DOI: 10.1111/jdv.15077 JEADV

ORIGINAL ARTICLE

Psoriasis Area and Severity Index response in moderate-severe psoriatic patients switched to adalimumab: results from the OPPSA study

M. Talamonti,[1,*,†] M. Galluzzo,[1,*] N. Bernardini,[2] G. Caldarola,[3] S. Persechino,[4] F. Cantoresi,[5] C.G. Egan,[6] C. Potenza,[2] K. Peris,[3] L. Bianchi[1]

[1]Department of Dermatology, University of Rome 'Tor Vergata', Rome, Italy

[2]Department of Medical and Surgical Sciences and Biotechnologies, Division of Dermatology 'Daniele Innocenzi', University of Rome 'La Sapienza', Polo Pontino, Italy

[3]Institute of Dermatology, Catholic University of the Sacred Heart, Rome, Italy

[4]Department of Dermatology, NESMOS Unit, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

[5]Department of Dermatology, Policlinico Umberto I, 'Sapienza' University of Rome, Rome, Italy

[6]CE Medical Writing, Pisa, Italy

†Correspondence: M. Talamonti. E-mail: talamonti.marina@gmail.com

Abstract

Background Few studies have compared the efficacy of switching to adalimumab in the real-life setting in plaque psoriasis patients.

Objective To evaluate the effect of adalimumab in psoriasis patients previously treated with other biologics.

Methods In this multicentre study, psoriasis patients ($N = 262$) treated with an anti-TNF-alpha agent, ustekinumab or naïve to biologics then switched to adalimumab were included. Disease severity was assessed by the Psoriasis Area and Severity Index (PASI) at baseline and after 3, 6, 12, 24 and 36 months. The association between clinical risk factors and achievement of PASI response was evaluated by logistic regression.

Results Adalimumab treatment resulted in a decrease in PASI (15.1 $\pm$ 6.2 at baseline vs. 2.7 $\pm$ 4.8 at 6 months, $P < 0.0001$), regardless of previous biologic treatment. Furthermore, adalimumab allowed 92.5%, 79% and 56% of patients to achieve PASI response (PASI 50, 75 and 90, respectively) and complete remission (PASI 100 response) in 48.4% of patients, by 6 months and maintained over 3 years, independent of prior biologic treatment. The absence of metabolic syndrome, dyslipidemia, hypertension and lower PASI and lower age at baseline was associated with achievement of PASI response at 3, 6 and 12 months, whereas at later time points (24 and 36 months), PASI 90 and PASI 100 response was associated with diagnosis of psoriasis/psoriatic arthritis.

Conclusion Adalimumab was effective at reducing PASI score over 3 years, irrespective of whether patients were biologic naïve or previously treated with a TNF-alpha or IL-12/23 inhibitor.

Received: 30 January 2018; Accepted: 4 May 2018

Conflict of interests

Authors have no conflict of interest to declare.

Funding sources

None.

Introduction

Psoriasis is characterized as a chronic inflammatory autoimmune skin disease with a prevalence of 1–3% worldwide.[1] The most frequent form of psoriasis, plaque psoriasis is (approximately 90% of patients) characterized by painful and itchy erythematous plaques localized on the elbows and knees and scalp or generalized disease across wider areas of the body.[2,3] Approximately 25 million patients worldwide are affected by severe-to-moderate psoriasis, defined as a PASI score >10 or BSA >10% and DLQI >10.[3] This severe form of psoriasis usually requires treatment with systemic medications or phototherapy.[4]

For the past few decades, treatment of this disease has included traditional systemic drugs; (e.g. methotrexate, acitretin and cyclosporine) however, their use is hampered by

*These authors contributed equally to this paper and conceived this study.

intolerance or organ-specific toxicity, particularly following long-term use.[5]

National and International Guideline Treatment strategies of severe or refractory/recalcitrant psoriasis are based on disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and cyclosporine.[6,7] In cases of inadequate response, contraindication or intolerance to at least one DMARD, a therapy with a biologic drug such as tumour necrosis factor (TNF)-alpha inhibitors (e.g. adalimumab, infliximab or etanercept) or anti-interleukin therapies (ustekinumab, secukinumab, ixekizumab and brodalumab) is recommended.[5–12] Although these treatments are effective in treating psoriasis (without severe adverse events), between 10% and 30% of patients show inadequate response, necessitating switching to a second-line biologic.[13] In real-life clinical practice, switching is relatively common; however, few studies have evaluated the efficacy of secondary biologic treatment in these patients.[14,15]

Adalimumab is a TNF-alpha inhibitor indicated for the treatment of psoriasis and psoriatic arthritis and several randomized controlled trials and meta-analysis studies have demonstrated short- and long-term benefit.[16–23] Less understood, however, is whether the extent of benefit granted by adalimumab is similar in patients previously treated with another biologic agent, particularly in the real-life setting.[22]

The purpose of this study was to evaluate the effect of adalimumab treatment in moderate-to-severe psoriasis on PASI response in patients naïve to biologics or in patients previously treated with a different anti-TNF-alpha agent or previously treated with the IL-12/23 inhibitor ustekinumab. The association between dependent variables (clinical characteristics, comorbidities and risk factors for psoriasis) associated with achievement of PASI response was also evaluated.

Materials and methods

Patients and study design

Outcome of Psoriatic Patients Switched to Adalimumab (OPPSA) was a retrospective longitudinal non-interventional epidemiological investigation performed by consulting a clinical database of psoriasis patients (with or without psoriatic arthritis) consecutively arriving for their routine visit. Patients were being treated with biologic drugs in five centres of the Lazio region of Italy between 1 January 2010 and 31 December 2015.

Inclusion criteria included male or female patients diagnosed with moderate-severe psoriasis and/or psoriatic arthritis treated with adalimumab (using standard dosing regimen as prescribed within the EU[24]) for at least 16 weeks from 1 January 2010 to 31 December 2015 after conventional or biologic therapy; patients ≥18 years of age and having signed an informed consent form and having undertaken at least two specialist visits for treatment of psoriasis during the 16 weeks after initiating adalimumab treatment. Reasons for switching to adalimumab were inefficacy, intolerance or presence of adverse events and included a washout period of approximately 1 month, according to clinical practice guidelines.[3] Reasons for suspension of adalimumab treatment were primary inefficacy (failure to achieve PASI 50 after 12 weeks of treatment) or secondary inefficacy (loss of PASI 50 after 12 weeks of treatment) in patients without arthritis only. Exclusion criteria included patients with other autoimmune/inflammatory diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis; patients treated with a biologic <16 weeks or patients that had received systemic treatment or phototherapy in combination with biologic agent within 4 weeks of the first visit. Diagnosis of psoriasis was clinical. Demographic and anamnestic data, comorbidities, current and previous biologic treatments and Psoriasis Area Severity Index (PASI) score at the moment of enrolment were recorded using a dedicated database. Ethics committee approval from all five participating centres and written informed consent was obtained from all patients. This study complies with the ethical standards laid down in the 1975 Declaration of Helsinki.

Outcome measures

To evaluate the efficacy of adalimumab, the 50%, 75%, 90% and 100% improvement in PASI score (PASI 50, 75, 90 and 100) was calculated at the moment of enrolment and compared to values prior to undergoing treatment (baseline values). Secondary endpoints were to evaluate the potential effect of previous anti-TNF-alpha treatment (e.g. etanercept, infliximab, golimumab), anti-interleukin treatment (e.g. ustekinumab) or biologic naive patients on PASI response (50, 75, 90 and 100) following adalimumab treatment over the 3-year follow-up. The association between dependent variables (age, sex, height, waist circumference, HLA-C*06:02 status, PASI at baseline, age of onset of psoriasis, disease duration, presence of hypertension, diabetes, dyslipidemia, metabolic syndrome, smoking history, alcohol intake, use of adalimumab as first biologic, number of anti-TNF-alpha drugs used before adalimumab, use of ustekinumab before adalimumab) and achievement of PASI 50, 75, 90 and 100 at 3, 6, 12, 24 and 36 months was also evaluated.

DNA extraction and HLA typing

Venous blood for genotyping was collected in EDTA tubes and stored at −70°C. Genomic DNA was isolated from whole blood using DNAeasy blood and tissue kit (Qiagen, Inc., Hilden, Germany). The HLA-C*06:02 locus was detected by standard polymerase chain reaction (PCR) using the allele-specific primers: forward 5′-TACTACAACCAGAGCGAGGA-3′ and reverse 5′-GGTCGCAGCCATACATCCA-3′, as previously described.[25]

Statistical analysis

Data are presented as mean ± SD for continuous variables, and number and percentage for categorical variables. Comparisons between groups were performed by the chi-squared test for

categorical variables and the one-way analysis of variance or Wilcoxon test for continuous variables. Stepwise multivariate logistic regression models were performed to evaluate the association between dependent variables (e.g. clinical characteristics and risk factors for presence of psoriasis) and achievement of PASI 50, 75, 90 and 100 at 3, 6, 12, 24 and 36 months. In the case of missing data, the last observation carried forward method (LOCF: if a patient dropped out of the study the last value available was 'carried forward' until the end of the treatment).[26] $P < 0.05$ was considered statistically significant. All analysis was performed using Stata 13 (Statacorp LP Inc., College Station, TX, USA).

Results

Patient demographic and clinical characteristics

A total of 262 patients with psoriasis were included in the OPPSA study. Patient clinical and demographic characteristics are summarized in Table 1. Approximately 63% of patients were male (mean age of 52.1 ± 14.3 years), with psoriasis disease duration of 18 ± 12 years and mean baseline PASI score of 15.1 ± 6.2. Of the 262 patients, 88 (33.6%) also had psoriatic arthritis and 66 (25.2%) had hypertension. Clinical characteristics of patients among the three treatment groups (naïve to biologics before adalimumab treatment, anti-TNF-alpha agent before adalimumab and ustekinumab prior to adalimumab) revealed some differences (Table 1). Patients previously treated with anti-TNF-alpha agents had elevated BMI (28 ± 7.9 vs. 25.6 ± 4.5 in ustekinumab-treated patients, $P < 0.05$) and higher prevalence of psoriatic arthritis (62.9% vs. 18.5% in ustekinumab-treated patients, $P < 0.0001$). In contrast, patients treated with ustekinumab before switching to adalimumab had lower psoriasis familiarity (31.5% vs. 68.5% in anti-TNF-alpha-treated patients, $P < 0.0001$), slightly higher baseline PASI (17.3 ± 8.7 vs. 14.2 ± 5.2 in anti-TNF-alpha-treated patients, $P < 0.05$) and higher burden of comorbid diseases (59.3% vs. 41.6% in patients naïve to biologics, $P < 0.05$). Although these differences were statistically significant, other clinically relevant variables such as age, gender and disease duration were similar among the different groups.

PASI response

Mean PASI was significantly decreased in all patients following adalimumab treatment over the follow-up period (Fig. 1a). Compared to baseline levels (15.1 ± 6.2), PASI declined by 12.4 points to 2.7 ± 4.8 by 6 months. This reduction was maintained for the remainder of the 3-year follow-up period (Fig. 1a). Adalimumab also granted a high proportion of patients to achieve PASI 50, 75 and 90 (92.5%, 79% and 56%, respectively) and complete remission (PASI 100 response) in 48.4% of patients, by 6 months (Fig. 1b). We next wanted to evaluate whether a differential effect on PASI improvement could be observed following adalimumab treatment among the three groups. Mean PASI was significantly decreased compared to baseline values in all three groups, with no difference observed among them (Fig. 2a). Although not attaining statistical significance, PASI was decreased to a greater extent in biologic naïve patients over the follow-up period (Fig. 2a). A similar profile was observed when

Table 1 Clinical characteristics of psoriasis patients

Anti-TNF agent	Total (*N* = 262)	Naive (*n* = 154)	Anti-TNF → Ada (*n* = 54)	Uste → Ada (*n* = 54)	*P*-value†
Male patients, *n* (%)	166 (63.3)	97 (62.9)	34 (62.96)	32 (59.3)	0.88
Age (years)	52.1 ± 14.3	51.1 ± 14.9	55.1 ± 12.7	50.5 ± 12.2	0.15
BMI (kg/m^2)	26.2 ± 4.4	26.3 ± 4.1	28 ± 7.9 vs. UA*	25.6 ± 4.5	0.043
Current smoker	115 (44.2)	69(44.8)	30 (55.6)	19 (35.2)	0.1
Alcohol consumption	89 (33.96)	53 (34.4)	22 (40.7)	14 (25.9)	0.26
Psoriasis familiarity, *n* (%)	150 (57.3)	93 (60.4)	37 (68.5)	17 (31.5) vs. N+TA****	0.0001
Psoriatic arthritis, *n* (%)	88 (33.6)	44 (28.6)	34 (62.9)	10 (18.5) vs. TA****	<0.0001
Disease duration (years)	18 ± 12	16.7 ± 10.2	17.9 ± 12.8	19.8 ± 11.6	0.2
PASI (baseline)	15.1 ± 6.2	14.5 ± 5.8	14.2 ± 5.2	17.3 ± 8.7 vs. N+TA*	0.013
Comorbidities, *n* (%)	125 (47.7)	64 (41.6)	29 (53.7)	32 (59.3) vs. N*	0.049
Hypertension	66 (25.2)	34 (22.1)	16 (29.6)	16 (29.6)	0.28
Dyslipidemia	45 (17.2)	22 (14.3)	8 (14.8)	15 (27.8)	0.068
Diabetes	43 (16.4)	21 (13.6)	13 (24.1)	9 (16.7)	0.2
Cardiovascular disease	20 (7.6)	9 (5.8)	9 (16.7)	2 (3.7) vs. TA*	0.017
Metabolic syndrome	18 (6.9)	6 (3.9)	4 (7.4)	8 (14.8) vs. N**	0.024

BMI, body mass index; PASI, Psoriasis area severity index; Ada, adalimumab; Uste, ustekinumab.
Data are presented as mean ± SD or number (%). *N* refers to number of patients.
†*P*-values refer to statistically significant differences among the three groups (naive, N; anti-TNF → Ada; TA, Uste → Ada; UA) by one-way ANOVA.
Comparison between specific groups by Bonferroni post hoc analyses among specific groups are indicated where *<0.05, **<0.01, ***<0.001 and ****<0.0001.

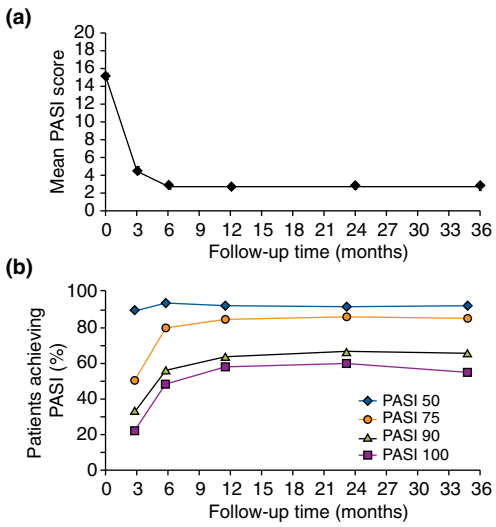

Figure 1 Effect of adalimumab in psoriatic patients (N = 262) on PASI score and achievement of PASI 50, 75, 90 and 100 response. (a) PASI is presented as mean values. Error bars represent SD. (b) PASI response is presented as % patients achieving PASI 50, 75, 90 and 100 response.

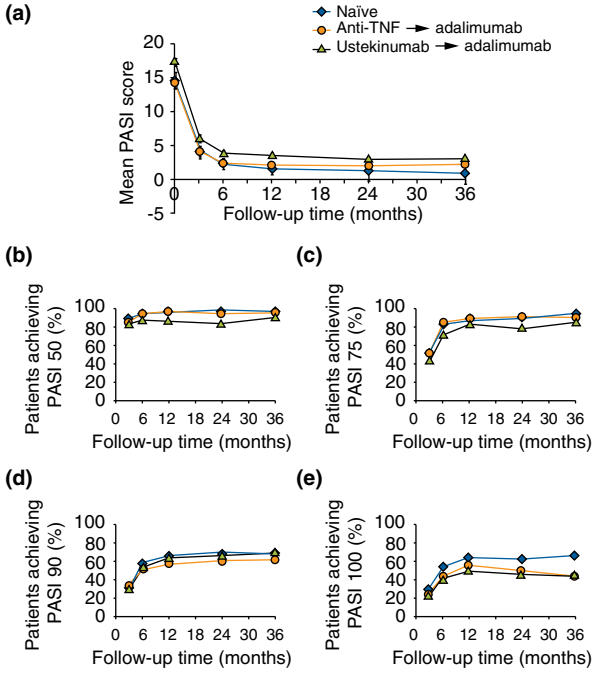

Figure 2 Effect of adalimumab in psoriatic patients naive to biologics, previously treated with another anti-TNF-alpha agent and patients previously treated with ustekinumab on PASI score and achievement of PASI 50, 75, 90 and 100 response. (a) PASI is presented as mean values. (b–e) PASI response is presented as % patients achieving PASI 50, 75, 90 and 100 response.

the effect of adalimumab on PASI response was compared among the three groups (Fig. 2b–e, Table 2). A lower proportion of patients previously treated with ustekinumab before being switched to adalimumab achieved PASI 50 (86.7% at 12 months) and PASI 75 response (82.2%), compared to a more favourable improvement observed over the study period in both anti-TNF → adalimumab (96.1% and 88.2%, respectively) and biologic naïve patients (95.8% and 86%, respectively; Fig. 2b,c). Approximately 65% of all patients achieved a PASI 90 response by 3 years and a similar proportion of biologic naïve patients achieved complete remission by 3 years, although this response was slightly lower (about 45%) in the anti-TNF → adalimumab and ustekinumab → adalimumab groups (Fig. 2e).

Association between dependent variables on PASI response

A stepwise logistic regression model was used to evaluate the association between a range of dependent variables (complete list of variables provided in Methods) and achievement of PASI 50, 75, 90 and 100 at 3, 6, 12, 24 and 36 months of adalimumab treatment. No significant difference was observed in terms of response rate between the group of patients treated in first-line with adalimumab (biologic naïve) and patients treated with other anti-TNF-alpha agents (e.g. infliximab or etanercept) before adalimumab treatment or patients treated with ustekinumab before starting adalimumab treatment. However, several dependent variables were observed to be significantly associated with an improvement in PASI response at specific time points (Table 3). Multivariate analysis revealed that the absence of metabolic syndrome, dyslipidemia, hypertension, lower PASI and lower age at baseline was associated with achievement of PASI response (PASI 50, 75, 90 and 100) at 3, 6 and 12 months. In contrast, at later time points (24 and 36 months), a diagnosis of psoriasis and concomitant psoriatic arthritis was associated with an approximately threefold increase in odds of achievement of PASI 90 and PASI 100 response, regardless of baseline disease severity (Table 3).

Discussion

Results from the OPPSA provide evidence that adalimumab can be considered as an optimal therapeutic choice in psoriatic patients over the long term, regardless of their prior exposure to biologics.

The short- and long-term benefit of adalimumab for the treatment of psoriasis and psoriatic arthritis is well established from several randomized controlled trials and meta-analyses.[16–23] However, little evidence is available documenting the effect of adalimumab administered as second-line biologic treatment compared to first-line treatment in the real-life setting.[22]

Our findings revealed that adalimumab permitted 92.5%, 79% and 56% of patients to achieve PASI 50, 75 and 90,

Table 2 PASI response rate for psoriasis patients to adalimumab treatment and over the 3-year follow-up period

PASI response	Follow-up (months)				
	3 months	6 months	12 months	24 months	36 months
All psoriasis patients					
N (%)	255	252	239	227	166
PASI 50	226 (88.6)	233 (92.5)	219 (91.6)	206 (90.8)	151 (91.2)
PASI 75	127 (49.8)	199 (79)	200 (83.7)	194 (85.3)	140 (84.1)
PASI 90	83 (32.5)	141 (56)	150 (62.8)	150 (66.1)	108 (64.8)
PASI 100	54 (21.2)	122 (48.4)	137 (57.3)	134 (59.2)	90 (54.2)
Biologic naive patients					
N (%)	150	151	143	142	112
PASI 50	134 (89.3)	142 (94)	137 (95.8)	138 (97.2)	108 (96.4)
PASI 75	75 (50)	122 (80.8)	123 (86)	127 (89.4)	106 (94.6)
PASI 90	50 (33.3)	88 (58.3)	95 (66.4)	98 (69)	77 (68.8)
PASI 100	45 (30)	83 (55)	92 (64.3)	89 (62.7)	73 (65.2)
Anti-TNF → adalimumab patients					
N (%)	52	52	51	48	34
PASI 50	44 (84.9)	49 (94.2)	49 (96.1)	45 (93.8)	32 (94.1)
PASI 75	26 (50.9)	43 (82.7)	45 (88.2)	43 (89.6)	30 (88.2)
PASI 90	18 (34)	27 (51.9)	29 (56.9)	29 (60.4)	21 (61.8)
PASI 100	13 (24.5)	23 (44.2)	28 (54.9)	24 (50)	15 (44.1)
Ustekinumab → adalimumab patients					
N (%)	53	49	45	37	20
PASI 50	44 (83)	43 (87.8)	39 (86.7)	31 (83.8)	18 (90)
PASI 75	23 (43.4)	35 (71.4)	37 (82.2)	29 (78.4)	17 (85)
PASI 90	16 (30.2)	27 (55.1)	29 (64.4)	25 (67.6)	14 (70)
PASI 100	12 (22.6)	20 (40.8)	22 (48.9)	17 (45.9)	9 (45)

N, number of patients; PASI, Psoriasis area severity index.

respectively) and complete remission (PASI 100 response) in just under half (48.4%) of patients by 6 months, this benefit being maintained over the 3-year follow-up. These improvements in PASI are in line with those reported in clinical trials.[16–23,27] Our efficacy results closely reflect values observed after 4 months of adalimumab treatment in 100 psoriatic patients in daily practice by Arnesto *et al.*[22] for PASI 50, PASI 90 and PASI 100 (85.7%, 78.7% and 40%, respectively). Furthermore, no significant difference was observed between efficacy in patients previously naïve vs. those not naïve to biologics in this study.[22] Similar findings were observed by van Lümig *et al.*[28] in 85 patients treated with adalimumab for 1.4 years. Although PASI 75 response at 3 months was significantly higher in biologic naïve (56%) vs. non-naïve (29%) patients, no difference was observed at later time points. Our study confirms these results and extends them further by demonstrating that previous biologic therapy does not influence the efficacy of adalimumab in the short (up to 6 months) as well as long term (up to 3 years).

Variability in treatment efficacy of adalimumab has been observed among these controlled and real-life studies, and causal factors have already been identified.[22,28–32] While no difference was observed in terms of PASI response between biologic naïve, previous anti-TNF-alpha or previous ustekinumab treatment on the effect of adalimumab, stepwise logistic regression in our study revealed that younger patients, no diabetes/metabolic syndrome, no dyslipidemia, no hypertension or a lower PASI at baseline were significantly associated with better achievement of PASI response by 3 and 6 months. Interestingly, at later time points (1, 2 and 3 years), absence of hypertension and a positive diagnosis for psoriasis/psoriatic arthritis were significantly associated with increased odds of achieving PASI 90 and complete remission (PASI 100).

It is recognized that switching is prescribed at a moment when patients are doing relatively poorly and will probably do better again at a later time point, termed a regression-like effect.[33] Although previous analysis of psoriasis patients has identified several factors as being associated with response to biologics, information is still scarce on predictor variables for treatment response over the long term.[34] Our analysis identified that patients without diabetes/metabolic syndrome were associated with better achievement of PASI response, particularly in the first 6 months following adalimumab treatment. Actually, moderate-to-severe psoriasis is frequently associated with the metabolic syndrome and its disorders such as type 2 diabetes, dyslipidemia and obesity.[35,36] The underlying mechanisms affecting the efficacy of adalimumab in psoriasis patients with

Table 3 Stepwise multivariate logistic regression analysis of dependent variables associated with achievement of PASI response at different time points

PASI response rate	OR (95% CI)	*P*-value
PASI 50		
3 months		
Metabolic syndrome (absence)	0.15 (0.05–0.44)	<0.0001
PASI 75		
3 months		
Dyslipidemia (absence)	0.29 (0.12–0.69)	0.006
Metabolic syndrome (absence)	0.11 (0.014–0.94)	0.043
PASI 90		
3 months		
Dyslipidemia (absence)	0.088 (0.02–0.37)	0.001
Lower PASI at baseline	0.93 (0.89–0.99)	0.014
6 months		
Lower age at baseline	0.98 (0.96–0.99)	0.024
Metabolic syndrome (absence)	0.34 (0.11–0.99)	0.05
12 months		
Hypertension (absence)	0.29 (0.15–0.56)	<0.0001
Diagnosis of PsA and PsO	2.5 (1.3–4.9)	0.008
PASI 100		
3 months		
Dyslipidemia (absence)	0.054 (0.007–0.4)	0.005
Lower PASI at baseline	0.89 (0.83–0.95)	<0.0001
6 months		
Lower age at baseline	0.97 (0.95–0.99)	0.001
Lower PASI at baseline	0.93 (0.89–0.98)	0.004
12 months		
Hypertension (absence)	0.39 (0.2–0.75)	0.005
Diagnosis of PsA and PsO	2.9 (1.5–5.6)	0.001
24 months		
Diagnosis of PsA and PsO	2.9 (1.4–5.9)	0.004
36 months		
Diagnosis of PsA and PsO	3.5 (1.3–4.9)	0.008

BMI, body mass index; CI, confidence interval; NI, variables not included in multivariate model; OR, odds ratio; PASI, Psoriasis area severity index; PsA, psoriatic arthritis; PsO, psoriasis.

the metabolic syndrome are still poorly understood; however, studies exploring the genetic predispositions of patients may provide insight as to why patients respond to one biologic but not another.[34] While the presence of the HLA-C*06:02 polymorphism in psoriatic patients has been shown to be associated with the efficacy of other biologics,[25] our group has previously demonstrated that the effect of adalimumab treatment was not associated with this allele.[37] Similarly, in the present study, HLA-C*06:02 allele was not found to be associated with PASI response at any of the time points examined. However, a diagnosis of psoriatic arthritis (combined with psoriasis) emerged from our multivariate analysis as being strongly associated with complete PASI remission in the long term (1- to 3-year follow-up). This association has also been previously observed[32] but a negative association has already been implicated.[31] However, these studies were limited by short follow-up and small sample sizes.

The efficacy of anti-TNF-alpha biologics is also known to be reduced in patients with elevated BMI and in elderly patients.[38–40] While BMI did not emerge as a predictor for improved PASI response, lower age at baseline was found to be significantly associated with improved PASI response with the first month of treatment. A pattern also emerged from our analysis whereby predictors of an improvement in PASI response in the short term predominantly included absence of metabolic syndrome, absence of dyslipidemia and lower age at baseline, whereas long-term treatment improvement was mainly associated with psoriasis and psoriatic arthritis diagnosis. These temporal differences remain to be examined further in a larger sample size with longer follow-up to ascertain whether the presence of early metabolic and late articular involvement may play an important role in the therapeutic management of these patients. Taken together, these results confirm that adalimumab is a valid therapeutic option for the management of severe-to-moderate plaque psoriasis (with or without psoriatic arthritis), as recommended by National guidelines and International guidelines.[6,7]

Limitations

There are some potential limitations that need to be addressed. Weaknesses of observational registries such as the reliability of results and incompleteness of data have already been established.[41,42] Furthermore, the lack of randomization may have also introduced selection bias, and the presence of other unmeasured confounders may have been missed in our analysis. Patient adherence was not the aim of this study and was therefore not evaluated. Some differences in baseline characteristics among patients previously treated with different biologics were noted. A higher proportion of psoriatic arthritis patients were observed in the anti-TNF-alpha group (62.9%) compared to biologic naïve (28.6%) and ustekinumab group (18.5%). This may be due to the fact that anti-TNF-alpha biologics have shown greater improvement in psoriatic arthritis patients compared to ustekinumab.[29]

However, stepwise logistic regression analysis adjusted for baseline PASI or presence of psoriatic arthritis therefore precluding these variables as being attributed to any potential bias.

Conclusion

Findings from the present study demonstrate that adalimumab granted a significantly high proportion of patients to achieve PASI 50, 75 and 90 (92.5%, 79% and 56%, respectively) and complete remission (PASI 100 response; 48.4% of patients), by 6 months. This improvement in PASI response was maintained up to 3 years. The effect of adalimumab was independent of prior biologic treatment or type of biologic previously used (anti-TNF-alpha or IL12/23). Real-world data represent an

important source of information to determine the efficacy of different biologic agents currently available in day-to-day conditions of clinical practice and among heterogeneous groups of patients, typically excluded from randomized controlled trials. Findings from the OPPSA study will aid dermatologists in their choice of biologic for the treatment of psoriasis patients. Additional studies are still needed to assess the differential effectiveness of biologic agents as rescue therapy in the case of primary or secondary failure over the long term.

Acknowledgements

The authors would like to thank Mauro Bavetta, Antonella Bidoli, Simone D'Adamio, Clara De Simone, Carmen Cantisani, Gaia Moretta, Federico Romaniello, Arianna Zangrilli for their support.

References

1 Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; **370**: 263–271.
2 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**: 496–509.
3 Mrowietz U, Kragballe K, Reich K *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1–10.
4 Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. *J Am Acad Dermatol* 2009; **60**: 218–224.
5 Menter A, Korman NJ, Elmets CA *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009; **61**: 451–485.
6 Salvarani C, Pipitone N, Marchesoni A *et al.* Recommendations for the use of biologic therapy in the treatment of psoriatic arthritis: update from the Italian Society for Rheumatology. *Clin Exp Rheumatol* 2011; **29**: S28–S41.
7 Gisondi P, Altomare G, Ayala F *et al.* Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol* 2017; **31**: 774–790.
8 Menter A, Gottlieb A, Feldman SR *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; **58**: 826–850.
9 Gottlieb A, Korman NJ, Gordon KB *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol* 2008; **58**: 851–864.
10 Gossec L, Smolen JS, Gaujoux-Viala C *et al.* European league against rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012; **71**: 4–12.
11 Gossec L, Smolen JS. Treatment of psoriatic arthritis: management recommendations. *Clin Exp Rheumatol* 2015; **33**: S73–S77.
12 Talamonti M, Galluzzo M, Bianchi L *et al.* What happened after the clinical trials: long-term safety and efficacy of ustekinumab in daily clinical practice. *Dermatology* 2014; **229**: 324–332.
13 Honda H, Umezawa Y, Kikuchi S *et al.* Switching of biologics in psoriasis: reasons and results. *J Dermatol* 2017; **44**: 1015–1019.
14 Papoutsaki M, Chimenti M-S, Costanzo A *et al.* Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. *J Am Acad Dermatol* 2007; **57**: 269–275.
15 Strober BE, Poulin Y, Kerdel FA *et al.* Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. *J Am Acad Dermatol* 2011; **64**: 671–681.
16 Papp K, Okun M, Vender R. Adalimumab in the treatment of psoriasis: pooled efficacy and safety results from three pivotal studies. *J Cutan Med Surg* 2009; **13**(Suppl 2): S58–S66.
17 Ortonne J-P, Chimenti S, Reich K *et al.* Efficacy and safety of adalimumab in patients with psoriasis previously treated with anti-tumour necrosis factor agents: subanalysis of BELIEVE. *J Eur Acad Dermatol Venereol* 2011; **25**: 1012–1020.
18 Papp K, Ho V, Teixeira HD *et al.* Efficacy and safety of adalimumab when added to inadequate therapy for the treatment of psoriasis: results of PRIDE, an open-label, multicentre, phase IIIb study. *J Eur Acad Dermatol Venereol* 2012; **26**: 1007–1013.
19 Gordon K, Papp K, Poulin Y *et al.* Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: results from an open-label extension study for patients from REVEAL. *J Am Acad Dermatol* 2012; **66**: 241–251.
20 López-Ferrer A, Vilarrasa E, Gich IJ, Puig L. Adalimumab for the treatment of psoriasis in real life: a retrospective cohort of 119 patients at a single Spanish centre. *Br J Dermatol* 2013; **169**: 1141–1147.
21 Burmester GR, Panaccione R, Gordon KB *et al.* Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013; **72**: 517–524.
22 Armesto S, Coto-Segura P, Mayorga J *et al.* Efficacy of adalimumab in the treatment of moderate-to-severe psoriasis: a retrospective study of 100 patients in daily practice. *J Dermatolog Treat* 2015; **26**: 49–53.
23 Papp KA, Armstrong AW, Reich K *et al.* Adalimumab efficacy in patients with psoriasis who received or did not respond to prior systemic therapy: a pooled post hoc analysis of results from three double-blind, placebo-controlled clinical trials. *Am J Clin Dermatol* 2016; **17**: 79–86.
24 Psoriasis: assessment and management|Guidance and guidelines|NICE [WWW Document]. URL https://www.nice.org.uk/guidance/CG153/ (last accessed on 13 June 2017).
25 Talamonti M, Galluzzo M, van den Reek JM *et al.* Role of the HLA-C*06 allele in clinical response to ustekinumab: evidence from real life in a large cohort of European patients. *Br J Dermatol* 2017; **177**: 489–496.
26 Papp KA, Fonjallaz P, Casset-Semanaz F *et al.* Approaches to reporting long-term data. *Curr Med Res Opin* 2008; **24**: 2001–2008.
27 Carrera CG, Dapavo P, Malagoli P *et al.* PACE study: real-life Psoriasis Area and Severity Index (PASI) 100 response with biological agents in moderate-severe psoriasis. *J Dermatolog Treat* 2017. http://doi.org/10.1080/09546634.2017.1395805.
28 van Lümig PPM, van de Kerkhof PCM, Boezeman JBM *et al.* Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naïve vs. non-naïve patients. *J Eur Acad Dermatol Venereol* 2013; **27**: 593–600.
29 Davison NJ, Warren RB, Mason KJ *et al.* Identification of factors that may influence the selection of first-line biologic therapy for people with psoriasis: a prospective, multi-centre cohort study. *Br J Dermatol* 2017; **177**: 828–836. https://doi.org/10.1111/bjd.15551.
30 Sbidian E, Giboin C, Bachelez H *et al.* Factors associated with the choice of the first biologic in psoriasis: real life analysis from the Psobioteq cohort. *J Eur Acad Dermatol Venereol* 2017; **31**: 2046–2054. https://doi.org/10.1111/jdv.14406.
31 Edson-Heredia E, Sterling KL, Alatorre CI *et al.* Heterogeneity of response to biologic treatment: perspective for psoriasis. *J Invest Dermatol* 2014; **134**: 18–23.
32 De Simone C, Caldarola G, Maiorino A *et al.* Clinical predictors of non-response to anti-TNF-α agents in psoriatic patients: a retrospective study. *Dermatol Ther* 2016; **29**: 372–376.
33 van Vollenhoven RF. Switching between anti-tumour necrosis factors: trying to get a handle on a complex issue. *Ann Rheum Dis* 2007; **66**: 849–851.

34 Gupta R, Debbaneh MG, Liao W. Genetic epidemiology of psoriasis. *Curr Dermatol Rep* 2014; **3**: 61–78.
35 Gisondi P, Galvan A, Idolazzi L, Girolomoni G. Management of moderate to severe psoriasis in patients with metabolic comorbidities. *Front Med* 2015; **2**: 1. https://doi.org/10.3389/fmed.2015.00001.
36 Gisondi P, Fostini AC, Fossà I *et al.* Psoriasis and the metabolic syndrome. *Clin Dermatol* 2018; **36**: 21–28.
37 Talamonti M, Galluzzo M, Zangrilli A *et al.* HLA-C*06:02 does not predispose to clinical response following long-term adalimumab treatment in psoriatic patients: a retrospective cohort study. *Mol Diagn Ther* 2017; **21**: 295–301. https://doi.org/10.1007/s40291-017-0261-4.
38 Menter A, Gordon KB, Leonardi CL *et al.* Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. *J Am Acad Dermatol* 2010; **63**: 448–456.
39 Di Lernia V, Tasin L, Pellicano R *et al.* Impact of body mass index on retention rates of anti-TNF-alfa drugs in daily practice for psoriasis. *J Dermatolog Treat* 2012; **23**: 404–409.
40 Di Lernia V, Ricci C, Lallas A, Ficarelli E. Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study. *J Dermatolog Treat* 2014; **25**: 73–74.
41 von Elm E, Altman DG, Egger M *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.
42 Vandenbroucke JP, von Elm E, Altman DG *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007; **147**: W163–W194.