The assessment of the drug retention rate of secukinumab in patients with psoriatic arthritis in a real-life multicentre cohort

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Abstract

Objective

We aimed to evaluate the drug retention rate (DRR) of secukinumab, an anti-IL-17A monoclonal antibody, in patients with psoriatic arthritis (PsA) in a real-life cohort, and to assess the impact of comorbidities and patient clinical characteristics on the DRR of secukinumab.

Methods

A retrospective study of prospective followed-up patients was performed to evaluate the DRR of secukinumab on patients with PsA attending the recruiting centres between January 2016 and June 2022.

Results

In 207 patients with PsA, a 60-month DRR of secukinumab of 57.0% was estimated (mean time of administration of 21.5±17.1 months). Male gender, age ≥65 years, disease duration ≥5 years and ≥10 years did not influence the DRR of secukinumab. The presence of comorbidities, considering any concomitant disorder, did not affect the DRR of secukinumab. In patients with cardiometabolic multimorbidity, a trend toward a better DRR of secukinumab was recorded. In fact, patients with high blood pressure, dyslipidaemia, and type 2 diabetes showed a trend toward an improved DRR of secukinumab. Furthermore, the presence of obesity did not influence the DRR of secukinumab. Different dosages, previous bDMARDs, and concomitant therapy with csDMARDs did not influence the DRR of secukinumab.

Conclusion

A cumulative 60-month DRR of secukinumab of 57.0% in patients with PsA was retrieved. The presence of cardiometabolic multimorbidity could be associated with an improved DRR of secukinumab, whereas obesity did not affect this feature in our cohort. Previous bDMARDs, concomitant csDMARDs, and different drug dosages could not influence the DRR of secukinumab over time.

Key words

psoriatic arthritis, secukinumab, drug retention rate

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Introduction

Psoriatic arthritis (PsA) is a chronic disease characterised by widespread musculoskeletal inflammatory manifestations in patients with psoriasis (1). PsA is characterised by a heterogeneous clinical presentation and different disease courses (2, 3). However, many patients may develop a destructive form of arthritis with a consequent morbidity and relevant disability (1-5). Beyond disease features, PsA is frequently associated with comorbidities which may increase the burden of the disease and may worse the outcome of these patients over time (6, 7). As far as pathogenesis is concerned, the mechanisms leading to the development of PsA have not been fully elucidated yet (8). A complex interplay has been suggested among individual genetic background, environmental factors, and an aberrant immune response in inducing the disease (9, 10). In this context, multiple lines of evidence have recently highlighted the pathogenic role of interleukin (IL)-17A in PsA (11, 12). This is a pro-inflammatory cytokine which functions within a complex network of cytokines (11, 12). IL-17A signalling results in the production of inflammatory cytokines and chemokines, and in the activation of IL-17 receptor-bearing target cells, including fibroblasts, epithelial cells and synoviocytes (11, 12). On these bases, diverse IL-17A inhibitors have recently been used in managing PsA (13). Amongst these drugs, secukinumab, an anti-IL-17A IgG1-κ monoclonal antibody, has been already approved for the treatment of these patients (14, 15). Robust evidence, derived from randomised clinical trials, showed the efficacy of secukinumab on different manifestations of the disease (16-19). Thus, both EULAR and GRAPPA recommendations for management of PsA have lately suggested the administration of IL-17 inhibitors in patients, who are identified as non-responders to the first line therapies (20, 21). However, although randomised clinical trials may provide an unbiased estimate of the comparative efficacy between patients in the treated and control groups, the strict enrolment criteria may limit the generalisation of the results since trial populations are often not fully representative of the patients encountered in daily clinical practice (22). Therefore, real-life studies may give relevant insights into effects of therapies in a more heterogenous clinical setting, where many patients may have multiple comorbidities or other clinical features influencing the management (23-24). The drug retention rate (DRR) is an accepted method to study the effectiveness in cohorts of patients from clinical practice by the assessment of the persistence of therapy over time. In the context of PsA, few studies have investigated the effectiveness of secukinumab in real-life studies (26-28). In addition, the impact of comorbidities on the DRR of secukinumab has not been fully investigated yet (29-31). On these bases, we aimed to evaluate the DRR of secukinumab in patients with PsA in a real-life cohort. We also assessed the impact of comorbidities on the DRR of secukinumab and stratified the results according to patient clinical characteristics.

Methods

Study design, patients and settings

A retrospective study of prospective followed-up patients was performed to evaluate the DRR of secukinumab, but also the impact of comorbidities and patient clinical characteristics on that. Consecutive patients with PsA, fulfilling CASPAR criteria (32) and attending the outpatient clinics of the recruiting centres, were included in this analysis if treated at least for 3 months with secukinumab between January 2016 and June 2022.

The local Ethics Committee (*Comitato Etico Azienda Sanitaria Locale 1 Avezzano/Sulmona/L'Aquila, L'Aquila*, Italy; protocol no. 0204194/22) approved the study, which was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki. Informed consent was obtained from each patient for the use of clinical features for the purposes of the study. In reporting the results, we followed the STROBE guidelines.

Variables to be assessed

The DRR of secukinumab was evalu-

ated by assessing the months of therapy. The reasons of discontinuation of secukinumab were also registered due to inefficacy and/or side effects. The following demographic and disease features were collected at the time of first administration of secukinumab: age, gender, weight, height, disease duration, and clinical manifestations (*i.e.* peripheral, axial, enthesis involvement, features of dactylitis, skin and/or nail involvement, extra-articular manifestations). The presence of comorbidities was also registered and defined as coexisting medical conditions distinct from the principal diagnosis for which the patient was included in this study. The researchers verified the presence of such comorbidities reviewing the clinical charts, by interview, and extensive medical examinations of patients. The comorbidities were also identified according to the therapies given to the patients, as performed in another setting (33, 34). The patient was defined as having cardiometabolic multimorbidity if affected by 2 or 3 among high blood pressure (HBP), type 2 diabetes (T2D), and/or dyslipidaemia. We used this approach since cardiometabolic multimorbidity (≥2 of 3 risk factors) may be considered as a clinical feature which may differ from a single cardiometabolic comorbidity, as elsewhere shown (35). Obesity and severe obesity were defined according to the values of body mass index (BMI) ≥30 and ≥35, respectively. Finally, duration of secukinumab therapy expressed in months, lines biologic disease-modifying anti-rheumatic drug (bDMARD) therapy, reasons of discontinuation (*i.e.* inefficacy, side effects), concomitant glucocorticoids (GCs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and non-steroidal anti-inflammatory drugs (NSAIDs) were also registered in our cohort of patients.

Data sources, bias, and study size

Relevant data were retrospectively collected by a review of clinical charts, registered during the scheduled visits for each involved patient. All clinical features, recorded between January 2016 and June 2022, were fully anonymised before we accessed them. Data were collected between June 2022 and November 2022, by a review of clinical charts, which were stored in each involved centre. All findings generated by the analysis are included into the body of the present work. Considering the retrospective design, our study may be subjected to a number of possible biases. We tried to minimise the main methodological problems by a careful definition of each variable to be assessed. Furthermore, patients with significant missing data, which were considered to be meaningful for the analyses, were removed, if one or more missing data in the main outcomes. Finally, given the retrospective design and the "real-life" aims of our study, no specific sample size was estimated.

Statistical methods

Statistics firstly provided descriptive analysis of the collected data. Kaplan-Meier curve was exploited to assess the cumulative DRR of secukinumab with the event being drug discontinuation due to inefficacy. Furthermore, Kaplan-Meier curves were carried out to evaluate the impact of comorbidities and patient clinical characteristics on the DRR of secukinumab. Survival curves were compared by using long-rank test. The statistical significance was set to $p<0.05$ and all p-values were two-sided. GraphPad for Windows (v. 8.0, San Diego, USA) was used for all analyses.

Table I. Descriptive statistics of assessed patients with PsA.

Clinical characteristics	207 patients with PsA
Demographic characteristics	
Age, years, mean ± SD	55.1 ± 11.9
Male gender (%)	40.1%
Weight, kg, mean ± SD	79.7 ± 17.3
Height, m, mean ± SD	1.67 ± 0.1
BMI, mean ± SD	28.6 ± 5.9
Clinical characteristics	
Peripheral involvement (%)	80.2%
Skin and/or nail involvement (%)	78.3%
Axial involvement (%)	50.3%
Enthesis involvement (%)	40.1%
Dactylitis features (%)	29.1%
Extra-articular manifestations (%)	1.1%
Comorbidity features	
Comorbidities (%)	57.2%
High blood pressure (%)	38.9%
Dyslipidaemia (%)	35.1%
Type 2 diabetes (%)	14.9%
Cardiometabolic multimorbidity (%)	28.6%
Obesity, BMI ≥30 (%)	38.7%
Severe obesity, BMI ≥35 (%)	18.3%
Other comorbidities (%)	24.8%
Secukinumab features	
Dosage of 300 mg (%)	76.0%
Ongoing at the last observation (%)	76.3%
Discontinuation due to inefficacy (%)	21.4%
Discontinuation due to side effects (%)	2.3%
Previous therapy with bDMARDs (%)	48.9%
Concomitant therapy with csDMARDs (%)	37.4%
Concomitant therapy with MTX (%)	71.8%
Concomitant therapy with NSAIDs (%)	29.3%
Concomitant therapy with GCs (%)	16.1%

PsA: psoriatic arthritis, BMI: body mass index; bDMARDs: biologic disease-modifying anti-rheumatic drugs, csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; GCs: glucocorticoids.

Results

Clinical characteristics of assessed patients

In this study, 207 patients with PsA (mean age 55.1±11.9 years, male gender 40.1%) and treated with secukinumab were assessed among those attending the recruiting centres between January 2016 and June 2022 (Table I). Almost

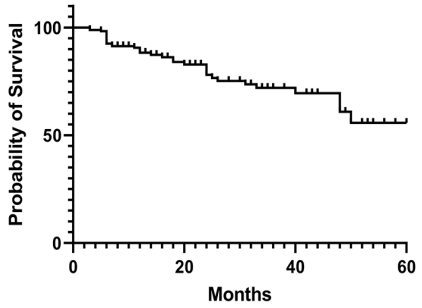

Fig. 1. The cumulative DRR of secukinumab is reported over a 60-month of follow-up. A cumulative DRR of secukinumab of 57.0% was estimated with a mean time of administration of 21.5±17.1 months (median 18.0 [IQR 24] months) in our cohort.

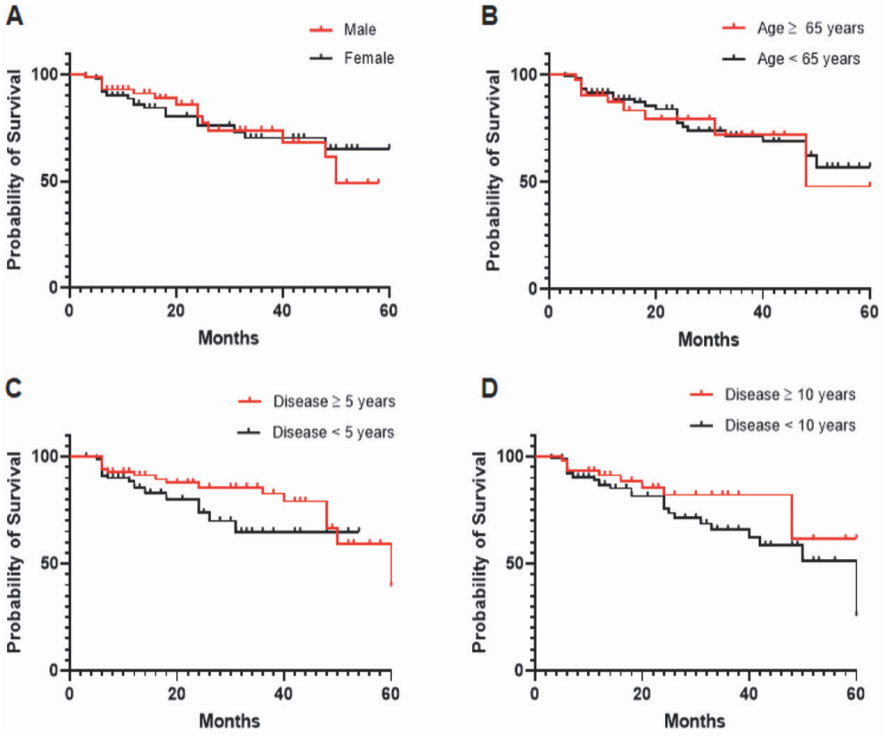

Fig. 2. The DRR of secukinumab is stratified according to male/female gender (**A**), age ≥65 years (**B**), disease duration ≥5 years (**C**), and disease duration ≥10 years (**D**), respectively. None of these features significantly influenced the DRR of secukinumab.

all assessed patients were characterised by a disease of the peripheral joints (80.2%) in association with skin and/or nail involvement (78.3%). Assessed patients also showed manifestations of axial (50.3%) or enthesis (40.1%) involvement. Features of dactylitis were recorded in 29.1% of patients. A mean disease duration of 8.4±5.5 years (median 7.5 (IQR 10] years) was retrieved in assessed patients.

In this cohort, 57.2% of patients showed concomitant comorbidities, mostly HBP (38.9%) and dyslipidaemia (35.1%). Furthermore, 28.6% of patients were affected by a cardiometabolic multimorbidity, since affected by 2 or 3 concomitant diseases among HBP, dyslipidaemia, and/or T2D. In addition, obesity was frequently recognised in our cohort, 38.7% of patients were characterised by BMI ≥30 and 18.3% by BMI ≥35, respectively. In our cohort, 8.6% of patients were affected by clinical atherosclerosis and 5.7% by metabolic syndrome. Other comorbidities were recognised in 24.8% of patients. Specifically, 15.1% of patients were affected by fibromyalgia, 13.6% by thyroid diseases, 6.4% by osteoporosis, 5.7% by hepatic diseases, 5.7% by gastrointestinal diseases, 5.3% by chronic obstructive pulmonary disease, 5.1% by latent mycobacterium tuberculosis infection, 4.3% by mood disorders, 3.5% by neurologic diseases, and 2.1% by chronic kidney failure.

Secukinumab was given in the majority of patients (76.0%) at the dosage of 300 mg/monthly. This feature is mostly related due to the concomitant presence of plaque psoriasis and/or to the previous therapy with TNF inhibitors. The discontinuation of secukinumab due to inefficacy was recorded in 21.4% of patients, whereas 2.3% stopped the drug due to the occurrence of side effects. No life-threatening side effects were recorded; we did not register the new-onset or exacerbation of an inflammatory bowel disease in our cohort during the follow-up. Secukinumab was administered as first-line bDMARD therapy in 51.1% of patients, whereas in others after having failed at least one bDMARD. The most common prior administered bDMARDs were TNF inhibitors in 89.6% of patients, less frequently patients (10.4%) were previously treated with non-TNF inhibitors, namely ixekizumab, an IL-17A inhibitor, or ustekinumab, an IL-12/IL-23 inhibitor. In addition, 6.5% of patients were previously treated with apremilast, a PDE4 inhibitor. In patients treated with previous bDMARDs, secukinumab was given in 31.2% after having failed one bDMARD, whereas in others after 2 or more bDMARDs. Concomitant therapy with csDMARDs was registered in 37.4% of patients, the most common was MTX (71.8%). In our cohort, patients were less frequently treated with NSAIDs (29.3%) or GCs (16.1%).

Drug retention rate of secukinumab

A cumulative DRR of secukinumab of 57.0% was estimated with a mean time of administration of 21.5±17.1 months (median 18.0 [IQR 24] months) in our cohort of patients with PsA (Fig. 1). After that, we analysed the results of the DRR of secukinumab according to patient clinical characteristics. Male gender (p=0.843) and age ≥65 years (p=0.082) did not influence the DRR of secukinumab in our cohort. We also stratified the results of DRR of secukinumab for disease duration. Patients with disease duration ≥5 years (p=0.181) or with disease duration ≥10 years (p=0.223) did not show a reduced DRR of secukinumab than others (Fig. 2), respectively. The presence of comorbidities, considering any concomitant disorder, did not affect the DRR of secukinumab in our cohort (p=0.258) (Fig. 3). Conversely, in patients with cardiometabolic multimorbidity, a trend toward a better DRR of

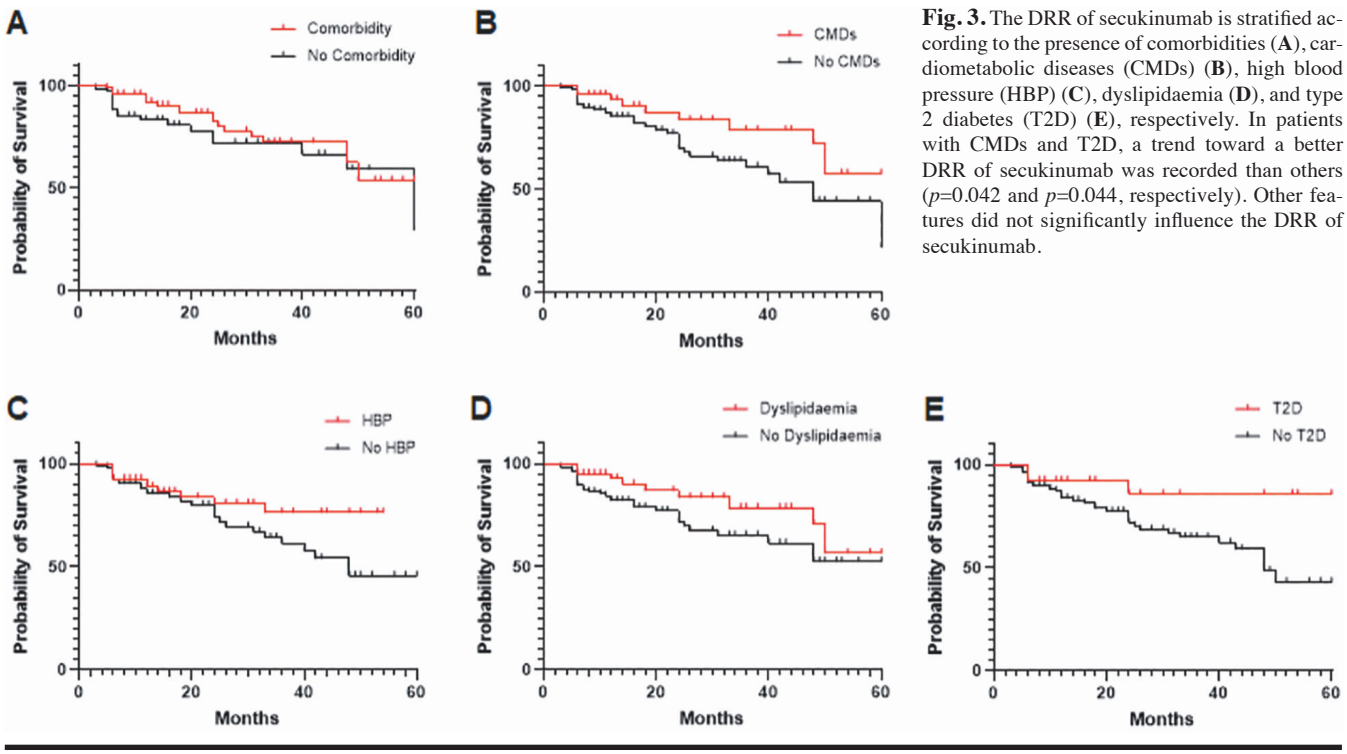

Fig. 3. The DRR of secukinumab is stratified according to the presence of comorbidities (**A**), cardiometabolic diseases (CMDs) (**B**), high blood pressure (HBP) (**C**), dyslipidaemia (**D**), and type 2 diabetes (T2D) (**E**), respectively. In patients with CMDs and T2D, a trend toward a better DRR of secukinumab was recorded than others (p=0.042 and p=0.044, respectively). Other features did not significantly influence the DRR of secukinumab.

secukinumab was recorded than others (p=0.042). In fact, in patients with HBP (p=0.062), dyslipidaemia (p=0.084), and T2D (p=0.044), a trend toward an improved DRR of secukinumab was observed when compared with those without these comorbidities. We also assessed the DRR of secukinumab according to the presence of obesity (Fig. 4). Patients characterised by a BMI ≥30 did not show a reduced DRR of secukinumab than others (p=0.747). Similarly, our analysis did not show a reduced DRR of secukinumab in patients characterised by a BMI ≥35 (p=0.905).

Finally, we stratified the results of the DRR according to drug features (Fig. 5). The different dosages of secukinumab did not influence the DRR of secukinumab over time, patients treated with 300 mg/monthly did not have a different DRR than those treated with 150 mg/monthly (p=0.098). Furthermore, patients treated with secukinumab as first-line bDMARD did not show a different DRR than those treated after having failed previous bDMARDs (p=0.923). In addition, the concomitant therapy with any csDMARD (p=0.417) or MTX (p=0.177) did not influence the DRR of secukinumab in our cohort.

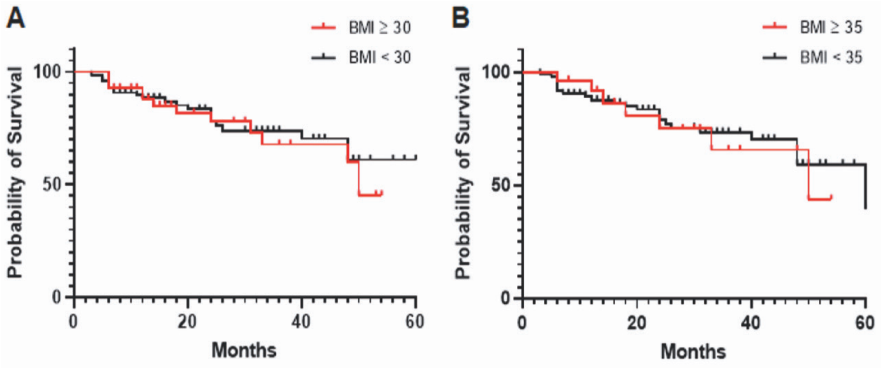

Fig. 4. The DRR of secukinumab is stratified according to BMI ≥30 (**A**), and BMI ≥35 (**B**), respectively. None of these features significantly influenced the DRR of secukinumab.

Discussion

In this study, we provided an assessment of the DRR of secukinumab in patients with PsA in a real-life multicentre cohort. We also showed that the presence of cardiometabolic multimorbidity could be associated with an improved DRR of secukinumab, whereas obesity did not affect this feature. Previous bDMARDs, concomitant csDMARDs, and different drug dosages could not influence the DRR of secukinumab over time.

In our cohort, a 60-month cumulative DRR of secukinumab of 57% was estimated with a mean duration of 21.5 months of drug administration. Although a longer follow-up of our analysis, this result may parallel previous experiences suggesting a good DRR over time of this drug in patients with PsA 26-31). Furthermore, a similar DRR comparing secukinumab and TNFis has been recently reported (27), although additional data are needed to entirely clarify this issue.

In our study, we also assessed the possible influence of demographic features on the DRR of secukinumab in patients with PsA. Paralleling with previous experiences (26-28), male gender did not appear to impact the DRR of this drug. However, in other works (29, 30), male gender was associated with a longer retention rate of secukinumab. These apparent conflicting findings could be

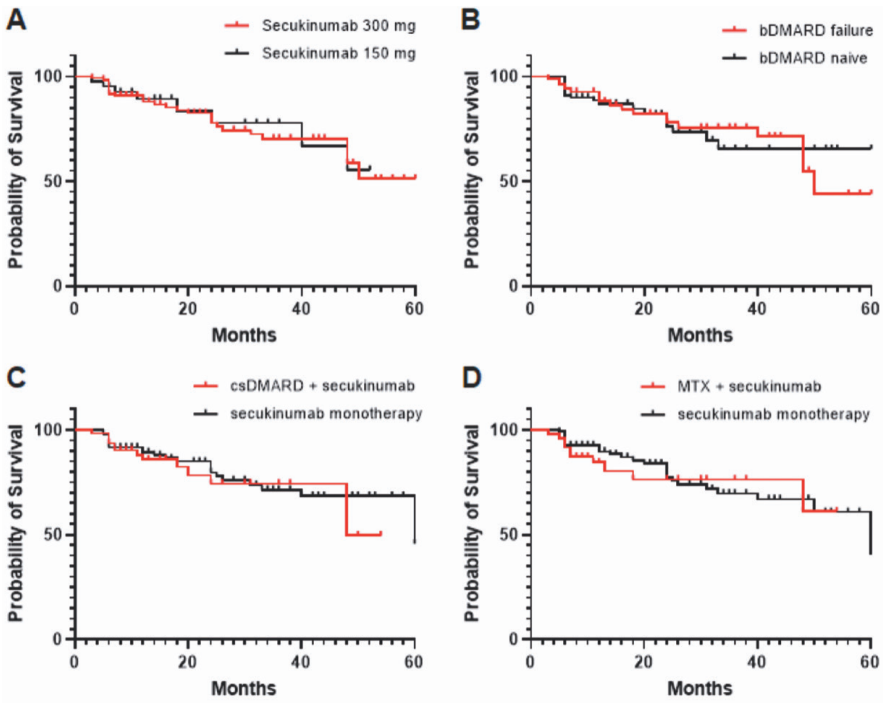

Fig. 5. The DRR of secukinumab is stratified according to drug dosages (**A**), line of bDMARD administration (**B**), combination therapy between conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) and secukinumab (**C**), and combination therapy between methotrexate (MTX) and secukinumab (**D**), respectively. None of these features significantly influenced the DRR of secukinumab.

related to different settings and diverse study designs. Therefore, the need of further studies is suggested to fully elucidate this finding according to possible gender-related differences in PsA (36). We also observed that older age of administration did not influence the DRR of secukinumab. This would be of importance since older age is usually associated with polypharmacy, consequently increasing the risk of iatrogenic effects, and making more difficult the treatment of these patients (37). The management of older patients could be furtherly complicated by frailty, a common aging-associated clinical syndrome characterised by an increased risk for poor health outcomes including disability, hospitalisation, and mortality (38).

In addition, we stratified the results of the DRR of secukinumab according to the presence of comorbidities in our cohort of patients. In fact, the clinical picture of PsA may be complicated by the presence of comorbidities which could make more difficult the management of these patients (6, 7). Independently from the main disease, patients with comorbidities may be at higher risk of complications and mortality as well as less responsive to therapy, in respect to patients with the same disease but without these conditions (39). Conversely, in our cohort, the presence of comorbidities, considering any concomitant disorder, did not influence the DRR of secukinumab. In addition, patients with cardiometabolic multimorbidity showed a trend toward a possible improved DRR of secukinumab. In fact, patients with HBP, dyslipidaemia, and T2D showed a longer DRR of secukinumab. In this context, IL-17A could play a central role in inflammation, endothelial dysfunction, insulin resistance, and the consequent cardiometabolic burden of patients with PsA (40-43). Consequently, paralleling with these observations, our study reported that patients with this cardiometabolic inflammatory profile, due to the presence of cardiometabolic multimorbidity, could have a better DRR of secukinumab. On these bases, IL-17A could have a central role in the pathogenesis of this clinical phenotype of patients with PsA and cardiometabolic multimorbidity. In addition, we also assessed our results according to the presence of obesity. Interestingly, the DRR of secukinumab appeared to be not influenced by values of BMI higher than 30 and 35, respectively. This finding would be of importance considering that obesity is associated with a poor prognosis PsA. In fact, obese patients may less frequently achieve a minimal disease activity, show a lower skin clearance rate, and more likely discontinue the administered therapies (44, 45). Therefore, as reported in a previous experience (30), obesity could not influence the DRR of secukinumab suggesting its clinical usefulness in these patients. Moreover, the effectiveness of secukinumab has been recently reported to be not influenced by BMI in patients with PsA (46).

In our cohort, we observed that previous bDMARDs, concomitant csDMARDs, and different drug dosages could not influence the DRR of secukinumab over time. Thus, these findings may support the effectiveness of secukinumab, which could be considered a valid option for monotherapy and in non-responder patients to previous bDMARDs. The latter could be also a feature of patients with a long disease. To date, the disease duration did not appear to influence the DRR of secukinumab in our cohort of patients with PsA. Taking together these observations, our result may mostly mirror previous experiences in this setting (26-31) reinforcing the idea that secukinumab could be a suitable therapeutic option in real-life settings.

Taking together all these results from our cohort, some key findings may be suggested about the DRR of secukinumab in patients with PsA. The persistence of treatment appeared to be not influenced by certain patient clinical characteristics, including male gender, older age, and disease duration. Furthermore, the presence of comorbidities, considering all possible concomitant disorders, and obesity did not reduce the DRR of secukinumab. In addition, a trend toward a better DRR of this drug was observed in patients with cardiometabolic multimorbidity. Finally, different dosages, diverse lines of treatment, and concomitant therapy with csDMARDs did not impact the DRR of secukinumab. Thus, the clini-

cal usability of secukinumab may be suggested in treating patients with PsA in a real-life setting.

Despite providing further insights in the DRR of secukinumab in patients with PsA, our study has some limitations which could reduce the validity of the results. The retrospective study design may indeed limit the generalisation of the data. Another limitation would be the lack of assessment of disease activity in our cohort. However, our study is aimed to assess the impact of patient characteristics and comorbidities on the DRR of secukinumab rather than its efficacy, which has been largely investigated and documented in randomised clinical trials and other real-life experiences (13-19, 26-31). Taking together these findings, further reports are needed to fully elucidate this topic and our data could provide the basis to arrange future confirmatory studies according to a more tailored management of these patients with PsA (47-49).

In conclusion, a cumulative 60-month DRR of secukinumab of 57.0% was retrieved in patients with PsA. The presence of cardiometabolic multimorbidity could be associated with an improved DRR of secukinumab, whereas obesity did not affect this feature in our cohort. Previous bDMARDs, concomitant csDMARDs, and different drug dosages could not influence the DRR of secukinumab over time. Although additional studies are needed to fully elucidate this issue, the clinical usability of secukinumab may be further suggested in the treatment of patients with PsA in real-life settings.

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