Rheumatol Ther (2022) 9:1031–1047
https://doi.org/10.1007/s40744-022-00446-9

ORIGINAL RESEARCH

Real-World Effectiveness and Treatment Retention of Secukinumab in Patients with Psoriatic Arthritis and Axial Spondyloarthritis: A Descriptive Observational Analysis of the Spanish BIOBADASER Registry

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Received: February 9, 2022 / Accepted: April 4, 2022 / Published online: April 25, 2022

ABSTRACT

Rheumatic diseases are extensively managed with biological disease-modifying antirheumatic drugs (bDMARDs), but a notable proportion of patients withdraw in the long term because of lack of effectiveness, adverse events, or the patient's decision. The present real-world analysis showed the effectiveness, retention, and safety data collected in the Spanish BIOBADASER registry for patients with psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA, including ankylosing spondylitis (AS) and non-radiographic axSpA) treated with secukinumab, a human antibody against interleukin-17A (IL-17A), for more than 12 months. Six hundred and

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-022-00446-9.

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thirty-nine patients were analysed (350, 262, and 27 PsA, AS, and nr-axSpA patients, respectively). The results showed an improvement in the disease activity after 1 year of treatment, in terms of decreases of the mean Disease Activity Score 28 using C-reactive protein (DAS28-CRP), the mean Disease Activity Psoriatic Arthritis (DAPSA) score, swollen joint counts (SJC), and tender joint counts (TJC) in PsA patients and decreases in the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the mean Ankylosing Spondylitis Disease Activity Score (ASDAS) in axSpA patients. This improvement was maintained or increased after 2 and 3 years of treatment, indicating that secukinumab is effective in both naïve and non-responder patients. Retention rates were higher when secukinumab was used as the first-line biological treatment, although they were also adequate in the second and third lines of treatment. Collected safety data were consistent with previous reports.

Keywords: Psoriatic arthritis; Ankylosing spondylitis; Axial spondyloarthritis; Non-radiographic axial spondyloarthrtis; Secukinumab; IL-17

Key Summary Points

Why carry out this study?

Since a notable number of patients with rheumatic diseases are treated with biological disease-modifying antirheumatic drugs (bDMARDs), real-world data analysis in routine clinical practice provides useful information.

What did this study ask?

The objective of this non-interventional study was to describe, as part of routine care in Spain, effectiveness, retention, and safety data for patients with psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) (including ankylosing spondylitis (AS) and non-radiographic axSpA) treated with secukinumab (human antibody against interleukin-17A).

What were the study outcomes/conclusions?

In the study, 639 patients (54.8% PsA and 45.2% axSpA) were analysed, and results showed effectiveness in terms of improvement in disease activity in both pathologies and in both first and second lines of treatment in real clinical practice. Adequate retention rates when secukinumab was used as the first, second, and third lines of treatment and satisfactory safety data were also observed.

What has been learned from the study?

Secukinumab is effective and safe in routine clinical practice in the first and second lines of treatment in patients with PsA and axSpA.

INTRODUCTION

Immune-mediated rheumatic diseases have been extensively managed during the last decade with biological disease-modifying antirheumatic drugs (bDMARDs), which reduce the signs and symptoms and improve physical function and quality of life [1]. Since rheumatic diseases are chronic conditions, biological therapies are long-term treatments. Currently, different biological therapies are approved and present long-term efficacy and safety data in the management of psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) (a summary of the available long-term open-label extension studies of the different molecules is presented in Supplementary Tables 1 and 2). However, a notable proportion of patients withdraw after 4 years because of a lack of effectiveness, adverse events, or the patient's decision [2, 3]. The Spanish BIOBADASER registry was established in 1999 to collect real-life data on patients with rheumatic disorders treated with biological therapies and to assess the long-term safety of bDMARDs. BIOBADASER involves 28 hospitals, providing an estimated national coverage of 25% of all biological and targeted synthetic

DMARD (b/tsDMARD)-treated rheumatoid arthritis (RA) patients [4].

Secukinumab is a human monoclonal antibody against interleukin-17A (IL-17A) approved by the European Medicines Agency (EMA) since 2015 for the treatment of moderate to severe psoriasis, active PsA and axSpA [5–7]. According to the recent EULAR recommendations, PsA and axSpA patients should commence therapy with a bDMARD if their activity is persistently high despite treatment with conventional synthetic DMARDs (csDMARDs) [8–10]. The treatment goal is to control symptoms and prevent disability and joint deterioration [8, 10]. Regarding PsA, TNFi agents are the first choice after csDMARDs in both the EULAR and GRAPPA recommendations [8, 11]. However, GRAPPA includes IL-12/23i and IL-17i as options for the first choice after csDMARDs [11]. On the contrary, switching therapy recommendations among patients who have failed a first TNFi is vague in the EULAR and GRAPPA treatment guidelines, since all potential biological therapies (TNFi, IL-12/23i, IL-17i) are listed as options [8, 11]. In the case of axSpA, ASAS-EULAR management recommendations indicate that bDMARD treatment should be initiated with TNFi therapy, according to the current practice [10]. If first-line TNFi therapy fails, ASAS-EULAR recommends switching to another TNFi or considering an IL-17i [10]. On the other hand, recommendations by the Spanish Society of Rheumatology on treatment with biological therapies indicate the use of IL-17i from the first line of treatment in both PsA and axSpA cases [9, 12, 13].

Therefore, the treatment choice should take into account the comprehensive treatment effect across the six PsA manifestations, the radiographic data, and the safety profiles of these treatments [14–19]. Most studies assessing TNFi effectiveness and retention have been performed with naïve patients, i.e. those who have not undergone previous long-term treatment with biologicals. Published data from several registries showed that median survival decreased from 2.2 years with the first TNFi to 1.3 and 1.1 years with the second and third, respectively [20]. Moreover, the ratio of withdrawal after 3 years of treatment in patients who switched from one TNFi to another was 36%. [21]. Overall, real-world studies show that the response to biologicals is better in naïve patients compared to those in whom a TNFi has already failed [20–25]. However, data on how and when patients are switched from a TNFi to another class of biological are limited.

Real-world data on secukinumab use has been accumulating over the years since its market authorization. A real-life observational study described data from 39 patients with axSpA in Italy [26], where secukinumab demonstrated remarkable effectiveness regardless of the biological treatment line and a notable rate of long-term retention. Another observational study from the Swiss Clinical Quality Management cohort suggested comparable effectiveness of secukinumab and an alternative TNFi after prior TNFi failure [27]. Recently, a multicentre retrospective observational study in Spain including 154 patients who were not included in the BIOBADASER registry (59 diagnosed with PsA and 95 with axSpA) showed a 66% retention rate at the first year in a population mainly refractory to biological treatment (median of three previous biologics) [28]. Moreover, the largest observational study to date, with published data on 1860 axSpA patients and 2017 PsA patients treated with secukinumab from 13 European registers (including the Spanish BIOBADASER), showed that secukinumab retention rates after 6 and 12 months of treatment were high (82% and 72% for axSpA and 86% and 76% for PsA, respectively) [29, 30]. Although there were significant differences between the participating registries, secukinumab effectiveness was better for biological-naïve patients, independently of the time since diagnosis.

The present study aimed to expand the current body of evidence on the effectiveness, retention, and safety of secukinumab in patients with PsA and AS and, importantly, to provide the first data on non-radiographic axSpA (nr-axSpA) in Spain.

METHODS

Study Design

BIOBADASER is a prospective national registry of patients with rheumatic diseases treated with bDMARDs, including biosimilars and tsDMARDs [4]. Patients are enrolled when they initiate a b/tsDMARD therapy and are followed up prospectively until treatment discontinuation. The Spanish Agency of Medicines and the Spanish Society of Rheumatology support the registry. The present study is an observational, retrospective, descriptive, non-comparative analysis of the effectiveness of secukinumab therapy in PsA or axPsA patients enrolled in BIOBADASER after 12, 24, and 36 months of treatment.

Participants and Setting

The present study analysed effectiveness in all adult PsA or axSpA (including nr-axSpA and AS) patients who had been treated with secukinumab for more than 12 months before the analysis date for an approved indication. The retention rate was analysed in all patients who had ever been treated with secukinumab for these indications, and was evaluated based on the percentage of patients who remained on the treatment continuously (from the start of the treatment to a dose change or treatment interruption). Data extraction occurred in October 2020.

Outcome Variables

The outcome variables in PsA patients were the mean Disease Activity Score 28 using C-reactive protein (DAS28-CRP) and the proportions of patients in remission (DAS28-CRP < 2.6) and with low disease activity (DAS28-CRP ≥ 2.6; ≤ 3.2) [31, 32]. The outcome variables in axSpA patients were the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores and the proportions of patients in remission (BASDAI score < 2) and with low disease activity (BASDAI < 4) [33, 34].

Other outcome variables included the mean Disease Activity Psoriatic Arthritis (DAPSA) scores [35], swollen joint counts (SJC), and tender joint counts (TJC) in patients with PsA and the mean Ankylosing Spondylitis Disease Activity Score (ASDAS) scores [36] in patients with axSpA. The retention rates for PsA and axPsA patients took into account the start date of treatment (the date secukinumab was prescribed for the first time) and the date of treatment discontinuation (the date secukinumab was definitively stopped).

Statistical Analysis

Summary descriptive statistics were presented as means with standard deviations, medians with percentiles, and percentages when applicable. Kaplan–Meier analysis was used to study the survival of secukinumab, and various analyses were performed according to the line of treatment. Patients were right censored if data were not available for a specific time point, and for patients remaining on treatment at the time of data analysis. Differences according to indication were evaluated using the log-rank test. The analysis was performed using Stata statistical software (release 13.1, 2013; StataCorp LP, College Station, TX, USA).

Ethical Considerations

Ethical approval was granted by the Hospital Clinic of Barcelona Ethics Committee acting as a reference committee (approval code FER-ADA-2015-01). All patients had signed an informed consent to be included in the BIOBADASER registry, which covered subsequent analyses such as the present analysis. Patient information was managed as anonymized aggregated data and, as approved by the Clinical Research Committee Hospital Universitario Virgen de la Arrixaca (Murcia, Spain; 2021-1-9-HCUVA), specific informed consent for this analysis was not required.

The study was performed following Good Pharmacoepidemiology Practice standards and the principles of the Declaration of Helsinki of 1964 and its later amendments.

RESULTS

General Characteristics of the Overall Population

The main characteristics of 724 patients treated with secukinumab who were in BIOBADASER at the time of data extraction are summarized in Table 1. The median duration of disease and mean age at the initiation of secukinumab treatment were 7.0 (interquartile range 2.7–14.4) years and 49.3 years, respectively, and 55.7% were men. At the time of data extraction, 639 patients fulfilled the inclusion criteria; 54.8% were PsA and 45.2% were axPsA patients (262 AS patients and 27 nr-axSpA patients).

Psoriatic Arthritis

Effectiveness

Overall Population At the time of data extraction, the median duration of PsA at the initiation of secukinumab treatment was < 2 years and ≥ 2 years for 68 and 282 patients, respectively.

The mean (standard deviation, SD) DAS28-CRP score decreased from 3.0 (1.2) at baseline to 2.0 (0.8) at the first year, was maintained during the second year of treatment, and decreased to 1.9 (0.8) in the third year of follow-up (Table 2 and Supplementary Fig. 1A). Mean (SD) SJC decreased from 5.4 (5.8) at baseline to 1.3 (2.6) in the third year, and mean TJC (SD) decreased from 2.7 (3.4) at baseline to 1.2 (2.7) in the third year. Furthermore, mean patient visual ana-

Table 1 General characteristics of patients on secukinumab treatment

Parameter	Order of secukinumab treatment		
	First biological (*N* = 206)	Second or later (*N* = 525)	All (*N* = 724)[a]
Age			
Years, mean (SD)	49.2 (12.1)	52.5 (11.7)	51.6 (11.9)
Age at treatment initiation			
Years, mean (SD)	47.1 (12.2)	50.1 (11.5)	49.3 (11.8)
Gender			
Male, *n* (%)	126 (61.2)	278 (53.1)	403 (55.7)
Female, *n* (%)	80 (38.8)	247 (46.9)	321 (44.3)
Duration of disease			
Years, median (range)	2.8 (1.1–7.5)	8.3 (4.0–15.3)	7.0 (2.7–14.4)
Observations included in the analysis, *n* (%)	185	454	639
PsA	96 (51.9)	254 (55.9)	350 (54.8)
axSpA			
AS	81 (43.8)	181 (39.9)	262 (41)
nr-axSpA	8 (4.3)	19 (4.2)	27 (4.2)

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *nr-axSpA* non-radiographic axial spondyloarthritis, *PsA* psoriatic arthritis, *SD* standard deviation

[a]Note that in 7 patients, secukinumab was prescribed in more than one line (a second or subsequent line) of treatment

Table 2 Summary of effectiveness in psoriatic arthritis patients treated with secukinumab as a first or second line of treatment or as any line of treatment (overall)

Parameter	Overall				First line				Second line			
	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years
DAS28-CRP	*n* = 250	*n* = 150	*n* = 84	*n* = 31	*n* = 71	*n* = 34	*n* = 22	*n* = 7	*n* = 49	*n* = 27	*n* = 3	*n* = 3
Mean score (SD)	3.0 (1.2)	2.0 (0.8)	2.0 (0.8)	1.9 (0.8)	3.2 (1.3)	1.9 (0.9)	1.7 (0.7)	1.8 (0.4)	3.1 (1.1)	2.0 (0.9)	1.6 (0.7)	1.8 (0.9)
Disease status, *n* (%)	*n* = 250	*n* = 150	*n* = 84	*n* = 31	*n* = 71	*n* = 34	*n* = 22	*n* = 7	*n* = 49	*n* = 27	*n* = 3	*n* = 3
Remission (DAS28-CRP $\leq$ 2.6)	88 (35.2)	103 (68.7)	65 (77.4)	25 (80.7)	25 (35.2)	26 (76.5)	19 (86.4)	6 (85.7)	22 (44.9)	18 (66.7)	2 (66.7)	2 (66.7)
Low activity (DAS28-CRP: 2.6–3.2)	54 (21.6)	35 (23.3)	13 (15.5)	5 (16.1)	12 (16.9)	5 (14.7)	3 (13.6)	1 (14.3)	13 (26.5)	6 (22.2)	1 (33.3)	1 (33.3)
Moderate–high activity (DAS28-CRP > 3.2)	108 (43.2)	12 (8.0)	6 (7.1)	1 (3.2)	34 (47.9)	3 (8.8)	0 (0.0)	0 (0.0)	14 (28.6)	3 (11.1)	0 (0.0)	0 (0.0)
SJC	*n* = 282	*n* = 167	*n* = 90	*n* = 34	*n* = 75	*n* = 39	*n* = 23	*n* = 8	*n* = 61	*n* = 33	*n* = 13	*n* = 3
Mean (SD)	5.4 (5.8)	2.2 (4.1)	1.5 (2.7)	1.3 (2.6)	5.7 (6.0)	2.6 (5.4)	0.6 (1.2)	1.3 (1.4)	5.6 (5.8)	2.4 (4.0)	0.9 (1.6)	1.3 (2.3)
TJC	*n* = 282	*n* = 166	*n* = 90	*n* = 34	*n* = 75	*n* = 38	*n* = 23	*n* = 8	*n* = 61	*n* = 33	*n* = 13	*n* = 3
Mean (SD)	2.7 (3.4)	0.8 (1.6)	0.7 (1.4)	1.2 (2.7)	3.0 (3.6)	1.2 (2.6)	0.6 (1.5)	0.0 (0.0)	3.0 (3.8)	0.6 (0.9)	0.6 (1.1)	1.0 (1.7)
ptVAS	*n* = 280	*n* = 160	*n* = 87	*n* = 33	*n* = 76	*n* = 38	*n* = 22	*n* = 7	*n* = 58	*n* = 29	*n* = 12	*n* = 3
Mean (SD)	6.3 (2.4)	4.2 (2.8)	4.1 (2.8)	4.0 (2.7)	6.4 (2.3)	3.7 (3.0)	3.5 (2.9)	2.3 (2.5)	6.2 (2.5)	3.8 (2.6)	3.7 (2.0)	3.0 (2.7)
CRP (mg/L)	*n* = 287	*n* = 172	*n* = 91	*n* = 33	*n* = 80	*n* = 41	*n* = 27	*n* = 8	*n* = 64	*n* = 35	*n* = 12	*n* = 3
Mean (SD)	11.3 (59.0)	4.5 (10.4)	5.3 (20.3)	3.7 (8.3)	11.5 (23.1)	3.5 (5.1)	3.0 (5.5)	2.0 (1.3)	13.1 (80.5)	5.0 (11.1)	17.3 (55.1)	1.3 (0.8)
DAPSA, *n* (%)	*n* = 39	*n* = 10	*n* = 5	*n* = 0	*n* = 23	*n* = 8	*n* = 2	*n* = 0	*n* = 11	*n* = 1	*n* = 2	*n* = 0
< 4	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)	NA
4–14	7 (18.0)	1 (10.0)	1 (20.0)	NA	3 (13.0)	1 (12.5)	0 (0.0)	NA	3 (27.3)	0 (0.0)	1 (50.0)	NA
> 14	32 (82.1)	9 (90.0)	4 (80.0)	NA	20 (87.0)	7 (87.5)	2 (100)	NA	8 (72.7)	1 (100)	1 (50.0)	NA

CRP C-reactive protein, *DAPSA* Disease Activity in Psoriatic Arthritis, *DAS28-CRP* Disease Activity Score 28 using CRP, *NA* not available, *SD* standard deviation, *SJC* swollen joint count, *TJC* tender joint count, *ptVAS* patient visual analogue score

logue scale (ptVAS) scores and CRP levels decreased from 6.3 (2.4) and 11.3 (59.0) mg/l at baseline to 4.0 (2.7) and 3.7 (8.3) mg/l in the third year, respectively. The percentage of patients in remission (DAS28-CRP < 2.6) or with low disease activity (2.6 < DAS28-CRP < 3.2) increased from 56.8 to 93% after 2 years of treatment, while the percentage of patients with moderate–high activity (DAS28-CRP > 3.2) decreased from 43.2 to 3.2% after 3 years of treatment (Supplementary Fig. 1B). Regarding DAPSA scores, most of the analysed patients did not have available observations.

First and Second Lines of Treatment Of the included patients with PsA, secukinumab was prescribed as a first-, second-, and subsequent-line biological in 96, 80, and 174 patients, respectively. The sub-analysis of secukinumab treatment prescribed as first or second line showed that the mean DAS28-CRP score decreased from baseline to the third year [from 3.2 (1.3) to 1.9 (0.9) (first year) and 1.8 (0.4) (third year) in the first line of treament and from 3.1 (1.1) to 2.0 (0.9) (first year) and 1.8 (0.9) (third year) in the second line of treatment] (Table 2 and Supplementary Fig. 2A). The percentage of patients in remission (DAS28-CRP < 2.6) or with low disease activity (DAS28-CRP 2.6–3.2) increased over the years in both the first and second lines of treatment (from 52.1% and 71.4%, respectively, to 100% after 2 years of treatment; Supplementary Fig. 2B). In contrast, no patients with moderate–high activity (DAS28-CRP > 3.2) in the second and third years were registered.

Probability of Retention

Retention of secukinumab was similar for patients with PsA, independently of the line of treatment (Fig. 1). Overall, the probability of retention in years 1, 2, and 3 was 74.1%, 59.1%, and 54.2%, respectively (Fig. 1A). The probability of retention in the first line of treatment was higher [80.7% (first year), 69.8% (second year), and 67.2% (third year); Fig. 1B] than the probability of retention in the second line of treatment [72.1% (first year), 57.6% (second year), and 54.3% (third year); Fig. 1C].

Axial Spondyloarthritis

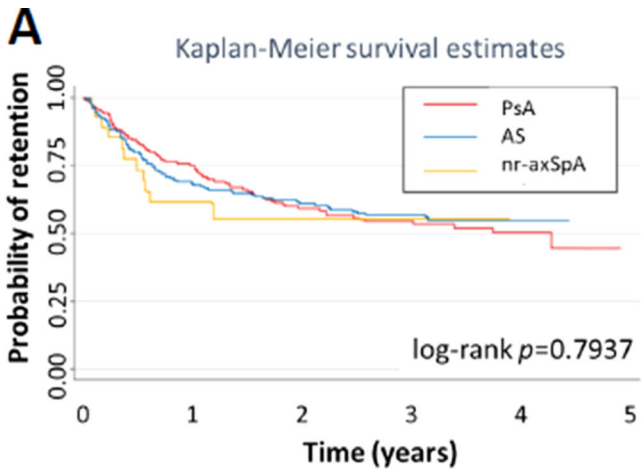
Secukinumab was prescribed as a first and second line of biological treatment in 89 (AS $n = 81$; nr-axSpA $n = 8$) and 76 (AS $n = 68$; nr-axSpA $n = 8$) patients with axSpA, respectively. Its use as a third or subsequent line of treatment was registered in 124 patients (AS $n = 113$; nr-axSpA $n = 11$). At the time of data extraction, the median duration of AS and nr-axSpA at the onset of secukinumab treatment was < 2 years for 32 AS and 13 nr-axSpA patients and ≥ 2 years for 230 AS and 14 nr-axSpA patients.

The mean BASDAI and ASDAS scores decreased from baseline to year 3 in the overall axSpA population, independently of the line of treatment (Table 3 and Supplementary Fig. 3). The sub-analysis of secukinumab administration by line of treatment showed that BASDAI mean scores decreased from 5.7 (2.1) and 5.3 (2.5) at baseline to 3.5 (2.1) and 2.6 (1.3) at the third year in the first and second lines, respectively. The same trend was observed in mean ptVAS and CRP, independently of the line of treatment. The ASDAS mean scores decreased from 3.3 (0.9) and 3.1 (0.9) at baseline to 1.8 (0.6) and 1.9 (0.9) at the third year in the first and second lines, respectively. This sub-analysis also showed an increase in the percentage of patients with controlled AS disease or low disease activity (BASDAI < 4 or ASDAS < 2.1) and a decrease in patients with high or very high activity (BASDAI ≥ 4 and ASDAS ≥ 2.1).

Ankylosing Spondylitis

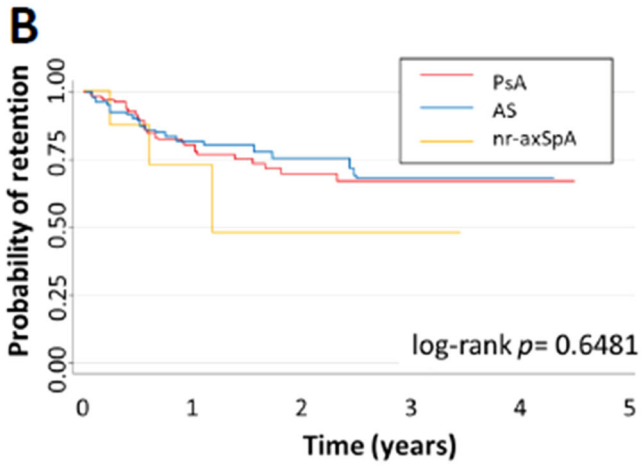
Effectiveness

Overall Population The mean BASDAI score decreased from 5.9 (2.3) at baseline to 3.9 (2.4) after 1 year of treatment and to 3.3 (2.1) at the third year of treatment (Table 4). Moreover, data from AS patients showed that the percentage of patients in remission (BASDAI ≤ 2) increased and that the percentages of patients with high activity (BASDAI ≥ 4), ptVAS scores, and CRP levels decreased. The ASDAS score decreased throughout follow-up, from 3.4 (1.1) at baseline to 2.1 (1.0) after the first year of treatment and to 2.3 (1.0) at the third year. The



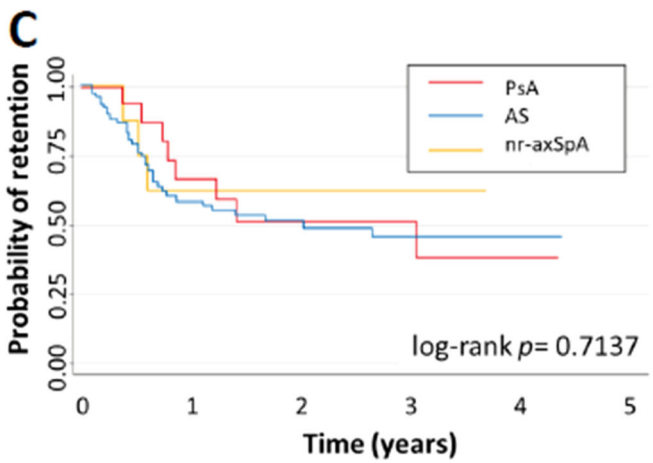
Overall

Diagnosis	Year	Probability of retention [% (95CI)]
PsA	1st year	74.1 (69.1-78.4)
	2nd year	59.1 (53.3-64.5)
	3rd year	54.2 (47.9-60.1)
AS	1st year	68.2 (62.1-73.6)
	2nd year	60.9 (54.3-66.9)
	3rd year	56.1 (48.9-62.7)
nr-axSpA	1st year	61.1 (39.7-77.0)
	2nd year	55.0 (32.8-72.6)



First line

Diagnosis	Year	Probability of retention [% (95CI)]
PsA	1st year	80.7 (70.7-87.5)
	2nd year	69.8 (57.9-78.9)
	3rd year	67.2 (54.5-77.0)
AS	1st year	81.5 (70.8-88.6)
	2nd year	75.4 (62.9-84.2)
	3rd year	68.2 (52.7-79.6)
nr-axSpA	1st year	72.9 (27.6-92.5)
	2nd year	48.6 (7.7-81.6)



Second line

Diagnosis	Year	Probability of retention [% (95CI)]
PsA	1st year	72.1 (60.3-80.9)
	2nd year	57.6 (44.5-68.7)
	3rd year	54.3 (40.3-66.3)
AS	1st year	59.1 (46.3-69.9)
	2nd year	49.5 (36.4-61.4)
	3rd year	46.0 (32.2-58.7)
nr-axSpA	1st year	62.5 (22.9-86.1)

Fig. 1 Rate of retention of treatment with secukinumab according to diagnosis and line of treatment. *95CI* 95% confidence interval, *AxSpA* axial spondyloarthritis, *nr-axSpA* non-radiographic axial spondyloarthritis, *PsA* psoriatic arthritis, *undef* undifferentiated

proportions of patients with high or very high disease activity (BASDAI ≥ 4 and ASDAS ≥ 2.1) decreased yearly, from 82.8% and 45.1% at baseline to 48.6% and 10.2% at the first year of

Table 3 Effectiveness in the total axial spondyloarthritis population* of secukinumab used as a first or second line of treatment or as any line of treatment (overall)

Parameter	Overall				First line				Second line			
	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years
BASDAI	$n = 289$	$n = 152$	$n = 77$	$n = 40$	$n = 89$	$n = 49$	$n = 22$	$n = 13$	$n = 76$	$n = 39$	$n = 16$	$n = 8$
Mean score (SD)	5.9 (2.2)	3.9 (2.4)	4.0 (2.6)	3.3 (2.1)	5.7 (2.1)	3.2 (2.2)	3.9 (2.5)	3.5 (2.1)	5.3 (2.5)	4.4 (2.4)	4.4 (3.0)	2.6 (1.3)
Disease state, *n* (%)	$n = 289$	$n = 152$	$n = 77$	$n = 40$	$n = 89$	$n = 49$	$n = 22$	$n = 13$	$n = 76$	$n = 39$	$n = 16$	$n = 8$
Remission (BASDAI $\leq$ 2)	17 (5.9)	36 (23.7)	24 (31.2)	13 (32.5)	5 (5.6)	18 (36.7)	8 (36.4)	4 (30.8)	7 (9.2)	4 (10.3)	4 (25.0)	2 (25.0)
Low activity (BASDAI $>$ 2; $<$ 4)	30 (10.4)	40 (26.3)	13 (16.9)	10 (25.0)	13 (14.6)	13 (26.5)	3 (13.6)	2 (15.4)	11 (14.5)	15 (38.5)	6 (37.5)	5 (62.5)
High activity (BASDAI $\geq$ 4)	242 (83.7)	76 (50.0)	40 (52.0)	17 (42.5)	71 (79.8)	18 (36.7)	11 (50.0)	7 (53.9)	58 (76.3)	20 (51.3)	6 (37.5)	1 (12.5)
ASDAS	$n = 79$	$n = 62$	$n = 31$	$n = 24$	$n = 18$	$n = 24$	$n = 12$	$n = 8$	$n = 20$	$n = 13$	$n = 6$	$n = 3$
Mean score (SD)	3.4 (1.2)	2.1 (1.0)	2.2 (0.9)	2.2 (0.9)	3.3 (0.9)	1.7 (0.9)	1.9 (1.0)	1.8 (0.6)	3.1 (0.9)	2.6 (1.0)	1.9 (0.3)	1.9 (0.9)
Disease state, *n* (%)	$n = 79$	$n = 62$	$n = 31$	$n = 24$	$n = 18$	$n = 24$	$n = 12$	$n = 8$	$n = 20$	$n = 13$	$n = 6$	$n = 3$
Inactive (ASDAS $<$ 1.3)	1 (1.3)	14 (22.6)	6 (19.4)	4 (16.7)	0 (0.0)	8 (33.3)	4 (33.3)	2 (25.0)	0 (0.0)	2 (15.4)	0 (0.0)	1 (33.3)
Low activity (ASDAS $\geq$ 1.3; $<$ 2.1)	5 (6.3)	17 (27.4)	10 (32.3)	9 (37.5)	1 (5.6)	8 (33.3)	3 (25.0)	4 (50.0)	2 (10.0)	2 (15.4)	5 (83.3)	1 (33.3)
High activity (ASDAS $\geq$ 2.1; $\leq$ 3.5)	40 (50.6)	25 (40.3)	14 (45.2)	8 (33.3)	8 (44.4)	7 (29.2)	5 (41.7)	2 (25.0)	11 (55.0)	6 (46.2)	1 (16.7)	1 (33.3)
Very high activity (ASDAS $>$ 3.5)	33 (41.8)	6 (9.7)	1 (3.2)	3 (12.5)	9 (50.0)	1 (4.2)	0 (0.0)	0 (0.0)	7 (35.0)	3 (23.1)	0 (0.0)	0 (0.0)
VAS	$n = 52$	$n = 39$	$n = 26$	$n = 15$	$n = 23$	$n = 16$	$n = 4$	$n = 4$	$n = 13$	$n = 7$	$n = 2$	$n = 3$
Mean (SD)	6.1 (2.8)	4.5 (2.7)	2.5 (3.0)	3.3 (2.0)	6.4 (2.7)	3.3 (2.6)	2.8 (4.2)	3.0 (2.5)	6.1 (2.7)	6.4 (1.6)	0.5 (0.7)	1.7 (1.2)
CRP (mg/L)	$n = 124$	$n = 59$	$n = 25$	$n = 14$	$n = 45$	$n = 20$	$n = 5$	$n = 5$	$n = 35$	$n = 16$	$n = 7$	$n = 4$
Mean (SD)	8.4 (19.7)	2.7 (5.1)	4.0 (6.2)	2.7 (3.2)	5.0 (6.5)	1.9 (2.8)	0.8 (0.9)	2.9 (2.8)	6.8 (12.4)	1.7 (2.8)	6.0 (6.4)	2.7 (2.6)

ASDAS Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *SD* standard deviation

*Total population refers to ankylosing spondylitis and non-radiographic axial spondyloarthritis patients

Table 4 Effectiveness in ankylosing spondylitis patients of secukinumab used as a first or second line of treatment or as any line of treatment (overall)

Parameter	Overall				First line				Second line			
	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years
BASDAI	*n* = 262	*n* = 144	*n* = 74	*n* = 39	*n* = 81	*n* = 47	*n* = 22	*n* = 13	*n* = 68	*n* = 36	*n* = 15	*n* = 8
Mean score (SD)	5.9 (2.3)	3.9 (2.4)	4.1 (2.6)	3.3 (2.1)	5.2 (2.2)	3.9 (2.5)	3.5 (2.1)	5.3 (2.5)	5.7 (2.1)	4.3 (2.4)	4.5 (3.1)	2.6 (1.3)
Disease state, *n* (%)	*n* = 262	*n* = 144	*n* = 74	*n* = 39	*n* = 81	*n* = 47	*n* = 22	*n* = 13	*n* = 68	*n* = 36	*n* = 15	*n* = 8
Remission (BASDAI ≤ 2)	17 (6.5)	35 (24.3)	23 (31.1)	12 (30.8)	5 (6.2)	17 (36.2)	8 (36.4)	4 (30.8)	7 (10.3)	4 (11.1)	4 (26.7)	2 (25.0)
Low activity (BASDAI > 2; < 4)	28 (10.7)	39 (27.1)	12 (16.2)	10 (25.6)	12 (14.8)	13 (27.7)	3 (13.6)	2 (15.4)	10 (14.7)	15 (41.7)	5 (33.3)	5 (62.5)
High activity (BASDAI ≥ 4)	217 (82.8)	70 (48.6)	39 (52.7)	17 (43.6)	64 (79.0)	17 (36.2)	11 (50.0)	7 (53.9)	51 (75.0)	17 (47.2)	6 (40.0)	1 (12.5)
ASDAS	*n* = 71	*n* = 59	*n* = 29	*n* = 23	*n* = 17	*n* = 22	*n* = 12	*n* = 8	*n* = 15	*n* = 13	*n* = 5	*n* = 3
Mean score (SD)	3.4 (1.1)	2.1 (1.0)	2.2 (0.9)	2.3 (1.0)	3.7 (0.9)	1.9 (1.0)	1.8 (0.6)	3.2 (0.9)	3.4 (0.9)	2.6 (1.0)	1.9 (0.4)	1.9 (0.9)
Disease state, *n* (%)	*n* = 71	*n* = 59	*n* = 29	*n* = 23	*n* = 17	*n* = 22	*n* = 12	*n* = 8	*n* = 15	*n* = 13	*n* = 5	*n* = 3
Inactive (ASDAS < 1.3)	1 (1.4)	13 (22.0)	6 (20.7)	4 (17.4)	0 (0.0)	7 (31.8)	4 (33.3)	2 (25.0)	0 (0.0)	2 (15.4)	0 (0.0)	1 (33.3)
Low activity (ASDAS ≥ 1.3; < 2.1)	4 (5.6)	17 (28.8)	9 (31.0)	8 (34.8)	1 (5.9)	8 (36.4)	3 (25.0)	4 (50.0)	1 (6.7)	2 (15.4)	4 (80.0)	1 (33.3)
High activity (ASDAS ≥ 2.1; ≤ 3.5)	34 (47.9)	23 (39.0)	13 (44.8)	8 (34.8)	7 (41.2)	6 (27.3)	5 (41.7)	2 (25.0)	8 (53.3)	6 (46.2)	1 (20.0)	1 (33.3)
Very high activity (ASDAS > 3.5)	32 (45.1)	6 (10.2)	1 (3.5)	3 (13.0)	9 (52.9)	1 (4.6)	0 (0.0)	0 (0.0)	6 (40.0)	3 (23.1)	0 (0.0)	0 (0.0)
VAS	*n* = 47	*n* = 36	*n* = 13	*n* = 12	*n* = 19	*n* = 4	*n* = 4	*n* = 4	*n* = 12	*n* = 6	*n* = 2	*n* = 3
Mean (SD)	6.1 (2.8)	4.5 (2.7)	2.5 (3.0)	3.3 (2.0)	3.4 (2.6)	2.8 (4.2)	3.0 (2.5)	5.9 (2.8)	6.7 (2.7)	6.2 (1.6)	0.5 (0.7)	1.7 (1.2)
CRP (mg/L)	*n* = 111	*n* = 54	*n* = 25	*n* = 15	*n* = 42	*n* = 5	*n* = 5	*n* = 5	*n* = 29	*n* = 14	*n* = 7	*n* = 4
Mean (SD)	8.1 (17.8)	2.7 (5.3)	4.1 (6.3)	2.7 (3.2)	1.9 (2.8)	0.8 (0.9)	2.9 (2.8)	8.1 (13.3)	5.3 (6.6)	1.9 (3.0)	6.0 (6.4)	2.7 (2.6)

ASDAS Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *SD* standard deviation

treatment and to 43.6% and 13% at the third year, respectively (Supplementary Fig. 4). In contrast, the proportions of patients with controlled disease or low disease activity (BASDAI < 4 or ASDAS < 2.1) increased from 17.2% and 7% at baseline to 51.4% and 50.8% after the first year of treatment and to percentages of 56.4% and 52.2% at the third year, respectively.

First and Second Lines of Treatment The sub-analysis of secukinumab administration by line of treatment showed that the BASDAI mean scores decreased from 5.2 (2.2) at baseline to 3.9 (2.5) (at the first year) and 5.3 (2.5) (at the third year)] in the first line and from 5.7 (2.1) to 4.3 (2.4) (at the first year) and to 2.6 (1.3) (at the third year) in the second line (Table 4). The ASDAS mean scores showed similar decreasing trends, from 3.7 (0.9) at baseline to 1.9 (1.0) (at the first year) and 1.8 (0.6) (at the second year) in the first line and from 3.4 (0.9) at baseline to 2.6 (1.0) (at the first year) and to 1.9 (0.4) (at the second year) in the second line (Supplementary Fig. 5A). This sub-analysis also showed that the percentage of patients with remission (BASDAI ≤ 2) or controlled AS disease activity (BASDAI < 4) increased from 21% at baseline to 63.9% at the first year, 50% at the second year, and 46.2% at the third year in the first line. In the second line of treatment, this proportion increased from 25% at baseline to 52.8% at the first year, 60% at the second year, and 87.5% at the third year. The percentage of patients by disease activity measured by ASDAS is shown in Supplementary Fig. 5B.

Probability of Retention

In the first line of treatment, the probability of retention of the AS patients in years 1, 2, and 3 was 81.5%, 75.4%, and 68.2%, respectively (Fig. 1B). In the second line of treatment, the probability of retention in years 1, 2, and 3 was 59.1%, 49.5%, and 46%, respectively (Fig. 1C).

Non-radiographic Axial Spondyloarthritis

Effectiveness

Overall Population The mean BASDAI score decreased from 6.2 (1.6) at baseline to 5.0 (2.0) at the first year and 3.4 (2.4) at the second year (Table 5). The ASDAS score decreased throughout follow-up, from 3.5 (2.2) at baseline to 2.2 (1.3) at the first year and 2.3 (1.0) at the second year of treatment. The percentage of nr-axSpAP patients with high disease activity (BASDAI ≥ 4) and the CRP level also decreased from 92% at baseline to 75% (at the first year) and 33% (at the second year) and from 11.4 (32.8) mg/L at baseline to 1.8 (2.1) mg/L at the first year, respectively. The number of patients with available observations of the variables was small at the second and third years of treatment.

First and Second Lines of Treatment Due to the limited number of patients in the nr-axSpA population, analysis by treatment line was not possible, especially given the absence of observations on the second line of treatment with secukinumab. In the first line of treatment, the mean BASDAI and ASDAS scores decreased from 5.8 (1.3) and 2.1 (–) at baseline, respectively, to 3.9 (3.8) and 1.6 (1.1) at year 1.

Probability of Retention

The probability of retention for the patients with nr-axSpA treated with secukinumab in the first line was 72.9% (at the first year) and 48.6% (at the second and third years) (Fig. 1C). The probability of retention in the second line was 62.5% (at the first to third years), but the number of patients with available observations was small.

Safety

The main cause of discontinuation was lack of effectiveness (67.9%), followed by AEs (48 cases, 16.4%). Overall, 622 AEs were registered during the treatment with secukinumab (Table 6). The rate of severe AEs was 55.2 per 1,000 patient-years (95% CI: 43.4–70.3). The most frequent AEs were infections and infestations (27.5%; 148.2 cases/1000 patient-years), gastrointestinal disorders (17.7%; 96.3 cases/1000 patient-years), among which were three IBD cases (two cases of Crohn's disease were reported: one patient with PsA and another patient with AS; only one case of ulcerative colitis was reported

Table 5 Effectiveness in non-radiographic axial spondyloarthritis patients of secukinumab used as a first or second line of treatment or as any line of treatment (overall)

Parameter	Overall				First line				Second line			
	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years	Baseline	1 year	2 years	3 years
BASDAI	*n* = 27	*n* = 8	*n* = 3	*n* = 1	*n* = 8	*n* = 2	*n* = 0	*n* = 0	*n* = 8	*n* = 3	*n* = 1	*n* = 0
Mean score (SD)	6.2 (1.6)	5.0 (2.0)	3.4 (2.4)	2.0 (–)	5.8 (1.3)	3.9 (3.8)	– (–)	0.0 (0.0)	5.6 (1.6)	5.9 (0.7)	3.0 (–)	– (–)
Disease state, *n* (%)	*n* = 27	*n* = 8	*n* = 3	*n* = 1	*n* = 8	*n* = 2	*n* = 0	*n* = 0	*n* = 8	*n* = 3	*n* = 1	*n* = 0
Remission (BASDAI ≤2)	0 (0.0)	1 (12.5)	1 (33.3)	1 (100)	– (–)	1 (50.0)	0 (0.0)	0 (0.0)	– (–)	0 (0.0)	0 (0.0)	– (–)
Low activity (BASDAI >2; <4)	2 (7.4)	1 (12.5)	1 (33.3)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (100)	– (–)
High activity (BASDAI ≥4)	25 (92.6)	6 (75.0)	1 (33.3)	0 (0.0)	7 (87.5)	1 (50.0)	0 (0.0)	0 (0.0)	7 (87.5)	3 (100)	0 (0.0)	– (–)
ASDAS	*n* = 8	*n* = 3	*n* = 2	*n* = 1	*n* = 1	*n* = 2	*n* = 0	*n* = 0	*n* = 5	*n* = 0	*n* = 1	*n* = 0
Mean score (SD)	3.5 (2.2)	2.2 (1.3)	2.3 (1.0)	1.4 (–)	2.1 (–)	1.6 (1.1)	0.0 (0.0)	0.0 (0.0)	2.8 (0.8)	– (–)	1.6 (–)	– (–)
Disease state, *n* (%)	*n* = 8	*n* = 3	*n* = 2	*n* = 1	*n* = 1	*n* = 2	*n* = 0	*n* = 0	*n* = 5	*n* = 0	*n* = 1	*n* = 0
Inactive (ASDAS <1.3)	0 (0.0)	1 (33.3)	– (–)	0 (0.0)	– (–)	1 (50.0)	0 (0.0)	0 (0.0)	– (–)	– (–)	0 (0.0)	– (–)
Low activity (ASDAS ≥1.3; <2.1)	1 (12.5)	– (–)	1 (50.0)	1 (100)	– (–)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	– (–)	1 (100)	– (–)
High activity (ASDAS ≥2.1; ≤3.5)	6 (75.0)	2 (66.7)	1 (50.0)	0 (0.0)	1 (100)	1 (50.0)	0 (0.0)	0 (0.0)	3 (60.0)	– (–)	0 (0.0)	– (–)
Very high activity (ASDAS >3.5)	1 (12.5)	– (–)	– (–)	0 (0.0)	– (–)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	– (–)	0 (0.0)	– (–)
VAS	*n* = 5	*n* = 3	*n* = 3	*n* = 0	*n* = 4	*n* = 1	*n* = 0	*n* = 0	*n* = 1	*n* = 1	*n* = 0	*n* = 0
Mean (SD)	5.6 (2.5)	4.7 (3.5)	– (–)	– (–)	5.0 (2.5)	1.0 (–)	0.0 (0.0)	0.0 (0.0)	8.0 (–)	8.0 (–)	– (–)	– (–)
CRP (mg/L)	*n* = 13	*n* = 5	*n* = 5	*n* = 0	*n* = 3	*n* = 0	*n* = 0	*n* = 0	*n* = 6	*n* = 2	*n* = 0	*n* = 0
Mean (SD)	11.4 (32.8)	1.8 (2.1)	1.0 (–)	– (–)	1.3 (1.7)	– (–)	0.0 (0.0)	0.0 (0.0)	0.5 (0.4)	0.4 (0.3)	– (–)	– (–)

ASDAS Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *SD* standard deviation

Table 6 Description of the adverse events reported during treatment with secukinumab

Adverse events	Cases per 1000 patient-years (CI 95%)
Total	539.9 (499.8–583.3)
Severe AEs	55.2 (43.4–70.3)
Main AEs (≥ 10 cases per 1000 patient-years)	
Infections and infestations	148.2 (127.9–171.7)
Gastrointestinal disorders	96.3 (80.2–115.6)
General symptoms and local injection site reactions	28.5 (20.3–39.8)
Traumatic injuries, intoxications, and complications of therapeutic procedures	26.0 (18.3–36.9)
Disorders of the skin and subcutaneous tissue	25.1 (17.6–35.9)
Musculoskeletal and connective tissue disorders	23.4 (16.2–33.9)
Respiratory, thoracic, and mediastinal disorders	23.4 (16.2–33.9)
Eye disorders	22.6 (15.5–33.0)
Medical and surgical procedures	21.8 (14.8–32.0)
Disorders of the nervous system	20.9 (14.1–31.0)
Disorders of the ear and vestibular maze	16.7 (10.8–26.0)
Heart disorders	13.4 (8.2–21.9)
Immune system disorders	12.6 (7.6–20.8)
Psychiatric disorders	10.9 (6.3–18.7)

AEs adverse events, *95%CI* 95% confidence interval

in a patient with AS), and general symptoms and local injection site reactions (5.5%; 28.5 cases/1000 patient-years). Table 6 describes the AEs reported.

DISCUSSION

The present analysis of the BIOBADASER Spanish Registry showed that patients with PsA, AS, and nr-axSpA treated with secukinumab improved after 1 year of treatment. This improvement was maintained or increased after 2 and 3 years of treatment and was numerically—although not remarkably—better in biological-naïve patients, indicating that secukinumab is effective in both naïve and non-responder patients [5, 7, 27–29, 37]. The overall probability of retention of secukinumab patients was high in the short term and the long term. Retention rates were higher when secukinumab was used as the first-line biological treatment. Regarding safety, the frequency of AEs and SAEs was consistent with previous reports.

A treat-to-target approach to the treatment of rheumatic diseases could be of interest to achieve remission or low disease activity [38]. Previous studies analyzing the suitability of treat-to-target strategies in these conditions from different points of view (safety, efficacy, and cost-effectiveness) have shown that adopting these strategies leads to better outcomes but with higher costs [39, 40]. However, to date, there is no optimal T2T strategy. In this sense, the results for the effectiveness and probability of retention of secukinumab presented here show that therapy with this biological is appropriate in patients with an inadequate response, those who are intolerant to TNFi, or naïve patients.

The high retention rates of secukinumab observed in the BIOBADASER registry are consistent with previous data from phase III clinical trials [5, 41, 42] and real-world evidence studies [27–30]. As these are chronic diseases managed with long-term treatments, retention data go hand in hand with long-term effectiveness data. In this sense, studies in real clinical practice endorse the results of open-label extension (OLE) studies (Supplementary Tables 1 and 2). In this way, secukinumab treatment led to a sustained improvement in the signs and symptoms of PsA and axSpA (including AS and nr-

axSpA) with consistent safety over 2 and 5 years [43–45].

The most frequent treatment-emergent AEs were infections and infestations (148.2 cases per 1,000 patient-years). It is worth noting that immunomodulatory biological agents are associated with an increased risk of infections [46]. In addition, immune modifications underlying severe rheumatic diseases are risk factors for developing infections [47]. Furthermore, the number of IBD cases was low (two patients were diagnosed with CD, and one patient with UC). It is important to note that most of the patients analysed here were previously treated with a biological agent—mostly TNFi treatments, and prior exposure to TNFi agents is an identified risk factor for IBD exacerbation [48]. Overall, no new safety signals were identified within the available data. Nevertheless, as this is a retrospective analysis of safety outcomes, adverse events, especially those that were mild or not considered to be treatment related, might have been under-reported.

Limitations of the current analysis include the lack of a control group, missing information on the medical history, comorbidities, and concomitant medications, and selection bias, as the patients were treated for at least 12 months with secukinumab. Furthermore, for some of the outcomes, a limited number of observations were available, e.g. there were a small number of patients with nr-axSpA and data on some variables such as DAPSA were limited. Regarding safety data, registry results were not separated by indication.

The main strength of this analysis is that it reflects the treatment of PsA, AS, and nr-axAsp patients with secukinumab in routine clinical practice in the real-world setting. Importantly, this is the first time that effectiveness, retention, and safety data in patients diagnosed with nr-axSpA and treated with secukinumab have been described. Regarding safety data analysis, the description of AEs by calculating the exposure-adjusted incident rates per 1000 patient-years for the reported AEs is more robust, since it allows results to be adjusted by treatment duration. Furthermore, the BIOBADASER registry collects information not only about prescription and dispensation, but also about safety and disease activity. This reduces the possibility of overestimating the retention rate, since it is possible to confirm the administration of the treatment to the participants. Finally, 28 centres in Spain are a representative sample for providing valuable evidence on the effectiveness and safety profile of secukinumab in everyday clinical practice in Spain.

CONCLUSION

In summary, the results of this analysis of PsA, AS, and nr-axSpA patients treated with secukinumab in Spain showed an improvement in disease activity at the first year, which increased at the second and third years of treatment. This improvement was observed not only in the first-line treatment, but also in the second line. Safety data were good and consistent with previous reports. Finally, the probability of secukinumab treatment retention in this patient profile was high and increased in naïve patients. Overall, these data provide information to be considered by clinicians regarding the use of secukinumab as both the first and subsequent lines.

ACKNOWLEDGEMENTS

Funding. This study has been sponsored by Novartis Spain. The Rapid Service Fee was funded by Novartis Spain.

Medical Writing and/or Editorial Assistance. Editorial assistance was funded by Novartis Spain and performed by Alicia Subtil-Rodriguez (Evidenze Group).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. J.M.-R., C.S.-P., M.J.M.-M., F.S.-A., and C.S. were involved in the

design of the study. C.S.-P. and F.S.-A. performed independent statistical analysis. C.S. was involved in the design of the study but was not involved in data collection and had no access to the data source. The rest of the authors are regular investigators of BIOBADASER, and they were involved in data collection and made substantial contributions to the current work. All authors reviewed and approved the final version of the manuscript.

Disclosures. Manuel José Moreno-Ramos, Carlos Sanchez-Piedra, Olga Martínez-González, Carlos Rodríguez-Lozano, Carolina Pérez-García, Mercedes Freire, Cristina Campos, Rafael Cáliz-Cáliz, Jerusalem Calvo, Juan María Blanco-Madrigal, Ana Pérez-Gómez, Maria José Moreno-Martínez, Luis Linares, Fernando Sánchez-Alonso, and Isabel Castrejón have nothing to disclose. Carlos Sastré is an employee of Novartis.

Compliance with Ethics Guidelines. Ethical approval was granted by the Hospital Clínic of Barcelona Ethics Committee, acting as a reference committee (approval code FER-ADA-2015-01). All patients had signed an informed consent to be included in the BIOBADASER registry, which covered subsequent analyses such as the present analysis. Patient information was managed as anonymized aggregated data and, as approved by the Clinical Research Committee Hospital Universitario Virgen de la Arrixaca (Murcia, Spain), 2021-1-9-HCUVA, specific informed consent for this analysis was not required. The study was performed following Good Pharmacoepidemiology Practice standards and the principles of the Declaration of Helsinki of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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