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ORIGINAL RESEARCH ARTICLE

Drug Survival of IL-12/23, IL-17 and IL-23 Inhibitors for Psoriasis Treatment: A Retrospective Multi-Country, Multicentric Cohort Study

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Abstract

Background Drug survival analysis of biologic agents in psoriasis is of extreme importance, as it allows not only the evaluation of objective clinical outcomes (such as effectiveness and safety) but also of factors that are associated with patients' adherence to treatment. The aim of this study was to evaluate and compare the drug survival of the most recent biologic agents approved for the treatment of moderate-to-severe psoriasis—ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and risankizumab—and to identify clinical predictors that can influence the drug survival of these drugs.

Methods This retrospective multicentric cohort study from 16 dermatology centers in Portugal, Spain, Italy, Switzerland, Czech Republic, Canada, and the United States included patients that started IL-12/23, IL-17 (IL-17A and IL-17R) and IL-23 inhibitors for the treatment of psoriasis between January 1, 2012 and December 31, 2019. Survival analysis was performed using a Kaplan-Meier estimator, to obtain descriptive survival curves, and proportional hazard Cox regression models.

Results A total of 3312 treatment courses (total patients: 3145) were included in the study; 1118 (33.8%) with an IL-12/23 inhibitor (ustekinumab), 1678 (50.7%) with an IL-17 inhibitor [911 (27.5%) on secukinumab, 651 (19.7%) on ixekizumab, 116 (3.5%) on brodalumab], and 516 (15.5%) with an IL-23 inhibitor [398 (12.0%) on guselkumab, 118 (3.5%) on risankizumab]. At 18 months, the cumulative probability of survival was 96.4% for risankizumab, 91.1% for guselkumab, 86.3% for brodalumab, 86.1% for ustekinumab, 82.0% for ixekizumab, and 79.9% for secukinumab. Using ustekinumab as reference, drug survival of guselkumab was higher (HR 0.609; 95% CI 0.418–0.887) and that of secukinumab was lower (HR 1.490; 95% CI 1.257–1.766). In the final multivariable model, secukinumab, female sex, higher BMI, and prior exposure to biologic agents significantly increased the risk of drug discontinuation, whereas risankizumab was protective.

Conclusion In this multinational cohort with 8439 patient-years of follow-up, the cumulative probability of drug survival for all drugs was >79% at 18 months. Prescribed biologic, female sex, higher BMI, and previous exposure to biologic agents were predictors of drug discontinuation. Drug survival of guselkumab and risankizumab was higher than that of ustekinumab, and secukinumab was lower.

1 Introduction

Psoriasis is an inflammatory, immune-mediated skin disease. Knowledge on the pathogenesis of psoriasis has markedly increased in recent years and led to a dramatic expansion in the psoriasis armamentarium [1, 2]. Due to their high efficacy and safety, biologic drugs have changed treatment expectations and goals for moderate-to-severe psoriasis [2]. However, discontinuation of ongoing treatment due to loss/lack of response, or the development of adverse events (AEs) is a frequent occurrence, often requiring a change in biologic agents [3].

Drug survival is defined as the duration of time a patient remains under a specific therapy, from the day of the first administration to the point in time when the treatment is discontinued [4]. Drug survival is an important measure of therapeutic success, not only because it embraces objective

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Key Points

Drug survival is determined by multiple factors, including therapeutic effectiveness, safety, drug availability, patient profiling and prescription patterns.

Current real-world drug survival data for biologics used in psoriasis provides clinically relevant information.

Current biologic therapy, female sex, higher BMI and previous exposure to biologic agents seem to be predictors of drug discontinuation. Drug survival of guselkumab and risankizumab was higher than that of ustekinumab, and secukinumab was lower.

clinical outcomes (such as effectiveness and safety) but also because it enables the analysis of other meaningful factors that are associated with both physician's drug management (i.e., rescue therapy) and patient's adherence to treatment, including minor adverse events and tolerability [5, 6]. Drug survival analysis of biologic agents in psoriasis is important, not only because it allows the identification of drugs that have the longest drug survival rate, but also because it can identify the clinical variables that may predict the most durable treatment for each patient [6].

The results from clinical trials are extremely important to guide dermatologists in their clinical practice, but clinical research conditions and inclusion criteria are not representative of the real-world setting. For this reason, it is crucial to provide updated data from patients in real-world practice [7, 8]. Several studies over the last decade have provided vital information about drug survival and predictors of biologic agents' persistence as treatment of moderate-to-severe psoriasis. However, the available data, mostly from national registries, is focused on inhibitors of tumor necrosis factor (TNF)-α (adalimumab, infliximab, etanercept), interleukin (IL)-12/23 (ustekinumab) and some IL-17 inhibitors (secukinumab, ixekizumab) [9–12]. With the growing importance of more recently approved biologic agents for the treatment of moderate-to-severe psoriasis, such as another IL-17 inhibitor (brodalumab) and the IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab), it is essential to obtain updated data on these drugs' survival profile. To our knowledge, no large-scale studies including data from these new drugs have been published yet.

The objective of this study, developed across several countries, is to provide large, multicentric data on drug survival from the most recent biologic agents approved for the treatment of moderate-to-severe psoriasis—ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and risankizumab—and to identify clinical predictors that can influence the drug survival of these drugs.

2 Materials and Methods

This retrospective cohort study was designed to compare the drug survival of different biologic agents for the treatment of moderate-to-severe chronic plaque psoriasis, and to identify clinical predictors of drug survival. It included treatment courses of patients that started treatment with an IL-12/23 inhibitor (ustekinumab), an IL-17 inhibitor (secukinumab, ixekizumab, brodalumab), or an IL-23 inhibitor (guselkumab, risankizumab) for the treatment of psoriasis between January 1, 2012 and December 31, 2019, in 16 specialized hospital and non-hospital-based dermatology centers in the treatment of psoriasis from Portugal, Spain, Italy, Switzerland, Czech Republic, Canada, and the United States. Whenever the patient started a new treatment, all data were reassessed and reintroduced. Tildrakizumab was excluded due to an extremely low number of treatment courses.

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; gender; disease duration; severity and impact of the disease (through 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 body mass index (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. All data was extracted from patients' records.

2.2 Definition of Outcomes

Drug survival was defined as the duration of time a patient remains under a specific therapy—from initiation to definitive discontinuation of treatment (due to loss of efficacy, safety, patient decision, loss of follow-up, or other) or last clinical observation. Primary failure was defined as stopping the drug due to lack of efficacy at the end of the induction phase for each drug; 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 given as frequencies (n) associated with percentages for categorical variables and means with standard deviations (SD) for continuous variables. Survival analysis was performed using a Kaplan-Meier estimator, to obtain descriptive survival curves, and proportional hazard Cox regression models. The selected biologic drug, gender, BMI, PsA, diabetes, naïve to systemic therapies, and naïve to biologic therapies were included as covariates in the adjusted model. Data were analyzed using IBM SPSS 26.0 for Windows. A significance level of 0.05 was considered in all analyses.

3 Results

3.1 Baseline Characterization

A total of 3312 treatment courses (total patients: 3145) were included in the study (US and Canada 37.6%, Italy 26.4%, Portugal 16.1%, Spain 15.1%, Czech Republic 2.7%, Switzerland 2%), 1118 (33.8%) with an IL-12/23 inhibitor (ustekinumab), 1678 (50.7%) with an IL-17 inhibitor (911 [27.5%] on secukinumab, 651 [19.7%] on ixekizumab, 116 [3.5%] on brodalumab), and 516 (15.5%) with an IL-23 inhibitor (398 [12.0%] on guselkumab, 118 [3.5%] on risankizumab).

The overall mean age of patients was 49.0 years (SD 14.1) and 61.5% were male. The mean BMI was 28.3 kg/m^2 (SD 5.7). The mean duration of the disease was 21.2 years (SD 13.0), and 959 of 2755 (34.8%) patients had PsA. The mean baseline values of PASI, BSA, and DLQI were 13.8 (SD 8.0), 16.3% (SD 12.9%), and 14.2 (SD 5.7), respectively. PsA was more prevalent in patients treated with ixekizumab (43.0%) and secukinumab (41.8%) than in patients treated with ustekinumab (27.3%) and guselkumab (27.1%).

Patients were biologic-naïve at the start of treatment in 1533 out of 3312 (46.3%) courses. This proportion was highest with ustekinumab (56.8%) and lowest with guselkumab (33.9%). Combination treatment with methotrexate was started in 120 (3.6%) patients; this proportion was highest in the secukinumab group (6.3%).

Further baseline demographic and disease characteristics are available in Table 1.

3.2 Causes of Discontinuation

A total of 615 patients discontinued treatment owing to ineffectiveness of the selected drug, with a greater proportion of patients discontinuing due to this cause in the groups receiving ustekinumab and secukinumab (23.2% and 24.3%, respectively), mainly on account of secondary failure. At the opposite end, only 6.3% and 3.4% of the treatment courses with guselkumab and risankizumab, respectively, ended due to ineffectiveness.

Safety issues were the cause of discontinuation in only 48 (1.4%) of total treatment courses, with infection by any agent as the main cause—a total of seven cases specifically due to *Candida* infection (most cases in patients being treated with IL-17 inhibitors), and 23 cases due to other infectious agents. A total of 35 (1.1%) treatment courses ended due to patient decision, and 20 (0.6%) due to loss of follow-up. Further data is available in Table 2.

3.3 Events of Inadequate Response

In a total of 447 (13.5%) treatment courses, the dose of the biologic was increased due to inadequate response; this occurrence was most frequent in patients receiving ustekinumab (23.3%). In 202 (6.1%) treatment courses, another systemic therapy was added to the biologic agent to improve efficacy, mainly in patients being treated with secukinumab (8.9%); methotrexate was the most used drug (131 [3.9%] courses). Further details are available in Table 2.

3.4 Safety

There was at least one episode of infection in 311 treatment courses. The highest rates were noted with secukinumab and ustekinumab—12.0% and 11.8%, respectively. On the opposite end, guselkumab and risankizumab had the lowest rate of infectious events during treatment—3.8% and 4.2%, respectively. *Candida* infections were more frequently reported in patients receiving IL-17 inhibitors (44 of a total of 51 events reported in all groups). Further information is available in Table 2.

Table 1 Baseline demographic data, baseline evaluation, previous treatments, and comorbidities, by treatment drug

	Data collected from *n* patients	Total	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab
Total number of treatment series, n (%)	3312	3312 (100.0)	1118 (33.8)	911 (27.5)	651 (19.6)	116 (3.5)	398 (12.0)	118 (3.6)
Age (years), mean (SD)	3312	49.0 (14.1)	46.8 (14.7)	49.3 (13.8)	50.2 (13.1)	51.3 (14.3)	51.2 (14.3)	50.9 (14.7)
Gender (male), *n* (%)	3312	2037 (61.5)	694 (62.1)	547 (60.0)	408 (62.7)	81 (69.8)	233 (58.5)	74 (62.7)
Family history of PsO, *n* (%)	2072	840 (40.5)	334 (43.4)	228 (40.5)	134 (36.5)	41 (42.3)	74 (37.9)	29 (35.8)
Disease duration (years), mean (SD)	2743	21.2 (13.0)	22.5 (13.2)	20.7 (12.7)	20.6 (13.0)	19.9 (12.6)	20.3 (12.5)	20.5 (13.6)
Baseline evaluation								
Height (m), mean (SD)	3119	1.71 (0.10)	1.71 (0.09)	1.71 (0.10)	1.72 (0.10)	1.73 (0.09)	1.71 (0.09)	1.72 (0.10)
Weight (kg), mean (SD)	3119	83.4 (19.1)	82.5 (18.9)	82.4 (18.6)	84.4 (19.4)	88.5 (20.0)	84.5 (18.2)	84.9 (22.5)
BMI, mean (SD)	3255	28.3 (5.7)	28.1 (5.8)	28.0 (5.6)	28.4 (5.5)	29.6 (6.6)	28.8 (5.5)	28.6 (6.5)
Baseline PASI, mean (SD)	2909	13.8 (8.0)	14.8 (8.6)	13.8 (7.7)	13.3 (8.0)	14.2 (7.3)	12.7 (6.9)	12.1 (7.6)
Baseline BSA, mean (SD)	2643	16.3 (12.9)	17.1 (13.2)	17.1 (13.5)	15.2 (11.7)	16.8 (10.6)	14.7 (12.6)	14.1 (12.4)
Baseline DLQI, mean (SD)	2139	14.2 (5.7)	14.0 (5.4)	14.7 (6.0)	14.6 (5.8)	13.4 (5.6)	13.0 (5.6)	15.0 (6.1)
Baseline MTX, *n* (%)	3312	120 (3.6)	30 (2.7)	57 (6.3)	18 (2.8)	4 (3.4)	10 (2.5)	1 (0.8)
PsA, *n* (%)[a]	2755	959 (34.8)	267 (27.3)	336 (41.8)	221 (43.0)	30 (28.0)	73 (27.1)	32 (38.1)
Peripheral, *n* (%)		858 (31.1)	248 (25.4)	294 (36.6)	192 (37.4)	29 (27.1)	66 (24.5)	29 (34.5)
Axial, *n* (%)		201 (7.3)	48 (4.9)	77 (9.6)	56 (10.9)	4 (3.7)	11 (4.1)	5 (6.0)
Comorbidities								
Obesity, *n* (%)	3312	1024 (30.9)	342 (30.6)	261 (28.6)	202 (31.0)	41 (35.3)	140 (35.2)	38 (32.2)
Hypertension, *n* (%)	3312	1081 (32.6)	353 (31.6)	294 (32.3)	223 (34.3)	46 (39.7)	129 (32.4)	36 (30.5)
Diabetes, *n* (%)	3312	518 (17.5)	171 (15.3)	141 (15.5)	106 (16.3)	21 (18.1)	56 (14.1)	23 (19.5)
Dyslipidemia, *n* (%)	3312	1037 (31.3)	388 (34.7)	276 (30.3)	198 (30.4)	43 (37.1)	99 (24.9)	33 (28.0)
Family history of CVD, *n* (%)	1794	330 (18.4)	138 (23.0)	88 (17.1)	51 (15.6)	17 (20.0)	30 (16.3)	6 (7.2)
Previous CVD, *n* (%)	3312	194 (5.9)	71 (6.4)	48 (5.3)	37 (5.7)	8 (6.9)	22 (5.5)	8 (6.8)
Inflammatory bowel disease, *n* (%)	3312	53 (1.6)	22 (2.0)	10 (1.1)	9 (1.4)	0 (0.0)	10 (2.5)	2 (1.7)
Smoker?	3042							
No, *n* (%)		1996 (65.6)	680 (63.3)	541 (67.2)	372 (65.0)	64 (55.2)	256 (71.9)	83 (70.3)
Yes, *n* (%)		749 (24.6)	301 (28.0)	194 (24.1)	136 (23.7)	28 (24.1)	72 (20.2)	18 (15.3)
Former smoker, *n* (%)		297 (9.8)	93 (8.7)	70 (8.7)	65 (11.3)	24 (20.7)	28 (7.9)	17 (14.4)
Hepatitis B, *n* (%)	3312	93 (2.8)	30 (2.7)	32 (3.5)	20 (3.1)	3 (2.6)	6 (1.5)	2 (1.7)
Hepatitis C, *n* (%)	3312	45 (1.4)	13 (1.2)	17 (1.9)	4 (0.6)	3 (2.6)	5 (1.3)	3 (2.5)
Latent tuberculosis (any time), *n* (%)	3312	394 (11.9)	165 (14.8)	108 (11.9)	76 (11.7)	19 (16.4)	21 (5.3)	5 (4.2)

3.5 Drug Survival, Model Development and Interaction Factors

At 12 months, IL-23 inhibitors were the biologic agents with the higher overall cumulative probability of drug survival: 96.4% for risankizumab and 92% for guselkumab. On the other end, secukinumab had the lowest cumulative probability of drug survival at 12 months: 85.5%. At 18 months, IL-23 inhibitors were the only drugs with a cumulative probability of drug survival above 90%: 96.4% for risankizumab, and 91.1% for guselkumab; secukinumab had the lowest (79.9%). At 24 months, guselkumab had the highest cumulative probability of drug survival (90.2%); the drug survival of risankizumab at 24 months could not be assessed, due to its more recent approval date. At the other end, brodalumab was the biologic drug with the lowest cumulative

Table 1 (continued)

	Data collected from *n* patients	Total	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab
Previous treatments[b]								
Naive to systemic therapy?	3312							
Yes		542 (16.4)	189 (16.9)	135 (14.8)	108 (16.6)	12 (10.3)	73 (18.3)	25 (21.2)
No. Which were used?		2770 (83.6)	929 (83.1)	776 (85.2)	543 (83.4)	104 (89.7)	325 (81.7)	93 (78.8)
Retinoids		854 (25.8)	301 (26.9)	251 (27.6)	149 (22.9)	37 (31.9)	87 (21.9)	29 (24.6)
MTX		1722 (52.0)	548 (49.0)	529 (58.1)	349 (53.6)	61 (52.6)	183 (46.0)	52 (44.1)
CyA		1275 (38.5)	530 (47.4)	362 (39.7)	224 (34.4)	46 (39.7)	93 (23.4)	20 (16.9)
Phototherapy		1345 (40.6)	432 (38.6)	372 (40.8)	230 (35.3)	63 (54.3)	189 (47.5)	59 (50.0)
Apremilast		256 (7.7)	28 (2.5)	73 (8.0)	67 (10.3)	12 (10.3)	59 (14.8)	17 (14.4)
Fumarate		21 (0.6)	4 (0.4)	10 (1.1)	0 (0.0)	3 (2.6)	3 (0.8)	1 (0.8)
Naive to biologic therapy?	3312							
Yes		1533 (46.3)	635 (56.8)	388 (42.6)	278 (42.7)	46 (39.7)	135 (33.9)	51 (43.2)
No. Which were used?		1779 (53.7)	483 (43.2)	523 (57.4)	373 (57.3)	70 (60.3)	263 (66.1)	67 (56.8)
Previous TNFi		1473 (44.5)	462 (41.3)	445 (48.8)	292 (44.9)	48 (41.4)	181 (45.5)	45 (38.1)
Adalimumab		962 (29.0)	277 (24.8)	306 (33.6)	197 (30.3)	32 (27.6)	118 (29.6)	32 (27.1)
Etanercept		859 (25.9)	293 (26.2)	262 (28.8)	166 (25.5)	32 (27.6)	85 (21.4)	21 (17.8)
Infliximab		359 (10.8)	100 (8.9)	116 (12.7)	79 (12.1)	12 (10.3)	46 (11.6)	6 (5.1)
Previous IL-12/23i (ustekinumab)		611 (18.4)	0 (0.0)	238 (26.1)	186 (28.6)	28 (24.1)	139 (34.9)	20 (16.9)
Previous IL-17i		454 (13.7)	60 (5.4)	22 (2.4)	160 (24.6)	43 (37.1)	130 (32.7)	39 (33.1)
Secukinumab		357 (10.8)	44 (3.9)	0 (0.0)	160 (24.6)	30 (25.9)	96 (24.1)	27 (22.9)
Ixekizumab		152 (4.6)	17 (1.5)	20 (2.2)	0 (0.0)	21 (18.1)	73 (18.3)	21 (17.8)
Brodalumab		19 (0.6)	7 (0.6)	2 (0.2)	3 (0.5)	0 (0.0)	5 (1.3)	2 (1.7)
Previous IL-23i		34 (1.0)	4 (0.4)	8 (0.9)	6 (0.9)	6 (5.2)	1 (0.3)	9 (7.6)
Guselkumab		31 (0.9)	4 (0.4)	7 (0.8)	6 (0.9)	5 (4.3)	0 (0.0)	9 (7.6)
Risankizumab		1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tildrakizumab		2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)	0 (0.0)
No. previous biologics, mean (SD)	3312	1.01 (1.23)	0.66 (0.91)	1.05 (1.17)	1.22 (1.42)	1.39 (1.55)	1.41 (1.46)	1.16 (1.36)

BMI body mass index, *BSA* body surface area, *CVD* cardiovascular disease, *CyA* cyclosporin A, *DLQI* Dermatology Life Quality Index, *i* inhibitor, *IL* interleukin, *MTX* methotrexate, *PASI* Psoriasis Area Severity Index, *PsA* psoriatic arthritis, *PsO* psoriasis, *SD* standard deviation, *TNF* tumor necrosis factor

[a]Patients can present both peripheral and axial PsA

[b]Patients may have been previously treated with more than one therapy

probability of drug survival at 24 months (64.7%). Considering only discontinuations due to ineffectiveness, drug survival of risankizumab and guselkumab showed a higher cumulative probability of drug survival at 12 (96.4% and 93.3%, respectively) and 18 months (96.4% and 92.8%, respectively), while secukinumab had the lowest (88.5% and 83.2%, respectively). At 24 months, guselkumab maintained the highest cumulative probability of drug survival at >90% (92.0%), while secukinumab presented a cumulative probability of drug survival of 77.5%. Detailed information is provided in Table 3 and Fig. 1a, b.

Univariable analysis identified the following as potential predictive factors of discontinuation ($p < 0.05$): selected drug, female sex, higher BMI, higher weight, presence of PsA, presence of peripheral PsA, obesity, presence of diabetes, previous exposure to systemic therapies, previous exposure to biologic therapies, and number of previous biologic therapies (Table 4).

As some of these factors were related, they were not included concomitantly in the multivariable model. Therefore, the final multivariable model contained the non-significant factor age, as well as the following variables: current

Table 2 Characterization of treatment management identifying causes of discontinuation, biologic dose optimization, combination with systemic therapy, and safety events related to biologic agents

	Total ($n = 3312$)	Ustekinumab ($n = 1118$)	Secukinumab ($n = 911$)	Ixekizumab ($n = 651$)	Brodalumab ($n = 116$)	Guselkumab ($n = 398$)	Risankizumab ($n = 118$)
Causes of discontinuation							
Ineffectiveness	615 (18.6)	259 (23.2)	221 (24.3)	96 (14.7)	10 (8.6)	25 (6.3)	4 (3.4)
Primary failure	101 (3.0)	31 (2.8)	34 (3.7)	23 (3.5)	3 (2.6)	7 (1.8)	3 (2.6)
Secondary failure	514 (15.6)	228 (20.4)	187 (20.6)	73 (11.2)	7 (6.0)	18 (4.5)	1 (0.8)
Safety	48 (1.4)	11 (0.9)	20 (2.2)	13 (2.0)	3 (2.6)	1 (0.2)	0 (0.0)
Candida infection	7 (0.2)	1 (0.1)	3 (0.3)	2 (0.3)	1 (0.9)	0 (0.0)	0 (0.0)
Infection by other agents	23 (0.7)	3 (0.2)	12 (1.4)	6 (0.9)	2 (1.7)	0 (0.0)	0 (0.0)
Inflammatory bowel disease	3 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)
Malignancy	9 (0.3)	4 (0.3)	3 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	6 (0.2)	3 (0.2)	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Loss of follow-up	20 (0.5)	15 (1.3)	3 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Patient decision	35 (1.1)	22 (2.0)	6 (0.7)	3 (0.5)	2 (1.7)	2 (0.5)	0 (0.0)
Other causes (not specified)	42 (1.3)	12 (1.1)	12 (1.3)	15 (2.3)	0 (0.0)	3 (0.8)	0 (0.0)
Total	760 (22.9)	319 (28.5)	262 (28.8)	129 (19.8)	15 (12.9)	31 (7.8)	4 (3.4)
Biologic dose optimization and combination with systemic therapy							
Biologic dose optimization	447 (13.5)	261 (23.3)	93 (10.2)	61 (9.4)	3 (2.6)	28 (7.0)	1 (0.8)
Combination with systemic therapy							
No	3110 (93.9)	1051 (94.0)	830 (91.1)	615 (94.5)	113 (97.4)	384 (96.5)	117 (99.2)
Yes	202 (6.1)	67 (6.0)	81 (8.9)	36 (5.5)	3 (2.6)	14 (3.5)	1 (0.8)
MTX	131 (3.9)	47 (4.2)	51 (5.7)	20 (3.1)	3 (2.6)	9 (2.3)	1 (0.8)
CyA	11 (0.3)	5 (0.4)	5 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Retinoids	23 (0.7)	11 (1.0)	7 (0.8)	3 (0.5)	0 (0.0)	2 (0.5)	1 (0.0)
Phototherapy	12 (0.4)	4 (0.4)	4 (0.4)	3 (0.5)	0 (0.0)	1 (0.2)	1 (0.0)
Fumarate	3 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.5)	1 (0.0)
Apremilast	22 (0.7)	0 (0.0)	14 (1.5)	8 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Safety events							
Any infectious event	311 (9.4)	132 (11.8)	109 (12.0)	43 (6.6)	7 (6.0)	15 (3.8)	5 (4.2)
Need for hospitalization	55 (1.7)	32 (2.9)	11 (1.2)	6 (0.9)	3 (2.6)	2 (0.5)	1 (0.8)
Candida infection	51 (1.5)	6 (0.5)	32 (3.5)	9 (1.4)	3 (2.6)	1 (0.3)	0 (0.0)
MACE	14 (0.4)	7 (0.6)	4 (0.4)	2 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
IBD	4 (0.1)	0 (0.0)	2 (0.2)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)
Depression	50 (1.5)	16 (1.4)	15 (1.6)	8 (1.2)	0 (0.0)	9 (2.3)	2 (1.7)
Malignancy	17 (0.5)	8 (0.7)	6 (0.7)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

For each drug, details on reason for discontinuation (ineffectiveness, safety, loss to follow-up, patient decision, or unspecified) are displayed. Similarly, data on biologic dose optimization (i.e., increased dosage, shortened drug administration interval) or combination therapeutic regimen, and safety events (namely infectious events, MACE, IBD, depression, and malignancies) are provided

Data are presented as *n* (proportion of events regarding the total number of treatment courses in each group, value presented as a percentage)

CyA cyclosporine A, *IBD* inflammatory bowel disease, *MTX* methotrexate, *MACE* major adverse cardiovascular event

biologic therapy, gender, BMI, PsA, diabetes, previous exposure to systemic therapies, and previous exposure to biologic therapies (Table 4). Drug remained as a significant variable in the multivariable model; using ustekinumab as reference and after adjusting for the other variables, discontinuation was more likely for treatment courses started on secukinumab (hazard ratio [HR] 1.297; 95% CI 1.076–1.563), and less likely for those started on risankizumab (HR 0.135; 95% CI 0.019–0.967). After adjusting for the other variables, the hazard of discontinuation was higher for female patients, biologic-experienced, and systemic-experienced patients compared with their counterparts, as well as increasing BMI (Table 4).

A significant interaction between obesity and brodalumab or secukinumab treatment was also found (Table 5); in obese patients, the HR of discontinuation for brodalumab and secukinumab was 3.753 (95% CI 1.250–11.26) and 1.558 (95% CI 1.105–2.196), respectively, compared with ustekinumab. Also, a significant interaction between prior biologic experience and secukinumab was found (Table 5). Among biologic-experienced patients, the HR of discontinuation was 1.727 (95% CI 1.211–2.462) for secukinumab as compared with ustekinumab treatment.

4 Discussion

This study provides important data on the drug survival of several options in the recently introduced biologic armamentarium for the real-world treatment of psoriasis. It not only provides data on biologic agents whose drug

Table 3 Drug survival rates stratified by reason of drug discontinuation**.** Evaluation of drug survival rates at different timepoints based on any reason of discontinuation and, in particular, based on ineffectiveness

Reasons for drug discontinuation	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Risankizumab
All reasons						
N events observed	319	262	129	15	31	4
Survival 3 months	0.974 (0.005)	0.959 (0.007)	0.966 (0.007)	0.957 (0.019)	0.980 (0.007)	1.0
Survival 6 months	0.946 (0.007)	0.919 (0.009)	0.924 (0.010)	0.947 (0.021)	0.957 (0.010)	0.974 (0.015)
Survival 12 months	0.899 (0.009)	0.855 (0.012)	0.867 (0.014)	0.890 (0.035)	0.920 (0.014)	0.964 (0.018)
Survival 18 months	0.861 (0.011)	0.799 (0.014)	0.820 (0.016)	0.863 (0.043)	0.911 (0.015)	0.964 (0.018)
Survival 24 months	0.828 (0.012)	0.741 (0.016)	0.791 (0.018)	0.647 (0.190)	0.902 (0.018)	
Ineffectiveness						
N events observed	259	221	96	10	25	4
Survival 3 months	0.980 (0.004)	0.973 (0.005)	0.974 (0.006)	0.965 (0.017)	0.985 (0.006)	1.0
Survival 6 months	0.953 (0.006)	0.943 (0.008)	0.945 (0.009)	0.956 (0.019)	0.967 (0.009)	0.974 (0.015)
Survival 12 months	0.915 (0.008)	0.885 (0.011)	0.900 (0.012)	0.908 (0.034)	0.933 (0.014)	0.964 (0.018)
Survival 18 months	0.884 (0.010)	0.832 (0.013)	0.867 (0.014)	0.880 (0.042)	0.928 (0.015)	0.964 (0.018)
Survival 24 months	0.857 (0.011)	0.775 (0.015)	0.839 (0.016)	0.880 (0.042)	0.920 (0.017)	

Log-rank test: $p < 0.001$

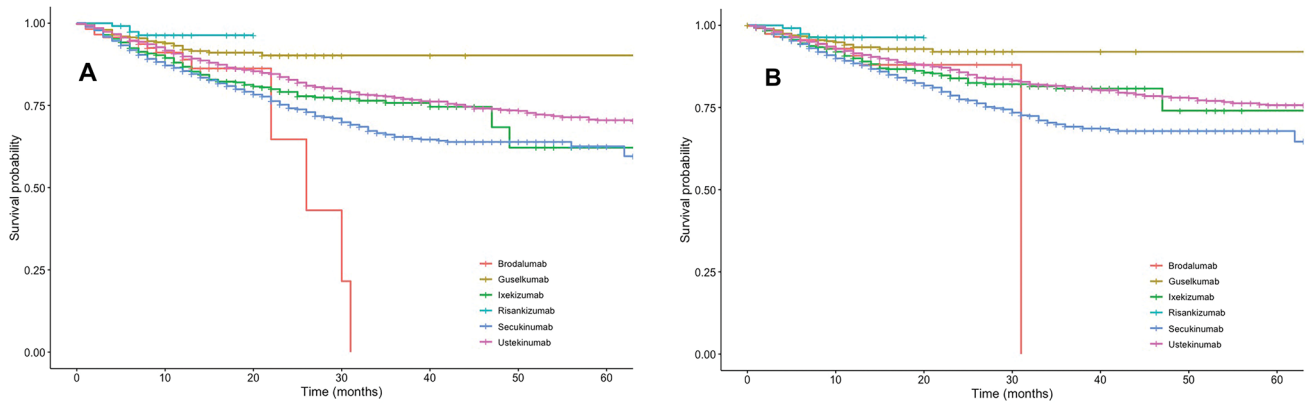

Fig. 1 Drug survival rates. **a** Overall drug survival rates; **b** drug survival for discontinuation due to inefficacy

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

	Univariable		Multivariable	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Treatment (ref: ustekinumab)		***<0.001***		***0.003***
Secukinumab	1.490 (1.257–1.766)	***<0.001***	1.297 (1.076–1.563)	***0.006***
Ixekizumab	1.191 (0.963–1.473)	0.107	1.031 (0.811–1.309)	0.805
Brodalumab	1.359 (0.804–2.298)	0.252	1.124 (0.638–1.980)	0.686
Guselkumab	0.609 (0.418–0.887)	***0.010***	0.670 (0.426–1.056)	0.085
Risankizumab	0.409 (0.152–1.102)	0.077	0.135 (0.019–0.967)	***0.046***
Age (years)	1.005 (0.999–1.010)	0.084	0.999 (0.993–1.005)	0.643
Gender, male	0.807 (0.699–0.933)	***0.004***	0.844 (0.720–0.989)	***0.036***
Family history of PsO, yes	0.993 (0.828–1.190)	0.940		
Disease duration (years)	0.998 (0.992–1.004)	0.602		
BMI (kg/m^2)	1.024 (1.012–1.036)	***<0.001***	1.022 (1.008–1.035)	***0.002***
Weight (kg)	1.006 (1.002–1.009)	***0.003***		
Baseline PASI	1.001 (0.992–1.011)	0.782		
Baseline BSA	1.000 (0.994–1.007)	0.880		
Baseline DLQI	1.001 (0.985–1.017)	0.901		
Baseline MTX	1.161 (0.801–1.683)	0.430		
PsA	1.187 (1.014–1.390)	***0.033***	1.014 (0.859–1.198)	0.868
Peripheral	1.251 (1.066–1.468)	***0.006***		
Axial	0.937 (0.683–1.286)	0.689		
Obesity	1.332 (1.149–1.543)	***<0.001***		
Hypertension	1.156 (0.995–1.343)	0.057		
Diabetes	1.207 (1.001–1.455)	***0.049***	1.021 (0.825–1.264)	0.848
Dyslipidemia	1.056 (0.908–1.229)	0.479		
Smoking (no)				
Yes	1.111 (0.934–1.321)	0.233		
Ex	1.263 (0.988–1.613)	0.062		
Naive to systemic therapy	0.632 (0.504–0.793)	***<0.001***	0.840 (0.637–1.107)	0.215
Naive to biologic therapy	0.546 (0.470–0.635)	***<0.001***	0.603 (0.508–0.717)	***<0.001***
Previous TNFi	1.576 (1.365–1.819)	***<0.001***		
Previous IL12/23i	1.826 (1.541–2.163)	***<0.001***		
Previous IL17i	2.191 (1.809–2.654)	***<0.001***		
Previous IL23i	3.723 (2.190–6.330)	***<0.001***		
Number of previous biologics	1.299 (1.235–1.368)	***<0.001***		

Data marked with bold means that *p* was inferior to 0.05

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *i* inhibitor, *IL* interleukin, *MTX* methotrexate, *PASI* Psoriasis Area Severity Index, *PsA* psoriatic arthritis, *PsO* Psoriasis, *TNFi* tumor necrosis factor inhibitor

survival has been analyzed over recent years [9–12], but also assesses the drug survival of IL-17 receptor inhibitor brodalumab and IL-23 inhibitors guselkumab and risankizumab. To our knowledge, this is the first study providing data from a large number of treatment series with IL-23 inhibitors. Additionally, by using a multicentric approach with dermatology centers from several countries, including data from non-hospital-based dermatologists, we seek to provide a much more comprehensive view of the global panorama than national registries regarding these therapeutic options and their impact on psoriasis.

The evolution of therapeutic strategies in psoriasis reached its peak with the development of IL-17 and IL-23 inhibitors. Their efficacy and safety profiles defined in both clinical trials and real-world settings have completely modified the disease treatment paradigm. Regarding the

Table 5 Interaction between current treatment and BMI >30 and between current treatment and biologic experience

	HR	95% CI	*p*-Value
BMI >30 *current therapy (ref: ustekinumab)			
Secukinumab	1.558	1.105–2.196	***0.011***
Ixekizumab	1.096	0.711–1.688	0.678
Brodalumab	3.753	1.250–11.26	***0.018***
Guselkumab	1.972	0.938–4.144	0.073
Risankizumab	1.968	0.273–14.17	0.501
Bio-experienced *current therapy (ref: ustekinumab)			
Secukinumab	1.727	1.211–2.462	***0.003***
Ixekizumab	1.458	0.931–2.286	0.100
Brodalumab	1.766	0.489–6.379	0.385
Guselkumab	2.839	0.971–8.302	0.057
Risankizumab	1.606	0.165–15.60	0.683

Data marked with bold means that *p* was inferior to 0.05

BMI body mass index

armamentarium for psoriasis, we now face a period where small differences can have a huge impact in the initial drug decision and also, once a drug is started, in how to react to the adversities that may arise, with so many other options available. Because of this large array of new therapeutic options providing excellent results, the dermatologists' choice may be influenced and the threshold for switching medications, as well as drug survival, tends to be reduced [13].

Ustekinumab has been previously shown to be associated with the best survival when compared with anti-TNFs as well as with secukinumab in some studies [11, 14, 15]. For that reason, it was taken as a reference in this study.

We found, in accordance to some previous studies, higher drug survival rates for IL-12/23, IL-17, and IL-23 inhibitors compared with the available published data on anti-TNFs [7–9, 11, 14–16]. Guselkumab and risankizumab had the highest overall drug survival at 6, 12, 18, and 24 months. When ineffectiveness was the cause of discontinuation, this pattern persisted. However, it is important to mention that no data was available to predict the drug survival of risankizumab at 24 months. One possible explanation for the advantage of IL-23 inhibitors over IL-17 inhibitors regarding drug survival may be the better results of efficacy and safety of IL-23 inhibitors over IL-17 inhibitors in comparative studies such as ECLIPSE and IMMerge [17, 18]: in a real-world setting, total clearance of the affected skin is usually the goal for both patients and dermatologists, and if this response is not achieved in the short term, it can lead to an early drug switch and consequent shorter drug survival. Also, the biologic agent with the best safety profile will likely also be associated with a higher drug survival.

Another somewhat speculative explanation for the superiority of IL-23 inhibitors over IL-17 inhibitors regarding drug survival may be associated with the importance of tissue resident memory cells and T-regulatory cells in psoriasis' pathogenesis and relapse [18–20]. Tissue resident memory cells may be sustained in their pathogenic state through the local production of IL-23 by different types of antigen-presenting cells. T-regulatory cells seem to have a suppressive activity and are responsible for the induction and maintenance of immunological tolerance [21]. Since guselkumab was associated with a significantly greater reduction in the number of tissue resident memory cells in affected skin when compared with secukinumab at weeks 4 and 24, and T-regulatory cell levels were maintained in patients treated with guselkumab while reduced in the secukinumab group, the ratio of tissue resident memory cells/T-regulatory cells was higher in the guselkumab group [19, 20]. By directly blocking the IL-23 pathway and inducing a reduction in tissue resident memory cells instead of acting on IL-17A, there is a possibility that we are impacting long-term efficacy, increasing the drug survival of IL-23 inhibitors compared with the IL-17 inhibitors. Further studies are needed to better understand this interaction and its impact on the overall disease pathophysiology.

The drug survival rate of ustekinumab in this study is in accordance with the available data [11, 16]. However, we found that nearly 23% of patients that were on ustekinumab needed a dose optimization (updose and/or shortening of administration interval) to remain with that therapeutic option and to achieve the desired efficacy. In several countries, the 90-mg dose is provided at a different price to the 45-mg dose. In such scenarios, the cost–benefit ratio of the drug may have a negative impact on the choice of biologic agent when compared with the other therapeutic options and their results. On the other hand, the flat price of both doses in many countries drives off-label use of the 90-mg dose in patients weighing <100 kg to achieve improved therapeutic results [22].

Regarding predictors of drug discontinuation, secukinumab presented a decreased drug survival compared with ustekinumab; this finding is consistent with those of some national registries [14, 23, 24], but at odds with recently published evidence from the BADBIR registry [11]. BADBIR reflects the real-world evidence of UK and Ireland, whereas our study includes many different countries and practices, where prior exposure to biologics, goals of treatment, and incentives to remain on a given drug might change. Risankizumab was found to be at the opposite end, with a lower hazard of discontinuation compared with ustekinumab. The results on the IL-17 inhibitor are not surprising and in line with previous reports [9, 25]; arguably, they might be related

to early change of treatment due to dissatisfaction with the results upon availability of newer drugs, differences in mechanism of action and drug indications (IL-17 inhibitors are approved for treatment of psoriatic arthritis and are primarily chosen for patients with an increased burden of psoriatic disease), and increased therapeutic expectations, based on the results of head-to-head trials.

Female patients presented a higher hazard of discontinuation when compared with male patients; this is consistent with previously published data, and seems to be related to the decreased tolerance of women to side effects, and to the fact that female patients are globally less satisfied with biologic treatment, discontinuing treatment more often [10, 26]. Higher BMI was associated with a higher hazard of discontinuation, which also corroborates the existent literature showing that a higher BMI can be associated with higher side effects and lower efficacy, with an important impact on drug survival [10, 27]. Patients that were naïve to biologic therapies presented a lower hazard of discontinuation, reinforcing the importance of choosing the correct agent *ad initium*. In this study, at baseline, patients being treated with IL-23 and IL-17 inhibitors have been previously exposed to a higher number of biologic agents when compared with ustekinumab (it is important to note that the guselkumab group had the highest percentage of biologic-experienced patients at baseline). This shows that, although many patients need to switch biologic agents during their course of disease, most of the currently available biologic drugs show encouraging results in this scenario. Recently, a small study of 50 patients with difficult-to-treat psoriasis treated with guselkumab (100% of the patients had previously failed on or experienced adverse events to other biologic treatments) showed a lower drug survival compared with our study. However, the population in this study was small in number and highly bio-experienced, which might provide explanations for their different findings [28].

When the baseline data are analyzed, there are some facts that should be highlighted. First of all, the guselkumab group had the highest percentage of biologic-experienced patients, and the ustekinumab group had the lowest. Second, since IL-17 inhibitors are approved for PsA, this class was highly selected by dermatologists in patients with concomitant PsA. Interestingly, risankizumab was also selected in a high number of patients with PsA. Since risankizumab was the drug with the highest drug survival at 6, 12, and 18 months, a good control of PsA with this drug may be implied, raising the possibility that in the near future this drug may be approved as a therapeutic option for PsA, similarly to guselkumab [29–31]. Lastly, the use of methotrexate concomitantly with secukinumab was an option observed not only at baseline, but also during the treatment course. This decision may have been made in order to achieve greater efficacy, but could also be due to the high prevalence of patients with PsA treated with secukinumab.

Regarding interaction between factors, both obesity and previous exposure to biologic agents were shown to have a differentiating effect on therapy, with an impact on drug discontinuation. Analyzing Table 5, among patients with BMI >30, drug discontinuation was more likely with secukinumab and brodalumab than with ustekinumab, whereas no significant interaction was seen with the other agents. Among biologic-experienced patients (Table 5), secukinumab had a significantly higher hazard of discontinuation than ustekinumab. Confirmation of our findings in future studies might have clinical implications.

This study has some limitations. Firstly, its retrospective nature; secondly subjects were not randomized to receive different treatment options, and selection bias should be taken into consideration; thirdly, this study assesses a long period of time during which several drugs were being approved on different dates and therapeutic goals have also become more ambitious, recently shown to influence drug survival [13, 24]; fourthly, brodalumab and risankizumab groups have a very small number of treatment courses compared with the other treatment groups; and finally, the existence of many therapeutic options with excellent results may influence dermatologists' choices and reduce the threshold for switching medications. Our multicentric approach improves the generalizability of the results, but also increases variability, since dermatologists and patients from different medical centers may decide differently on the same side effect, or other factors influencing therapeutic choice and discontinuation, and access to therapies may differ between countries. Finally, we acknowledge that less adherent patients can dictate the early termination of a treatment course, which may also be considered a limitation. Thus, more data are needed to corroborate these findings on the drug survival of IL-23 inhibitors and possible predictors of discontinuation for IL-12/23, IL-17, and IL-23 inhibitors.

5 Conclusion

This multicentric study revealed that guselkumab and risankizumab seem to be associated with higher drug survival at 6, 12, 18, and 24 months when compared with the other therapeutic options approved for the treatment of psoriasis. Current biologic therapy, female sex, higher BMI, and previous exposure to biologic agents seem to be predictors of drug discontinuation.

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Ethics approval 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 Not applicable.

Consent for publication Not applicable.

Availability of data and materials Raw data are available on request from the authors.

Code availability Not applicable.

Author contributions TT and AC contributed to the study concept and design. TT, LP, LT and AC conducted the statistical analyses on the data. All authors participated in data collection, interpreted 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.

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