Voting in the aftermath of a pension reform: the role of financial literacy

J Am Acad Dermatol. 2014 Feb;70(2):257-62.e3.
doi: 10.1016/j.jaad.2013.10.019. Epub 2013 Dec 16.

Efficacy of switching between tumor necrosis factor-alfa inhibitors in psoriasis: Results from the Italian Psocare Registry

Stefano Piaserico, MD, PhD,a Simone Cazzaniga, PhD Math,b Sergio Chimenti, MD, PhD,c Alberto Giannetti, MD, PhD,d Mara Maccarone, BA,e Mauro Picardo, MD,f Andrea Peserico, MD,a and Luigi Naldi, MD,b Psocare Study Group*

Padua, Bergamo, Rome, and Modena, Italy

From the Dermatology Unit, Department of Medicine, University of Padua
a; Centro Studi Gruppo Italiano Studi In Epidemiologia (GISED), Papa Giovanni XXIII Hospital, Bergamo
b; Department of Dermatology, University of Rome ''Tor Vergata''
c; Department ofDermatology, University of Modena and Reggio Emilia
d; Italian Psoriatic Patient Association (Associazione Difesa Pazienti Psoriasici [ADIPSO]), Rome
e; and Laboratory of Cutaneous Physiopathology, San Gallicano Dermatological Institute Rome.
f*The PSOCARE study centres are listed in the Appendix at http://www.jaad.org.

ABSTRACT

Background: Some studies have shown that switching patients from one tumor necrosis factor (TNF)-alfa inhibitor to another may be beneficial when they have an inadequate response or an adverse event.

Objective: We sought to assess the variables predicting the efficacy of the second TNF-alfa inhibitor in patients discontinuing the first TNF-alfa inhibitor.

Methods: Data from all 5423 consecutive patients starting TNF-alfa inhibitor therapy for psoriasis between September 2005 and September 2010 who were included in the Italian Psocare registry were analyzed.

Results: In 105 patients who switched to a second TNF-alfa inhibitor who had complete follow-up data, 75% improvement in the Psoriasis Area Severity Index score (PASI 75) was reached by 29% after 16 weeks and by 45.6% after 24 weeks. Patients who switched because of secondary loss of efficacy (loss of initial PASI 75 response) or adverse events/intolerance were more likely to reach PASI 75 than those who switched as a result of primary inefficacy (PASI 75 never achieved) (hazard ratio 2.7, 95% confidence interval 1.3-5.5 vs hazard ratio 2.0, 95% confidence interval 1.0-3.9 and 1, respectively). Limitations: There was a small number of patients with complete follow-up data.

Conclusion: PASI 75 response in patients who switched from one antieTNF-alfa agent to another was significantly reduced in patients who showed primary inefficacy of the first antieTNF-alfa. (J Am Acad Dermatol 2014;70:257-62.)

Key words: biologics; efficacy; primary inefficacy; psoriasis; secondary loss of efficacy; switching; tumor necrosis factor-alfa inhibitors.

It is well established that tumor necrosis factor (TNF)-alfa inhibitors have markedly improved the management of psoriasis. Several randomized clinical trials have reported that 50% to 90% of patients are likely to experience a short-term improvement in symptom severity when treated with biological agents.1

Patients' clinical response to treatment with TNF-alfa inhibitors has, nevertheless, been found to vary enormously. Some patients may fail to respond at all to a first cycle of treatment with a TNF-alfa inhibitor (primary inefficacy). Others may respond well initially, but may later show an inadequate response (secondary loss of efficacy or acquired drug resistance). Even others may present drug intolerance or other adverse events.

It is not uncommon for physicians to switch patients from one TNF-alfa inhibitor to another when there is an inadequate response or an adverse event.2 As new biological agents with different mechanisms of

action are becoming available for the management of this condition, clinicians' and patients' treatment options continue to increase. The optimal therapeutic strategy for patients with an inadequate response to a first cycle of biologics remains, nevertheless, an unanswered question that often arises in clinical practice.

The aim of this study was to assess the efficacy of switching to a second TNFalfa inhibitor in patients discontinuing a first one because of an inadequate response (primary inefficacy or secondary loss of efficacy) or to adverse events. The reasons for switching and the efficacy of the second TNF-alfa inhibitor used were also evaluated.

METHODS

Setting

Involving 155 dermatology clinics appointed by the Italian Regional Health Authorities (see Appendix at http://www.jaad.org) as reference centers for the treatment of moderate to severe psoriasis in Italy, the Italian Psocare Registry was instituted on September 1, 2005. The ethical committees of the hospitals contributing to this registry approved the study protocol. The registry's goals and methods have been described in detail elsewhere.3

Patients

All consecutive patients presenting at the participating centers who were prescribed TNF-alfa inhibitor treatment for psoriasis between September 2005 and September 2009 were considered for this study. Only adults (aged $18 years) with a clinically confirmed diagnosis of chronic plaque psoriasis or psoriatic arthritis were considered eligible for the study. The drug agents used were etanercept, infliximab, and adalimumab.

Patients with a diagnosis of guttate, pustular, or erythrodermic psoriasis at presentation were excluded. Those receiving combination therapies (eg, methotrexate associated with TNF-alfa inhibitor treatments), receiving off-label dosages (eg, infliximab infusions every 6 weeks, adalimumab injections every week), and who had unspecified baseline treatments or who were unable to provide Psoriasis Area Severity Index (PASI) assessment scores at baseline or during the follow-up period were also excluded.

Patients for whom there was information about the reason the first TNF-alfa inhibitor was discontinued were likewise excluded.

After giving their written informed consent, the patients considered eligible were included in the Italian Psocare Registry and assigned a distinctive personal code to ensure data anonymity.

Follow-up and data collection Study participants agreed to take part in at least 3 years of follow-up. Data were collected at baseline and at regular intervals thereafter. Information was gathered by the investigators using World Wide Webebased electronic data collection forms endowed with internal quality controls, which also guaranteed confidentiality.

The data collected at baseline included: (1) patients' demographic details and personal habits (smoking and average alcohol consumption);

(2) patients' comorbidities and medications;

(3) dermatologic and family history of psoriasis and arthritis; and (4) severity of psoriasis at entry, dosages and drugs prescribed, and the results of laboratory tests performed before their prescription.

The PASI was adopted as the measure of disease severity. A 75% improvement in the PASI score (PASI 75) was considered a clinically meaningful improvement.

The following information were collected during follow-up examinations: (1) patients' demographic details and personal habits were updated; (2) psoriasis progression/regression was updated as was medication information; (3) any adverse events, new diagnoses, hospitalizations, or examinations by specialists were recorded; and (4) laboratory tests and results were recorded.

The reasons for discontinuing prior TNF-alfa inhibitor therapy were classified as follows:

(1) PASI 75 was never achieved (primary inefficacy); (2) loss of initial PASI 75 response (secondary loss of efficacy); or (3) adverse event or other, including drug intolerance or physician's decision.

Statistical analysis In all, 105 patients who were switched to second TNF-alfa inhibitor were eligible for the study.

For descriptive purposes, continuous variables are presented here as means with SD and categorical variables as numbers with percentages. For univariate and multivariate analyses, continuous variables were

categorized using tertiles of their distribution as cut-offs. The Kaplan-Meier productlimit estimate was used for univariate analysis of the duration of the treatment with a second TNF-alfa inhibitor using a PASI 75 as the end point. The log rank test was used to compare cumulative response rates between different levels of selected variables.

We also compared the PASI 75 response achieved in the 105 patients who switched therapy with that achieved in 2933 patients who did not but were able to provide complete data (body mass index, PASI assessment scores, and prescribed treatments) to make adjustments for potential baseline confounders.

All variables with a P value less than .10 at univariate analysis were considered for inclusion in the multivariate analysis. Cox proportional hazards regression with forward stepwise algorithm selection was used to identify significant predictor factors of PASI 75 response. The effects of the factors identified were expressed in terms of hazard ratios along with their 95% confidence intervals and P values.

A P value less than .05 was considered significant.

The analysis was conducted using software (SPSS, Version 17.0, IBM Corp, Armonk, NY).

RESULTS

Demographic details and treatments Overall 5423 patients who were treated with a first cycle of TNF-alfa inhibitors were identified. Of these 1034 (19.1%) were excluded from the study because not all patient data needed for this study were available. Of the remaining 4389 patients, 228 switched to a second TNF-alfa inhibitor after discontinuing the first one, but salient information about the first treatment (including the reason for switching) and all outcome assessment values during follow-up were available only for 105 (Table I).

Adalimumab was found to be more frequently prescribed as a second TNF-alfa inhibitor than as the first one. The majority of patients (60% of cases) switched from etanercept to a monoclonal antibody, 20.9% switched from a monoclonal antibody to etanercept, and 18.1% switched from one monoclonal antibody to another.

The reason for switching to a second TNF-alfa inhibitor was primary inefficacy (PASI 75 never achieved) in 47 cases (44.8%), secondary loss of efficacy (loss of initial PASI 75 response) in 23 (21.9%), and adverse events/other in 35 (33.3%).

Patients who switched had been treated with the first TNF-alfa inhibitor for a mean of 58.4 (637.9) weeks.

Cumulative PASI 75 response A cumulative PASI 75 response rate was attained in 29%, 45.6%, and 74.1% of the patients after switching to the second TNF-alfa inhibitor after 16, 24, and 52 weeks, respectively. These scores were quite similar to those in patients who did not switch TNF-alfa inhibitors (30.6%, 42.5%, and 67.5% after 16, 24, and 52 weeks, respectively, P = .090).

After 16 and 24 weeks of treatment with a second TNF-alfa inhibitor, PASI 75 was reached by 14.4% and 29.8%, respectively, being treated with etanercept; by 26.6% and 40.4%, respectively, being treated with infliximab; and by 38.3% and 58%, respectively, being treated with adalimumab. Univariate and multivariate analyses on variables associated with the efficacy of the second TNF-alfa inhibitor Univariate analysis showed that the reason for switching and the length of time the first TNF-alfa inhibitor was taken were associated to the cumulative PASI 75 at 52 weeks. Notably, the cumulative PASI 75 response rates for patients stratified according to the reason the first cycle of TNF-alfa inhibitors was discontinued were higher for the those who switched because of: (1) a secondary loss of efficacy; or (2) adverse events, drug intolerance, or as a consequence of their physician's decision; than for (3) those who had from the beginning failed to respond to the first TNF-alfa inhibitor (31.4%, 34.3%, and 11.6% at 12 weeks, and 58.4%, 57.1%, and 30.2% at 24 weeks, respectively) (Fig 1).

Multivariate analysis confirmed the data obtained at univariate analysis, showing a statistically significant positive correlation between a clinical response (PASI 75) and secondary loss of efficacy as the reason for withdrawal (Table II).

DISCUSSION

The findings emerging from this large Italian cohort of patients with moderate to severe psoriasis in whom a cumulative PASI 75 response was achieved in 29% and 45.6% after 16 and 24 weeks, respectively, confirmed that some patients benefit from switching to a second TNF-alfa inhibitor after the first proves to be inefficacious. Most of the patients studied who switched were treated with adalimumab during the

second cycle and this was to be expected in view of the fact that it was introduced into clinical practice at a later date with respect to the other 2 TNF-alfa inhibitors.

Only a limited amount of data is available in the literature concerning patients with psoriasis who switched biological agents with the greater part coming from short-term, nonrandomized studies concentrating on small population samples.

Those observational studies have, nevertheless, described improved disease severity in the patients studied2,4-11 although their response rate appeared lower than what might have been expected in clinical trials focusing on patients na€ıve to biological agents.

BothWoolf et al12 and Van L€umig et al13 reported a PASI 75 response, respectively, in 29% (at 16 weeks) and 27% (at 12 weeks) of the psoriatic patients who switched from etanercept to adalimumab and this finding was confirmed by our study, with 14.4%, 26.6%, and 38.3% of our patients reaching a PASI 75 at 16 weeks who were being, respectively, treated with etanercept, infliximab, and adalimumab.

The differences in response to several TNF-alfa inhibitors can be linked to the differences in their bioavailability and stability and in patients' genetics. These drugs also differ in terms of their immunogenicity or potential to induce antidrug antibodies, which may be associated to a secondary loss of response over time.

Nearly all published studies on patients switching from one TNF-alfa inhibitor to another failed to analyze the reasons for abandoning the first.

Biological treatment is considered a failure when: a patient does not respond to treatment at all (primary inefficacy), when the patient shows secondary loss of efficacy with time after an initially satisfactory response (this may be a result of the production of antibodies against the drug),14-16 or when a patient develops an intolerance to the biological agent (with drug reactions or various adverse events, which may differ in the 3 TNF-alfa inhibitors considered).

Some studies on patients with rheumatoid arthritis and ankylosing spondylitis did, nevertheless, indicate that the response to a second TNF-alfa inhibitor seems to differ depending on the reason the first one was abandoned. A second TNF-alfa inhibitor might be more effective in patients with a history of secondary loss of efficacy than in those with a primary inefficacy.17-20 In our study, achieving a PASI 75 response was, indeed, significantly associated with the reason for switching: patients with secondary loss of response or adverse events/intolerance achieved a PASI 75 response more often than those who failed to respond to the first TNF-alfa inhibitor. This correlation was confirmed by the 2 studies on psoriatic patients who switched biological agents that did examine the reason for discontinuing the first cycle.11,13 In particular, a subanalysis of the double-blind, randomized, controlled BELIEVE trial showed that 53.8% of patients who had previously not responded at all to a prior antieTNF treatment achieved a PASI 75 by week 16 as did 65.7% of the patients with a history of an initially satisfactory response that was lost.11 The fact ours was a prospective, observational, cohort study of patients with psoriasis attending dermatology clinics and that the choice of treatment was not randomized but at the discretion of the treating physician can be considered study limitations; likewise the fact that data needed to carry out our analyses were available for only a small proportion of the patients.

In conclusion, this prospective, open, registrybased study shows that switching to a second TNF-alfa inhibitor can be effective in some psoriatic patients, particularly in cases of a secondary loss of response to a previous TNF-alfa inhibitor or to drug intolerance.

Improvement in symptom severity in patients with a history of primary inefficacy is of course advantageous and desirable despite a debatable cost-benefit profile. Using a drug with a different mechanism of action seems opportune in these cases in view of the patients' lower rate of response to a second TNF-alfa inhibitor with respect to that noted in patients continuing with the first. Needless to say, treatments should always be tailored to each patient's needs taking into account his/her characteristics (traditional drug use and tolerance, comorbidities, weight) and preferences (mode and frequency of drug administration) and, when it comes to switching from a TNF-alfa inhibitor to another drug, the reason the first was discontinued.

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Table I. Demographics, and disease and treatment characteristics of 105 patients who were prescribed a tumor necrosis factor-alfa inhibitor and then switched, after failure, to another one

Gender	
Male (%)	68 (64.8)
Female (%)	37 (35.2)
Age, y, mean (SD)	47.4 (12.5)
BMI, mean (SD)	28.8 (5.6)
PASI score on starting first TNF-alfa inhibitor [baseline], mean (SD)	18.1 (12.6)
PASI score on starting second TNF-alfa inhibitor [switch], mean (SD)	8.8 (8.4)
Time on first TNF-alfa inhibitor [baseline], mean (SD)	58.4 (37.9)
≤24 wk	16 (15.2%)
>24 wk	89 (84.8%)
Time on second TNF-alfa inhibitor [switch], wk, mean (SD)	29.0 (26.4)
First TNF-alfa inhibitor [baseline]	
Adalimumab	5 (4.8%)
Etanercept	63 (60.0%)
Infliximab	37 (35.2%)
Second TNF-alfa inhibitor [switch]	
Adalimumab	43 (41.0%)
Etanercept	23 (21.9%)
Infliximab	39 (37.1%)
Switching order	
Adalimumab to etanercept	4 (3.8%)
Adalimumab to infliximab	1 (1.0%)
Etanercept to adalimumab	25 (23.8%)
Etanercept to infliximab	38 (36.2%)
Infliximab to adalimumab	18 (17.1%)
Infliximab to etanercept	19 (18.1%)
Total 105	

BMI, Body mass index; PASI, Psoriasis Area Severity Index; TNF, tumor necrosis factor.

Table II. Multivariate analysis of variables associated with a 75% improvement in the Psoriasis Area Severity Index score response

Variables	Hazard ratio (95% CI)	P value
Reason for switching:		
Primary inefficacy	1	
Secondary loss of efficacy	2.7 (1.3-5.5)	.008
Adverse events/other	2.0 (1.0-3.9)	.037
Time on first TNF-alfa inhibitor, wk		
≤35	2.1 (1.1-4.1)	.035
35-65	1	
>65	2.9 (1.4-5.7)	.003

CI, Confidence interval; TNF, tumor necrosis factor.

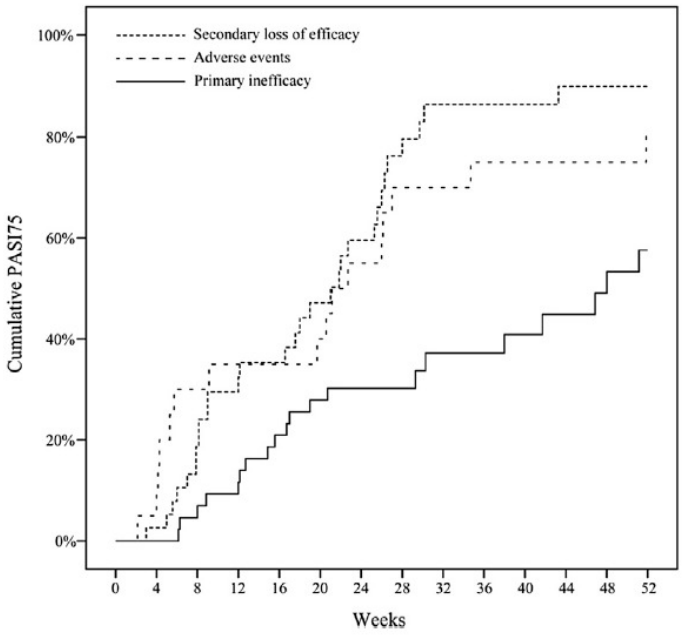

Fig 1. Cumulative 75% improvement in the Psoriasis Area Severity Index score (PASI75) response stratified according to the reason the first tumor necrosis factor-alfa inhibitor was discontinued.