ADVERSE REACTIONS OF BIOLOGICAL THERAPY FOR PSORIASIS

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ADVERSE REACTIONS OF BIOLOGICAL THERAPY FOR PSORIASIS (Abstract): Aim: To detect in patients with psoriasis the adverse effects during TNF-α inhibitor therapy. Material and methods: Fifty-seven patients with psoriasis, aged between 12 and 75 years were analyzed. They were treated with different TNF-α antagonists, the maximum treatment duration being 59 months. All patients were followed monthly after the initiation of therapy by clinical checkup, then every 3 months during the first 6 months of treatment by laboratory screening, and then every 6 month. Chest x-ray and tuberculin intradermal skin test were performed annually or as needed. All symptoms reported by patients were recorded, the treating doctor deciding the need for additional investigations or specialist consult. Results: Of the total of 57 patients with psoriasis on biological therapy, 9 patients developed diseases requiring temporary or permanent discontinuation of therapy. The recorded adverse reactions were: infectious (pulmonary tuberculosis, pulmonary empyema), oncologic (rectal cancer, renal cancer), dermatologic (vesiculobullous erythema multiforme major, nodular hypodermis, secondary erythroderma, and hives) disorders. Conclusions: Despite its adverse reactions, biological therapy is safe and is a necessary tool in the treatment of moderate and severe forms of psoriasis unresponsive to other treatments. Keywords: PSORIASIS, BIOLOGICAL THERAPY, ANTI-TNF-α.

Psoriasis is a chronic inflammatory disease, affecting the growth and differentiation of the epidermis, with polygenic predisposition and various trigger factors (infections, drugs, physical or emotional trauma, stress) (1, 2). Its prevalence ranges from 0.1 to 11.8% in Europe and the United States, with an average incidence of 2-2.5% and equal gender distribution (3, 4).

Biological therapy in dermatology represented an important step in treating chronic conditions with significant impact on patient quality of life. For the treatment of psoriasis there are already a number of molecules with favorable results, some approved for years, others new, of which we mention the anti-CD11a agents (efalizumab), anti-TNF-alpha agents (etanercept, adalimumab, infliximab), and IL-12/IL-23 antagonists (ustekinumab). The mechanism of action of these agents consists in specific blocking of certain steps in the cascade of molecular events involved in the pathogenesis of this complex disease. Being a
last generation therapy, trials to assess its side effects and compare the effects of these molecules are in progress, and their long-term safety is continuously assessed (3, 4).

MATERIAL AND METHODS
The study group included 57 patients with psoriasis, aged 12 to 75 years, most of them from rural areas (35 patient = 61.4%). They received different TNF alpha antagonists, the maximum treatment duration being 59 months. During treatment, 9 (15.78%) of the 57 patients developed adverse reactions. All patients were followed up monthly after the initiation of therapy by clinical checkup, then every 3 months during the first 6 months of treatment by laboratory screening (blood count, ESR, creatinine, SGOT, SGPT, urine test), and then every 6 months. Chest x-ray and tuberculin intradermal skin test (IDR) were performed annually or as needed, depending on patient complaints and findings of pneumology consultation. All symptoms reported by patients were recorded, the treating doctor deciding the need for additional investigations or specialist consults. The correct administration was rigorously followed no matter of the molecule recommended for treatment.

RESULTS
Of the total of 57 psoriasis patients on biological treatment, 9 (15.78%) patients developed diseases requiring temporary or permanent discontinuation of therapy. The recorded adverse reactions were: infectious (tuberculosis, pulmonary empyema), oncologic (cancer, rectal cancer, renal cancer), dermatologic (vesiculobullous erythema multiforme major, nodular hypodermitis, secondary erythroderma, hives).

Of these, 4 presented lung infections: 3 (5.26%) patients developed pulmonary tuberculosis, 1 (1.75%) patient on treatment with infliximab and another (1.75%) patient on adalimumab. Another (1.75%) patient was diagnosed with pulmonary tuberculosis after the switch from infliximab to adalimumab due to lack of efficiency. The fourth patient developed pulmonary empyema after therapy with etanercept (1.75%). The shortest interval between the initiation of biologic therapy and the occurrence of infectious complications was 3 months for infliximab, 5 months for etanercept, and the longest, 59 months, for adalimumab.

In the patient in whom the pathologically confirmed left secondary infiltrative nodular pulmonary occurred short time after the initiating biologic therapy with infliximab, i.e. three months, we suspect a poor screening, resulting in the reactivation of a latent form of tuberculosis. Before the lung disease was detected, treatment with infliximab resulted in a moderate decrease in PASI score (Psoriasis Area Severity Index) from 39.3 to 30.8. After 38 months, following triple TB treatment (isoniazid, rifampicin and pyrazinamide) and confirmation of clinical and bacteriological cure, a switch to adalimumab was initiated. The patient is still on adalimumab treatment, totaling 28 months.

The patient who after 22 months of infliximab treatment was switched to adalimumab due to lack of efficiency (initial PASI = 55.2, PASI at 22 months = 29.4, < 50% of baseline PASI) developed pulmonary tuberculosis 10 months after switching. Incriminated were the socioeconomic status, conditions, underweight, diet low in vitamins and nutrients, and poor rural area he lives in.
The patient on systemic treatment with adalimumab for 57 months, with an obviously favorable course of skin symptoms (PASI score at onset = 26.8, then it gradually decreased to 6.1 at 3 months, 1.2 at 6 months, reaching 0 after 12 months of treatment) was diagnosed with pulmonary tuberculosis, pathologically confirmed by bronchoscope biopsy. The onset form of skin disease was psoriasis vulgaris, but subsequently after applying a topical irritant (Swedish bitters) it turned into a generalized pustular psoriasis treated with long-term systemic corticosteroids. Disease-induced immunosuppression and exacerbated by prolonged systemic corticosteroids probably favored the occurrence of active tuberculosis.

In the study group, malignancies were recorded in 2 (3.50%) patients none of them with a family history of cancer. One of these 2 patients with psoriasis was treated with infliximab for 28 months and due to the lack of response reflected in PASI score = 18.2 (PASI score <50% of baseline PASI = 24.5) he was switched to adalimumab. The course of psoriasis lesions was favorable (PASI at 3 months = 12.4, at 6 months =1.2, and at 12 months =0). But, after 11 months of treatment with adalimumab the presence of a left renal tumor stage cT1bN0M0 was detected, and consequently adalimumab was discontinued. Left radical nephrectomy was performed and pathology findings confirmed the diagnosis.

The second patient was treated with adalimumab for 40 months, with a favorable course of skin lesions and psoriasis-related joint disease (PASI score decreased gradually from 24.2 at baseline to PASI = 8.1 at 3 months, PASI = 0.4 at 6 months, and PASI = 0), until because of fresh blood rectorrhages he was referred to the gastroenterology unit. Colonoscopy revealed a vegetant, friable tumor mass, 10-12 cm from the anus, for which the pathology diagnosis was of infiltrating, moderately differentiated adenocarcinoma. A Hartmann operation with mesorectal excision was performed, the final diagnosis being ampullary mid-rectal cancer.

Adverse dermatological reactions were reported in 4 (7.01%) patients. After 5 months of etanercept, 1 (1.75%) patient presented pleural empyema, so the treatment was discontinued. One month after the last etanercept administration the same patient developed nodular hypodermitis, diagnosis confirmed by pathological examination of skin biopsies. Immediately after this event, the patient received treatment with sulfasalazine for 1 year and for 54 months she is on therapy with adalimumab. After 24 months, due to the severity of joint lesions methotrexate 7.5 mg/week was added at the recommendation of a rheumatologist, with a slowly favorable course, without complete remission of skin lesions, in the context of an unfavorable family climate (husband with lower limb amputation, daughter's death). Initial PASI was 51.2, and decreased gradually during the 54 months to PASI = 4.3.

Another (1.75%) patient developed severe vesiculobullous erythema multiforme after 4 weeks of infliximab administration, namely after 2 injections of infliximab, which responded well to short-term average-dose systemic corticosteroids. After the remission of allergy episode the patient resumed the biologic treatment regimen for the treatment of psoriasis with a favorable outcome. After 4 months the patient decided to discontinue the treatment in view of conceiving a child, but the occurrence of
psoriasis lesions within the 16-week free interval required the introduction of a new biological treatment, namely adalimumab, followed for 59 months with a favorable course of psoriasis.

The other two (3.50%) patients, one on etanercept and the other one on infliximab, developed secondary erythroderma after 19 and 30 months, respectively. On therapy, PASI score had an undulating course in both cases, starting from PASI = 10.8 and PASI = 26.2, respectively, with a tendency to decrease and then increase due to lesion accentuation and extension. Additionally, the patient receiving infliximab also presented at the next infusion, after another two months, an episode of acute urticaria, resolved by the administration of antihistamines. In both cases, treatment was discontinued due to its lack of efficiency, PASI score reaching 26.2 and 52.6, respectively at last reassessment.

Three of the patients experiencing adverse reactions to the administered biologic therapies, namely the patient with pulmonary tuberculosis occurred after 3 months of infliximab, the patient with ampullary mid-rectal cancer and the patient with pleural empyema and nodular hypodermitis were also diagnosed with psoriatic arthropathy. These patients have an additional depression of their immune status due to the aggressiveness of the arthropathy disease itself.

In our patients the degree of immunosuppression differed, being higher in those who received treatment with methotrexate and general corticotherapy (patient with pulmonary tuberculosis after 57 months of adalimumab treatment), followed by therapy with methotrexate (therapy administered prior to biologic therapy in 6 of the 9 patients), less affected being the only patient on PUVA (Psoralen and ultraviolet A light) therapy prior to biologic therapy (who developed erythema multiforme after 2 infliximab infusions, subsequently switched to adalimumab).

**DISCUSSION**

Before the introduction of mandatory screening for active pulmonary tuberculosis, its rate was high during biologic therapies, accounting for 19/100,000 patients a year (5). Later, when all patients on biologic therapy were screened for tuberculosis, between 2002 and 2006 its incidence has decreased to 7 (5). In case of 100% compliance with the screening protocol tuberculosis rate decreased to 1.8 per 100,000 patients a year but increased to 13 if compliance was below 100% (5).

In our study group the screening for active pulmonary tuberculosis was performed in 100%. Of all 57 patients on biologic therapy, 25 underwent isoniazid chemoprophylaxis as recommended by the pulmonologist. None of the 3 patients who developed pulmonary tuberculosis required prophylactic medication according to the screening performed prior to the initiation of biologic therapy.

Most cases of tuberculosis on adalimumab treatment occurred during the first 8 months of treatment (6). In our study, 1 of the 57 patients developed tuberculosis after 57 months of treatment with adalimumab.

The literature (7) suggests an increased incidence of neoplasms among patients with psoriasis without biologic treatment, compared with the general population. Patients with psoriasis are at a 76% higher risk for developing skin cancer and a 82% higher risk for developing lymphoma compared to subjects in the control group.
(without psoriasis), with a statistically significant p value <0.001.

In patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease, malignancies, except lymphoma and non-melanoma skin cancer, have occurred at a rate of 0.6 per 100 patient-years versus a rate of 0.4 per 100 patient-years for placebo-treated patients. The mean treatment duration was 5.7 months for adalimumab and 5.5 months in the control group (7). In clinical trials (7), the most common cancers other than lymphoma and non-melanoma skin cancer were breast, colon, prostate, and lung cancers and melanoma. The incidence rate of these cancers is similar to that in general population.

Dermatological adverse reactions reported in the literature (6) were: cellulitis, erysipelas, cutaneous vasculitis, *erythema multiforme*, Stevens-Johnson syndrome, alopecia, worsening of psoriasis or occurrence of other forms of psoriasis in the same patient.

As to etanercept, new cases or reactivation of tuberculosis have been reported, including patients on treatment for latent or active tuberculosis. Studies suggest that the risk of latent tuberculosis reactivation is lower compared with therapy with TNF-alpha blocking monoclonal antibodies (8, 9). Tuberculosis was reported in approximately 0.01% of patients in trials globally. The risk of developing severe infections is higher in those on therapy associated with immunosuppressive drugs such as methotrexate, and patients older than 65 years. As to malignancies, it was found that in patients on treatment with etanercept the risk of developing lymphoma is about 3 times higher than in general population. Cases of acute or chronic leukemia (0.06 cases per 100 patient-years) *versus* 0 in the control group have been reported. Duration of controlled treatment ranged from 3 to 48 months (10). Sixty-seven malignancies other than lymphoma have been reported, among which the most common are colon, breast, lung, and prostate cancers. In patients with psoriasis, 22 of 1261 (1.74%) patients were diagnosed with cancer. Of these, 9 were non-cutaneous solid tumors, 12 non-melanoma tumors (8 basal cells, 5 squamous cells) and 1 patient had Hodgkin lymphoma. Among placebo-treated patients only one developed two squamous cell cancers (10). Of the cutaneous adverse reactions we mention: *lupus erythematosus*, cutaneous vasculitis (including leukocytoclastic vasculitis), *erythema multiforme*, Stevens-Johnson syndrome, Lyell syndrome, subcutaneous nodules, worsening or occurrence of a new type of psoriasis in the same patient (10).

As to infliximab, during clinical trials tuberculosis was reported in 14 patients, of whom four died. Most tuberculosis cases were diagnosed during the first 2 months after the initiation of infliximab therapy (11). In our study group, one patient developed tuberculosis 3 months after the initiation of therapy. Infliximab treatment was discontinued and after 3 years therapy with adalimumab was initiated, the patient still being on this treatment, with a favorable course for 26 months.

Cases of lymphoma, skin, breast, and colorectal cancer, leukemia, Sezary syndrome, Merkel cell carcinoma, hepatosplenic T-cell lymphoma (most often in patients treated with infliximab - 20 compared with one in patients on etanercept, and 2 on adalimumab) have been reported. The risk of developing lymphoma is 3 times higher in those treated with inflixi-
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mab compared to general population (12). The following cutaneous side effects have been reported: rash, which is the most common, followed in frequency of pruritus, cellulitis, ulceration, interstitial granulomatous dermatitis, furunculosis, psoriasiform rash, cutaneous vasculitis, erysipelas, atopic dermatitis, necrotizing fasciitis, bullous skin lesions, tinea corporis, varicelliform exanthema, palmoplantar pustulosis, atypical cutaneous leishmaniasis, alopecia areata, herpes labialis, cutaneous lymphomas, erythema multiforme, seen in patients with rheumatoid arthritis or Crohn's disease. In the interval August 1998 - August 2006, FDA (13) reported 21 severe skin reactions in patients treated with infliximab, of which 15 patients had erythema multiforme, 5 Stevens - Johnson syndrome and one case toxic epidermal necrolysis. The mean time to the occurrence of adverse reactions was 28 days after the first infusion, in this case exactly 4 weeks.

Studies comparing the effectiveness, safety and rate of side effects of these three molecules are useful. For example, Sallit et al. (8) in a recent retrospective study compared the infection rate in the same patients before and during treatment with TNF-alpha blockers. The infection rate after biologic treatment initiation was 34.5%, compared to 6.7% before treatment. Etanercept, adalimumab and infliximab were compared. The fewest infectious events were reported in patients on adalimumab (15.3% of patients), followed by etanercept (34.5%) and infliximab with the highest rate of infection (50.5 %). Instead, the rate of serious infections was lowest with etanercept (4%) (8). Other studies (9, 10) have also shown that the risk of developing certain infections is lower when using etanercept.

CONCLUSIONS

Despite the adverse reactions reported in this study, biologic therapy is safe and is a necessary tool in the treatment of moderate and severe psoriasis that do not respond to other therapies. Adverse reactions are usually very rare, but they must be quickly diagnosed and properly monitored. Systematic international reporting on adverse reactions to biologic therapy helps creating a clear image on the safety profile useful to the practitioner.

REFERENCES


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**NEWS**

**COMPARISON OF THE EFFECTIVENESS AND ANTIBIOTIC COST AMONG CEFTRIAXONE, ERTAPENEM, AND LEVOFLOXACIN IN TREATMENT OF COMMUNITY-ACQUIRED COMPLICATED URINARY TRACT INFECTIONS**

Most of urinary tract infections (UTIs) are uncomplicated for healthy young women that are easily managed with short-term antimicrobial therapy. Complicated UTIs (cUTIs) may occur in both sexes at all age groups and are frequently associated with anatomical or functional urinary tract deficiencies. This research has compared the treatment of urinary tract infections with ceftriaxone, ertapenem and levofloxacin. At the same time, in this study, it was analyzed the quality-price ratio of the three antibiotics. The primary outcome was the time to defervescence after admission and the secondary outcome was duration of hospital stay. The antibiotic cost was calculated as the sum of all antibiotic usage during hospital course. The study compared the clinical characteristics and antibiotic costs in patients with cUTIs receiving three different antibiotics. Compared to patients in the other two groups, ertapenem group had shorter time to defervescence since admission and shorter hospitalization stay. The antibiotic cost was significant lower in ceftriaxone group. This study is subject to several limitations regularly found in retrospective studies. A well-conducted prospective study may be necessary in the future to elucidate the differences in treating cUTIs among the three agents. In conclusion ETP, CRO, and LVX in the treatment of cUTIs had good clinical response. (Lin H-A, Yang Y-S, Wang J-X et al. Comparison of the effectiveness and antibiotic cost among ceftriaxone, ertapenem, and levofloxacin in treatment of community-acquired complicated urinary tract infections. *J Microbiol Immunol Infect*, 2015.

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