

# Psoriasis Induced by Anti-Tumor Necrosis Factor Alpha Agents: A Comprehensive Review of the Literature

**Fedra Ciccarelli, Massimo De Martinis, Maria Maddalena Sirufo, Lia Ginaldi**

Allergy and Clinical Immunology Unit, Department of Life, Health & Environmental Sciences, University of L'Aquila, L'Aquila, Italy

## Corresponding author:

Prof. Massimo De Martinis, MD  
Department of Life, Health  
& Environmental Sciences  
University of L'Aquila  
L'Aquila  
Italy  
[demartinis@cc.univaq.it](mailto:demartinis@cc.univaq.it)

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**ABSTRACT** Tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors revolutionized the management of patients affected by autoimmune diseases such as inflammatory bowel diseases, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis. The biologic agents targeted to block TNF- $\alpha$  such as infliximab, adalimumab, certulizumab pegol, etanercept, and golimumab, have a good safety profile; however, with increasing, broader, and prolonged use, patients could be exposed to an increased risk of adverse reactions including a wide spectrum of dermatological conditions of different etiology and morphology. Among these, of particular interest is the development of skin immune-mediated diseases that seem to be the consequence of the paradoxical inflammation induced by anti-TNF- $\alpha$  therapy. The majority of these lesions are identified as psoriasiform with three main morphologies and different frequency: pustular psoriasis, signs of psoriasis, and guttate; although erythrodermic or inverted psoriasis, among others, may be observed with less frequency. The increased incidence of these dermatological immune-mediated lesions highlight the importance of the skin as a main target of the side effect of anti-TNF- $\alpha$  agents, while the immunopathogenetic hypothesis of these paradoxical effects are quite intriguing. The aim of this review is to collect and to analyze existing knowledge to better understand the pathogenetic mechanism of these complications and suggest new fields of investigation, improve therapeutic strategies of autoimmune diseases, and prevent and/or better address such complications.

**KEY WORDS:** anti-TNF- $\alpha$  therapy; autoimmune diseases; pustular psoriasis; psoriasis; arthritis; biologic therapy; tumor necrosis factor; translational medicine; translational immunology

## INTRODUCTION

Since the late 1990s, the therapeutic approach to rheumatologic conditions, such as rheumatoid arthritis and seronegative arthritis, has changed dramatically with the introduction of biological therapies such as tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors (1,2). Over the years, numerous publications have demonstrated their efficacy against chronic inflammatory diseases and their relative safety, and consequently

the use of anti-TNF- $\alpha$  agents in patients with several immune-mediated inflammatory diseases, not only in the field of rheumatology, is increasing (3). Nevertheless, in parallel with their spread, rising numbers of pharmacological monitoring reports have described their association with unusual reactions, namely the *de novo* development or flaring of conditions that usually respond to these therapeutic agents,

including psoriasiform eruption. Due to the astonishing nature of this induced dermopathy, as TNF- $\alpha$  inhibitors are also largely and successfully used in the treatment of psoriasis, the term paradoxical psoriasis has been coined (4).

## OVERVIEW

In 2004, the first case of anti-TNF- $\alpha$  agent (infliximab) induced psoriatic lesions was described in a patient with Crohn's disease (5). A few months later, the British Journal of Dermatology reported two unusual cases of cutaneous psoriatic lesions appearing in patients with rheumatoid arthritis treated with TNF- $\alpha$  inhibitors (in one case etanercept and in the other infliximab) (6). Afterwards, the British Society for Rheumatology Biologics Registry notified, from the beginning (January 2001) until the end of the observation (July 2007), 25 cases among a group of 9826 patients who developed new onset of psoriasis as a consequence of anti-TNF- $\alpha$  treatment. In the comparison group of 2880 patients treated with the traditional disease-modifying antirheumatic drugs (DMARDs), none developed psoriasis during the same observation period. This prospective study also detected a higher incidence of paradoxical reactions in patients treated with adalimumab (7). However, the latter has not been confirmed in subsequent studies. In the meantime, Wollina *et al.* (8) reported 116 patients from the literature plus six new patients (three men and three women) who developed psoriatic skin lesions during treatment with anti-TNF- $\alpha$  agents. Subsequently, Collamer and Battafarano (9) reported 207 cases of psoriasis induced by TNF $\alpha$  inhibitors until August 2009, while at almost the same time a French study (10) found 57 cases in the National Pharmacovigilance Database. More recently, Shmidt *et al.* (11) reviewed 56 additional cases from the Mayo Clinic between January 1998 and July 2010 and determined the prevalence of plaques (48% of cases) and palmoplantar pustulosis (45%). Lately, with the increased use of anti-TNF- $\alpha$  in the treatment of inflammatory bowel diseases, two studies (12,13) evaluated the induction of psoriasis by anti-TNF- $\alpha$  agents in these patients, and several case reports have been published on the appearance of psoriatic skin lesions in patients taking TNF- $\alpha$  inhibitors for other immunological diseases, such as SAPHO syndrome, juvenile arthritis, and Behcet's disease (14,15). All the aforementioned studies assessed the three classical anti-TNF- $\alpha$  agents (infliximab, adalimumab, and etanercept), however, after the appearance of certolizumab (16) and golimumab (17) there have been case reports of paradoxical psoriasis associated also with the use of these new anti-TNF- $\alpha$  agents, suggesting a class effect rather than a drug-specific effect.

According to data from rheumatology literature, psoriasiform eruptions induced by anti-TNF- $\alpha$  have a low incidence rate (1.04-3.0 per 1 000 person-years) and a prevalence ranging from 0.6% to 5.3%, depending on the different studies, that clearly exceeds the 1-2% prevalence expected by chance (18,19). No statistically significant predisposing factors or effect of personal or family history of psoriasis have yet been identified, but it is likely that genetic susceptibility could have a role in these paradoxical reactions. Men and women appear to be equally affected, and no predilection for any age group has been described, with some reports in children as well (20). The slight sex discrepancy found in some reviews is probably due to the prevalence of women in the distribution of primary diseases for which anti-TNF- $\alpha$  agents have been used (21). Concomitant treatment with other immunosuppressive drugs for psoriasis has not proven effective as a preventive measure for the development of these skin lesions. Regarding the clinical presentation, the typical manifestations are plaques and pustular psoriasis with palmoplantar involvement, but development of guttate psoriasis and psoriasis of the nail and scalp with alopecia have also been described (22,23). Reports are also heterogeneous with regards to the most frequent underlying disease, although most of the cases found in the literature concern patients affected by rheumatoid arthritis. Likewise, authors do not agree on the type of anti-TNF- $\alpha$  agent more closely related with the induction of psoriasis. Some reviewers found higher incidence of psoriatic skin lesions in patients treated with monoclonal antibodies (such as infliximab and adalimumab) while others proposed that monoclonal antibodies could be more commonly associated with the development of *de novo* psoriasis and etanercept with the worsening of pre-existent psoriasis (24). The treatment duration before the appearance of skin lesions also seems extremely variable, although the reaction tends to occur after the first two weeks of treatment, helping to distinguish this condition from a hypersensitivity drug reaction.

To date, the underlying pathophysiological mechanism by which TNF- $\alpha$  blockade therapy could induce the development of psoriasis is still obscure, although several theories have been proposed to explain this immunologic phenomenon. The full action of anti-TNF- $\alpha$  agents probably changes the balance between regulatory and inflammatory cytokines and cells, disrupting the homeostasis of the skin.

Initially, some authors considered these skin lesions a hypersensitivity reaction, but then skin biopsies of selected cases ruled out this theory, having shown the same histological lesions present in individuals with idiopathic psoriasis (25).

Other authors postulated that these cases could be a misdiagnosis and that they were actually patients with psoriatic arthritis with a later onset of the skin involvement. However, the majority of cases referred to patients with a definite diagnosis of rheumatoid arthritis or spondyloarthropathies. Moreover, the coexistence of psoriasis with other rheumatic inflammatory diseases, such as rheumatoid arthritis, is extremely rare, while psoriasis induced by TNF- $\alpha$  inhibitors has been reported with a much higher incidence.

One of the most plausible hypotheses suggests the disruption of the balance between TNF- $\alpha$  and interferon- $\alpha$  (INF- $\alpha$ ). Indeed, TNF- $\alpha$  inhibits both maturation of plasmacytoid dendritic cells, known to be the natural INF- $\alpha$  producing cells, and release of INF- $\alpha$  (26), the latter recently having been proven to be a pivotal cytokine in the early phase of psoriasis (27). The onset and the worsening of psoriasis after injection of recombinant INF- $\alpha$  has been demonstrated, corroborating the association between psoriasis and INF- $\alpha$  (28). Furthermore, plasmacytoid dendritic cells have been shown to infiltrate the skin in patients with psoriasis and release INF- $\alpha$  (29). Moreover, the INF- $\alpha$  signaling pathway is also activated in these patients (30), and it seems that T-cells in psoriatic skin acquire an increased sensitivity to INF- $\alpha$  (31). INF- $\alpha$  seems to also increase T-cell expression of chemokine receptors, such as CXCR3, promoting the migration of autoreactive T-cells to the psoriatic dermis and consequently causing skin damage (32). The central role of INF- $\alpha$  in the induction of psoriatic skin lesions was suggested because of the cross-regulation between TNF- $\alpha$  and INF- $\alpha$ , which means that TNF- $\alpha$  blockade may lead to INF- $\alpha$  over-expression with consequent onset of psoriasis. In support of this theory, one study (33) reported higher levels of perivascular and epidermal myxovirus-resistance protein A (MxA), an indicator of local INF- $\alpha$  release, in the inflammatory cells of skin samples of psoriasis induced by anti-TNF- $\alpha$  compared to samples of psoriasis vulgaris.

An injury or superinfection (mainly bacterial infection) on the inflammatory lesion may also have a key role by inducing INF- $\alpha$  production in plasmacytoid dendritic cells (34). It has been proposed that palmopustular lesions could indeed represent a form of keratoderma blenorrhagicum elicited by persistent *Yersinia* or *Chlamydia* (35).

Finally, according to another possible hypothesis, anti-TNF $\alpha$  agents may induce a disruption of the immune system equilibrium, enhancing Th17 function and down-regulating T<sub>reg</sub> expansion (36).

Psoriasiform skin lesions induced by TNF- $\alpha$  may be caused by a combination of all these mechanisms,

which may differ in magnitude from patient to patient. However, it may be that TNF- $\alpha$  is not solely involved, but that other cytokine and T-cell pathways are potential key players, in the pathogenesis of this paradoxical effect, explaining the appearance of psoriasiform lesions, although rarely, in patients treated with different biological therapy such as rituximab (37,38), anakinra (39), and tocilizumab (40). Furthermore, while it is true that the anti-TNF- $\alpha$  agents can induce the occurrence of psoriasiform reactions in patients with arthritis, the opposite scenario is also true. Indeed, unusual cases of arthritis induced by anti-TNF- $\alpha$  in patients with psoriasis vulgaris have been reported in the literature (41,42). It is evident that further studies are required to better clarify the pathophysiology of this unexpected skin reaction in patients undergoing biological treatment.

## TREATMENT APPROACH

To date, no guidelines exist for treating psoriasis induced by anti-TNF- $\alpha$  agents, so finding an effective treatment can be extremely challenging. It is imperative to exclude infection, and close collaboration with a dermatologist is recommended since a skin biopsy can be of value to rule out other possible causes and a variety of cutaneous therapies are often required.

There is a wide range of therapeutic approaches. All patients should remain under close and continual surveillance, and the appearance of skin complications should receive the utmost attention. The appearance of psoriasiform lesions can be treated using several treatment modalities, ranging from suspension of the offending anti-TNF- $\alpha$  agent to topical and systemic therapies to avoid the discontinuation of an effective treatment.

Collamer *et al.* (9) proposed a therapeutic algorithm based on the severity of psoriasis. In cases of skin eruptions affecting less than 5% of body surface area, a topical treatment (corticosteroids, keratolytics, and vitamin D analogs) should be recommended without withdrawing the TNF- $\alpha$  inhibitor. For more severe systemic reactions covering more than 5% of body area, or in case of pustular psoriasis and unsuccessful topical treatment, the addition of systemic therapy including methotrexate, retinoids, and cyclosporine or PUVA may be beneficial in treating psoriatic lesions. Discontinuation of the anti-TNF- $\alpha$  agent, which usually results in a complete or partial resolution of the skin lesions in the majority of cases, should be taken into account in patients who do not respond to the previous treatment and develop severe psoriasis or erythrodermic presentation, and also when skin lesions reduce the



quality of life or tend to increase in size and severity after each injection treatment.

With regard to the switch to another anti-TNF- $\alpha$  agent, this therapeutic approach is not recommended by all authors since this paradoxical reaction is a class effect with a high risk of reappearance of the skin lesions when using another anti-TNF- $\alpha$  agent, although the recurrence rate varies among the case series (48-85%). Ustekinumab has recently been used effectively in several cases of refractory palmoplantar pustulosis induced by anti-TNF- $\alpha$  agents (43), although an exacerbation of infliximab-induced palmoplantar psoriasis in a patient with ankylosing spondylitis has also been reported (44).

Interestingly, according to Werner de Castro *et al.* (45) vitamin D may have a therapeutic role in the treatment of psoriasis induced by anti-TNF- $\alpha$  agents.

## CONCLUSION

In conclusion, it seems a paradox that TNF- $\alpha$  inhibitors, which are widely used in the therapy of psoriasis, are able to aggravate or even induce the disease. However, since the use of TNF- $\alpha$  antagonists has increased, this adverse effect is becoming more and more important in the therapeutic management of rheumatic patients. In fact, the cases of psoriasis developed after administration of anti-TNF- $\alpha$  agents are becoming more and more common, and it is increasingly easy to come across one of these cases and have to recognize and treat it promptly. Apart from the disagreeable nature of this dermatopathy, ranging from slight predominant cosmetic impairment to severe and diffuse skin eruptions, the major impact of this side effect lies in the fact that a considerable percentage of patients need either to switch to another TNF- $\alpha$  inhibitor (often with recurrence of psoriatic lesions) or discontinue anti-TNF- $\alpha$  treatment. This wide variation both in the cutaneous manifestations and in the response to treatment suggests an individual susceptibility. Moreover, it highlights the important and complex role of TNF- $\alpha$  in the pathogenesis of psoriasis, which is not yet completely known, and a better pathogenetic understanding would likely finally help to define and improve treatment strategies for this complication. Bringing back the clinical issues to the laboratory bench seems particularly important in these cases, in order to fully understand the immunopathogenesis and molecular mechanisms that induce the appearance of these paradoxical effects.

Meanwhile, patients should be informed of these paradoxical effects prior to the start of anti-TNF- $\alpha$  treatment, and treating physicians should maintain close surveillance of their patients with

an early referral to a dermatologist in case of side effects occurrence. Close cooperation among specialists is needed to achieve the best treatment.

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