.2)	31(72.1)	55 (83.3)	73 (73.7)	0.69	0.18
<b>HLA*B27 positive</b>	139 (74.7)	112 (80.0)	27 (64.3)	57 (89.1)	67 (69.1)	0.04	0.004
<b>Dactylitis</b>	5 (2.7)	5 (3.5)	0	2 (3.0)	2 (2.0)	0.59	0.68
<b>Enthesitis</b>	46 (24.7)	35 (24.5)	11 (25.6)	17 (25.8)	25 (25.3)	0.88	0.94
<b>Psoriasis</b>	8 (4.3)	7 (4.9)	1 (2.3)	3 (4.5)	4 (4.0)	0.46	0.87
<b>Uveitis</b>	36 (19.4)	28 (19.6)	8 (18.6)	12 (18.2)	21 (21.2%)	0.88	0.69
<b>IBD</b>	4 (2.2)	4 (2.8)	0	1 (1.5)	3 (3.0)	0.27	0.65
<b>Baseline measurements</b>							
<b>CRP (mg/L), median (Q1-Q3)</b>	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
<b>BASDAI, mean ± SD</b>	5.6±1.9	5.5±1.8	6.0±1.9	5.4 ±1.9	5.9±1.8	0.11	0.08
<b>ASDAS, mean ± SD</b>	3.3±1.0	3.2± 1.0	3.8±0.8	3.2 ±0.9	3.4 ±1.0	0.005	0.27
<b>PhyGA, median (Q1-Q3)</b>	40 (20-50)	40 (20-50)	35.6 (20-50)	40 (20-60)	30 (20-50)	0.84	0.47
<b>PtGA, median (Q1-Q3)</b>	60 (50-80)	60 (50-76.2)	70 (54-80)	60 (50-70.5)	66.5 (50-80)	0.04	0.25
<b>Concomitant treatment</b>							

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

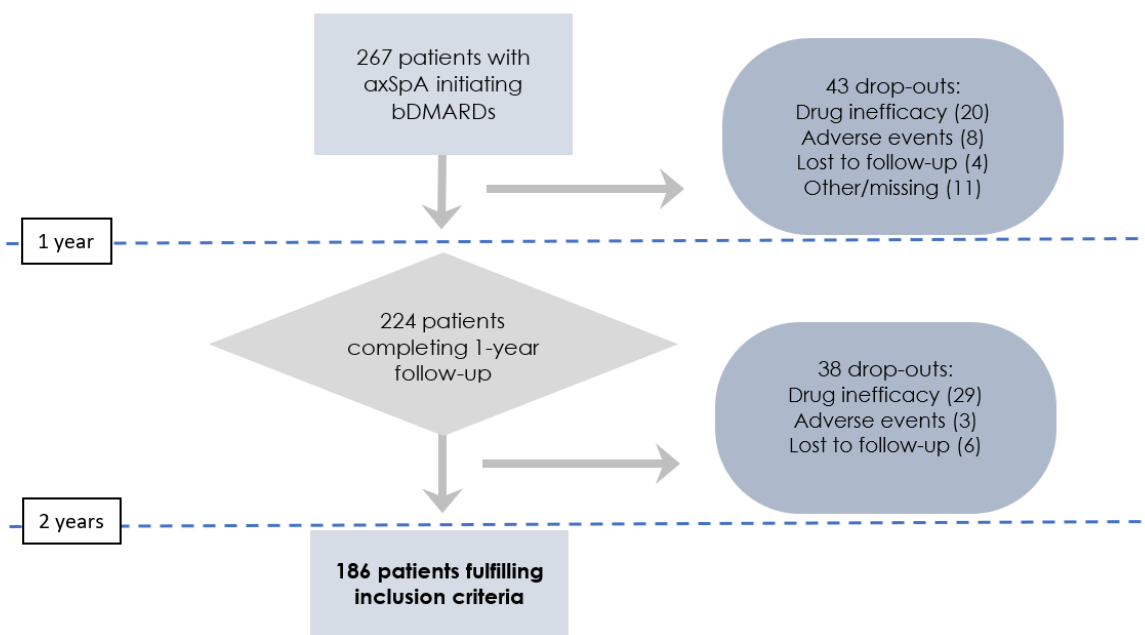
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3 **Figure 1. Patient disposition during the 2-year follow-up**  
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10 **Figure 2. Momentary and sustained outcomes (remission and low disease activity).**

11 REM: remission; LDA: Low disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-Reactive  
12 Protein; ASDAS: Ankylosing Spondylitis Disease Activity Score.  
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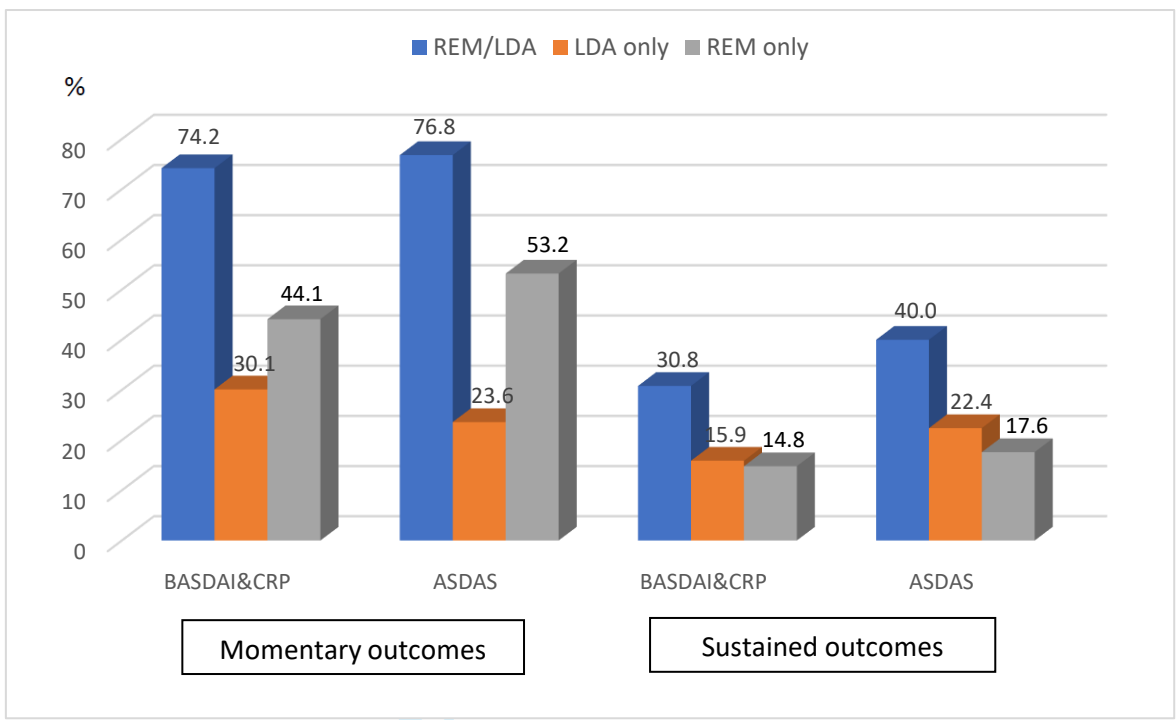
17 **Figure 3. Momentary and sustained outcomes (remission or low disease activity, as**  
18 **measured by ASDAS-CRP) stratified by gender.**

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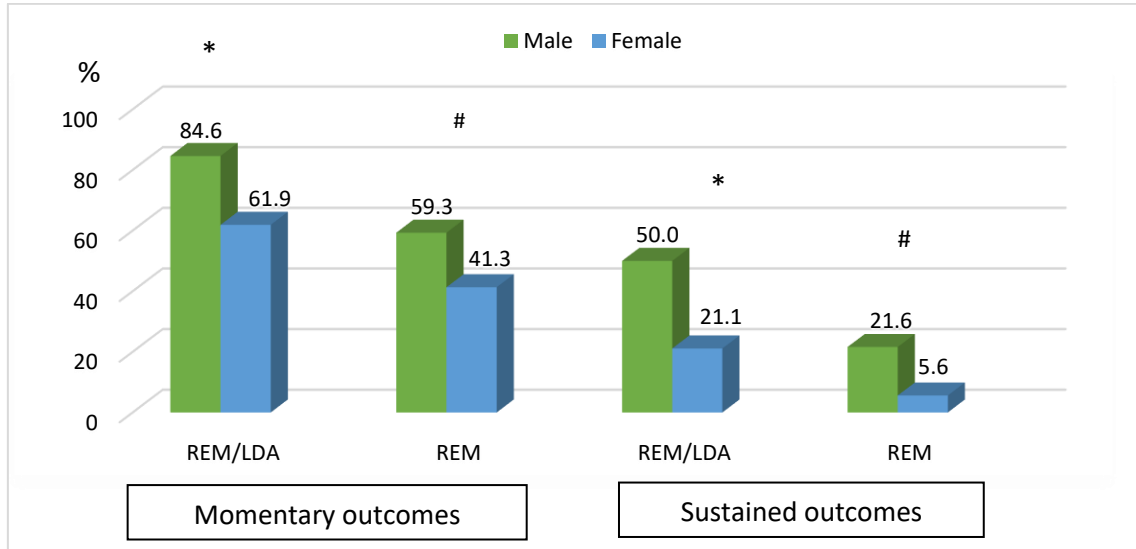


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**Figure 3. Momentary and sustained outcomes (remission or low disease activity, as measured by ASDAS-CRP) stratified by gender.**

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



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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).