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Outcome following a short period of adalimumab dose escalation as rescue therapy in psoriatic patients

Background: Advances in biologic treatments have led to a new therapeutic frontier for moderate-to-severe psoriasis. Nevertheless, the efficacy of anti-TNFα decreases with time, requiring adjustments to maintain valuable Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index (DLQI) responses. *Objectives:* To evaluate the efficacy and safety of adalimumab dose escalation (40 mg, subcutaneous, once a week for 24 weeks) in psoriatic adult patients with secondary loss of response (PASI ≥50 to ≤75 or PASI≥75 and DLQI ≥5). *Materials and Methods:* A multicentre, observational study involving different Italian third-level referral centres for psoriasis enrolled a total of 64 adult patients with moderate-to-severe psoriasis who were treated with adalimumab and experienced a secondary loss of response. Primary endpoints were PASI> 75 or PASI ≥50 to ≤ 75 with DLQI ≤ 5, and the secondary end-point was the ability to maintain a therapeutic response, resuming adalimumab every other week. *Results:* At Week 16 and Week 24, 29/64 (45.3%) and 35/64 (54.6%) responded based on PASI, and mean DLQI was 4.9 and 4.09, respectively. At Week 36 and Week 48, 45.3% and 28.1% patients achieved the second end-point, respectively. No adverse events were recorded except for one patient with recurrent tonsillitis. *Conclusion:* Adalimumab escalation could be considered in cases with loss of response before switching to alternative biologic therapy.

Key words: psoriasis, Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), anti-TNFα, adalimumab,

Psoriasis is a systemic, immune-mediated, inflammatory disease with a chronic-relapsing course, particularly disabling patients' quality of life [1]. Moderate-to-severe psoriasis is strongly associated with several comorbidities, including psoriatic arthritis (PsA), inflammatory bowel disease, metabolic syndrome and an increased risk of cardiovascular disease and mortality [2-5]. Thus, successful long-term control of the inflammatory state is mandatory [4, 5].

In recent decades, various biologic therapies, such as anti-TNFα, have been shown to be effective for the management of moderate-to-severe psoriasis over the long term [6]. Nevertheless, in clinical practice, drug survival for all anti-TNFα preparations has been shown to decrease with time, dropping from 60% at Year 1 to 40% at Year 4 [7]. This is defined as primary loss of response (LOR) and lack of initial efficacy; while secondary LOR identifies those cases in which an optimal initial response is lost over time [8]. A primary treatment failure is defined as Psoriasis Area and Severity Index (PASI) <50 [8, 9]. In accordance with the European Consensus Programme (ECP) goals [9] and the European S3 guidelines [10], "treatment success" is defined as a ≥75% reduction of PASI, and an "intermediate response" is defined as a PASI reduction of ≥50% to <75% and Dermatology Life Quality Index (DLQI) ≤5%. Mrowietz *et al.* recommended to continue treatment whether the regimen results in PASI ≥75 or PASI ≥50 to <75 combined with a DLQI ≤ 5 [9]. In contrast, for cases with PASI <50 or PASI ≥50 to <75, combined with DLQI >5, treatment modifications can be considered [9]. Hence, a secondary LOR may be considered if a patient loses an initial optimal response to treatment over time, with a PASI <75 or ≥50 to <75, combined with DLQI >5 [9].

Thus, potential therapeutic adjustments include drug dose escalation, reduced intervals, combination therapies, or switching to another drug [9, 11]. In particular, dose escalation of adalimumab (ADA) to weekly dosing has been recently approved [12].

Thus, the aim of the present study was to evaluate the efficacy and safety of ADA dose escalation in psoriatic patients with secondary LOR as a strategy to regain treatment success.

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Materials and methods

Study design and population

We performed a multicentre, observational, retrospective study from 1st January 2017 to 31st December 2017 in selected dermatology departments of Emilia Romagna and Marche, Italy. The patients included in the analysis met the following criteria: adult patients (≥ 18 years) with chronic moderate-to-severe plaque psoriasis undergoing treatment with ADA who experienced a secondary LOR. All patients previously received therapy according to the scheduled regimen dose: 80 mg, subcutaneous (sc), as loading dose, then 40 mg sc one week later and then every other week for at least 16 weeks. Participants entered the study if they met one of the following conditions:

– PASI ≥50 to <75
– PASI 75 with DLQI ≥5

Data collection and outcome

Patients were clinically observed at the beginning of ADA dose escalation. Data were gathered from the electronic medical files from each department. For each patient, the following were recorded: age, sex, body weight, Body Mass Index (BMI), PASI, DLQI, mean duration of the disease at enrolment of the current study, affected areas of the body (nails, face, scalp, genitalia, palms and soles), comorbidities (obesity, smoke, alcohol habit, familiarity of psoriasis or PsA, PsA, hypertension, hyperlipidaemia, metabolic syndrome, diabetes, and other significant comorbidities), number of prior systemic treatments for psoriasis, and both traditional and biologics (*table 1*).

The weekly protocol consisted of administration of ADA, at 40 mg sc once a week, for 24 weeks. In particular, the first 16 weeks were set as the minimum treatment period necessary to evaluate the efficacy of the weekly intervention, whereas the other eight weeks were established to evaluate the maintenance of the treatment effects. Moreover, after these 24 weeks, we continued the patients' follow-up for an additional 24 weeks in order to evaluate the clinical outcomes following the weekly intervention over a year. Time points for the evaluation of rate of therapeutic response to ADA dose escalation were set at Week 16 and 24 using PASI and DLQI as quantitative parameters for the outcomes. The number of patients who regained clinical response with the weekly intervention and maintained it, returning to ADA administration every other week, as well as those patients with LOR over the study period, despite dosage escalation, were also determined.

Furthermore, the safety of ADA escalation was evaluated considering adverse events (AEs).

Assessment of efficacy

Primary end-points were PASI> 75 at Week 24 or PASI ≥50 to ≤ 75 combined with DLQI ≤ 5. The secondary end-point was based on the ability to maintain a therapeutic response, resuming dosing every other week.

Table 1. Baseline demographic and disease characteristics of patients.

Characteristics	*n* = 64
Age (years), mean ±SD (range)	28.7 ±14.3 (4-74)
Male sex	36 (56.2)
Body weight (kg), mean ±SD (range)	80.3 ±19.9 (49-144)
BMI (kg/m^2), mean ±SD (range)	27.8 ±5.7 (19-44)
PASI score, mean ±SD (range)	10.4 ±7.1 (1-40)
DLQI	9.8 ±4.2 (2-20)
Mean duration of the disease (years)	22.8 ±14.2 (4-74)
Affected areas of the body	
Nails	5 (7.8%)
Face	1 (1.5%)
Scalp	35 (54.6%)
Genitalia	2 (3.1%)
Palms and soles	5 (7.8%)
At least one comorbidity	46 (71.8)
Obesity	17 (26.6)
Smoker	25 (39.1)
Alcohol consumption	12 (18.8)
Familiarity of Pso/PsA	22 (34.4)
PsA	27 (42.2)
Hypertension	25 (39.7)
Hyperlipidaemia	27 (42.2)
Metabolic syndrome	11 (17.2)
Diabetes	9 (14.1)
Number of failures with previous systemic traditional therapy	
1	16 (25.0)
2	29 (45.3)
3	17 (26.5)
4	1 (1.6)
5	1 (1.6)
Number of failures with previous biologic therapy	
0	35 (54.7)
1	23 (35.9)
2	3 (4.7)
3	3 (4.7)

PsA: psoriatic arthritis; Pso: psoriasis; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; BMI: Body Mass Index.

Statistical analysis

Descriptive statistics for continuous variables were reported as means with standard deviation (SD), and dichotomous variables were recorded as frequencies with percentages in parentheses. Baseline characteristics were compared to assess the statistical significance of any differences among the groups of responders (R) and non-responders (NR) at Weeks 16 and 24. Furthermore, clinical response rates were evaluated and compared based on baseline PASI and DLQI scores over the entire 24-week period.

Where appropriate, the Mann-Whitney U-test or Student's t-test was used for continuous variables, and analyses for dichotomous variables were based on Pearson's χ2-test or Fisher's exact test without imputation of missing data. $P < 0.05$ was considered statistically significant. In addition, a univariate logistic regression and multivariate

logistic regression analysis was used to assess the adjusted effect of clinical factors on clinical response.

Results

Baseline patient characteristics

A total of 64 adult patients were included in the analysis. The demographic data, disease-specific characteristics and associated comorbidities of the study population at baseline (T0) are summarized in *table 1*. Moreover, in the same table, we include former systemic therapies, both traditional and biologic, administered for psoriasis.

The mean age (±SD) of the study population was 28.75 ±14.3 years, and more than half were male (56.2%). The mean body weight was 80.3 ±19.9 kg and BMI 27.8 ±5.7 kg/m^2; 17 patients were obese (BMI ≥30 kg/m^2).

At T0, mean duration of the disease before the beginning of the study was 22.8 years ±14.2 years and mean values of PASI and DLQI were respectively, 10.4 ±7.1 and 9.8 ±4.2. Comorbidities were not present in 29.7% (*n*= 19) patients. Based on analysis of the other patients, one comorbidity was present in 29.7% (*n*= 19), and at least two comorbidities in 40.6 % (*n*= 26). The two most (equally) common comorbidities were elevated blood lipids 42.2% (*n* = 27) and PsA 42.2% (*n* = 27), followed by arterial hypertension in 39.1% (*n* = 25) and metabolic syndrome detected in 17.2% (*n* = 11). Among the patient population, 39.1% (*n* = 25) had a smoking habit.

With regards to previous treatments, traditional systemic therapies were unsuccessful for the majority of patients. A total of 45.3% (*n* = 29) failed two different traditional

Table 2. Demographic and disease characteristics of patient responders and non-responders at weeks 16 and 24.

	Week 16			Week 24		
Characteristics	**Non-responders 35 (54.6%)**	**Responders 29 (45.3%)**	***p* value**	**Non-responders 29 (45.3%)**	**Responders 35 (54.6%)**	***p* value**
Age (years), mean ±SD (range)	28.7 ±11.4 (6-53)	28.8 ±17.2 (4-74)	0.981	28.4 ±11.1 (4-70)	29.0 ±16.6 (4-74)	0.880
Male sex	21 (60.0)	15 (51.7)	0.506	18 (62.1)	18 (51.4)	0.393
Body weight (kg), mean ±SD (range)	86.4 ±21.6 (58-144)	72.9 ±14.7 (49-105)	0.006	87.8 ±22.0 (58-144)	74.0 ±14.0 (49-108)	0.004
BMI (kg/m^2), mean ±SD (range)	29.1 ±5.7 (219-40)	26.3 ±5.4 (19-38)	0.055	29.4 ±6.1 (21-44)	26.6 ±5.1 (19-38)	0.05
PASI score, mean ±SD (range)	11.9 ±8.7 (1-40)	8.5 ±3.9 (2-21)	0.059	12.7 ±9.2 (1-40)	8.5 ±3.7 (2-21)	0.01
DLQI, mean ±SD (range)	10.4 ±4.7 (2-20)	9.2 ±3.6 (4-18)	0.298	11.2 ±4.4 (2-20)	8.9 ±3.6 (3-18)	0.051
At least one comorbidity	27 (77.1)	19 (65.5)	0.303	25 (86.2)	21 (60.0)	0.020
Obesity	10 (28.6)	8 (27.6)	0.814	9 (31.0)	9 (25.7)	0.624
Smoker	12 (34.3)	13 (44.8)	0.498	11 (37.9)	14 (40.0)	0.880
Alcohol consumption	8 (22.8)	4 (13.8)	0.327	7 (24.1)	5 (144.3)	0.282
Familiarity of Pso/PsA	9 (25.7)	13 (44.8)	0.019	6 (20.7)	16 (45.7)	0.036
PsA	18 (51.4)	9 (31.0)	0.100	16 (55.2)	11 (31.4)	0.050
Hypertension	17 (48.6)	8 (27.6)	0.070	16 (55.2)	9 (25.7)	0.011
Hyperlipidaemia	15 (42.8)	12 (41.4)	0.747	14 (48.3)	13 (37.1)	0.352
Metabolic syndrome	8 (22.8)	3 (10.3)	0.153	8 (27.6)	3 (8.6)	0.043
Diabetes	5 (14.3)	4 (13.7)	0.918	5 (17.2)	4 (11.4)	0.469
Number of failures with systemic Pso therapy						
1	7 (20.0)	9 (31.0)	0.399	4 (13.7)	12 (34.2)	0.210
2	17 (48.60)	12 (41.4)		16 (55.2)	13 (37.1)	
3	11 (31.4)	6 (20.7)		9 (31.0)	8 (22.8)	
4	0 (0.0)	1 (3.4)		0 (0.0)	1 (2.8)	
5	0 (0.0)	1 (3.4)		0 (0.0)	1 (2.8)	
Number of failures with biologic Pso therapy						
0	19 (54.2)	16 (55.2)	0.377	16 (55.2)	19 (54.2)	0.267
1	11 (31.4)	12 (41.4)		8 (27.6)	15 (42.8)	
2	2 (5.7)	1 (3.4)		2 (6.9)	1 (2.8)	
3	1 (2.8)	0 (0.0)		1 (3.4)	0 (0.0)	
4	2 (5.7)	0 (0.0)		2 (6.9)	0 (0.0)	

PsA: psoriatic arthritis; Pso: psoriasis; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; BMI: Body Mass Index.

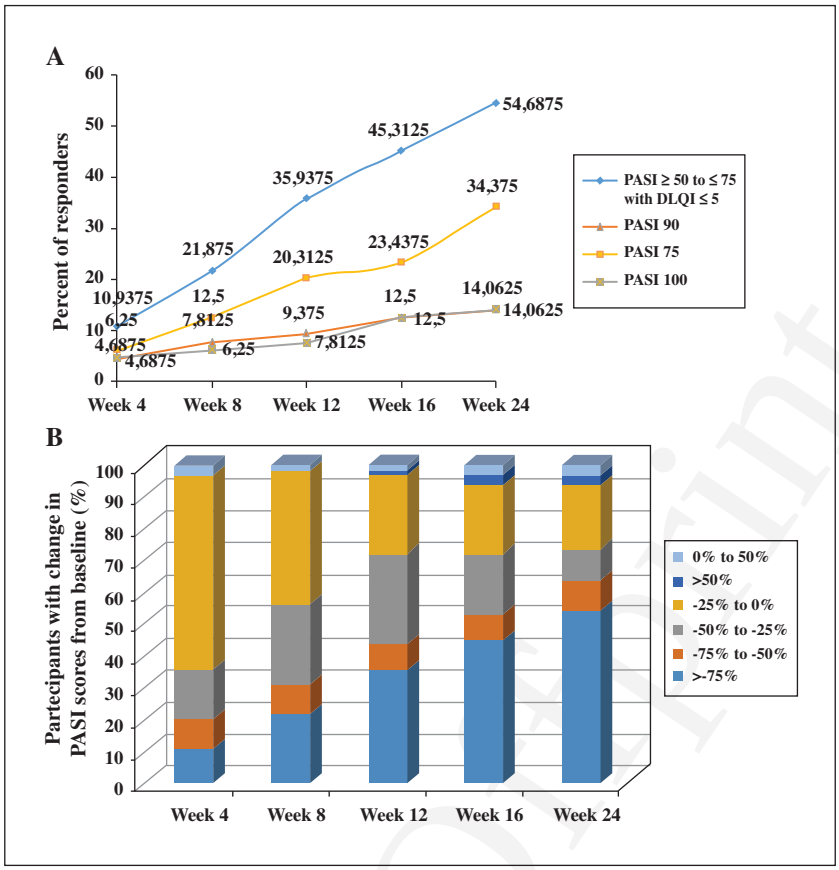

Figure 1. Proportion of patients with clinical response over the whole study period: from Week 0 to Week 24. **A**) Percentage of patients with PASI ≥50 to ≤ 75 and DLQI≤5, PASI75, PASI 90 and PASI 100. **B**) Proportion of patients with change in PASI scores from baseline to Week 24 (PASI: Psoriasis Area and Severity Index).

systemic therapies among methotrexate, cyclosporine A, phototherapy and acitretin. In contrast, as with biological therapies, the majority were drug-naïve (54.7%; $n=35$) or failed only one former monoclonal antibody (35.9%; $n=25$), including other anti-TNFα drugs (etanercept and infliximab) and anti-interleukin (IL) -12 and 23 (ustekinumab).

Univariate analysis

The study population was divided into two groups and compared at Week 16 and 24 (*table 2*).
We considered "*responders*" as those patients who achieved PASI >75, or at least PASI ≥50 to ≤ 75 combined with DLQI ≤ 5. In contrast, "*non responders*" were those who failed to achieve such improvements in PASI and/or DLQI.
The responder group encompassed 29 patients (15 males and 14 females) at Week 16 and increased to 35 (18 males and 17 females) at Week 24.
Following univariate analysis, body weight was significantly higher among non-responders (86.4 [±21.6] kg vs 72.9 [+/- 14.7] kg, $p=0.006$ at Week 16 and 87.8 [±22.0] kg vs 74.0 [±14.0], $p=0.004$ at Week 24 for non-responders vs responders, respectively). Moreover, familiarity of psoriasis and/or PsA was significantly higher among responders during the whole study; at Week 16 (44.8%; $p=0.019$) and Week 24 (45.7%; $p=0.036$). Furthermore, at Week 24, the prevalence of arterial hypertension and metabolic syndrome was significantly higher among non-responders than responders; 55.2% ($p=0.011$) and 27.6% ($p=0.043$), respectively.
In addition, the safety profile of the weekly administration of ADA was confirmed. No AEs were recorded, apart from a frequent recurrence of tonsillitis in one of the 64 patients, which triggered worsening of cutaneous psoriasis and required antibiotic administration.

Effectiveness of adalimumab dose escalation

The number of patients with improvements in PASI and DLQI scores gradually increased over time throughout the 24 weeks of ADA weekly administration.
With regards to PASI, the number of responders at Week 16 was 29 out of 64 (45.3%) and rose to 35 (54.6%) at Week 24 (*figure 1A*). Both PASI 90 and PASI 100 were reached by 23.4% ($n=8$) at Week 16 and 32.8% ($n=14$) at Week 24; while, PASI ≥50 to ≤ 75 with DLQI≤5 was achieved by 20.3% ($n=13$) at Week 16 and 18.8% ($n=12$) at Week 24 (*figure 1B*).
Moreover, the mean DLQI score was 9.9 at baseline and, along with PASI, demonstrated a decreasing trend over the whole study; 4.9 at Week 16 and 4.09 at Week 24 (*figure 2A*). Furthermore, the proportion of patients with DLQI response

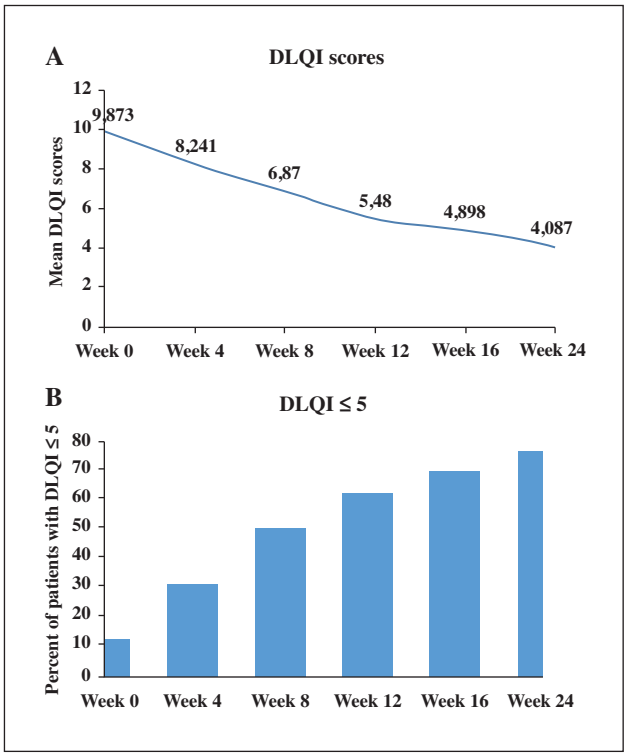

Figure 2. **A**) Dermatology Life Quality Index (DLQI) scores over the whole study: from Week 0 to Week 24. **B**) The percentage of patients with DLQI ≤ 5 at all visits.

≤ 5 increased from 13% at baseline to 69% at Week 16 and 76.1% at Week 24 (*figure 2B*).
The response rate of patients maintaining PASI > 75 or ≥50 to ≤75 with DLQI ≤5, resuming ADA administration every other week, was 45.3% at Week 36 and 28.1% at Week 48.

Logistic regression

We examined whether all the variables considered were independent using logistic regression analysis. For the univariate logistic regression, the explanatory variables employed were sex, age, BMI, smoking habit, alcohol consumption, familiarity of psoriasis or PsA, PsA, hypertension, hyperlipidaemia, metabolic syndrome and diabetes. However, among these variables, we did not find any significant difference between the two groups (*table 3*).

Discussion

Our results show that ADA dose escalation may be considered an appropriate drug management strategy to regain and maintain a favourable PASI and DLQI score in patients with secondary LOR. More than half of the patients included in the study regained a favourable PASI response during the ADA dose escalation (54.6% at Week 24), and the DLQI response improved in more patients (76.1% at Week 24). Moreover, no significant AEs were reported apart from one patient presenting with recurrent tonsillitis triggering a worsening of psoriasis.

Table 3. Logistic regression analyses of responder patients versus non-responder patients: adjusted effect of clinical factors among responders.

		Multivariate OR (95% CI)	*p* value
Weight		1.12 (1.00-1.25)	0.042
BMI		0.71 (0.49-1.01)	0.061
PsA	No	reference	
	Yes	4.23 (0.93 -19.09)	0.060
Familiarity of Pso/PsA	No	reference	
	Yes	0.19 (0.03 -0.98)	0.047
PASI score at T0		1.09 (0.96-1.23)	0.143
DLQI score at T0		1.28 (1.03-1.60)	0.025

PsA: psoriatic arthritis; Pso: psoriasis; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; BMI: Body Mass Index.

These data are in line with those of Leonardi *et al.* who evaluated the efficacy and safety of ADA weekly administration among patients with a suboptimal response to ADA every other week [13]. Moreover, based on the univariate analysis, we observed that patients with greater body weight, arterial hypertension, metabolic syndrome and familiarity of psoriasis and/or PsA were more likely to be non-responders to ADA dose escalation. Though, following multivariate analysis, we did not observe any specific profile for responder patients.
Furthermore, among responders resuming ADA every other week, a considerable percentage maintained the PASI response gained during ADA escalation. In particular, at Week 36 and 48 (three and six months after the de-escalation), 45.3% and 28.1% of patients maintained PASI ≥75 and/or ≥50 to ≤75 and DLQI < 5, respectively. This therefore represents a further improvement relative to the study of Leonardi *et al.* in which only PASI 75 and 50 were considered [13]. Moreover, this is the first multicentric analysis to evaluate the effectiveness of this rescue therapy in a real-life setting.
Furthermore, as patients are becoming more demanding in terms of treatment satisfaction relative to PASI, we consider that ADA dose escalation could be considered for secondary LOR as it could allow patients to regain and maintain PASI and DLQI responses before switching to another biologic. Furthermore, according to the analysis performed by Puig on the additional cost of temporary dose escalation of biological therapies, ADA is one of the treatments with the lowest increase in annual cost [14]. Thus, dose escalation and de-escalation might enable clinicians to fulfil patients' concerns without overlooking the rising healthcare costs.
To conclude, in order to obtain more extensive and conclusive data, we suggest that a randomized controlled trial should be performed to compare the efficacy and safety of ADA, at 40 mg every other week or weekly as a dosage regimen, as first-maintenance treatment. ■

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