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Research Article

Can Biologics Be Discontinued in Patients with Psoriatic Arthritis in Stable Remission? A Prospective Single-Center Clinical and Ultrasound Study

Dario Graceffa,[1] **Francesca Sperati**,[2] **Claudio Bonifati**,[1] **Gabriele Spoletini**,[3] **Fulvia Elia**,[4] **Mauro Caterino**,[4] **Antonio Cristaudo**,[1] **and Aldo Morrone**[5]

[1]*Department of Clinical Dermatology, San Gallicano Dermatological Institute, IRCCS, Rome, Italy*
[2]*Biostatistics Unit, San Gallicano Dermatological Institute IRCCS, Rome, Italy*
[3]*General Surgery and Liver Transplantation, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*
[4]*Radiology and Diagnostic Imaging Unit, San Gallicano Dermatological Institute, IRCCS, Rome, Italy*
[5]*Scientific Direction, San Gallicano Dermatological Institute, IRCCS, Rome, Italy*

Correspondence should be addressed to Dario Graceffa; medialta@virgilio.it

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Biologic disease-modifying antirheumatic drugs (bDMARDs) and particularly tumor necrosis factor inhibitors (TNFi) have dramatically changed the natural history of psoriatic arthritis (PsA), making complete clinical remission possible in most patients. However, TNFi drugs are not without potential adverse effects such as increased infectious risk. In addition, their extensive use is associated with a significant economic burden. This prospective longitudinal cohort study involving 45 PsA patients treated with TNFi in stable remission aimed to evaluate by both clinical examination and ultrasound timing and predictive factors of disease relapse after discontinuation of TNFi treatment. Thirty-nine (86.6%) of 45 enrolled patients experienced disease relapse during the follow-up period, while six patients (13.4%) maintained remission beyond the scheduled 104 weeks. The median survival time of drug-free remission after TNFi discontinuation was 24 weeks (95% confidence interval (CI): 22.6–25.4). Disease relapse was characterized by marked clinical and ultrasound worsening of dermatologic and rheumatologic conditions. However, resuming previously discontinued treatment allowed all patients to quickly regain clinical remission. Interestingly, axial involvement was a key feature of the symptomatological pattern of disease relapse, being the main reason for treatment restart in 26% of our cohort. Based on a multivariate Cox model, three variables (VAS pain, tender joint count, and swollen joint count) of the clinical assessment performed at the time point of TNFi treatment onset negatively influenced the time to disease relapse. In conclusion, temporary discontinuation of TNFi drugs is feasible and relatively safe. However, as few predictors of the risk and timing of disease relapse have been identified, patients should be closely monitored when therapy is discontinued.

1. Introduction

Psoriasis is a common, chronic, inflammatory skin disease with a worldwide prevalence of 2-3% [1].

Regardless of the extension of skin involvement, any form of chronic inflammatory arthritis complicates the clinical course of around 30% of psoriasis patients, significantly affecting their quality of life and physical functioning [2]. The development of a concomitant arthritis markedly changes the pharmacological approach to the psoriatic patient. Even with limited skin involvement, treatment with systemic drugs becomes mandatory to minimize the risk of irreversible damage to tendons and joints [3].

The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) has dramatically changed the natural history of psoriasis and psoriatic arthritis, making the target of a complete clinical remission achievable in most treated patients [4].

However, the long-term use of bDMARDs is associated with a significant economic burden and potential adverse

effects, mainly related to their immunomodulatory action and the consequent increased risk of infection. Tumor necrosis factor inhibitors (TNFi) have been extensively associated with an increased risk of pulmonary infections and reactivation of quiescent viral or mycobacterial infections. Moreover, although most cohort studies are rather reassuring, the severity of the clinical course of COVID-19 in this subgroup of patients is also currently debated [5–11].

Consequently, concerns have been raised about the lifelong, uninterrupted treatment of patients with psoriatic disease even when in complete remission, and periodic dosing tapering or complete discontinuation of bDMARDs have been investigated [12, 13].

Although periodic discontinuation of biologics could result in substantial cost savings and a reduction in potential adverse effects, an increased risk of relapse of both skin and joint components of the disease is to be considered.

Evidence of a real need to continuously treat patients with biologic drugs is limited. Nevertheless, therapy is commonly maintained without interruption to maintain complete control of the disease and prevent possible irreversible permanent joint damage.

In addition, no guidelines for the management of PsA include any clear recommendation on the option of discontinuing treatment in patients who have achieved sustained complete remission.

Most of the studies on this topic have demonstrated that discontinuation of the drug is followed by loss of remission in the vast majority of cases [14–16].

Still, there is no clear evidence that discontinuation of therapy results in the rapid progression of bone damage. To date, no study has prospectively evaluated patients with PsA in stable remission after discontinuation of TNFi with power Doppler ultrasound (PDUS) and contrast enhanced ultrasound (CEUS).

PDUS is currently employed by many rheumatology centers as an essential diagnostic tool for the follow-up of patients with PsA [17, 18].

Alternatively, CEUS is a relatively new ultrasound imaging technology, which is extensively used, primarily in solid tumors diagnostics. Although its use in daily clinical practice in rheumatology is rather limited, a number of studies have demonstrated its particular sensitivity, especially in confirming or excluding the presence of subclinical synovitis. For this reason, CEUS is particularly suitable for our purpose of assessing patients with PsA in complete clinical remission [19, 20].

The aim of the present study was to monitor patients with PsA in stable remission after discontinuation of TNFi and to assess the timing and predictors of disease relapse by clinical assessment, PDUS, and CEUS in an outpatient clinical setting.

2. Methods

2.1. Study Design. This is a longitudinal prospective cohort study involving 45 PsA patients in stable remission under continuative treatment with TNFi.

2.2. Setting. Patients were recruited from January 2018 to January 2021 among those referred to the Psoriasis Clinic of the San Gallicano Dermatological Institute, Rome, Italy.

2.3. Ethics. The study received full approval from the local ethics committee (Comitato Etico Centrale IRCCS Lazio project number: GR-2013-02354935), and all patients involved signed informed consent before enrollment.

2.4. Subjects. Patients were included in the study if they met the following characteristics: (1) age ≥ 18 years; (2) diagnosis of peripheral or axial psoriatic arthritis lasting more than 12 months according to CASPAR criteria [21]; (3) condition of complete remission (i.e., no clinical signs of skin and joint disease activity or minimal disease activity (MDA). MDA is defined by the presence of 5 of the 7 following criteria: tender joint count ≤ 1; swollen joint count ≤ 1; Psoriasis Activity and Severity Index (PASI) ≤ 1 or body surface area $\leq 3\%$; patient pain visual analogue score (VAS) ≤ 15; patient global disease activity VAS ≤ 20; health assessment questionnaire (HAQ) ≤ 0.5; tender entheseal points ≤ 1 [22]; (4) stable disease for at least 12 months; absence or minimal signs of joint and/or tendon inflammation at PDUS; continuous therapy with TNFi drug at baseline assessment time point.

2.5. Interventions. Participants underwent a baseline visit (time point 0; TP0) during which remission status was confirmed by means of clinical and ultrasound assessment. Clinical assessment included tender and swollen joints count (TJC/SJC), evaluation of entheses according to Leeds enthesitis score [23], administration of the following assessment questionnaires: Dermatology Life Quality Index (DLQI); HAQ; Bath Ankylosing Spondylitis Functional Index (BASFI); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); visual analogue scale (VAS) for pain; and patient-reported global health assessment (PGA). Safety blood tests (full blood count, liver function tests, urea, and electrolytes) and inflammation biomarkers (CRP and ESR) were collected at each visit. To assess any potential dysmetabolic and atherosclerotic comorbidities, ultrasound of the liver and epiaortic vessels was performed.

Ultrasound assessment was performed with MyLab Eight Exp scanner (Esaote, Genoa, Italy) equipped with an IH 6–18 linear array transducer by a single rheumatologist (DG) with expertise in musculoskeletal ultrasound. A systematic multiplanar PDUS examination of each clinically involved joint was performed, and power Doppler activity was graded as absent, low, moderate, and high according to the degree of synovial inflammation.

To detect any possible subclinical involvement of the entheses, an examination of the entheses, according to Madrid sonographic enthesitis index (MASEI) score was performed. The MASEI score includes six entheses (the triceps, the quadriceps, both proximal and distal patellar and Achilles tendons, and the proximal insertion of the plantar aponeurosis) and six elementary lesions (structure, thickening, erosion, enthesophytes, PD, and bursa), with

weighted punctuations that can be summed to a maximum score of 136 [24].

Within seven days of the enrollment visit (TP0), all patients underwent CEUS of a target joint selected among those previously most affected by the inflammatory process. Patients were clinically monitored for 104 weeks at 12- to 16-week intervals and provided with a phone number to perform unscheduled visits in the event of a disease relapse. A final study exit visit (time point 1; TP1) was performed at the time of disease relapse, defined as the occurrence of significant joint or skin symptoms. On the TP1 visit, the same procedures performed on TP0 were repeated.

2.6. CEUS. A contrast agent composed of sulfur hexafluoride-filled microbubbles (SonoVue, Bracco International B.V., Amsterdam, Netherlands) was used. A 7.5 MHz dedicated linear transducer was used in conjunction with a specific continuous mode contrast-enhanced harmonic imaging technology, contrast-tuned imaging technology (CnTI), which allows the transmission of the specific resonance frequency of sulfur hexafluoride-filled microbubbles and the selective registration of harmonic frequencies. The acoustic pressure was set at 45 kPa in each patient, and the mechanical index (MI) was selected automatically by the sonography scanner in relation to beam focus depth. All patients gave their informed consent for the use of contrast agent. A 4.8 mL bolus of contrast agent was injected into a peripheral vein, followed by an injection of 10 mL of physiologic saline solution. Immediately after the injections, the synovial tissue under examination was scanned in CnTI mode with a frame rate of 15 frames per second. The transducer was kept in a fixed position to highlight all the phases of enhancement. The beam focus was placed at the level of the synovial proliferation or immediately below it, and beam gain was set at the minimum level. Images were recorded in digital forms.

2.7. Statistics. Categorical variables were reported through absolute and relative frequencies, whereas the continuous variables were reported through mean, standard deviation (SD), median, and the first ($Q1$) and third ($Q3$) quartiles. The Kolmogorov–Smirnov normality test was calculated for all the continuous variables. To explore the differences between continuous variables, the Mann–Whitney test was utilized. The Wilcoxon and McNemar tests were applied to compare variables at the TP1 and TP0 time points, according to the nature of the variables. The agreement between CEUS and joint ultrasound was calculated using Cohen's kappa statistics, interpreted with the Landis and Koch classification criteria. The Kaplan–Meier product-limit method and the log-rank test were used for estimating and comparing survival curves. Hazard ratios and their relative 95% confidence intervals were estimated for each variable using the univariate Cox proportional hazard model. A multivariate Cox model was then implemented considering the variables significant at univariate analysis. A p value of <0.05 was considered statistically significant. Statistical analyses were carried out using SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

Forty-five patients with PsA (female = 11; male = 34) were enrolled in the study. Three of 45 patients (6.6%) were affected by spondylitis in addition to peripheral arthritis. At the time of discontinuation, 36/45 patients (80%) were on Etanercept, 7/45 (15.6%) were on adalimumab, 1/45 (2.2%) were on Certolizumab Pegol, and 1/45 (2.2%) were on intravenous Infliximab. In accordance with the study inclusion criteria, the assessment performed on TP0 showed all enrolled patients to be in complete clinical remission or in a state of MDA. The remission was maintained for a median time of 6.37 years before enrollment (range 1–12 years).

PDUS on TP0 showed minor or insignificant signs of synovial inflammation (low power Doppler activity) in 36 patients (80%), while in nine (20%) no power Doppler activity was detectable.

The TP0 CEUS examination revealed modest synovial inflammatory activity (low enhancement) in 26 patients (57.7%) and no enhancement in 19 patients (42.2%).

The median MASEI index measured on TP0 was 25 (range 17–30), significantly above the cut-off value of 18 used to identify enthesis involvement in PsA [25].

Liver ultrasound on TP0 detected mild-to-moderate hepatic steatosis in 21/45 patients (46.6%) while epiaortic vessels scan revealed carotid plaques in 5/45 patients (11.1%).

The baseline characteristics of the study population are summarized in Table 1.

Thirty-nine patients (86.6%) experienced disease relapse during the follow-up period while six patients (13.4%) maintained their remission status beyond the scheduled 104 weeks.

Three of the 39 patients (7.6%) who experienced a relapse were still in MDA when therapy was resumed. Psoriasis worsening in sensitive sites (most commonly hands, face, and genitals) and synovial activity on PDUS led to treatment resumption in this subgroup of patients.

The median survival time of drug-free remission after TNFi discontinuation was 24 weeks (95% confidence interval (CI): 22.6–25.4) (Figure 1).

Comparative analysis of the survival time of drug-free remission after discontinuation of Etanercept vs Adalimumab showed a higher value for the monoclonal antibody as compared to the receptor fusion protein (adalimumab time to relapse = 46 weeks, 95% CI: 0–102.4 vs. Etanercept time to relapse = 22 weeks, 95% CI: 19.1–24.9). Such a difference did not reach statistical significance probably due to the small sample size of the adalimumab group (log-rank p value = 0.140) (Figure 2).

To identify factors potentially influencing the persistence of remission after drug discontinuation, the following variables were included in Cox's multivariate model: sex, BMI, smoking, family history of psoriasis, duration of disease, duration of remission state (prior to enrollment), presence of dysmetabolic, cardiovascular, clinical dermatologic, and rheumatologic assessment at the time of biologic treatment start and at the time of study enrollment (Table 2).

Table 1: Study population clinical characteristics on TP0 (baseline) vs. TP1 (disease relapse).

	TP0 (baseline)	TP1 (disease relapse)	Wilcoxon test p value
BMI	27.4 (20.4–42.6)	27.8 (21.1–37.7)	0.045
BASDAI	0.5 (0.0–5.5)	3.8 (0.0–8.1)	<0.001
BASFI	0.1 (0.0–4.0)	1.8 (0.0–7.5)	<0.001
HAQ	0.0 (0.0–1.0)	0.5 (0.0–1.6)	<0.001
MASEI	25.0 (17.0–30.0)	26.0 (19.0–33.0)	<0.001
PASI	0.4 (0.0–2.1)	1.2 (0.0–9.6)	<0.001
DLQI	0.0 (0.0–3.0)	1.0 (0.0–16.0)	<0.001
CRP (mg/dl)	0.2 (0.1–1.0)	0.6 (0.1–2.1)	<0.001
ESR (mm/h)	11.0 (2.0–38.0)	20.0 (3.0–50.0)	<0.001
VAS pain	0.0 (0.0–30.0)	50.0 (0.0–100.0)	<0.001
VAS PGA	0.0 (0.0–20.0)	50.0 (0.0–100.0)	<0.001
TJC	0.0 (0.0–1.0)	3.0 (0.0–16.0)	<0.001
SJC	0.0 (0.0-0.0)	1.0 (0.0–16.0)	<0.001
LEI	0.0 (0.0-0.0)	0.0 (0.0–2.0)	<0.001

Data are expressed as median (range); BMI, body mass index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; MASEI, Madrid sonography enthesitis index; PASI, Psoriasis Area Severity Index; DLQI, Dermatology Life Quality Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; PGA, patient-reported global health assessment; TJC/SJC, 66/68-swollen and tender joint counts; LEI, Leeds enthesitis index.

None of the included variables negatively influenced the time to disease relapse. However, three variables belonging to the clinical evaluation performed at the time of biological treatment onset bordered on statistical significance: VAS pain (HR: 1.02, 95% CI 1.01–1.03, $p = 0.04$); SJC (HR: 1.07, 95% CI 0.99–1.16, $p = 0.05$); and HAQ (HR: 1.89, 95% CI 0.99–3.60, $p = 0.05$).

A comparison between baseline and TP1 was performed for all dermatologic and rheumatologic clinical parameters, resulting in a statistically significant worsening of all variables on TP1 (Table 1).

Similarly, ultrasonography demonstrated marked worsening of synovitis and enthesitis through (1) increased power Doppler activity, (2) higher levels of postcontrast enhancement, and (3) elevation of MASEI index.

In fact, none of the 45 enrolled patients showed significant power Doppler signal or postcontrast enhancement at the baseline, yet TP1 assessment showed moderate-to-high power Doppler signal in 22 patients (49%) and moderate-to-high contrast enhancement in 27 (60%). The agreement of the two ultrasound methods measured by Cohen's kappa coefficient was 0.487, consistent with a moderate level of concordance. However, despite a specific sensitivity analysis was not performed, CEUS detected a higher number of active patients as compared to simple PDUS (Table 3).

The analysis of the major psoriasis-related comorbidities revealed no cases of significant worsening after therapy discontinuation (Table 4).

Baseline assessments of axial involvement showed BASDAI and BASFI scores around 0 for all patients. Spondylitis patients did not differ significantly from those with peripheral involvement only (Mann–Whitney test p value = 0.702). The relapse evaluation showed BASDAI to increase from a median value of 0.5 (min. 0–max. 5.5) to 3.8 (min. 0–max. 8.1) and the BASFI from 0.1 (min. 0–max. 4.0) to 1.8 (min. 0–max. 7.5), Wilcoxon test p value < 0.001. Interestingly, in five out of 42 patients (12%) with exclusive peripheral involvement and for the three spondylitis patients, axial pain was the main cause of treatment restart.

4. Discussion

We investigated the effects of TNFi discontinuation in 45 patients with PsA in sustained clinical remission. We followed this cohort of patients until the onset of disease relapse or for 104 weeks. Differently from previous studies, to increase diagnostic reliability, we confirmed disease remission and the occurrence of relapse by PDUS and CEUS.

A low grade of ultrasound-detected joint inflammation was observed at baseline in a small proportion of patients in complete clinical remission, confirming a higher sensitivity of the ultrasound techniques employed over clinical examination in detecting enthesitis and joint synovitis.

This finding is in agreement with previous ultrasound studies that revealed a residual disease activity in a variable percentage of patients in complete clinical remission [26–28].

However, we did not report an increased risk of relapse among this subgroup of patients when compared to those with a completely silent ultrasound assessment.

Similarly, ultrasound assessment of entheses by MASEI score showed baseline levels exceeding the cut-off of normality. However, it should be clarified that the MASEI score includes not only abnormalities related to active inflammation but also to chronic damage such as thickening and calcification of the entheses.

Previous studies evaluating the maintenance of remission after discontinuation of TNFi drugs demonstrated a high incidence of relapse with variable timing. Of the 45 patients we enrolled, 6 maintained remission beyond the established follow-up period with no need to restart therapy, and 3 resumed therapy, although on MDA. We can therefore conclude that during the scheduled follow-up, we observed a clear relapse of the disease in 80% of the patients who discontinued treatment. Although the evidence of a superior long-term effectiveness of continuous therapy compared with intermittent therapy and the potential risk of antidrug antibody production is documented in a few studies, we observed that remission was promptly regained once the previously discontinued treatment was resumed. Nevertheless, the long-term effects of this approach remain largely unexplored [29–31].

In a small cohort of 11 patients, Moverley et al. found a relapse incidence of 54.6% after discontinuation of TNFi plus methotrexate combination therapy, with a median time to relapse of approximately 8 weeks after drug discontinuation [15].

In 2015, Araujo et al. found in a small group of patients with PsA (12 patients, only 5 of whom were on TNFi monotherapy and 7 on methotrexate combination therapy), a relapse incidence similar to that observed by us but with

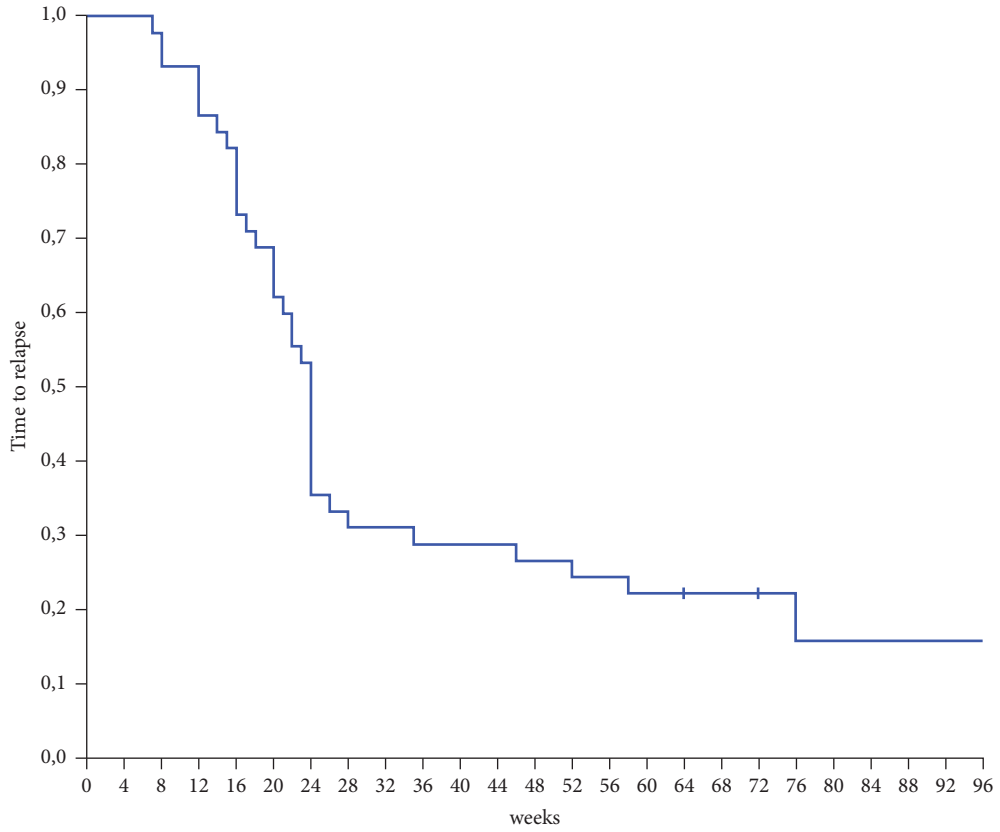

Figure 1: Kaplan–Meier survival curve of drug-free remission after discontinuation of TNFi.

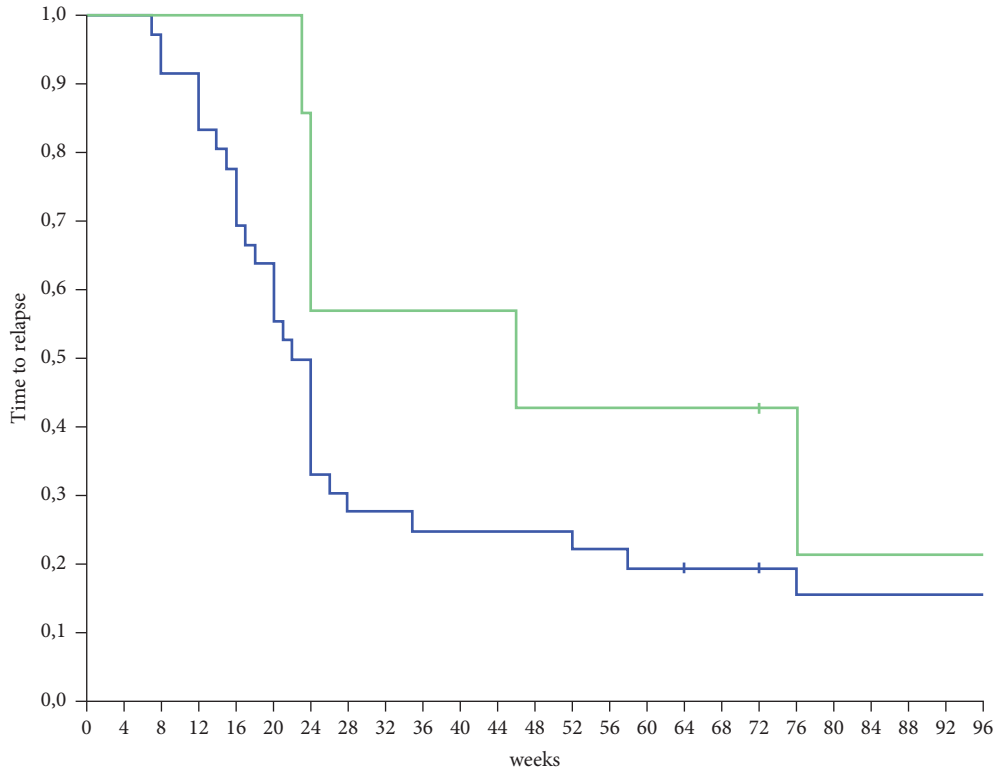

Figure 2: Comparison of survival curves of drug-free remission after discontinuation of etanercept (blue line) vs. adalimumab (green line).

Table 2: Cox regression analysis for factors potentially affecting the time to relapse after drug discontinuation.

		Relapse risk	
		HR (95% CI)	*p* value
Gender	Female vs. male	0.90 (0.44–1.86)	0.784
BMI	≥25 vs. <25	0.99 (0.93–1.06)	0.852
Age		1.00 (0.98–1.03)	0.845
Psoriasis duration		0.99 (0.97–1.02)	0.738
Spondylitis	Yes vs. no	1.05 (0.25–4.39)	0.945
Duration of remission	>5 vs. ≤5	1.40 (0.74–2.67)	0.298
Family history of psoriasis/PsA	Yes vs. no	0.74 (0.39–1.44)	0.381
Dyslipidemia	Yes vs. no	1.04 (0.46–2.37)	0.919
Obesity	Yes vs. no	1.24 (0.57–2.70)	0.591
Hypertension	Yes vs. no	1.46 (0.77–2.78)	0.246
Ischemic heart disease	Yes vs. no	2.17 (0.83–5.69)	0.116
Ultrasound nonalcoholic fatty liver	Yes vs. no	0.80 (0.42–1.53)	0.500
Peripheral arterial disease	Yes vs. no	3.56 (0.46–27.56)	0.225
Autoimmune thyroiditis	Yes vs. no	2.91 (0.38–22.62)	0.304
Depression	Yes vs. no	0.77 (0.18–3.24)	0.720
VAS pain TP0	Yes vs. no	1.00 (0.96–1.03)	0.838
VAS PGA TP0	Yes vs. no	0.99 (0.94–1.05)	0.753
TJC TP0		0.87 (0.36–2.09)	0.751
HAQ		2.18 (0.43–11.0)	0.343
PASI		1.03 (0.57–1.85)	0.924
DLQI		1.04 (0.65–1.67)	0.870
BASFI		0.92 (0.57–1.48)	0.739
BASDAI	≥4 vs. <4	0.83 (0.62–1.12)	0.221
Psoriasis onychopathy	Yes vs. no	0.90 (0.21–3.76)	0.883
ESR		1.00 (0.96–1.04)	0.950
CRP		3.22 (0.66–15.63)	0.148
PDUS	Low activity vs. no activity	1.04 (0.48–2.28)	0.912
CEUS	Low enhancement vs. no enhancement	1.61 (0.84–3.09)	0.148
MASEI		1.02 (0.91–1.14)	0.752
Smoke	Yes vs. no	1.09 (0.52–2.25)	0.825
VAS pain at biologic treatment onset	Yes vs. no	1.02 (1.01–1.03)	**0.004**
HAQ at biologic treatment start		1.89 (0.99–3.61)	**0.050**
TJC at biologic treatment start		1.05 (1.00–1.12)	0.069
SJC at biologic treatment start		1.07 (1.00–1.16)	**0.050**

PsA, psoriatic arthritis; BMI, body mass index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; MASEI, Madrid sonography enthesitis index; PASI, Psoriasis Area Severity Index; DLQI, Dermatology Life Quality Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; PGA, patient-reported global health assessment; TJC/SJC, 66/68-swollen and tender joint counts; PDUS, power Doppler ultrasound; CEUS, contrast-enhanced ultrasound. Bold values represent statistically significant results.

Table 3: Agreement of the two ultrasound methods measured by Cohen's kappa coefficient.

		CEUS on TP1 (disease relapse)			
		No enhancement *N* (%)	Low enhancement *N* (%)	Moderate enhancement *N* (%)	High enhancement *N* (%)
PDUS on TP1 (disease relapse)	No activity	5 (50.0)	4 (40.0)	1 (10.0)	0 (0.0)
	Low activity	0 (0.0)	8 (61.5)	4 (30.8)	1 (7.7)
	Moderate activity	0 (0.0)	1 (5.9)	10 (58.8)	6 (35.3)
	High activity	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)

Cohen' kappa = 0.487, $p < 0.001$ (moderate level of concordance). PDUS, power Doppler ultrasound; CEUS, contrast-enhanced ultrasound.

a significantly shorter time to relapse after drug discontinuation [32].

In our patients, the survival time of drug-free remission was significantly longer than in the cited works. To date, the present study was the only one that included the ultrasound assessment of the remission. Presumably, this approach allowed us to increase the sensitivity of baseline assessment and to exclude cases that, although asymptomatic, still had joint inflammation, potentially affecting the drug-free remission time.

Although the increased duration of drug-free remission in our patients treated with adalimumab versus etanercept did not reach statistical significance, to our knowledge, there are no studies showing similar results. This interesting result is worthy of further evaluation by means of more extensive studies.

Table 4: Psoriasis comorbidities on TP0 (baseline) vs TP1 (disease relapse).

		TP1 (disease relapse)		McNemar test
		No *N* (%)	Yes *N* (%)	*p* value
TP0 (baseline)				
COPD	No	44 (97.8)	1 (2.2)	0.999
	Yes	0 (0.0)	0 (0.0)	
Ischemic heart disease	No	40 (100.0)	0 (0.0)	0.999
	Yes	0 (0.0)	5 (100.0)	
Depression	No	42 (100.0)	0 (0.0)	0.999
	Yes	1 (33.3)	2 (66.7)	
Type II diabetes	No	38 (100.0)	0 (0.0)	0.999
	Yes	0 (0.0)	7 (100.0)	
Dyslipidemia	No	36 (100.0)	0 (0.0)	0.999
	Yes	0 (0.0)	9 (100.0)	
Ultrasound carotid plaque	No	40 (100.0)	0 (0.0)	0.999
	Yes	1 (20.0)	4 (80.0)	
Ultrasound nonalcoholic fatty liver	No	25 (92.6)	2 (7.4)	0.999
	Yes	1 (5.5)	17 (94.5)	
Hypertension	No	26 (96.3)	1 (3.7)	0.999
	Yes	1 (5.5)	17 (94.5)	
Obesity	No	34 (94.6)	2 (5.4)	0.500
	Yes	0 (0.0)	9 (100.0)	
Psoriasis onychopathy	No	36 (85.7)	6 (14.3)	**0.031**
	Yes	0 (0.0)	3 (100.0)	
Autoimmune thyroiditis	No	44 (100.0)	0 (0.0)	0.999
	Yes	0 (0.0)	1 (100.0)	
Peripheral arterial disease	No	44 (100.0)	0 (0.0)	0.999
	Yes	0 (0.0)	1 (100.0)	

Bold values represent statistically significant results.

In contrast to Arujo et al., our regression analyses did not show any baseline clinical and/or ultrasound factors influencing the risk of relapse and the disease-free interval after drug discontinuation. On the contrary, our data show that the clinical course after treatment discontinuation could be influenced by clinical parameters (pain VAS, TJC, and SJC) recorded at the start of biologic treatment. However, this finding just borders on statistical significance without fully reaching it.

Disease relapse was characterized by marked clinical worsening of both dermatologic and rheumatologic conditions, as confirmed by PDUS and CEUS. However, in agreement with most authors, no patient reported clinical impairment so severe as to require urgent pharmacological intervention. On the contrary, restarting previously discontinued treatment allowed all patients to rapidly regain clinical remission.

Interestingly, axial involvement was a key feature of disease relapse, not only in patients with spondylitis but also in those with peripheral arthritis, being in 26% of our cohort the main reason for treatment reintroduction.

In most studies conducted on patients with spondyloarthritis, an axial disease relapse (defined as BASDAI ≥ 4) was found in 76% to 100% of cases after TNFi discontinuation, with median disease-free intervals ranging from 6 to 24 weeks [33].

Analysis of psoriasis-related cardiovascular and dysmetabolic disorders did not reveal progression of these comorbidities during the period between TNFi discontinuation and the onset of relapse. According to scientific evidence, these comorbidities are largely caused by chronic inflammation [34].

We may speculate the clinical remission to be characterized by quiescence of general inflammation, so the short follow-up we planned was not sufficiently long to reveal any clinical or ultrasound changes in the above conditions.

Our study had limitations. The sample size was small, and a control group on continuous therapy was not included to make appropriate comparisons. Ultrasound examination was always performed at the time of symptom onset to confirm recurrence, so we could not assess the sensitivity of ultrasound in predicting disease relapse in patients who were still asymptomatic. The operator who performed the ultrasound assessment was not blinded to the patient's clinical condition. Finally, radiographic evaluation aimed at excluding any increased cumulative bone damage was not included.

In conclusion, our study shows the temporary discontinuation of TNFi drugs to be feasible and relatively safe. However, because few factors are known to predict the risk and timing of disease relapse, close clinical monitoring after treatment discontinuation is mandatory.

Data Availability

The rows data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Dario Graceffa and Francesca Sperati share first authorship.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Dario Graceffa and Francesca Sperati contributed equally to this work.

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