Actas Dermosifiliogr. 2014;105(8):752–761

ACTAS Dermo-Sifiliográficas

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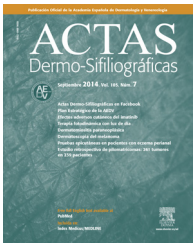

PRACTICAL DERMATOLOGY

Clinical Management of Paradoxical Psoriasiform Reactions During TNF-α Therapy☆

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Received 31 December 2012; accepted 25 May 2013
Available online 4 September 2014

KEYWORDS
Psoriasis;
Palmoplantar pustulosis;
Guttate psoriasis;
Erythrodermia;
Tumor necrosis factor;
Psoriasiform reactions;
Adverse effects;
Induced psoriasis

Abstract There have been reports of paradoxical induction or worsening of psoriasis during treatment with tumor necrosis factor (TNF) α agents (infliximab, etanercept, adalimumab, and certolizumab). It has been hypothesized that an imbalance between TNF-α and interferon α might have a role in the etiology and pathogenesis of these reactions. Paradoxical psoriasiform reactions can be divided clinically into de novo psoriasis and exacerbation of preexisting psoriasis. The first, which is more common and more extensively described in the literature, occurs in patients without a history of psoriasis who are receiving TNF-α therapy for another inflammatory disorder. The second can occur with or without changes in the morphology of the lesions. In this article, we review the literature on the clinical and histologic features of paradoxical psoriasiform reactions, analyze their clinical course and treatment, and propose a clinical management model for use in routine practice.

PALABRAS CLAVE
Psoriasis;
Pustulosis palmoplantar;
Psoriasis guttata;
Eritrodermia;
Factor de necrosis tumoral;
Reacciones psoriasiformes;
Efectos adversos;
Psoriasis inducida

Reacciones psoriasiformes paradójicas durante el tratamiento con terapia anti-factor de necrosis tumoral. Manejo clínico

Resumen Paradójicamente se han descrito casos de inducción o empeoramiento de una psoriasis durante el tratamiento con todos los agentes anti-factor de necrosis tumoral α (anti-TNFα) (infliximab, etanercept, adalimumab y certolizumab). Se ha postulado que la alteración del equilibrio entre el TNFα y el interferón α estaría implicada en su etiopatogenia. Clínicamente se distinguen varios patrones de reacciones psoriasiformes paradójicas: la psoriasis *de novo* en pacientes que no han presentado anteriormente esta enfermedad y que reciben este tratamiento por otra enfermedad inflamatoria, que es la más frecuente y la mejor descrita, y la exacerbación de una psoriasis preexistente durante la terapia anti-TNFα, que puede presentarse con o sin un cambio de morfología. En este trabajo realizamos una revisión de la literatura

☆ Please cite this article as: Navarro R, Daudén E. Reacciones psoriasiformes paradójicas durante el tratamiento con terapia anti-factor de necrosis tumoral. Manejo clínico. Actas Dermosifiliogr. 2014;105:752–761.
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1578-2190/$ - see front matter

en relación con las características clínicas e histológicas de este tipo de reacciones, así como de su evolución y tratamiento, y planteamos un esquema de manejo en la práctica clínica.

Introduction

Psoriasis, a chronic inflammatory disease of unknown etiology, affects approximately 2% to 3% of the population worldwide.[1] It has been speculated that it could be the result of a combination of genetic and environmental factors; a genetic predisposition does exist, but it has not been possible to establish a classic Mendelian pattern of inheritance.

Numerous factors that trigger the onset of psoriasis or aggravate established psoriasis have been described, including infections, stress, and drugs (β-blockers, lithium, . . .).[1,2]

Several hypotheses and models have been proposed to try to explain the pathogenesis of psoriasis; these have led us to look not only at the skin, but also at the multiple associated comorbid conditions, such as psoriatic arthritis and cardiovascular disease.[3,4] A unifying hypothesis is the model of the cytokine network, which states that both external stimuli, such as stress, and endogenous ones, such as viruses, neuropeptides, or drug ingestion, can act as triggers that activate a cytokine cascade. These cytokines include tumor necrosis factor (TNF) α, derived from antigen-presenting dendritic cells and keratinocytes, and interferon (IFN) γ produced by activated type 1 helper T cells.[1]

Around 90% of individuals with psoriasis have the most common form, the so-called plaque psoriasis or psoriasis vulgaris. In the majority of cases, the disease is mild and can be controlled with topical therapy. However, up to a third of patients develop moderate or severe psoriasis and require systemic therapy, such as phototherapy, acitretin, methotrexate, or ciclosporin.[5] The toxicity of these drugs and the frequent lack of response to them has led to the appearance over the past 15 years of the so-called biologic therapies, which act at different levels of the inflammatory cascade that gives rise to the plaques of psoriasis.

The use of biologic therapy is increasing worldwide for the treatment not only of psoriasis, but also of other chronic immune-mediated inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease. At the present time, the most widely employed drugs are those that inhibit TNF-α (infliximab, etanercept, and adalimumab), though a number of side effects have been reported during their use, including infections, reactivation of latent tuberculosis, demyelinating diseases, and congestive heart failure.[6–8]

It has been reported that the cutaneous side effects of anti-TNF-α therapy are more prevalent than was previously thought.[9] These effects include reactions at the site of infusion or injection, skin infections, eczema, and even psoriasis or psoriasiform reactions.[10] Though paradoxical (as these drugs are of demonstrated efficacy in the treatment of psoriasis[11–17]), case reports and some case series describe patients with exacerbations of their psoriasis or even the new onset of distinct subtypes of psoriasis during anti-TNF-α therapy.[9,10,18–73] The most relevant articles and reviews are summarized in Tables 1 and 2.

Moustou et al.[10] published a literature review in which they established the strength of the association between published side effects and the use of 1 or more anti-TNF-α agents, classifying the association as poor, moderate, strong, or definitive. The authors used descriptions of the side effects in meta-analyses, randomized trials, retrospective or prospective studies, case series, and case reports. They analyzed the number of anti-TNF-α agents implicated, the number of distinct inflammatory diseases in which the side effect had occurred during treatment with anti-TNF-α drugs, and the clinical course after withdrawal and reintroduction of the drug. The authors not only described the clinical manifestations of these cutaneous reactions, but they also established that there was a strong relationship between anti-TNF-α therapy and new onset psoriasis or psoriasiform reactions.

Classification

Distinct patterns of paradoxical psoriasiform reactions can be distinguished during treatment with TNF-α-inhibitors (Fig. 1):

- The induction of new onset psoriasis, which is the appearance of psoriasis lesions in patients who have not previously been diagnosed with this disease and who are receiving anti-TNF-α treatment for another inflammatory disease.
- An exacerbation of pre-existing psoriasis, with or without morphologic differences, during anti-TNF-α therapy.

Pathogenesis of Psoriasiform Reactions

The pathophysiology of the induction or exacerbation of psoriasis during treatment with TNF-α inhibitors is still unknown. A number of theories have been proposed, such as a disruption of the balance between TNF-α and IFN-α, activation of self-reactive T lymphocytes, wrong diagnosis, natural course of the primary disease, or infections that trigger such reactions.[9,10,25,37] In their article on the pathogenesis of psoriasiform reactions, Collamer et al.[25] explained that a disruption of cytokine balance could lead to increased IFN-α production by dendritic cells in genetically predisposed individuals, and that genetic polymorphisms could play a role in this paradoxical reaction secondary to TNF-α blockade.

De Gannes et al.,[52] in an article published in 2007, demonstrated that patients who developed new onset psoriasis during treatment with anti-TNF-α agents presented