Secukinumab real world drug retention compared to TNF-alpha inhibitors in psoriatic arthritis

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Abstract

Objective

To prospectively study real-world efficacy and safety of secukinumab in psoriatic arthritis (PsA) patients from the Israeli registry of inflammatory diseases.

Methods

PsA patients fulfilling the CASPAR criteria were included in the analysis from 2010 to 2019. The primary endpoint was secukinumab drug retention compared to other TNF-α inhibitors (TNFi). Bivariate and multivariate analyses were made by Cox regression analysis. Drug retention according to treatment line was examined with Kaplan-Meier curves.

Results

Included were 404 PsA patients who had 709 treatment courses during the study period. Ninety patients had been treated with secukinumab (22%). The secukinumab-treated patients were significantly older and their disease duration was longer. Secukinumab was less likely to be the first line of treatment compared to TNFi. Secukinumab had a drug retention comparable to TNFi, and a better drug retention than TNFi among biologic-experienced patients. Neither methotrexate combination nor body mass index affected the inefficacy event rate. Secukinumab had a similar rate of adverse events as TNFi.

Conclusion

This multicentre real-world study demonstrated that secukinumab had a drug retention comparable to TNFi. Secukinumab had a better drug retention than TNFi among biologic-experienced patients. IL-17 inhibition is an effective mechanism of action to treat PsA in real life.

Key words

secukinumab, psoriatic arthritis, drug retention, real-world, TNFα inhibitors

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Introduction

Psoriatic arthritis (PsA) is a seronegative spondyloarthritis with peripheral and axial inflammation, enthesitis and dactylitis, which have a major impact on patient function and quality of life (1, 2). The treatment of PsA has been revolutionised by the advances in the understanding of its pathogenesis (3). It has been shown that the interleukin (IL)-17 pathway plays a pivotal role in PsA. The role of IL-17 in psoriatic disease is supported in studies that have demonstrated elevated levels of IL-17 in the serum, skin lesions and synovial tissues of patients with active psoriasis and PsA (4-6), correlating with measures of disease activity (4, 7).

Secukinumab (Cosentyx) is a human immunoglobulin-G1 monoclonal antibody that selectively binds to and neutralises IL-17A. Several prospective randomised controlled trials have demonstrated the efficacy and safety of secukinumab (8). In the FUTURE 1 and FUTURE2 studies (9-11), biologic naïve as well as experienced patients who received secukinumab were significantly more likely to achieve an ACR20 response compared with patients receiving placebo at week 24, with the benefit having been sustained at 52 and 104 weeks. The drug was well-tolerated in patients treated with either the drug or placebo. These pivotal trials have led to approval of the drug for PsA by both the European Medicines Agency (2015) and the Food and Drug Administration (2016). Although randomised controlled trials are instrumental for introducing drugs into clinical use, they do not always represent real-world patients. Therefore, describing real-world experience with drugs is essential and can contribute to informed clinical decisions.

To date, few descriptions of real-world experiences with secukinumab in PsA have been published (12-14).

Given the paucity of real-world data on secukinumab for the treatment of PsA, the aim of our study was to assess its drug retention and to compare it to tumour necrosis factor α inhibitor (TNFi) agents in a cohort of patients with PsA included in the Israeli registry of inflammatory diseases.

Patients and methods

Study design

Our study was designed to examine secukinumab drug retention compared to TNFi treatments in PsA patients registered in the Israeli registry of inflammatory diseases. The Israeli registry has been collecting prospective data of rheumatologic patients treated in 6 medical centres in Israel since 2010. The registry was approved by the institutional ethical committee in each hospital according to the declaration of Helsinki (approval 0322-10TLV). PsA patients fulfilling the CASPAR criteria (15) who signed an informed consent form were included. In order to be eligible for inclusion in the analysis, the patient had to have at least one follow-up visit until study closure in November, 2019. In Israel, biologic disease-modifying anti-rheumatic drugs (bDMARDs) can be prescribed for PsA patients after failure of 2 conventional synthetic DMARDs, and in axial disease after failure of 2 non-steroidal anti-inflammatory drugs. Secukinumab is prescribed in the 150 mg dose if it is given as the first-line bDMARD, and in the 300 mg dose when given for a biologic-experienced patient.

Methods

Follow-up visits were recorded in the registry at 6-month intervals. Data on demographics, comorbidities (including body mass index [BMI]), and disease characteristics (duration since first musculoskeletal manifestation and type of involvement) were collected at the first visit. Additional information on disease activity, drug therapy or change and reason for change was collected at all subsequent visits. The primary endpoint was secukinumab drug retention compared to the other available TNFi drugs, specifically, infliximab (IFX), etanercept (ETA), adalimumab (ADA), and golimumab (GOL). Certolizumab-pegol was not included due to its unavailability in Israel until recently.

We recorded treatment courses so that every PsA patient who switched from one biologic treatment to another could be included more than once. A treatment course was included if the medication was used for a minimum of 3 months and up to 3 years of follow-up.

Table I. Patient characteristics and adverse events according to drug.

	SEC n=90	ETA n=202	IFX n=87	ADA n=227	GOL n=103
Female (%)	45 (50)	113 (56)	47 (54)	120 (53)	54 (52)
Age at diagnosis (yrs)	41.2 ± 14.4	42.6 ± 14.5	41.2 ± 4.2	41.5 ± 14.0	39.9 ± 15.7
Age at episode (yrs)	54.8 ± 13.1	50.1 ± 14.1*	49.7 ± 13.8*	50.1 ± 14.2*	52 ± 15.4
Disease duration (yrs)	13.7 ± 13.1	7.8 ± 8.6**	8.5 ± 9.4**	8.7 ± 9.0**	12.1 ± 11.3
Disease phenotype [missing] (%)†					
Oligoarthritis	19 [9] (23)	74 [7] (38)*	28 [7] (35)	79 [12] (37)*	38 [4] (38)*
Polyarthritis	68 [2] (77)	117 [2] (59)*	56 [3] (67)	132 [5] (59)*	59 [3] (59)*
Axial disease	25 [5] (29)	42 [7] (22)	19 [8] (24)	49 [12] (23)	23 [3] (23)
Enthesitis	49 [7] (59	75 [4] (38)*	31 [7] (39)*	82 [13] (38)*	43 [3] (43)*
Dactylitis	40 [4] (47)	76 [4] (38)	29 [4] (35)	81 [7] (37)	48 [0] (47)
DIPs involvement	45 [6] (54)	78 [4] (39)*	33 [6] (41)	90 [8] (41)	39 [4] (39)
BMI, n (%)					
<24.9	17 (19)	49 (28)	14 (17)	53 (26)	26 (29)
25-34.9	57 (63)	107 (60)	57 (69)	125 (62)	53 (58)
≥35	16 (18)	21 (12)	12 (14)	25 (12)	12 (13)
Missing	0	25	4	24	12
Smoking status, n (%)					
Never smoked	42 (50)	81 (52)	43 (54)	104 (56)	52 (62)
Past and current smokers	42 (50)	76 (48)	37 (76)	83 (44)	32 (38)
Missing	6	45	7	40	19
MTX combination n (%)	48 (53)	125 (62)	68 (78)**	147 (65)	58 (56)
DAS28 ESR, n (%)					
<3.2	8 (15)	23 (28)	8 (17)	32 (32)*	14 (33)*
≥3.2	47 (85)	58 (72)	39 (83)	67 (68)	29 (67)
Missing	35	121	40	128	60
Adverse events, total n††	7	18	8	16	3
Infectious (n)	Epidermal cyst (1) Recurrent infections (1)			Viral disease (1)	
Allergy (n)		2	Urticaria (1)	Allergic rash (1)	Facial oedema (1)
Dermatologic (n)	Rash (1)	Psoriasis (1) Rash (1)		Psoriasis ex. (1) Rash (1)	
Gastrointestinal (n)	IBD (1)	IBD ex. (1) Abnormal LFT (1)	Abnormal LFT (1)	Abnormal LFT (1)	
Haematologic (n)		Leukopenia (1)			
Malignancy (n)	1	1		Adenocarcinoma (1) Lymphoma (1)	
Neurologic (n)		2			Headache (1)
Miscellaneous (n)	Hot flushes (1) Dizziness (1)		Weight loss (1) Chills (1)	Chest pain (1)	SVT (1)
Missing (n)		8	4	7	

*$p \leq 0.05$; **$p \leq 0.001$; †Oligoarthritis and polyarthritis are mutually exclusive, while axial disease, enthesitis, dactylitis and involvement of DIPs can exist concomitantly. ††If the specific reaction/adverse event manifestation is not known – only the total number of events is written.
SEC: secukinumab; ETA: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab**;** DIPs: distal interphalangeal joints; BMI: body mass index; MTX: methotrexate; DAS28: disease activity score-28; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease; ex: exacerbation; SVT: supraventricular tachycardia.

Medication cessation was recorded as being due to inefficacy event or adverse effects. Drug retention was defined as proportion of patients remaining on the treatment for 1, 2 and 3 years after treatment initiation.

Statistical analysis

Differences between baseline patient characteristics in drug courses were analysed with the Chi-square test. Bivariate and multivariate analysis of the factors that affect the drug event-free retention was done by Cox regression analysis with hazard ratio (HR) and 95% confidence interval (CI). A two-tailed *p*-value of 0.05 or less was considered statistically significant. Drug retention according to treatment line (all treatment lines, or 2nd and above treatment lines) was examined by Kaplan-Meier curves. Statistical analyses were made using SPSS software v. 25 for windows (IBM corp., Armonk, NY).

Results

Baseline characteristics

The study population consisted of a total of 404 PsA patients with 709 treatment courses during the study period from 2010 until 2019.

Fifty-two percent of the patients were females, and 94% were of Jewish origin. The mean age at diagnosis of PsA was 41.5±14.5 years, and the mean age at the start of a treatment course was 50.9±14.2 years. The mean disease

Table II. Inefficacy events according to treatment and drug retention at 1, 2, and 3 years.

Drug	Total episode n	Inefficacy events, *n* (%)	HR	95% CI	*p*-value	1st yr retention %	2nd yr retention %	3rd yr retention %
SEC	90	30 (33.3)	1		0.095	86	58	41
ETA	202	86 (42.6)	1.16	0.77-1.76	0.479	75	58	50
IFX	87	34 (39.1)	1.01	0.62-1.65	0.966	82	64	52
ADA	227	103 (45.4)	1.36	0.9-2.04	0.143	71	53	46
GOL	103	50 (48.5)	1.64	1.05-2.59	0.031	63	50	42

HR: hazard ratio; CI: confidence interval; SEC: secukinumab; ETA: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab

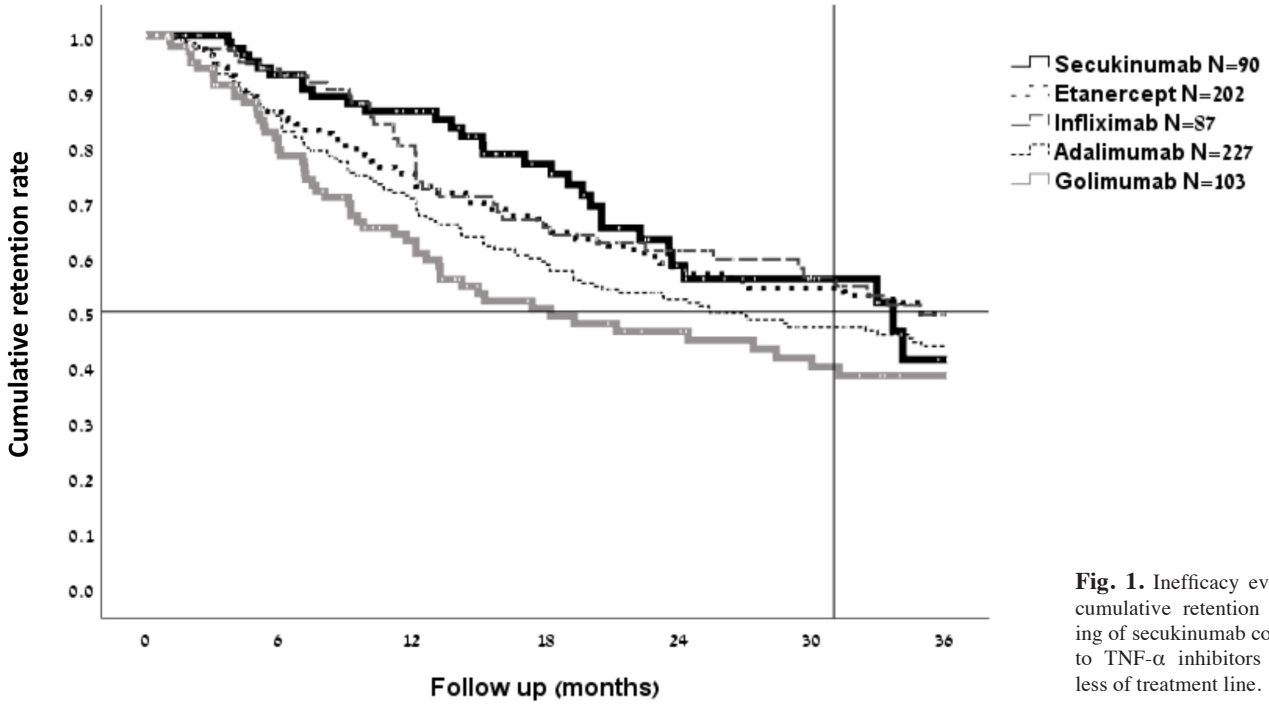


Fig. 1. Inefficacy event-free cumulative retention according of secukinumab compared to TNF-α inhibitors regardless of treatment line.

duration at treatment initiation was 9.5±10.1 years. The patients were taking methotrexate (MTX) in combination with the biologic treatment in 446 out of 709 (62.9%) of the courses. One-quarter of the patients were of normal weight (body mass index [BMI] 18.5–24.9), 55% were considered overweight or class I obese (BMI 25–34.9), and 11% were class II or class III obese (BMI >35). The BMI data for 9% of the study population were missing. Forty-five percent of patients never smoked, 22% were past smokers, and 15% were current smokers (smoking status was missing in 19%). There were significantly more drug inefficacy events and drug switches in recent years (2016–2019: 104 out of 233, HR (95%CI) 1.62 (1.25–2.09) compared to before 2013 (144 out of 328, HR 1, $p \leq 0.001$). Biologic-experienced patients had more inefficacy events than biologic-naïve patients (124 out of 299, HR 1, compared to 190 out of 410, HR (95%CI) 1.34 (1.06–1.68), $p=0.013$).

Patients treated with secukinumab

Ninety of the 404 study patients had been treated with secukinumab (22%), 87 (22%) with IFX, 202 (50%) with ETA, 227 (57%) with ADA, and 103 (25%) with GOL, for a total of 709 treatment courses. Patient characteristics according to the drug used are presented in Table I. Secukinumab treatment courses took place significantly more recently, with 91% (82 courses) beginning between 2016 and 2019 compared to 33% (233 courses) of TNFi courses ($p<0.0001$). Patients treated with secukinumab were not significantly different from those treated with TNFi with regard to gender, ethnicity, or BMI (Table I). Age at secukinumab treatment initiation (54.8±13.1 years) was significantly older than age at ETA initiation (50.1±14.1, $p=0.018$), IFX (49.7±13.8, $p=0.01$) and ADA (50.1±14.2, $p=0.009$), but similar to that of GOL (52±15.4, $p=0.214$). Disease duration was also significantly longer for secukinumab and GOL treatment courses (13.7±13.1 years and 12.1±11.3 years, respectively, $p=0.377$) compared to IFX (8.5±9.4), ETA (7.8±8.6), and ADA (8.7±9) ($p<0.001$ for all).

Secukinumab was used as a first-line treatment in 13 patients, and it was more likely to be a second- (17%), third- (21%), fourth- (23%) or beyond (24%) line of treatment than all of the other TNFi (30%, 15%, 8%, and 4% re-

spectively, $p<0.0001$ for IFX, ETA, and ADA, and $p=0.003$ for GOL). More patients treated with secukinumab had polyarthritis (77%), similarly to those treated with IFX, but significantly different from the population treated with ETA (59%, $p=0.002$), ADA (59%, $p=0.004$), and GOL (59%, $p=0.008$). In contrast, there were significantly fewer secukinumab courses for patients with oligoarthritis (23%) compared to ETA (38%, $p=0.025$), ADA (37%, $p=0.037$), and GOL (38%, $p=0.037$). A similar trend was observed for IFX (35%, $p=0.121$), although the difference did not reach statistical significance. Patients treated with secukinumab were more likely to have enthesitis and involvement of distal interphalangeal joints (DIPs), but axial involvement was similar for all treatments (Table I).

Secukinumab drug retention: primary outcome

The drug retention of secukinumab after 1 year of treatment was 86%, higher than that of TNFi. After 3 years of treatment, the drug retention of secukinumab was 41%, which was not significantly different than that of TNFi (Table II and Fig. 1). The mean inefficacy event free survival of secukinumab was 26.6 months (95% CI 23.9–29.2), and of ETA 24.9 (23–26.8), IFX 25.9 (23.2–28.6), ADA 23.1 (21.3–25) and GOL 20.9 (18–23.7) (p-values for ETA, IFX, ADA are non-significant, and for GOL $p=0.016$). Figure 1 demonstrates time to inefficacy events of secukinumab and other TNFi during 3 years of follow-up regardless of treatment line. Time to an inefficacy event was longer for secukinumab than any other TNFi. The multivariate analysis for the model controlled for year of episode (2010-2015 or 2016-2019), DAS28-ESR (high disease activity or remission to medium disease activity), polyarthritis disease type, and biologic treatment line. The HRs for inefficacy events were significantly higher for all TNFi: ETA 2.42 (95% CI 1.46–4.0, $p=0.001$), IFX 1.92 (95% CI 1.10–3.36, $p=0.022$), ADA 2.7 (95% CI 1.66–4.40, $p<0.001$), and GOL 2.58 (95% CI 1.6–4.16, $p<0.001$).

As a first-line treatment, secukinumab drug retention was similar to other TNFi, except for GOL which had a worse drug retention (Table III). After 3 years, 76% of the biologic-naïve patients remained on secukinumab compared to 50% of those on ETA, 52% on IFX, 56% on ADA, and 34% on GOL. Even though secukinumab was used more often as fourth-line biologic or even beyond, secukinumab drug retention was still better than other TNFi in biologic-experienced patients. When only the second-line and beyond treatment courses were taken into account in the multivariate analysis, it was still significantly higher than ETA (2.0, 95% CI 1.09–3.68, $p=0.026$), ADA (3.31, 95% CI 1.89–5.81, $p<0.001$), and GOL (2.26, 95% CI 1.34–3.82, $p=0.002$) compared with secukinumab, while it was not significantly different for IFX (HR 1.73, 95% CI 0.91–3.30, $p=0.093$) (Supplementary Fig. S1).

Table III. Inefficacy events and drug retention according to line of treatment.

Drug	Inefficacy events/ Tx episodes *n/n* (%)	HR (95% CI)	1st yr retention %	2nd yr retention %	3rd yr retention %
Biologic naïve (treatment as 1st line)					
SEC	2/13 (15.4)	1	92	92	76
ETA	56/130 (43.1)	3.3 (0.81-13.54)	76	59	50
IFX	11/28 (39.3)	2.89 (0.64-13.3)	81	63	52
ADA	39/103 (37.9)	2.77 (0.67-11.46)	79	63	56
GOL	16/25 (64)	5.21 (1.2-22.65)*	60	43	34
Biologic experienced (treatment as 2nd line and above)					
SEC	28/77 (36.4)	1*	85	51	32
ETA	31/72 (43.1)	1.02 (0.61-1.71)	73	57	50
IFX	26/59 (44.1)	0.97 (0.57-1.66)	80	60	49
ADA	68/124 (54.8)	1.62 (1.04-2.51)*	63	43	32
GOL	37/78 (47.4)	1.48 (0.9-2.41)	64	48	41

*$p\leq0.05$.

Tx: treatment; HR: hazard ratio; CI: confidence interval; SEC: secukinumab; ETA: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab.

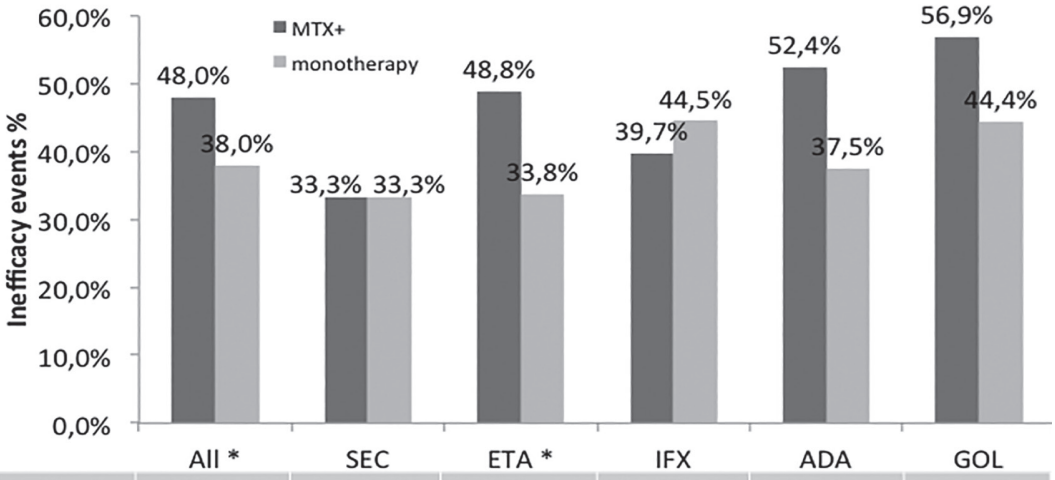
MTX, BMI, and inefficacy events

In an attempt to better characterise the patient populations most likely to benefit from the use of secukinumab, we examined the relationship between MTX use, BMI, and the occurrence of inefficacy events. Patients treated with MTX were more likely to be younger than 50 years of age (66%, compared to 38% in patients over 70 years of age, $p<0.001$) and weighing over 100 kilograms (77% compared to 59% weighing 89 kilograms or under, $p=0.002$). MTX was used in combination with the bDMARD in 72% of treatment initiations before 2013 compared to 48% after 2016 ($p<0.001$). The PsA phenotype did not have any significant effect on MTX use. MTX was used more often with IFX (78%) than with secukinumab (53%), ($p=0.001$) (Table I). In general, patients treated with combination therapy with MTX were more likely to have an inefficacy event (Fig. 2), especially the biologic-naïve patients [87 inefficacy events out of 191 (HR (95%CI) 1.65 (1.12–2.43] in patients given MTX with a first-line biologic compared to 37 out of 108 in patients on first-line monotherapy, $p=0.011$]. On the other hand, when MTX was administered in combination with secukinumab, it did not have a significant effect on the inefficacy event rate.

An increased BMI did not affect the drug retention of secukinumab, while it significantly affected the drug retention of all treatments as a group. Drug retention of treatments in the high BMI group (≥35) was 65% and 29% at 1 and 3 years, respectively, compared to 76% and 50%, respectively for a BMI <35. The rate of inefficacy events of secukinumab, as for IFX and GOL, was not affected by the BMI group (Suppl. Table S1).

Secukinumab adverse events

Secukinumab had a similar rate of adverse events compared to TNFi, and a similar adverse event-free drug retention after 1, 2, and 3 years (Table I; Fig. 3).



	All *	SEC	ETA *	IFX	ADA	GOL
MTX combination (n/total)	214/446	16/48	61/125	27/68	77/147	33/58
Monotherapy (n/total)	100/263	14/42	26/77	10/19	30/80	20/45
Hazard ratio (95% CI) **	1.32 (1.04-1.67)	0.75 (0.37-1.55)	1.59 (1.01-2.53)	0.82 (0.4-1.7)	1.46 (0.96-2.23)	1.44 (0.82-2.5)

Fig. 2. Effect of methotrexate on rate of inefficacy events according to biologic treatment.
*$p \leq 0.05$; **MTX combination compared to monotherapy.
MTX: methotrexate; SEC: secukinumab; ETA: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab; n: number; CI: confidence interval.

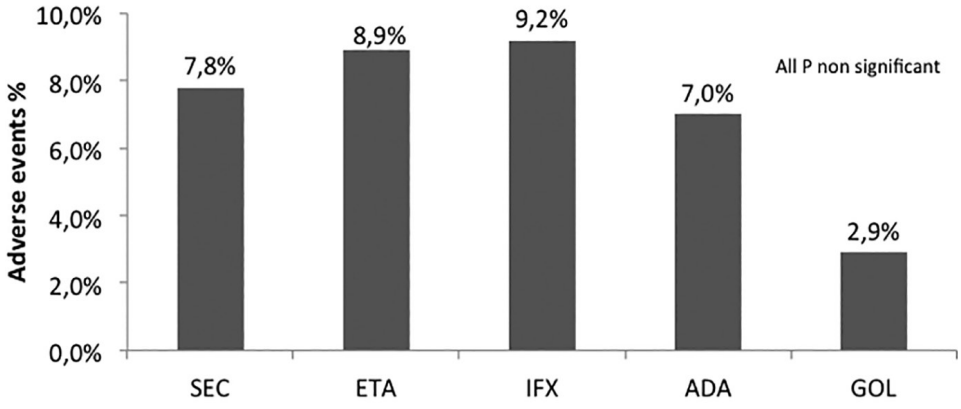
Discussion

This real-world multicentre study on PsA patients in Israel found that secukinumab had a similar rate of inefficacy events and retention compared to TNFi treatments, even though secukinumab was usually given as a second-line treatment or beyond, and for patients with longer disease duration. Most secukinumab courses were given in recent years (91% after 2016), in line with the recent local approval of the drug for the treatment of PsA. In general, drug retention and survival rates of TNFi in PsA patients are better for biologic-naïve compared to biologic-experienced patients. A recent study by the EuroSpa collaboration of 12 registries from Europe (16) reported TNFi retention rates in over 14,000 biologic-naïve PsA patients. The 1-year retention rate was 77% for all TNFi, and the 2-year retention rate was 68%. For their biologic-experienced patients, the Portuguese registry (17) indicated lower retention rates for second and third TNFi therapy in PsA patients, with a 2-year retention for second and third TNFi therapy of 50.3% and 34%, respectively, in comparison to 61.7% for first-line TNFi treatment. In the Finnish registry ROB-FIN (18), TNFi drug survival for PsA patients was 80%, 72%, and 66% for the first, second, and third year and the rate was similar between first-line and the second- or third-lines of therapy. The NOR-DMARD study from Norway (19) reported a 1-year drug survival of 74% for all PsA patients, and a rate of 83% for biologic-naïve compared to 56% for patients on second-line TNFi therapy.

The practice of prescribing secukinumab as other than first-line therapy is endorsed by the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation guideline of PsA (20). The IL-17 inhibition mechanism of action is reserved for the third line of treatment, or after primary failure or a severe adverse event to TNFi, and in some cases of severe psoriasis. The 2019 European League against Rheumatism (EULAR) recommendation (21) changed the 2015 (22) specification of TNFi as first-line biologic therapy, and now IL-17 inhibitors can be considered first-line when there is relevant skin involvement in peripheral and axial disease.

Three small studies investigated PsA patients who were prescribed secukinumab in various countries. Sunkureddi *et al*. reported the characteristics of 153 patients with PsA receiving secukinumab and the reasons for its initiation (12). Secukinumab was the first biologic treatment in 25% of their cohort. The most common reasons for secukinumab prescription were its known efficacy (84.2%) and the failure of other prior biologics (80.9%). Similar to our experience, a study from the Musgrave Park Hospital in Belfast (14) on 45 axial spondyloarthritis and PsA (peripheral and axial) patients also showed that secukinumab was mostly given to patients failing 2 or 3 TNFi drugs. Of 34 patients of their patients who continued the drug after 4 months, 27% of them stopped treatment after one year. Those figures are higher than ours where only 14% of the patients discontinued secukinumab after 1 year (Table II). Data on both axial spondyloarthropathy and PsA patients from the ATTRA registry (13) from the Czech Republic showed that practitioners chose to use secukinumab as frequently as TNFi for naïve patients, but that they usually chose to treat with another TNFi after a first TNFi failure.

Real-world data of secukinumab in PsA are rare, but there are some publications on its use in psoriasis. A recent meta-analysis (23) of 43 real-world



Adverse events (n/total)	7/90	18/202	8/87	16/227	3/103
Hazard ratio (95% CI)	1	1.07 (0.45-2.58)	1.07 (0.39-2.96)	0.9 (0.37-2.19)	0.4 (0.1-1.55)

Fig. 3. Adverse events rate of secukinumab and TNF-α inhibitors in study period.
SEC: secukinumab; ETA: etanercept; IFX: infliximab; ADA: adalimumab; GOL: golimumab**;** HR: hazard ratio; n: number; CI: confidence interval.

studies on secukinumab in psoriasis reported an 80% 1-year survival, which is close to our results of 86%. A European multicentre study (24) included 330 psoriasis patients from 11 centres: 52.4% used secukinumab as a second or beyond biologic line of treatment, and 21.5% of those patients had also PsA. The 1-year drug survival was 83%, and the biologic-naïve patients had better drug survival, similar to our results. Contrary to our results, however, obese patients did more poorly than non-obese patients, and MTX combination therapy was associated with lower drug survival (as seen in the TNFi-treated patients in our study). A single-centre study from Greece (25) on 83 psoriasis secukinumab-treated patients found that the 2-year drug survival was 74.5%, which is higher than in our experience (58%). In the Greek study, 56.3% of the patients were biologic naïve, and that may partly explain the higher rate of drug survival. Of note, 43.9% of the Greek patients had coexisting PsA, and those patients had statistically significant lower PASI response rates.

Numerous studies demonstrated that switching between TNFi treatments results in lower response rates than first-line therapy (19, 26, 27). In our study, secukinumab had a better drug retention and a lower HR for an inefficacy event than TNFi in biologic-experienced patients. This finding may suggest that switching to a drug with the same mechanism of action is more likely to result in failure compared to switching to a drug with another mechanism, namely IL-17 inhibition.

We observed that the HR for an inefficacy event in biologic-experienced patients was significantly higher for all TNFi compared to secukinumab, even though secukinumab-treated patients were more likely to have long-standing polyarticular disease with enthesitis, dactylitis and DIPs involvement. A recent meta-analysis (28) of RCTs of biologic treatments for PsA showed that IL-17 inhibitors had the best relative risk of response for enthesitis and dactylitis. The EXCEED performed a head-to-head comparison between secukinumab 300 mg and ADA for biologic-naïve patients. The superiority endpoint was not reached for secukinumab, although it was numerically higher (67% *vs*. 62% ACR20) and had a better retention rate (29). A recent head-to-head trial of ixekizumab *versus* ADA (30) proved superiority of ixekizumab, which shares the anti-IL-17 mechanism, in achieving a combined endpoint of PASI100 and ACR50 at 24 weeks. A number of matching-adjusted indirect comparisons (MAIC) have been published in an attempt to compare other TNFi to secukinumab. A MAIC that compared IFX and secukinumab (31) used data from the IMPACT2 trial and the FUTURE 2 and 3 trials and found that the ACR20 response rates were higher at 1 year for patients treated with secukinumab 150 mg and 300 mg. Another MAIC (32) used data of biologic-naive patients from FUTURE 2, 3, and 5 and compared them to patients from NCT00317499, an ETA trial of biologic-naïve patients who used the 25 mg twice weekly dosing. At week 24, there was a significant difference in favour of secukinumab 150 mg over ETA only in the ACR70 response rate, and in the ACR20, 50 and 70 with the 300 mg dosage.

The effect of MTX combination therapy in PsA is controversial. The rate of patients taking MTX is 53–62.3% in most studies (16-18, 27, 33-35) with a mixed effect on drug survival. In the FUTURE2 study (11), more patients treated with MTX achieved ACR20 response than patients not taking MTX. In contrast, the SEAM study (36), that examined response rates in PsA patients treated with ETA monotherapy, ETA plus MTX combination and MTX alone did not find any advantage of the combination therapy over ETA monotherapy. A systematic review of all TNFi (37) also found no effect of combination therapy on response rates, although an MTX combination did affect drug survival of monoclonal antibodies. When all of the patients in our study were taken together, treatment with MTX was associated with a higher rate of inefficacy events, and the same trend was evident in all TNFi drugs with the exception of IFX. The DANBIO registry also found an unfavourable effect of csDMARDs on drug survival (33). The fact that the immunomodulatory effect of MTX on immunogenicity is most important in patients receiving

IFX may explain the better IFX drug survival in combination therapy with MTX (27, 34).

IFX and GOL can be given in weight-adjusted doses. The usual starting dose of secukinumab is 150 mg in PsA, but the dose is titrated up to 300 mg when it is given to biologic-experienced patients (usually after TNFi failure), as it was in most cases in this study. Accordingly, none of the 3 drugs showed decreased efficacy in obese patients. We did not find any study on PsA that examined the relationship between BMI and response to secukinumab. A Swiss registry (38) showed that secukinumab was prescribed more often to overweight psoriasis patients. In contrast to our results, a pooled data analysis from phase 3 secukinumab psoriasis trials (39) found that the BMI decreased as the response rate increased. A Spanish multicentre study on psoriasis patients (40) found that a BMI >30 was associated with significantly lower response rates, although normal weight and overweight patients achieved similar response rates. In contrast, and in agreement with our results, a subgroup analysis of 3 UNCOVER studies on ixekizumab (41) demonstrated that body weight did not influence the response to the drug in psoriasis patients.

The rate of adverse events was 7.8% in the secukinumab-treated patients, and 7% had stopped the drug due to adverse events at 2 years. This was slightly higher than in the FUTURE2 study (11) that reported a rate of 3.4-5.6% for the various secukinumab dosage groups at 2 years. In most real-world studies on secukinumab in psoriasis, as shown in a meta-analysis (23), the rates of adverse events are comparable to those reported in clinical trials, and they are generally low.

The limitations of our study are the relatively small number of patients and the lack of PsA-specific disease activity and response measures scores recorded in the registry. The drug retention rate can be used as a surrogate marker of efficacy in the real-world setting. However, this study provides useful new real-world information on secukinumab in PsA.

Our multicentre real-world study demonstrated that all lines of treatment with secukinumab had a drug retention rate comparable to that of TNFi, and that secukinumab had better drug retention and a lower HR for an inefficacy event in biologic-experienced patients. Co-medication with MTX and BMI, did not affect secukinumab drug retention. More real-world studies are needed to determine and to confirm secukinumab efficacy in the treatment of PsA. Our results may imply that this is a good monotherapy option for patients who are obese, a common trait in PsA. Finally, IL-17 inhibition is an effective mechanism of action to treat PsA in real life, and it should be used more frequently as first- and second-line treatment.

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