Persistence rates of second-line biologics in psoriasis following first-line biologic treatment based on nationwide data from Greece

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INTRODUCTION

The introduction of newer generation biologics in moderate-to-severe psoriasis (PsO) treatment algorithm has widened the arsenal of effective therapeutic options[1]. Antibodies against cytokines involved in the pathogenesis of the disease, namely interleukin (IL)-17/23 and tumor necrosis factor alpha (TNFα)[2,3], are currently the first choice. Antibodies against IL-17/23 seem to have higher persistence rates (i.e. time between initiation and discontinuation) than antibodies against TNFα indicating increased treatment success[4]. However, discontinuation or switching to another agent may occur due to lack or loss of efficacy, adverse events[5,6] and comorbidities[7].

OBJECTIVES

We aimed to evaluate the persistence of biologics in the second treatment line (2L) according to prior biologic exposure in the first treatment line, and to determine associated factors.

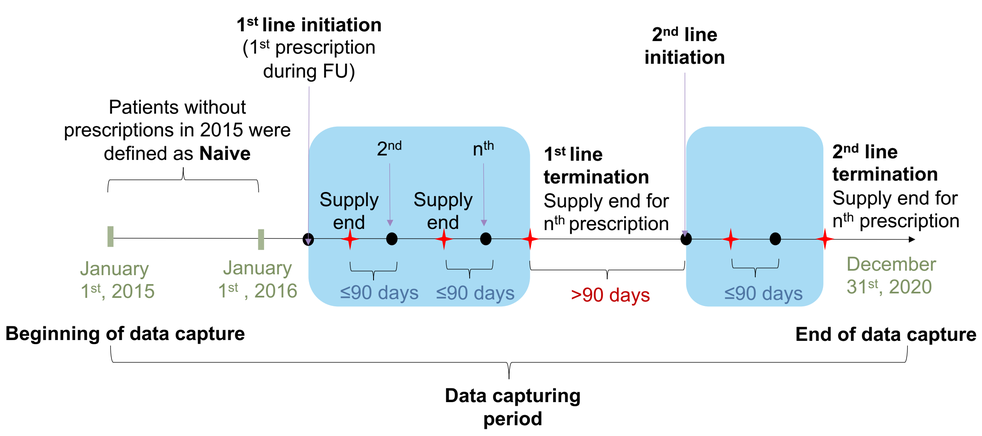
METHODS

Study design: observational, retrospective, longitudinal cohort study

Patients: Psoriatic patients that had initiated a second-line biologic treatment in Greece after Jan 1st, 2016 until the end of data capturing period, without other autoimmune diseases (e.g., Crohn's disease, rheumatoid arthritis), except for psoriatic arthritis (PsA) based on national prescription database (IDIKA S.A.).

Data capturing period: January 1st, 2015 - December 31st, 2020 (**Figure 1**).

Figure 1: Data capturing period and definitions



Data extraction: all prescriptions issued through **national prescription system** (IDIKA S.A) from Jan 1, 2015, to Dec 31, 2020, under

- ICD-10 codes of L40.0-L40.4, L40.8, L40.9, and
- ATC code of the biologics: infliximab, adalimumab, etanercept, secukinumab, ustekinumab, brodalumab, certolizumab pegol.

Setting

- Persistence was defined as the period between the date of the first executed prescription for each biologic treatment during the follow-up, to the date of discontinuation, end of the study, or death, whichever came first. Biologic treatment discontinuation was considered when a patient switched to a different agent irrespectively of the time passed or re-initiated the same drug >90 days after the initial drug halt. Persistence was summarized with median, and 95% confidence interval (CI) and persistence rates were derived by Kaplan-Meier (KM) curves.
- The impact of potential factors [sex, age at baseline, diagnosis group ("PsO only" vs. "PsO/PsA"), drug, in the 2L persistence was tested with Cox models. The interaction of 1L and 2L drugs was assessed as well. The significance level was set at 5% for all analyses. All analyses were performed using STATA v.17.0.

RESULTS

Patient characteristics (1L)

- Collectively, 6,772 patients received a biologic therapy in 1L with a median overall persistent rate of 51.1 (95% CI: 47.1 - not reached (NR)] months. Patients being treated with agents against TNFα (adalimumab, certolizumab pegol, infliximab and etanercept) had the lowest median persistence rate compared to the other antibodies (secukinumab, ustekinumab, brodalumab).

Patient characteristics (2L)

- Among them,1,857 patients initiated a 2L biologic treatment. Most patients were male (60.5%) while the mean age (standard deviation, SD) at initiation of 2L was 50.3 (14.6) years. Among patients within the total cohort, 17.8% were diagnosed with concomitant PsA (**Table 1**). Most patients were treated with secukinumab in 2L (n=701, 37.7%) followed by those treated with anti-IL-12/23 (ustekinumab) (n=522, 28.1%) (**Table 2**).

Table 1: Patient demographics stratified by 2nd treatment drug

	Anti-TNFα	IL17RA	Anti-IL17A	Anti-IL12/23	Total
	N=371	N=263	N=701	N=522	N=1857
Sex, n (%)					
Male	217 (58.5%)	161 (61.2%)	426 (60.8%)	319 (61.1%)	1123 (60.5%)
Female	154 (41.5%)	102 (38.8%)	275 (39.2%)	203 (38.9%)	734 (39.5%)
Diagnosis, n (%)					
Only PsO	261 (70.4%)	234 (89.0%)	593 (84.6%)	438 (83.9%)	1526 (82.2%)
PsO & PsA	110 (29.6%)	29 (11.0%)	108 (15.4%)	84 (16.1%)	331 (17.8%)
Age (years) at initiation of 2L, mean (SD)	50.7 (14.3)	52.8 (14.0)	49.1 (15.0)	50.5 (14.6)	50.3 (14.6)

Note: Anti-TNFα; adalimumab, etanercept, infliximab, certolizumab pegol, anti-IL17RA; brodalumab, anti-IL17A; secukinumab, anti-IL12/23; ustekinumab.

Table 2: Disposition of patients at the 2nd treatment line

1st line	2nd line:	Anti-TNFα	Anti-IL17RA	Anti-IL17A	Anti-IL12/23
	Anti-TNFα [n=527]	230	66	133	98
	Anti-interleukin 17RA [n=120]	36	49	23	12
	Anti-interleukin 17A [n=778]	77	115	472	114
	Anti-interleukin 12/23 [n=432]	28	33	73	298
	Total	371	263	701	522

Note: Anti-TNFα; adalimumab, etanercept, infliximab, certolizumab pegol, anti-IL17RA; brodalumab, anti-IL17A; secukinumab, anti-IL12/23; ustekinumab.

Persistence

- The overall median persistence of 2L was 30.8 [95% CI: 27.2 – 39.0] months with the corresponding rates at 12 and 24 months being 70.0% and 55.4%, respectively. Patients treated with anti-IL12/23 and with anti-IL17RA had the highest rates at 12 and 24 months, respectively (**Table 3, Figure 2**).

Table 3: Overall persistence rates at 2nd treatment line

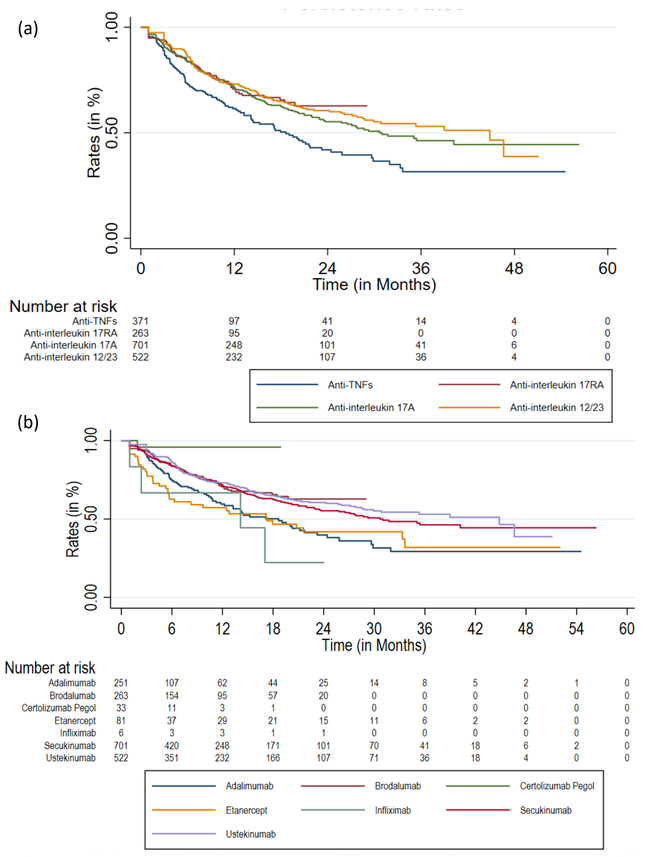
Months	Overall	Anti-TNFs	Anti-IL17RA	Anti-IL17A	Anti-IL12/23
12	70.0	61.5	70.7	71.4	73.0
24	55.4	41.9	62.8	55.3	60.5
36	46.5	31.5	.	46.3	53.0
48	40.6	31.5	.	44.4	38.7
Median	30.8	18.6	NR	30.7	44.8
(95% CI)	(27.2, 39.0)	(14.1, 23.2)	(NR, NR)	(23.7, NR)	(28.8, NR)

Note: Anti-TNFα; adalimumab, etanercept, infliximab, certolizumab pegol, anti-IL17RA; brodalumab, anti-IL17A; secukinumab, anti-IL12/23; ustekinumab.

Associated factors

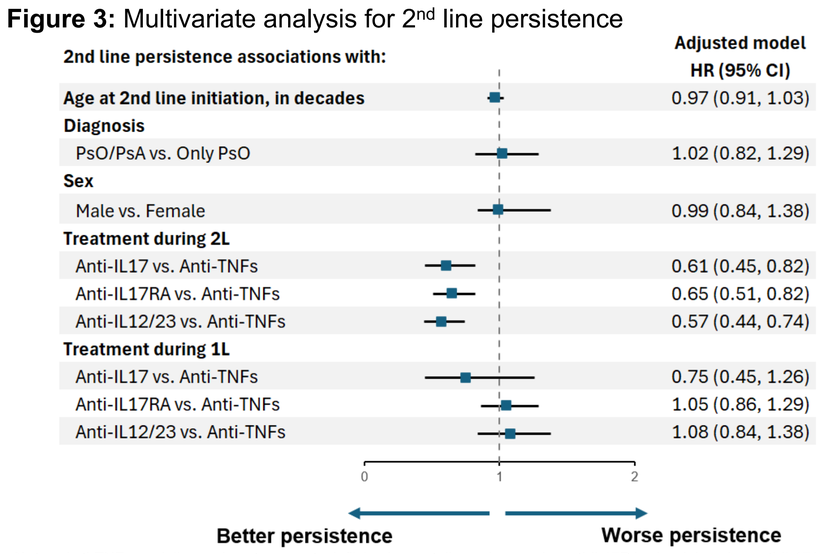
- Multivariate analysis demonstrated that patients treated with anti-IL17 (HR=0.61), anti-IL17RA (HR=0.65) and anti-IL12/23 (HR=0.57) had significantly increased drug persistence compared to the reference (anti-TNFα). These results are adjusted for age, sex, diagnosis and biologic received during 1L. None of these was statistically significant (**Figure 3**).
- Following stratification by 1L drug, patients treated with anti-TNFα at 2L had lower persistence compared with patients treated with anti-ILs, only in the case an anti- TNFα was used at 1L (**Figure 4**).

Figure 2: Overall 2L drug persistence by (a) drug class and (b) drug



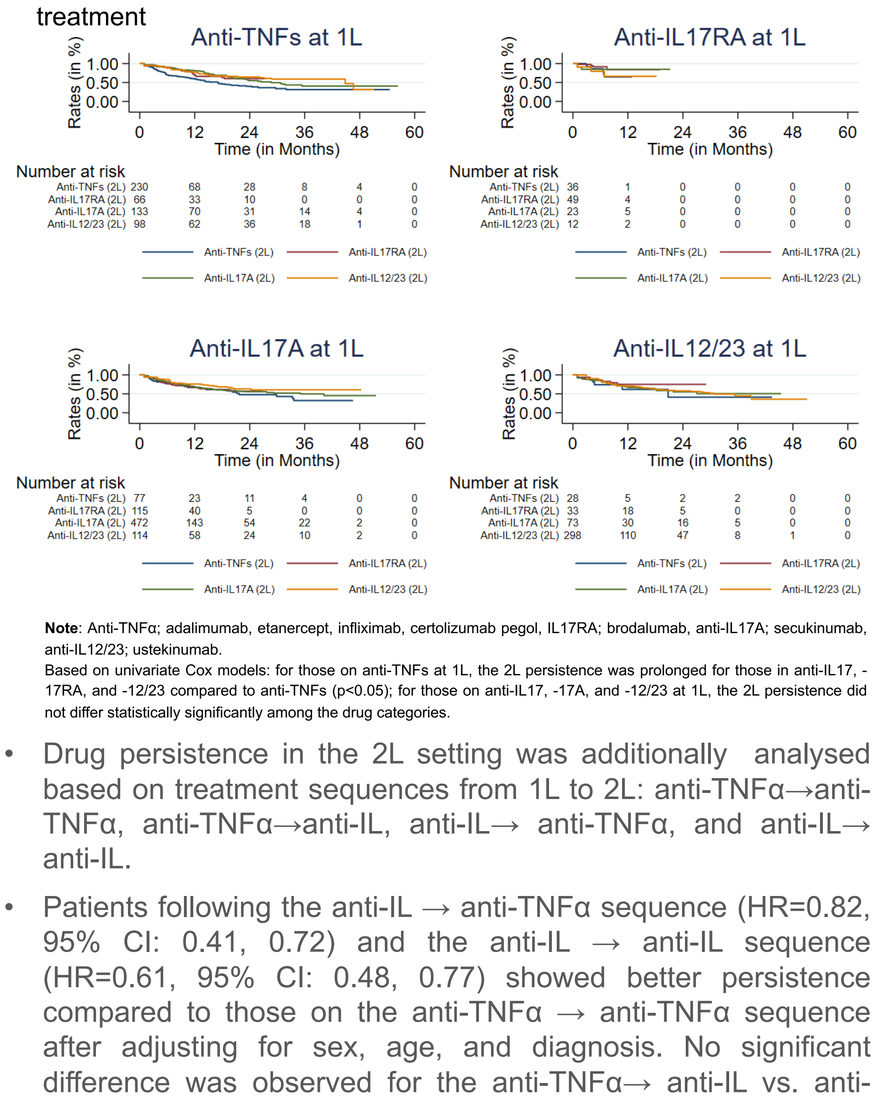
Note: Anti-TNFα; adalimumab, etanercept, infliximab, certolizumab pegol, anti-IL17RA; brodalumab, anti-IL17A; secukinumab, anti-IL12/23; ustekinumab.

Figure 3: Multivariate analysis for 2nd line persistence



Note: Anti-TNFα; adalimumab, etanercept, infliximab, certolizumab pegol, anti-IL17RA; brodalumab, anti-IL17A; secukinumab, anti-IL12/23; ustekinumab.

Figure 4: Drug persistence of 2nd line treatment stratified by 1st line treatment



Note: Anti-TNFα; adalimumab, etanercept, infliximab, certolizumab pegol, IL17RA; brodalumab, anti-IL17A; secukinumab, anti-IL12/23; ustekinumab.
Based on univariate Cox models: for those on anti-TNFs at 1L, the 2L persistence was prolonged for those in anti-IL17, -17RA, and -12/23 compared to anti-TNFs ($p<0.05$); for those on anti-IL17, -17A, and -12/23 at 1L, the 2L persistence did not differ statistically significantly among the drug categories.

- Drug persistence in the 2L setting was additionally analysed based on treatment sequences from 1L to 2L: anti-TNFα→anti-TNFα, anti-TNFα→anti-IL, anti-IL→ anti-TNFα, and anti-IL→ anti-IL.
- Patients following the anti-IL → anti-TNFα sequence (HR=0.82, 95% CI: 0.41, 0.72) and the anti-IL → anti-IL sequence (HR=0.61, 95% CI: 0.48, 0.77) showed better persistence compared to those on the anti-TNFα → anti-TNFα sequence after adjusting for sex, age, and diagnosis. No significant difference was observed for the anti-TNFα→ anti-IL vs. anti-TNFα → anti-TNFα sequence.

CONCLUSIONS

- Second-line treatment with anti-IL17, -IL17RA and -IL12/23 showed significantly better persistence compared to anti-TNFα, suggesting improved treatment success with these newer agents. Age, sex, and 1L treatment did not affect significantly the overall 2L persistence.
- Patients who switched from anti-IL in the 1L to anti-IL in 2L, or from anti-IL to anti-TNFα, demonstrated better 2L persistence than those on a continuous TNFα sequence.
- These results support prioritizing IL-targeted biologics for improved persistence in 2L treatment, potentially enhancing long-term outcomes in moderate-to-severe psoriasis.

Limitations: Persistence was measured using prescription data, which may not fully capture actual patient adherence or reasons for discontinuation, such as side effects or disease progression. While the study adjusted for certain confounders, unmeasured factors—like patient preference, disease severity, or comorbidities—may still affect persistence outcomes.

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