TREATMENT NON-ADHERENCE – A MAJOR FACTOR OF THERAPY FAILURE IN PATIENTS WITH SEVERE PSORIASIS

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Abstract: *Systemic immunosuppressive therapy and/or anti-TNF-α, anti IL 12-23, anti IL 17 biological treatments can improve the long-term prognosis of patients with moderate and severe forms of psoriasis. Forgoing such treatments may be due to side effects that can occur during the treatment process, as well as to patients' noncompliance and non-adherence to treatment. As such, a relapse of the psoriasis can occur - sometimes in even more severe forms than previously - as well other pathologies that are linked to treatment complications. We present the case of a patient with a severe form of psoriasis vulgaris and arthropathic psoriasis who, during disease evolution, received alternative systemic treatment with Methotrexate, Acitretin and Cyclosporine, as well as biological therapy with Infliximab. The evolution of the disease in this case can be described as fluctuating, due to either treatment noncompliance, or to medication related-side effects. Based on this clinical case, we have reviewed relevant literature sources documenting chronic treatment adherence, successes in psoriasis and the factors related to the patient or medication administered that influences the therapeutic success.*

INTRODUCTION

Psoriasis is a multifactorial chronic inflammatory disease in whose etiopathogenesis environmental, genetic, metabolic and immunological factors play an essential part. Approximately 2-3% of the world's population is affected by psoriasis.(1)

In the treatment of severe psoriasis, long-term systemic therapies are necessary in order to maintain control of the disease and prevent complications.

Adherence to topical therapy (the patient's voluntary decision to continue to take medication, rather than simply complying with medical prescriptions) is probably the determining factor in ensuring the effectiveness of a long-term treatment. The Heritage American Medical Dictionary distinguishes between adherence and compliance in the following way: adherence as the extent to which the patient continues the agreed-upon mode of treatment under limited supervision when faced with conflicting demands; compliance as the degree of consistency and accuracy with which a patient follows a prescribed regimen.(2)

Some researchers believe that compliance (where the patient acts according to the medical advice of the prescribing physician) reveals a paternalistic attitude towards the patient and therefore it should not be used. For this reason, they introduce the idea of concordance, meaning that the patient and doctor should jointly agree on the regimen that the patient will follow.

The most commonly used term, however, is adherence, which, according to the Oxford English Dictionary is defined as "persistence in a practice or tenet; steady observance or maintenance", a definition that adequately evokes the tenacity that patients need to adhere to and to maintain a regimen.(2)

Treatment noncompliance and non-adherence is the patient's failure, intentionally or unintentionally, to observe and implement therapeutic recommendations in terms of quality or quantity. This (in this case, relevant to the psoriasis) leads to a compromised therapeutic outcome, disease exacerbations (relapses, erythrodermias, complications (systemic, articular, metabolic damage), with an overall decreased quality of life and, by association, high socio-economic costs.

Treatment noncompliance can be reduced by involving the patient in planning the treatment and by providing instructions alongside complete and clear information on the therapeutic regimen.

In light of these data, we present the case of a patient with psoriasis vulgaris and arthropathic psoriasis, who repeatedly did not adhere to the recommended treatments, and as a result experienced severe relapses of the psoriasis as well as secondary complications.

CASE REPORT

A 49-year old patient, who had been diagnosed with psoriasis vulgaris for 22 years and with arthropathic psoriasis for 10 years, and whose associative symptoms included hypertension, grand mal seizure and depressive syndrome, was hospitalized in the Dermatology Clinic of Sibiu with a generalized erythematous-squamous infiltrative rash, with flexural cracks and ulcerations following scratching on legs and arms, polyarthralgias, moderate ankle swelling, low grade fever, interphalangeal joints swelling of toe 2, left hand, and coughing up mucous in small quantities.

The patient's disease history revealed that since his psoriasis' onset in 1994, he had been following various systemic therapies, but which had been regularly interrupted due to treatment noncompliance, the occurrence of severe infections or due to poor response to the treatment. Initially, he had followed a systemic treatment with Methotrexate over a period of six months, but which was interrupted by infectious complications (pneumonia). Subsequently, the psoriasis was aggravated, evolving towards a generalization of the eruption and erythrodermia. The lung infection was treated and the treatment with topical corticosteroid and exposure to natural UV radiation continued, with a relative good evolution for a period of 6 years.

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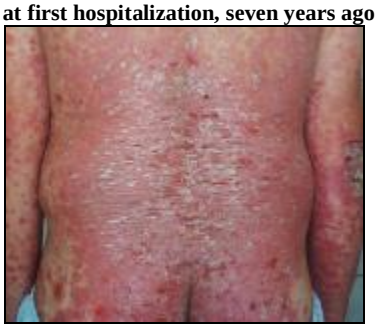
In 2009, he was hospitalized for a new erythrodermic episode (figure no.1) which was controlled by the administration of Acitretin 0.5mg/kgc/day, with a gradual decrease of the dose. 10 months later, the psoriasis became non-responsive to the treatment with Acitretin. Given the severity and extent of the patient's lesions (without being erythrodermic), a treatment with Infliximab 400mg in endovenous perfusion every 2 months was initiated, to which therapeutic response was very good, achieving PASI 75. After 3 years of anti TNF-α biological therapy, well tolerated and with good clinical response, with PASI > 50 3 years later, the patient decided to discontinue it on his own initiative, without retuning for follow-ups.

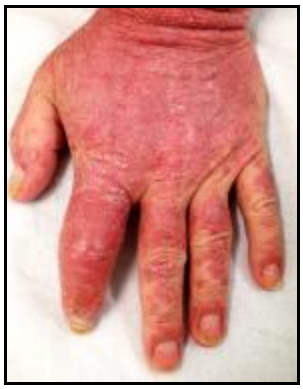
Figure no. 1. Generalized erythematous-squamous infiltrative rash at first hospitalization, seven years ago



In 2013, the psoriasis flared up again, prompting the patient to follow a treatment with Cyclosporine. This process was dermatologically monitored for 6 months. Subsequently, the patient continued to follow the treatment with Cyclosporine (on his own initiative, without medical supervision) for 2 years until a severe Enterobacter pneumonia, conjunctivitis and otitis media with SAH led to the interruption of the administration of Cyclosporine at the physician's recommendation.

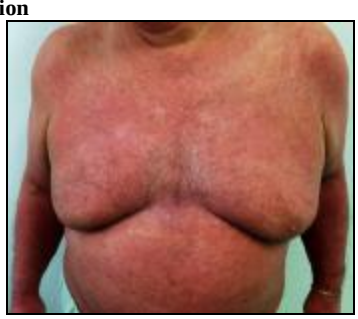
The general clinical examination upon admission revealed an altered general condition, low grade fever (37.4°C), chills, BMI 40.83 kg/m^2, hypotonic, hypokinetic muscular system, gynecomastia, pain upon spinal percussion test, arthralgia at knee and tibiotarsal bilateral joints level, swelling and stiffness in the left hand, toe II interphalangeal joint (figure no. 2), emphysematous chest with vesicular murmur enhanced on both lung fields, 160/100 mmHg blood pressure, liver 3 cm below the costal margin with rounded edge and organ consistency.

Figure no. 2. Dactylitis in toe 2, left hand - current hospitalization



A local exam revealed generalized erythemato-squamous infiltrating plaques (figure no. 3), covered by pearly-white, layered, abundant micaceous squamae, including at the scalp level, with positive spermaceti sign and positive Auspitz sign. There were flexural cracks and multiple ulcerations as a result of scratches on upper and lower limbs. Nail pitting, subungual hyperkeratosis and salmon patches were typical manifestations for nail psoriasis.

Figure no. 3. Erythrodermic eruption - the current hospitalization



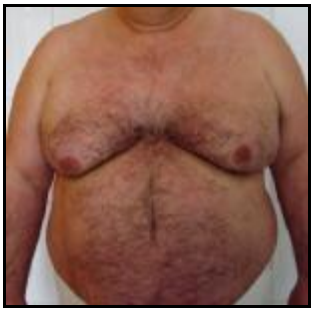
Laboratory investigations later revealed a biological inflammatory syndrome (ESR 81 mm/h, fibrinogen 486.8 mg/dl, CRP 24 U/L), leukocytosis and neutrophilia (L 10.500/uL, N 83.6%), anemic syndrome with reactive thrombocytosis (RBC 3.150.00/uL, Hb 9.2 g/dL HCT 28.1%, normal morphology, PLT 476.000/mm^3), hyperglycemia (Glucose 143 mg/dL) and SAH in nasal and conjunctival secretion. A radiography and CT of the chest excluded any scenarios involving congestive processes or tumour proliferation, while a TB skin test and QuantiFERON ruled out any TB infection.

After cleaning the infection sites with Ceftazidime, local corticosteroids treatment and emollients, the patient resumed treatment with Methotrexate 15mg/week and Folic acid 5mg/week, which led to a favourable evolution of the psoriasis.

One year after having resumed the systemic treatment with Methotrexate and local treatment with topical emollients, joints inflammation had wholly subsided (figure no. 4) and skin lesions were entirely absent (figure no. 5).

Figure no. 4. Interphalangeal joint remaining swelling in toe II, painless, without skin manifestations, 1 year after treatment with Methotrexate + Folic acid

Figure no. 5. Remission of lesions 1 year after treatment with Methotrexate + Folic acid



DISCUSSIONS

Low levels of compliance by patients to the recommended treatment in chronic diseases, such as psoriasis, represent a significant difficulty in administering successful dermatological treatments. Richards et al. suggest that the rate of noncompliance to a treatment regimen in psoriasis is of 39%. It has been found that the noncompliant group reported a higher self-rated severity of the psoriasis, particularly in younger patients who had suffered an onset of the disease at a younger age than the compliant group. Also, in the noncompliant group, psoriasis had a greater impact on daily life, but the quality of life was not significantly different from those that were compliant to treatment.(3)

Medication adherence is recognized as an important issue in the management of psoriasis. A meta-analysis reveals that 22 studies conducted between 1980 and 2011 were aimed at treatment adherence in psoriasis. Nine of them were aimed at the frequent application of topical treatment. Of these, five studies showed that the frequency of applications ranged between 50% and 60% of that which had been predicted. A controlled, randomized study on the frequency of the application of topical treatment reported an adherence rate ranging between 55% and 100%. In terms of the amount of the product used, 35% up to 72% of patients used the recommended dosage during a treatment period that lasted between 14 days and 8 weeks. The most commonly cited reasons for not adhering to the topical treatment were low efficiency, time consumption and poor cosmetic characteristics of the topical agents. Patients who experienced adherence problems were younger, mostly male, who had had an early onset of the psoriasis and a higher self-assessed severity of the disease. To improve treatment adherence, the following strategies were suggested: providing patients with clear information about psoriasis, recognising the social impact of the disease, providing written instructions for applications, explaining the possible side effects of the topical therapy, choosing the appropriate treatment and cosmetic properties of topical agents in agreement with the patient.(4)

The PSOLAR study followed the rate of severe infections in a total of 12,095 patients with psoriasis who were treated with biological therapies. The cumulative rate of serious infections were 1.50/100 per year. The rates of serious infections for Infliximab (2.78/100 per year) were numerically higher than those for Ustekinumab (0.95/100 per year).(5)

A meta-analysis of 820 studies counting a total of 6810 patients with psoriasis vulgaris and psoriatic arthritis who had undergone anti-TNF therapy (Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumab) analyzed the risk of severe infections. The probability of occurrence of the total infections and severe infections for an average treatment period of time of 17.8 weeks was 1.18.(6)

There was a slight increase in the risk of infections associated with short-term use of anti-TNF therapy in the treatment of psoriasis, which can be attributed to the difference in follow-up time between the treatment group and the placebo group. There was no statistically significant evidence of an increased risk of serious infections or of an increased risk of cancer associated with the short-term use of TNF inhibitors.(6)

Powers et al. analyzed the risk of severe infections associated with treatment with Methotrexate and found no significant increases in the risk of infections, neither in patients with psoriasis nor in patients with psoriatic arthritis.(7)

In our case, infectious complications (pneumonia) occurred during the treatment with Methotrexate even when the patient was monitored properly. Another lung infection occurred when the patient continue to follow an immunosuppressive treatment with Cyclosporine for a further 2 years, without medical supervision and on his own initiative.

With regard to the involvement of streptococcal infections in the exacerbation of psoriasis, especially in the guttate form, a study conducted on comparative groups - i.e. psoriasis/control groups - showed that patients with psoriasis had reported neck pains significantly more often than the controls (61 of 208 vs 3 of 116). Also, β-hemolytic streptococci of Lancefield groups A, C, and G (M protein-positive streptococci) were isolated more frequently in the throat swab cultures of patients with psoriasis than in controls (19 of 208 vs. 1 of 116).(8)

Several studies have confirmed that the evolution of psoriasis is exacerbated by the presence of different strains of bacteria or their toxins. A study published by Noorbakhsh et. al isolated SAH 25 times more frequently in patients with psoriasis. Toxic shock syndrome toxin (TSST) was detected in 47% (20/41) of the cases, as opposed to 6% (1/28) of the controls, marking a significant difference.(9)

In our case, the identified infectious factor (SAH in nasal and conjunctival secretion) aggravated the eruption of psoriasis and led to a discontinuation of the immunosuppressive therapy with Cyclosporine.

The adipose tissue is an important source of pro-inflpieammatory substances (adipokines (leptin, visfatin, resistin), IL-6, TNF-α and IL-8) and substances with anti-inflammatory effects (adiponectin).(10) It is recognised that Visfatin plays a significant role in chronic inflammationm while also contributing to the process of atherosclerosis, and increasing the cardiovascular risk.(11,12) An imbalance of adiponectin levels (low) and IL-6 (high) occurs in patients manifesting both psoriasis and obesity.(13)

In cases of obesity there exists a certain degree of adipocyte inflammation, characterised by the production of adipokines, that plays an important role in chronic inflammation.(14)

In our case, psoriasis was associated with class IV obesity and type 2 diabetes.

Regarding the association of psoriasis and obesity, an observational study by MEDLINE, EMBASE and the Cochrane Central Register identified 16 trials with 2.1 million participants in between 1980 and 2012, of whom 201,831 were patients with psoriasis. Using random effects of meta-analysis, the odds-ratio report for obesity among patients with psoriasis was 1.66 when compared to those without psoriasis. Among the studies that reported psoriasis severity, odds-ratio for obesity among patients with mild psoriasis was 1.46, while for patients with severe psoriasis, the figure was at 2.23. One study found that patients with psoriasis had a higher risk of 1.18 for new-onset obesity.(15)

A population study conducted on 34,781 Danish twins in whom the degree of association between psoriasis, diabetes and obesity was followed revealed that the prevalence of psoriasis in the sample of twins was of 4.2%, while the prevalence of diabetes was of 1.4%. Psoriasis prevalence in the patients with diabetes was 7.6% vs 4.1% in patients without diabetes, thus highlighting the existence of a significant association between psoriasis and type 2 diabetes.(16)

CONCLUSIONS

In our case, the treatment of the psoriatic disease was difficult, both because of the side effects that resulted from the systemic immunosuppressive therapies (Enterobacter pneumonia, rhinitis and pharyngitis with SAH) and because of the patient's non-adherence to the suggested biological immunosuppressive therapy. Other relevant factors which contributed to the worsening of the psoriasis were endocrine and

metabolic disorders (obesity, diabetes), associated cardio-vascular diseases (hypertension) and the existence of a mental illness (depressive syndrome).

The pervasiveness of these factors in a non-compliant patient who consults the doctor irregularly - particularly during periods of acute exacerbation of the disease - was ultimately reflected in the long-term management capabilities of the disease.

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