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REVIEW ARTICLE

Dermatological adverse reactions during anti-TNF treatments: Focus on inflammatory bowel disease

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Abstract

The clinical introduction of tumour necrosis factor (TNF) inhibitors has deeply changed the treatment of inflammatory bowel diseases (IBD). It has demonstrated impressive efficacy as compared to alternative treatments, allowing for the chance to achieve near-remission and long-term improvement in function and quality of life and to alter the natural history of Crohn's disease (CD) and ulcerative colitis (UC). As a consequence of longer follow-up periods the number of side effects which may be attributed to treatment with biologics is growing significantly. Cutaneous reactions are among the most common adverse reactions. These complications include injection site reactions, cutaneous infections, immune-mediated complications such as psoriasis and lupus-like syndrome and rarely skin cancers. We review the recent literature and draw attention to dermatological side effects of anti-TNF therapy of inflammatory bowel disease.

Contents

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1. Introduction

TNF is a pro-inflammatory cytokine implicated in the pathogenesis of chronic inflammatory diseases such as IBD, CD and UC as well as rheumatologic and dermatological diseases such as rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, and psoriasis. During the last two decades, TNF antagonists, including infliximab (a chimeric monoclonal anti-tumour necrosis factor antibody), adalimumab (human monoclonal antibody), certolizumab (the Fab fraction of human IgG monoclonal antibody) and etanercept (a soluble receptor fusion protein), were developed and have been used worldwide to treat more than 2 million patients affected by various autoimmune and idiopathic inflammatory diseases.[1,2] Anti-TNF agents are generally well tolerated, even if they are not free of side effects. The main side effects include serious infections, malignancies, demyelinating disease, aplastic anaemia, congestive heart failure, and induction of autoimmune conditions.[3] The use of TNF blockers may also provoke a broad spectrum of dermatological side effects, including injection site reactions, cutaneous manifestations of infusion reactions, cutaneous infections, non-melanoma skin cancer (NMSC), and psoriasis. Other cutaneous side effects are rare lesions including lupus-like syndrome, Stevens–Johnson syndrome (SJS), erythema multiforme (EM), and toxic epidermal necrolysis (TEN).[4,5] Different factors can be responsible for the immunogenicity of the anti-TNF agents. The degree of humanization, the content of adjuvants, the IgE or not IgE mediated immune responses can cause acute or delayed reactions (local or systemic urticaria, erythema, local dermatitis, serum sickness). A deregulated TNF production has also been associated with autoimmunity and autoinflammatory disorders such as psoriasis or lupus-like syndrome.[6] Rheumatologic studies have demonstrated that almost 25% of patients undergoing anti-TNF therapy had a dermatological complication,[7,8] and more recently, these data have also been confirmed in IBD cohorts.[9,10] In this clinical review, we focused on the most frequent dermatologic complications. We also examined the clinical management of the different dermatological situations induced by TNF antagonist therapy (Table 1).

Table 1 Anti-TNF and IBD: skin manifestations.

- Injection site reactions.
- Infusion reactions.
- Infectious complications
  - *Bacterial cellulitis, erysipelas, abscess*
  - *HSV, VZV, CMV, HPV, MC*
  - *Candida species*
- Immune-mediated and toxic complications:
  - *Psoriasis*
  - *Cutaneous lupus*
  - *Lupus like-syndrome*
  - *Cutaneous vasculitis*
  - *Erythema multiforme*
  - *Stevens Johnson syndrome*
  - *Toxic epidermal necrolysis*
- Skin cancers:
  - *Melanoma*
  - *Non-melanoma skin cancer*
    - *Basal cell carcinoma*
    - *Squamous cell carcinoma*

2. Reactions to injection/infusion

Injection site reactions occur with the use of adalimumab, etanercept and certolizumab pegol. These reactions manifest as redness, itching, bruising, pain, swelling and/or irritation at the site of injection. An allergic hypersensitivity reaction and local trauma are the most important mechanisms for injection reactions. Usually, clinical presentation is mild and occurs in the first months. Reactions typically last for 3–5 days, subsequently disappear[11] (Fig. 1). Injection site reaction based on an allergic mechanism may later present as systemic allergic reaction when treatment is continued. Food and Drugs Administration (FDA) labels for TNF inhibitors demonstrate that these local reactions occurred more often in TNF treated patients compared to those treated with placebo. Further, the incidence of such local reactions is up to 20% in adalimumab-treated patients compared to 14% in the placebo group and up to 37% in etanercept-treated patients compared to 10% in patients receiving placebo.[11] The higher number of injection site reactions with etanercept compared to adalimumab are likely due to more frequent dosing, longer availability on the market, and because it is a larger treatment group, as this drug has been available for longer than other agents. Injection site reactions are generally well tolerated and should be treated with supportive and preventive measures such as cool packs with a temperature around 4 °C, topical corticosteroids, rotation of injection sites and pain control if necessary. However, very few patients require discontinuation of TNF inhibitors.

Infusion reactions occur with infliximab (IFX) and are classified as acute or delayed, both of which can have cutaneous manifestations.[4,12] Acute reactions to IFX are infusion-related reactions that occur during or within 1 h after infusion.[10,13,14] These reactions appear in 10–40% of IFX-treated patients and include urticaria, erythematous rash, fever, bronchospasm, laryngopharyngeal oedema, dyspnoea, and hypotension.[4,10,11,13,14] Pruritus, flushing and urticaria are the most common symptoms and are observed in up to 2.2% of these patients compared to 0.3% of controls.[15] Acute reactions to IFX can be further categorised as mild-moderate,

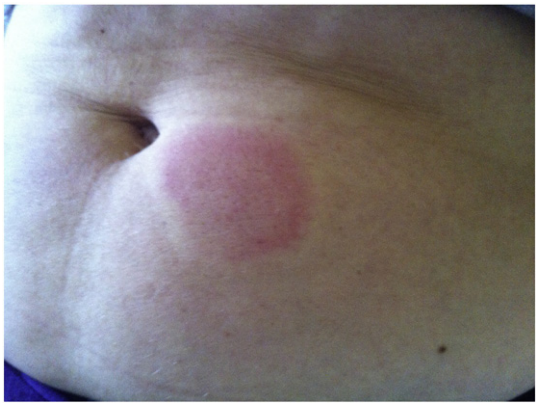

Figure 1 Injection site reaction with the use of adalimumab.

Table 2 Acute and delayed reactions under infliximab therapy.

	No. of patients	Acute	Delayed	IBD
Hanauer 2002[25]	573	97 (17%)		CD
Cheifetz 2003[18]	165	14 (8.5%)	3 (1.8%)	CD
Colombel 2004[22]	500	19 (3.8%)	14 (2.8%)	CD
Rutgeerts 2005[26]	484	55 (11%)	3 (0.6%)	UC
Moss 2008[27]	287	52 (18%)	–	CD
Lees 2009[21]	202	19 (9.4%)	8 (3.9%)	CD and UC
Fidder 2009[10]	682	115 (17%)	50 (7%)	CD and UC
Ducharme 2010[17]	2036	158 (8%)		CD and UC
Steenholdt 2011[12]	315	8 (2.5%)	–	CD and UC

which may be associated with nausea, fever, itching erythema and/or mild wheal formation, and severe, which may present with fever, generalized urticaria, angioedema, chest discomfort, dyspnoea, hypotension, and allergic shock.[12–14,16,17] The management of these types of reactions is different. Mild to moderate reactions in the most cases are self-limited and simply require slowing the infusion rate or a temporary interruption of the infusion. They may however be the first manifestations of hypersensitivity against the compound, with worsening with every infusion. However, acute severe infusion reactions constitute a serious clinical problem requiring immediate patient stabilisation and vital sign monitoring, discontinuation of the infusion and consequent indefinite contraindication to IFX therapy.[14,17] Furthermore, practice guidelines recommend premedication with anti-histamines and acetaminophen to reduce the incidence and severity of acute infusion reactions.[18–20] Interestingly, some authors investigating potential risk factors associated with acute severe infusion reactions have observed that the risk of reaction is higher during episodic or re-initiation therapy, especially during the 2nd infusion in a new series,[11] whereas the risk decreased with concomitant use of immunosuppressive therapy.[10,15,21,22] However, the risk of these reactions in two rheumatologic cohorts was not reduced by pre-treatment with systemic betamethasone or diphenhydramine.[23,24]

Finally, delayed infusion reactions are serum sickness-like reactions that occur 1–14 days after infusion. They typically manifest as myalgias, arthralgias, headache, fever, facial oedema, rash and fatigue.[12–14] FDA data and post-marketing reviews show an overall occurrence rate of about 2% of those patients treated with IFX.[10,12–14,21]

Table 2 shows pooled data for the incidence of acute and delayed infusion reactions with IFX in IBD from various registers and reviews.

Mechanisms for infusion reactions include immune and non-immune-mediated pathways. It is hypothesised that these reactions are caused by IFX immunogenicity.[14,16] In the ACCENT I trial, 42/254 infusions (16%) were given to anti-IFX antibody-positive patients compared with 55/656 (8%) given to anti-IFX antibody-negative patients.[25] Higher antibody titres were not associated with more infusion reactions in ACCENT I,[28] even though other studies reported that concentrations of 8 mcg/ml or higher predicted a higher risk for infusion reaction (relative risk 2.4).[29] In order to evaluate the role of immunogenicity in acute severe reactions systematically, a Danish group measured anti-IFX IgG and IgE antibodies levels in 25 IBD patients after these reactions.[12] Surprisingly, the authors found a clear association between these reactions and the presence of high levels of circulating anti-IFX IgG antibodies, but not with the presence of anti-IFX IgE antibodies. They thus concluded that most acute severe infusion reactions to IFX are not true anaphylactic reactions. Moreover, by measuring the levels of these antibodies before re-initiation of IFX infusion after a period of drug discontinuation, the same authors demonstrated that patients negative for anti-IFX antibodies before re-initiation still had infusion reactions.

3. Infectious complications

It has become clear from both randomised controlled trials (RCTs) and post-marketing surveillance that patients with rheumatoid arthritis treated with anti-TNF agents are at increased risk of bacterial, viral, fungal and opportunistic infections of all aetiologies.[30–37] Data are less robust in IBD patients because the pivotal trials on biological therapy in this population have not demonstrated an increased risk of serious infections.[38–40] Alternatively, cohort studies from several centres suggest that the risk for serious cutaneous infections is increased significantly.[22] In terms of skin infections, particularly in the subgroup of serious cutaneous infections defined as those that result in new or prolonged hospitalisation or are life-threatening, permanently disabling, or fatal, the precise incidence is not fully known. At present, there are only a few data from rheumatological cohorts showing an incidence of cutaneous infections and serious cutaneous infections of about 7–8% and 1.5%, respectively.[32,41,42] Data from the British Society for Rheumatology Biologics Register (BSRBR, a registry of 9018 patients, 7664 treated with adalimumab, etanercept and IFX) and the German register (1529 patients of whom 858 have had therapy with IFX or etanercept) follow-up the use of biologics in RA. The data of these cohorts have confirmed

that the skin is the second most common site of serious infections after infections of the respiratory tract.[42–44]

Many risk factors have been identified as causes of increased cutaneous infections during anti-TNF therapy, including a dose increase, concomitant immunosuppressive therapy, malnutrition, age, and comorbidities such as chronic lung disease, alcoholism, organic brain disease and diabetes mellitus.[45–47] The rheumatologic literature has demonstrated that each immunomodulator carries an increased risk of infection, and combinations of immunosuppressive therapy are associated with an incremental increase in the relative risk of opportunistic infections.[48] For patients under corticosteroids, the relative risk of occurrence of infectious complications is 1.6. The overall risk of infection increases for doses of Prednisolone >10 mg/day or cumulative doses >700 mg. Moreover, a duration of steroid therapy >2 weeks predisposes patients to infections.[47–50]

Cutaneous bacterial infections include cellulitis, erysipelas, abscess formation and pharyngitis and occur in less than 0.1% to 7% of anti-TNF treated patients.[7,10,15,22,32] Fungal infections (Candida species) are more commonly associated with corticosteroid and anti-TNF therapy, but the exact incidence of cutaneous fungal infections is unknown.[7,8,32,48]

With regard to viral infections, TNF is involved in the regulation of herpes virus replication and dissemination.[51] Reactivation of herpes virus infection in patients undergoing anti-TNF therapy is relatively common, with an incidence of 1–5% in the various registers and reviews.[7,10,32] In particular, shingles (Herpes zoster), a neurocutaneous disease typically characterised by a painful, unilateral, vesicular rash distributed in one or more dermatomes, is the result of reactivation of the varicella zoster virus (VZV). VZV reactivation is well documented in patients receiving anti-TNF therapy, with an incidence of about 3%, and appears to be particularly associated with IFX and adalimumab therapies.[52,53] Concomitant immunosuppressive therapy increases the risk of dissemination and complications such as bacterial superinfection, post-herpetic neuralgia, thrombocytopenia and disseminated intravascular coagulopathy.[54] In the European Crohn's and Colitis Organisation (ECCO) Consensus on the prevention, diagnosis and management of infections in IBD patients, experts concluded that previous VZV infection is not a contraindication to immunomodulator therapy but that biologics should not be started during an active infection. A serologic test for chickenpox and VZV infection should be recommended in order to assess immunologic status of a patient and to decide if vaccination is necessary or not: vaccination should be performed at least 3 weeks before the onset of immunomodulator therapy. In the case of VZV infection during immunomodulator therapy, antiviral treatment should be started, and immunomodulator and/or anti-TNF therapy should be discontinued if possible. Finally, anti-TNF therapy can be safely restarted after complete clearance of lesions.[46]

There are also reported cases of CMV infections that may present as cutaneous ulcers or retinitis.[55]

Recently, few case reports of human papilloma virus (HPV) and molluscum contagiosum (MC) infection in patients under anti-TNF treatment for psoriasis, were reported.[56,57] One case of genital condylomata in a patient receiving IFX for CD was described.[58] HPV and MC viral proteins seem to interfere with the apoptotic pathway of the host cell signalled by TNF receptors. Anti-TNF agents block TNF directly, so HPV and MC could develop or flare. For females, PAP smear test before and during anti-TNF therapy is highly recommended.[59]

4. Immune-mediated complications

4.1. Psoriasis

TNF inhibition is effective and approved for the treatment of moderate to severe psoriasis.[60,61] However, as experience with the use of biological therapeutic is increasing, a significant number of cases of psoriasis induced by anti-TNF therapy have been reported.[62] This paradoxical side effect has been described in nearly all conditions treated with anti-TNF and with all anti-TNF agents. In a series of 127 patients treated with biologic agents for a number of primary autoimmune conditions (70 on IFX, 35 on etanercept, and 22 on adalimumab), authors have reported a prevalence of new-onset psoriasis ranging from 0.6% to 5.3%.[63] The majority of these cases have been described in rheumatologic diseases, but this side effect has also been described in IBD patients.[64,65] New-onset psoriasis during treatment with TNF blockers is not rare: 15% of all cases are RA patients.[66,67] The prevalence of psoriasis is greater in CD than in UC.[68–70] Moreover, a great majority of cases have been described after IFX therapy, perhaps due to the fact that IFX was the first anti-TNF agent used for the treatment of IBD, whereas adalimumab is a far more recent addition to the therapeutic arsenal for the treatment of CD.[66–88]

The pathogenic mechanism of this paradox reaction has not yet been completely clarified. A possible aetiology might be the balance between TNF and interferon-α (IFNα), an important cytokine for the early phase of induction of psoriasis produced by the dermal plasmocytoid dendritic cells (DPDC). According to this hypothesis, TNF can inhibit the release of IFNα by DPDC; therefore, TNF blockade may induce a local uncontrolled and unlimited production of IFNα that may cause the onset of psoriatic lesions. However, because only few patients on anti-TNF therapy develop psoriasis, a genetic predisposition is likely.[86–90]

Cullen et al., in a recent work, identified 30 subjects who developed a psoriatic rash while receiving anti-TNF therapy for IBD and combined these new data with those from 120 published cases of anti-TNF-induced psoriasis in IBD. In this analysis, anti-TNF-induced psoriasis in IBD seems to be more common in women (70%).[91]

Denadai et al. published a review, including 47 studies, that documented 222 cases of IBD patients with psoriasis induced or exacerbated by anti-TNF. Of the 222 patients, 78% were affected by CD, 48% were female. IFX was the anti-TNF that caused psoriatic lesions in most of these patients (69%); none of them had previous history of psoriasis.[92,93]

The most frequent clinical presentation of psoriasis occurring during TNF blockade is the palmoplantar type, which differs from the classic plaque-type that occurs in over 80% of psoriasis patients.[63,66,91] Psoriatic lesions can appear at any moment after drug initiation, but the most frequent time of onset is between the 3rd and 4th IFX infusion.[66,68,84]

In the majority of cases, psoriatic lesions resolved after discontinuation of TNF blockers. In some patients who

showed resolution of psoriasis after discontinuation of IFX, skin lesions reappeared after the start of etanercept or adalimumab.[66,91,94]

A prospective study on dermatological side effects under adalimumab therapy in IBD patients shows 9 cases of eczema and 9 cases of acne-like dermatitis: 6 of these patients developed psoriatic lesions.[95]

The management of this paradoxical side effect is not conclusive, and various treatment options have been employed with mixed results. Biopsy should be considered in all patients with new-onset psoriatic lesions. For mild skin lesions responsive to topical therapy, it is reasonable to try continuation of anti-TNF therapy. According to Collamer's algorithm, patients with psoriasis covering <5% of body surface area should be treated with topical treatments (corticosteroids, keratolytics and vitamine D analogs); for lesions covering >5% of body surface area and palmoplantar disease, topical therapies, occlusive therapy to the palms and soles, and UV phototherapy should be given.[62]

However, in the severe cases, treatment should include both withdrawal of anti-TNF and consequent treatment of psoriasis.[63,91,96] In most cases, topical treatments such as steroids, UVB-radiation and PUVA will be sufficient. In some patients systemic treatment (metotrexate, fumaric acid, other biologicals) will be necessary. Finally, the switch to another anti-TNF agent can be considered in patients with a general skin disease and/or aggressive IBD.

We show seven examples of psoriatic lesions manifested under IFX treatment, in our centres (Figs. 2–8).

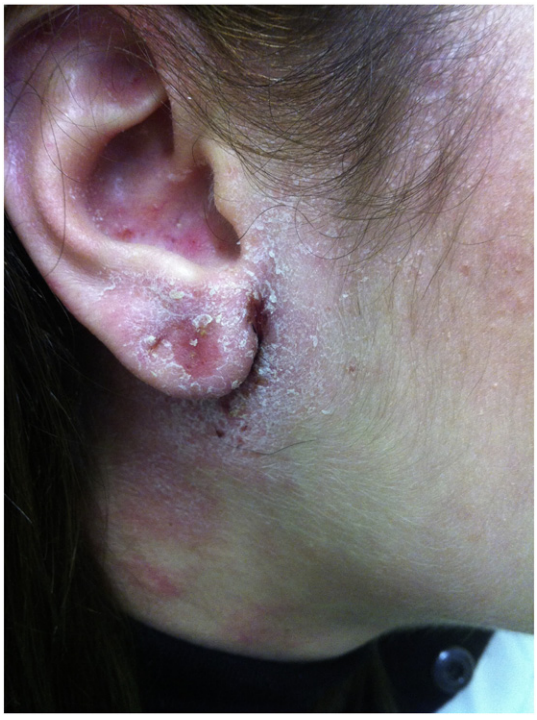

Figure 3 Psoriatic lesion under infliximab therapy: Ear lobe.

4.2. Cutaneous lupus and lupus-like syndrome

Biological agents have been reported to cause a drug-induced lupus-like syndrome defined more specifically as TAILS (TNF alpha antagonist-induced lupus-like syndrome).[4,97] TAILS is a rare condition with an incidence of less than 1% overall, and, as a recent study on a Spanish cohort of 105 patients with TAILS has confirmed, it occurs most often in women in the fifth decade of life.[98,99] TAILS has been observed in patients treated with TNF blockers for various autoimmune diseases, mostly RA and CD.[98–103] IFX and etanercept are the two most common biological agents associated with this syndrome. To date, there are only a few cases of adalimumab-induced lupus-like syndrome and one case of certolizumab-induced lupus-like syndrome.[98,100,102,103] It is likely that the increased incidence of TAILS associated with IFX and etanercept is due to the larger population that has been treated with these drugs. Nevertheless, it has been shown that each anti-TNF agent has particular structural and pharmacokinetic features that may contribute to the different incidence rates of TAILS. Indeed, IFX is the most immunogenic of the anti-TNF agents, due to its chimeric structure. The fully humanised structure of adalimumab is the least immunogenic. They have different capacities to stimulate autoantibody production.

An aetiology has not been determined, and several hypotheses have been proposed. Some investigators have suggested that anti-TNF induced apoptosis of inflammatory cells may release DNA and other lupus auto-antigens,

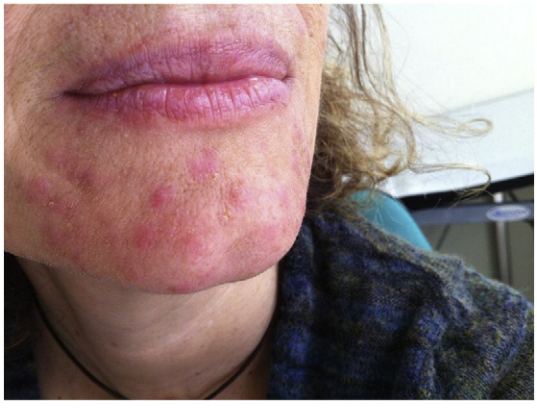

Figure 2 Psoriatic lesion under infliximab therapy: Chin.

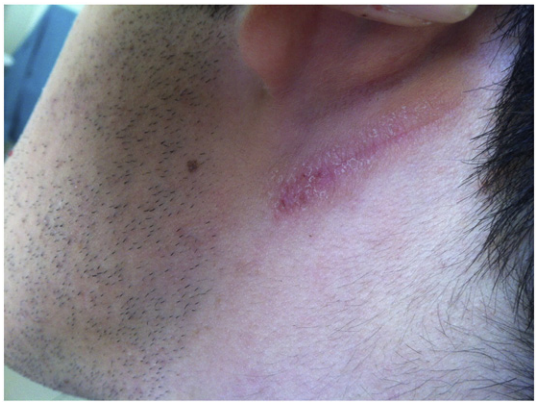

Figure 4 Psoriatic lesion under infliximab therapy: Auricolar region.

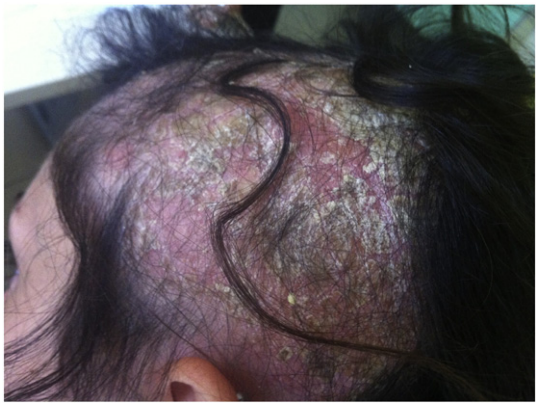

Figure 5 Psoriatic lesion under infliximab therapy: Scalp psoriasis with alopecia.

which may elicit the development of autoantibodies.[104] However, this mechanism should not be implied in TAILS caused by etanercept, as this agent does not cause cell apoptosis. A second possible mechanism of pathogenesis includes immune suppression that favours increased rates of infection with the consequent activation of B lymphocytes and autoantibody production.[105] Finally, a third possible mechanism hypothesises that anti-TNF agents may promote humoural autoimmunity by blocking T-helper 1 cells and favouring T-helper 2 immune responses.[104,106]

TAILS can appear in two different clinical variants. The limited skin lupus type is characterised by cutaneous symptoms of lupus (malar rash, photosensitive rash, purpura, alopecia)

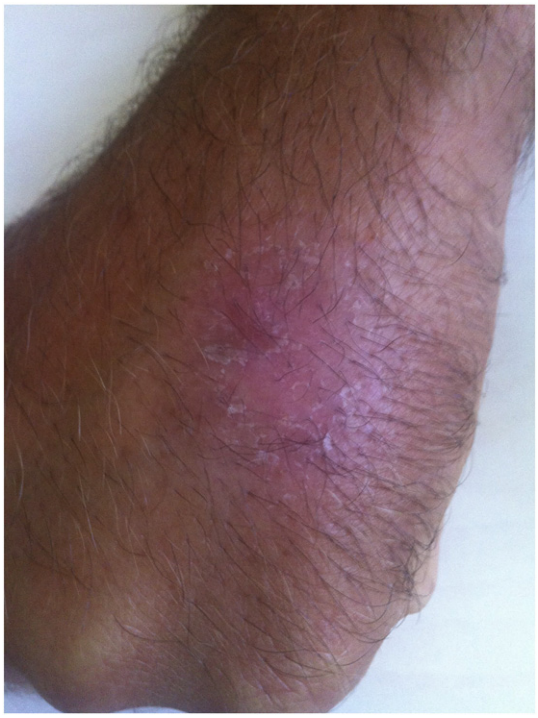

Figure 6 Psoriatic lesion under infliximab therapy: Right arm.

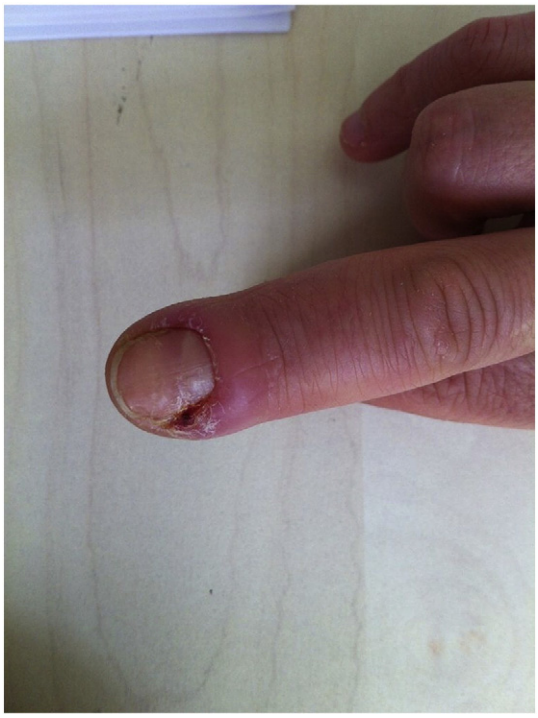

Figure 7 Psoriatic lesion under infliximab therapy: Ungual psoriasis.

together with antinuclear antibodies (ANAs) and anti-dsDNA autoantibody. The complete lupus type is characterised by both autoantibodies and skin manifestations as well as extra-cutaneous manifestations such as arthritis, myositis, serositis, haematological abnormalities, and renal and

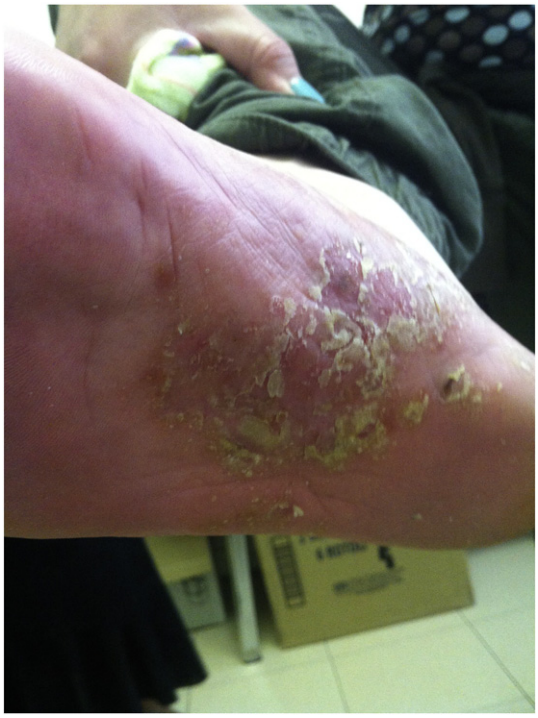

Figure 8 Psoriatic lesion under infliximab therapy: Plantar psoriasis.

neurological disorders.[97–99,107,108] There are no differences in terms of clinical presentation between the different TNF agents. The time for onset of symptoms varies very much (10 days to 54 months after start of therapy).[98–100]

It has been well documented that anti-TNF therapy is associated with the induction of autoantibodies.[101,109,110] New onset, positive ANAs have been reported in up to two-thirds of previously negative-ANA patients treated with TNF inhibitors. Anti-dsDNA was found in 70–90% of patients treated with TNF inhibitors and was observed in 20% of IFX patients. Notably, the majority of new anti-dsDNA antibodies are of the IgM subtype; these are not more pathogenic than the IgG subtype.[4,15] Anti-phospholipid antibodies have been found in 11–50% of patients.[99,102] In a prospective cohort study of 125 CD patients under IFX therapy, a cumulative incidence of ANAs of 56.8% was found. ANAs were associated with the female sex and skin manifestations. In this cohort only 2 patients developed drug-induced lupus erythematosus.[111]

Specific criteria for the diagnosis of TAILS have not been established. The most rigorous criteria include the following: a temporal relationship between clinical manifestations and anti-TNF therapy, at least one of the serologic criteria for systemic lupus erythematous according to the American Congress of Rheumatology (ACR) (i.e., ANAs or anti-dsDNA), and at least one non-serologic ACR criteria (i.e., arthritis, serositis, malar rash, or hematologic disorder).[100]

The management of TAILS depends on the severity of clinical presentation because TNF antagonists need to be discontinued only in patients with organ involvement. Moreover, patients with severe reactions may require additional treatment, such as systemic or topical corticosteroids and immunosuppressives.[108] In nearly all cases, TAILS may be reversible, when the harmful drug is stopped, within a period from three weeks to six months.[98,100,109] Authors agree that the induction of autoantibodies in asymptomatic patients is not an indication for the discontinuation of therapy.[4,108]

An interesting question is whether patients with TAILS can receive another anti-TNF agent without the recurrence of adverse effects. Reports regarding this issue are scarce, and there are only 10 patients that have been challenged with the same or different agents to date.[98,112,113] Adalimumab and etanercept have been used with success, whereas, to our knowledge, successful re-challenge has not been documented with IFX. Interestingly, there are three cases of etanercept-induced TAILS that tolerated re-challenge with the same anti-TNF agent without recurrence.[113]

4.3. Cutaneous vasculitis, erythema multiforme, Stevens Johnson syndrome and other cutaneous reactions

Ramos–Casals and colleagues conducted a baseline Medline search of articles published between January 1990 and May 2008. They identified a total of 379 cases of autoimmune diseases and other intolerance reactions; 118 cases of cutaneous vasculitis were reported. However, these data are sparse, due to a lack of biopsy data, and confounded by the concomitant presence of RA (more than 80% of cases), which is frequently associated with vasculitis. Purpura is the most common presentation, and nearly all cases disappear when anti-TNF therapy was discontinued.[99] The management of cutaneous vasculitis consists of evaluation for and treatment of systemic involvement. Discontinuation of TNF blockade may be suggested.

Safety reviews of TNF antagonists, including IFX, etanercept, and adalimumab, identified rare cases of serious skin reactions, including erythema multiforme (EM), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), associated with the use of these biological products.[114–116] Most affected patients were female with rheumatoid arthritis, and nearly half of the cases resulted in hospitalisations (22 of 50). Although most had co-administration of one or more medications associated with EM, SJS and/or TEN, several reports described a temporal relationship between the start or most recent dose of an anti-TNF agent and the onset of the skin reactions. Moreover, more than half of the patients had a positive de-challenge test.[114]

The development of any severe skin reaction while receiving TNF antagonist therapy may require urgent work-up to determine the appropriate diagnosis and treatment and to guide consideration of an alternative therapy. IFX and other anti-TNF agents must be stopped in cases of SJS or TEN.

5. Skin cancers

Several case reports have documented that the use of TNF inhibitors may be associated with an increased incidence of non-melanoma skin cancer (NMSC), particularly squamous cell carcinoma.[7,10,15,30] A recent meta-analysis of randomised controlled trials of adalimumab, IFX and etanercept demonstrated that the relative risk associated with all anti-TNF therapies for NMSCs was 2.02.[117]

In a cohort of 108,579 IBD patients, IBD was associated with an increased incidence of melanoma and NMSC (IRR 1.29, IRR 1.46 respectively), especially for individuals with CD.[118] Burmester et al. revised 71 global clinical trials including 23,458 patients exposed to adalimumab for different autoimmune disorders, and showed that standardised incidence rates (SIRs) for NMCS were based on 22 events from CD trials (14 basal cell carcinoma, 6 squamous cell carcinoma and 2 not classified). In CD, SIRs for melanomas did not show a higher incidence relative to the general population.[119] In a meta-analysis of data from registries and systematic reviews about patients with RA treated with anti-TNF, no evidence was found that anti-TNF therapy exacerbated the risk of NMSC, but this cannot be excluded.[120]

So, the responsibility of TNF in skin cancer remains unclear, and data for actual rates of NMSCs are confounded by other past or concomitant aetiologic factors.

Specifically, psoralen and ultraviolet A (PUVA), ultraviolet B (UVB) and other immunosuppressive therapies, such as cyclosporine, methotrexate or thiopurines, can influence malignancy rates.[7,10,30,121–125] Ongoing and past exposure to thiopurines seems to significantly increase the risk of NMSC in IBD patients even before the age of 50 years.[126]

All patients treated with anti-TNF should be protected against UV radiation and receive a dermatologic examination before starting therapy and then once a year thereafter. Newly diagnosed NMSCs must be completely removed and

followed, but anti-TNF agents do not necessarily have to be discontinued.

6. Conclusion

Anti-TNF agents actually offer a significant improvement in IBD. As a result of their use, and of the longer follow-up periods of treatments, there are a growing number of cutaneous side effects during anti-TNF treatment in IBD patients. These are typically mild and are treated using standard topical therapies without discontinuing or switching the anti-TNF agent. But in the most severe cases, the discontinuation of the drug is necessary. So, a close surveillance by a physician who deals with IBD patients is very important and a consultation with a dermatologist is highly recommended before and during anti-TNF treatment.

Conflict of interest

There is no financial conflict of interest for all authors.

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