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Chapter

Skin Adverse Reactions Related to TNF Alfa Inhibitors: Classification and Therapeutic Approach in Psoriatic Patients

Karolina Vorčáková, Tatiana Péčová, Klára Martinásková, Katarína Nováčeková and Juraj Péč

Abstract

Tumor necrosis factor alpha (TNF alpha) inhibitors are widely and effectively used for inflammatory and autoimmune diseases in rheumatology, gastroenterology, and dermatology. Adalimumab, etanercept, and infliximab are indicated for the treatment of patients with moderate to severe chronic plaque psoriasis. This target treatment is very effective and lead to control the most severe cases, which were formerly fatal. Biologic treatment is strictly monitored. These large molecules, even with the same mechanism of action in the form of inhibiting TNF alpha, may act differently, and they may have other adverse effects. Skin complications of anti-TNF alpha treatment include a wide range of manifestations which can be divided into four groups: infections, reactions directly associated with drug administration, immune-mediated skin reaction, and malignancy. This chapter describes currently available information regarding the occurrence of individual complications and defines possible therapeutic options in case of individual adverse reactions.

Keywords: anti-TNF alpha, adverse reactions, infection, drug-related reactions, immune-mediated reactions, malignancy

1. Introduction

Tumor necrosis factor alpha (TNF alpha) inhibitors have been successfully used in the treatment of various immune-mediated inflammatory diseases since the early 1990s. In dermatology, chronic plaque psoriasis is treated by three biologics belonging to the group of TNF alpha inhibitors: infliximab, adalimumab, and etanercept.

Biologic therapy offers new treatment options for psoriatic patients with high levels of efficacy and convenience; such treatments have immunomodulatory or immunosuppressive effects that may predispose patients to potential adverse events [1–4]. The skin is one of the most frequently affected organs. Adverse effects of anti-TNF alpha on the skin represent nearly 25% of all adverse effects [5, 6]. Despite the strict observation of preclinical studies, many adverse effects were manifested only following the implementation of biologics in clinical practice. In 2004, a paper on anti-TNF alpha treatment-induced psoriasis was first published [7]. Since then,
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Skin adverse reactions

1. Skin infections
2. Reactions directly associated with drug administration
3. Immune-mediated skin reactions
4. Malignancy

Table 1. Classification of skin adverse reactions.

A whole group of so-called immune-mediated adverse effects which includes a large group of so-called paradoxical reactions has emerged. Likewise, new cases of hypersensitivity reactions continue to arise with ambiguous pathogenesis. Skin complications of anti-TNF alpha treatment include a wide range of manifestations which can be divided into four groups: skin infections, reactions related with drug administration, immune-mediated reactions, and malignancies (Table 1). In this chapter, we describe currently available information regarding the occurrence of individual complications and define possible therapeutic approach in the case of individual adverse reaction necessary for such adverse reaction to be resolved.

2. Infections

Early randomized and postmarketing studies proved that patients undergoing anti-TNF alpha therapy are at increased risk of infectious diseases namely, bacterial, viral, fungal, and opportunistic [8]. Data from the British and German rheumatology registry confirm that the skin is the second most common location of serious infections, immediately after the respiratory system [9–11]. Besides other risk factors which may impact the onset on infections, combined immunosuppressive treatment, which increases the number of infectious complications, is regarded as the most significant. The majority of skin infections are nonserious adverse effects that go unreported in studies and registries but which nevertheless cause problems to patients and may have a fundamental impact on their quality of life. Infectious skin complications can be divided into three groups:

- Viral infections
- Bacterial infections
- Fungal infections

2.1 Viral infections

2.1.1 Herpes infections

Herpes infections are the most common viral complications. According to registries and article reviews, the incidence of reactivated herpes infections in patients on anti-TNF alpha therapy is around 1–5% [5, 12, 13].

2.1.1.1 Varicella-zoster virus

Varicella-zoster virus (VZV) reactivation and occurrence of herpes zoster infection is a common serious adverse event. According to Burmester et al., the incidence of
herpes zoster (HZ) infection in a group of 23,458 patients treated with adalimumab in 71 studies of dermatological, rheumatological, and gastrointestinal indications is 0.3/100 patient-year (PY) [14]. Yet in contrast, one of the most recent publications regarding the long-term follow-up of psoriatic patients did not confirm the association of increased HZ risk in patients treated with ustekinumab, TNF alpha inhibitors, and methotrexate. However these authors also stated that a larger number of HZ events would be needed to assess the presence or absence of risk [15]. In the case of the VZV infection, early diagnosis and timely treatment are a precondition for the prevention of VZV complications. Most feared complications include meningoencephalitis, myositis, pneumonitis, hepatitis, and herpes zoster ophthalmicus. The most frequent complication is postherpetic neuralgia. Caution is required in patients on combined immunosuppressive treatment, in whom the disease may take a severe course. In the case of a localized infection, oral virostatic agents are the treatment of choice (Table 2). Disseminated herpetic manifestations require patient hospitalization in order to administer intravenous treatment. Biologic treatment is immediately suspended due to the severity of herpes infection. Further doses of biologics are never administered in the acute stage of the disease. Biologic agents are subsequently not contraindicated, and biological treatment may continue after the complete return of body temperature to normal and the suppression of skin manifestations. Primary VZV infection is very dangerous in patients on anti-TNF alpha and may take a very complicated course. Vaccination is recommended in patients who failed to previously overcome VZV, which must be administered 3 weeks before the initiation of biologic therapy at the latest [16]. If the patient contracts a primary VZV infection, it is necessary to immediately suspend anti-TNF alpha therapy and initiate treatment with aciclovir 10 mg/kg every 8 h for at least 7 days (Figure 1). Complicated cases require diagnostic examinations. Serologic tests are most important for the diagnosis of previous disease and also at the acute stage. PCR, viral culture, and IHC or hybridization methods are more sensitive for the confirmation of a diagnosis of current VZV infection or reactivation in the event of clinical uncertainty [16].

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV1, HSV2</td>
<td>p.o. Aciclovir 400 mg 3 times a day</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>i.v. Aciclovir 5–10 mg/kg every 8 h</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>p.o. Aciclovir 400 mg 3 times a day</td>
</tr>
</tbody>
</table>

**Herpes zoster—VZV**

| VZV localized | Aciclovir 800 mg 5 times a day | Brivudin 125 mg once a day | Famciclovir 500 mg 3 times a day | Valaciclovir 1000 mg 3 times a day | Duration until complete healing of lesions occurs |
| VZV disseminated or visceral | i.v. Aciclovir 5–10 mg/kg every 8 h | Duration until complete healing of lesions occurs, usually 7-10 days |
| VZV primo infection | i.v. Aciclovir 5–10 mg/kg every 8 h | Duration until complete healing of lesions occurs, usually 7-10 days |

Table 2. Management of herpesvirus infections in patients on anti-TNF alpha treatment (adapted from [16, 17]).
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2.1.1.2 Herpes simplex virus (HSV)

Herpes simplex virus 1 (HSV1) and herpes simplex virus 2 (HSV2) herpes infections are a relatively frequent complication which may if recurrent impact patient quality of life. Due to the relatively benign course of HSV infections, the majority are not recorded in registries—hence the limited data on incidence in patients on anti-TNF alpha therapy. Our experience with 1 year follow-up of skin viral infection in 239 psoriatic patients taking anti-TNF alpha confirms 12 cases with HSV 1 and HSV2 infection, which is incidence 5,0/100 PY.

In the general population, an occurrence of more than five episodes a year is regarded as a recurrent HSV infection that initiates prophylactic virostatic therapy. Repeated or disseminated infection in patients on anti-TNF alpha therapy is an indication for prophylactic treatment (Table 2). In adult patients, acute primary infections are not encountered which may be manifested as herpetic gingivostomatitis. In the majority of herpes simplex labialis infections, anti-TNF alpha therapy is not suspended. If the disease has a more severe course, therapy is suspended until the suppression of skin or system manifestations [16]. HSV1 and HSV2 are only diagnosed in clinically unclear manifestations.

2.1.2 Other viral infections

The manifestation of clinical skin human papillomavirus (HPV) infection during anti-TNF alpha therapy is frequent. HPV and molluscum contagiosum (MC) viral proteins seem to interfere with the apoptotic pathway of the host cell signaled by TNF receptors. Anti-TNF alpha agents block TNF directly, so HPV and MC could develop or flare [18].

Clinically, HPV infection is manifested as verrucae vulgaris and condylomata accuminata. When treating condylomata accuminata, we avoid topical treatment with imiquimod, since this may induce the formation of psoriatic lesions or psoriasis-like plaque.

2.2 Bacterial infections

Erysipelas and cellulitis are common severe skin bacterial complications. Cellulitis is one of the most common infectious skin diseases that occur in the course of biological therapy (0.3/100 PY). The first manifestations of cellulitis and
erysipelas require immediate antibiotic treatment. These data have been confirmed not only in all patients (rheumatological, gastroenterological, and dermatological) undergoing anti-TNF alpha therapy [14]. The early initiation of therapy may prevent subsequent complications. If the disease is resistant to the oral form, intravenous antibiotic treatment or sometimes combined therapy is initiated. In the case of acute manifestations of the disease, biological therapy is suspended immediately. After the successful treatment of an acute attack, long-term antibiotic prophylaxis may continue.

As stated by Andrade et al., bacterial infections were most frequent when observing adverse effects in patients with inflammatory bowel disease (IBD) (732 patients, 10-year follow-up) on anti-TNF alpha therapy, accounting for 45% of all infections. Most common were folliculitis in 38% of patients and abscesses in 31%. Psoriatic patients are likely to have less abscesses, since IBD diseases have specific extraintestinal manifestations and are also associated with hidradenitis suppurativa comorbidity which may be evaluated as folliculitis and abscesses [19].

### 2.3 Fungal infections

Fungal infections are not as frequent as viral and bacterial infections. Likewise, such depend on whether the patient is on combined immunosuppression. In the case of opportunistic infections, association between anti-TNF alpha and oral candidiasis has been described but only in a very small number of cases (less than 0.1 patient per 100/PY). Cases of esophageal candidiasis have occurred in particular in patients with Crohn’s disease (CD). Rare cases of aspergillosis, candida sepsis, and coccidioidomycosis have been reported [14]. To a large degree incidence is impacted by concurrent systemic corticosteroid treatment, which is not indicated for the treatment of psoriasis [20]. In practice we can observe cases of tinea pedis and onychomycosis, which are also very common in the general population; data on comparison of incidence with the general population are very limited. If joints are severely affected by psoriatic arthritis with deformation of toes, interdigital fungal manifestations are more common. Treatment of the fungal infection is essential in prevention of skin cracking, which is a portal for the entry of bacterial infections.

![Figure 2. Female patient treated with adalimumab, who was working as a nurse at a psychiatric department. A follow-up examination revealed green-brown nail color (A). Culture test findings: Pseudomonas aeruginosa ++, Klebsiella pneumoniae +, Kosciura kristinae ++, Candida albicans ++, Candida tropicalis +. Topical antibiotic treatment in combination with antymycotic therapy was initiated. (B) Condition after 6 weeks of treatment.](image-url)
Superficial skin mycoses in patients on anti-TNF alpha therapy may be mistaken for psoriasis, and if such occur following anti-TNF alpha therapy, they may be mistaken for paradoxically induced psoriasis. In complicated cases, it is therefore necessary to conduct a direct microscopic and culture fungal examination (Figure 2).

3. Reactions directly associated with therapy administration

Reactions associated with therapy administration have a heterogeneous nature. Their classification and etiopathogenesis are complicated. Due to the different structure and properties of anti-TNF alpha preparations, reactions are described separately for infliximab, adalimumab, and etanercept.

3.1 Infliximab

Most data in literature and reactions following administration are associated with infliximab. Infliximab is a chimeric monoclonal antibody (murine/human) of immunoglobulin (Ig) G1 class anti-TNF alpha. Due to its chimeric element and intravenous administration, patients are premedicated prior to therapy.

Acute reaction to infusion occurs in 10–40% of infliximab-treated patients and usually starts during administration or within an hour of administration of the biologic agent. Delayed reaction to infusion occurs in 1–14 days following the administration of the biologic agent and is typically associated with myalgia, arthralgia, headache, rash, and fatigue. In some cases, a serum sickness-like reaction develops [21, 22]. According to FDA data and post-marketing surveillance, this reaction occurs in 2% patients.

Acute reactions can be divided into mild, moderate, and severe. Mild and moderate reactions may be dealt with by slowing the infusion rate or momentary interruption or infusion, with symptoms spontaneously resolving. Clinical manifestation is accompanied by headache, itching, nausea, and erythema [21, 22].

Severe forms of acute reactions are described in 5% cases, with manifestations of severe anaphylactic reaction [21]. Treatment must be suspended and readministration of the biologic agent is not recommended. It is assumed that the reaction is not a standard anaphylactic reaction, but rather an anaphylactoid one. In recent years, many papers describing the formation of antibodies against biologic agents have been published. The formation of antibodies against biologics is called immunogenicity of biological treatment and is associated with acute reactions. Steenholdt et al. evaluated the formation of antibodies against infliximab and the formation of IgE antibodies during acute reactions. Their work confirmed that serious acute reactions following infliximab are closely associated with the production of anti-IFX IgG antibodies while having no relation to anti-IFX IgE antibodies. The reactions are therefore not called anaphylactic but rather anaphylactoid. In the observed set, reactions occurred most frequently with second administration. Low levels of anti-IFX IgG antibodies prior to subsequent administration do not exclude the possibility of reaction [23]. In contrast, works confirm the association between the occurrence of acute reactions and specific IgEs against a biologic agent [24, 25]. Likewise, works have successfully implemented desensitization with a biologic agent following acute urticarial and anaphylactic reaction [26].

While the precise mechanisms of individual reactions have not been explained, it transpires that monitoring the formation of antibodies against biologics may be important to differentiate certain reaction types. In daily practice it has become common to administer combined suppressing biologics with low doses of...
methotrexate or in the case of chronic inflammatory bowel disease in combination with azathioprine. Combined suppression should reduce the formation of antibodies against biologics and thus reduce adverse reactions [27].

3.2 Adalimumab

Adalimumab is a recombinant human high-affinity immunoglobulin G1 (IgG1) monoclonal antibody that inhibits TNF alpha. A reaction at the injection site is most frequent, which may occur after administration or within 1–2 days and usually resolves within 3–5 days. It occurs in nearly 20% of patients, and occurrence is much less frequent compared to etanercept [28]. Anaphylactic and anaphylactoid reactions are rare.

Benucci et al. also described a case of an immediate systemic reaction to adalimumab with positive skin prick and intradermal tests. Nevertheless, serum-specific IgE to adalimumab results were not detectable. This was the first case of immunologic but not IgE-mediated immediate systemic reaction to adalimumab [29].

3.3 Etanercept

Etanercept is a dimeric human recombinant protein constituted by the binding of two soluble TNF receptors (p75 and human IgG1 Fc). It binds irreversibly and competitively to circulating and membrane-bound TNF-α and TNF-β, thus preventing its interaction with membrane receptors of effector cells of the immune system [30]. According to the Food and Drug Administration (FDA), up to 37% of patients have injection site reaction to etanercept, while other types of reaction are rare with this biologic agent [31]. As described in the case of adalimumab, the reaction resolves within several (3–5) days. Most of these reactions are type IV delayed-type hypersensitivity (DTH) reactions [31]. Benucci et al. described two cases of etanercept-induced ISR consisting of edema, erythema, and itching [29]. In both patients, intradermal tests with etanercept were positive at the immediate reading and negative at the later reading, suggesting an immediate reaction, possibly IgE-mediated (“Type I” reaction).

Borrás-Blasco et al. and Skyttä et al. described three cases of severe urticaria induced by etanercept [32, 33]. Although the overall risk of urticaria appears low, clinicians should be aware of this reaction.

3.4 Testing and invoking tolerance

Due to various mechanisms of injection site reactions, as well as anaphylactic or anaphylactoid reactions, it is appropriate to supplement patient testing.

Literature contains publications which describe various protocols for the dilution of biologic agents when testing using prick and intradermal tests; some authors have also conducted patch tests [30, 34]. Likewise, various procedures invoking drug tolerance and the detection of antibodies against biologics from IgG and IgE class are becoming more available. In the case of serious reactions, it is preferred to switch biological therapy prior to desensitization, which is only carried out in exceptional cases when there is no other therapeutic modality available.

4. Immune-mediated complications

As we mentioned at the beginning, immune-mediated adverse effects are a new group of diseases. We recently published a chapter on immune-mediated adverse
effects, analyzing pathogenesis and reactions in all indications of anti-TNF alpha therapy [35]. The following section is therefore only about diseases that occur in psoriasis patients on anti-TNF alpha therapy, followed by a description of the potential therapeutic procedures in the event of immune-mediated complications.

4.1 Psoriasis

Psoriasis or psoriasiform reaction is one of the most common immune-mediated reactions. This reaction may occur in psoriasis patients successfully treated with anti-TNF alpha therapy. The formation of anti-TNF alpha-induced psoriasis is also called a paradoxical reaction. Psoriasis or psoriasiform reaction is one of the most common immune-mediated reactions.

The clinical symptom of paradoxical psoriasis can be of variable nature. Paradoxical psoriasis includes newly developed psoriasis as well as the significant worsening of existing psoriasis. The disease is most commonly manifested in the palms and soles as palmoplantar pustulosis reported in 56% of cases; other common forms include chronic plaque psoriasis (50%) and guttate manifestations (12%). Patients may also suffer from multiple forms of disease simultaneously (15%) [36]. Other manifestations include scalp or nail involvement. The clinical picture of the disease in patients with chronic plaque psoriasis most often includes the formation of palmoplantar pustulosis, which they did not suffer before (Figures 3 and 4). While the pathogenic mechanism of this paradox reaction remains unclear, the most widespread theory links the relationship between TNF alpha and type 1 interferon alpha: TNF alpha blockers can lead to the overproduction of INF-alpha. In papers that confirm this theory, the increased expression of interferon alpha was demonstrated in skin biopsy compared to common psoriatic findings [37]. One of the latest theories involves the Th 17 pathway. TNF alpha inhibitor may cause dysregulation in the immune system, which may cause the following changes. We describe possible therapeutic approaches in patients with psoriasis and paradoxical reactions in Figure 5.

4.2 Alopecia areata

Etiopathogenesis of alopecia areata is not clear. Some authors explain the occurrence of alopecia areata similar to TNF alpha-induced psoriasis. Inhibition of TNF alpha results in dysregulation of cytokines and subsequent production of IFN-alpha, which results in a pathological process [38].

Alopecia areata could be solitary finding or could accompany other immunologically mediated reaction. In practice we can see that alopecic lesions can regress

Figure 3.
Patient with positive family history for psoriasis with palmar ragdiform eczema, nail lesions, and erythema around wrist. Lesions started immediately after 1 month of initiation adalimumab therapy sent to our department like paradoxical psoriatic reaction. Fungal culture proves Trichophyton rubrum.
to normal, even without biologic agent discontinuation or switching. Along with biologic treatment, local treatment or cyclosporin can be added to the treatment regime to manage less severe cases of alopecia areata. In cases which lead to generalized or universal alopecia, immediate biologic treatment discontinuation is indicated. Corticosteroid pulses are not recommended due to possible rebound of primary disease [35].

Figure 4.
(A) Patient in whom palmoplantar pustular reaction with concomitant alopecia areata started 2 months after adalimumab treatment initiation for chronic plaque psoriasis. In the time of adverse event, the patient was already without chronic plaque psoriasis. Discontinuation of anti-TNF alpha and switch to secukinumab resolve skin reactions (B).

Figure 5.
Literature data indicate a possible occurrence of sarcoidosis in 0.04% of the patients treated with TNF alpha inhibitors [39]. The skin symptoms were manifested as erythema nodosum, pigmented scars, and nodular lesions [40]. Differential diagnosis of symptoms along with histological examination is important (Figure 6). In most cases, the anti-TNF alpha agent was discontinued. Rechallenge was not performed, but a limited number of patients switched therapy without relapse.

4.4 Other reactions

A wide range of skin immune-mediated adverse reactions have been described in relation with using anti-TNFα agents. Frequently reported reactions are vasculitis, lupus-like syndrome, vitiligo, lichen and lichenoid reaction, and hidradenitis suppurativa. Some cases reports about pyoderma gangrenosum, morphea, and dermatomyositis induced by anti-TNF alpha agents [35].

5. Malignancy

Many studies examining the carcinogenic risk of TNF-α inhibitors suggest that they can slightly increase the risk of cancer, mainly non-melanoma skin cancer (NMSC).

In their summary work, Burmester et al. assessed the incidence of malignancies in patients treated with adalimumab against the general population. Overall, the incidence of malignancies in patients undergoing biologic therapy with adalimumab was comparable to the general population. A higher incidence of non-melanoma skin cancer (NMSC) compared to the general population in all indications of the biologic agent was also unconfirmed. The occurrence of melanoma was not significantly higher vs. the general population [14]. A recent meta-analysis of 77
randomized controlled trials of adalimumab, infliximab, and etanercept associated with all anti-TNF alpha therapies for NMSCs was 2.02 [41].

The risk of melanoma with TNF inhibitors is controversial. The meta-analysis of registries found increased but insignificant risk of developing melanoma in patients treated with anti-TNF, because the pooled estimate from two studies was 1.79 (95% CI, 0.92–2.67). In addition, a combined analysis of 11 European registries did not find any increased risk of melanoma with anti-TNF [42].

Comparisons of biologic agents and malignancies in patients with psoriasis are included in outputs from the PSOLAR database (long-term follow-up, 12,000 psoriasis patients), with higher incidence of malignancies detected in the case of infliximab vs. adalimumab and etanercept [43]. When assessing cancer diseases, we have to consider the potential previous combined immunosuppression that patients may already receive (Figure 7). We know that most patients on biological therapy previously received high doses of conventional immunosuppressive systemic therapy, and in psoriasis patients we have to take into account the impact of phototherapy as well. HPV infection is a factor which may contribute to the development of squamous cell carcinoma.

All patients on anti-TNF alpha therapy should be regularly (annually) monitored for skin changes and undergo examination prior to the initiation of anti-TNF alpha therapy. Patients should use appropriate photoprotection and be advised of potentially increased risk of NMSC. In the case of a newly detected NMSC, the removal of skin cancer is recommended in most cases with the subsequent continuation of biologic therapy. We do not recommend the application of topical imiquimod, which may induce the formation of psoriatic lesions. In psoriasis patients, it is sometimes difficult to distinguish between a superficial basocellular carcinoma and a psoriatic lesion. So if a psoriatic lesion is refractory to topical treatment, we have to consider a potential superficial basal cell carcinoma as part of differential diagnostics.

In the case of squamous cell carcinoma, the staging and grading of the carcinoma should be reviewed, and subsequently consider whether biological therapy should continue. Alternatives would be systemic retinoids [44].

6. Conclusion

Biologic therapy with anti-TNF alpha agents is a first-line and highly effective biologic therapy of psoriasis but is commonly associated with complications and adverse events. In the case of long-term, lifelong therapy, such events can be seen...
in almost every patient. The correct management of an adverse effect may prevent subsequent complications or the avoidable switching to another biologic preparation—if a biologic agent is highly effective for an underlying psoriatic disease, we continue its use for as long as possible. Every other biologic agent is less effective than in a naïve patient. In contrast, the abrupt termination of biologic therapy may protect from potential and even fatal complications. Therefore, collecting information on the incidence of individual adverse effects, even minor ones, but which have a significant impact on quality of life and the optimum handling of such effects, is crucial for long-term biologic therapy.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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