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ORIGINAL ARTICLE

Impact of body mass index on retention rates of anti-TNF-alfa drugs in daily practice for psoriasis

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Abstract

Background: Psoriasis is a chronic inflammatory skin disease which often requires life-long treatment. *Objective/aim:* Our objective was to assess the role of the body mass index (BMI) on the retention rates of anti-TNF-alfa therapies in patients with moderate to severe plaque psoriasis. *Material and methods*: Retrospective observational study of psoriasis patients included in local databases of three public Italian hospitals. All patients, who received anti-TNF-alfa treatment in referral centers, were included. Only patients with at least 1-year follow-up were considered eligible. The outcome was the conservation of the treatment at 1 and 2 years of follow-up. *Results*: 194 patients were enrolled. 307 treatment courses with a minimum follow-up of 12 months and 263 with a follow-up of 24 months were analyzed. The proportion of patients receiving the same treatment at months 12 and 24 was 67.43% and 42.21%, respectively. The proportion steadily decreased with increased values of BMI. *Conclusions*: The overall efficacy of TNF-alfa inhibitors diminishes with time. The BMI affects the long-term survival rate of anti-TNF-alfa in psoriatic patients. A high BMI can be considered a potential predictor of drug discontinuation.

Key words: *adalimumab*, *BMI*, *etanercept*, *infliximab*, *obesity*

Background

Psoriasis is a chronic inflammatory condition; therefore, patients affected by psoriasis often need life-long treatment (1). Conventional therapies have not completely met the needs of psoriatic patients, because of contraindications in presence of comorbidities which are common in the general population. Cumulative toxicity is another concern which limits to circumscribed intervals of time the administration of conventional treatments, such as methotrexate, cyclosporine, and PUVA. Thus, safe long-term treatment options for these patients are considered imperative.

In recent years, the recognition of the central role of tumor necrosis factor (TNF)-alfa led to the introduction of a number of biologic drugs belonging of the group of anti-TNF-alfa inhibitors. These drugs have been developed with the goal to produce a more targeted approach to immunomodulation compared with conventional systemic agents. Currently, three TNF-alfa blockers are approved for chronic plaque psoriasis: infliximab, a chimeric monoclonal IgG antibody directed against TNF-alfa; etanercept, a recombinant TNF-alfa receptor fusion protein; and adalimumab, a human anti-TNF-alfa monoclonal antibody. There are no concerns about cumulative toxicity of these treatments, however, most available data are derived from relatively short-term trials.

Among the range of evaluable parameters to assess product performance of a drug, long-term efficacy and safety, defined respectively by the extent to which a biologic can achieve disease improvement and the safety profile of a biologic beyond 24 weeks of therapy, are two attributes considered both to be critical when

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managing a chronic disease such as plaque psoriasis (2). So far, there are still insufficient records about the long-term efficacy and toxicity of biologics. In addition, to date, there are limited published data concerning the relative performance of individual biologic agents.

Little is known about long-term drug persistence of anti-TNF therapies in patients with psoriasis in daily practice. A recently published study, covering records from the Danish registry of patients treated with a biologic agent, showed that the overall efficacy of anti-TNF-alfa drugs diminishes with time, as envisaged by the progressive loss of patient adherence to treatment due mainly to loss of efficacy, followed by adverse events (3). There is no doubt that it is crucial to identify also patient factors, particularly if modifiable, affecting response to treatment and disease outcome.

Body mass index (BMI) is somewhat responsible for the comorbidities associated with psoriasis, among which diabetes and cardiovascular disease and may, in principle, affect disease severity, response to treatment, and disease outcome. A study from the Italian Registry, the Psocare Project, showed that the BMI affects the early clinical response to systemic treatment for psoriasis with both conventional and biologic therapies (4). Previously a small cohort of Japanese study had shown that an increased BMI could represent prognostic factors for psoriasis outcome predicting more severe and persistent clinical manifestations (5).

On the basis of this evidence, we investigated the drug survival (i.e., continuation) rates of anti-TNF agents in 194 consecutive psoriatic patients and assessed the impact of BMI on long-term persistence with these therapies in patients with psoriasis.

Material and methods

Study design: Retrospective, observational study.

Setting: Three hospital-based Italian secondary referral dermatology units.

Selection of patient files: All patients with a clinical diagnosis of chronic moderate to severe plaque psoriasis who received at least one course of treatment of a TNF blocker, as infliximab, etanercept or adalimumab and had data available for a minimum of 12 months were selected through a computer examination of patient files. Time of exposure was considered from the beginning of therapy with a TNF antagonist to date of the last administration. In all cases, the three TNF blockers were administered in conventional doses for psoriasis: etanercept as a subcutaneous injection of 50 mg once a week, with the option to administer the dose of 50 mg twice weekly for the first 12 weeks of treatment; infliximab at the dose of 5 mg/kg administered at weeks 0, 2, 8, and then every 8 weeks thereafter; adalimumab as two subcutaneous injection of 40 mg at day 0, a subcutaneous injection of 40 mg at day 7 and every 14 days thereafter.

One hundred and ninety-four patients were included in a multicentre retrospective chart review. Data covering individual treatment series for each anti-TNF-alfa agent were extracted and contained a patient identification number, gender, age, weight and height, previous systemic treatments for psoriasis, presence of psoriasis arthritis, presence of comorbidities by the following categories: hypertension, ischemic heart disease, diabetes, alcohol abuse, hepatic disease, chronic renal insufficiency, duration of the treatment series, reason for treatment termination, side effects, combination therapy with conventional treatments. Each patient's weight and height were obtained at entry and the BMI was calculated as weight in kilograms divided by height in square meters. Patients were visited by the same dermatologist after 1 month and every 2-months interval. Before treatment initiation, complete blood cell count (CBC) and routine biochemical analysis were performed, including testing for hepatitis B and C markers, antinuclear antibodies, anti-DNA antibodies, chest X-rays, and Mantoux test or QuantiFERON® TB Gold. CBC were performed monthly for the first 2 months and then at 2-months interval during the treatment period.

As patients may stop treatment during an infection or elective surgery, any gaps in the use of the same treatment of less than 3 months were considered as continuous treatment. Patients with psoriatic arthritis were included only if psoriasis at baseline had a PASI (Psoriasis Area and Severity Index) score ≥10. Patients with psoriatic arthritis who discontinued treatment due to inefficacy on articular symptoms or worsening of arthritis were excluded.

The patients were followed for a minimum of 12 months. With this selection we obtained 307 treatment series with a TNF blocker with a follow-up of 12 months and 263 treatment series with a follow-up of 24 months administered to 194 patients with moderate to severe psoriasis. In patients treated successively with more than one TNF blocker, each TNF treatment course was separately analyzed. Thus, a given patient may have been analyzed more than one time.

Statistical analysis

The effect of BMI on retention rate was evaluated by calculating for BMI the odds ratio (OR) of getting the

same treatment at 12 and 24 months together with its 95% confidence interval (CI).

Results

The characteristics of the 194 patients included in the cohort are depicted in Table I. All patients were psoriasis subjects with moderate to severe disease who had failed to respond to conventional drugs, had become intolerant to conventional systemic therapy, and/or could not receive conventional systemic therapy because of contraindications, according to the guidelines of the National Drug Agency (AIFA). All patients underwent biological therapies and had at least 1-year follow-up. The proportion of treatment courses that were continued at 12 and 24 months was 67.43% and 42.21%, respectively. The proportion of treatments being maintained in all patients with etanercept, infliximab, or adalimumab was 65.65%, 71.43%, or 65.38%, respectively after 12 months and 37.07%, 46.07%, or 46.55%, respectively at 24 months (Table II). The proportion of patients maintaining the treatment at 12 and 24 months steadily decreased with higher values of BMI (Table III) and ranged from 77.78% in patients with BMI 20–24 to 56.99% in those with a BMI ≥ 30 at 12 months and from 60.94% in subjects with a BMI 20–24 to 25.51% in patients with a BMI ≥ 30 at 24 months. Compared with treatment performed in patients with normal weight (BMI 20–24), treatments in obese patients (BMI ≥ 30) had less chances of being maintained at 12 and 24 months. The adjusted OR for maintaining the treatment in obese patients compared with normal-weight patient was 2.64 (95% CI 1.32 to 5.27) at 12 months and 4.52 (95% CI 2.21 to 9.24) at 24 months. The proportion of treatments being maintained in obese patients (BMI ≥ 30) with etanercept, infliximab, or adalimumab was 63.89%, 61.54%, or 45.16%, respectively after 12 months; 29.41%, 28.57%, or 17.39%, respectively after 24 months (Table IV).

Table I. Demographic and comorbidity presence of the complete psoriasis patient cohort at baseline.

Characteristics	
Age	52, 3 (median)
Male	123
Female	71
Patients with psoriatic arthritis	64
Patients with other baseline comorbidites	75

Table II. Retention rates at 12 and 24 months according to treatments.

	12 months Drug continuation (%)	24 months Drug continuation (%)
Etanercept	65.65	37.07
Infliximab	71.43	46.07
Adalimumab	65.38	46.55
All together	67.43	42.21

Discussion

The advent of biologic agents has enlarged the treatment armamentarium for psoriasis. However the role of biologics, in particular of TNF-alfa inhibitors, as long-term therapies has yet to be characterized. Only few studies have examined the long-term clinical response of biologic agents in psoriasis (6). In general, it is expected to continue the therapy with anti-TNF agents uninterruptedly if the treatment is efficacious and well tolerated. Indeed long-term efficacy is one of the most important attributes considered by dermatologists when selecting a biologic therapy (2). The safety and efficacy profiles of these agents have been extensively investigated in several well-conducted clinical trials, but the efficacy rates are limited to a short-term analysis. Some of these studies excluded patients with several comorbidities, in the presence of which the discontinuation rate of the therapies could raise. In the clinical practice, it is common to see that, whereas many patients treated with biologics obtain reliable long-term results, others show only an initial improvement with the need of following therapeutic changes or adjustments which can consist of a combination with conventional drugs or a reduction of the interval of time between the approved scheduled doses of treatment. Thus, a full understanding of the efficacy and tolerability of these drugs with longer courses of therapy is crucial to provide reliable prospective care to the patients. Adherence to treatment is considered an overall marker of treatment success, since it is based on drug efficacy and the occurrence of relevant side effects conditioning the maintenance of the cure. Since adherence to treatment in patients with psoriasis to anti-TNF-alfa agents decreases with time (3), recognition of factors improving or worsening drug adherence are essential. In this context, we conducted a study on the role of BMI as a significant predictor of drug survival in the retention rate of TNF-alfa inhibitors in patients affected by moderate to severe psoriasis.

Our study was a long-term observational, retrospective cohort study which included all consecutive

Table III. Distribution of all treatment courses according to BMI of patients at entry and retention rates at 12 and 24 months.

	12 months Drug suspension	12 months Drug continuation	% Retention	OR (95% CI)	24 months Drug suspension	24 months Drug continuation	% Retention	OR (95% CI)
BMI < 20	1	4	80.00	NC	1	4	80.00	NC
BMI 20–24	16	56	77.78	1	25	39	60.94	1
BMI 25–29	43	94	68.61	1.60 (0.83 to 3.11)	68	48	41.31	2.21 (1.18 to 4.12)
BMI ≥ 30	40	53	56.99	2.64 (1.32 to 5.27)	58	20	25.51	4.52 (2.21 to 9.24)
All	100	207	67.43	–	152	111	42.21	

CI = confidence interval; OR = odds ratio; NC = not calculated due to small sample size.

patients treated with TNF-alfa antagonists for plaque psoriasis in three hospital-based dermatology departments. The purpose of this choice was to minimize bias due to different baseline severity and therapeutic medical decisions.

The overall retention rate of treatment was about 67% at 12 months and 42% at 24 months in our patients. Infliximab was associated with the lowest rate of discontinuation at 12 months, while the rates at 24 months for infliximab and adalimumab were similar. Different results were observed in obese patients with lower retention rates at 12 and 24 months. In obese subjects (BMI ≥ 30), etanercept was associated with the lowest rate of discontinuation at 12 and 24 months, while adalimumab showed the highest rate of discontinuation at both 12 and 24 months.

A meta-analysis of randomized controlled trials (7) showed that the overall rates and withdrawal from treatment were similar between the different biologics, these agents differing substantially in the rates of specific events. Schmitt et al. confirmed that the differences in response rates of biologic treatments seem to become less pronounced with increased duration of treatment (7). In a retrospective cohort study comparing tolerability and safety of biological therapies, Brunasso et al. showed a mean treatment duration of 16 months per patient and a high long-term tolerability for etanercept with respect to infliximab (8). Infliximab had the best patient retention ability among the anti-TNF-alfa blockers, with 70% of patients being still on drug after 4 years of treatment (3). Plotting patient numbers for the studies greater than 30 weeks, Noiles and Vender reported that adherence to treatment seemed to be highest for etanercept followed by adalimumab and infliximab (9). However, it is challenging to achieve definitive conclusions from comparison of data from different studies. Although the outcome measures between clinical trials are generally similar, there are disparities between patient selection, drug combination and statistical analysis complicating these assessments (10). In addition, the potential effect of individual factors

Table IV. Distribution of treatment courses according to BMI < 30 and > 30 and retention rates at 12 and 24 months*.

	BMI < 30 Treatments total/continued 12 months	% Retention	BMI ≥ 30 Treatments total/continued	% Retention	OR (95% CI)
12 months					
Etanercept	95/63	66.32	36/23	63.89	1.11 (0.50 to 2.48)
Infliximab	72/54	75.00	26/16	61.54	1.88 (0.72 to 4.86)
Adalimumab	47/37	78.72	31/14	45.16	4.49 (1.66 to 12.14)
Total	214/154	71.96	93/53	56.99	1.94 (1.17 to 3.22)
24 months					
Etanercept	82/33	40.24	34/10	29.41	1.62 (0.68 to 3.82)
Infliximab	68/35	51.47	21/6	28.57	2.65 (0.92 to 7.65)
Adalimumab	35/23	65.71	23/4	17.39	9.10 (2.52 to 32.89)
Total	185/91	49.19	78/20	25.64	2.81 (1.57 to 5.04)

*OR for retention rate of treatment courses in patients with BMI ≥ 30 compared with treatment courses in patients with BMI < 30 in the different treatment groups.

has to be considered. In this perspective, our analysis shows that BMI works as an independent factor for treatment discontinuation. Therefore, a drug comparison should consider the burden of this risk factor on the patient population which is the object of investigation.

To the best of our knowledge our study may be the first to identify BMI as potential predictor of drug discontinuation in patients with psoriasis treated with anti-TNF therapies in the long-term routine clinical practice. Since the relation between the short-term response to all systemic treatment, both conventional and biologics, and BMI emerged from a recent study we have contributed to (4), a possible relation between BMI and discontinuation rate in the long-term could be theoretically postulated. Bardazzi et al. showed a correlation between BMI and PASI in patients affected by moderate to severe psoriasis undergoing biological therapy (11). It has been suggested that adipose tissue can noticeably modify the volume of drug distribution and, as a consequence, limit drug efficacy (12). Otherwise, the presence of high levels of inflammatory cytokines in obese patients could make anticytokine therapy more difficult to implement, requiring higher doses of such drugs. As many systemic therapies for psoriasis are administered on a fixed-dose basis, some of them might be inadequately dosed for heavier or overweight patients. Gniadecki et al. assumed that advantageous discontinuation rates for infliximab with respect to other TNF-alfa antagonists in their study could be ascribed to weight-based dosage of this treatment (3). It is also possible that, due to higher costs of weight-based drugs in high-weight patients, clinician avoid to choose such drugs as first biologic in obese subjects. In our group of patients, we did not find a highest retention rate for infliximab in obese patients. Adalimumab was associated with a greater rate of discontinuation in obese subjects. We cannot exclude that higher dosages, BMI based, of adalimumab can achieve a better performance of retention rates in patients with high BMI. However, the very large width of 95% CI for treatment courses with adalimumab (Table IV) indicates an inadequate sample size, so further studies are necessary to confirm our findings.

Our study investigated a single factor, BMI, which likely influences efficacy of TNF-blocker therapy in a real-life cohort of patients affected by psoriasis, with the limitations being those of many retrospective studies. All three hospitals involved in the study were secondary referral centers that treat patients with potentially more severe disease. As TNF-alfa blockers are licensed in Italy only through hospitals, the selection bias was minimized. The sample size was not similar for all drugs, in particular treatment courses with adalimumab were lower and could be considered inadequate to draw authoritative conclusions from a statistical point of view. Our study design, focusing on daily practice, had the gain of showing the effect of a treatment under typical everyday situations. However, potential limitations should be considered when interpreting the findings. For example, we cannot exclude a possible role of concomitant conventional treatments (methotrexate or cyclosporine) in retention rates of TNF-alfa blockers. Data of Gniadecki et al. did not show any effect of PASI or DLQI score at baseline, concomitant methotrexate, and presence of any comorbidity or the metabolic comorbidities on drug survival (3). Treatment decisions could not be randomized but were left to the discretion of the treating physician, based on clinical opinion as to whether a treatment had failed and the TNF blocker should be discontinued or combined to a conventional treatment.

Long-term studies, including observational analysis, remain crucial to identify individual patient factors as predictive factor of long-term efficacy outcomes and to supplement data from clinical trials.

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References

1. Papp KA. The long-term efficacy and safety of new biologic therapies for psoriasis. Arch Dermatol Res. 2006; 298:7–15.
2. Guibal F, Iversen L, Lluis P, Strohal R, Williams P. Identifying the biologic closest to the ideal to treat chronic plaque psoriasis in different clinical scenarios: using a pilot multi-attribute decision model as a decision-support aid. Curr Med Res Opin. 2009;25:2835–2843.
3. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol. 2011;164: 1091–1096.
4. Naldi L, Addis A, Chimenti S, Giannetti A, Picardo M, Tomino C, et al. Impact of Body Mass Index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare Project. Dermatology. 2008;217: 365–373.
5. Sakai R, Matsui S, Fukushima M, Yasuda H, Miyauchi H, Miyachi Y. Prognostic factor analysis for plaque psoriasis. Dermatology. 2005;211:103–106.
6. Alwawi EA, Krulig E, Gordon KB. Long-term efficacy of biologics in the treatment of psoriasis: what do we really know? Dermatol Ther. 2009;22:431–440.
7. Schmitt I, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008;159: 513–526.

8. Brunasso AMG, Puntoni M, Salvini C, Delfino C, Curcic P, Gulia A, Massone C. Tolerability and safety of biological therapies for psoriasis in daily clinical practice: a study of 103 Italian patients. Acta Derm Venereol. 2011; 91:44–49.
9. Noiles K, Vender R. Biologic survival. J Drugs Dermatol. 2009;8:329–333.
10. Papoutsaki M, Talamonti M, Giunta A, Costanzo A, Ruzzetti M, Teoli M, Chimenti S. The impact of methodological approaches for presenting long-term clinical data on estimates of efficacy in psoriasis illustrated by three-year treatment data on infliximab. Dermatology. 2010; 221(Suppl 1):43–47.
11. Bardazzi F, Balestri R, Baldi E, Antonucci A, De Tommaso S, Patrizi A. Dermatol Ther. 2010;23(Suppl 1):S14–S19.
12. Briot K, Garnero P, Le Henanff A, Dougados M, Roux C. Body weight, body composition, and bone turnover changes in patients with spondyloarthropathy receiving anti-tumour necrosis factor (alpha) treatment. Ann Rheum Dis. 2005;64:1137–1140.