Diffuse skin reaction after changing the etanercept formulation

Sirs,

It is well known that therapy with anti-TNF-α inhibitors is often associated with cutaneous reactions (1, 2). In particular, controlled clinical trials carried out to evaluate the safety of etanercept in rheumatoid arthritis (RA) patients showed that this drug may be responsible for a variety of skin rashes (3-8). The main part of these manifestations are mild and only a small percentage are severe such as delayed skin rash, erythema multiform, lichenoid rash, atopic dermatitis, vulgaris psoriasis, vasculitis (9). Usually the skin reaction appears two or three weeks after the start of treatment (6, 7). A careful monitoring of patients who start treatment with anti-TNF-α drugs is recommended, even if not codified, during the first two or three weeks of therapy due to possible appearance of major post-administration reaction including anaphylactic shock.

It is also known that anti-TNF-α therapy may be associated with the onset of psoriasis (10). As a matter of fact, it has been recently described in a work of Harrison *et al*., a higher rate of psoriasis with TNF-α inhibitors in RA patients, compared to DMARDs treated patients (11). The exact pathogenetic mechanism leading to this skin manifestation remains uncertain (10). For Berg *et al*. TNF-α may have suppressive regolatory role of autoreactive T cells (12). Some authors suggest that TNF-α inhibition may be induced by dermal plasmacytoid dendritic cells locally increased INF-α production, which have recently been shown to have a central role in the induction of psoriasis (13, 14).

Here, we describe the first case of a severe and diffuse skin eruption concurrently with replacement of previous etanercept formulation with the new pre-filled preparation of drug.

A 58-year-old woman, with RA refractory to conventional DMARDs, started treatment with etanercept (50mg/w) plus methotrexate (15mg/w) in June 2004 at the Department of Rheumatology of the Pavia University Hospital and was prospectively followed up.

The patient achieved a good EULAR clinical response to therapy after 14 weeks of treatment and maintained a Disease Activity Score (DAS) between 2.00 and 1.5 until the last visit on the 24th August 2007. On this date, the first subcutaneous administration of pre-filled etanercept formulation was performed. After two weeks of using this new formulation, the patient presented onset of severe diffuse skin manifestation. At physical examination there was a diffuse papular erythematosus eruption with periorbital and palmoplantar desquamation, associated with itching and urente pain. A dermatologist evaluated the patient and confirmed the diagnosis of adverse reaction related to drug exposure. The clinical manifestation quickly disappeared after stopping of etanercept and with systemic anti-histaminic and steroidal therapy.

Table I.

Excipient	Etanercept powder and solvent for solution for injection	Etanercept pre-filled formulation
Saccharose	+	+
Mannitol	+	
Tromethamine	+	
Sodium chloride		+
L-arginine chloridrate		+
Monobasic nonohydrate Sodium phosphate		+
Dibasic anhydrus Sodium phosphate		+

Laboratory tests revealed a normal ESR, CRP, blood count, renal function, liver enzymes, levels of C3-C4. ANA were low positive (1:160 homogeneous) but stable since the 6th week of treatment, while anti-dsDNA remained negative over the course of treatment. Now the patient is continuing the treatment with methotrexate plus low doses of prednisone with good control of the disease activity.

In our case, the possible acute onset of psoriasis has been considered. However, the kind of cutaneous lesion, as well as the rapid disappearance and the link between this event and the change in etanercept formulation has been suggested as more likely to be a skin reaction linked to the new formulation of the drug.

The appearance of an important skin reaction in association with replacement of formulation of etanercept could be caused by different kind of excipients. As a matter of fact, the first form of etanercept was a soluble formulation and contains only a few excipients in comparison with those contained in the new pre-filled form (Table I). In our case, the onset of skin reaction occurred soon after the use of this new formulation of etanercept and early resolution after treatment stopped suggests a causal relationship.

In conclusion, we reported for the first time that the replacement of enbrel formulation can cause the onset of severe diffuse skin reaction probably related to a different composition of excipients and we suggest monitoring the patients, who did not show allergic manifestations during treatment with soluble etanercept form, when they start to receive the new pre-filled formulation.

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