Case Report

A case of figurate urticaria by etanercept

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ABSTRACT

Etanercept is a competitive inhibitor of tumor necrosis factor-alpha (TNF-α) a polypeptide hormone, involved in the development of the immune system, in host defense and immune surveillance. Even if the etanercept mechanism of action is not completely understood, it is supposed that it negatively modulates biological responses mediated by molecules (cytokines, adhesion molecules, or proteinases) induced or regulated by TNF. For this reason, it is widely used in the treatment of immunologicals diseases, such as rheumatoid and psoriatic arthritis, polyarticular juvenile idiopathic active, ankylosing spondylitis, and plaque psoriasis. Etanercept has a good tolerability profile. Adverse events related to skin are rare, arising usually in about 5% of patients treated with anti-TNF α. In this scenario, we describe a case of figurate urticaria arose after the re-administration of etanercept in a patient affected by psoriasis and hepatitis B. A 65-year-old man, affected by psoriasis, was hospitalized in September 2014 to the Regional Center for the treatment of psoriasis and Biological Drugs of Second University of Naples for progressive extension of psoriatic skin lesions. The laboratory analysis detected positivity for hepatitis B virus (HBV) antigens. For this reason, it was administered to him lamivudine 100 mg/die about 30 days before to start etanercept treatment. The etanercept therapy has resulted in a progressive improving of skin manifestations, and the patient decided individually to stop the therapy. Afterwards, for worsening of the psoriatic lesions, he was again hospitalized and treated with the same therapeutic schedule (lamivudine followed by etanercept). Ten days after the start of therapy, the patient showed the onset of urticarial rash. Due to this, the treatment with lamivudine and etanercept was suspended and the patient's clinical conditions improved. It is probably that immunological disorders due to etanercept therapy and HBV infection could explain the onset of figurate urticaria in our patient. In this contest, the post-marketing surveillance confirms its important role in the monitoring of drugs tolerability and effectiveness.

Key words: Adverse drug reaction, anti-tumor necrosis factor-alpha, urticaria figurate

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INTRODUCTION

Etanercept is a competitive inhibitor of tumor necrosis factor (TNF) binding to cell surface TNF-Receptor, preventing TNF-mediated cellular responses by rendering

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TNF biologically inactive. Even though its mechanism of action is not completely known, it is supposed to modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.[1] TNF-α and lymphotoxin-alpha (LF-α), formerly known as TNF-β, are polypeptides hormones, members of the superfamily of TNF, composed of about 30 related molecules, encoded in the major histocompatibility complex Class III region. The TNF, mainly produced by monocytes/macrophages and activated T-cells, is involved in the development of the immune system, in host defense and immune surveillance.[2-4] Both TNF-α and LF-α share the same two monomeric receptors on the cell surface (p55 TNF receptor [TNFR] and p75 TNFR), part of the signal transduction system and both exist in soluble TNFR (sTNFR) forms produced by enzymatic cleavage induced by cell activation.[5-9] Etanercept is widely used in the treatment of rheumatoid arthritis in adults, psoriatic polyarticular juvenile idiopathic active in children and adolescents more than 2-year-old, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis.[1] The Summary of Product Characteristics of etanercept include a long list of severe and non-severe adverse event. Infections due to immunosuppression, which was related to anti-TNF- α pharmacodynamics effects of etanercept. The skin-related adverse event usually arises in about 5% of patients treated with anti-TNF α.[10]

Regarding this, we reported an etanercept-induced figurate urticaria onset after re-administration of etanercept and lamivudine in a patient affected by psoriasis and hepatitis B virus (HBV) infection. The patient was followed with periodic follow-up at the Regional Centre for the treatment of psoriasis and Biological Drugs of the Second University of Naples.

CASE REPORT

A 65-year-old man, affected by psoriasis from the young age, was hospitalized in September 2014 to Regional Centre for the treatment of psoriasis and Biological Drugs of Second University of Naples for progressive extension of psoriatic skin lesions. The patient denied the previous history of herbal medicines and drugs hypersensitivity. Laboratory result was positive for HBV antigens. Since other systemic drugs are contraindicated in this condition, a biological agent was preferred drug orienting clinicians to administer a biologic drug.[1] The patient started hepatitis B therapy with lamivudine tablets 100 mg/day. Hence, about 30 days after lamivudine administration, we began the treatment of psoriasis with etanercept 50 mg 2 fl by subcutaneous injection (s.c.)/week for 3 months, and then 1 fl s.c./week. Two medical examinations followed 30 and 90 days after first etanercept administration, showing a progressive resolution of cutaneous manifestations. For this reason, the patient decided on his own to stop the therapy. Afterward, for worsening of the psoriatic lesions, the patient was hospitalized again. During hospitalization, lamivudine was re-administered followed by etanercept after 30 days. Ten days after etanercept re-administration, the patient was hospitalized due to the onset of urticarial rash composed of lesion involving trunk and upper limbs. The lesions converged and assumed the character of figurate urticaria with well-delimited polycyclic pinkish contours, more marked at the periphery and itchy. Due to this, the treatment with lamivudine and etanercept was suspended, and the adverse event got better. The drug-adverse event association was postulated using Naranjo Probability Scale resulting possible (score of 4).[11]

DISCUSSION

Etanercept is a TNF blocker used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis. Apart from infections, the most common adverse events due to etanercept, severe skin reactions were also observed. Among these, in particular, erythematous skin lesions, multiform erythema localized to the trunk, legs, arms, shoulders, hands, and face were commonly observed.[1,12,13] Regarding multiforme erythema, a case-series reporting five cases of annular erythematous lesions was published in the literature in 2006. These types of adverse events were observed in patients treated with anti-TNF α, and particularly one of these patients was treated with etanercept.[12] In 2010, another case of multiform erythema raised 11 days after the first administration of adalimumab in a 67 years patient suffering from psoriasis and chronic infection by herpes simplex 2. The patient already presented the same adverse event during the previous treatment with etanercept.[13] According to literature, several etiopathogeneses could determine this condition, including allergic, infectious, neoplastic, autoimmune, and iatrogenic.[14] In our experience, we observed a case of figurative urticaria characterized by annular, ovular, and polycyclic shaped lesions with well-defined itchy margins that followed the administration of etanercept. Considering the potential role of drug–drug interactions in inducing adverse events in HBV patients,[15,16] we assessed the interactions using the software Micromedex 2.0 (Truven Health Analytics, Inc. Greenwood Village, Colarodo). No drug–drug interactions were detected between lamivudine and etanercept. Therefore, we supposed a possible immunological mechanism to explain this adverse event. In particular, we cannot rule out the possibility that the previous exposure to etanercept-induced antidrug antibodies production from B-cell.[17] Antidrug antibody were commonly observed with biologic drugs, included anti-TNF. When a second etanercept administration was

performed, these antibodies had to complement activation with immunocomplex deposition in dermis vessels, collagen damage, and consequently dermic vessels inflammation and onset of clinical manifestation. On the other hand, we cannot exclude the fact that positivity to HBV antigens could play a role in etiopathogeneses of this case of figurate urticaria. Several authors described the role of deposition of circulating immune complexes anti-HBV antigens in the pathogenesis of HBV-related urticaria. Skin lesions related to HBV could be considered as a prodromal sign of acute hepatitis B infection. For this type of reactions immune-mediated mechanism have been supposed to this kind of clinical manifestations. HBV-related hepatic complications may be associated with extrahepatic manifestations such as urticaria skin lesion.[13,18] Our case contributes to the current body of literature on this topic, mainly characterized by cases obtained from post-marketing surveillance. Post-marketing surveillance represents the cornerstone of pharmacovigilance especially for those adverse event, which are rare, to obtain additional information potentially useful to better understand the safety profile of the drugs in a real life contest.[19-28]

CONCLUSION

We described a case of figurate urticaria arose after the re-administration of etanercept inpatient HBV positive. It is probably that immunological disorders due to etanercept therapy and HBV infection could explain the onset of figurate urticaria in our patient. In this scenario, the post-marketing surveillance confirms its important role in the monitoring of drugs tolerability and effectiveness, especially for drugs such as anti TNF-α, whose safety profile is not yet fully known.

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Conflicts of interest
There are no conflicts of interest.

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