Aspects concerning patient adherence to anti-TNFα therapy in psoriasis: A decade of clinical experience

MADALINA MOCANU[1], MIHAELA-PAULA TOADER[1], ELENA REZUS[2] and TATIANA TARANU[1]

[1]Dermatology Clinic, Railways University Hospital Iasi, 'Grigore T. Popa' University of Medicine and Pharmacy, 700506 Iasi;
[2]Rheumatology Clinic, University Rehabilitation Hospital,
'Grigore T. Popa' University of Medicine and Pharmacy, 700115 Iasi, Romania

Abstract. Non-adherence to psoriasis treatment has an important impact in controlling chronic disease evolution and the occurrence of systemic comorbidities. Biologic therapy represents a revolutionary treatment, many of the undesirable psychological and socio-economical consequences of conventional topical or systemic therapies being avoided. Nevertheless, the discontinuation of biological therapy may occur due to facts related to the patient, to the lack of good communication between the patient and the physician or to the adverse or paradoxical reactions. We studied the non-adherence reasons to anti-TNFα agents (Infliximab, Adalimumab, Etanercept) used for treating 84 cases with moderate-severe psoriasis. The results of our study over the past 10 years showed a 76.2% adherence rate, lowest in patients treated with Etanercept (70.9%). Relative to the anti-TNF agent used, the highest adherence rate was recorded in Adalimumab (80.8%), followed by Infliximab (76.5%) and Etanercept (70.9%). We have noticed differences between the rates of adhesion to therapy with different anti-TNFα agents, but with no statistical significance. The main adverse effects that occurred during anti-TNFα therapy were: local reaction to the drug, mild infectious events, allergic reactions, cardiotoxicity, alopecia areata, pancreatitis, eosinophilia, thrombocytopenia. Anti-TNF therapy was discontinued in one case of endocarditis, one case with tuberculous laryngitis and another one with polydiscitis (Adalimumab), a case of colon cancer and one of pregnancy (Etanercept) and one paradoxical reaction (Infliximab).

Introduction

Psoriasis is an inflammatory condition with chronic evolution, multifactorial etiology and complex pathogenesis, involving genetic, immunological and environmental factors. Skin lesions, erythematous-squamous plaques with inconstant osteo-articular and nail involvement may be associated with systemic damage, such as cardiovascular diseases, metabolic syndrome or autoimmune disorders (1,2). Psoriasis is a disease with a severe psychosocial impact, comparable to diabetes and cancer (3,4).

The treatment is adapted to the extent of the lesions, the duration of the disease evolution, the comorbidities and the general biological status of the patient. In mild or moderate clinical forms of psoriasis, with lesions not exceeding 10% of the skin surface, local therapy is recommended. In severe forms of psoriasis, with extensive lesions or resistant to either topical therapy or UVA/NB-UVB therapy, a systemic treatment with antiproliferative medicines (methotrexate, retinoids) or immunomodulators, such as cyclosporine or fumaric acid is established (5,6). Lack of response constitutes an eligibility criterion for biological therapy (7).

Biological agents are a class of revolutionary pharmaceuticals useful in many immunological-mediated diseases. Those intended for psoriasis include selective inhibiting biological agents of anti-TNFα tumor necrosis factor, of interleukin 12/23 or interleukin 17A (8,9). The longest experience has been gained by anti-TNFα agents (infliximab, etanercept, adalimumab).

Despite the modern therapeutic options being destined to patients with psoriasis, obtaining satisfactory clinical and biological results requires optimal patient compliance with the treatment. The term 'compliance' has been criticized for having an authoritative message and referring in particular to the rigor with which a patient is following the prescribed treatment, not to the doctor's additional recommendations on appropriate diet or change of lifestyle (10). For these reasons, the term adhesion or even therapeutic alliance is currently preferred to suggest an approach that indicates a high degree of involvement of both the patient and the physician in the therapeutic act (11). As an extended definition, adherence is expressed in patients who have been treated for a certain period of time and who have followed both the indications and the doctor's prescription following treatment without interruption. According to the World Health Organization (WHO), adherence is 'the extent to which the behavior of a person taking medication, following a diet, making lifestyle changes corresponds to the recommendations accepted by the physician' (12).

Correspondence to: Dr Mihaela-Paula Toader, Dermatology Clinic, Railways University Hospital Iasi, 'Grigore T. Popa' University of Medicine and Pharmacy, 1st Garabet Ibraileanu Street, 700506 Iasi, Romania
E-mail: toaderpaula@gmail.com

Biological agents, targeted, rational and long-term individualized therapy are able to increase adherence to treatment for patients with psoriasis, due to the ease of drug administration, the costs incurred by the national health insurance system, the clinical effectiveness shortly after treatment initiation, the long-term safety profile. Non-adherence to biological therapy is found, however, correlated with a number of factors that involve both the patient and the attending physician (13,14).

This study aimed to identify the main factors involved in the non-adherence of patients with psoriasis to anti-TNFα biological therapy, as well as to analyze the optimal methods of combating this phenomenon with negative echoes in terms of disease evolution over time.

Patients and methods

The current retrospective, observational study includes patients with moderate-severe psoriasis vulgaris treated with biological anti-TNFα agents. The study group encompassed 84 patients who underwent therapy with anti-TNFα biological agents in the Department of Dermatology at CF University Hospital Iasi (Iasi, Romania) between January 2009 and October 2018. The Ethics Committee of the Railways University Hospital Iasi (Iasi, Romania) approved the current study. The patients were aged 9-82 years, 48 women and 35 men, 66 from urban areas and 18 from rural areas.

Depending on the biological agent administered, the patients were divided into 3 groups: group 1 included 34 patients who received Infliximab (5 mg/kg iv every 8 weeks), group 2 consisted of 26 patients treated with Adalimumab (40 mg subcutaneously every 2 weeks) and group 3 had 24 patients treated with Etanercept (50 mg subcutaneously every week). The patients' eligibility was based on the inclusion and exclusion criteria regarding the general protocol for biological therapy. The analysis of the clinical and paraclinical parameters during the biological therapy allowed the evaluation of the adherence to treatment, as well as the investigation of the factors responsible for non-adherence.

Statistical analysis. Descriptive and analytical methods were used in the statistical analysis. Once the data were collected, in an accessible form to ensure their informational character, the processing was performed. The confidence intervals, at the significance threshold of 95%, were used in the data presentation, and the χ^2 and Student's t-tests were used to assess the differences. The data were centralized in EXCEL and SPSS 13.0 databases and processed with the statistical functions they are suitable for. In calculating the significant difference between two environments, the Student's t-test takes into account the variability measurement and the weight of the observations. The accepted significance threshold was 95%. χ^2 test is a nonparametric test comparing two or more frequencies distributed from the same population; it applies when the expected events are excluded.

Results

From an epidemiological point of view, the study group consisted predominantly of male patients (57.1%) with a M/F ratio of 1.4/1 (Fig. 1). Most subjects were from the urban area, the U/R ratio being 3.7/1 (Fig. 2). The distribution by areas of origin and
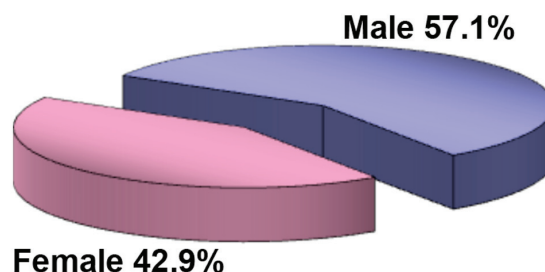

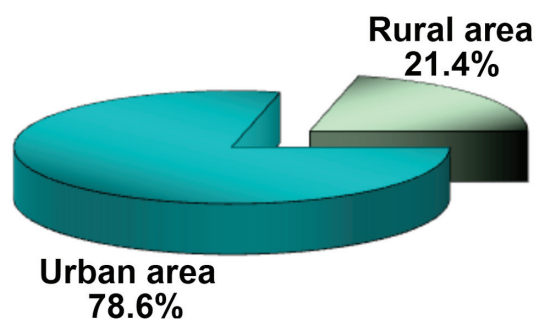Figure 1. Distribution of the patients in the study group by sex.

Figure 2. Distribution of the patients in the study group by area of origin.
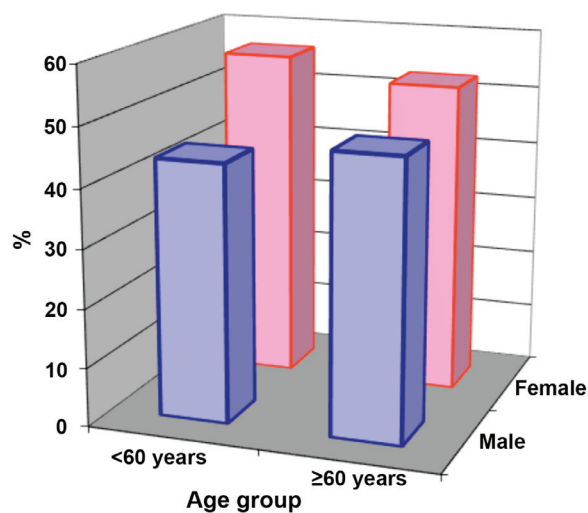

Figure 3. Distribution of patients by age and sex.

sex did not show significant differences: 75% of women and 83.3% of men came from the urban environment (P=0.514), statistically revealing the homogeneity of the study group.

Distribution by age group reveals the high proportion of cases in the 60-69 age group, both in women and men. Since the mean age of the group was 58.88 years and the highest weight of cases is found in patients >60 years (54.8%), we chose this age as reference in the statistical processing (Fig. 3).

Infliximab was used in 40.5% of the cases, the majority in men (72.7 vs. 27.3%, P=0.038) and Adalimumab was recommended in 30.9% of the patients, frequently women (60 vs. 40%, P=0.038) (Fig. 4).

Discontinuation of therapy was observed in 20 of the 84 patients enrolled in the study (22.6%) for reasons related either to therapy (adverse events) or to the patient. The

Table I. Distribution of events leading to discontinuation of therapy.

| Adverse effects	Infliximab (n=8/34)		Adalimumab (n=5/26)		Etanercept (n=7/24)	
	% of Infliximab group	% of all patients	% of Adalimumab group	% of all patients	% of Etanercept group	% of all patients
Angioedema urticarial	8.82	3.57	-	-	-	-
Infectious endocarditis			3.84	1.19	-	-
Hypereosinophilic syndrome	-	-	3.84	1.19	-	-
Paradoxical psoriasis	2.94	1.19	-	-	-	-
Cataract	2.94	1.19				
Eosinophilic cellulite	-	-	-	-	8.33	2.38
IC class III NYHA	2.94	1.19	-	-	-	-
Hepatitis C virus	2.94	1.19	-	-	-	-
Tuberculous laryngitis	-	-	3.84	1.19	-	-
Thrombocytopenia	-	-	-	-	4.16	1.19
Pancreatitis	-	-	-	-	4.16	1.19
Breast cancer	-	-	3.84	1.19	-	-
Colon cancer	-	-	-	-	4.16	1.19
Polydiscitis	-	-	3.84	1.19	-	-
Move home	2.94	1.19	-	-	-	-
Pregnancy	-	-	-	-	4.16	1.19
Alopecia	-	-	-	-	4.16	1.19
Total adverse effects	23.5	9.52	19.2	5.95	29.1	8.33
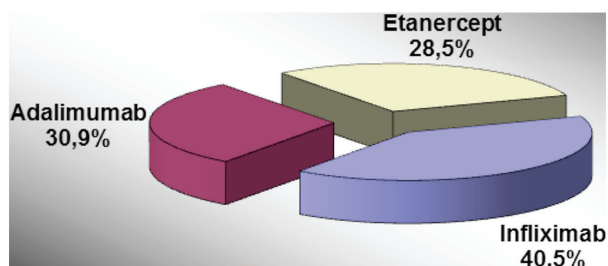
Figure 4. Distribution of groups according to therapy.
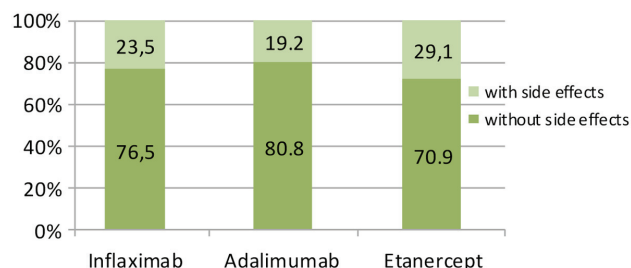

Figure 5. Treatment discontinuation according to the biological agent administered (P=0.00213).

highest rate of treatment discontinuation was observed in the Etanercept group (29.1), followed by the Infliximab group (23.5%) and Adalimumab group (19.2%) (Fig. 5).

In most cases, the reasons for discontinuing biological therapy were represented by adverse events. In the Infliximab group these were: allergic reactions (angioedema and deep urticaria) in three cases (8.82% of all patients treated with Infliximab) representing 3.57% of the total number of patients enrolled in the study, NYHA class III heart failure one patient (2.94% of all patients in the Infliximab group), viral hepatitis with C virus in one patient (2.94% of all patients treated with Infliximab). One patient developed paradoxical psoriasis and cataract (2.94% of all patients treated with Infliximab). Home relocation was the reason for discontinuing the therapy in one patient (2.94% of all patients in the Infliximab group). Patients who discontinued Infliximab accounted for 8.3% of the total number of patients.

In the Adalimumab group, the therapy was discontinued in the context of the following adverse events: polydiscitis in one case (3.84% of all patients in the Adalimumab group), infectious endocarditis in one case (3.84%), laryngeal tuberculosis, one case (3.84%), hypereosinophilic syndrome, one case (3.84%) and breast cancer, one case (3.84%), each adverse event representing 1.19% of the total. Patients who discontinued Adalimumab accounted for 5.95% of the total number of patients.

In the Etanercept group, adverse events that led to the interruption of therapy were: eosinophilic cellulitis in two cases (8.33% of all patients in the Etanercept group), accounting for 2.38% of the total number of patients, colon cancer occurred in one patient (4.16% of all patients in the Etanercept group), representing 1.19% of the total number of patients, alopecia areata in one case (4.16%), pancreatitis in one case (4.16%) and thrombocytopenia in one case (4.16%). Pregnancy occurred during biologic therapy in one patient (4.16% of all patients in the Etanercept group) and led to interruption of Etanercept. Patients who interrupted Etanercept accounted for 8.3% of the total number of patients (Table I).

Overall adverse events that led to treatment discontinuation occurred in 52.6% of men and 47.4% of women (P=0.179). There were no significant differences in the reason for non-adherence to treatment based on the background (P=0.280). In conclusion, the study group had a predominantly male distribution (57.1%), from urban areas (68.6%) aged between 28 and 82 years. Statistically, the homogeneity of the group by sex, age groups, and background was demonstrated. Non-adherence to therapy was noted in 22.6% of the patients, most commonly in those treated with Etanercept (29.1%). The adherence rate for the entire patient population was of 76.2%, statistical analysis revealing a lack of direct correlation between the incidence of adverse events and biologic therapy (P=0.00213).

Discussion

Biological therapy in psoriasis is a modern treatment alternative with long-term proven efficacy and safety profile. Clinical experience with biological agents from the anti-TNFα class allows them to be categorized as superior to conventional systemic therapy for moderate-severe psoriasis. Rapid remission of symptomatology, its maintenance over treatment, easy administration, significant improvement in the quality of life are the arguments that reinforce this idea (15,16).

The adhesion of patients with psoriasis to anti-TNFα therapy is an essential condition for obtaining and maintaining the expected therapeutic outcome, but also a long-term indicator of patient satisfaction. The risk of reactivating the disease in the context of cessation of treatment confers a key role in maintaining the favorable clinical effects to the notion of adherence to therapy (17,18).

The rate of adherence to biological therapy is clearly superior compared to adherence to classical topical or systemic treatments, but the literature data on this topic varies, depending on the size of the group studied and the biological agent used (19).

Thus, a 2017 study conducted in Germany for 31 months in 13 dermatology centers showed a rate of adhesion to anti-TNFα therapy of ~85%. Other studies concluded that adherence rates ranged between 65 and 96.7% one year after initiation of anti-TNFα therapy with a 40-70% decrease in adherence after 4 years of therapy (20). Another large study on 747 patients concludes on a high adherence to Infliximab of 70% after 4 years of treatment as compared to Etanercept and Adalimumab with a 40% adherence rate (21).

The results of the current study, which included 84 patients treated with anti-TNFα (Infliximab, Adalimumab, Etanercept) over the past 10 years, showed an overall 76.2% adherence rate, lowest in patients treated with Etanercept (70.9%). Relative to the anti-TNF agent used, the highest adherence rate was recorded in Adalimumab (80.8%), followed by Infliximab (76.5%) and Etanercept (70.9%). We noted differences between the rates of adhesion to therapy with different anti-TNFα agents, but with no statistical significance (P=0.00213).

The main adverse events of anti-TNFα therapy reported in literature are cardiovascular diseases, increased risk of latent tuberculosis reactivation, increased risk of infections, malignancy, injection site reactions, haematological

disorders (22,23). These events may be a factor of non-adherence to therapy. In our study, patients treated with Infliximab experienced: allergic reactions (8.8%), cardiotoxicity (NYHA class III congestive heart failure 2.9%), hepatitis C (2.9%), results which are comparable to those published in other studies (23,24).

The most common adverse events reported during treatment with Adalimumab are minor injection site reactions, occurring in 12-37% of the treated cases. In addition, Adalimumab increases the risk of infection or reactivation of chronic latent infections, such as viral hepatitis or TB (22). Only one case of tuberculous infection (tuberculous laryngitis 3.8%) and a bacterial endocarditis (3.8%) were recorded in our study during Adalimumab therapy.

Numerous research studies focused on the efficacy and safety profile of Etanercept. The main side effects to Etanercept reported in the literature are local reactions on injection site (eosinophilic cellulitis) and the risk of infection. In our study, 8.3% of the patients treated with Etanercept developed eosinophilic cellulitis. Other events recorded during Etanercept therapy were: malignancies (4.1% colon cancer), alopecia areata (4.1%), and pancreatitis (4.1%). Various studies have focused on the analysis of long-term safety of Etanercept administration and concluded on a similar rate of side effects after 96 and 144 weeks of monitoring. They have also concluded that the rate of major adverse events, such as severe infections and tumors, is higher than in the general population (24,25).

On the one hand, adherence to long-term treatment is influenced by its nature; on the other hand, it is influenced by the patient's compliance based on an optimal physician-patient relationship. Two cases of non-adherence due to factors independent of therapy (home relocation and pregnancy) were reported in our study. There were no matters involving refusal to follow the prescribed treatment, under or overdosing, intermittent dosing, premature discontinuation, addition or waiver of medicine without medical advice, non-compliance to the protocol regimen. Serious side events were rare and difficult to interpret widely on a small batch of patients.

Other non-adherence reasons reported in literature are loss of insurance, long-term remission of the skin lesions or lack of confidence in pharmaceutical drugs. Even though vitamins, minerals and herb supplements (zinc, selenium, B12, fish oil, curcumin, aloe vera extract) are sometimes prescribed in psoriasis due to their mainly antioxidant action, we consider it a complementary therapeutical instrument (26,27).

The case with PR and aggravated psoriasis under Infliximab therapy benefited from switch to anti-IL17 therapy. Potential causes for paradoxical psoriasis under TNFα are the imbalance of the key cytokines in the pathophysiological chain of the disease (TNFα, IFNα, IL12/23, IL17), the differences between the immunological properties of monoclonal antibodies and soluble TNFα receptor, as well as the change of the immunological profile from Th1 to Th2, with the consequent increase in antibody production (28,29).

Malignancy caused interruption of anti-TNF biologic therapy in two patients in the study (breast cancer: Adalimumab/ colon cancer: Etanercept), but it is difficult to interpret the contribution of biologic therapy in the etiopathogenesis of

these neoplasms (30)]. Prior to the biological treatment, no tumor markers were used to stratify the risk of patients treated with anti-TNF to develop a form of cancer. Studies do not indicate a clear correlation between anti-TNFα treatment and an increased risk of malignancy, which allows us to interpret the occurrence of these events independently of the biological therapy for psoriasis.

In conclusion, adherence is a complex process, which represents an important parameter in assessing the long-term effectiveness of biological therapy. Improved adhesion is based on the patient's transformation into an active co-participant to his/her own healing through an optimal communication with the treating physician, as well as on an easy way to carry out the treatment, on its safety and the application of pharmaco-vigilance principles.

Availability of data and materials

The data that support the findings of this study are available from the archives of the Railways University Hospital Iasi, (Iasi, Romania), but restrictions apply to the availability of these data which are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Railways University Hospital Iasi.

Author's contributions

MM, MPT, ER, TT contributed equally to acquisition, analysis and systematization of data, manuscript writing and critical revision of it for important intellectual content. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Ethics Committee of the Railways University Hospital Iasi (Iasi, Romania) approved the current study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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