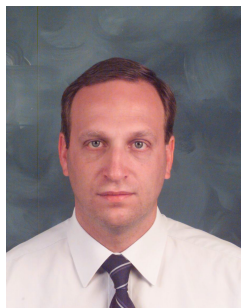


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Psoriasis occurring during anti-TNF- α therapy: causal effect or unrelated?



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'Psoriasis has also been observed with all three available anti-TNF- α agents, suggesting a class rather than drug-specific effect.'

The introduction of biologic agents, such as tumor necrosis factor (TNF) inhibitors, has transformed our therapeutic approach to rheumatic diseases in recent years. Anti-TNF- α therapy has shown a significant reduction in disease activity in a variety of inflammatory joint conditions, such as rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis [1–3]. In addition, TNF- α antagonists have been effectively used for the treatment of other inflammatory conditions, such as Crohn's disease, Adamantiades-Behçet's syndrome and refractory plaque-type psoriasis [4–6]. At present, there are three TNF-blocking agents that are used in rheumatology: two monoclonal anti-TNF- α antibodies (infliximab and adalimumab) and one soluble TNF- α receptor (etanercept).

With the expanded use of these agents in clinical practice, outside the setting of randomized clinical trials, an increasing number of cutaneous adverse reactions have been observed [7,8]. Severe cutaneous reactions, such as urticaria, erythema multiforme, cutaneous lupus erythematosus, necrotizing vasculitis, dermatomyositis and lymphomatoid papulosis-like and bullous skin lesions have been described, either in anecdotal case reports or in larger prospective studies [7–10]. One of the most striking reactions has been the development of psoriatic or psoriasiform eruptions in patients without a previous history of psoriasis following the administration of TNF- α inhibitors [11–19]. This contradicts the documented efficacy of these agents in plaque-type psoriasis by virtue of their role in decreasing the activity of proinflammatory mediators in psoriatic inflammation [10]. Although there is an open debate as to whether the development of these psoriasiform lesions is triggered by anti-TNF- α treatment or whether it is a coincidental manifestation of a previously 'latent' psoriasis, the accumulating evidence in

the literature suggests that psoriasis can occur with TNF- α inhibition and that its early recognition and treatment can spare the patient from substantial morbidity, without necessarily discontinuing a beneficial treatment for the underlying inflammatory condition.

Clinical manifestations of the eruption

Several case reports have been published describing the onset of psoriasis during anti-TNF- α treatment [11–19]. The exact prevalence is not clear, although it has been reported to range from 4–5% in a small series of patients [6,11]. In a recent online survey, 63% of rheumatologists responded positively when asked if they had seen psoriasis or other skin lesions in their patients during anti-TNF- α treatment, suggesting that the frequency of the eruption may be even higher [10]. The psoriasiform reaction has been observed more frequently in patients with rheumatoid arthritis or seronegative spondylarthropathies, but has also been reported in the setting of Crohn's disease, ulcerative colitis and Adamantiades-Behçet's syndrome [11,12,19]. It has also been observed with all three available anti-TNF- α agents, suggesting a class rather than drug-specific effect. The onset of the lesions varies, in some patients developing as early as a few days after the initiation of treatment and in others appearing in a more delayed fashion (up to 4 years after initiation of treatment) [8,11]. Interestingly, psoriasis has occurred in patients who were receiving concomitant immunosuppressive treatment, such as methotrexate, which is itself a potent antipsoriatic agent [6,16]. The lesions usually have the typical psoriasiform morphology, appearing as scaly erythematous plaques on the trunk, extremities or scalp. In some patients, the eruption may first appear or predominate at the flexural areas, such as the axillary and inguinal folds and the pubic area [19]. The new onset of nail psoriasis has also been noted, manifesting in the form of nail pitting, onycholysis, yellow discoloration and subungual keratosis [11]. The most characteristic pattern of psoriasis associated with anti-TNF- α treatment is a localized pustular eruption occurring symmetrically on

the palms and soles, resembling palmoplantar pustulosis. The eruption has been consistently reported in more than half of all reported cases and consists of painful or itchy pustular lesions based on erythematous areas of the acral sites, with or without concomitant psoriatic plaques or pustular lesions in other cutaneous sites [11,13–15,18]. Apart from the clinical presentation, the histology of the lesions supports the diagnosis of psoriasis, showing salient features of the disease: acanthosis, parakeratosis, dilated capillaries in the dermal papillae and a dense inflammatory infiltrate consisting mainly of neutrophils, lymphocytes and monocytes. In most cases, the lesions usually subside with the use of topical treatment, although discontinuation of the offending anti-TNF- α agent or switching to an alternative anti-TNF- α regimen have also been reported as successful modalities in severe or persistent cases [11].

Even though the occurrence of the psoriasiform eruption does not conform to the classic type of a drug-induced cutaneous hypersensitivity reaction, there are several clues that support a causal link between the eruption and the TNF- α -blocking therapy. The absence of a personal or family history of psoriasis in the affected patients, the lack of obvious exacerbating factors of psoriasis preceding the onset of the eruption and the temporal relation with the drug administration, although not always consistent, argue in favor of a causative role for TNF- α antagonists. In addition, the improvement of the rash after discontinuation of anti-TNF- α treatment and, conversely, its recurrence after re-administration of the same or a different anti-TNF- α agent (positive challenge), provide further evidence of a causative relationship between TNF- α inhibition and psoriasis development [11,18].

Potential mechanisms of anti-TNF- α -induced psoriasis

The mechanisms underlying the paradox of induced or exacerbated psoriasis by agents that show such a remarkable efficacy profile in the treatment of the disease remain elusive. One simple explanation could relate to the nature of the treated arthritic disorder: given the considerable overlap between the various spondyloarthropathies, particularly the seronegative group, it is possible that some of these patients have psoriatic arthritis and are, therefore, expected to develop clinically overt psoriasis over the course of their arthritic disease. This hypothesis may stand

true for some of the patients, but is strongly disputed by the occurrence of the eruption in cases with typical, clinical and serological findings of rheumatoid arthritis and ankylosing spondylitis. Furthermore, no concomitant arthritis flare was observed in any of the patients, which would have been anticipated given the similar immunological mechanism underlying the joint and skin involvement in psoriatic arthritis [21]. Another hypothesis that has been put forward suggests that the affected patients suffer from Reiter's syndrome and that the pustular eruption of the palms and soles are, in fact, a manifestation of keratoderma blennorrhagicum, a condition that is clinically indistinguishable from pustular psoriasis [101]. The eruption may therefore occur in the setting of a triggering chlamydial infection, either new or a re-activation of a latent infection, under the immunosuppressive influence of anti-TNF- α treatment. So far, there have been no specific studies performed on these patients that would indicate a genetic predisposition to Reiter's syndrome or serological evidence of a chlamydial infection.

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Based on our experience, none of the patients who developed psoriasis had symptoms of reactive arthritis or any of the other manifestations that characterize Reiter's syndrome, such as circinate balanitis, apthous stomatitis or ocular symptoms. With an estimated chlamydial seropositivity of more than 10% in the general population, and with the current widespread use of anti-TNF agents, one would expect the hypothesis of re-activation to be confirmed on a much larger scale.

What then is the most likely explanation of this phenomenon? In everyday practice, we are constantly reminded of the clinical heterogeneity of psoriasis and the various clinical expressions of the disease. Although little is known regarding the genetic background of the disease, it is probably reasonable to speculate that the different phenotypic expressions of the disease correspond to diverse pathogenetic and genetic mechanisms. A classic example is palmoplantar pustulosis (PPP), a key feature of anti-TNF- α -induced psoriasis. There is now evidence to suggest that PPP is a distinct clinical and genetic disease, although it is frequently seen in the context of plaque-type psoriasis [22,23]. It has recently been proposed that PPP originates from an inherent disfunction of

the palmoplantar sweat glands. TNF- α may play a crucial role in the function of the eccrine glands, as shown by TNF- α expression studies, and anti-TNF treatment may worsen an already existing TNF- α disfunction in PPP [18]. Nevertheless, the role of TNF- α in the pathogenetic mechanisms of psoriasis remains a puzzling question, despite the work of numerous investigators.

‘The role of TNF- α in the pathogenetic mechanisms of psoriasis remains a puzzling question’

The inhibition of its action at the cutaneous level, although beneficial in a large proportion of patients with psoriasis, may, in a subset of patients, alter the immunological milieu of the skin promoting an immunological response that

favors the development of psoriasis [24]. Until a larger number of patients who develop psoriasis under anti-TNF- α treatment are studied and more is understood regarding the pathophysiology of this cutaneous adverse reaction, we should remain attentive to the possibility of psoriasis occurring or worsening in patients receiving TNF- α antagonists. In their pretreatment evaluation, patients should be asked for a history of plaque-type psoriasis or PPP and, if positive, should be informed about the possibility of exacerbation of their cutaneous disease after initiation of anti-TNF- α treatment. Finally, the management of a psoriasiform outbreak in patients under treatment should be guided by the severity and extent of the eruption and by the overall cost-benefit ratio of anti-TNF- α treatment for the underlying inflammatory condition.

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