Skin manifestations associated with anti TNF-α therapy

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Summary

The efficacy of anti-TNFα agents in the treatment of patients with moderate-to-severe psoriasis is well recognized in several clinical trials as well as in daily clinical practice. However, in a proportion of patients these agents can induce skin adverse events that are usually well tolerated. Secondary reactions induced by these agents are variable with regard to symptoms and severity and may be divided into two main groups: 1) skin reactions that could be defined as paradoxical, essentially being psoriasis exacerbations; 2) skin adverse reactions which can be of various kinds. There are some skin reactions which are secondary to the immunosuppressive drug effect, including sarcoidosis, induced lupus-like skin manifestations, skin lupus, Hodgkin-type lymphoproliferative skin disorders, skin mycobacterial infections. Besides the above, there are also the classical drug reactions: eczema reactions, erythema multiforme major, Stevens-Johnson syndrome, skin vasculitides, lichen planopilaris induction, morphea and skin reactions at the site of injection including erythema, edema, burning which are generally mild. The authors will present and discuss this data.

KEY WORDS: TNF-α inhibitors; skin adverse events; psoriasis; lupus-like syndrome.

Skin manifestations that may occur during treatment with anti TNF-α drugs are classified as definite, possible or fortuitous according to their likelihood of direct relationship with the drug. Figure 1 shows the main associations classified as definite and probable.

Among the reactions that are definitely drug-related there are infusion-associated skin reactions: from a semiotic point of view, these reactions are characterized by the appearance of erythema, urticaria, eczema and urticarial-like skin rash. In most cases, these reactions are of mild to moderate intensity, with rare severe cases that usually do not require treatment discontinuation.

Infusion-associated reactions can be either acute or chronic. In literature, cases of acute reactions – occurring during infusion or within 24 hours – during therapy with infliximab (1) have been reported to account for 3-6% of all cases, and are mostly of mild to moderate intensity. Of these, only less than 1% are considered to be severe reactions. The mechanism is not immune complex-mediated, and reactions usually resolve by reducing infusion rate and administering pre-medication with anti-histamines and/or corticosteroids; these measures have allowed to reduce the number of infusion-associated reactions in the last few years (2). Chronic reactions associated with infliximab infusion usually appear from 24 hours to 14 days after infusion. They occur in 1-2.8% of cases and generally involve face swelling and urticaria; these are type III immune complex-mediated reactions, as demonstrated by the presence of high levels of infliximab antibodies.

Injection-related skin reactions usually appear during the first month of therapy, with a tendency to reduce afterwards. They are characterized by mild to moder-
Adalimumab induces ANA and anti-dsDNA in 5.3% and 12.9% of pts.

Etanercept induces ANA and anti-dsDNA in 11% and 15% of pts.

Infliximab induces ANA and anti-dsDNA in 63% and 13% of pts with RA and in 49% and 21.5% of pts with Crohn disease.

Histone, n (%) 16/28 (57) Not reported 2 (17)

dsDNA, n (%) 29/32 52 (72) 11(92)

ANA, n (%) 32/32 (100) 57 (79) 12 (100)

aPL, n (%) Not reported 8 (11) 6 (50)

Anti-RNP 5 (7)

Anti-Sm 7 (10), Anti-RO/La 9 (12), Anti-RNP 5 (7)

Table 1 - Skin manifestations associated with anti TNF-α therapy: lupus and lupus-like syndromes.

Comparison of Antibodies in Anti-Tumor Necrosis Factor-α Induced Lupus Erythematosus as Reported in Three Different Studies

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Costa et al., 2008, (UK), (n=33)</th>
<th>Ramos et al., 2007, (Spain), (n=72)</th>
<th>De Bandt et al., 2005, (France), (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA, n (%)</td>
<td>32/32 (100)</td>
<td>57 (79)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>dsDNA, n (%)</td>
<td>29/32</td>
<td>52 (72)</td>
<td>11(92)</td>
</tr>
<tr>
<td>Histone, n (%)</td>
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<td>2 (17)</td>
</tr>
<tr>
<td>aPL, n (%)</td>
<td>Not reported</td>
<td>8 (11)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>ENAs, n (%)</td>
<td>10/19 (53)</td>
<td>Anti-Sm 7 (10), Anti-RO/La 9 (12), Anti-RNP 5 (7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibodies; dsDNA, double-stranded DNA; aPL, antiphospholipid antibodies; ENAs, extractable nuclear antigens.

- Infliximab induces ANA and anti-dsDNA in 63% and 13% of pts with RA and in 49% and 21.5% of pts with Crohn disease.
- Etanercept induces ANA and anti-dsDNA in 11% and 15% of pts.
- Adalimumab induces ANA and anti-dsDNA in 5.3% and 12.9% of pts.
after the beginning of therapy) (11, 12). In this cases, the pathogenesis is not completely clear; on the one hand, anti TNF-α drugs may induce apoptosis, immunosuppression or humoral autoimmunity, on the other hand they could cause type 1 interferon-α dysregulation, development of ANA and therefore a lupus-like syndrome (13, 14). In most cases, therapy discontinuation is followed by complete remission of the disease (12).

The literature describes anecdotal cases of morphea or localized scleroderma that have developed during therapy with biological drugs: in these cases, TNF-α inhibition may have acted on the cascade of TGF-β1 and other pro-fibrotic cytokines, while suppressing Th1 lymphocytes and activating Th2 lymphocytes, that are responsible for tissue damage and amplification of fibrosis (15-18).

Studies available in literature have shown that the incidence of skin infections in patients receiving anti TNF-α therapy has increased by 2-4 times compared to controls: skin infections during infliximab therapy were reported in 11.6% of cases, while those reported with adalimumab accounted for 6.6% (19, 20).

In a retrospective study, 28 out of 709 observed patients reported skin infections: in approximately half of cases, these infections were of bacterial etiology, 30.5% of viral origin and 6.5% were fungal infections. The clinical severity of these infections was modest and easy to treat (19).

Among the clinical manifestations regarded as probably associated with anti TNF-α therapy there are vasculitides. Leukocytoclastic vasculitis (LCV), the necrotizing form, Schönlein Henoch purpura and urticarial vasculitis are the most commonly reported forms. There have been reports of 35 cases of LCV in 116,000 patients treated with etanercept and 344,000 receiving infliximab, of which 17 cases were histologically confirmed. The close chronological association and the resolution of vasculitides (in 22 of 35 affected patients) following therapy discontinuation support the correlation between vasculitides and anti TNF-α drugs (21).

Cutaneous granulomatous reactions are also regarded as probably associated with anti TNF-α therapy. They may develop as atypical granuloma annulare or the disseminated form. Atypical granuloma annulare has been associated with the use of infliximab, etanercept and adalimumab; it is characterized, in its classical form, by ring-like macules, papules with raised edges – with a typical central clearing – usually asymptomatic and with a rapid development. The trigger role of anti TNF-α drugs seems to be supported by the close chronological association between the therapy and the development of lesions, as well as by the resolution of the condition following treatment discontinuation (22).

Regarding disseminated granuloma annulare, 9 cases have been reported in literature, all of which were treated with topical corticosteroids; only two cases required discontinuation of the systemic therapy (23). Only a few cases of vitiligo during anti TNF-α therapy, usually infliximab therapy, have been reported in literature (12).

With regard to alopecia areata, there are only a few cases reported in literature, i.e. 15 patients who developed total or universal alopecia areata associated with anti TNF-α therapy from 1-2 days to 24 months after starting the treatment; despite therapy discontinuation, alopecia had a clinical progression in 50% of cases. The observation of several cases associated with different anti TNF-α drugs is suggestive of a probable relationship (12). For this condition too, the suggested pathogenesis is much like those described up to now: anti TNF-α drugs might induce a dysregulation of cytokines such as interferon-α, and the activation of autoreactive T-cell clones that are able to induce the disease in genetically predisposed subjects (12).

Finally, among probable associations there are autoimmune bullous diseases. Very few cases have been reported, including a 72-year-old woman with a diagnosis of rheumatoid arthritis who was treated with etanercept, infliximab and eventually with adalimumab, and who developed a bullous pemphigoid of mucous membranes; another case concerned a 62-year-old patient treated with infliximab who developed, after the 7th infusion, a pemphigus foliaceous confirmed by the target antigen test (24).

Figure 2 shows the skin reactions that are classified as possible and fortuitous.

From a clinical viewpoint, the observed eczema presentations are mainly of the nummular or dyshydrosic form, but may also present as atopic dermatitis (19). Other possible associations include lichen planus and lichenoid reactions. The number of cases is limited: 15 cases of lichen planus or lichenoid reactions, mainly associated with infliximab, but also with etanercept and adalimumab. These skin reactions usually develop during the first two months of therapy (19).

There have also been reports of a certain number of cases of erythema multiforme, Stevens-Johnson syndrome and TEN induced by anti TNF-α drugs. These reactions seem to be more frequently associated with infliximab (4-22%), while a certain relationship has been observed between adalimumab and localization of these affections in the oral cavity (25, 26).

About sarcoidosis there have been reports of 28 cases in literature, of which 16 during etanercept therapy, 8 with infliximab and 4 with adalimumab. The time to onset of this condition may vary, ranging from none to 60 months, and in the majority of cases a complete or partial remission of the condition following treatment discontinuation is followed by complete remission of the disease (22).

Skin manifestations associated with anti TNF-α therapy

- **Possible associations**: eczema reactions, lichen and lichenoid reactions, sarcoidosis

- **Fortuitous associations**: cutaneous lymphoma, non melanocytic skin cancer, melanoma

Figure 2 - Skin manifestations associated with anti TNF-α therapy: possible and fortuitous associations.
partial resolution can be achieved (27). The pathogenesis is unknown, it may be secondary to an infection caused by Mycobacterium tuberculosis and Corynebacterium acnes which would be activated by the anti TNF-α drug, or the granulomatous reaction could be part of an auto-immune response resulting from cytokine changes secondary to TNF-α suppression (28).

An increased incidence of lymphoma in patients treated with anti TNF-α drugs has been reported in literature, although there have been no studies that provided real evidence of such association (2).

The development of actinic keratosis, Bowen’s disease, spinocellular carcinoma, basal cell carcinoma and acanthoma in patients receiving anti TNF-α drugs (etanercept, infliximab) has been reported in literature, but their incidence was comparable to that observed in the normal control population (29, 30).

Regarding melanoma, there have been reports of anecdotal cases of development or relapse of the disease in subjects receiving anti TNF-α drugs, which suggested a possible relationship; for the time being, these cases have been included in the class of fortuitous associations. There have been reports of two cases of locoregional relapse occurring 90 days after anti TNF-α therapy (etanercept, adalimumab), after 6 and 9 years from the diagnosis of melanoma, respectively (31). A case of melanoma (Breslow’s depth, 0.51 mm) occurring 25 weeks after the start of adalimumab therapy has been reported in a patient with a past history of PUVA therapy (32).

In conclusion, literature provides a wide range of skin manifestations related to the use of anti TNF-α drugs, although only some of them (infusion-related reactions and reactions at the site of injection) are definitely related to the therapy. Many of these reactions are validated by the literature because of the chronological association with the treatment and by the observation that the disease resolves following drug discontinuation. In the majority of cases, such manifestations are of mild or moderate intensity and resolve either spontaneously or with a short topical or systemic treatment; only rare cases require therapy discontinuation.

References

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