Abstract. – Multiple bioengineered agents has been recently developed to attack other parts of the immune/inflammatory system, achieving therapeutic implications for dermatologic diseases. On the other side, each new therapy has the potential for adverse cutaneous reactions.

We present herein the first two cases of Gibert’s pityriasis rosea occurring during etanercept therapy and discuss possible links between this common, etiologically still unexplained exanthema and anti-tumor necrosis factor-α drugs.

Key Words: Pityriasis rosea, Etanercept, TNF-α inhibitors.

Introduction

Tumor necrosis factor-α (TNF-α) antagonists, commonly termed as “biologics”, have established themselves as highly effective and relatively safe therapeutic alternatives for several inflammatory conditions, including psoriasis and psoriatic arthritis. Although anti-inflammatory and disease-modifying action of these bioengineered agents are well known, there are concerns for development of side effects such as autoimmune disorders, infections and neoplasms as the physiologic activities of TNF-α are blocked.

A broad spectrum of skin eruptions has been also reported during treatment with these drugs:\(^1\). On this topic, we describe two cases of pityriasis rosea occurring during etanercept therapy and discuss possible links between this common, etiologically still unexplained exanthema and anti-tumor necrosis factor-α drugs.

Case Report

Case Report #1. A 35-year-old woman with a longstanding psoriatic arthritis refractory to different therapeutic regimens including corticosteroids, cyclosporine A, and methotrexate, was recently started on etanercept (50 mg subcutaneously, twice weekly), with improvement of arthritic symptoms after 8 weeks. Then she sought medical advice for the onset of a cutaneous rash, composed of multiple, oval, 0.5-1.5 cm pinkish bilateral and symmetrical macules and papules of trunk and arms, arranged with their long axes parallel to the lines of cleavage and resulting in a suggestive “Christmas Tree” pattern (Figures 1 and 2). A single, salmon-pink, oval patch on the lower abdomen preceded the eruption, gradually enlarging, then presenting an elevated border with fine scale (Figure 3). She denied fevers, symptoms or history of previous skin lesions.

Routine blood exams, liver function tests and VDRL were in the normal limits. A 3 mm-punch biopsy specimen was obtained, histopathological examination revealing epidermal focal spongiosis and parakeratosis, with a superficial perivascular infiltrate of lymphocytes, histiocytes and eosinophils in the dermis.

She was diagnosed with Gibert’s pityriasis rosea. The patient was reassured on the benignity of the condition while treatment with etanercept was continued. The eruption resolved spontaneously, in absence of further treatment, in 5 weeks without any residual signs.

Case Report #2. A 40-year-old man was referred with an asymptomatic rash for three weeks, originally starting as a single patch on the abdomen (Figure 4). He denied fevers, symptoms or history of previous skin lesions.

Routine blood exams, liver function tests and VDRL were in the normal limits. A 3 mm-punch biopsy specimen was obtained, histopathological examination revealing epidermal focal spongiosis and parakeratosis, with a superficial perivascular infiltrate of lymphocytes, histiocytes and eosinophils in the dermis.

He was diagnosed with Gibert’s pityriasis rosea. The patient was reassured on the benignity of the condition while treatment with etanercept was continued. The eruption resolved spontaneously, in absence of further treatment, in 5 weeks without any residual signs.
and shapes, with flesh-colored central areas surrounded by pink borders and light scaling, involving trunk and proximal limbs following Langer’s lines (Figures 5 and 6). Headache and mild gastrointestinal discomfort were also present. The histopathological examination of a biopsy specimen supported the clinical suspicion of pityriasis rosea. Etanercept administration was continued under close surveillance; the rash persisted for three weeks, then progressively resolved in additional two weeks, without specific therapy.

**Discussion**

Pityriasis rosea (PR) is an acute, self-limited papulosquamous disorder commonly observed in healthy young adults during the fall, winter and spring, thought to represent a viral exanthema².
Recent studies have focused on the role of human herpes viruses 6,7 (HHV-6, HHV-7), which particles were detected in approximately 70% of PR patients with the invasion of the extravascular dermal spaces from the blood vessels and the damage of the dermal and epidermal tissues, either directly or by their interaction with the host immune system.

Herpesviruses, including HHV-6 and HHV-7, establish latency after primary infection and reactivate in immunocompromised and immunocompetent adults and children. The lymphotropic nature of HHV-6 and HHV-7, the in vitro observation that these viruses affect the expression of interferon, interleukin (IL)-8, IL-1β and TNF-α, and their ability to modulate other immunologically important cell surface molecules suggest that these viruses may have immunomodulatory potential.

Patients treated with TNF-α inhibitors show a decreased production of interferon-γ and a decreased expression of Toll-like receptor-4 (TLR-4), which is necessary for the recognition of microorganisms by phagocytes and dendritic cells, causing an increased susceptibility to pathogens.

Etanercept (Enbrel™, Immunex Corp., Thousand Oaks, CA) is a biological response modifier and is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF-receptor. This molecule is linked to the FC portion of human IgG1 and prevents the interaction of both TNF-α and TNF-β with their respective receptors. The TNF-α antagonists do not act in the same way, as etanercept binds primarily to soluble TNF whereas the others bind to both soluble and membrane-bound TNF.

Although the risk of infectious complications in association with etanercept is lower and it has a safer side effect profile as compared with more traditional immunosuppressive agents, due to its blockade of TNF-α, a theoretical risk of infections during this biologic treatment definitely exists, and patients should still be monitored very closely for any potential adverse event.

Assuming the viral origin (HHV-6, HHV-7) of PR, it is theoretically possible that TNF-in-
hibitors could play a role in viral reactivation by lowering immunity. However, there are few studies in literature concerning the development of viral related diseases during therapy with TNF-α inhibitors, and the results are controversial.

TNF-α plays a key role in host defence mechanism, especially for intracellular infections; moreover, TNF-α was shown to be a crucial cytokine in skin immunity due to its effects on inflammatory cells recruitment, antigen presenting cells mobilization to the lymph nodes and cytokines’ production. In fact, the use of TNF-α inhibitors has been associated with an increased risk of infections.

Levalampi et al. recently reported three cases of herpes zoster infection of the left part of the upper body that led to discontinuation of adalimumab, although it was administered in combination with other disease modifying antirheumatic drugs (DMARD). In the same study, etanercept, in association with DMARDs, was discontinued in one patient for the emergence of recurrent generalized herpes. On the other hand, TNF-α inhibitors did not modify Epstein-Barr viral load over time in 68 patients treated with infliximab and in 48 patients treated with etanercept for rheumatoid arthritis. Furthermore, Zein et al. have reported that when etanercept was associated with interferon and ribavirin in 19 patients treated for chronic hepatitis C infection, not only improved virologic response but it was also found to decrease the side-effects related to interferon and ribavirin.

Another study, on TNF-α inhibitors in patients with rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis, revealed no changes on viral loads or serum aminotransferases levels. On the contrary, HBV reactivation was demonstrated in a patient treated with a single injection of infliximab, as well as two cases of fulminant hepatitis 2 weeks after a second dose of infliximab.

Finally, Calabrese et al. have reviewed the few studies on TNF-α inhibitors in the setting of HIV-infection, a disease that affects and that it is highly affected by the multiple effects of TNF-α especially on HIV-1 replication, suggesting that this biological agents can be used if the patients are not extremely immunocompromised, without major side effects.

Since the above mentioned studies were performed in a small number of individuals, and different baseline conditions or concurrent treatments may bias the side effect profiles of TNF-α inhibitors, further investigations have to be performed to better characterize these data.

In regard to our patient, although a fortuitous association cannot be ruled out, it is possible to speculate that etanercept might have played a role in viral reactivation by lowering immunity. To the best of our knowledge, there is only a single report in literature describing PR during administration of a TNF-α inhibitor (adalimumab). Our cases, however, clinically presented as relatively typical, without any “particular” features (larger lesions, lack of the herald patch, oral lesions, longer duration) of a drug-induced form, not requiring pharmacological treatment or TNF-blocker discontinuation/termination.

Nonetheless, further larger studies are needed to investigate the role of TNF-α inhibitors in the development of viral disease, especially for latent viruses such as herpes and retroviruses.

References


