

## PARADOXICAL ADVERSE REACTIONS TO ANTI-TNF $\alpha$ THERAPY IN PSORIASIS

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### Summary

#### Introduction

Biological therapy with anti-TNF $\alpha$  agents used in the treatment of psoriasis as well as other immunologically mediated pathologies has become a common therapeutic option that offers certain therapeutic benefits but is not without adverse reactions. The paradoxical ones are signs and symptoms that occur during therapy with biological agents similar to those under the pathological conditions that constitute an indication for biological therapy. The overall incidence as well as the etiopathogenic mechanism underlying these reactions are still unclear.

#### Material and method

We will present a female patient with psoriasis vulgaris and seronegative rheumatoid arthritis, who followed a treatment with an anti-TNF $\alpha$  biological agent for 3 years, with favourable therapeutic effect until the recurrence of severe skin lesions and an exacerbated osteo-articular algic syndrome, manifestations considered in this context as paradoxical adverse reactions to the anti-TNF $\alpha$  therapy.

#### Discussions and conclusions

Paradoxical adverse reactions (PAR) are rare and unusual during anti-TNF $\alpha$  therapy and are not limited to agents in this class. Their management is a challenge, and prognosis depends on severity and accessibility to therapeutic alternatives.

**Key words:** anti-TNF $\alpha$  agents, paradoxical adverse reactions, psoriasis, therapeutic alternatives.

Received: 10.12.2018

Accepted: 7.02.2019

### Introduction

The use of biological therapy in many autoimmune diseases has led to radical changes in the view regarding the treatment and evolution of these pathologies. Anti-TNF $\alpha$  agents have proven effective in immune-mediated skin diseases (psoriasis, hidradenitis suppurativa), rheumatic diseases (rheumatoid polyarthritis, spondyloarthritis) or gastrointestinal diseases (Crohn's disease, ulcerative colitis) (1,2). The clinical experience accumulated during over 15 years of biological therapy in dermatology has allowed the accumulation of important pharmacovigilance data, so that local and systemic adverse reactions

are known. Rarer and less known are the paradoxical adverse effects, as well as the appearance de novo or the changes in the pattern of the psoriasis lesions, the worsening of symptoms in known patients, who have associated psoriatic arthritis or not, the installation of signs of uveitis, scleritis, sarcoidosis, granuloma annulare, vasculitis, vitiligo or alopecia areata (3,4). Paradoxical psoriasis occurs in approximately 5% of patients treated with anti-TNF $\alpha$  agents, mostly females (5).

Real paradoxical adverse reactions (PAR) are immunologically-mediated pathological conditions arising during biological therapy and usually respond to the treatment with the triggering biological agent. The emergence

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mechanisms of these reactions and their incidence are not yet fully known (6, 7) .

These anti-TNF $\alpha$  responses should be known and monitored, patients currently benefiting from alternatives to biological therapy.

## Material and method

We present the case of a female patient aged 55 years, diagnosed with psoriasis in 2002 and seronegative rheumatoid arthritis in 2005, with a history of pathologic stage 2 hypertension, type 2 diabetes and fatty liver who was consulted in our department in 2012 for a severe eruption of psoriasis vulgaris.

As an eligible case for biological therapy (PASI-21, DLQI-17, history of systemic therapy with Methotrexate 20mg/week, per os, from 2005 with partial results), in January 2013, she was recommended a treatment with Remicade i.v. 5 mg/kg at 8 weeks, while maintaining the Methotrexate therapy on recommendation of the rheumatologist.

For three years, the efficacy parameters of the biological therapy were within the limits allowed by the protocol, but at the re-evaluation in November 2017, the patient had a PASI-19.2 score, DLQI-15 and exacerbated osteo-articular algic syndrome. The newly emerged lesions were placed in erythematous-squamous plates and plaques, with an ostraceous appearance, infiltrative, intensely itchy, with significant expansion in the territory of the thorax (anterior/posterior), upper limbs (arms/lower arms/elbows) and lower limbs (hips/legs/knees), including in the palmar-plantar regions. Considering the severity of the clinical picture, it was decided to discontinue the biological therapy and continue the treatment with Methotrexate 20mg/week in combination with NB-UVB phototherapy.

In March 2018 the patient is re-admitted for clinical and biological balance, the value of the PASI score being 20.8. The ophthalmological consultation detects a cataract attributed to Infliximab therapy. It is decided to associate Neotigason, 30mg/day, and six weeks after the initiation of retinoid therapy, there is ascertained the stagnation of skin lesions and the persistence of osteo-articular algic syndrome. The case meets

the diagnostic criteria of paradoxical psoriasis triggered during anti-TNF $\alpha$  therapy.

## Discussions

Biological agents are the modern option for the treatment of many chronic inflammatory diseases, and their use has become increasingly common, including in dermatological clinical practice, psoriasis vulgaris being one of their indications. The mechanism of action targets key points in the etiopathogenic chain of the disease, the therapeutic efficacy being demonstrated in forms of moderate and severe psoriasis vulgaris, whether or not accompanied by psoriatic arthritis. Currently, biological agents primarily target selective inhibition of activity of TNF $\alpha$  factor, interleukin-12/23 and interleukin 17 (8, 9).

Despite the stable safety profile and the targeted mechanism of action, biological therapy does not lack predictable adverse effects. Clinical experience also demonstrates possible paradoxical reactions. These consist in the emergence of new pathological manifestations or the exacerbation of the background disease during treatment with biological agents, manifestations that should favourably respond to this class of drugs. There are two major categories of PARs, the real (authentic) one represented by diseases where anti-TNF $\alpha$  biological agents have been shown to be efficacious (de novo/aggravated psoriasis, Chron's disease, hidradenitis suppurativa) and the borderline one – immunologically-mediated conditions that can be observed during biological therapy but which cannot be treated (uveitis, scleritis, sarcoidosis, granuloma annulare, vasculitis, vitiligo, alopecia areata) (10,11).

Paradoxical adverse reactions have been described primarily in patients treated with anti-TNF $\alpha$  agents, as is the case presented in this paper. The emergence of new psoriasis lesions as well as the exacerbation of pre-existing psoriasis lesions is part of the clinical picture of PARs (12). The pathophysiological mechanism of these PARs is partially elucidated due to the polymorphism of the complex individual immunological manifestations and profiles of the patients to whom biological therapy is addressed. The pathophysiological hypotheses that attempt to explain the occurrence of PAR are mainly the



*Fig. 1. Paradoxical adverse reaction (November 2017)*



*Fig. 2. May 2018 reevaluation*

imbalance of the key cytokines in the pathophysiological chain of the disease (TNF $\alpha$ , IFN $\alpha$ , IL12/23, IL17), the differences between the immunological properties of monoclonal antibodies and soluble TNF $\alpha$  receptor, as well as the change of the immunological profile from Th1 to Th2, with the consequent increase in antibody production (13).

Paradoxical psoriasis occurs more frequently in patients with rheumatoid arthritis undergoing biological treatment. Statistically, the British Rheumatology Register (BSRBR), shows that the incidence rate of paradoxical psoriasis in the rheumatoid arthritis population treated with biological therapy is 1.04/1,000 patients-years compared to the rheumatoid arthritis population without biological treatment, where the rate was close to zero. The Spanish Register of Biological Therapies (BIOBADASER) reveals a rate of global incidence of paradoxical psoriasis in patients under biological treatment of 2.31/1,000 patients-years (14, 15). Therefore, there are concrete statistical data supporting the hypothesis of occurrence of paradoxical psoriasis in patients treated with biological agents compared to those not included in such a protocol.

The case presented may be considered an example of paradoxical reactivity to anti-TNF $\alpha$  therapy in the context of the underlying articular disease treated for long periods with methotrexate. In rheumatoid arthritis, TNF- $\alpha$  inhibition induces the predominant migration of Th1 lymphocytes in circulation and a low traffic to synovial cells inflamed by the rheumatic disease and the concentration of T cells in the skin (cell homing) (16).

The management of paradoxical psoriasis varies according to the severity of cutaneous lesions in terms of intensity, enlargement, discomfort created for the patient. After some data, prognosis is generally favourable and the onset of clinical expression of PARs does not always require interruption of the biological agent, especially in cases where the background disease is controlled and the new lesions are mild

and tolerable. In this situation only specific topical treatment is recommended. Studies show that despite the continuation of biological therapy, total lesion resolution may occur in 32.9% of cases or partial improvement in 57.3% of patients. The safety of the remittance of lesions is nonetheless given by the interruption of the biological treatment in a significant percentage of cases (47.7%) (17).

The severity of the paradoxical reaction in the case presented required the cessation of anti-TNF $\alpha$  treatment and the initiation of another systemic immunosuppressive regimen, NB-UVB phototherapy, which was associated with a retinoid after 4 months, with partial clinical effects at both skin and osteo-articular level. It has been decided to switch to another biological agent belonging to the class of IL-17 inhibitors.

## Conclusions

The biological therapy with anti-TNF $\alpha$  agents is currently the therapeutic pillar of moderately-severe psoriasis vulgaris and psoriatic arthritis. Although it has a demonstrated therapeutic efficacy and an optimal pharmacological safety profile, the risk of occurrence of common and paradoxical adverse reactions should not be neglected. Paradoxical adverse reactions are rare and unusual during anti-TNF $\alpha$  therapy and are not limited to agents in this class. The accuracy of their diagnosis and management are the key points for the subsequent development of background disease. The prognosis and therapeutic attitude are closely correlated with the severity of the lesions, the particularities of the case, as well as the accessibility to therapeutic alternatives.

The case presented above is an example of a severe paradoxical reaction occurring after a prolonged period of treatment with an anti-TNF $\alpha$  agent accompanied by a borderline adverse reaction (cataract) and underlines the importance of pharmacovigilance measures during biotherapy.

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Conflict of interest  
NONE DECLARED

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