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Effectiveness and safety of secukinumab in ankylosing spondylitis and psoriatic arthritis: a 52-week real-life study in an Italian cohort

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Abstract

Background Secukinumab has shown high efficacy in randomized controlled trials in both ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Here, we investigated its real-life effectiveness and tolerability in a cohort of AS and PsA patients.

Methods We retrospectively analyzed medical records of outpatients with AS or PsA treated with secukinumab between December 2017 and December 2019. ASDAS-CRP and DAS28-CRP scores were used to measure axial and peripheral disease activity in AS and PsA, respectively. Data were collected at baseline and after 8, 24, and 52 weeks of treatment.

Results Eighty-five adult patients with active disease (29 with AS and 56 with PsA; 23 males and 62 females) were treated. Overall, mean disease duration was 6.7 years and biologic-naïve patients were 85%. Significant reductions in ASDAS-CRP and DAS28-CRP were observed at all time-points. Body weight (in AS) and disease activity status at baseline (particularly in PsA) significantly affected disease activity changes. ASDAS-defined inactive disease and DAS28-defined remission were achieved in comparable proportions between AS and PsA patients, at both 24 weeks (45% and 46%) and 52 weeks (65.5% and 68%, respectively); male sex was found an independent predictor of positive response (OR 5.16, $P=0.027$). After 52 weeks, achievement of at least low disease activity and drug retention were observed in 75% of patients. Secukinumab was well-tolerated and only mild injection-site reactions were recorded in 4 patients.

Conclusion In a real-world setting, secukinumab confirmed great effectiveness and safety in both AS and PsA patients. The influence of gender on treatment response deserves further attention.

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Keywords Ankylosing Spondylitis (AS), ASDAS-CRP, Body weight, DAS28-CRP, Male sex, Interleukin-17 (IL-17), Psoriatic Arthritis (PsA), Secukinumab, Spondyloarthritis (SpA), Treatment.

Background

Spondyloarthritis (SpA) is a group of chronic diseases characterized by entheseal and synovial inflammation of axial and/or peripheral joints, which accounts for chronic pain and stiffness, structural joint damage and disability, reduced quality of life and work inefficiency [1–3]. A number of interrelated disorders are encompassed within the spectrum of SpA, including predominantly axial forms, such as ankylosing spondylitis (AS), and predominantly peripheral forms, such as psoriatic arthritis (PsA) [4, 5]. Nonetheless, patients with PsA may also experience axial symptoms, especially in the long-standing disease, while patients with AS often show peripheral involvement and about 10% also have psoriasis; indeed, approximately one fourth of patients with AS or PsA fulfill classification criteria for both conditions [3, 6]. Whether AS and PsA are separate entities with some common features or, rather, represent different manifestations of the same disease is, therefore, still a matter of debate.

Treatment of AS and PsA aims to achieve the lowest possible level of disease activity, in order to improve functional status and quality of life, and to prevent structural damage and complications [7, 8]. Although peripheral arthritis may respond to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), axial disease is poorly controlled by these drugs and only a subgroup of AS patients (up to 50–60%) can be adequately controlled by first-line use of nonsteroidal anti-inflammatory drugs (NSAIDs) [7–9]. In recent years, tumor necrosis factor inhibitors (TNFi) have certainly revolutionized the management of AS and PsA but, not infrequently, patients present contraindications to this class of drugs, poorly respond, or show a subsequent loss of response [10]. Indeed, some AS patients do not achieve complete and persistent drug-free remission and still show radiographic progression despite several years of TNFi treatment [11, 12].

Interleukin (IL)-17 is a key player in the pathogenesis of SpA [13–16] and a new class of biologics blocking IL-17 has been developed and approved for treatment as an alternative to TNFi [17, 18]. In clinical trials, secukinumab, a fully human anti-IL17A IgG1/κ monoclonal antibody, has in fact shown good efficacy and safety in both AS and PsA [17, 18]. However, an important goal is to confirm its effectiveness and tolerability profile in the real-life management of these patients, and to investigate patient adherence to treatment. For this purpose, we retrospectively analyzed real-world data from an Italian cohort of AS and PsA patients during secukinumab therapy.

Methods

Study design

We conducted a retrospective study of patients with AS or PsA treated with secukinumab and followed-up for up to 52 weeks.

Data source and patient populations

We extracted and analyzed the data of consecutive anonymized outpatients affected by AS (axial disease) or PsA (peripheral disease), attending the Clinic of the Rheumatology Unit at Papardo Hospital in Messina (Sicily), Italy, and treated with secukinumab between December 2017 and December 2019. All included patients were adult, met the modified New York criteria for AS [19] or the CASPAR classification criteria for PsA [20], and had moderate-to-severe active disease despite previous treatments. Only patients with regular follow-up visits available were enrolled. Patients with severe comorbidities (e.g., tumoral or advanced heart, kidney or liver diseases) were excluded. Concomitant use of NSAIDs, methotrexate (MTX) or other csDMARDs, glucocorticoids, and analgesics was allowed. Patients whose treatment with secukinumab was discontinued due to lack or loss of response were considered dropouts.

The study was approved by the Ethics Committee of the Institution and conforms to the provisions of the Declaration of Helsinki as revised in Brazil, 2013. All patients gave their informed consent to participate in the study.

Drug administration

According to the approved protocols, secukinumab was administered subcutaneously to AS and PsA patients at a loading dose of 150 mg at weeks 0, 1, 2, 3 and 4, followed by a monthly maintenance dose of 150 mg thereafter. In PsA patients with an inadequate response to previous biologics, secukinumab was administered at a dose of 300 mg, with the same time schedule.

Assessments

Demographics, including age, gender, body weight and disease duration, disease activity state at study entry, concomitant treatments, and previous use of TNFi were recorded. Disease activity was evaluated by means of the ankylosing spondylitis disease activity score using C-reactive protein (ASDAS-CRP) [21] and the 28-joint disease activity score using C-reactive protein

(DAS28-CRP) [22] in AS and PsA patients, respectively, at baseline and after 8, 24, and 52 weeks of treatment.

Outcomes

The main outcomes of the study were the changes in ASDAS-CRP or DAS28-CRP and the rates of inactive disease or remission achieved at 24 and 52 weeks. Proportions of patients with different disease activity status, according to the ASDAS or DAS28 approved cut-offs, and proportions of patients achieving various grades of ASDAS-based improvement or DAS28-based response, according to the ASAS and EULAR response criteria, were also assessed [21, 22]. Drug survival and safety were examined. Data were further analyzed to detect any potential association between treatment response and baseline patient characteristics, and to identify any independent factors that could predict a successful response.

Statistical analysis

Data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables and as percentages or absolute counts for categorical variables. For univariate analyses, Kruskal-Wallis test with Dunn's multiple comparison test (non-parametric ANOVA) and Mann-Whitney U test were used to analyze changes in disease activity at different time points (statistical significances were further confirmed by Friedman and Wilcoxon tests for matched data after removing dropouts from analysis). Mann-Whitney U test was also used to detect differences between patient groups or subgroups divided according to patient characteristics. Differences in categorical and binary variables between groups, such as use of co-treatments and achievement of treatment outcomes (yes/no), were analyzed using Fisher exact test. Drug survival curves were obtained using Kaplan-Meier curve and differences in drug survival between two curves were analyzed using log-rank (Mantel-Cox) test. For bivariate analyses, correlations between two variables were examined using Spearman test. For multivariate analyses, multiple linear regression or multiple logistic regression were used to identify any independent predictors of treatment response among various continuous or categorical variables, respectively. Results were expressed as odds ratio (OR) with 95% confidence interval (CI). P values <0.05 were considered statistically significant. Statistical analysis was performed using GraphPad Prism software, version 9.4.1 for Mac OS (La Jolla, CA, USA).

Table 1 Baseline characteristics of the patients

	All patients	AS patients	PsA patients
N.	85	29	56
Gender, F/M	62/23	20/9	42/14
Age (years), mean ± SD (median ± IQR)	55.5 ± 12 (56 ± 17)	50.5 ± 14 (52 ± 16)	58 ± 10 (57 ± 15.5)*
Body weight (Kg), mean ± SD (median ± IQR)	75 ± 17 (75 ± 25)	72 ± 14 (72 ± 23)	77 ± 18 (76 ± 26)
Disease duration (years), mean ± SD (median ± IQR)	6.7 ± 1.3 (7 ± 2)	6.6 ± 1.35 (6 ± 3)	6.8 ± 1.2 (7 ± 2)
HLA-B27 carriers, N. (%)	N/A	23 (79)	N/A
Highest disease activity status at baseline, N. (%)	68 (80)	22 (76)	46 (82)
Baseline ASDAS-CRP or DAS28-CRP, mean ± SD (median ± IQR)	-	3.7 ± 0.3 (3.7 ± 0.2)	5.8 ± 0.7 (5.7 ± 0.8)
Concomitant csDMARDs, N. (%)	61 (72)	7 (24)	54 (96)****
Concomitant MTX, N. (%)	58 (68)	7 (24)	51 (91)****
Concomitant NSAIDs, N. (%)	N/A	26 (90)	N/A
TNFi-experienced, N. (%)	13 (15)	4 (14)	9 (16)

Highest disease activity status: ASDAS > 3.5 (AS patients) or DAS28 > 5.1 (PsA patients)

N/A, not available

(AS vs. PsA) * $P<0.05$ (=0.0194); **** $P<0.0001$

Results

Patient characteristics

Overall, 85 patients were enrolled, 29 with AS and 56 with PsA. Baseline characteristics of the patients are summarized in Table 1.

The mean age in the whole cohort was 55.5 years, with AS patients being on average younger than PsA patients (50.5 vs. 58 years old; $P<0.05$). The mean disease duration was 6.7 years. Overall, there was a predominance of female patients in both groups (20 of 29 in AS and 42 of 56 in PsA).

Most of the patients showed the highest disease activity status at baseline, according to their respective scores (i.e., ASDAS-based "very high disease activity" [VHDA] in 76% of AS patients and DAS28-based "high disease activity" [HDA] in 82% of PsA patients).

No patients received secukinumab as first-line treatment, but it was the first biologic therapy in 85% of patients; the remaining 15% had previous experience with at least one TNFi. Secukinumab was administered as monotherapy in 28% of patients, while the remaining 72% was concomitantly treated with csDMARDs (i.e., MTX, leflunomide or cyclosporine), especially in the PsA group (96 vs. 24%, $P<0.0001$).

Treatment effectiveness

Treatment outcomes in AS and PsA patients at 8, 24 and 52 weeks, are reported in Table 2 and illustrated in Fig. 1.

Continuous improvement in disease activity scores was recorded throughout the follow-up, with significant reductions observed at all time-points. Mean ASDAS-CRP values in AS patients decreased from 3.7 at baseline (i.e., on average VHDA status) to 2.5 at week 8 (i.e., HDA), 1.7 at week 24 (i.e., "low disease activity" [LDA]), and 1.3 at week 52 (i.e., sustained LDA or nearly "inactive disease"). Mean DAS28-CRP values in PsA patients

Table 2 Outcomes after 8, 24 and 52 weeks of treatment with Secukinumab

	All patients	AS patients	PsA patients
Effectiveness			
Week 8			
ASDAS-CRP or DAS28-CRP value, mean ± SD (median ± IQR)	-	2.5 ± 0.8 (2.1 ± 1.5)	4.2 ± 0.85 (4 ± 0.6)
(at least) Low disease activity, N. (%)	15 (18)	11 (38)	4 (7)**
Inactive disease or Remission, N. (%)	0 (0)	0 (0)	0 (0)
Change in ASDAS-CRP or DAS28-CRP, mean ± SD (median ± IQR)	-	-1.1 ± 0.75 (-1.5 ± 1.6)	-1.6 ± 0.9 (-1.6 ± 0.95)
(at least) CII or Moderate response, N. (%)	67 (79)	19 (65.5)	48 (86)*
Major improvement or Good response, N. (%)	4 (5)	0 (0)	4 (7)
Week 24			
ASDAS-CRP or DAS28-CRP value, mean ± SD (median ± IQR)	-	1.7 ± 0.8 (1.2 ± 0.6)	2.7 ± 0.8 (2.5 ± 0.85)
(at least) Low disease activity, N. (%)	58 ***(68)***	19 ***(65.5)***	39 ***(70)***
Inactive disease or Remission, N. (%)	39 ***(46)***	13 ***(45)***	26 ***(46)***
Change in ASDAS-CRP or DAS28-CRP, mean ± SD (median ± IQR)	-	-2 ± 0.8 (-2.3 ± 0.65)	-3.1 ± 1.1 (-3.1 ± 1.3)
(at least) CII or Moderate response, N. (%)	70 (82)	21 (72)	49 (87.5)
Major improvement or Good response, N. (%)	55 (65)	16 (55)	39 (70)
Week 52			
ASDAS-CRP or DAS28-CRP value, mean ± SD (median ± IQR)	-	1.3 ± 0.5 (1.2 ± 0)	2.2 ± 0.7 (2.2 ± 0.45)
(at least) Low disease activity, N. (%)	64 ***(75)***	20 ***(69)***	44 ***(79)***
Inactive disease or Remission, N. (%)	57 ***(67)***	19 ***(65.5)***	38 ***(68)***
Change in ASDAS-CRP or DAS28-CRP, mean ± SD (median ± IQR)	-	-2.3 ± 0.6 (-2.4 ± 0.3)	-3.6 ± 0.9 (-3.6 ± 1.2)
(at least) CII or Moderate response, N. (%)	67 (79)	20 (69)	47 (84)
Major improvement or Good response, N. (%)	63 (74)	19 (65.5)	44 (79)
Retention rate (Drug survival *after 52 weeks*), N. (%)	64 ***(75)***	20 ***(69)***	44 ***(79)***
Safety			
Serious adverse events, N.	0	0	0
Injection-site reactions, N.	4	1	3

ASDAS- and DAS28-based disease activity states:

- Low disease activity: ASDAS < 2.1; DAS28 ≤ 3.2.

- Inactive disease: ASDAS < 1.3. Remission: DAS28 < 2.6.

ASDAS-based (ASAS-EULAR) response criteria (for AS patients) [Ref. 21]:

- Clinically important improvement (CII): ASDAS change compared to baseline ≥-1.1

- Major improvement: ASDAS change ≥-2

- No improvement: ASDAS change <-1.1

DAS28-based (EULAR) response criteria (for PsA patients) [Ref. 22]:

- Moderate response: DAS28 change compared to baseline >-1.2 with current DAS28 value > 3.2 or DAS28 change >-0.6 to ≤-1.2 with current DAS28 ≤ 5.1.

- Good response: DAS28 change >-1.2 with current DAS28 ≤ 3.2.

- No response: DAS28 change ≤-0.6 or DAS28 change >-0.6 to ≤-1.2 with current DAS28 value > 5.1

(AS vs. PsA) * $P < 0.05$ (= 0.0484); ** $P < 0.001$ (= 0.0008)

decreased from 5.8 at baseline (i.e., on average HDA status) to 4.2 at week 8 (i.e., "moderate disease activity" [MDA]), 2.7 at week 24 (i.e., LDA), and 2.2 at week 52 (i.e., "remission") (Fig. 1a).

Notably, ASDAS-defined inactive disease and DAS28-defined remission were achieved in comparable proportions between AS and PsA patients, at both 24 weeks (45% and 46%, respectively) and 52 weeks (65.5% and 68%, respectively) (Fig. 1b).

ASDAS-CRP and DAS28-CRP responses were significant throughout the whole study period (Fig. 1c). Nevertheless, at earlier time points, statistical significances were stronger in the PsA group compared to the AS group (Fig. 1a-c). At week 8, in fact, higher rates of substantial responses to treatment were observed in PsA (i.e., "moderate response" + "good response", according to the EULAR criteria) compared to AS patients (i.e., "clinically important improvement" [CII] + "major improvement", according to the ASAS-EULAR criteria) (86% vs. 65.5%, $p < 0.05$) (Fig. 1d). On the other side, higher proportions of AS patients more rapidly achieved the LDA status compared to PsA patients (38% vs. 7%, $p < 0.01$) (Fig. 1b).

Achievement of substantial control of the disease (i.e., inactive disease/remission + LDA) was overall observed in 68% of patients at week 24 and in 75% of patients at week 52, with no significant differences between AS and PsA patients (Fig. 1b; Table 2).

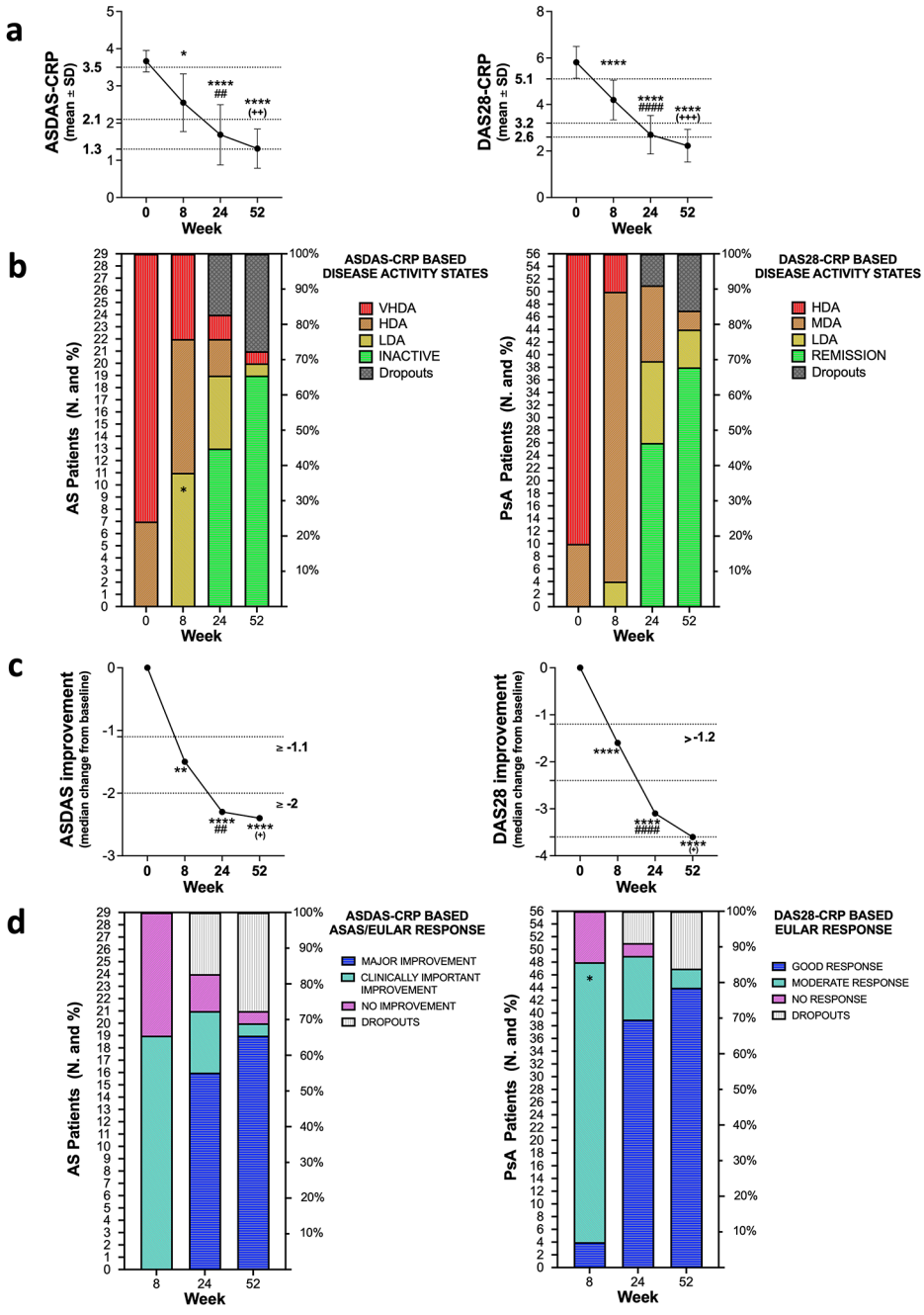

Fig. 1 Disease activity scores and treatment responses in patients with AS or PsA during therapy with secukinumab. ***a)*** Mean values (± standard deviation) of ASDAS-CRP and DAS28-CRP at baseline and at 8, 24 and 52 weeks of treatment in patients with AS and PsA, respectively. $^{*}P < 0.05$, $^{****}P < 0.0001$ (compared to week 0); $^{\#\#}P < 0.01$, $^{\#\#\#\#}P < 0.0001$ (week 24 vs. 8); $^{++}P < 0.01$, $^{+++}P < 0.001$ (week 52 vs. 24). ***b)*** Numbers and percentages of AS or PsA patients with different disease activity states according to ASDAS and DAS28 cut-offs. VHDA, very high disease activity (ASDAS > 3.5); HDA, high disease activity (2.1 ≤ ASDAS < 3.5 or DAS28 > 5.1); MDA, moderate disease activity (3.2 < DAS28 ≤ 5.1); LDA, low disease activity (ASDAS < 2.1 or DAS28 ≤ 3.2); inactive disease or remission (ASDAS < 1.3 or DAS28 < 2.6). $^{*}P < 0.05$ (LDA at week 8 in AS vs. PsA). ***c)*** Median changes of ASDAS-CRP and DAS28-CRP at the various time points in patients with AS and PsA, respectively. ΔASDAS ≥ 1.1, clinically important improvement; ΔASDAS ≥ 2, major improvement; ΔDAS28 > 1.2, moderate response with current DAS28 > 3.2 or good response with current DAS28 ≤ 3.2. $^{**}P < 0.01$, $^{****}P < 0.0001$ (compared to week 0); $^{\#\#}P < 0.01$, $^{\#\#\#\#}P < 0.0001$ (week 24 vs. 8); $^{+}P < 0.05$ (week 52 vs. 24). ***d)*** Numbers and percentages of AS or PsA patients with different treatment responses according to ASAS and EULAR criteria (see above cut-offs). $^{*}P < 0.05$ (significant responses at week 8 in PsA vs. AS).

Influence of baseline patient characteristics on disease activity changes and drug survival

We looked at potential differences in treatment response based on patient characteristics at study entry. We found that patients with the highest disease activity status at baseline (i.e., DAS28-CRP > 5.1 or ASDAS-CRP > 3.5) overall had the greatest changes in disease activity scores at the end of follow-up (Fig. 2a). Specifically, the extent of DAS28-CRP reduction in PsA patients was significantly affected by baseline disease activity and significantly correlated with it at week 52, as well as at weeks 8 and 24, whereas ASDAS-CRP reduction in AS patients was significantly associated with baseline disease activity only at week 52 (Fig. 2b). On the other hand, baseline disease activity did not significantly affect drug survival in either group.

Body weight was observed to modestly influence the magnitude of ASDAS-CRP change at week 52, electively in AS patients (Fig. 2c).

The relationship between secukinumab response and sex was composite. Although gender did not affect the overall extent of either ASDAS-CRP or DAS28-CRP change, it did affect the rates of achievement of LDA (i.e., ASDAS-CRP < 2.1 or DAS28-CRP ≤ 3.2) and/or inactive disease or remission (i.e., ASDAS-CRP < 1.3 or DAS28-CRP < 2.6) (Fig. 3a), as well as the overall drug survival (Fig. 3b), in the whole cohort of AS and PsA patients, in favor of males.

No significant differences in treatment response or drug survival were observed based on age, disease duration, HLA-B27 status, concomitant MTX, and previous experience with TNFi. In particular, treatment failure and drug discontinuation after 52 weeks were recorded in 22% of TNFi-naïve patients (16 of 72) and in 24% of TNFi-experienced patients (4 of 13).

Predictors of inactive disease or remission

Finally, we performed multivariate analyses to identify any independent factors that could predict a positive response to secukinumab treatment at 52 weeks. In accord with the above data, at multiple linear regression analysis (also including age, body weight and disease duration), only disease activity scores at baseline predicted the magnitude of score changes at the end of follow-up in both AS (β-coefficient =-1.19; 95% CI: -2.04 to -0.34; $P=0.0093$) and PsA groups (β-coefficient =-0.96; 95% CI: -1.31 to -0.61; $P<0.0001$), while, at multiple logistic regression, the male gender emerged as a strong independent predictor of achievement of inactive disease or remission (OR = 5.16; 95% CI: 1.35 to 26.63; $P=0.0271$) (Table 3), as well as inactive disease/remission + LDA (OR = 6.44; 95% CI: 1.44 to 47.64; $P=0.0296$).

Drug discontinuation and safety

The overall retention rate at one-year follow-up was 75%. A total of 21 patients (25%) dropped out of the study because of treatment failure. Of these, 14 patients (67%) discontinued secukinumab owing to primary failure (i.e., lack of response and persistently high disease activity); 4 (19%) because of suboptimal responses (i.e., lack of achievement of LDA); and 3 (14%) because of secondary failure (i.e., loss of response and relapse of active disease). The highest rate of dropouts was observed among female patients with AS (40%) (Fig. 3c).

The treatment was well tolerated and none of the patients discontinued secukinumab due to adverse events; only 4 patients (5%) experienced mild local reactions at the injection site.

Discussion

Secukinumab, a first-in-class IL-17 inhibitor (IL-17i), has repeatedly shown its efficacy in several phase-3 randomized controlled trials (RCTs) that were part of a large development program, such as MEASURE trials in AS and FUTURE trials in PsA; more recently, other clinical trials, such as MAXIMISE and PREVENT, have demonstrated its efficacy also in axial manifestations of PsA and in non-radiographic axial SpA [17, 18]. Furthermore, secukinumab demonstrated a good safety profile, including lack of tuberculosis reactivation, and high patient adherence [17, 18, 23].

Real-world evidence is gradually emerging from observational data, surveys and registries [24–27], although often available as abstracts [28, 29]. Among full-length articles, our study adds up to the real-life Italian studies that have recently been published in AS, PsA and axial SpA [30–32].

Our data clearly show analogous effectiveness profiles of secukinumab in AS and PsA patients, with very similar rates of inactive disease or remission and comparable rates of inactive disease/remission + LDA between the two groups. Only modest numerical differences in favor of PsA were observed in the rates of significant improvement at 24 and 52 weeks, according to the ASAS and/or EULAR response criteria, and in the drug retention rates. As also reported by others [31], inactive disease/remission or LDA were mostly achieved within the first 24 weeks of treatment and sustained during the 52-week follow-up period.

Our study included many biologic-naïve patients. This might have favored higher rates of inactive disease/remission compared to those observed in previous trials or real-world reports in which proportions of biologic-experienced patients were higher. In fact, lower successful responses and retention rates have sometimes been reported among subjects previously treated with one or more lines of biologics [26, 32–34]. On the other hand,

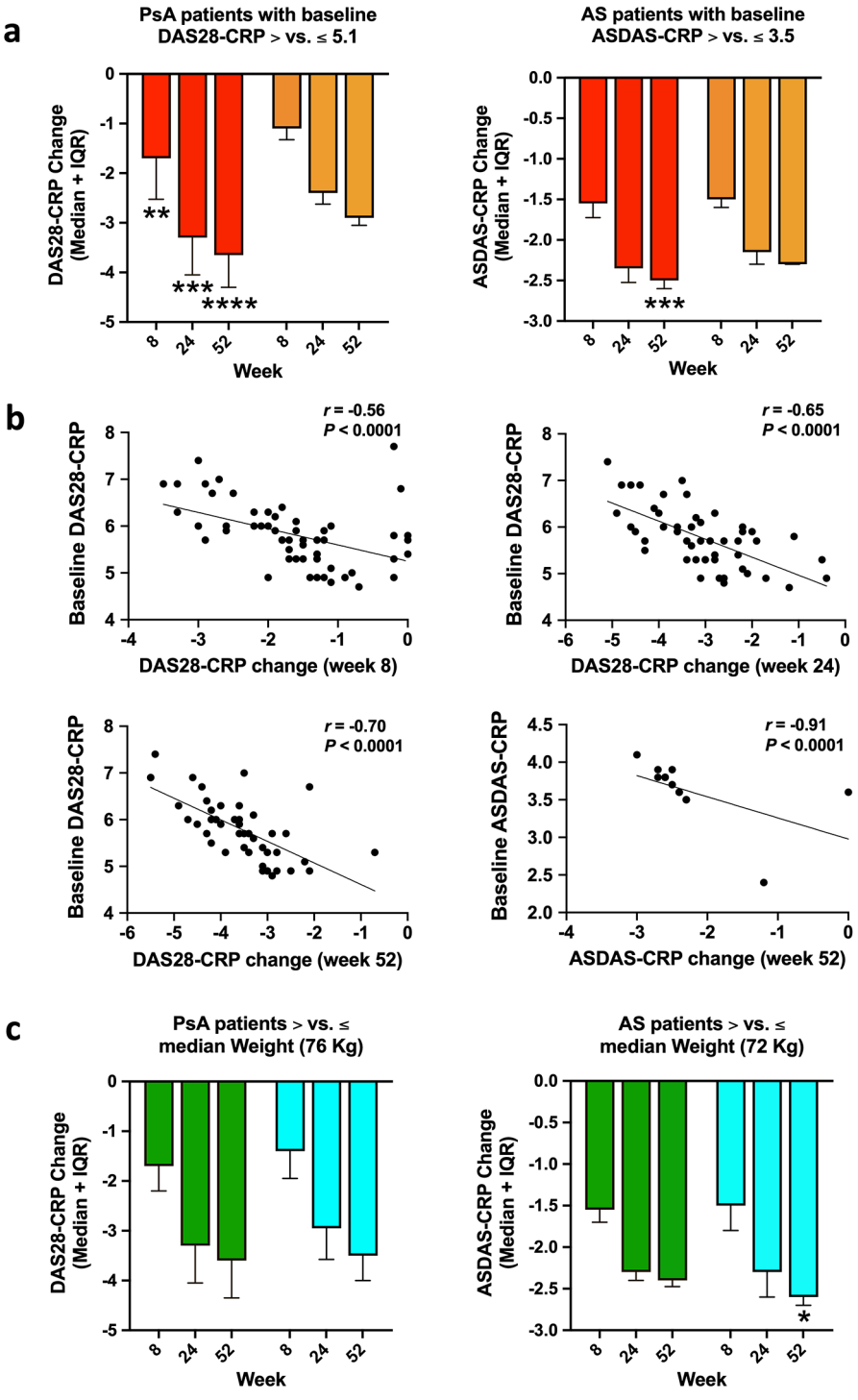

Fig. 2 Influence of baseline disease activity and body weight on response to secukinumab. ***a)*** Differences in median changes (+interquartile range) of DAS28-CRP and ASDAS-CRP at 8, 24 and 52 weeks between patients with the highest vs. lower disease activity scores at baseline. $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. ***b)*** Significant correlations between baseline disease activity and disease activity score changes at the various time points (Note: events in the fourth graph appear to be fewer than the number of patients analyzed due to overlapping dots). ***c)*** Differences in median changes (+interquartile range) of DAS28-CRP and ASDAS-CRP at 8, 24 and 52 weeks between patients with body weights above and below median values. $^{*}P < 0.05$.

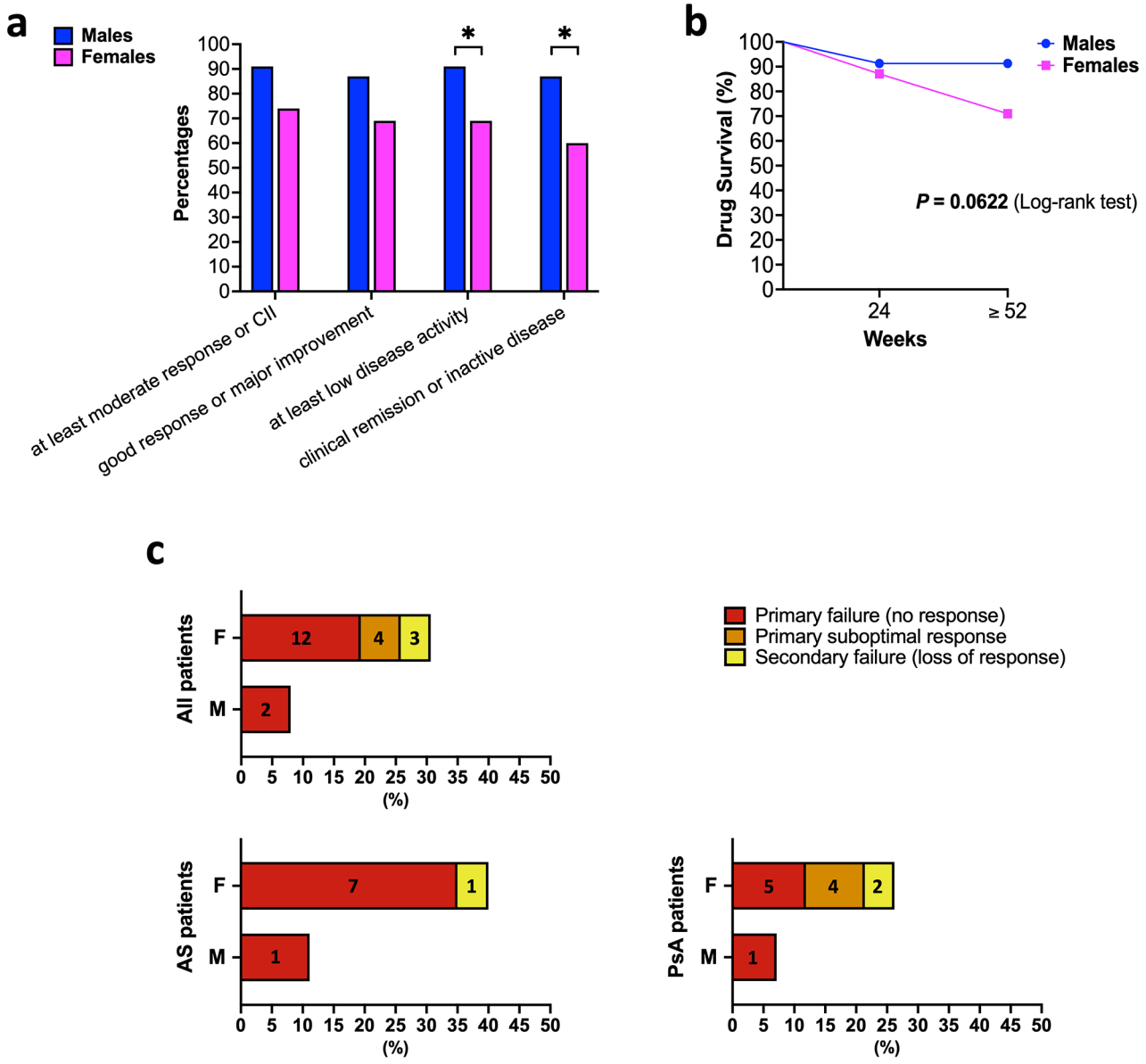

Fig. 3 Impact of gender on response to secukinumab. ***a)*** Percentages of male and female patients with AS or PsA achieving different outcomes at 52 weeks of treatment. CII, clinically important improvement. *$P < 0.05$ (males vs. females). ***b)*** Kaplan-Meier drug survival curves of male and female patients during one year of follow-up. ***c)*** Percentages (and numbers) of male and female patients who experienced poor outcomes during follow-up (i.e., primary and secondary failures or suboptimal responses accounting for subsequent drug discontinuation), in the whole cohort and separately in the AS and PsA groups.

as generally seen in several studies [17, 18, 30, 31], we did not observe substantial differences in treatment outcomes between TNFi-naïve and TNFi-experienced patients.

Our study also included many women. In fact, the number of women diagnosed with AS has increased dramatically over the last decades [35–37]. Moreover, in axial SpA, the M:F ratio decreases with disease onset after age 40 [36], as is the case of AS patients in our series. Such an abundance of female patients ultimately allowed us to better grasp the role of gender in the response to secukinumab. Women are known to show poorer responses to TNFi compared to men in both AS and PsA, while the influence of gender in IL-17i responses appears more controversial [38]. In AS, male patients more frequently achieved inactive disease (ASDAS-ID response) in a *post-hoc* pooled analysis of all MEASURE trials, although no other efficacy outcomes were substantially affected by sex [38]. Furthermore, real-world evidence with secukinumab suggests that male patients show higher retention rates than females in AS and axial SpA, either statistically [31, 32] or at least numerically

Table 3 Multiple logistic regression aimed to identify possible independent predictors of achievement of inactive disease (ASDAS-ID: ASDAS < 1.3) or remission (DAS28 < 2.6) after 52 weeks of treatment with Secukinumab in the whole cohort of patients with AS or PsA.

Variable	β value	Standard error (SE)	Odds ratio (OR)	95% profile likelihood confidence interval (CI)	*P* value
Age (above median)	-0.8037	0.5448	0.4477	0.1474 to 1.274	0.1402
Body weight (above median)	-0.1398	0.5536	0.8695	0.2879 to 2.570	0.8006
Disease duration (above median)	-0.8409	0.5687	0.4313	0.1372 to 1.304	0.1392
Male gender	1.641	0.7426	**5.161**	1.347 to 26.63	**0.0271 (*)**
Concomitant use of MTX	0.1278	0.7524	1.136	0.2576 to 5.172	0.8651
Previous treatment with TNFi	-0.7003	0.7168	0.4965	0.1201 to 2.101	0.3286
Highest disease activity status at baseline	-0.3904	0.7162	0.6768	0.1491 to 2.626	0.5857
Diagnosis of PsA	0.2529	0.6994	1.288	0.3137 to 5.145	0.7177

[39]. Our study confirms, in the whole cohort of patients with AS or PsA, the disadvantageous role of female sex in drug survival and in achieving inactive disease or clinical remission (± LDA) with secukinumab after one year of follow-up, although the overall extent of disease activity score reductions did not substantially differ between the two genders. Sex does not affect the pharmacokinetics of secukinumab [18], nor does the influence of gender in the response to secukinumab appear to be related to HLA-B27 status. Rather, a possible sexual dimorphism in SpA associated with a different immunological phenotype has been suggested, with a greater expression of IL-17A and IL-17 receptor (TH17 signature) being reported in men [40]. This might concur to explain the increased response of males to IL-17 pathway blockade. On the other hand, the subjective perception of pain and fatigue, substantially uncoupled to inflammation, is notoriously greater in women due to a more frequent concomitance of fibromyalgia [41], and might account for not achieving complete disease control.

High disease activity is not *per se* a limitation to treatment with secukinumab. In our experience, in fact, patients with more active disease eventually had greater reductions in activity scores at the end of follow-up (particularly in PsA, for which significant correlations were found as early as 8 and 24 weeks). This is consistent with previous observations of a favorable response to secukinumab in patients with high inflammatory indices (e.g., ESR) [31], and probably reflects the key role of IL-17 in orchestrating inflammation in general, both at the systemic [42, 43] and joint level [15, 44], and in driving the immune pathogenesis of axial SpA and PsA in particular [13–16, 45].

In addition, we found that elevated body weight may affect, to some extent, the 1-year effectiveness of secukinumab, specifically in patients with AS. This could reflect the impact of physical load and biomechanical stress particularly on axial disease. Given the lack of effects on peripheral PsA, this association does not appear to be based on obesity-related inflammation. However, we lack body mass index data for many of our patients, so we cannot draw definitive conclusions. Indeed, the effects of increased body mass index on secukinumab response have been controversial in previous studies, ranging from no influence [31], to some numerical but not statistical difference [46], to an even favorable role [47].

Finally, we recorded good adherence to secukinumab, which settled on average at 75%, in line with other real-world observations [29, 30]. In agreement with RCTs [48], we were able to confirm an excellent tolerability and safety profile of the drug. None of the patients discontinued secukinumab due to adverse events, while the rate of local reactions stood at 5%, similar to that observed in the EXCEED trial [23].

During the observation period of this study (i.e., 2017–2019), DAS28-CRP was still widely used to assess disease activity in PsA, in RCTs [18, 22] as in daily practice [49]; one of the limits of this retrospective study is, in fact, the unavailability of the most recently validated outcome measures in PsA, such as the disease activity index for psoriatic arthritis (DAPSA) or the minimal and very low disease activity responses [50], as well as the lack of records relating to assessment tools for other clinical domains. On the other hand, DAS28-CRP has been shown to have a very high degree of correlation with DAPSA [49], and the use of DAS28-CRP in PsA patients has allowed us to draw a parallel with ASDAS-CRP in AS patients, thus comparing treatment outcomes both in terms of remission/inactive disease±LDA achievement and according to ASAS/EULAR response criteria [21, 22].

Overall, our study has several limitations, including retrospective design, small size, and lack of a control cohort. Nevertheless, it provides considerable real-world information and interesting insights into secukinumab responders and confirms the validity in clinical practice of this first-in-class IL-17i for the treatment of AS and PsA.

Conclusion

This study supports a high effectiveness and tolerability profile for secukinumab in the real-life management of patients with AS or PsA, in accordance with results previously obtained in RCTs. We report significant reductions in disease activity scores in both groups, with comparable high proportions of patients achieving optimal disease control, and high drug retention rates at one year of follow-up. Secukinumab is overall effective regardless of disease duration and previous experience with TNFi. Patients with the highest disease activity at baseline ultimately show the greatest score reductions. The predictive role of gender on treatment response is newly emerging from real-world evidence and certainly deserves further attention. We underscore that male patients are more likely to achieve inactive disease or remission at 52 weeks and show higher retention rates. The possible influence of body weight on axial disease control is also of interest and needs confirmation. Larger real-life studies with longer follow-up are warranted.

Abbreviations

AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score using C-reactive protein
CI	Confidence interval
csDMARDs	Conventional synthetic disease-modifying anti-rheumatic drugs
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAS28-CRP	Disease Activity Score calculated in 28 joints and using C-reactive protein
HDA	High disease activity
IL	Interleukin
IL-17i	IL-17 inhibitors
LDA	Low disease activity
MDA	Moderate disease activity
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PsA	Psoriatic Arthritis
SD	Standard deviation
SpA	Spondyloarthritis
TNFi	Tumor necrosis factor inhibitors
VHDA	Very high disease activity

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Authors' contributions

Study conception and design: ABMC. Patient recruitment and data collection: FMC, MTF, ABMC. Statistical analysis, tables and figures: GZ. Literature search and manuscript writing: GZ. Manuscript review: FMC, VP, MTF, RC, FF, ABMC, AM. Supervision: ABMC, AM. All authors have read and approved the final version submitted.

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Availability of data and materials

Data supporting the findings of this study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the local Ethics Committee and was conducted in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki and its subsequent amendments. All patients gave their informed consent prior to their inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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