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ORIGINAL ARTICLE

Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs

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Abstract The aim of this study is to compare effectiveness and safety of Infliximab (INF), Etanercept (ETN), and Adalimumab (ADA) in patients with psoriatic arthritis (PsA) with inadequate response to a previous disease-modifying antirheumatic drug (DMARD). One hundred consecutive PsA patients with inadequate response to a previous DMARD entered this study. Clinical and laboratory assessment at baseline (T0) and 12 (T12) months were performed and included physical examination, vital signs, global Psoriasis Area and Severity Index (PASI; extension of psoriasis), tender joints count (TJC), swollen joint count, health assessment questionnaire (HAQ; questionnaire for measuring disability), and monitoring of adverse events (AEs). After enrolment, all patients were randomly given INF 5 mg/Kg every 6–8 weeks, ETN 50 mg weekly, or ADA 40 mg every other week. Baseline therapy with DMARD remained unchanged. Effectiveness was defined as percentage of ACR20 responders and as clinical remission and/or minimal disease activity at 12 months treatment. INF, ETN, and ADA all effectively controlled signs and symptoms of PsA. All variables tested showed at T12 for each treatment a significant variation from the baseline value. In particular, patients on INF and ADA showed the greatest improvement in terms of PASI, while patients on ETN showed the greatest improvement on TJC and HAQ. ACR response rates were 72% of patients on ETN, 70% of those on ADA, and 75% of those patients on INF. Occurrence of AEs was reported in 15% of the cases. Only two AEs in patients on INF were considered drug related, pneumonitis and thrombocytopenia, respectively. All tumor necrosis factor-α blockers significantly controlled signs and symptoms of PsA. An increased knowledge of the different profiles of these agents may help in optimizing their use.

Keywords Minimal disease activity · Psoriatic arthritis · Remission · TNF-α blockers

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Introduction

Psoriatic arthritis (PsA) is a spondyloarthropathy occurring in patients with skin and/or nail psoriasis [1]. Recent evidences underline its severity, which leads to progressive joint damage with radiographic changes, usually appearing within 2 years of clinical onset [2]. Therefore, appropriate therapy has to be promptly started in order to control symptoms, inflammation, and to prevent progression of articular damage.

Traditionally, treatment for the established form of arthritis primarily includes nonsteroidal anti-inflammatory drugs (NSAIDs) and, in addition, disease-modifying anti-

rheumatic drugs (DMARDs). NSAIDs are used with the sole aim of controlling joint symptoms, not showing any effect on the progression of structural damage. Traditional DMARDs are employed with the aim of restraining inflammatory process, but their usefulness still remains controversial. In fact, a recent meta-analysis of therapies of PsA found methotrexate, sulfasalazine, and leflunomide to be effective, but their benefits appear modest at best [3].

Tumor necrosis factor (TNF)-α is a pro-inflammatory cytokine that acts a complex role in the pathogenesis of psoriasis and PsA.

The recent use of TNF-α blockers in the treatment of psoriasis and PsA has generated an increased interest in this field. TNF-α blockers have efficacy in providing a clinical response and in preventing the progression of articular damage. Their use is expensive, and also the Italian Society of Rheumatology provided clinical suggestions to discipline this therapy in patients with recalcitrant PsA [4].

Therefore, this study was conducted with the aim of comparing the effectiveness and the safety of three different TNF-α blockers in a cohort of Italian patients with established PsA who experienced an inadequate response to a previous DMARD therapy.

Study design

The study was designed as longitudinal, and it was carried out as single-center, enrolling consecutive patients affected by PsA, attending their follow-up visit at the outpatient clinic for PsA patients, regardless of the disease duration. PsA was based on the CASPAR classification criteria [5]. Inclusion criteria were age >18 years and an inadequate response to a previous DMARDs therapy.

The study protocol considered a recruitment period from January 2005 until December 2007. During that period of time, 1,240 patients with PsA were consecutively seen at our outpatient clinic; out of them, 100 were considered active and eligible for the present study.

The exclusion criteria were previous usage of anti-TNF-α inhibitors; the usage of DMARDs other than sulfasalazine, methotrexate, azathioprine, and leflunomide within 4 weeks of enrolment; the usage of more than 10 mg prednisone daily; and variation of dosage of NSAIDs or prednisone within 2 weeks of enrolment. None of the 100 PsA patients showed any of the exclusion criteria. All patients treated with DMARDs were on stable dosage for at least 6 months.

All patients gave their written informed consent, and the study protocol was approved by the local Ethical Committee.

Patients and methods

One hundred consecutive patients with active PsA, routinely attending the Psoriatic Arthritis Clinic at the University Federico II (60 females and 40 males, mean age 48.5± 12.5 years; median duration of disease 80 months, range 20–140) who experienced an inadequate response to a previous DMARD therapy (Table 1) entered this study.

In patients eligible for therapy with TNF-α blockers, we performed tuberculin skin test and interferon gamma release assay tests to screen latent tubercular infection.

After the screening, all patients were randomly given Infliximab (INF) at dosage of 5 mg/Kg every 6–8 weeks (increasing or decreasing the dosage when warranted), Etanercept (ETN) 25 mg twice weekly, and Adalimumab (ADA) 40 mg every other week.

Disease activity

The patients were followed up every 3 months for a total of 1 year. Clinical and laboratory assessment was carried out at baseline (T0) and at every 3 months (T3, T6, and T9) and at 12 months (T12), including physical examination, vital signs, global Psoriasis Area and Severity Index (PASI; measure of the extension of psoriasis), tender joints count (TJC; 68 tender joints), swollen joint count (SJC; 66 swollen joints), and health assessment questionnaire (HAQ) score (measure of function and disability).

Data were collected at inclusion and at each visit, and in this paper, we report on the effectiveness and safety of

Table 1 Demographic, baseline, clinical, and therapeutic characteristics of patients

	Overall (n=100)	Etanercept (n=36)	Adalimumab (n=34)	Infliximab (n=30)	p
Gender (male)	40 (40)	15 (42)	14 (41)	11 (37)	0.91
Age (years)	48.5±12.5	49.3±13.4	47.5±11.5	48.5±12.9	0.84
PASI	19 (18.2)	26 (18.5)	18 (16.5)	15 (14.8)	0.08
HAQ	1.2 (0.4)	1.2 (0.4)	1.2 (0.3)	1.5 (0.5)	0.03
Tender joints	12 (6)	13 (5)	13 (7)	12 (4.8)	0.41
Swollen joints	4 (2)	4 (3.2)	5 (3.8)	3 (3)	<0.01

Values are mean±SD, median (interquartile range) or absolute frequency (percentage)

therapy with TNF-α blockers based on the variation between T0 and T12 on the various endpoints. ACR20 responses rates were taken into account to measure the effectiveness of the three medications. However, we calculated also the clinical remission that was defined by the physician as absence of swollen and tender joints, as previously defined [6], while minimal disease activity (MDA) was defined by the physicians as absence of swollen joints, no more than two tender joints associated to a HAQ score <0.5, at 12 months observation.

Statistical analysis

Age is expressed as mean±SD, while other continuous variables are expressed as median (interquartile range), and categorical variables are expressed as absolute frequency (percentage).

Differences between treatment groups on baseline measures and after 1-year follow-up were tested using analysis of variance, Kruskal–Wallis tests, or the χ^2 tests, as appropriate.

The analyses were made using R statistical software (R Development Core Team, 2008).

Results

Demographic and clinical characteristics of the studied cohort measured at baseline and after 1 year are tabulated in Tables 1 and 2, respectively. Fifty-one patients were on combination methotrexate and biologic agent (ETN 40%, INF 90%, and ADA 30%), and 20% of them showed a disease duration ≤24 months. Patients treated with INF tended to have higher HAQ values ($p=0.03$) and lower number of swollen joints ($p<0.01$) than the patients treated with ADA and ETN at baseline. On the other hand, the patients on ETN had the highest PASI score at baseline, but no significant differences were found with the other two biologic agents.

The distributions of the endpoint variables at baseline and at 1 year for the three treatment groups are depicted in Fig. 1. In particular, all endpoints at 1-year observation were significantly different compared to those at baseline visit.

ETN, INF, and ADA effectively controlled signs and symptoms of patients with PsA included in this study. In fact, all variables tested showed at T12, for each treatment, a significant variation from the baseline value T0. However, ACR response rates were 72% of patients on ETN, 70% of those on ADA, and 75% of those patients on INF.

A statistical significant difference among the drugs at 1 year was found in terms of PASI by means of univariate analysis ($p<0.01$). In particular, patients treated with ADA and INF showed the greatest improvement of the extension of the psoriatic rash when compared to those treated with ETN ($p<0.01$ and $p<0.001$).

When compared to ADA and IFN, patients treated with ETN showed better improvement of TJC ($p<0.018$ and $p<0.012$, respectively), while no significant differences for SJC were found among the three groups of patients included in this study.

Finally, patients taking ETN showed better decrease of HAQ when compared with patients taking ADA ($p<0.002$).

No patients reached the remission as previously defined, while they reached the MDA as a group. In particular, 26 patients on ETN reached an MDA status, as defined, and 16 on ADA, with a cumulative number on this latter group not satisfying the complete definition.

Adverse events

Adverse events (AEs) were recorded in 15% of cases. Patients under ADA when compared to those under INF or ETN showed the lowest rate of events (INF 23%, ETN 17%, and ADA 6%; $p<0.001$). No cases of tuberculosis or demyelinating disease were reported during this study. The majority of AEs were mild to moderate in all groups. Only two serious AEs occurring in patients under INF were considered drug related and consisted of pneumonitis and thrombocytopenia. Both were resolved with treatment withdrawal and with the appropriate therapy.

Discussion

Recent evidence demonstrated that PsA is a relatively frequent condition which shows a profound impact on the

Table 2 Clinical and therapeutic characteristics of patients after 1 year

	Overall ($n=100$)	Etanercept ($n=36$)	Adalimumab ($n=34$)	Infliximab ($n=30$)	p
PASI	0.6 (2)	2 (4.4)	0.1 (1.9)	0 (1)	<0.01
HAQ	0.1 (0.1)	0.1 (0)	0.1 (0.2)	0.1 (0)	0.60
Tender joints	1 (1)	1 (1)	1 (2)	1 (1.8)	0.12
Swollen joints	0 (1)	0 (1)	0.5 (1)	1 (1)	0.23

Values are median (interquartile range)

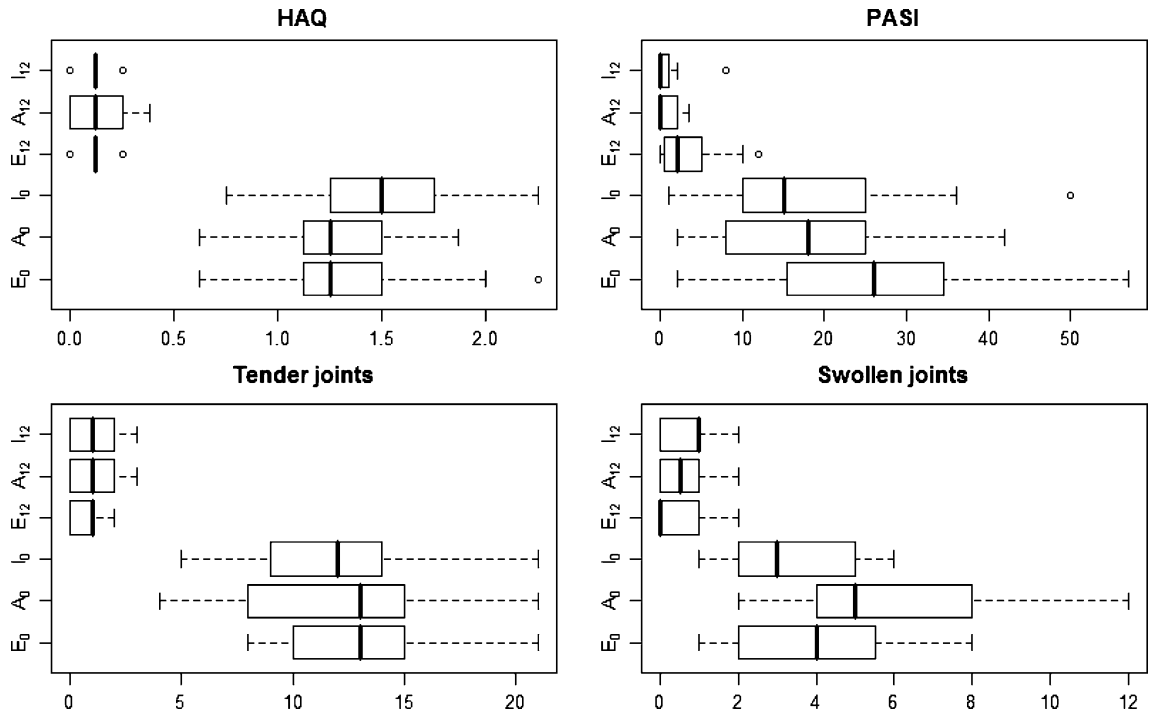

Fig. 1 Box-plots of health assessment questionnaire, Psoriasis Area and Severity Index, tender joints count, and swollen joint count for the three treatment groups, Etanercept (*E*), Adalimumab (*A*), and Infliximab (*I*), measured at baseline (0) and after 1 year (12)

lives of patients. In fact, it develops in up to one third of the patients with psoriasis, and articular inflammation frequently leads to a stable structural damage [7], even if it is often still difficult to assess the real impact of the disease. In fact, it has been noted that patients with PsA are less tender than those with rheumatoid arthritis [8].

Moreover, traditional DMARDs used in PSA have not demonstrable consistent efficacy in clinical practice [9].

Our recent experience outlines controversial results with MTX at full dosage also in patients with PsA in early clinical stages [10]. Finally, we do not have reliable tools that may predict the onset of arthritis and its clinical outcome.

In the last 20 years, the potentially devastating joint destruction of PsA has been clearly evidenced, and the need for a rapid detection and a quick therapeutic intervention has become mandatory in this condition as well.

The recent introduction of TNF-α blockers in the therapy of PSA patients developed a great interest because these drugs showed their ability to control symptoms and signs of articular inflammation and to prevent radiographic progression of structural damage.

The results of this study confirmed that all TNF-α blockers employed improved signs of articular and cutaneous involvement and ameliorating the function and quality of life of patients treated as previously described [11]. Our study, based on clinical practice and aimed to assess the effectiveness of these biologic agents, seems to show some therapeutic peculiarities of the three drugs used. In fact, ETN seems to be more effective on the articular involvement and function, while ADA seems to be more effective on the cutaneous involvement, and this is in keeping with the literature [12–14]. Indeed, the patients on ETN had the highest level of PASI at baseline, and the dosage of 50 mg weekly is recommended for joint disease and not for skin involvement, and our group of patients showed a level of PASI quite unusual for a rheumatological clinic because our center represents the only tertiary center for the region.

Therefore, the results from this study could be interpreted as the three biologic agents are an effective and safe treatment for PsA patients, but with some differences that should be taken into account when the treatment is tailored based on the predominant clinical feature of the disease at the time of the starting therapy. However, similar results were already obtained from randomized controlled trials and in observational studies [12, 15], but not in a "head-to-head" study based on real clinical practice. The MDA status, defined by us as a predominant improvement of articular manifestations and function, was reached from all three biologic agents as a group and with some differences among the three TNF-α blockers.

This definition is, in some ways, keeping with that obtained by the GRAPPA group a few months ago from a survey among 60 experts in PsA [16].

Moreover, all the three biologic agents showed a good safety profile, and all patients carried out the treatment.

The discovery of anti-TNF-α agents that specifically block a crucial molecule implicated in the inflammatory cascade leading to PsA represents a significant advancement in our ability to control disease activity and to inhibit the progression toward a structural damage. The rapid improvement of skin rash and of tenderness and swelling of joints and/or entheses has allowed patients to regain a relatively normal life. The better knowledge in clinical practice of TNF-α blockers therapeutic ability could permit a use that optimizes their peculiarities at most. The results of this study may support this hypothesis.

Disclosures None.

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