



ASSESSMENT OF IMMUNOLOGICAL THERAPY WITH INFLIXIMAB AND ETANERCEPT IN THE TREATMENT OF PSORIASIS ARTHROPATHY

Liana Suciu, Carmen Cristescu, Mirela Voicu, Maria Suciu, B. Bumbăcilă

University of Medicine and Pharmacy Timisoara, Faculty of Pharmacy, Department of Pharmacology and Clinical Pharmacy

Abstract. Psoriasis arthritis is a seronegative chronic inflammatory arthropathy, which occurs in patients with psoriasis and is accompanied by characteristic symptoms. Shortcomings of conventional therapy, frequent and sometimes severe side effects induced by classical immunomodulatory substances (methotrexate, cyclosporine, leflunomide), lack of ethyo-pathogenic theories has been leading to research on new therapeutic perspectives in psoriasis, including for psoriasis arthropathy. Pathogenesis of psoriasis has highlighted a number of changes related to keratinocytes, T lymphocytes, dermal fibroblasts and a number of genes encoding several types of proteins involved in proliferation of keratinocytes. The aim of the present study was to highlight the effectiveness of therapy with biological agents (infliximab and etanercept), assessed by improvement of PASI score, and to assess the incidence of adverse effects detected in patients during the study group. Patients enrolled in the study were selected by eligibility criteria and the final number was 14, from which eight patients were treated with infliximab and six were treated with etanercept in Dermatology Clinic from Timisoara. In the infliximab - treated group to whom the drug was administered iv 5mg/kgc for two hours at weeks 0, 2, 6 and 8 weeks thereafter until week 24, a rate of 62.5% of cases showed a 75% improvement in index PASI, in 12 weeks . Evaluation performed at week 24 showed improvement of symptoms (objective by index steps) to 87.5% of patients, thus proving efficacy. Administration over 24 weeks resulted in adverse effects: myalgia and fever in 32% of patients, the increase of transaminases in 25% of patients. No patient treated with infliximab did not show de novo appearance of antibodies antiADN DC. The group of patients treated with Etanercept, administered in doses 25mg/twice a week, for 24 weeks, were obtained the following results: after 12 weeks of treatment PASI index improved to 50% of cases, after 24 weeks the percentage of patients which occurred improvement was 66.66. Adverse effects in this group were represented by: transient leukopenia and thrombocytopenia (one case), autoimmune events (one case) and local reactions as redness and induration at the site of administration, delivered spontaneously (two patients). This study has shown considerable clinical effects in psoriasis arthropathy, but it is not considered a first-line therapy because of the incidence of adverse events which has to be monitored and interpreted in the context of each patient's clinical condition on such therapy and not least because of the extremely high cost of the treatment.

Keywords: psoriasis arthropathy, therapy, biological agents

Introduction

Psoriasis arthropathy is a chronic seronegative inflammatory arthritis

which occurs in patients with psoriasis and is accompanied by characteristic symptoms. The onset is insidious for the articular manifestations in most patients. The onset of psoriasis lesions precedes in most cases the articular manifestation, only about 10% of the cutaneous manifestations appear simultaneously with those of the joint [1,2]. The joint, in addition to events occurring in the skin and nails of patients with psoriasis, presents features

Liana Suciu

University of Medicine and Pharmacy
2 Piata Eftimie Murgu Str., Timișoara
email: lianads@yahoo.com

that suggest the diagnosis of psoriatic arthritis:

a) it relatively frequently involves isolated distal interphalangeal joints of the upper fingers and lower limbs, with asymmetric oligoarthropathy;

b) axial affliction of the spine and sacroiliac joint;

c) the presence of osteolysis.

Psoriasis arthropathy is considered less aggressive than rheumatoid arthritis. However, disease progression is variable from destructive forms, mild to mutilating forms, leading to severe bone loss and change fingers. Presently, it is known that 40-50% of patients have distorting arthritis; in a cohort study from Toronto, Gladman observed that 11-19% of patients have increased disability and mortality rates than those of the general population [1,6].

The axial form of psoriatic arthritis develops slowly, with limited repercussions on the backbone, in contrast to radiological changes which increase over time. Among the complications seen in patients with psoriatic arthritis we can distinguish: i) psoriatic enteropathy described by Sushter M. (1967) which manifests itself by malabsorption syndrome and small bowel villous atrophy; ii) renal amyloidosis; iii) heart failure, atrioventricular block.

Currently, it is considered that psoriasis is an immune-mediated disease; its pathogenesis highlights a number of changes related to keratinocytes, T lymphocytes, endothelial cells, dermal fibroblasts. The main pathological changes of psoriasis are: rapid proliferation and differentiation of keratinocytes and abnormal and inflammatory infiltrate in the dermis, epidermis and the synovial [1,3].

Shortcomings of conventional therapy and frequent and sometimes severe side effects are induced by conventional systemic therapy (methotrexate, cyclosporine, leflunomide); the lack of etiopathogenic theories have led to research on new therapeutic perspectives in psoriasis, including arthropathy psoriasis.

A number of studies have demonstrated the role of T lymphocytes in the initiation and maintenance of abnormal proliferation and differentiation process of keratinocytes. The interaction between activated T lymphocytes and keratinocytes is achieved mainly through proinflammatory cytokines: interferon-gamma, TNF-alpha. Other molecules involved in this process are: E selectins and HLA-DR molecules. On the activated T lymphocytes' surface, there were identified markers of the type CD2 + CD3 +, CD5 +, CD28 +, CLA +, CD25 (IL-2 receptor), CD27. Cytokine production has the effect of keratinocyte

proliferation, neutrophil migration, angiogenesis and increased expression of adhesion molecules.

Experimental models demonstrated that epithelial hyperplasia is dependent in particular of TNF-alpha, a cytokine secreted by keratinocytes. Keratinocytes have a basal secretion of TNF-alpha, but in the epithelial hyperplasia processes, TNF-alpha is significantly elevated both in the serum and on local level. For these reasons it sought to block the activity of this cytokine and reduced epithelial hyperplasia [4,5,7].

Infliximab is a chimera monoclonal antibody that is a human immunoglobulin constant region and murine variable region. Infliximab is able to pair both serum TNF alpha and the transmembrane forms of TNF-alpha. By this coupling, TNF-alpha cannot exercise its proinflammatory activity. Infliximab is currently used to treat Crohn's disease, rheumatoid arthritis and moderate to severe forms of psoriasis and psoriatic arthritis.

Prolonged administration of infliximab has led to several adverse effects, including myalgia, arthralgia, pyrexia, rash, increased transaminases, headache, vertigo, infections. A special reaction is given by the occurrence of autoimmune biological changes: anti-DNA antibodies in patients treated with infliximab. The clinical significance of these antibodies is not known. The risk of a malignant tumor, by blocking TNF-alpha is an important element; it seems to be increased, but this is hard to prove in clinical trials [2,4].

Etanercept is a recombinant protein containing the p75 TNF receptor and the Fc portion of human IgG1 immunoglobulin. This molecule binds competitively to TNF alpha and TNF beta, preventing them from interacting with their membrane receptors and therefore, from exercising their proinflammatory effects. Etanercept has proven to be effective in spondylitis and medium and severe forms of psoriasis. In this case there were reported autoimmune phenomena and theoretical risk of developing cancer by inhibiting the TNF [5,6].

The aim of the study is to assess: the effectiveness of therapy with these biological agents and incidence of adverse effects arising from administering the two drugs.

Materials and methods

In this retrospective study the information was extracted from the files of patients treated as outpatient in the Dermatology Clinic of Timișoara.

Initially, the group consisted of 80 patients receiving conventional systemic therapy and topical therapy with methotrexate, retinoids, cyclosporine, pimecrolimus. Of these, 14 patients corresponded to one of the following criteria and were included in the study:

- have developed or are at risk to develop toxicity from therapies used, so the standard therapy could not be used;
- have become intolerant to standard therapies;
- became non-responsive to therapy with methotrexate, acitretin or their combination (clinical response <50% in terms of improving the PASI score);
- have a disease that requires repeated hospitalizations (more than three hospitalizations per year);
- present comorbidities which excluded systemic therapy.

Based on clinical and biological evaluation, the following patients were excluded from the study group:

- patients with active infections: sepsis, an active tuberculosis, opportunistic infections;
- heart failure patients, class NYHA III/IV;
- concomitant administration of live vaccines with germ;
- pregnancy/lactation;
- patients under the age of 17 years;
- patients with malignancy or premalignant stage of disease;
- patients with demyelination;
- patients with a hypersensitivity to one of the components of the product.

From the group of 14 patients, 8 were treated with infliximab and six were treated with etanercept over a period of 24 weeks.

Effectiveness evaluation was conducted by analyzing changes in the PASI index (psoriasis area and severity index); although it is the most common score, it presents limitations. PASI score was assessed for each group initially, when the patient was included in the study and then at weeks 12 and 24.

Laboratory tests were conducted bimonthly (blood count, liver tests) and clinical consultations were held monthly.

Infliximab was administered to 8 patients, three female and five male, with a mean age of 49 years (30-75). Infliximab was administered at a dose of 5 mg/kg, by intravenous infusion over 2-3 hours at weeks 0, 2, 6 and then again as one injection every eight weeks.

In the group treated with etanercept there were three females and three males, with a mean age of 56 years (40-80). Etanercept was administered at doses of 25 mg subcutaneously twice weekly for 24 weeks.

Results and discussions

It can be noticed from table no. I that the group of patients treated with infliximab achieved an improvement of PASI score with 75% after 12 weeks of treatment in 62.5% of the cases, percentage that increased to 87.5% at week 24 of treatment.

The incidence of adverse events was as follows:

- upper respiratory tract infection: 2 patients;
- headache: 2 patients;
- increase in serum transaminases: 2 patients;
- fatigue: 2 patients;
- myocardial infarction: one patient.

No patients treated with infliximab showed the de novo appearance of antibodies Anti dsDNA.

In the group treated with infliximab, the average PASI score was 59 ± 13.1 . After 12 weeks of

No.	Patient Name	Age (years)	Sex	Initial PASI Score	PASI Score after 12 weeks of therapy	PASI Score after 24 weeks of therapy	Final variation of PASI Score (%)
1	M.I.	50	F	70	17	17	75,7
2	N.O.	75	M	65	16	15	76,9
3	P.C.	42	F	45	11	11	75,5
4	B.I.	39	M	67	49	16	76,1
5	C.C.	50	F	70	17	16	77,1
6	G.I.	48	M	34	8	8	76,4
7	A.M.	60	M	56	42	27	51,7
8	T.F.	30	M	65	47	16	75,3
Avg±SD		49,2 ± 13,6		59 ± 13,1	26,1 ± 16,8	15,7 ± 5,4	73 ± 8,6

Table I. Characteristics of patients treated with infliximab

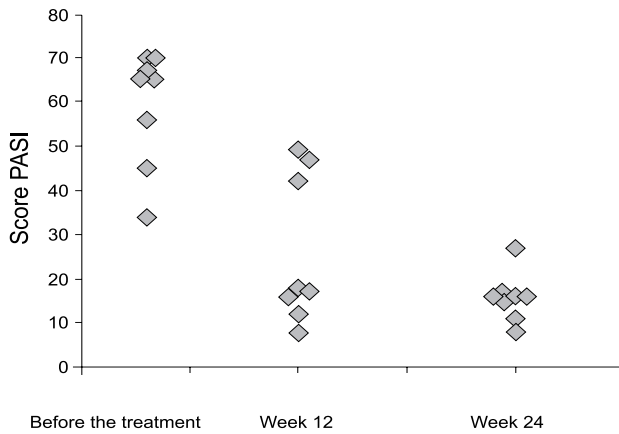


Figure 1. Evolution of PASI score in the group of patients treated with infliximab

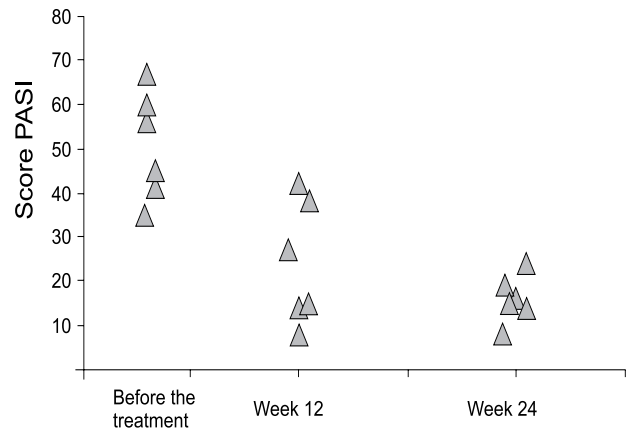


Figure 2. Evolution of PASI score in the group of patients treated with etanercept

treatment, PASI average score decreased significantly (26.1 ± 16.8 , $p = 0.003$, non-parametric test Mann-Whitney).

In week 24 of treatment, the scores decreased compared to the PASI score at 12 weeks, but without reaching statistical significance (15.75 ± 5.4 , $p = 0.2$, non-parametric test Mann-Whitney).

The overall average PASI score improved with 73% from baseline ($p = 0.0002$, non-parametric test Mann-Whitney) (figure 1).

It should be noted that occasionally, anti-inflammatory treatments have been used, according to symptoms. A patient with psoriasis, skin and nail lesions that presented a score of 80 at the beginning of NAPS nail treatment showed a very good recovery of the nail blade at 12 weeks of treatment.

The group treated with etanercept achieved a score improvement of 75% after 12 weeks of treatment in 50% of cases, and the score reached this value in 66.66% of patients at 24 weeks.

Side effects were the following:

- gastrointestinal disorders: two patients;
- infections: one patient;
- psychiatric symptoms: one patient;

- autoimmune manifestations: one patient;
- local reactions at the injection administration of etanercept which was reversible: two patients;
- transient leukopenia and thrombocytopenia: one patient.

In the group treated with etanercept, the mean PASI score was 50.8 ± 12.1 . After 12 weeks of treatment, the PASI average score decreased significantly (24 ± 13.8 , $p = 0.005$, t-test for independent values). In week 24 of treatment, the PASI score decreased compared with the PASI score at 12 weeks, but without reaching statistical significance (16 ± 5.3 , $p = 0.21$, t-test).

There were no statistically significant differences detected in terms of therapeutic response between the two groups: in the group treated with infliximab, the average PASI score improved by 73% and in the group treated with etanercept, the average PASI score improved by 67.4 % ($p = 0.27$, non-parametric test Mann-Whitney).

Side effects were present in both groups of patients, but it can be noticed that the group treated with etanercept has a greater incidence of them. It can be mentioned that only one patient presented

No.	Patient Name	Age (years)	Sex	Initial PASI Score	PASI Score after 12 weeks of therapy	PASI Score after 24 weeks of therapy	Final variation of PASI Score (%)
1	N.C	58	M	35	8	8	77,1
2	V.N.	69	M	42	27	19	54,7
3	S.O.	80	F	67	42	16	76,1
4	A.S.	40	M	56	14	14	75
5	L.N.	50	F	45	38	24	46,6
6	A.D.	40	F	60	15	15	75
Avg±SD	56,1 ± 16,1			50,8 ± 12,1	24 ± 13,8	16 ± 5,3	67,4± 13,2

Table II. Characteristics of patients treated with etanercept

an autoimmune manifestation and there hasn't been evidence of any malignant process.

Conclusions

This study has shown considerable clinical effects in psoriasis arthropathy by PASI assessment score. However, the biological therapy cannot be considered as a first-line therapy because of the incidence of side effects. It should be monitored and interpreted in the clinical context of each patient.

Because the number of studied patients was not very large and because the treatment protocols provided a period of therapy no longer than 24 weeks without a break, the patients were monitored and there were no serious adverse effects revealed which could be connected with the treatment.

The initiation of immunological therapy in psoriasis involves assessing the balance of benefit/risk/cost for each patient, so that currently the number of patients receiving such therapy is quite limited.

References

1. Guidelines of care for the management of psoriasis and psoriatic arthritis, *The American Academy of Dermatology*, 2008.
2. **Baker BS, Fry Lionel.** Immunotargeting: A biological approach to the treatment of psoriasis; *Drug Discovery today:Therapeutic Strategies*, 2007.
3. **Zaragoza V, Perez A, Sanchez JL, et al.** Long-term safety and efficacy of Etanercept in the treatment of psoriasis, *ACTAS Dermo-Sifiliograficas*, 2009.
4. **Alecu M, Coman G, Costache I, Agraviloaie A.** Terapia imunologică în psoriasis, *DermatoVenerol (București)*,53: 123-131.
5. **Kormeili T, Lowe NJ, Yamauchi PS.** Psoriasis: immunopathogenesis and evolving immunomodulators and systemic therapies. US experiences. *Br.J.Dermatol.* 2004; 151:3-15.
6. **Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler D, et al.** British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005, *Br. J. Dermatol.* 2005; 153: 486-97.
7. **Mehlis SL, Gordon KB.** The Immunology of psoriasis and biologic immunotherapy. *J. Am. Acad. Dermatol.* 2003; 49:S44-50.