Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Treatment of Psoriasis with Il-17 Inhibitors: Comparison of Long-Term Effectiveness and Drug Survival of Secukinumab vs Ixekizumab in Real-World Practice

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Introduction: The emergence of IL-17A inhibitors, has led to improvements in psoriasis treatment. However, comparative studies addressing their long-term efficacy and drug survival with associated predictors are scarce. The study aimed to compare the characteristics of patients treated with secukinumab or ixekizumab and in addition to analyze associated factors and independent predictors of drug survival in a real-world setting.

Methods: This study was designed as a single-center retrospective study. Kaplan–Meier analysis was used to assess drug survival. Log rank test and Cox regression analysis were performed to identify associated factors and possible independent predictors for drug discontinuation.

Results: 81 patients have been included in the study. Ixekizumab showed a trend toward faster and higher Psoriasis Area and Severity Index (PASI) 75 and 90 response rates compared to secukinumab at weeks 52 (74.6% versus 55.4%) and 104 (41.5% versus 31.1%). Overall, drug survival rates for ixekizumab were always higher than secukinumab, although the differences were not statistically significant (P = 0.26). Four predictors were identified. For secukinumab, nail psoriasis (hazard ratio [HR]: 0.27, 95% confidence interval [CI]: 0.09–0.83; P = 0.02) was assessed to be a protective factor favoring drug continuation, while five or more previous therapies (HR: 5.52, 95% CI: 1.98–15.40, P = 0.007) were considered a risk factor for discontinuation. In the ixekizumab group, psoriasis inversa was identified as a protective factor (HR: 0.15, 95% CI: 0.03–0.72; P = 0.02), and female sex (HR: 3.47, 95% CI: 1.09–10.99, P = 0.03) was considered a risk factor.

Conclusion: Ixekizumab exhibited a non-significant trend toward better long-term efficacy and drug survival compared to secukinumab with slightly lower tolerability. Patient characteristics, including nail psoriasis and treatment history, influenced drug survival differently for each treatment. These findings underscore the importance of personalized treatment strategies in managing psoriasis.

Keywords: psoriasis, IL-17-blocker, ixekizumab, secukinumab, drug survival, real world, associated factors, predictors

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease with cutaneous and systemic manifestations affecting 2–4% of the population in western countries.[1,2] The discovery that dominant interleukin-23/interleukin-17 (IL-23/ IL-17) axis has a pathogenetic influence on keratinocyte proliferation and inflammation established the basis for the development of the newer generation of biologics consisting of IL-17 and −23 blockers. These new biologics have revolutionized the treatment of psoriasis.[3–6] Still, therapeutic strategy depends on numerous factors, such as disease severity, medical history, tolerability of therapies, potential for side effects, and patient's preference.[5] In Switzerland, three IL-17 blockers are available on the market, namely secukinumab (approved February 2015), ixekizumab (approved December 2016), and bimekizumab (approve 2021).[3,7]

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Secukinumab is a completely human IgG1κ anti-IL-17A monoclonal antibody, while ixekizumab is a humanized IgG4 anti-17A monoclonal antibody.[8] Both secukinumab and ixekizumab showed a rapid and high efficacy and good safety profile as demonstrated in several clinical trials. Both showed higher efficacy when compared with placebo, the tumor necrosis alpha (TNFα)-inhibitor etanercept, and the IL-12/IL-23 inhibitor ustekinumab.[9–13] Furthermore, ixekizumab even showed a faster response than secukinumab with a higher number of patients achieving psoriasis area and severity indices (PASI) 75 and 100 when compared with the IL-23 inhibitor guselkumab at week 12 in a head-to-head trial.[14] Despite both, secukinumab and ixekizumab block IL-17A, the specific differences in their structure and pharmacokinetics may contribute to variations in individual clinical outcomes and responses.[15–17] Besides clinical trials, real-world data are also needed in treatment-related decision-making.[18] Up to now, drug survival studies for ixekizumab and secukinumab have been relatively short-term, whereas minimal data about long-term drug survival comparisons exist. The aim of this study was to analyze and compare the characteristics of patients treated with secukinumab or ixekizumab in a real-world setting and evaluate drug effectiveness and survival. Furthermore, associated factors and independent predictors of drug survival were analyzed.

Methods

Study Design and Patient Population

This study was a single-center retrospective cohort analysis that was conducted at the Inselspital, University Hospital in Bern, Switzerland. All psoriasis patients treated with at least one dose of secukinumab or ixekizumab between February 2012 and July 2022 were included in this study. Written informed consent was obtained. This study was approved by the Cantonal Ethics Committee Bern (KEK nr. 2022–00645) and was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki.

Data Collection and Outcome Measures

Data were retrieved from electronic patient records. Several sets of patient demographic characteristics and clinical records were collected: demographics (age and gender), type of psoriasis, lifestyle factors (smoking, alcohol consumption), body mass index (BMI), family history of psoriasis, comorbidities, duration of psoriasis (defined as the time from first psoriasis diagnosis to initiation of secukinumab/ixekizumab treatment), PASI, and Dermatology Life Quality Index (DLQI). Records of previous and concomitant treatments, including topical therapy (steroids, vitamin D analogues, and others), phototherapy (ultraviolet [UVB], psoralen and ultraviolet A [PUVA], and others) and systemic therapy (non-steroidal anti-inflammatory drugs [NSAIDs], fumaric acids, retinoids, methotrexate, cyclosporine, apremilast, biologics, and others) were also obtained. We also evaluated drug intake duration, reasons for drug discontinuation, and adverse events.

To evaluate efficacy, PASI 75 and 90 corresponding to a reduction in baseline PASI of 75% and 90%, respectively, were selected.

Statistical Analysis

Data were presented as means ± standard deviations (SD) for continuous variables and as absolute numbers with percentages for categorical variables. Differences between patient characteristics at therapy start were assessed by using Pearson's χ^2 (or Fisher's exact in places where required) and Mann–Whitney *U*-tests for nominal and continuous variables, respectively.

Cumulative drug survival and PASI response estimates were calculated by using Kaplan-Meier analysis, and differences between groups of patients were tested using the Log rank test. Median times to event were also calculated and presented with their 95% confidence interval (CI). Drug survival differences between groups of patients in each stratum of the investigated variables were also explored by using univariate Cox regression analysis.

To identify independent predictors of drug discontinuation, all variables with P-values <0.10 in the univariate analysis and with <30% of missing data were assessed for inclusion in multivariable Cox regression.

Measures of association were presented as hazard ratios (HR) along with their 95% CI and P-values. All tests were considered statistically significant at P <0.05. Analyses were performed with SPSS software v.26.0 (IBM Corp, Armonk, NY, US).

Results

Patient Characteristics

A total of 81 patients were included in this study. Forty-four (54.3%) were receiving secukinumab, and 37 (45.7%) were receiving ixekizumab. Patient characteristics, lifestyle factors, type of psoriasis, and comorbidities are presented in Table 1. The mean baseline age of all included patients was 50.9 ± 16.1 years. The two groups were comparable in terms of sex, age, lifestyle factors, disease duration, and/or family history.

Table 1 Demographics, Lifestyle Habits, General Characteristics, Type of Psoriasis, Comorbidities and Previous Therapies of Patients at Baseline, Overall and by Drug Prescribed

		Total		Secukinumab		Ixekizumab		P*
		N=81	%	N=44	%	N=37	%	
Sex	Male	44	54.3%	22	50.0%	22	59.5%	0.39
	Female	37	45.7%	22	50.0%	15	40.5%	
Age at start of therapy (years)	*Mean, SD*	*50.9*	*16.1*	*49.3*	*15.8*	*52.9*	*16.4*	0.42
Smoking habits	Never smoked	33	40.7%	15	34.1%	18	48.6%	0.18^
	Active smoker	31	38.3%	20	45.5%	11	29.7%	
	Ex-smoker	17	21.0%	9	20.5%	8	21.6%	
Alcohol abuse	No	71	87.7%	40	90.9%	31	83.8%	0.50
	Yes	10	12.3%	4	9.1%	6	16.2%	
BMI (kg/m^2)	N	55		33		22		
	Mean, SD	*30.1*	*6.4*	*29.9*	*7.2*	*30.4*	*5.0*	0.50
Family history of psoriasis	No	55	67.9%	29	65.9%	26	70.3%	0.68
	Yes	26	32.1%	15	34.1%	11	29.7%	
Disease duration (years)	*Mean, SD*	*19.8*	*15.6*	*19.3*	*16.7*	*20.4*	*14.5*	0.54
Type of psoriasis**	Plaque	76	93.8%	40	90.9%	36	97.3%	0.37
	No plaque psoriasis	5	6.2%	4	9.1%	1	2.7%	0.37
Special localization	Pustulosa palmoplantaris	16	19.8%	12	27.3%	4	10.8%	0.06
	Palmoplantaris	12	14.8%	4	9.1%	8	21.6%	0.11
	Nail	35	43.2%	13	29.5%	22	59.5%	0.007
	Capitillium	45	55.6%	21	47.7%	24	64.9%	0.12
	Inversa	21	25.9%	6	13.6%	15	40.5%	0.006
	Guttata	21	25.9%	9	20.5%	12	32.4%	0.22
	Paradoxical	7	8.6%	6	13.6%	1	2.7%	0.12
Comorbidity**	Psoriatic arthritis	48	59.3%	31	70.5%	17	45.9%	0.03
	Hypertonia	28	34.6%	18	40.9%	10	27.0%	0.19
	Obesity (BMI ≥30)	30	37.0%	16	36.4%	14	37.8%	0.89
	Diabetes	14	17.3%	7	15.9%	7	18.9%	0.72
	Cardiovascular diseases	19	23.5%	9	20.5%	10	27.0%	0.49
	Depression and other psychiatric disorder	13	16.0%	7	15.9%	6	16.2%	0.97
	Liver diseases	16	19.8%	5	11.4%	11	29.7%	0.04
	Kidney diseases	6	7.4%	3	6.8%	3	8.1%	1
	Thyroid diseases	10	12.3%	6	13.6%	4	10.8%	0.75
	Atopic diseases***	11	13.6%	5	11.4%	6	16.2%	0.53
	Other autoimmune diseases	13	16.0%	10	22.7%	3	8.1%	0.07

(*Continued*)

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Table 1 (Continued).

		Total		Secukinumab		Ixekizumab		P*
		N=81	%	N=44	%	N=37	%	
Number of comorbidities	*Mean, SD*	*3.3*	*2.6*	*3.2*	*2.6*	*3.3*	*2.7*	*0.89*
*Previous therapies***								
Topical therapy	Steroids	81	100.0%	44	100.0%	37	100.0%	nc
	Vitamin D analogue	53	65.4%	25	56.8%	28	75.7%	0.08
Phototherapy	UVB	30	37.0%	10	22.7%	20	54.1%	0.004
	PUVA	20	24.7%	10	22.7%	10	27.0%	0.65
	Other	15	18.5%	9	20.5%	6	16.2%	0.62
	Any	*55*	*67.9%*	*26*	*59.1%*	*29*	*78.4%*	*0.06*
Systemic non-biological	NSAIDs	10	12.3%	9	20.5%	1	2.7%	0.02
	Fumaric acid	11	13.6%	1	2.3%	10	27.0%	0.001
	Retinoid	24	29.6%	13	29.5%	11	29.7%	0.99
	Cyclosporine	5	6.2%	4	9.1%	1	2.7%	0.37
	Methotrexate	52	64.2%	28	63.6%	24	64.9%	0.91
	Systemic steroids	12	14.8%	7	15.9%	5	13.5%	0.76
	Leflunomide	2	2.5%	2	4.5%	0	0.0%	0.50
	Apremilast	23	28.4%	8	18.2%	15	40.5%	0.03
	Any	*67*	*82.7%*	*38*	*86.4%*	*29*	*78.4%*	*0.34*
TNFα-inhibitors	Adalimumab	27	33.3%	17	38.6%	10	27.0%	0.27
	Golimumab	8	9.9%	7	15.9%	1	2.7%	0.06
	Infliximab	15	18.5%	10	22.7%	5	13.5%	0.29
	Etanercept	20	24.7%	12	27.3%	8	21.6%	0.56
	Certolizumab	3	3.7%	3	6.8%	0	0.0%	0.25
	Any	*41*	*50.6%*	*27*	*61.4%*	*14*	*37.8%*	*0.03*
IL-12/23- or IL-23- inhibitors	Ustekinumab	16	19.8%	9	20.5%	7	18.9%	0.86
	Tildrakizumab	1	1.2%	0	0.0%	1	2.7%	0.46
	Any	*17*	*21.0%*	*9*	*20.5%*	*8*	*21.6%*	*0.90*
IL-17-inhibitors	Brodalumab	3	3.7%	3	6.8%	0	0.0%	0.25
	Secukinumab	6	7.4%	0	0.0%	6	16.2%	0.007
	Any	*9*	*11.1%*	*3*	*6.8%*	*6*	*16.2%*	*0.29*
Others (Alefacept, Efalizumab)		3	3.7%	2	4.5%	1	2.7%	1
Biologicals-naive		32	39.5%	12	27.3%	20	54.1%	0.01
Number of prior therapies	*(Mean, SD)*	*5.2*	*2.2*	*4.9*	*2.1*	*5.6*	*2.3*	*0.17*

Notes: *Pearson's X^2 test or Fisher's exact test where required for nominal variables and Mann–Whitney *U*-test for continuous variables. **Multiple types/comorbidities/therapies were possible. ***Atopic diseases including: allergic rhinoconjunctivitis, allergic asthma, atopic dermatitis. ^ Never smokers vs actively/ex-smokers were compared.
Abbreviations: BMI, body mass index; nc, not computable; NSAIDs, non-steroidal anti-inflammatory drugs; PUVA, psoralen and ultraviolet A; SD, standard deviation; UVB, ultraviolet B.

Types of Psoriasis

The percentage of involvement of special locations for each drug is listed in Table 1. Patients receiving secukinumab had more palmoplantar pustulosis (27.3% versus 10.8%) at baseline, although the difference was not statistically significant (P = 0.06). Nail involvement (59.5% versus 29.5%, P = 0.007) and psoriasis inversa (40.5% versus 13.6%; P = 0.006) were more frequent in patients receiving ixekizumab.

Patient Comorbidities

Comorbidities for each group are listed in Table 1. On average, patients presented with 3.3 ± 2.6 comorbidities. Psoriatic arthritis (PsA) was the most frequent comorbidity (59.3%) followed by obesity (BMI ≥30 in 37.0%) and arterial hypertension (34.6%). Significant differences between groups were found for PsA (70.5% versus 45.9%; P = 0.03) with higher prevalence in the secukinumab group, and for liver diseases (29.7% versus 11.4%; P = 0.04), which were more prevalent in the ixekizumab group.

Severity of Psoriasis at Baseline

PASI scores and DLQI scores at baseline are shown in Supplementary Table 1. In 73 (90.1%) patients, the baseline PASI score was documented with a mean of 11.2 ± 6.7. DLQI was documented in 25 (30.7%) patients with a mean of 13.9 ± 6.0. No significant differences were detected.

Previous Treatment

Previous treatments are presented in Table 1. The mean number of previous treatments in the secukinumab group was 4.9 ± 2.1, while this number was 5.6 ± 2.3 in the ixekizumab group with no significant differences between groups. Psoriasis patients in the ixekizumab group had previously received significantly more UVB (54.1% versus 22.7%; P = 0.004), fumaric acid (27.0% versus 2.3%; P = 0.001), apremilast (40.5% versus 18.2%; P = 0.03), and secukinumab (16.2% versus 0.0%; P = 0.007). Patients receiving secukinumab were previously treated significantly more frequently with TNFα-inhibitors (61.4% versus 37.8%; P = 0.03). A significantly higher number of patients in the ixekizumab group was biologic-naïve (54.1% versus 27.3%, P = 0.01).

Drug Survival and Discontinuation

All 81 patients were included in the drug survival analysis (Supplementary Table 2, Figure 1). The median survival time for secukinumab was 45.3 months (95% CI: 16.6–73.9), whereas for ixekizumab it could not be estimated since the 50% survival rate was never achieved within the observation period. Overall, drug survival rates for ixekizumab were always higher than for secukinumab, although the difference was not statistically significant (P = 0.26). Secukinumab was discontinued in 24 patients (54.5%) and ixekizumab in 13 patients (35.1%) as shown in Supplementary Table 3. The most common reasons for discontinuation of secukinumab and ixekizumab were lack of efficacy (41.7% versus 23.1%), loss of efficacy (25.0% versus 46.2%), and adverse events (12.5% versus 23.1%). Adverse events leading to discontinuation of

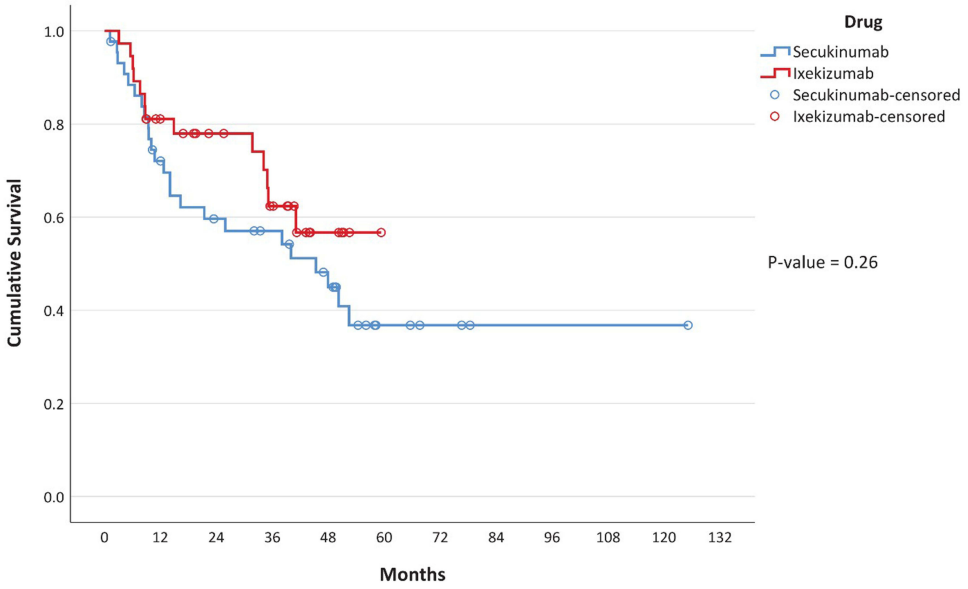

Figure 1 Kaplan-Meier plot of cumulative drug survival.

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secukinumab were exacerbation of Crohn's disease, drug-induced leukopenia and recurrent fungal infection (onychomycosis), each 1. Adverse events leading to discontinuation of ixekizumab were urticaria in all 3 patients as well as hair loss and dyspnea in 1 patient each. Overall, no significant difference between these two groups (P = 0.58) were found.

Biologic-naïve patients in both groups exhibited higher drug survival rates when compared with biologic-experienced patients (Figure 2). However, only biologic-naïve patients in the secukinumab group exhibited a significant superior drug survival (P = 0.01).

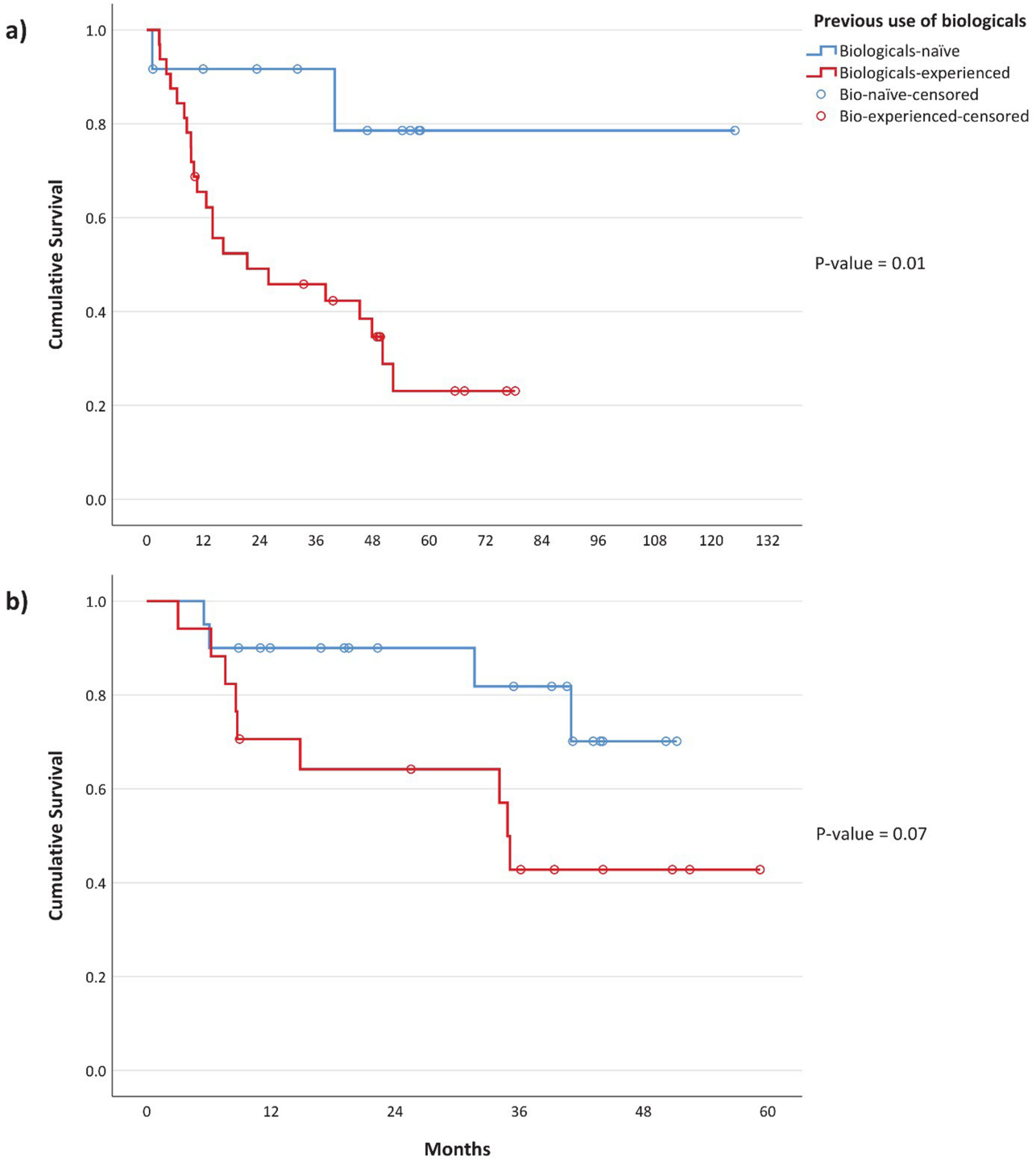

Figure 2 Kaplan-Meier plot of drug survival in patients undergoing secukinumab (**a**) and ixekizumab (**b**), according to the previous use of biologicals.

Drug Effectiveness

Forty patients in the secukinumab group and 36 patients in the ixekizumab were included in this analysis. At week 52, the cumulative rate of patients reaching PASI 75 was less in the secukinumab group (55.4%) than in the ixekizumab group (74.6%) as shown in Supplementary Table 4, Figure 3a. At week 104, 61.0% of patients in the secukinumab group and 87.3% in the ixekizumab group achieved PASI 75. However, no significant differences between groups were found (P = 0.15).

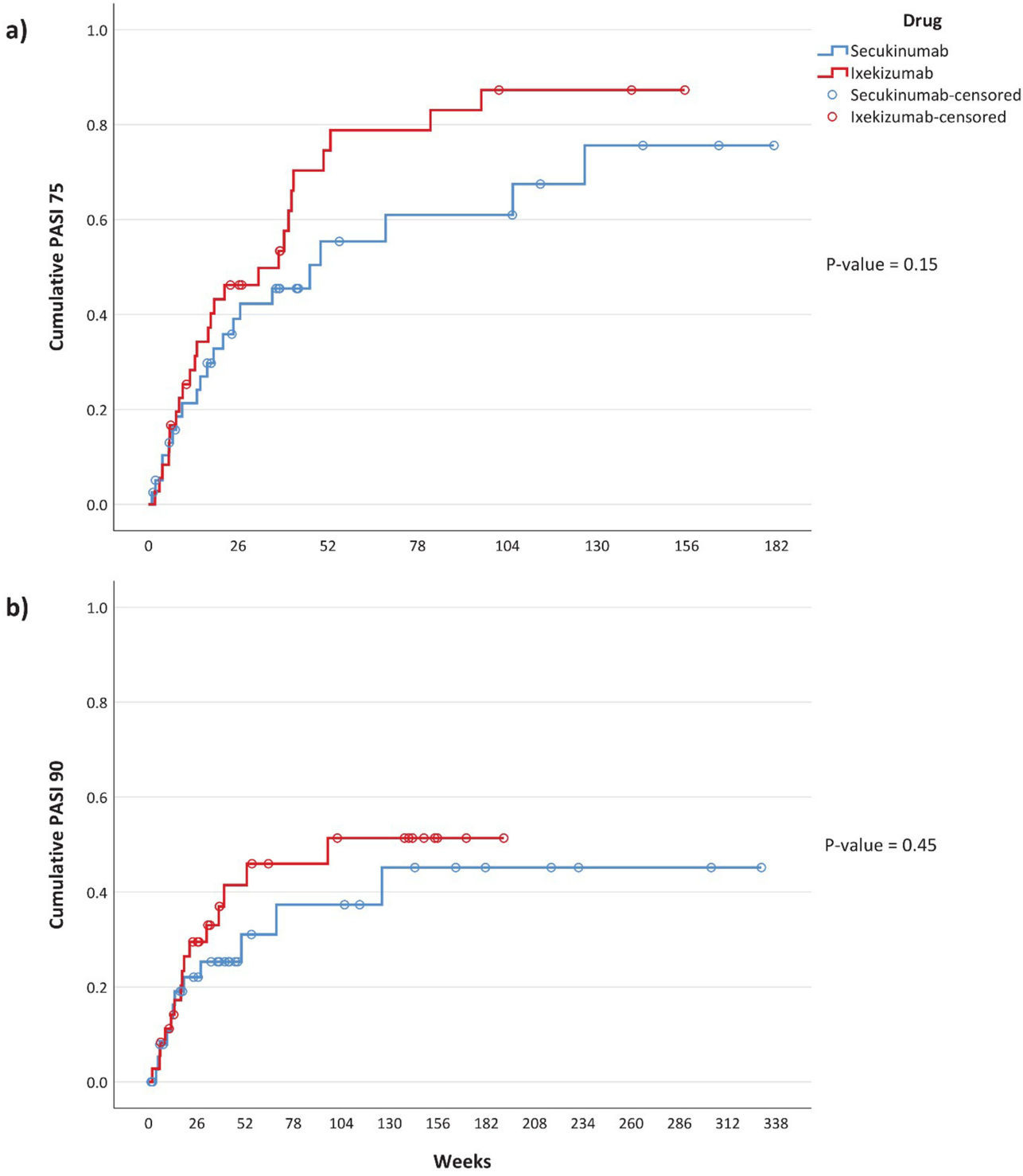

Figure 3 Kaplan-Meier plot of cumulative PASI 75 (**a**) and PASI 90 (**b**) response in patients undergoing secukinumab vs ixekizumab.

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PASI 90 response rates showed similar results (Supplementary Table 5, Figure 3b). After 52 weeks of therapy, 31.1% of patients in the secukinumab and 41.5% in the ixekizumab group achieved PASI 90. The cumulative PASI 90 at 104 weeks was 37.3% versus 51.4% in the secukinumab and ixekizumab groups. Overall, no significant differences between the groups were detected (P = 0.45).

Associated Factors and Independent Predictors for Drug Survival

Univariate analysis of factors associated with drug survival is presented in Table 2. For secukinumab, several factors were associated with lower drug survival: alcohol abuse (P = 0.008), no family history of psoriasis (P = 0.005), disease duration ≥15 years (p = 0.03), palmoplantar pustulosis (P = 0.04), absence of nail psoriasis (P = 0.04), obesity (P =

Table 2 Univariate Analysis of Factors Associated to Drug Survival, by Therapy Prescribed

		Secukinumab			Ixekizumab			HR** (95% CI)	P
		N Events	Survival at 36 Months	P*	N events	Survival at 36 Months	P*		
Demographics and general characteristics									
Sex	Male	13	55.8%	0.55	6	72.3%	0.06	0.43 (0.16–1.14)	0.09
	Female	11	58.0%		7	48.0%		1.23 (0.47–3.20)	0.67
Age at start of therapy (years)	<50	9	60.2%	0.28	8	58.3%	0.52	0.98 (0.37–2.63)	0.98
	50+	15	54.4%		5	67.5%		0.48 (0.17–1.34)	0.16
Smoking habits	Never	9	52.5%	0.56	8	57.8%	0.34	0.74 (0.28–1.92)	0.53
	Ex/Active	15	59.7%		5	66.5%		0.60 (0.21–1.69)	0.33
Alcohol abuse	No	20	63.0%	0.008	11	62.4%	0.75	0.86 (0.40–1.84)	0.70
	Yes	4	0.0%		2	62.5%		0.11 (0.01–1.01)	0.05
Family history of psoriasis	No	21	47.0%	0.005	11	57.1%	0.18	0.60 (0.29–1.25)	0.17
	Yes	3	77.9%		2	75.8%		0.97 (0.16–5.83)	0.98
Disease duration (years)	<15	6	67.7%	0.03	7	50.0%	0.18	1.65 (0.55–4.92)	0.37
	15+	18	48.9%		6	69.1%		0.35 (0.14–0.89)	0.03
Type of psoriasis									
Vulgaris	No	2	50.0%	0.86	1	0.0%	<0.001	3.46 (0.22–55.78)	0.38
	Yes	22	57.6%		12	64.1%		0.64 (0.31–1.30)	0.22
Palmoplantar pustulosis	No	15	66.8%	0.04	12	61.9%	0.97	0.90 (0.41–1.94)	0.78
	Yes	9	33.3%		1	75.0%		0.34 (0.04–2.67)	0.30
Palmoplantaris (plaque)	No	23	55.1%	0.24	8	65.7%	0.17	0.50 (0.22–1.12)	0.09
	Yes	1	75.0%		5	50.0%		2.78 (0.32–24.20)	0.35
Nail	No	20	49.2%	0.04	6	52.4%	0.42	0.65 (0.26–1.63)	0.36
	Yes	4	76.2%		7	68.5%		1.29 (0.37–4.53)	0.69
Capitillium	No	14	60.3%	0.60	4	69.2%	0.91	0.66 (0.21–2.03)	0.46
	Yes	10	53.6%		9	59.2%		0.76 (0.30–1.88)	0.55
Inversa	No	22	52.8%	0.18	11	40.3%	0.01	0.98 (0.47–2.03)	0.95
	Yes	2	83.3%		2	93.3%		0.69 (0.09–5.33)	0.72
Guttata	No	20	58.8%	0.71	10	51.8%	0.18	0.84 (0.39–1.82)	0.66
	Yes	4	50.0%		3	81.5%		0.45 (0.10–2.02)	0.30
Paradoxical	No	21	58.5%	0.98	12	64.1%	<0.001	0.64 (0.31–1.31)	0.22
	Yes	3	50.0%		1	0.0%		nc	–

(*Continued*)

Table 2 (Continued).

		Secukinumab			Ixekizumab			HR** (95% CI)	P
		N Events	Survival at 36 Months	P*	N events	Survival at 36 Months	P*		
Psoriatic arthritis	No	7	49.0%	0.78	7	66.7%	0.74	0.58 (0.20–1.65)	0.30
	Yes	17	60.2%		6	56.1%		0.79 (0.31–2.04)	0.62
Comorbidities									
Hypertonia	No	11	63.0%	0.08	10	62.2%	0.67	1.05 (0.43–2.55)	0.91
	Yes	13	48.9%		3	61.7%		0.38 (0.11–1.34)	0.13
Obesity (BMI >30)	No	12	61.9%	0.046	5	82.6%	0.046	0.53 (0.19–1.52)	0.24
	Yes	12	49.2%		8	35.4%		0.99 (0.38–2.60)	0.98
Diabetes	No	19	59.8%	0.30	8	74.7%	0.08	0.58 (0.25–1.33)	0.19
	Yes	5	42.9%		5	28.6%		0.83 (0.23–2.91)	0.77
Cardiovascular disease	No	16	57.3%	0.06	11	58.2%	0.27	0.96 (0.44–2.08)	0.91
	Yes	8	55.6%		2	72.9%		0.24 (0.05–1.13)	0.07
Depression and other psychiatric disorder	No	21	55.4%	0.54	11	62.4%	0.78	0.66 (0.32–1.38)	0.27
	Yes	3	66.7%		2	62.5%		0.94 (0.13–6.73)	0.95
Liver disease	No	20	61.9%	0.04	8	70.0%	0.33	0.67 (0.29–1.54)	0.35
	Yes	4	20.0%		5	43.0%		0.30 (0.08–1.13)	0.07
Kidney disease	No	22	59.5%	0.16	13	59.1%	0.22	0.81 (0.41–1.63)	0.56
	Yes	2	0.0%		0	100%		nc	–
Thyroid disease	No	18	61.3%	0.05	12	60.9%	0.75	0.82 (0.39–1.73)	0.61
	Yes	6	33.3%		1	75.0%		0.24 (0.03–1.97)	0.18
Atopic diseases	No	22	58.3%	0.60	11	62.3%	0.83	0.70 (0.34–1.46)	0.34
	Yes	2	37.5%		2	66.7%		0.56 (0.08–4.01)	0.57
Other autoimmune diseases	No	19	56.2%	0.92	12	62.4%	0.80	0.66 (0.32–1.36)	0.26
	Yes	5	60.0%		1	66.7%		0.91 (0.10–8.25)	0.93
Number of comorbidities	0–2	7	75.1%	0.001	5	75.0%	0.73	1.44 (0.43–4.83)	0.55
	3+	17	39.7%		8	53.3%		0.40 (0.17–0.92)	0.03
Severity and quality of life scores									
PASI	<10	10	68.0%	0.18	3	51.4%	0.84	1.08 (0.27–4.40)	0.91
	10+	12	39.4%		9	66.5%		0.41 (0.17–0.97)	0.04
DLQI	<15	4	76.2%	0.001	2	60.0%	0.10	1.62 (0.27–9.75)	0.60
	15+	4	0.0%		0	100%		nc	–
Prior therapies									
Number of previous therapies	<5	5	83.9%	0.001	5	67.4%	0.79	1.67 (0.47–5.96)	0.43
	5+	19	35.7%		8	59.0%		0.41 (0.18–0.95)	0.04
Previous biologicals	No	2	91.7%	0.01	4	81.8%	0.07	1.34 (0.24–7.38)	0.74
	Yes	22	45.8%		9	42.8%		0.78 (0.36–1.71)	0.54

Notes: *Log rank test. **Univariate Cox regression analysis of drug discontinuation differences between Ixekizumab and Secukinumab in each strata of the investigated variables.

Abbreviations: BMI, body mass index; CI, confidence interval; DLQI, dermatology life quality index; HR, hazard ratio; nc, not computable; PASI, psoriasis area severity index; SD, standard deviation.

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Table 3 Multivariable Analysis of Independent Predictors of Drug Discontinuation, by Therapy Prescribed

		Secukinumab		Ixekizumab	
		HR (95% CI)	**P***	**HR (95% CI)**	**P***
Sex	Male Female	–	–	1 3.47 (1.09–10.99)	0.03
Psoriasis inversa	No Yes	–	–	1 0.15 (0.03–0.72)	0.02
Nail psoriasis	No Yes	1 0.27 (0.09–0.83)	0.02	–	–
Number of previous therapies	<5 5+	1 5.52 (1.98–15.40)	0.007	–	–

Notes: *Multivariable Cox regression model with forward stepwise selection algorithm.
Abbreviations: CI, confidence interval; HR, hazard ratio.

0.046), liver disease (P = 0.04), three or more comorbidities (P = 0.001), DLQI ≥15 (P = 0.001), five or more previous therapies (P = 0.001), and previous use of biologics (P = 0.01). For ixekizumab, psoriasis other than vulgaris (P <0.001) or inversa (P = 0.01), paradoxical psoriasis (P <0.001), and obesity (P = 0.046) were associated with reduced drug survival.

In total, four independent predictors were identified in the multivariable regression analysis (Table 3). In the secukinumab group, nail psoriasis (HR: 0.27, 95% CI: 0.09–0.83, P = 0.02) was assessed to be a protective factor favoring drug continuation, while five or more previous therapies (HR: 5.52, 95% CI: 1.98–15.40; P = 0.007) was determined to be a risk factor. In the ixekizumab group, psoriasis inversa was identified as a protective factor (HR: 0.15, 95% CI: 0.03–0.72, P = 0.02), and female sex (HR: 3.47, 95% CI: 1.09–10.99, P = 0.03) was determined to be a risk factor for drug discontinuation.

Drug survival differences between ixekizumab and secukinumab in each stratum of the investigated variables are reported in Table 3, Figure 4. Overall, drug survival was higher in the ixekizumab group, especially for patients with ≥15 years of disease duration (HR: 0.35, 95% CI: 0.14–0.89; P = 0.03), 3 or more comorbidities (HR: 0.40, 95% CI: 0.17–0.92; P = 0.03), PASI >10 (HR: 0.41, 95% CI: 0.17–0.97; P = 0.04), and five or more previous therapies (HR: 0.41, 95% CI: 0.18–0.95; P = 0.04).

Discussion

This study with up to ten years of follow-up data demonstrates long-term efficacy and drug survival of secukinumab and ixekizumab in psoriasis patients. Patients receiving secukinumab were comparable to the ones receiving ixekizumab in terms of age, sex, and disease severity, but more of them had PsA and had undergone previous biologic treatment, especially consisting of TNFα-inhibitors. The higher frequency of TNFα inhibitors that were used as previous therapy could correlate with the higher number of PsA in this group. In contrast, patients with nail or psoriasis inversa were more likely to be treated with ixekizumab. Both, secukinumab and ixekizumab have demonstrated good effect in nail psoriasis in previous studies, but ixekizumab already leads to improvement within two weeks and more studies showed superiority to other systemic treatments.[19–21] A possible explanation for the higher number of patients with psoriasis inversa in the ixekizumab group could be the specific demonstration of its positive effect on genital psoriasis and impact of symptoms on sexual activity.[22]

Regarding efficacy at week 52, in our study, patients receiving ixekizumab achieved more rapidly and higher PASI 75 and 90 response rates than patients treated with secukinumab (74.6% versus 41.5%; 55.4% versus 31.1%), although the difference was not significant. The same trend was observed at week 104 (87.3% versus 61.0%; 51.4% versus 37.3%). At week 52, except for the comparable rate achieving PASI 75 with ixekizumab, the efficacy was slightly lower when compared to previous real-world studies. Our results differed from those of Herrera-Acosta et al in which PASI 75 was

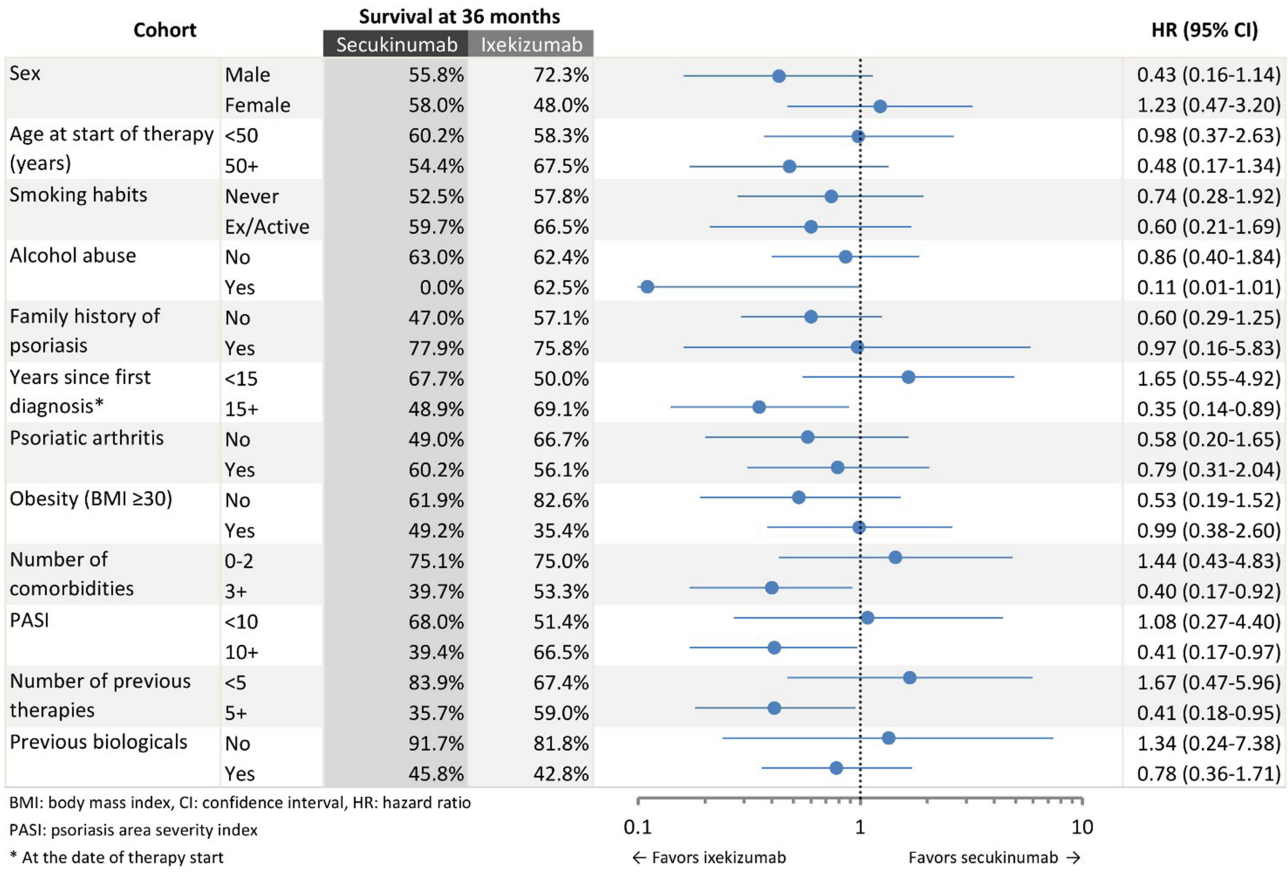

Figure 4 Estimated hazard ratios for drug discontinuation of ixekizumab vs secukinumab among selected factors.

achieved by 75.9% and 64.4% in the ixekizumab and secukinumab groups, respectively, and PASI 90 was reached by 62.1% and 49.2%, respectively, at week 52.[15] This difference could be explained by a higher representation of male and biologic-naïve patients (59.3% and 35.6%, respectively) than in our study (50% and 27.3%, respectively), two factors that have been described to be associated with higher efficacy of biologics in psoriasis.[23,24]

The median overall drug survival of secukinumab in our study population was 45.3 months. Previous studies have shown a lower median survival rate of 34.3 months.[23] The drug survival rate for secukinumab at week 52 (72.1%) in our analysis was comparable with previous studies (drug survival at week 52 between 68% and 88%).[15,23,25–28] For ixekizumab, drug survival was comparable with other studies.[23,27,28] Discrepancies in drug survival rates may occur due to various factors, such as different dosing regimens, disease-related characteristics of the study cohort (such as treatment experience and comorbidities, including PsA), different baseline demographic characteristics (such as age, sex, and risk factors, such as smoking), available treatment alternatives, patients' attitudes and preferences, and physician- and center-related factors (such as different experiences and preferences for specific drugs).[29] In our study, patients showed longer drug survival in terms of ixekizumab when compared with secukinumab even if the patient was biologic-naïve or -experienced, a result that is also consistent with those from previous studies.[23,27,30,31] In contrast to other studies, no significant difference in drug survival was detected between the two IL-17 inhibitors. An explanation for longer drug survival of ixekizumab could be the higher efficacy as explained by the 50–100 fold higher affinity of ixekizumab to IL-17A.[17] Drug survival was significantly superior among biologic-naïve patients in the secukinumab group, a finding that is also supported by other studies.[27,30] For secukinumab, a positive family history of psoriasis, no alcohol consumption, shorter disease duration, nail psoriasis, and/or absence of palmoplantar pustulosis, no obesity, no liver conditions, fewer previous therapies, no previous biologics, lower DLQI, and fewer comorbidities were significantly associated with a longer drug survival. The positive influence of family history on biologic drug survival in psoriasis has

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previously been demonstrated.[27] Previous studies suggest obesity as a risk factor for shorter drug survival, and PsA has been identified, although controversially, as protective factor in one study and negative factor for secukinumab survival in another.[27,32,33] This discrepancy could be demonstrated in our cohort for obesity only. For ixekizumab, a significantly higher survival rate could be observed in patients with pure psoriasis vulgaris without involvement of special locations, with psoriasis inversa, or without paradoxical psoriasis and in non-obese patients. A trend toward lower surveillance in females was found. Male sex is a well-known factor associated with higher biologic drug survival, including IL-17-inhibitors.[5,23,34] This factor was only of borderline significance in our analysis.

Independent predictors for longer drug survival were nail psoriasis and fewer previous therapies for secukinumab and male sex and psoriasis inversa for ixekizumab.

Reasons for discontinuation of secukinumab were most frequently primary lack of efficacy (41.7%) followed by loss of efficacy (25.0%) and adverse events (12.5%), while for ixekizumab, loss of efficacy (46.2%) was the most frequent reason followed by adverse events and lack of efficacy (both 23.1%). Previous studies confirmed these three reasons as the main cause for drug discontinuation.[23,30,35] Graier et al also reported that lack of efficacy occurred more often in patients receiving secukinumab (29.2%) than in those receiving ixekizumab (20.3%). Despite better clearance results associated with ixekizumab rather than secukinumab in our study, the tolerability of ixekizumab (23.1%) was worse when compared with secukinumab (12.5%). A recent meta-analysis supports our findings.[35]

The main limitation of this study is its retrospective design, which led to dependence on quality of available data in patient records. Also, the monocentric setting did not allow our results to be generalized to psoriasis-affected patients in other regions. Furthermore, the higher prevalence of bio-naïve and obese patients in the ixekizumab group could influence the comparison results. Finally, the modest number of patients in both study populations may have limited interpretation of performances of secukinumab and ixekizumab. Moreover, a limitation of our study is that the disease duration until initiation of the IL-17 inhibitor was very long in most of our patients. A recent study has shown that a therapy with the IL-23 inhibitor guselkumab leads to a better response and a longer-lasting effect after discontinuation of the therapy when used in patients with a short disease duration (<2 years).[36] Since only one patient in our cohort has a disease duration of less than 2 years, we cannot investigate the factor of early disease intervention.

In conclusion, in our study ixekizumab showed a non-significant better long-term efficacy and drug survival compared to secukinumab, although tolerability is lower compared to secukinumab. Well-known factors associated with longer drug survival of secukinumab, such as biologic-naïve patients, fewer previous therapies, no obesity, and positive family history, could be confirmed in addition to new factors, such as low DLQI, alcohol abstinence, nail- or palmoplantar pustulosis, and fewer comorbidities. Factors associated with longer drug survival of ixekizumab were psoriasis inversa, absence of paradoxical psoriasis, and non-obesity. Independent predictors for longer drug survival were nail psoriasis and fewer previous therapies for secukinumab and male sex and psoriasis inversa for ixekizumab.

Study Approval Statement

This study was approved by the Cantonal Ethics Committee Bern, Switzerland (KEK nr. 2022-00645).

Data Sharing Statement

The datasets presented in this article are not readily available due to ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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