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ORIGINAL RESEARCH ARTICLE

Drug Survival of Interleukin (IL)-17 and IL-23 Inhibitors for the Treatment of Psoriasis: A Retrospective Multi-country, Multicentric Cohort Study

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Abstract

Background Drug survival, defined as the length of time from initiation to discontinuation of a given therapy, allows comparisons between drugs, helps to predict patient's likelihood of remaining on a specific treatment, and achieving the best decision for each patient in daily clinical practice.

Objective The aim of this study was to provide data on drug survival of secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab in a large international cohort, and to identify clinical predictors that might have an impact on the drug survival of these drugs.

Methods This was a retrospective, multicentric, multi-country study that provides data of adult patients with moderate to severe psoriasis who started treatment with an interleukin (IL)-17 or IL-23 inhibitor between 1 February 2015 and 31 October 2021. Data were collected from 19 distinct hospital and non-hospital-based dermatology centers from Canada, Czech Republic, Italy, Greece, Portugal, Spain, and Switzerland. Kaplan–Meier estimator and proportional hazard Cox regression models were used for drug survival analysis.

Results A total of 4866 treatment courses (4178 patients)—overall time of exposure of 9500 patient-years—were included in this study, with 3164 corresponding to an IL-17 inhibitor (secukinumab, ixekizumab, brodalumab) and 1702 corresponding to an IL-23 inhibitor (guselkumab, risankizumab, tildrakizumab). IL-23 inhibitors had the highest drug survival rates during the entire study period. After 24 months of treatment, the cumulative probabilities of drug survival were 0.92 (95% confidence interval [CI] 0.89–0.95) for risankizumab, 0.90 (95% CI 0.88–0.92) for guselkumab, 0.80 (95% CI 0.76–0.84) for brodalumab, 0.79 (95% CI 0.76–0.82) for ixekizumab, and 0.75 (95% CI 0.73–0.77) for secukinumab. At 36 months, only guselkumab [0.88 (95% CI 0.85–0.91)], ixekizumab [0.73 (95% CI 0.70–0.76)], and secukinumab [0.67 (95% CI 0.65–0.70)] had more than 40 patients at risk of drug discontinuation. Only two drugs had more than 40 patients at risk of drug discontinuation at 48 months, with ixekizumab demonstrating to have a higher cumulative probability of drug survival [0.71 (95% CI 0.68–0.75)] when compared with secukinumab [0.63 (95% CI 0.60–0.66)]. Secondary failure was the main cause for drug discontinuation. According to the final multivariable model, patients receiving risankizumab, guselkumab, and ixekizumab were significantly less likely to discontinue treatment than those receiving secukinumab. Previous exposure to biologic agents, absent family history of psoriasis, higher baseline body mass index (BMI), and higher baseline Psoriasis Area and Severity Index (PASI) were identified as predictors of drug discontinuation.

Conclusion The cumulative probability of drug survival of both IL-17 and IL-23 inhibitors was higher than 75% at 24 months, with risankizumab and guselkumab demonstrating to have overall cumulative probabilities ≥ 90%. Biological agent chosen, prior exposure to biologic agents, higher baseline BMI and PASI values, and absence of family history of psoriasis were identified as predictors for drug discontinuation. Risankizumab, guselkumab, and ixekizumab were less likely to be discontinued than secukinumab.

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Key Points

Drug survival analysis in the real-world integrates several relevant factors besides effectiveness or safety, such as physicians' drug management or patients' adherence to treatment or drug tolerability, and may provide guidance to clinicians in their daily clinical practice.

At 24 months of treatment, the interleukin (IL)-23 inhibitors guselkumab and risankizumab were the drugs with higher cumulative probability of drug survival (nearly 0.90).

Biologic drug chosen, previous exposure to biologics, baseline BMI and PASI score, and absent family history of psoriasis were all identified as predictors of drug discontinuation. Risankizumab, guselkumab, and ixekizumab were all less likely to be discontinued than secukinumab.

1 Introduction

The use of biologic therapy has revolutionized the management of several immune-mediated diseases, and psoriasis is a paradigmatic example [1]. Several biologic agents are now approved for the treatment of moderate-to-severe plaque psoriasis, including tumor necrosis factor (TNF)-α and interleukin (IL)-12/23 inhibitors, and, more recently, IL-17 and IL-23 selective blockers [1]. In the last decade, data from both clinical trials and real-world studies have supported and reinforced the important role of these drugs in the management of patients with moderate-to-severe psoriasis [1].

In a real-world setting, undesired drug discontinuation is a major concern to both clinicians and patients and a common reason for switching to a different biologic agent [2]. Lack or loss of effectiveness and development of treatment-emergent adverse events (AEs) are considered the main causes for treatment discontinuation [2], and drug survival, defined as the length of time from initiation to discontinuation of a given therapy, is an important measure that must be considered [3, 4]. In daily clinical practice, drug survival allows us to compare different drugs and the predictability for a patient to remain under a specific treatment, considering not only its effectiveness but also its safety and patients' tolerability and adherence [3, 4].

According to our previous study [5], the overall probability of patients receiving either IL-12/23, IL-17, or IL-23 inhibitors to remain under treatment for at least 12 months was > 85% and superior to that previously reported for TNFα inhibitors [5, 6]. In that study, the IL-23 inhibitors guselkumab and risankizumab in particular had the highest overall drug survival at the evaluated timepoints, in contrast to secukinumab, which had the lowest drug survival [5]. We found several predictors of drug discontinuation, including female sex, higher body mass index (BMI), previous exposure to biologic agents, and the chosen drug (higher probability of staying in treatment with guselkumab or risankizumab, and lower when starting secukinumab).

Currently, more real-world data on drug survival of biologic agents are required to sustain the already existent evidence so that more accurate clinical decisions can be made when managing patients with psoriasis. The goal of this cohort study is to provide real-world, international, large-scale data on drug survival of six biologic drugs among those most recently approved for moderate-to-severe psoriasis, i.e. secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab, and to identify and discuss clinical predictors that might influence drug survival. With such a strategy and design, we aim to provide a broader view of the global panorama on biologic agents' drug survival in the real-world to complement data from national registries of psoriasis.

2 Materials and Methods

This is an extension from a previous multicentric cohort study [5]. Apart from the longer period of follow-up with each drug, the main difference in the current analysis when compared with our previous publication was that data on patients receiving ustekinumab were not included. Instead, this real-world study focused on patients with moderate-to-severe chronic plaque psoriasis treated with an IL-17 inhibitor (secukinumab, ixekizumab, brodalumab) or an IL-23 inhibitor (guselkumab, risankizumab, tildrakizumab) between 1 February 2015 and 31 October 2021, either as first choice or as a switching option. This study provides an extended follow-up (our previous study ended on 31 December 2019) and updated clinical data for all the included drugs. Patients with other subtypes of psoriasis were excluded from the analysis. Data were collected from 19 distinct hospitals and non-hospital-based dermatology centers from Canada, Czech Republic, Italy, Greece, Portugal, Spain, and Switzerland. Patients who were switched to a new drug during the study period were included in the analysis of drug survival as new treatment courses, and all baseline variables were reassessed accordingly. All data were extracted from patients' records. The present study was conducted in accordance with the Declaration of Helsinki, initially published in 1964, on Ethical Principles for Medical Research Involving Human Subjects and after approval by the local ethical committees.

2.1 Baseline Data

At baseline, patients' demographic data, disease characteristics, and previous treatments, comorbidities, and family medical history were collected. These included age; sex; disease duration; severity and impact of the disease (through the Psoriasis Area and Severity Index [PASI], body surface area [BSA], and Dermatology Life Quality Index [DLQI]), presence of psoriatic arthritis (PsA) and its characteristics; previous therapies and prior biologic experience and reason for discontinuation; family history of psoriasis; weight, height and BMI; concomitant presence of other diseases such as hypertension, diabetes mellitus, dyslipidemia, inflammatory bowel disease, latent tuberculosis (any time), anxiety and/or depression, skin cancer or other neoplasms, hepatitis B or C; history of smoking; past cardiovascular diseases; and family history of cardiovascular diseases.

Patients who discontinued a drug and started another were included in the analysis as a new treatment course with reassessment of all baseline parameters.

2.2 Definition of Outcomes

Drug survival was defined as the period of time that a patient remains under a specific drug, from its initiation to the definitive discontinuation of treatment (due to loss of effectiveness, safety, patient decision, loss of follow-up, or others) or last clinical observation. Primary failure was defined as discontinuing the drug due to lack of effectiveness at the end of the induction phase defined for each drug, while secondary failure was defined as definitively discontinuing the drug due to loss of response during the maintenance phase.

2.3 Statistical Analysis

Descriptive statistics are presented as means with standard deviations (SD) for continuous variables and frequencies (*n*) with percentages for categorical variables. Variables were handled in their native form. Biological drug survival curves were estimated using the Kaplan–Meier method, and data were censored at the last visit. Proportional hazard Cox regression models were used for multivariable analysis. The proportional hazards assumption was assessed by graphical diagnosis before the analysis. The main outcome was the drug survival of patients exposed to different biological drugs (an IL-17 inhibitor, i.e. secukinumab, ixekizumab, brodalumab, or an IL-23 inhibitor, guselkumab, risankizumab, tildrakizumab). Both adjusted and unadjusted hazard ratios (HR) were used to summarize the differences between groups. The respective 95% confidence intervals (CIs) were also estimated. Multivariable analysis was performed after the identification of significant variables in the univariate analysis. The included predictors were the biologic agent chosen; age; sex; family history of psoriasis; disease duration; presence of PsA; presence of peripheral PsA; presence of comorbidities such as obesity, hypertension, dyslipidemia or diabetes; exposition to tobacco; previous exposure to systemic therapies; previous exposure to biologic therapies; number of previous biologic therapies; baseline BMI; and baseline PASI and BSA. As some of the factors were closely related, they were not concomitantly included in the final multivariable model.

Data were analyzed using IBM SPSS 26.0 for Windows (IBM Corporation, Armonk, NY, USA). A significance level of 0.05 was considered in all analyses.

3 Results

3.1 Baseline Characterization and Time of Exposure

A total of 4866 treatment courses from 4178 patients were considered in this analysis. From these, 3164 (65.0%) corresponded to patients receiving an IL-17 inhibitor [1542 (31.7%) patients were receiving secukinumab, 1073 (22.1%) were receiving ixekizumab, and 549 (11.3%) were receiving brodalumab], and 1702 (35.0%) corresponded to patients receiving an IL-23 inhibitor [879 (18.1%) patients were receiving guselkumab, 693 (14.2%) were receiving risankizumab, and 130 (2.7%) were receiving tildrakizumab]. The detailed data by treatment group are presented in Table 1. Regarding exposure in patient-years (py), the final values of our study were 4203 py for secukinumab, 2305 py for ixekizumab, 1445 py for guselkumab, 750 py for brodalumab, 696 py for risankizumab, and 101 py for tildrakizumab.

Patients were predominantly male (60.7%) with an overall mean age of 52.5 years (SD 14.3), a mean BMI of 27.9 kg/m^2 (SD 5.4), and a mean duration of disease of 18.0 years (SD 13.1). The mean baseline PASI and BSA values were 13.9 (SD 17.5) and 15.3 (SD 11.4), respectively. PsA was present in 1288 (26.5%) patients, and a higher proportion of these patients [1009 of 1288 (78.3%)] received an IL-17 inhibitor compared with 279 of 1288 (21.7%) patients who received an IL-23 inhibitor. A total of 154 (3.2%) patients were receiving methotrexate concomitantly with the biologic agent at the beginning of the treatment course. A higher proportion of patients receiving methotrexate in combination occurred in the secukinumab group (5.3%), while the lowest proportion was seen with tildrakizumab (0.8%) and brodalumab (0.9%).

A total of 2289 (47.0%) patients were biologic-naïve, with the lowest proportion occurring in the guselkumab group (39.6%), whereas tildrakizumab (53.8%) and secukinumab (52.5%) were the treatment groups with the highest proportion of biologic-naïve patients. Regarding biologic exposure, 25.0% of patients overall had been previously

Table 1 Study population baseline characterization: demographic data, disease characteristics, comorbidities, and previous treatments

	N	Total	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Tildrakizumab	Risankizumab
Total number of treatment series [*n* (%)]	4866	4866 (100.0)	1542 (31.7)	1073 (22.1)	549 (11.3)	879 (18.1)	130 (2.7)	693 (14.2)
Age, years [mean (SD)]	4866	52.5 (14.3)	53.2 (13.6)	52.7 (14.1)	52.1 (14.3)	52.8 (14.6)	52.6 (16.4)	50.5 (15.4)
Sex, male [*n* (%)]	4866	2952 (60.7)	941 (61.0)	662 (61.7)	343 (62.5)	506 (57.6)	78 (60.0)	422 (60.9)
Family history of PsO [*n* (%)][a]	4377	1252 (28.6)	414 (29.8)	219 (23.9)	152 (28.2)	230 (30.8)	41 (31.5)	196 (29.8)
Disease duration, years [mean (SD)]	4241	18.0 (13.1)	19.1 (13.3)	17.9 (13.2)	16.8 (12.8)	17.9 (12.9)	17.2 (13.3)	16.8 (12.8)
Baseline evaluation								
BMI [mean (SD)]	4790	27.9 (5.4)	27.8 (5.5)	27.9 (5.2)	28.2 (5.5)	28.2 (5.7)	27.2 (4.8)	27.9 (5.5)
Baseline PASI [mean (SD)]	4576	13.9 (7.5)	14.8 (7.7)	13.8 (8)	14.2 (6.9)	12.5 (6.9)	13 (6.9)	13.4 (7.6)
Baseline BSA [mean (SD)]	4117	15.3 (11.4)	16.5 (12)	15 (11)	16.2 (12)	13.8 (10.8)	12.8 (8.3)	15.2 (11.4)
Baseline MTX [*n* (%)]	4866	154 (3.2)	82 (5.3)	30 (2.8)	5 (0.9)	20 (2.3)	1 (0.8)	16 (2.3)
Baseline latent tuberculosis [*n* (%)]	4866	220 (4.5)	85 (5.5)	63 (5.9)	14 (2.6)	19 (2.2)	8 (6.2)	31 (4.5)
PsA [*n* (%)]	4866	1288 (26.5)	539 (35.0)	359 (33.5)	111 (20.2)	161 (18.3)	13 (10.0)	105 (15.1)
Peripheral [*n* (%)]		1116 (22.9)	465 (30.2)	310 (28.9)	102 (18.6)	132 (15.0)	13 (10.0)	94 (13.6)
Axial [*n* (%)]		265 (5.4)	121 (7.8)	89 (8.3)	13 (2.4)	28 (3.2)	2 (1.5)	12 (1.7)
Comorbidities [n (%)]								
Obesity	4866	1423 (29.2)	428 (27.8)	314 (29.3)	174 (31.7)	265 (30.1)	33 (25.4)	209 (30.2)
Hypertension	4866	1466 (30.1)	468 (30.4)	329 (30.7)	174 (31.7)	265 (30.1)	38 (29.2)	192 (27.7)
Diabetes	4866	689 (14.2)	226 (14.7)	163 (15.2)	71 (12.9)	121 (13.8)	19 (14.6)	89 (12.8)
Dyslipidemia	4866	1475 (30.3)	470 (30.5)	312 (29.1)	174 (31.7)	248 (28.2)	41 (31.5)	230 (33.2)
Previous CV disease	4866	319 (6.6)	100 (6.5)	54 (5.0)	43 (7.8)	57 (6.5)	11 (8.5)	54 (7.8)
Inflammatory bowel disease	4866	73 (1.6)	16 (1.0)	16 (1.5)	1 (0.2)	29 (3.3)	3 (2.3)	8 (1.2)
Smoking	4866							
No		3355 (68.9)	1062 (68.9)	746 (69.5)	379 (69.0)	594 (67.6)	96 (73.8)	480 (69.3)
Yes		1090 (22.5)	352 (22.8)	229 (21.4)	111 (20.3)	208 (23.7)	25 (19.3)	165 (23.8)
Former smoker		419 (8.6)	128 (8.3)	98 (9.1)	59 (10.7)	77 (8.7)	9 (6.9)	48 (6.9)
Hepatitis B	4866	112 (2.3)	40 (2.6)	32 (3.0)	6 (1.1)	14 (1.6)	5 (3.8)	15 (2.2)
Hepatitis C	4866	68 (1.4)	30 (1.9)	13 (1.2)	6 (1.1)	6 (0.7)	1 (0.8)	12 (1.7)
Latent tuberculosis (any time)	4866	470 (9.7)	161 (10.4)	120 (11.2)	46 (8.4)	66 (7.5)	10 (7.7)	67 (9.7)
Past therapies [n (%)]								
Naive to systemic therapy?	4866							
Yes		661 (13.6)	221 (14.3)	154 (14.4)	74 (13.5)	117 (13.3)	7 (5.4)	88 (12.7)
No. Which were used?								
Retinoids		1153 (23.7)	367 (23.8)	237 (22.1)	143 (26.0)	200 (22.8)	39 (30.0)	167 (24.1)
MTX		2371 (48.7)	774 (50.2)	537 (50.0)	236 (43.0)	384 (43.7)	76 (58.5)	364 (52.5)
CyA		1734 (35.6)	621 (40.3)	375 (34.9)	233 (42.4)	249 (28.3)	56 (43.1)	200 (28.9)
Phototherapy		1827 (37.5)	558 (36.2)	373 (34.8)	195 (35.5)	335 (38.1)	72 (55.4)	294 (42.4)
Apremilast		544 (11.2)	128 (8.3)	102 (9.5)	74 (13.5)	117 (13.3)	15 (11.5)	108 (15.6)
Fumarate		54 (1.1)	15 (1.0)	4 (0.4)	8 (1.5)	9 (1.0)	9 (6.9)	9 (1.3)

Table 1 (continued)

	N	Total	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Tildrakizumab	Risankizumab
Naive to biologic therapy?	4866							
Yes		2289 (47.0)	810 (52.5)	517 (48.2)	260 (47.4)	348 (39.6)	70 (53.8)	284 (41.0)
No. Which were used?								
Previous TNF inhibitor		1825 (37.5)	622 (40.3)	418 (39.0)	190 (34.6)	329 (37.4)	41 (31.5)	225 (32.5)
Adalimumab		1247 (25.6)	420 (27.2)	286 (26.7)	139 (25.3)	210 (23.9)	29 (22.3)	163 (23.5)
Etanercept		894 (18.4)	352 (22.8)	219 (20.4)	88 (16.0)	138 (15.7)	15 (11.5)	82 (11.8)
Infliximab		435 (8.9)	157 (10.2)	98 (9.1)	39 (7.1)	87 (9.9)	5 (3.8)	49 (7.1)
Previous IL-12/23 inhibitor (ustekinumab)		1041 (21.4)	300 (19.5)	220 (20.5)	96 (17.5)	260 (29.6)	13 (10.0)	152 (21.9)
Previous IL-17 inhibitor		865 (17.8)	31 (2.0)	225 (21.0	135 (24.6)	246 (28.0)	14 (10.8)	214 (30.9)
Secukinumab		642 (13.2)	0 (0.0)	214 (19.9)	99 (18.0)	171 (19.5)	12 (9.2)	146 (21.1)
Ixekizumab		290 (6.0)	28 (1.8)	0 (0.0)	54 (9.8)	115 (13.1)	3 (2.3)	90 (13.0)
Brodalumab		87 (1.8)	3 (0.2)	19 (1.8)	0 (0.0)	27 (3.1)	2 (1.5)	36 (5.2)
Previous IL-23 inhibitor		122 (2.5)	18 (1.2)	19 (1.8)	21 (3.8)	5 (0.6)	5 (3.8)	54 (7.8)
Guselkumab		91 (1.8)	14 (0.9)	13 (1.2)	15 (2.7)	0 (0.0)	0 (0.0)	49 (7.1)
Tildrakizumab		15 (0.3)	0 (0.0)	4 (0.4)	3 (0.5)	3 (0.3)	0 (0.0)	5 (0.7)
Risankizumab		20 (0.4)	4 (0.3)	3 (0.3)	6 (1.1)	2 (0.2)	5 (3.8)	0 (0.0)
Number of previous biologics [mean (SD)]	4866	0.99 (1.3)	0.8 (1.1)	1 (1.3)	1 (1.3)	1.2 (1.3)	0.7 (0.9)	1.1 (1.4)
Number of previous biologics [*n* (%)]	4866							
0		2289 (47.0)	810 (52.6)	517 (48.2)	260 (47.4)	348 (39.6)	70 (53.9)	284 (41.0)
1		1361 (28.0)	384 (24.9)	284 (26.5)	159 (29.0)	260 (29.6)	44 (33.8)	230 (33.2)
2 or 3		938 (19.3)	292 (18.9)	206 (19.2)	94 (17.1)	210 (23.9)	13 (10.0)	123 (17.7)
> 3		278 (5.7)	56 (3.6)	66 (6.1)	36 (6.5)	61 (6.9)	3 (2.3)	56 (8.1)

BMI body mass index, *BSA* body surface area, *CV* cardiovascular, *CyA* cyclosporin A, *IL* interleukin, *MTX* methotrexate, *PASI* Psoriasis Area Severity Index, *PsA* psoriatic arthritis, *PsO* psoriasis, *SD* standard deviation, *TNF* tumor necrosis factor

[a]Data are expressed as *n* [proportion of events compared with the total number of treatment series that have information regarding that issue (value presented as a percentage)]

exposed to at least two biologic agents; the corresponding percentages were highest (30.8%) for guselkumab and lowest for tildrakizumab (12.3%) and secukinumab (22.5%).

3.2 Causes of Drug Discontinuation and Events of Inadequate Response

A total of 908 (18.7%) treatment courses were discontinued throughout the study period. Detailed data on treatment discontinuation are presented in Table 2. Lack/loss of effectiveness (mainly secondary failure) was the major cause of drug discontinuation and occurred globally in 773 (15.9%) treatment courses. Only 1.3% of treatment courses were discontinued due to safety reasons, with infections being the most common cause.

When an inadequate response was verified, a decision to intensify the biologic therapy (updosing and/or shortening of the administration interval) was made in 295 (6.1%) treatment courses. This occurred in a higher proportion of treatment courses with secukinumab (7.4%) and guselkumab (7.4%), whereas tildrakizumab (1.5%) and brodalumab (2.4%) had the lowest rates. Another systemic therapy was added to biologic therapy in 300 (6.2%) treatment courses, with methotrexate being the most common. Combination therapy was more frequent in patients treated with secukinumab (9.1%) and less frequent with tildrakizumab (2.3%) and risankizumab (2.4%).

3.3 Safety

A total of 390 safety events were reported (Table 2). A total of 313 events corresponded to infections—an incidence rate of 32.9 infections per 1000 py of exposure (32.9/1000 py; 95% CI 29.5–36.7). The highest incidence rate of any infection event corresponded to secukinumab ($n = 160$, 38.1/1000 py; 95% CI 32.7–44.3), and these were numerically lower with tildrakizumab ($n = 2$, 19.8/1000 py, 95% CI 5.0–78.1), guselkumab ($n = 39$,

Table 2 Causes of discontinuation, therapy adjustments during treatment, and safety events

	Total [*n* = 4866] ToE: 9500 py	Secukinumab [*n* = 1542] ToE: 4203 py	Ixekizumab [*n* = 1073] ToE: 2305 py	Brodalumab [*n* = 549] ToE: 750 py	Guselkumab [*n* = 879] ToE: 1445 py	Tildrakizumab [*n* = 130] ToE: 101 py	Risankizumab [*n* = 693] ToE: 696 py
Causes of discontinuation [n (%)]							
Loss of efficacy	772 (15.9)	417 (27.0)	176 (16.4)	75 (13.7)	63 (7.2)	11 (8.5)	30 (4.3)
Primary failure	162 (3.3)	72 (4.7)	34 (3.2)	18 (3.3)	19 (2.2)	5 (3.8)	14 (2.0)
Secondary failure	610 (12.5)	345 (22.4)	142 (13.2)	57 (10.4)	44 (5.0)	6 (4.6)	16 (2.3)
Safety	65 (1.3)	34 (2.2)	20 (1.9)	6 (1.1)	3 (0.3)	0 (0.0)	2 (0.3)
Candida infection	14 (0.3)	6 (0.4)	6 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Infection by other agents	23 (0.5)	15 (1.0)	5 (0.5)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Inflammatory bowel disease	8 (0.2)	3 (0.2)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)
Malignancy	14 (0.3)	7 (0.5)	4 (0.4)	1 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)
Depression	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	5 (0.1)	3 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Loss of follow-up	37 (0.8)	20 (1.3)	8 (0.7)	4 (0.7)	2 (0.2)	1 (0.8)	2 (0.3)
Patient decision	34 (0.7)	20 (1.3)	6 (0.6)	3 (0.5)	4 (0.5)	0 (0.0)	1 (0.1)
Not specified	53 (1.0)	32 (2.0)	21 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	961 (19.7)	523 (31.8)	231 (21.5)	88 (16.0)	72 (8.2)	12 (9.2)	35 (5.1)
Therapy adjustments [n (%)]							
Biologic dose optimization	295 (6.1)	114 (7.4)	69 (6.4)	13 (2.4)	65 (7.4)	2 (1.5)	32 (4.6)
Combination with systemic therapy	300 (6.2)	140 (9.1)	64 (6.0)	32 (5.8)	44 (5.0)	3 (2.3)	17 (2.5)
Which therapy?							
MTX	195 (4.1)	101 (6.6)	41 (3.8)	19 (3.5)	25 (2.8)	1 (0.8)	8 (1.3)
CyA	28 (0.6)	12 (0.8)	2 (0.2)	7 (1.3)	4 (0.5)	0 (0.0)	3 (0.4)
Retinoid	31 (0.6)	10 (0.6)	7 (0.7)	5 (0.9)	7 (0.7)	1 (0.8)	1 (0.1)
Phototherapy	12 (0.2)	2 (0.1)	3 (0.3)	0 (0.0)	4 (0.5)	1 (0.8)	2 (0.3)
Apremilast	34 (0.7)	15 (1.0)	11 (1.0)	1 (0.2)	4 (0.5)	0 (0.0)	3 (0.4)
Safety events (n)							
Any infection	313	160	70	23	39	2	19
Any infection with hospitalization	38	17	8	4	8	0	1
Candida infection	112	60	29	13	8	0	2
MACE	14	8	3	1	1	0	1
Inflammatory bowel disease	6	2	1	1	1	0	1
Depression	45	21	8	1	11	1	3
Cancer	12	8	3	0	1	0	0
Total (*n*)	390	199	85	26	53	3	24

CyA cyclosporin A, *MACE* major adverse cardiovascular event, *MTX* methotrexate, *py* patient-years, *ToE* time of exposure

27.0/1000 py; 95% CI 19.8–36.8), and risankizumab (n = 19, 27.3/1000 py; 95% CI 17.5–42.5). Infections requiring hospitalization were rare (n = 38, 4.0/1000 py; 95% CI 2.9–5.5). *Candida* infections were mainly reported with IL-17 inhibitors [92 of 102 events (91.1%)].

3.4 Drug Survival, Model Development and Interaction Factors

All the detailed information on drug survival is provided in Table 3 and Fig. 1. At 12 months of treatment, IL-23 inhibitors had higher overall cumulative probability of drug survival. The ranking was similar when solely considering ineffectiveness as the reason for drug discontinuation. Secukinumab had the lowest cumulative probability of drug survival at 12 months when considering

Table 3 Cumulative probability of drug survival evaluation at different timepoints based on any reason for drug discontinuation and, in particular, ineffectiveness

	Secukinumab [*n* = 1542]	Ixekizumab [*n* = 1073]	Brodalumab [*n* = 549]	Guselkumab [*n* = 879]	Tildrakizumab [*n* = 130]	Risankizumab [*n* = 693]
N events observed due to all reasons	502	231	88	72	12	35
N events observed due to ineffectiveness	396	176	75	63	11	30
6 months						
Patients at risk, *n*	1395	934	454	743	94	510
DS (95% CI)—all reasons	0.92 (0.91–0.94)	0.93 (0.92–0.95)	0.91 (0.89–0.94)	0.97 (0.95–0.98)	0.91 (0.87–0.96)	0.98 (0.96–0.99)
Events, *n*	119	71	47	28	11	15
DS (95% CI)—ineffectiveness	0.94 (0.93–0.95)	0.95 (0.93–0.96)	0.92 (0.90–0.95)	0.97 (0.96–0.98)	0.92 (0.88–0.97)	0.98 (0.97–0.99)
Events, *n*	90	56	41	25	10	14
12 months						
Patients at risk, *n*	1224	765	341	573	41	301
DS (95% CI)—all reasons	0.85 (0.83–0.87)	0.87 (0.85–0.89)	0.86 (0.83–0.89)	0.94 (0.92–0.95)	0.90 (0.85–0.96)	0.95 (0.93–0.97)
Events, *n*	107	56	22	20	1	10
DS (95% CI)—ineffectiveness	0.88 (0.86–0.89)	0.90 (0.88–0.92)	0.89 (0.86–0.92)	0.94 (0.93–0.96)	0.91 (0.85–0.96)	0.95 (0.93–0.97)
Events, n	93	42	14	18	1	10
24 months						
Patients at risk, *n*	953	561	146	335	–	96
DS (95% CI)—all reasons	0.75 (0.73–0.77)	0.79 (0.76–0.82)	0.80 (0.76–0.84)	0.90 (0.88–0.92)	–	0.92 (0.89–0.95)
Events, *n*	130	66	18	18	–	6
DS (95% CI)—ineffectiveness	0.79 (0.77–0.81)	0.83 (0.81–0.86)	0.84 (0.81–0.88)	0.91 (0.89–0.93)	–	0.92 (0.89–0.95)
Events, *n*	112	51	14	15	–	6
36 months						
Patients at risk, *n*	651	327	–[a]	121	–	–[a]
DS (95% CI)—all reasons	0.67 (0.65–0.70)	0.73 (0.70–0.76)	–[a]	0.88 (0.85–0.91)	–	–[a]
Events, *n*	89	32	–[a]	5	–	–[a]
DS (95% CI)—ineffectiveness	0.72 (0.69–0.74)	0.78 (0.76–0.82)	–[a]	0.90 (0.87–0.92)	–	–[a]
Events, n	73	25	–[a]	4	–	–[a]
48 months						
Patients at risk, *n*	424	131	–	–[a]	–	–
DS (95% CI)—all reasons	0.63 (0.60–0.66)	0.71 (0.68–0.75)	–	–[a]	–	–
Events, *n*	36	6	–	–[a]	–	–
DS (95% CI)—ineffectiveness	0.68 (0.65–0.71)	0.78 (0.75–0.81)	–	–[a]	–	–
Events, *n*	28	2	–	–[a]	–	–

Log-rank test: $p < 0.001$

CI confidence interval, *DS* drug survival

[a]Data shown only when there were 40 or more patients at risk of drug discontinuation

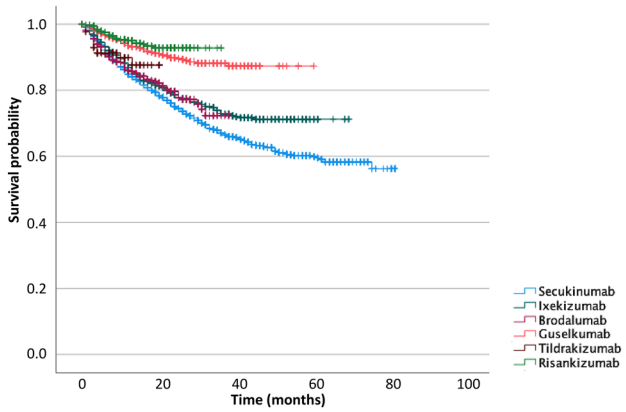

Fig. 1 Overall drug survival rates

both all reasons and ineffectiveness as causes of drug discontinuation.

At 24 months of treatment, all the IL-17 inhibitors had an overall cumulative probability of drug survival lower than 0.80, with the lowest corresponding to secukinumab (0.75, 95% CI 0.73–0.77). Patients receiving guselkumab or risankizumab remained with nearly 0.90 of cumulative probability of continuing with the drug when considering both all reasons and ineffectiveness as causes of drug discontinuation.

Guselkumab had the highest cumulative probability of drug survival when considering all reasons and solely ineffectiveness as the causes of drug discontinuation at 36 months, while secukinumab had the lowest. At 48 months of treatment, the cumulative probability of drug survival for ixekizumab was higher compared with secukinumab when considering both all reasons and ineffectiveness as causes of drug discontinuation.

In the univariable regression analysis, several potential predictive factors of drug discontinuation were found, i.e. the biologic agent chosen; age; family history of psoriasis; presence of PsA; presence of peripheral PsA; presence of comorbidities such as obesity, hypertension or diabetes; previous exposure to systemic therapies; previous exposure to biologic therapies; number of previous biologic therapies; baseline BMI; baseline PASI; and BSA (Table 4).

The final multivariable regression model included the biologic drug, patient's age, sex, family history of psoriasis, presence of PsA, hypertension, diabetes, number of previous biologic therapies, baseline PASI, and BMI (Table 4). When adjusted for the other variables, risankizumab (HR 0.291, 95% CI 0.196–0.433), guselkumab (HR 0.373, 95% CI 0.283–0.492), or ixekizumab (HR 0.728, 95% CI 0.608–0.872) were significantly less likely to be discontinued than secukinumab. Patients with a family history of psoriasis were less likely to discontinue treatment (HR 0.814, 95% CI 0.69–0.961) when compared with those who had not. Previous exposure to biologic agents was also identified as a significant predictor of drug discontinuation, and patients who had been exposed to a greater number of biological agents were at a higher risk of discontinuing the biologic agent; patients previously exposed to one biologic agent had an HR of discontinuation of 1.423 (95% CI 1.182–1.714), while those previously exposed to three or more biologic agents had an HR of discontinuation of 2.790 (95% CI 2.166–3.593). Baseline BMI (HR 1.016, 95% CI 1.002–1.029) and baseline PASI (HR 1.011, 95% CI 1.002–1.020) were also associated with a higher likelihood of drug discontinuation. The proportional hazards assumption was not violated for the models performed.

No interaction was found with the covariate weight (data not shown). Among biologic-experienced patients (data not shown), only guselkumab had a significantly lower hazard of drug discontinuation compared with secukinumab (HR 0.40, 95% CI 0.30–0.52).

4 Discussion

This multi-country, multicentric cohort study provides relevant data on drug survival for six biological drugs recently approved for the treatment of moderate-to-severe psoriasis, namely the IL-17 inhibitors secukinumab, ixekizumab, and brodalumab, and the IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab. This study analyzes one of the largest real-world study populations with data on drug survival, with a total of 4866 treatment courses and 9500 py of exposure. This study also includes large numbers of treatment courses with brodalumab and IL-23 inhibitors, including tildrakizumab. As in our prior publication [5], the main purpose of this study was to provide data on a crucial real-world measurement, drug survival, compounding multiple factors in addition to the effectiveness and safety of therapeutic agents [3, 4]. In a therapeutic scenario consisting of multiple options with great effectiveness and safety, this type of evidence aims to guide clinicians when selecting the best option for their patients in distinct settings.

The cumulative probability of drug survival for all the drugs in this study was 0.85 or superior 12 months after the start of treatment, either considering all causes for drug discontinuation [0.95 (95% CI 0.93–0.97) for risankizumab, 0.94 (95% CI 0.92–0.95) for guselkumab, 0.90 (95% CI 0.85–0.96) for tildrakizumab, 0.87 (95% CI 0.85–0.89) for ixekizumab, 0.86 (95% CI 0.83–0.89) for brodalumab, and 0.85 (95% CI 0.83–0.87) for secukinumab] or just ineffectiveness [0.95 (95% CI 0.93–0.97) for risankizumab, 0.94 (95% CI 0.93–0.96) for guselkumab, 0.91 (95% CI 0.85–0.96) for tildrakizumab, 0.90 (95% CI 0.88–0.92) for ixekizumab, 0.89 (95% CI 0.86–0.92) for brodalumab, and 0.88 (95% CI 0.86–0.89) for secukinumab].

Table 4 Univariable analysis and final multivariable prognostic model for overall drug survival

	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Treatment [ref: secukinumab]				
Ixekizumab	0.768 (0.657–0.898)	**0.001**	0.728 (0.608–0.872)	**0.001**
Brodalumab	0.835 (0.667–1.043)	0.112	0.804 (0.630–1.025)	0.078
Guselkumab	0.350 (0.273–0.449)	**< 0.001**	0.373 (0.283–0.492)	**< 0.001**
Tildrakizumab	0.773 (0.444–1.346)	0.363	0.857 (0.468–1.571)	0.618
Risankizumab	0.290 (0.202–0.416)	**< 0.001**	0.291 (0.196–0.433)	**< 0.001**
Age, years	1.007 (1.002–1.011)	**0.006**	1.003 (0.997–1.009)	0.320
Sex, male	0.898 (0.788–1.022)	0.104	0.885 (0.764–1.026)	0.105
Family history of PsO, yes	0.821 (0.703–0.958)	**0.013**	0.814 (0.690–0.961)	**0.015**
Disease duration, years	1.003 (0.998–1.008)	0.275		
Baseline BMI, kg/m^2	1.026 (1.015–1.037)	**< 0.001**	1.016 (1.002–1.029)	**0.020**
Baseline PASI	1.011 (1.002–1.013)	**0.008**	1.011 (1.002–1.020)	**0.013**
Baseline MTX	1.244 (0.910–1.701)	0.172		
PsA	1.392 (1.217–1.591)	**< 0.001**	1.029 (0.878–1.207)	0.723
Peripheral	1.461 (1.273–1.676)	**< 0.001**		
Axial	1.123 (0.869–1.450)	0.375		
Obesity	1.297 (1.134–1.484)	**< 0.001**		
Hypertension	1.159 (1.013–1.327)	**0.032**	0.984 (0.830–1.167)	0.854
Diabetes	1.279 (1.082–1.513)	**0.004**	1.052 (0.858–1.290)	0.624
Dyslipidemia	1.084 (0.945–1.244)	0.251		
Smoking [ref: no]				
Yes	1.128 (0.968–1.314)	0.123		
Ex smoker	1.063 (0.845–1.338)	0.601		
Naive to systemic therapy	0.546 (0.431–0.693)	**< 0.001**		
Naive to biologic therapy	0.602 (0.527–0.687)	**< 0.001**		
Previous TNF inhibitor	1.495 (1.316–1.699)	**< 0.001**		
Previous IL-12/23 inhibitor	1.680 (1.465–1.927)	**< 0.001**		
Previous IL-17 inhibitor	1.563 (1.336–1.828)	**< 0.001**		
Previous IL-23 inhibitor	1.539 (1.055–2.245)	**0.025**		
Number of previous biologics	1.231 (1.180–1.284)	**< 0.001**		
1			1.423 (1.182–1.714)	**< 0.001**
2 or 3			1.662 (1.370–2.015)	**< 0.001**
> 3			2.790 (2.166–3.593)	**< 0.001**

Bolded text indicates *p*-values inferior to 0.05

BMI body mass index, *CI* confidence interval, *HR* hazard ratio (of discontinuation), *IL* interleukin, *MTX* methotrexate, *PASI* Psoriasis Area Severity Index, *PsA* psoriatic arthritis, *PsO* psoriasis, *TNF* tumor necrosis factor

The 24-month timepoint appeared to be ideal for drug survival comparison between drugs, since 100 or more patients were at risk of drug discontinuation in all the treatment groups, except tildrakizumab. The higher cumulative probability of drug survival registered with risankizumab and guselkumab was sustained through the entire study period, reaching values of nearly 0.90 at 24 months when considering either all causes [0.92 (95% CI 0.89–0.95) for risankizumab, 0.90 (95% CI 0.88–0.92) for guselkumab] or ineffectiveness [0.92 (95% CI 0.89–0.95) for risankizumab, 0.91 (95% CI 0.89–0.93) for guselkumab] as the reason for drug discontinuation. This pattern was consistent with our previous findings [5]. In fact, in our previous study [5], we suggested that the superiority of IL-23 inhibitors was probably related to their greater effectiveness and safety in head-to-head trials, but also perhaps because of potential mechanistic effects on tissue resident memory cells and T-regulatory cells [7]. Since only selective IL-17 and IL-23 inhibitors were included in this study, the drug dosage schedule—longer time between administrations with IL-23 inhibitors compared with IL-17 inhibitors—might have influenced

treatment adherence and contributed to the higher drug survival rates observed with IL-23 inhibitors.

Regarding IL-17 inhibitors, our data demonstrated that both brodalumab and ixekizumab had higher overall cumulative probability of drug survival than secukinumab, at 12 months [0.87 (95% CI 0.85–0.89) for ixekizumab, 0.86 (95% CI 0.83–0.89) for brodalumab, and 0.85 (95% CI 0.83–0.87) for secukinumab] and 24 months [0.80 (95% CI 0.76–0.84) for brodalumab, 0.79 (95% CI 0.76–0.82) for ixekizumab, and 0.75 (95% CI 0.73–0.77) for secukinumab]. These differences might be related to differing affinities for the corresponding molecular targets and mechanisms of action. Ixekizumab binding affinity to IL-17A and the IL-17A/F heterodimer is higher than that of secukinumab [8, 9], whereas brodalumab inhibits the IL-17 receptor A subunit, impeding signaling of IL-17F, IL-17C, and IL-17E, in addition to IL-17A and the heterodimer IL-17A/F [10].

At 36 months of treatment, only guselkumab, ixekizumab, and secukinumab had more than 40 patients at risk for drug discontinuation. Only secukinumab and ixekizumab met that criterion at 48 months of treatment. Guselkumab and ixekizumab were the drugs with higher overall cumulative probability of drug survival at 36 months [0.88 (95% CI 0.85–0.91) for guselkumab, 0.73 (95% CI 0.70–0.76) for ixekizumab, 0.67 (95% CI 0.65–0.70) for secukinumab] and 48 months [0.71 (95% CI 0.68–0.75) for ixekizumab, 0.63 (95% CI 0.60–0.66) for secukinumab], respectively.

The greater overall cumulative probability of drug survival of IL-23 inhibitors, compared with that registered with IL-17 inhibitors and with previously published data on TNFα inhibitors or the IL-12/23 inhibitor ustekinumab, is consistent with the results of our previous study and comparable studies [5, 11–13]. On one hand, the better efficacy and safety results of IL-23 inhibitors over IL-17 inhibitors in comparative studies might justify the longer persistence with those drugs, which culminates in a higher cumulative probability of drug survival with IL-23 inhibitors [5]. On the other hand, according to the data of patients who received either guselkumab or secukinumab, the higher overall cumulative probability of drug survival of IL-23 inhibitors when compared with IL-17 inhibitors might also be justified by the greater reduction in the levels of tissue resident memory cells and T-regulatory cells with the former ones [14].

New relevant data have been published since our previous publication, but real-world evidence on drug survival of risankizumab and tildrakizumab is still limited [15–19]. The number of treatment courses included in those studies is rather limited, with fewer than 100 patients for treatment group in many instances. At 12 months of treatment, the overall drug survival observed in those studies ranged between 72.3% and 90% for secukinumab [15–19] and 75.9% and nearly 90% for ixekizumab [15–19], and > 85% for guselkumab [15, 17, 18]. Data on drug survival at 24 months were particularly limited by the number of patients, even in those who received IL-17 inhibitors, making any comparison with our study difficult.

The analysis of causes for drug discontinuation demonstrated that safety events led to treatment withdrawal in a limited number of treatment courses, i.e. only 1.3%. This finding confirms the excellent safety profile of newer biologic treatments in patients with moderate-to-severe plaque psoriasis. On the other hand, the leading cause for drug discontinuation was secondary failure in a total of 610 (12.5%) treatment courses. Differences among treatments in rates of secondary failure might be accounted for in part by the sequence of introduction into the market, with newer drugs being used for switching in patients with prior exposure/failure to multiple biologics, who are more likely to discontinue treatment.

Regarding predictors of drug discontinuation, the initial choice of biologic plays an important role. Patients treated with ixekizumab, guselkumab, or risankizumab had a lower hazard of drug discontinuation when compared with those treated with secukinumab. Previous treatments also interfered with drug survival; drug discontinuation was more likely in patients with increasing numbers of prior biologic treatments compared with biologic-naïve patients. Among biologic-experienced patients, the risk of discontinuation with guselkumab was significantly lower than with secukinumab. As mentioned in our previous study, all these findings highlight the importance of identifying and selecting the best treatment for each patient ab initio. On the other hand, failure in achieving therapeutic goals by prior biological treatment does not jeopardize the ability of other drugs to obtain those goals.

We also found that increasing baseline BMI was associated with a greater hazard of drug discontinuation, corroborating the results from our previous study. High BMI appears to be an important independent risk factor for drug withdrawal, being associated with a higher number of AEs and with lower treatment effectiveness, and ultimately impacting drug survival [20, 21]. Increasing baseline PASI and no family history of psoriasis were also associated with a higher hazard of drug discontinuation.

Regarding therapy adjustments during treatment, 6.2% of all patients combined a biological agent with another systemic therapy, which was mainly methotrexate (4.0%). While 9.1% of patients receiving secukinumab received another systemic therapy during treatment (methotrexate in 6.5% of patients), < 5.0% of patients treated with an IL-23 inhibitor received combination therapy. This might be explained by the greater proportion of patients with PsA starting treatment with IL-17 inhibitors, or perhaps their slightly lower effectiveness compared with IL-23 inhibitors, driving combination therapy to prevent a therapeutic switch [22].

Regarding baseline characterization, a higher proportion of patients receiving any of the IL-17 inhibitors had PsA when compared with those receiving IL-23 inhibitors. Furthermore, a higher proportion of patients receiving secukinumab and ixekizumab, compared with all IL-23 inhibitors, started treatment concomitantly with methotrexate. These two findings are possibly related to the fact that IL-17 inhibitors were approved for PsA before IL-23 inhibitors.

It is also important to highlight that IL-23 inhibitors, namely guselkumab and risankizumab, had the highest proportion of biologic-experienced patients. As previously mentioned, a possible explanation for these findings is the fact that these drugs were approved for moderate-to-severe plaque psoriasis a few years after the IL-17 inhibitors secukinumab and ixekizumab. Although previous exposure to biologics is recognized as a negative factor impacting on the effectiveness of further treatments, our drug survival analysis demonstrates that guselkumab and risankizumab were able to surpass this limitation. When we further analyze this biologic experience, some key points must be mentioned. First, about 30% of patients receiving guselkumab and 21% receiving risankizumab had been previously exposed to ustekinumab. This allows us to hypothesize that a more selective IL-23 inhibition is a successful option even when IL-12/23 inhibition is not able to control the disease. Second, as 21.0% of patients receiving ixekizumab and 24.6% of patients receiving brodalumab were previously exposed to an IL-17 inhibitor, we can infer dermatologists assume that different mechanisms of inhibition or binding affinity for the same cytokine may produce distinct final outcomes. Third, almost 50% of biologic-experienced patients in the guselkumab and risankizumab groups had been previously treated with an IL-17 inhibitor, which suggests these drugs were used as salvage therapy following the failure of IL-17 inhibitors. Lastly, about 10% of patients receiving risankizumab had been previously exposed to another IL-23 inhibitor, which suggests the dermatologists' confidence on the most recently introduced drug, even when treatment goals have not been met with other biologics of the same class.

Real-world studies are associated with several potential sources of bias, such as information bias (e.g. misclassification of data), selection bias (e.g. different clinicians might decide for different therapeutic options according to distinct patient or disease characteristics), recall bias (e.g. selective recall of impactful events by patients or closer family/friends), or detection bias (e.g. certain types of events are more likely to be detected in some treatment groups when compared with others). Despite our efforts of surpassing some of these potential sources of bias with a uniformized and easy-to-fill registry system for each clinician involved in our study, some were unable to be addressed.

As in our previous publication [5], this study has some limitations that should be addressed. First, its retrospective nature, depending on the quality of the available recorded data, and second, the biological agents included in the study were approved at different timepoints. The most recently approved drugs purportedly have superior effectiveness and safety and this may have interfered with the prescribers' threshold in switching medications along the study period. The importance of considering the time-dependent availability of drugs when analyzing and comparing drug survival rates has been subject to recent discussion [19]. Third, as subjects were not randomized to receive different biologic agents, selection bias is likely. In addition, the broad multicentric and multinational nature of our study not only improves the generalizability of its results but also introduces heterogeneity, and dermatologists with different backgrounds might have different thresholds for biologic discontinuation considering adverse effects, effectiveness, or other factors. In addition, patients' needs and their levels of adherence to treatments might also differ among countries, or even within the same country, and this may ultimately affect drug survival. Finally, we have to highlight that the tildrakizumab group had a small sample size and future studies are needed to reinforce our conclusions.

5 Conclusion

Guselkumab and risankizumab were associated with the highest cumulative probabilities of drug survival at months 6, 12, and 24. Guselkumab cumulative probability of drug survival registered at month 36 was higher than was seen with the IL-17 inhibitors secukinumab and ixekizumab. Initial choice of biologic drug, absence of family history of psoriasis, previous exposure to biologics, baseline BMI, and baseline PASI were all identified as predictors of drug discontinuation. Risankizumab, guselkumab, and ixekizumab were less likely to be discontinued when compared with secukinumab.

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Declarations

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Conflict of interest Tiago Torres has received honoraria for acting as a consultant and/or speaker for AbbVie, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, and Novartis. Luis Puig has received honoraria for acting as a consultant and/or speaker for AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, LeoPharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi, and UCB. Ron Vender has received grants/research support from, and/or acted as a speak-

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Paulo Ferreira has received honoraria for acting as a consultant and/or speaker for AbbVie, Janssen, LEO Pharma, Eli-Lilly, Novartis, and Pfizer. Pedro Mendes-Bastos has received honoraria for acting as a consultant and/or speaker for AbbVie, Pfizer, Janssen, LEO Pharma, Novartis, Sanofi, Teva, Bayer, and L'Oreal. Esteban Dauden has been an advisory board member and consultant, participated in clinical trials, and received grants, research support, and honorarium for speaking from AbbVie/Abbott, Almirall, Amgen-Celgene, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, MSD-Schering-Plough, Lilly, UCB, Bristol Myers, and Boehringer Ingelheim. Elena del Alcazar-Viladomiu has participated as an SI and/or invited speaker for AbbVie, Janssen, Novartis, Lilly, Leo Pharma, Almirall, Amgen, UCB, and Sanofi. Eva Vilarrasa Rull has received honoraria for acting as a consultant and/or speaker for AbbVie, Almirall, Boehringer, Celgene, Janssen, Leo Pharma, Eli Lilly, MSD, Novartis, Pfizer, and UCB. 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Ethics The present study was conducted in accordance with the Declaration of Helsinki (initially published in 1964) on Ethical Principles for Medical Research Involving Human Subjects and after approval by the local ethical committees.

Consent to participate Informed consent was waived due to the study's retrospective design. Data were properly anonymized before the analysis.

Consent for publication Not applicable.

Availability of data and materials Not applicable.

Code availability Not applicable.

Author contributions TT and AC contributed to the study conception and design. TT, LP, LT, MN and AC conducted the statistical analyses on the data. All authors participated in data collection and interpretation of the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the article.

References

1. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA. 2020;323(19):1945–60. https://doi.org/10.1001/JAMA.2020.4006.
2. Tsai Y-C, Tsai T-F. Switching biologics in psoriasis—practical guidance and evidence to support. Expert Rev Clin Pharmacol. 2020;13(5):493–503. https://doi.org/10.1080/17512433.2020.1767590.
3. Costanzo A, Malara G, Pelucchi C, et al. Effectiveness end points in real-world studies on biological therapies in psoriasis: systematic review with focus on drug survival. Dermatology. 2018;234(1–2):1–12. https://doi.org/10.1159/000488586.
4. van den Reek JMPA, Kievit W, Gniadecki R, et al. Drug survival studies in dermatology: principles, purposes, and pitfalls. J Investig Dermatol. 2015;135(7):1–5. https://doi.org/10.1038/JID.2015.171.
5. Torres T, Puig L, Vender R, et al. Drug survival of IL-12/23, IL-17 and IL-23 inhibitors for psoriasis treatment: a retrospective multi-country, multicentric cohort study. Am J Clin Dermatol. 2021;22(4):567–79. https://doi.org/10.1007/S40257-021-00598-4.
6. Mourad AI, Gniadecki R. Biologic drug survival in psoriasis: a systematic review & comparative meta-analysis. Front Med. 2021;7: 625755. https://doi.org/10.3389/FMED.2020.625755.
7. Mehta H, Mashiko S, Angsana J, et al. Differential changes in inflammatory mononuclear phagocyte and T-cell profiles within

psoriatic skin during treatment with guselkumab vs secukinumab. J Investig Dermatol. 2021;141(7):1707-1718.e9. https://doi.org/10.1016/J.JID.2021.01.005.
8. Azevedo A, Torres T. The successful treatment with ixekizumab in a multi-failure psoriasis patient. Dermatol Online J. 2018;24(9):13030/qt2qn1p4bz. https://doi.org/10.5070/D3249041420.
9. Liu L, Lu J, Allan B, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. J Inflamm Res. 2016;9:39–50. https://doi.org/10.2147/JIR.S100940.
10. Foulkes A, Warren R. Brodalumab in psoriasis: evidence to date and clinical potential. Drugs Context. 2019;8: 212570. https://doi.org/10.7573/DIC.212570.
11. Yiu ZZN, Mason KJ, Hampton PJ, et al. Drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). Br J Dermatol. 2020;183(2):294–302. https://doi.org/10.1111/BJD.18981.
12. Lin P-T, Wang S-H, Chi C-C. Drug survival of biologics in treating psoriasis: a meta-analysis of real-world evidence. Sci Rep. 2018;8(1):16068. https://doi.org/10.1038/S41598-018-34293-Y.
13. Augustin M, Jullien D, Martin A, Peralta C. Real-world evidence of secukinumab in psoriasis treatment—a meta-analysis of 43 studies. J Eur Acad Dermatol Venereol. 2020;34(6):1174–85. https://doi.org/10.1111/JDV.16180.
14. López-Sánchez C, Puig L. Guselkumab in the treatment of moderate-to-severe plaque psoriasis. Immunotherapy. 2020;12:355–71. https://doi.org/10.2217/imt-2020-0040.
15. Gooderham MJ, Lynde C, Turchin I, Avadisian M, Labelle M, Papp KA. Real-world, long-term treatment patterns of commonly used biologics in Canadian patients with moderate-to-severe chronic plaque psoriasis. J Dermatol. 2022;49(1):95–105. https://doi.org/10.1111/1346-8138.16214.
16. Schmitt-Egenolf M, Freilich J, Stelmaszuk-Zadykowicz NM, Apol E, Hansen JB, Levin LÅ. Drug persistence of biologic treatments in psoriasis: a Swedish National Population Study. Dermatol Ther. 2021;11(6):2107–21. https://doi.org/10.1007/S13555-021-00616-7.
17. Iznardo H, Vilarrasa E, López-Ferrer A, Puig L. Real-world drug survival of guselkumab, ixekizumab and secukinumab for psoriasis. Br J Dermatol. 2021;185(3):660–2. https://doi.org/10.1111/BJD.20416.
18. Dapavo P, Siliquini N, Mastorino L, et al. Efficacy, safety, and drug survival of IL-23, IL-17, and TNF-alpha inhibitors for psoriasis treatment: a retrospective study. J Dermatol Treat. 2021;13:1–6. https://doi.org/10.1080/09546634.2021.1961998.
19. Graier T, Salmhofer W, Jonak C, et al. Biologic drug survival rates in the era of anti-interleukin-17 antibodies: a time-period-adjusted registry analysis. Br J Dermatol. 2021;184(6):1094–105. https://doi.org/10.1111/BJD.19701.
20. Mourad A, Straube S, Armijo-Olivo S, Gniadecki R. Factors predicting persistence of biologic drugs in psoriasis: a systematic review and meta-analysis. Br J Dermatol. 2019;181(3):450–8. https://doi.org/10.1111/BJD.17738.
21. Carrascosa JM, Vilavella M, Garcia-Doval I, et al. Body mass index in patients with moderate-to-severe psoriasis in Spain and its impact as an independent risk factor for therapy withdrawal: results of the Biobadaderm Registry. J Eur Acad Dermatol Venereol. 2014;28(7):907–14. https://doi.org/10.1111/JDV.12208.
22. Gisondi P, Geat D, Pizzolato M, Girolomoni G. State of the art and pharmacological pipeline of biologics for chronic plaque psoriasis. Curr Opin Pharmacol. 2019;46:90–9. https://doi.org/10.1016/J.COPH.2019.05.007.

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