Received: 25 August 2022 | Accepted: 3 January 2023

DOI: 10.1111/jocd.15638

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Clinical course of psoriasis patients that discontinued biologics during the COVID-19 pandemic

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Abstract

Background: Since psoriasis is a chronic disease, it is not recommended to discontinue the treatment agents used. However, in real life, the treatment of psoriasis patients may be interrupted for various reasons. During the pandemic period, the treatment of many patients was also interrupted.

Objectives: To evaluate relapse and clinical worsening in psoriasis patients whose biological therapy was interrupted during the pandemic and reveal associated factors.

Methods: The study included patients aged ≥18 years, who were followed up with moderate and severe chronic psoriasis controlled by the last biological agent [Psoriasis Area Severity Index (PASI) 75 response achieved] but had to discontinue their treatment during the pandemic. The patients' demographic and clinical characteristics, clinical course after the discontinuation of these agents, presence of clinical worsening, and relapse were evaluated. Risk factors were analyzed with the logistic regression analysis.

Results: The study included 169 patients, with a mean age of 47.3 ± 14.5 (18–87) years. The mean biologics-free time was 18.2 ± 12.3 (2–56) weeks. Clinical worsening was detected in 41.4% and relapse in 48.5% of the patients. The significant risk factors for clinical worsening and relapse in both univariate and multivariate analyses

were alcohol use during the biologics-free period, total time off biologics, and the presence of an additional triggering factor. The use of secukinumab and ustekinumab was found to be a protective factor against clinical worsening in multivariate analyses. **Conclusion:** As the biologics-free period is prolonged, the likelihood of clinical worsening and relapse increases, therefore, we do not recommend discontinuing biological agents.

KEYWORDS
medical therapy, psoriasis, treatment

1 | INTRODUCTION

Psoriasis is a chronic inflammatory disease with periods of remission and exacerbation. In recent years, with the elucidation of the immunopathogenesis of psoriasis, biological agent therapy has become a good option to control the disease. Although the literature contains comprehensive data on biologics used for this purpose from efficacy and safety to the appropriate selection of these agents, there are not sufficient real-life data on when, how, and by whom biological agent therapy can be discontinued in patients whose lesions have regressed with the use of biologics.[1–3] Since psoriasis is a chronic disease, the recommendation is not to discontinue the therapeutic agent used. However, in real life, the treatment of psoriasis patients may be interrupted for various reasons, such as unresponsiveness to medication, side effects, patient requests, drug unavailability, or inability to see a physician.[4] During the COVID-19 pandemic, the biologic agent treatment of many psoriasis patients was interrupted due to problems in access to medication and safety concerns reducing patient visits to the hospital.[5–7] In this study, our aim was to evaluate patients that discontinued biological agent therapy in terms of relapse and clinical worsening and to contribute to the literature by revealing predictors that may be associated with relapse and clinical worsening.

2 | MATERIALS AND METHODS

This research was planned as a retrospective multicenter study and included patients aged 18 years and over, who were followed up with the diagnosis of moderate and severe chronic plaque psoriasis that was brought under control [Psoriasis Area Severity Index (PASI) 75 response achieved] following the most recently used biological agent (adalimumab, etanercept, infliximab, certolizumab, ustekinumab, secukinumab, and ixekizumab) but had to discontinue their biological agent therapy for physician- or patient-related reasons during the COVID-19 pandemic (March 1, 2020–May 1, 2021). These patients were evaluated in terms of demographic and clinical characteristics, reasons for not being able to continue using biologics, clinical course after the discontinuation of these agents, and presence of relapse and clinical worsening. Patients who could not maintain 50% of the initial PASI score (PASI 50 response) after stopping treatment were considered to have relapsed, and those with a PASI of ≥5 were considered to have clinical worsening. Biologics-free time was calculated by subtracting the recommended administration time for each biological agent from the total time of these agents. In patients with relapse and clinical worsening, risk factors that could be associated with these conditions were investigated. Data were obtained from the patient follow-up files and/or records in the computer systems of the university. The study was approved by the Non-Invasive Clinical Research Ethics Committee of the University. SPSS v. 15.0 for Windows software package was used for statistical analyses. Descriptive statistics were presented as numbers and percentages for categorical variables and mean, standard deviation, minimum, maximum, median, and interquartile range values for numerical variables. Risk factors were analyzed using the logistic regression analysis, and the statistical alpha significance level was accepted as $p < 0.05$.

3 | RESULTS

The study included a total of 169 patients, 79 women and 90 men, with a mean age of 47.3 ± 14.5 (18–87) years. The mean biologics-free time was 18.2 ± 12.3 (2–56) weeks. Of the patients, 41.4% had clinical worsening (PASI ≥5), 48.5% had a relapse (unable to maintain PASI 50 response), 17.3% had increased joint findings, and 20.9% had increased nail findings. During the biologics-free period, 82.2% of the patients developed new lesions. New lesions mostly emerged in the lower extremities (38.8%). Table 1 summarizes the data on the demographic and clinical characteristics of the patients, comorbidities, treatments, relapse, and clinical worsening. The results of the univariate logistic regression analyses of clinical worsening, relapse, and maximum PASI being 10 and above during the biologics-free period are shown in Table 2, and those of the multivariate logistic regression analyses are given in Table 3.

The significant risk factors for clinical worsening, relapse, and PASI score being ≥10 in the univariate analyses were alcohol use, total time off biologics, and presence of an additional triggering factor, such as stress, infection, and other medication use during the biologics-free period (Table 2). In the multivariate model, under the combined effect of all variables, and according to the backward method, the most significant risk factors of clinical worsening were

TABLE 1 Demographic and clinical characteristics of the patients

	n (%)
Gender	
Female	79 (46.7)
Male	90 (53.3)
Age mean ± SD (min–max)	47.3 ± 14.5 (18–87)
Disease duration (years) mean ± SD (min–max)	19.9 ± 11.5 (3–67)
Smoking during the biologics-free period	62 (36.7)
Alcohol use during the biologics-free period	9 (5.3)
BMI mean ± SD (min–max)	28.1 ± 5.1 (15.8–46.5)
Comorbidities	
Obesity[a]	
Obese	49 (29.0)
Overweight	79 (46.7)
Normal weight	41 (24.3)
PsA	57 (33.7)
Hypertension	42 (24.9)
Diabetes	39 (23.1)
CVD	15 (8.9)
Hyperlipidemia	55 (32.5)
Liver disease	29 (17.2)
CKD	5 (3.0)
History of biologics use	99 (58.6)
Adalimumab	48 (28.4)
Etanercept	28 (16.6)
Infliximab	24 (14.2)
Certolizumab	5 (3.0)
Ustekinumab	34 (20.1)
Secukinumab	18 (10.7)
Ixekizumab	5 (3.0)
Golimumab	1 (0.6)
Last used biologics	
Adalimumab	48 (28.4)
Etanercept	8 (4.7)
Infliximab	7 (4.1)
Certolizumab	5 (3.0)
Ustekinumab	38 (22.5)
Secukinumab	53 (31.4)
Ixekizumab	10 (5.9)
Additional systemic treatment along with the last biologics	17 (10.1)
Reason for discontinuation of biologics	
Physician's decision due to pandemic	58 (34.3)
Physician's decision for other reasons	14 (8.3)
Patient's decision due to pandemic	84 (49.7)
Patient's decision for other reasons	37 (21.9)
Due to COVID-19 infection	7 (4.1)
Relapse	82 (48.5)
Clinical worsening	70 (41.4)
Increased joint findings	24 (17.3)
Increased nail findings	29 (20.9)
New lesion emergence	139 (82.2)
Origin of new lesion emergence	
Scalp	15 (10.8)
Face	4 (2.9)
Trunk	34 (24.5)
Upper extremity	0 (0.0)
Lower extremity	54 (38.8)
Nails	3 (2.2)
Additional triggering factor during the biologics-free period	46 (27.2)
Stress	34 (20.1)
Infection	11 (6.5)
Other medication use	0 (0.0)
Trauma	0 (0.0)
Other	5 (3.0)
PASI before last biologics use mean ± SD (min–max)	16.5 ± 8.9 (5–49.3)
Last biologics use, months mean ± SD (min–max)	27.4 ± 26.5 (1–160)
Last PASI before discontinuation mean ± SD (min–max)	1.12 ± 1.59 (0–10.2)
Total time off biologics, weeks mean ± SD (min–max)	18.2 ± 12.3 (2–56)
Number of half-lives elapsed according to the last biologics used mean ± SD (min–max)	8.4 ± 11.7 (0.5–112)
PASI during the biologics-free period mean ± SD (min–max)	6.6 ± 8.1 (0–46.1)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis.

[a]Normal weight, BMI: 18.5–24.9; overweight, BMI: 25–29.9; obese, BMI ≥30.

determined to be the use of the last biological agent for ≥1 year, total time off biologics, and presence of an additional triggering factor, and those of relapse were the total time off biologics and presence of an additional triggering factor. The use of secukinumab and ustekinumab was found to be a protective factor for clinical worsening in the backward method (Table 3). The most significant risk factors for relapse in the multivariate analyses were determined as the total time off biologics and presence of an additional triggering factor during the biologics-free period (Table 3). In the multivariate analysis, the most significant risk factors for PASI score being ≥10 after treatment interruption were identified as alcohol use during the biologics-free period, number of comorbidities being ≥3, being experienced in biological agent use, PASI being ≥10 at the start of the last biological therapy, use of the last biological agent for ≥1 year,

TABLE 2 Risk factors of clinical worsening, relapse, and PASI score being ≥10 according to the univariate analysis

	Clinical worsening					Relapse					Relapse PASI during the biologics-free period				
	Present	Absent	Univariate logistic regression analysis			Present	Absent	Univariate logistic regression analysis			<10	≥10	Univariate logistic regression analysis		
	n (%)	*n* (%)				*n* (%)	*n* (%)	OR	95% CI	*p*	*n* (%)	*n* (%)	OR	95% CI	*p*
Gender															
Male	38 (54.3%)	52 (52.5%)	1.07	0.58–1.98	0.821	43 (52.4%)	47 (54.0%)	0.94	0.51–1.72	0.837	69 (53.5%)	21 (52.5%)	0.96	0.47–1.96	0.913
Female	32 (45.7%)	47 (47.5%)				39 (47.6%)	40 (46.0%)				60 (46.5%)	19 (47.5%)			
Age median (IQR)	46 (38–58)	46 (36–56)	1.00	0.98–1.02	0.913	45.5 (36–58)	46 (37–56)	1.01	0.99–1.03	0.562	46(36.5–56)	45.5 (38–58)	1.00	0.97–1.02	0.649
Disease duration (years) median (IQR)	18,5 (11,5–28)	18 (10–25)	1.01	0.98–1.04	0.560	18 (10–25)	19 (11–27)	0.99	0.97–1.02	0.622	19 (11–25)	17.5 (10–26.75)	1.00	0.97–1.03	0.981
Smoking during the biologics-free period	29 (41,4%)	33 (33.3%)	1.41	0.75–2.66	0.283	31 (37.8%)	31 (35.6%)	1.10	0.59–2.05	0.770	44 (34.1%)	18 (45.0%)	1.58	0.77–3.25	0.214
Alcohol use during the biologics-free period	7 (10,0%)	2 (2.0%)	5.39	1.08–26.78	0.039	8 (9.8%)	1 (1.1%)	9.30	1.14–76.07	0.038	3 (2.3%)	6 (15.0%)	7.41	1.76–31.18	0.006
BMI median (IQR)	27 (24,3–31)	28 (25–30.85)	1.04	0.98–1.11	0.189	27 (25–31.5)	27.55 (24.7–30)	1.004	0.95–1.07	0.907	26.8 (25–30.75)	27.2 (25–31)	1.03	0.95–1.12	0.494
Obesity[a] (Ref: Normal weight)		27 (27,3%)	14 (20.0%)			0.372	19 (21.8%)	22 (26.8%)			0.582	7 (21.9%)	33 (24.4%)		0.934
Overweight	42 (42.4%)	37 (52.9%)	1.70	0.78–3.72	0.184	40 (46.0%)	39 (47.6%)	0.842	0.40–1.79	0.656	16 (50.0%)	63 (46.7%)	0.84	0.31–2.32	0.820
Obese	30 (30.3%)	19 (27.1%)	1.22	0.52–2.90	0.650	28 ((32.2%)	21 (25.6%)	0.648	0.28–1.49	0.308	9 (28.1%)	39 (28.9%)	0.92	0.31–2.74	0.880
PsA	37 (37,4%)	20 (28.6%)	0.67	0.347–1.296	0.234	33 (37.9%)	24 (29.3%)	0.677	0.36–1.29	0.235	15 (46.9%)	42 (31.1%)	0.51	0.23–1.21	0.094
Number of comorbidities															
None or 1	41 (58.6%)	62 (62.6%)			0.868	48 (58.5%)	55 (63.2%)			0.800	79 (61.2%)	17 (42.5%)			0.899
2	14 (20.0%)	18 (18.2%)	1.18	0.53–2.62	0.692	16 (19.5%)	16 (18.4%)	1.15	0.52–2.53	0.737	25 (19.4%)	7 (17.5%)	0.92	0.35–2.39	0.867
≥3	15 (21.4%)	19 (19.2%)	1.19	0.55–2.61	0.658	18 (22.0%)	16 (18.4%)	1.29	0.59–2.80	0.522	25 (19.4%)	9 (22.5%)	1.19	0.49–2.88	0.708
History of biological therapy	41 (58,6%)	58 (58.6%)	1.00	0.54–1.86	0.999	42 (51.2%)	57 (65.5%)	0.55	0.30–1.03	0.060	70 (54.3%)	29 (72.5%)			
Previous biologics used															
Adalimumab	17 (24.3%)	31 (31.3%)	0.70	0.35–1.41	0.319	20 (24.4%)	28 (32.2%)	0.68	0.35–1.34	0.263	34 (26.4%)	14 (35.0%)	1.50	0.70–3.21	0.291
Etanercept	13 (18.6%)	15 (15.2%)	1.28	0.57–2.89	0.556	13 (15.9%)	15 (17.2%)	0.90	0.40–2.04	0.808	22 (17.1%)	6 (15.0%)	0.86	0.32–2.29	0.760
Infliximab	11 (15.7%)	13 (13.1%)	1.23	0.52–2.94	0.636	10 (12.2%)	14 (16.1%)	0.72	0.30–1.74	0.469	18 (14.0%)	6 (15.0%)	1.09	0.40–2.96	0.868
Certolizumab	1 (1.4%)	4 (4.0%)	0.34	0.04–3.15	0.345	1 (1.2%)	4 (4.6%)	0.26	0.03–2.34	0.228	5 (3.9%)	0 (0.0%)	0.00		0.999
Ustekinumab	9 (12.9%)	25 (25.3%)	0.44	0.19–1.01	0.052	12 (14.6%)	22 (25.3%)	0.51	0.23–1.11	0.087	25 (19.4%)	9 (22.5%)	1.21	0.51–2.86	0.667
Secukinumab	8 (11.4%)	10 (10.1%)	1.15	0.43–3.07	0.783	8 (9.8%)	10 (11.5%)	0.83	0.31–2.22	0.715	12 (9.3%)	6 (15.0%)	1.72	0.60–4.93	0.312
Ixekizumab	1 (1.4%)	4 (4.0%)	0.34	0.04–3.15	0.345	1 (1.2%)	4 (4.6%)	0.26	0.03–2.34	0.228	5 (3.9%)	0 (0.0%)	0.00		0.999
Golimumab	0 (0.0%)	1 (1.0%)	0.00	0.00	1.000	0 (0.0%)	1 (1.1%)	0.00		1.000	1 (0.8%)	0 (0.0%)	0.00		1.000

TABLE 2 (Continued)

	Clinical worsening					Relapse					Relapse PASI during the biologics-free period				
	Present	Absent	Univariate logistic regression analysis			Present	Absent	Univariate logistic regression analysis			<10	≥10	Univariate logistic regression analysis		
	n (%)	*n* (%)				*n* (%)	*n* (%)	OR	95% CI	*p*	*n* (%)	*n* (%)	OR	95% CI	*p*
Concomitant use of a systemic agent with last biologics	66 (94,3%)	94 (94.9%)	0.88	0.23–3.39	0.850	78 (95.1%)	82 (94.3%)	1.19	0.31–4.59	0.802	122 (94.6%)	38 (95.0%)	1.09	0.22–5.47	0.916
Duration of the last biological therapy, months median (IQR)	18 (12–36)	17 (9–36)	1.00	0.99–1.01	0.995	19(11.75–36)	16 (9–36)	1.00	0.99–1.02	0.532			0.99	0.97–1.01	0.284
Total time off biologics Median (IQR)	18,5 (12–28)	12 (8–20)	1.03	1.00–1.05	0.040	18.5 (12–28)	12 (8–20)	1.04	1.01–1.07	0.008	12 (8–24)	20 (12–29.5)	1.03	1.002–1.06	0.038
Number of elapsed half-lives according to the biologics used median (IQR)	7,1 (4,1-12,4)	5 (3–8)	1.02	0.99–1.05	0.196	6.7 (4–11.25)	5 (3–8)	1.02	0.99–1.05	0.275	5.2 (3–9.5)	6.7 (4.03–10.45)	1.00	0.97–1.03	0.942
Reason for discontinuation															
Physician-related	29 (41.4%)	39 (39.4%)				37 (45.1%)	31 (35.6%)				55 (42.6%)	13 (32.5%)			
Patient-related	41 (58.6%)	60 (60.6%)	0.92	0.49–1.71	0.790	45 (54.9%)	56 (64.4%)	0.67	0.36–1.25	0.209	74 (57.4%)	27 (67.5%)	1.54	0.73–3.26	0.255
Presence of an additional triggering factor during the biologics-free period	29 (41,4%)	17 (17.2%)	3.41	1.68–6.91	0.001	34 (41.5%)	12 (13.8%)	4.43	2.09–9.38	<0.001	24 (18.6%)	22 (55.0%)	5.35	2.49–11.49	<0.001
History of COVID-19 infection	10 (10.1%)	8 (11.4%)	1.15	0.43–3.07	0.783	9 (10.3%)	9 (11.0%)	1.07	0.40–2.84	0.894	4 (12.5%)	14 (10.4%)	0.81	0.25–2.65	0.727

Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; OR, odds ratio; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; Ref, reference.

[a]Normal weight, BMI: 18.5–24.9; overweight, BMI: 25–29.9; obese, BMI ≥30.

TABLE 3 Risk factors of clinical worsening, relapse, and PASI score being ≥10 during the biologics-free period according to the multivariate analyses

	Clinical worsening				Relapse				Relapse PASI ≥10 during the biologics-free period			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
Enter method												
Gender (Ref: Female)												
Male	0.223	0.58	0.25	1.39	0.321	0.65	0.28	1.52	0.019	0.15	0.03	0.73
Age	0.740	1.01	0.97	1.04	0.306	1.02	0.99	1.05	0.072	1.05	1.00	1.11
Disease duration	0.193	1.03	0.99	1.06	0.874	1.00	0.96	1.03	0.520	1.02	0.96	1.08
Smoking during the biologics-free period	0.534	1.34	0.53	3.36	0.936	0.96	0.38	2.41	0.642	0.72	0.17	2.93
Alcohol use during the biologics-free period	0.029	8.78	1.25	61.69	0.034	15.28	1.23	190.31	<0.001	551.6	18.12	16790
BMI	0.403	1.08	0.91	1.27	0.422	1.07	0.90	1.27	0.783	1.04	0.80	1.34
Obesity[a] (Ref: Normal weight)	0.301				0.716				0.332			
Overweight	0.765	0.71	0.07	6.93	0.421	0.40	0.04	3.72	0.245	0.09	0.00	5.03
Obese	0.447	1.65	0.45	6.04	0.479	0.63	0.17	2.27	0.138	0.18	0.02	1.73
PsA	0.016	0.33	0.13	0.82	0.057	0.42	0.17	1.03	0.116	0.31	0.07	1.33
Number of comorbidities (Ref: None or 1)	0.178				0.227				0.025			
2	0.669	1.26	0.44	3.62	0.741	1.19	0.42	3.40	0.401	0.43	0.06	3.05
≥3	0.067	2.96	0.93	9.50	0.090	2.66	0.86	8.22	0.016	17.41	1.69	179.51
History of biological therapy	0.938	0.96	0.39	2.41	0.311	0.62	0.25	1.56	0.001	26.22	3.61	190.48
Last used biologics												
Adalimumab	0.309	0.38	0.06	2.46	0.373	0.42	0.06	2.80	0.295	0.19	0.01	4.34
Etanercept	0.162	8.36	0.43	163.42	0.806	0.69	0.03	13.79	0.458	0.12	0.00	31.16
Infliximab	0.932	1.11	0.10	11.98	0.769	1.42	0.13	15.04	0.124	0.05	0.00	2.28
Certolizumab	0.494	2.41	0.19	29.94	0.597	1.99	0.15	25.83	0.255	7.66	0.23	254.14
Ustekinumab	0.082	0.17	0.02	1.26	0.169	0.25	0.03	1.81	0.022	0.01	0.00	0.48
Secukinumab	0.285	0.35	0.05	2.40	0.409	0.45	0.07	3.02	0.179	0.09	0.00	3.04
Concomitant use of a systemic agent with last biologics	0.780	0.79	0.16	4.00	0.642	1.51	0.27	8.48	0.228	0.19	0.01	2.86
PASI before the last biological therapy (Ref: <10)	0.438				0.643				0.006			

TABLE 3 (Continued)

	Clinical worsening				Relapse				Relapse PASI ≥10 during the biologics-free period			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
10–20	0.706	0.81	0.27	2.41	0.349	0.59	0.20	1.78	0.037	24.53	1.21	497.26
≥20	0.522	1.46	0.46	4.62	0.490	0.66	0.21	2.13	0.003	123.65	4.95	3091
Duration of the last biological therapy (Ref: <1 year)												
≥1 year(s)	0.017	3.05	1.22	7.66	0.088	2.12	0.89	5.03	0.039	5.63	1.10	28.93
Total time off biologics (weeks)	0.004	1.08	1.02	1.14	0.033	1.06	1.00	1.11	0.033	1.16	1.01	1.34
Number of elapsed half-lives according to the biologics used	0.082	0.95	0.90	1.01	0.688	0.99	0.93	1.05	0.529	0.91	0.67	1.23
Reason for discontinuation (Ref: Physician-related)												
Patient-related	0.810	0.90	0.38	2.14	0.529	0.76	0.32	1.79	0.430	1.78	0.42	7.48
Presence of an additional triggering factor	0.003	4.54	1.67	12.31	<0.001	7.56	2.68	21.34	0.001	20.15	3.71	109.40
History of COVID-19 infection	0.965	1.03	0.29	3.68	0.927	1.06	0.31	3.61	0.005	17.17	2.35	125.23
Backward method												
Gender (Ref: Female)												
Male									0.045	0.25	0.07	0.97
Age									0.086	1.04	0.99	1.08
Alcohol use during the biologics-free period	0.072	4.83	0.87	26.83	0.075	7.17	0.82	62.64	<0.001	159.43	10.70	2376
PsA									0.066	0.30	0.08	1.08
Number of comorbidities (Ref: None or 1)									0.027			
2									0.400	0.47	0.08	2.70
≥3									0.025	5.95	1.25	28.26
History of biological therapy									0.001	10.54	2.56	43.41
Last used biologics												
Adalimumab	0.076	0.39	0.14	1.10								
Etanercept												

(Continues)

TABLE 3 (Continued)

	Clinical worsening				Relapse				Relapse PASI ≥10 during the biologics-free period			
	p	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI	
Secukinumab	0.036	0.33	0.12	0.93								
Ustekinumab	0.012	0.23	0.08	0.73					0.017	0.13	0.02	0.69
Certolizumab									0.008	34.91	2.53	480.94
PASI before the last biological therapy												
<10									0.009			
10–20									0.045	20.38	1.06	390.36
≥20									0.006	72.74	3.41	1550.95
Duration of the last biological therapy (Ref: <1 year)												
≥1 year(s)	0.040	2.22	1.04	4.74					0.068	3.51	0.91	13.52
Total time off biologics (weeks)	0.012	1.04	1.01	1.07	0.005	1.04	1.01	1.07	0.005	1.14	1.04	1.25
Number of elapsed half-lives according to the biologics used									0.369	0.92	0.77	1.10
Presence of an additional triggering factor during the biologics-free period	0.001	4.22	1.86	9.57	<0.001	4.80	2.18	10.59	<0.001	10.65	3.00	37.78
History of COVID-19 infection									0.015	7.89	1.50	41.43

Abbreviations: BMI, body mass index; OR, odds ratio; CI, confidence interval; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis; Ref, reference.

[a]Normal weight, BMI: 18.5–24.9; overweight, BMI: 25–29.9; obese, BMI ≥30.

last used biological agent being certolizumab, total time off biologics, presence of an additional triggering factor during the biologics-free period, and having had a COVID-19 infection, while protective factors were determined to be male gender and the last used biological agent being ustekinumab (Table 3).

4 | DISCUSSION

In recent years, biological agents have attracted great interest in the treatment of psoriasis due to their proven long-term efficacy, drug retention, and better long-term safety profiles.[8,9] However, although complete and almost complete recovery can be achieved with biological agents currently used in the treatment of psoriasis, there is no cure for the disease.

Despite more than 20 years of clinical experience in biological therapy for psoriasis, optimal treatment strategies after achieving remission and/or low disease activity in patients with psoriasis are still not well defined.[4] The literature contains limited data on how to proceed in patients with long-term complete and near-complete recovery. There are also insufficient recommendations concerning which agent to use in which patient group biological agents can be discontinued, whether the treatment can be interrupted or applied intermittently. Due to the chronic course of the disease with relapses, long-term uninterrupted treatment is recommended.

However, in clinical studies evaluating the efficacy and safety of biological agents, the duration of treatment ranges from 3 months to a maximum of 5 years.[10] Very few studies have reported real-life data obtained over 10 years or longer.[11] However, although the discontinuation of biological therapy is associated with the risk of relapse, the temporary or permanent discontinuation of this treatment is common in patients with psoriasis who have achieved clinical remission, and this has a variety of reasons, such as cost-effectiveness of maintenance therapy, financial savings, government and private payer reimbursement policies, and long-term safety concerns.[12–14] In addition, in daily clinical practice, patients may present to their physicians with a request to discontinue their treatment. A group of patients, on the other hand, is willing to see if there is any relapse by extending the treatment interval. There are also patients who discontinue their treatment completely, thinking that they have achieved full recovery.

Although all biological agents approved for the treatment of psoriasis are immunosuppressants, their chemical composition, mechanism of action, and thus individual long-term benefits vary considerably.[15] Considering the time to relapse after drug discontinuation, alefacept has the longest clinical benefit, followed by ustekinumab, infliximab, adalimumab, and etanercept.[15] Significant differences have been reported between biological agents in terms of their duration of action.[15] In a study evaluating patients responding to biological therapy, the median time to the loss of PASI 50 response after the discontinuation of biologics was determined as 29.9, 22, 19.5, 18, and 12.1 weeks for those using alefacept, ustekinumab, infliximab, adalimumab, and etanercept, respectively.[4] In another study, the median time to the loss of PASI 75 response after the discontinuation of ustekinumab was reported to be approximately 15 weeks.[16] In a pooled analysis of phase III studies, the median time to the loss of PASI 50 response was 28.0 and 20.3 weeks after the discontinuation of secukinumab treatment at a dose of 300 mg and 150 mg, respectively.[4] In light of the available data, except for alefacept, the time to relapse is the longest for ustekinumab and secukinumab. In our study, the last biological agent used being secukinumab or ustekinumab was determined as a protective factor against clinical worsening.

In a previous study, after the data were adjusted for age, sex, body weight, psoriatic arthritis, and smoking status at baseline, the predictors of a longer relapse-free period following the discontinuation of ustekinumab were reported to be biologics naivety, recovery with a higher maximum PASI during treatment, shorter time to achieve PASI 50 response after starting ustekinumab, no family history of psoriasis, absence of chronic kidney disease, and use of immunosuppressants when not taking ustekinumab.[4] In the same study, the cumulative probability values of relapse-free status at six, 12, 18, 24, and 36 months of the discontinuation of ustekinumab treatment were reported to be 49.3%, 12.6%, 5.3%, 4.7%, and 1.6%, respectively. As in our study, the authors determined biologics-free time as one of the most important predictors of clinical worsening and relapse. Given the high relapse rates, the discontinuation of ustekinumab in patients with well-controlled psoriasis is not recommended.[4]

In a study by Huang and Tsai,[10] the rates of exacerbation without systemic treatment in psoriasis patients were reported as 16.8%, 7.4%, 4.3%, 3.2%, and 3.2% at the end of 1, 2, 3, 4, and 5 years, respectively. Biologics were restarted in 41.9%, 66.7%, 77.1%, 83.5%, and 86.1% of patients at the end of 1, 2, 3, 4, and 5 years, respectively. According to the multivariate generalized estimating equation regression analysis, the predictors of a longer relapse-free time were baseline PASI, improvement in PASI, biologics naivety, and early biological therapy intervention. In the same study, the log-rank test and Kaplan–Meier analysis showed a significantly higher relapse-free rate in patients who had received early biological therapy, those that had achieved PASI 90, and those that were biologics-naive. Furthermore, early biologics administration within 2 years of diagnosis resulted in a lower risk of relapse in patients with moderate-to-severe psoriasis.

In conclusion, we do not recommend completely discontinuing the used biologic agent in psoriasis patients with clinical improvement, as we found a high rate of clinical worsening and relapse in those whose treatment was interrupted, and the risk of clinical worsening and relapse increased as the duration of the drug-free period increased. Therefore, rather than discontinuation of biological agent therapy, we recommend extending the intervals between the doses in suitable patients. Large-scale controlled studies are needed to validate this recommendation.

AUTHOR CONTRIBUTIONS

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Oğuz Topal, Sezgi Sarıkaya Solak, Asude Kara Polat, and Ayşe Serap Karadağ performed the research. Filiz Topaloğlu Demir and Ayşe Serap Karadağ designed the research study. Filiz Topaloğlu Demir wrote the paper. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available within the article or its supplementary materials.

ETHICS STATEMENT

The Istanbul Medipol University Clinical Researchers Ethical Board approved this study (date: 10/12/2020, number: 890).

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How to cite this article: Topaloğlu Demir F, Polat Ekinci A, Aytekin S, et al. Clinical course of psoriasis patients that discontinued biologics during the COVID-19 pandemic. *J Cosmet Dermatol*. 2023;00:1-10. doi:10.1111/jocd.15638