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The effectiveness of a biologic agent on axial manifestations of psoriatic arthritis. A twelve-month observational study in a group of patients treated with etanercept

E. Lubrano[1], A. Spadaro[2], A. Marchesoni[3], I. Olivieri[4], R. Scarpa[5], S. D'Angelo[4-8], C. Salvarani[6], A. Mathieu[7], A. Cauli[7], N. Ferrara[1-8], P. Helliwell[9]

[1]*Department of Health Sciences, School of Medicine, University of Molise, Campobasso, Italy;*
[2]*Dipartimento di Clinica e Terapia Medica, Divisione di Reumatologia, Sapienza-Università di Roma, Italy;*
[3]*Rheumatology Department, "Istituto Ortopedico G. Pini", Milano, Italy;*
[4]*Rheumatology Department of Lucania, "S. Carlo Hospital", Potenza and Madonna Delle Grazie, Matera, Italy;*
[5]*Academic Rheumatology Unit, University of Naples Federico II, Naples, Italy;*
[6]*Rheumatology Unit, "Arcispedale S. Maria Nuova", Reggio Emilia, Italy;*
[7]*Chair of Rheumatology, Department of Medical Sciences, University of Cagliari, Cagliari, Italy;*
[8]*Fondazione Maugeri, Institute for Rehabilitative Medicine, Telese Terme, Italy;*
[9]*Academic Unit of Musculoskeletal and Rehabilitation Medicine, University of Leeds, Leeds, United Kingdom.*

Ennio Lubrano, Antonio Spadaro, Antonio Marchesoni, Ignazio Olivieri, Raffaele Scarpa, Salvatore D'Angelo, Carlo Salvarani, Alessandro Mathieu, Alberto Cauli, Nicola Ferrara

Please address correspondence and reprint requests to:
Dr Ennio Lubrano,
Dipartmento di Scienze per la Salute,
Università di Molise,
C/da Tappino,
86100 Campobasso, Italy.
E-mail: enniolubrano@hotmail.com

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ABSTRACT

Objectives. *To investigate the effectiveness of etanercept on axial manifestations of a group of patients with established psoriatic arthritis (PsA).*

Methods. *This was a multicentre observational study. PsA was classified based on the CASPAR criteria. Inclusion criteria were refractory PsA with axial manifestations and suitability for anti TNF-α therapy. Effectiveness was defined according to the ASAS response criteria (BASDAI: 50% relative or absolute change of 20mm and expert opinion in favour of continuation), and on the improvements of BASFI, anthropometric measures, PASI, ESR and CRP at 12 months. PASI 50 and 75 were also assessed, as well as the ACR20 and ACR50 response criteria for patients with peripheral arthritis. Comparisons between baseline and after 12-month treatment were done using the Wilcoxon signed rank test for the end-points considered.*

Results. *The study included 32 patients (25/7 M/F; median age 51yrs; 25th–75th percentiles: 34.5–58.7; median disease duration 14.5 yrs; 25th–75th percentiles: 9.2–17.00). Effectiveness of etanercept was observed in 72% of patients for the BASDAI ($p<0.001$), in 68% for the BASFI ($p<0.001$), in 76% for ESR ($p<0.001$) and in 68% of patients for CRP ($p<0.01$). The PASI improved in 72% of patients treated ($p<0.0001$), while PASI 50 and PASI 75 was reached in 81% and 55% of patients, respectively. ACR 20 and 50 was reached in 78 and 56% of patients with peripheral involvement respectively.*

Conclusion. *The present study has shown that etanercept is effective on axial manifestations of established PsA, confirming the positive effects of anti TNF-α therapy on clinical manifestations of the disease.*

Introduction

The definition and measurement of axial disease in psoriatic arthritis (PsA) remain problematic (1). Since the frequency of spondylitis in PsA patients is a function of the number and sensitivity of the diagnostic instruments, and of the disease duration, it may vary from 25% (early disease and clinical assessment only) to 75% (late disease and sophisticated imaging) (2). Psoriatic axial involvement is usually less severe than that of ankylosing spondylitis (AS) and dissimilar in many respects (3). Indeed, some radiographic features of psoriatic spondylitis, such as asymmetrical sacroiliitis, non-marginal syndesmophytes, asymmetrical syndesmophytes, paravertebral ossification, and more frequent involvement of cervical spine, seem to be so characteristic as to be potentially helpful in diagnosing PsA and in differentiating this condition from some cases of psoriasis with co-incidental AS (4, 5). Until recently there were no instruments validated to assess psoriatic spondylitis. However, some validation of previous radiological scores for AS (BASRI, m-SASSS) (6), as well as by a new instrument, has been proposed (7).

Effectiveness, defined as the effect of any intervention carried out in daily clinical practice and evaluated at the community as well as at individual levels, was assessed in a group of PsA patients with refractory disease and treated with etanercept (ETN) in monotherapy. The patients included in that study were affected by a predominant peripheral joint involvement, and the axial involvement was excluded from the study. The results showed that ETN was efficacious, effective and safe in the majority of PsA patients treated (8). On the other hand, at present no study based on the real clinical practice on axial manifestations in PsA patients has been carried out to assess the effectiveness of any biologic therapy. In 2005, we designed an observational study aimed at assessing the validity of radiological scores for the axial involvement of PsA (6, 7). We recruited patients from different centres throughout Italy. In the present paper, we report the effectiveness of an anti TNF-α therapy in a group of patients with axial manifestations treated with ETN and followed up for 12 months.

Patients and methods

Study design

The study was a multi-centre observational study involving patients with established PsA. Therefore, all patients

fulfilling the inclusion/exclusion criteria (see below) were then recruited and followed up for 12 months.

Out of the 77 patients enrolled for the radiological validation study, 32 were suitable to start ETN. These patients were re-evaluated at 12 months of treatment.

The study was approved by the local ethics committee. All patients gave their written informed consent. The study was carried out at the outpatient clinic for PsA by a group of rheumatologists with a specific expertise in PsA. The patients were recruited consecutively during their follow-up visit, regardless of the disease duration, and of which of them were eligible for treatment with biologic agents.

Inclusion criteria were:

1. satisfaction of ClASsification of Psoriatic ARthritis (CASPAR) classification criteria (9);
2. the presence of clinical (spinal inflammatory pain according to the Calin criteria) (10) and/or radiological axial involvement;
3. patients with refractory PsA recruited consecutively at the outpatients clinics from January to December 2006 and suitable for the anti TNF-α therapy, based on the recommendation for the use of these medications (11, 12)

Exclusion criteria were:

1. previous biological agents within the previous 6 months;
2. previous Disease Modifying Antirheumatic Drugs (DMARDs) treatments (including but not limited to methotrexate, sulfasalazine, CsA, and leflunomide) within the previous 6 months;
3. oral corticosteroids within the previous 4 weeks;
4. positive screening for tuberculosis

Once a week patients received subcutaneously 50mg of ETN, a soluble TNF-α receptor.

Clinical and functional assessment

In all patients a detailed clinical and functional assessment for the axial involvement was performed. Anthropometric measurements included cervical rotation, tragus to wall distance, the modified Schober test, intermalleolar distance (13-14) and lumbar side flexion. Other measures included the Italian version of BASMI, BASFI, HAQ, and the Italian version of RLDQ (Revised Leeds Disability Questionnaire) (15). The activity of the disease was assessed by the BASDAI as well as the acute phase reactants (ESR, CRP), and the patient's VAS on global disease activity (PGA). Moreover, the skin involvement measured by the PASI was carried out in all patients.

Patients with peripheral joint involvement were also evaluated by assessing the tender and swollen joint count (68/66, respectively).

Assessment of response

Effectiveness was defined according the ASAS response criteria: BASDAI with a 50% relative change or absolute change of 20mm, and expert opinion in favour of continuation, (11) and also as an improvement of single outcome measures such as BASFI, BASMI, HAQ, RLDQ, PGA, ESR, CRP, and anthropometric measures at 12 months. Finally, the effectiveness of the ETN on skin involvement was assessed by an improvement of PASI and by the number of patients reaching a PASI 50 and/or 75 at 12 months.

However, response to the biologic treatment was also evaluated by the ACR response criteria in those patients who had at the time of the recruitment a peripheral joint involvement.

Safety

At each visit, adverse events were noted and biochemical and peripheral blood analyses were performed. Serious adverse events prompted interruption of therapy at the discretion of the physician.

Statistical analysis

Descriptive data were expressed, if not otherwise specified, as median and 25^{th}–75^{th} percentile.

Changes from baseline to 12 months assessment were analysed using the Wilcoxon paired sign rank test for the endpoints considered. All statistical procedures were two-sided at a significance level of 0.05.

Statistical analysis was carried out using the SPSS package for Windows (version 13.0; Chicago, IL).

Results

Descriptive, clinical and functional data

Thirty-two patients were enrolled (25/7 M/F, median age 51 yrs, 25^{th}–75^{th} percentiles: 34.5–58.7) median disease duration 14.5, 25^{th}–75^{th} percentiles**:** 9.2–17.00). Peripheral joint involvement was present in 23/32 (72%) and the median (25^{th}–75^{th} percentiles) joint count was 2(0–10) for tender and 1(0–4.7) for swollen joints.

All the demographic, clinical and functional data, as well as the outcome measures considered are shown in Table I.

In particular, at the beginning of the ETN therapy the patients showed the following clinical spinal measurements (median/25^{th}–75^{th} percentiles): cervical rotation; degree (45/32.5–55 degree); tragus to wall, cm (13/12–18.5); chest expansion, cm (3/2–3.5); modified Schober test, cm (3/ 2.2–4); intermalleolar distance, cm (90/83–97.5), and lumbar side flexion, cm (5, 4.2–7.1). Finally, the median BASDAI was at the beginning of the ETN treatment 69 (25^{th}–75^{th} percentiles: 65–79.5).

Assessment of response

Effectiveness of ETN was observed in 72% of patients when measured by BASDAI, ($p<0.0001$) in 68% of patients for the BASFI, ($p<0.0001$), in 76% for ESR, ($p<0.0011$) and in 68% of the patients for CRP, ($p=0.002$). The PASI improved in 72% of the patients treated ($p<0.0001$), while PASI 50 and PASI 75 was reached in 22/27(81%) and in 15/27(55%), respectively. Moreover, a statistical significant improvement was also recorded for the RLDQ, HAQ and PGA.

In particular, with regard to spinal mobility, at 12 months we observed a statistical significant improvement of anthropometric measurements (median/25^{th}–75^{th} percentiles): cervical rotation, degree (52/43–70), $p<0.0001$; tragus to wall distance, cm (13/11–16), $p<0.001$; chest expansion, cm (3/2–5.4), $p<0.001$; modified Schober test, cm (4/3–5), $p<0.001$; intermalleolar distance, cm (99/90–110), $p<0.0001$; lumbar side flexion, cm (6, 4.7–8.4), $p<0.001$. However, BASMI showed a statistical improvement at 12 months

(3/2–4) when compared to the baseline value (3/3–5), $p<0.001$.
Finally, ACR 20 and ACR 50 were reached by 18/23(78%) and 13/23(56%) of patients with peripheral joint involvement.
All the main data on the assessment of response are summarised in Table II.

Adverse events
No serious adverse events (SAEs) were recorded. No cases of tuberculosis or demyelinating disease were observed. Mild Adverse events (AEs) were observed in 4 patients (11%) that did not require the interruption of ETN treatment.

Table I. Demographic and clinical data of the enrolled patients.

Number of patients (M/F ratio)	32 (25/7)
Age (yrs), median, (25^{th}–75^{th} percentiles)	51 (34.5–58.7)
Disease duration, median (25^{th}–75^{th} percentiles)	14.5 (9.2–17)
Evidence of psoriasis, n (%)	27/32 (84%)
Nail dystrophy, n (%)	18/32 (56)
Family history of psoriasis, n (%)	15/32 (47)
HLA B27 positive, n (%)	11/25 (44)
Patients with peripheral involvement, n (%)	23/32 (72%)
Patients with axial involvement without peripheral, n (%)	9/32 (28)
Tender joints (n), median (25^{th}–75^{th} percentiles)	2 (0–10)
Swollen joints (n), median (25^{th}–75^{th} percentiles)	1 (0–4.7)

Table II. Measurements of effectiveness at baseline and at week 52. All data are expressed as median (25^{th}–75^{th} interquartile).

	Baseline	Week 52	Significance
Measurements			
BASDAI	69 (65–79.5)	27 (10–39)	$p<0.0001$
BASFI	64 (55.7–69.7)	27 (4–34)	$p<0.0001$
BASMI	3 (3–5)	3 (2–4)	$p<0.001$
RLDQ	1.4 (1–1.7)	1 (0.31–1.9)	$p<0.0001$
HAQ	0.75 (0.5–1.1)	0.62 (0.15–1)	$p=0.003$
Cervical rotation (°)	45 (32.5–55)	52 (43–70)	$p<0.0001$
Tragus to wall distance (cm)	13 (12–18.5)	13 (11–16)	$p<0.001$
Chest expansion (cm)	3 (2–3.5)	3 (2.5–4)	$p<0.001$
Modified Shober Test (cm)	3 (2.25–4)	4 (3–5)	$p<0.001$
Intermalleolar distance (cm)	90 (83–97.5)	99 (90–110)	$p<0.0001$
PASI	3.3 (1.1–4.9)	1 (0.3–2)	$p<0.0001$
CRP (mg/l)	12 (7–18)	4.9 (3–8.9)	$p=0.002$
ESR (mm/1^{st} h)	34 (26–45)	11 (4–14)	$p<0.0001$
PGA	58 (41–69)	41 (12–60)	$p<0.0001$

Discussion

The present study dealt with the assessment of the effectiveness of an anti TNF-α agent, namely ETN, on the clinical and functional axial manifestations of a group of patients with established PsA. Our results showed that ETN was effective in a group of axial PsA.
Axial PsA represents one of the domains that are considered important to evaluate in randomised controlled trials (RCT) or in the Longitudinal Observational Study (LOS). However, it is not mandatory that it be done, as resulted in the OMERACT 8 (16), and at present it is not included in the inner core set of variables for RCT or LOS in PsA patients. This aspect is mainly related to the lack of evidence of data on two main aspects: 1) it is not clear whether axial PsA is a subset of the disease and independent of a coincidental AS; and 2) it is often associated with peripheral joint involvement, which could be a bias in assessing the real efficacy of any treatment. Both aspects, therefore, limit the design of any trials aimed at evaluating the role of any medication in a cohort of "true" axial PsA and, in fact, all the RCT have assessed only the efficacy and/or the effectiveness of PsA patients with predominant peripheral joint involvement. On the other hand, sometimes the axial involvement can be difficult to be recognised til to be underestimated and a subclinical or occult PsA should be considered (17).
Therefore, therapeutic guidelines, including assessment of disease activity and response criteria, have been borrowed from the AS literature to evaluate the axial PsA (16). In particular, the INSPIRE study (International Spondyloarthritis Interobserver Reliability Exercise) showed that the measures of spinal mobility used in primary AS performed well and are equally reproducible when applied to PsA patients with axial involvement (14). Moreover, a recent study showed that in a group of axial PsA patients who were followed up for 10 years, an improvement of neck and back pain was recorded but with a deterioration of lateral spinal flexion and cervical mobility (18).
Therefore, the axial involvement still represents the unmet clinical need, to be addressed, of formulating a better treatment strategy.
TNF-α antagonists (infliximab, etanercept and adalimumab) have demonstrated to be effective in spondyloarthritis with a clinical response rate ranging from 43% to 71% by BASDAI-50 in AS patients and from 62% to 87% by PsARC in subjects with PsA (19).
The rationale to use TNF-α in spondyloarthropathies is based on several issues, from pathogenetic aspects to the lack of alternative and disease-modifying therapies, particularly for the axial involvement. In PsA, TNF-α antagonists showed to be efficacious, effective and safe either in clinical trails (19) or in observational longitudinal studies (8, 20) where the peripheral joint involvement was predominant. The latter studies were designed to assess the effectiveness in a group of PsA patients with refractory disease and some of them treated with ETN in monotherapy. The patients included in those studies were affected by a predominant peripheral joint involvement and, in particular, the axial involvement was excluded from the study of De Vlam *et al*. (8). The results showed that ETN was efficacious, effective and safe in the majority of PsA patients treated (8, 20).
Our study was designed for PsA pa-

tients with axial manifestations consecutively attending the outpatients clinics of 6 different centres and suitable for the beginning of anti TNF-α treatment. A 12-month observational study was carried out to assess the effectiveness at the individual level of a group of PsA patients with established disease. Interestingly, patients reached a good response to the treatment, with more than 70% at the primary endpoint (BASDAI 50), which is a reliable indicator of overall disease activity. Moreover, a good response was obtained at the level of other secondary endpoints, particularly at the level of metrology measures and BASMI aimed to measure the spinal function, disability and skin severity, confirming that TNF-α antagonists have a multidimensional capacity to control the disease. The raised level of CRP and ESR at the baseline could be considered a predictor of good response to the anti-TNF therapy, as recently showed by BSRBR in patients with Ankylosing Spondylitis (21). Indeed, the largest longitudinal observational study on an unselected population of PsA patients, obtained from the British Society for Rheumatology Biologics Register (BSRBR), showed that TNF therapies were effective in PsA (22). The effectiveness, measured as EULAR responders was 70.3% of the cohort studied at 12 months, and this data is similar to that obtained in our small group of patients, measured by an improvement of BASDAI (72%).

Similar results have been recently obtained in AS patients (23), confirming the role of biologics in the treatment of AS (24).

Although the BASDAI in PsA may be influenced by peripheral involvement (25), the changes in the other axial measurements are consistent with a true effect of ETN on the axial component of arthritis.

It is worth noting that our results have been obtained from real clinical practice, which is in keeping with the growing attention on evidence-based clinical practice and recommendations (26-27), although the number of patients enrolled was not very high.

In conclusion, this study, based on real clinical practice, showed that the TNF-α antagonism is effective in dealing with PsA patients with axial involvement.

Competing interests

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