

Cutaneous adverse effects of biologic drugs in psoriasis: a literature review

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Abstract

Psoriasis is a chronic immune-mediated skin disease that affects 125 million people worldwide. Over the last two decades, biologic drugs have revolutionized the treatment of moderate to severe plaque psoriasis. They act on one or more molecular targets and thus modify or inhibit signal transduction pathways in the pathophysiological process of the disease. This article summarizes cutaneous adverse effects to biologic drugs used in the treatment of psoriasis. Because they were on the market first, most of the literature covers cutaneous adverse effects of tumor necrosis factor- α (TNF- α) inhibitors, but increasingly more data are also available for adverse effects caused by newer biologics that inhibit the interleukin (IL)-12/23, IL-17, and IL-23 pathways. Some cutaneous adverse effects are general—for example, injection site reactions—whereas others are more class-specific; namely, *Candida* infections in IL-17 inhibitors. However, because some biologic drugs used in psoriatic patients are also registered for the treatment of certain other immune-mediated diseases such as rheumatoid arthritis, data regarding cutaneous adverse effects come from various sources that differ in quality and often cannot be interpreted without bias.

Keywords: psoriasis, biologic drugs, biologics, targeted therapy, cutaneous side effects

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Introduction

Psoriasis is a chronic immune-mediated skin disease that affects 125 million people worldwide. The pathogenesis of psoriasis is complex and not yet been elucidated in detail (1). Over the last two decades, biologic agents have revolutionized the treatment of moderate to severe plaque psoriasis due to their efficacy and acceptable safety profiles. They act on one or more molecular targets and thus modify or inhibit signal transduction pathways in the pathophysiological process of the disease (2). The first biological drugs on the market for the treatment of psoriasis were from the group of tumor necrosis factor- α (TNF- α) inhibitors in 2004. With the advent of newer biologic drugs, which target mediators in the pathophysiological pathway of psoriasis with increasing precision, the set goal of improving in the Psoriasis Area and Severity Index (PASI) has increased from PASI 50 to PASI 100, or complete remission of skin changes. Detailed data about brand names, targets, types of antibodies, and indications of the individual biologics approved by the European Medicines Agency (EMA) for the treatment of moderate to severe plaque psoriasis until July 31st, 2021 are presented in Table 1. Treatment with biologics may be associated with heterogeneous adverse effects that depend on their targets and biological effects (3). To better understand them, it is important to know the differences between chemical and biological drugs, presented in Table 2. Based on these differences, a classification of adverse effects induced by biologics has been created, which groups them according to mechanism into five types denoted by Greek letters (α , β , γ , δ , and ϵ). This alternative classification is related but still distinct from the well-accepted classification of adverse effects observed with chemical drugs, and it is explained in Table 3 (2, 4). Regarding the diagnosis of adverse effects of biologics, various techniques are described; for example, detection of immunoglobulin (Ig) G and IgE antibodies by enzyme-linked immunosorbent assay, skin prick tests, intrader-

mal tests, and patch tests (5). Tryptase or basophil activation tests may be considered as an additional option to confirm immediate hypersensitivity. Finally, in milder non-IgE-mediated reactions, drug challenge may be performed (2).

This article reviews cutaneous adverse effects of biologic drugs approved by the EMA for the treatment of moderate to severe plaque psoriasis until July 31st, 2021. However, because some of these biologics are also registered for the treatment of certain other immune-mediated diseases, data regarding cutaneous adverse effects come from various sources that differ in quality—from registries to small case series and isolated case reports in which the causal effect of the adverse effect and the biologic drug must be critically assessed. The likelihood of an adverse effect association with the drug can be estimated by the Naranjo scale, presented in Table 4 (6). Management of skin adverse effects during treatment with biologics is beyond the scope of this article.

Type α reactions

Irritative subtype of injection site reactions (ISRs) should be categorized here.

Type β reactions

Infusion reactions

The pathomechanism of infusion reactions (IRs) is still debated; however, the immunogenicity of biologics with the formation of anti-drug antibodies (ADAs), the release of high concentrations of pro-inflammatory cytokines or histamine, and the activation of cells by Fc-IgG receptors or complement have been proposed (3, 4). Among biologics to treat psoriasis, only infliximab is administered by infusion. Occurrence of IRs was detected in 18% of treated patients compared to 5% in the placebo group (7). IRs can

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be acute or delayed, occurring within 24 hours and between 24 hours and 14 days (typically 5 to 7 days), respectively. Acute IRs are most commonly non-immune-mediated reactions, less often urticaria or anaphylaxis through IgE-mediated type I hypersensitivity mechanisms can occur. Delayed IRs or serum sickness-like reactions are usually type III hypersensitivity reactions that manifest with arthralgia, arthritis, myalgia, headache, fatigue, fever, sore throat, edema of the lips, face, or hands, and rash (8–10). Cutaneous manifestations occur in 21.1% of acute IRs (i.e., pruritus, flushing, urticaria, or rash) and 24.4% of delayed IRs (i.e., rash, urticaria, or pruritus) (11). The incidence of IRs is increased by an increased number of ADAs to infliximab and decreased by concomitant immunosuppressive treatment and dosing schedule, whereas premedication with paracetamol, antihistamines, and/or corticosteroids does not affect it (8). Mostly IRs are mild to moder-

ate, and in these patients further applications of infliximab may be continued with caution (8, 12).

Type I hypersensitivity reactions

Urticaria, angioedema, and anaphylactic reactions have been uncommonly to rarely reported in patients on therapy with TNF-α inhibitors, ustekinumab, IL-17 inhibitors, and guselkumab. Exceptions are adalimumab and infliximab, with which urticaria commonly occurs (7, 13–20).

Delayed reactions other than delayed infusion reactions

Erythema multiforme, toxic epidermal necrolysis, Stevens–Johnson syndrome, and acute generalized exanthematous pustulo-

Table 1 | Basic characteristics of biologics registered by the European Medicines Agency (EMA) until July 31st, 2021 for the treatment of moderate-to-severe plaque psoriasis (7, 13–20, 25, 26).

Target	Biologic drug/ brand name	Type of antibody	Pharmacodynamic properties	Indications approved by EMA
TNF-α	adalimumab/ Humira®	Human monoclonal IgG1 antibody	Binds specifically to TNF and blocks interaction with cell surface TNF receptors p55 and p75	PP* (≥ 4 y), PsA, HS* (> 12 y), JIA, CD* (≥ 6 y), UC* (≥ 6 y), uveitis* (> 2 y), RA, axSpA
	etanercept/ Enbrel®	Human p75 Fc fusion protein between TNF-α receptor protein and crystallizable fragment portion of IgG1	Binds to soluble, non-membrane-bound TNF and thus prevents binding of TNF to cell surface receptor TNFR	PP* (≥ 6 y), PsA (≥ 12 y), RA, JIA, axSpA
	infliximab/ Remicade®	Chimeric human–murine monoclonal IgG1	Binds to both transmembrane and soluble forms of TNFα and thus inhibits its activity	PP, RA, CD* (≥ 6 y), UC* (≥ 6 y), ankylosing spondylitis, PsA
	certolizumab pegol/ Cimzia®	Humanized antibody Fab' fragment	Binds to and consequently neutralizes membrane-associated and soluble TNF-α	PP, PsA, axSpA, RA
IL-12/23	ustekinumab/ Stelara®	Human IgGκ monoclonal antibody	Binds to p40 subunit shared by IL-12 and IL-23 and thus prevents binding of p40 to receptor IL-12Rβ1 on immune cells, thus inhibiting biological activity of IL12 and IL-23	PP* (≥ 6 y), PsA, CD, UC
IL-17A	secukinumab/ Cosentyx®	Human IgG1/κ monoclonal antibody	Binds to IL-17A and thus prevents binding to its receptor	PP* (≥ 6 y), PsA, axSpA
	ixekizumab/ Taltz®	Humanized IgG4 monoclonal antibody	Binds to IL-17A and neutralizes it	PP* (≥ 6 y), PsA, axSpA
	brodalumab/ Kyntheum®	Human IgG2 monoclonal antibody	Binds to IL-17RA, a protein that is a component of receptor complexes of multiple IL-17 family cytokines, consequently blocking IL-17 inflammatory pathway	PP
IL-23	guselkumab/ Tremfya®	Human IgG1λ monoclonal antibody	Inhibits p19 subunit of IL-23 and thus reduces cascading IL-23/TH17 pathway	PP, PsA
	risankizumab/ Skyrizi®	Humanized IgG1 monoclonal antibody	Inhibits p19 subunit of IL-23 and prevents it from binding to its receptor, thus preventing cascading TH17 pathway	PP
	tildrakizumab/ Ilumetri®	Humanized IgG1/κ monoclonal antibody	Binds to p19 subunit of IL-23 and consequently prevents interaction with its receptor	PP

*Also registered for the same indication in children.

axSpA = axial spondylarthritis, CD = Crohn’s disease, EMA = European Medicines Agency, HS = hidradenitis suppurativa, IL = interleukin, JIA = juvenile idiopathic arthritis, PP = plaque psoriasis, PsA = psoriatic arthritis, RA = rheumatoid arthritis, TNF = tumor necrosis factor, UC = ulcerous colitis, y = years.

Table 2 | Differences between chemical and biological drugs (3).

Key differences	Traditional small-molecule drugs	Biologic agents
Molecular weight	Small molecule (< 1 kDa)	Large complex molecules (> 1 kDa)
Manufacture	Synthesized chemicals (xenobiotics)	Foreign non-self proteins produced with molecular genetic techniques and purified from natural sources
Mode of administration	Oral or parenteral	Mostly parenterally (otherwise digested in gastrointestinal tract)
Metabolized (yes/no)	Yes	No, catabolized to endogenous amino acids
Side effects linked to	Pharmacological effect	Their targets and biological consequences of their action
Drug interactions	Yes	No
Dose-response	Linear	Non-linear
Effect	Pharmacological	Biological

sis are reported with TNF- α inhibitors, but they are very rare (7, 13–15). Paradoxically, researchers are studying the promising use of their target treatment with TNF- α inhibitors because TNF- α is considered a key mediator of epithelial cell death in these severe cutaneous adverse reactions (9, 21). Lichenoid drug eruption is also rare during TNF- α inhibitor therapy (13–15). A case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE or baboon syndrome) has been reported with infliximab (22). Cutaneous vasculitis can also be categorized in this group of skin adverse effects because it possibly develops due to immune complexes as a type III hypersensitivity reaction (9). It is uncommonly to rarely reported in patients on therapy with TNF- α inhibitors or secukinumab, most commonly as leukocytoclastic or non-specified cutaneous vasculitis (9, 18, 23). Recurrence is possible in 33% of patients if treatment is switched to another agent from the same group of biologics and also possible if switched to another class (23). Aside from the cutaneous manifestations of vasculitis, extra-cutaneous and systemic ones are possible, and autoantibodies can be detected (9).

Injection site reactions

ISRs are local and usually mild reactions to biologic drugs that may be manifested as erythema, edema, pruritus, erythema, hematoma, and/or pain around the injection site. They can be divided into irritative (immediate) and allergic (immune-mediated)

ISRs (immediate or delayed). Irritative ISRs are the most common and are caused by the proinflammatory actions of the drug substances. These ISRs are non-immunological and are dependent on injection techniques, the chemical and physical characteristics of the injected drug and its vehicle, etc. According to the mechanism described, this subtype should be categorized under type α reactions of biologics (5). They are thought to appear after the first application of the drug, disappear spontaneously over time, and do not require discontinuation of treatment (24). The second group of ISRs are immune-mediated ISRs, which can be further divided into immediate and delayed—which, according to the Coombs and Gell classification of hypersensitivity reactions, are categorized as types I–III and type IV, respectively (5). Immune-mediated ISRs develop because of ADAs, the isotype of which determines the subtype of these ISRs. In contrast to irritant ISRs, immune-mediated ISRs appear over time and recur with all subsequent applications of the drug with the possibility of developing immune tolerance (24). “Recall” reactions may also occur in immune-mediated ISRs with development of ISRs at the most recent sites of injections along with ISRs at previous injection sites. ISRs usually disappear in 3 to 5 days. Generally, ISRs are mild, do not necessitate discontinuation of biologic therapy, and are self-limiting (5).

The stated percentages of ISRs occurrence for different biologics are as follows: adalimumab 12.9% versus 7.2% in placebo (all indications), etanercept 13.6% versus 3.4% in placebo (psoriatic patients), and certolizumab pegol 5.8% versus 4.8% in placebo

Table 3 | Classification of adverse effects to biologic drugs according to mechanism (2–4).

Type	Mechanism	Examples	
α	Overstimulation: predicted by pharmacological activity of biological drug, due to administration or release of high concentrations of cytokines	Cytokine release syndrome	
β	Hypersensitivity: affected by degree of humanization of applied protein (humanized or fully human antibodies are less immunogenic compared to mouse and chimeric ones); development of ADAs depends on immunogenicity of the protein, type of immunoglobulin response elicited, containing adjuvants and excipients, manner of application, treatment regimens, amount of immunosuppressive co-treatment	Immediate reactions (usually within minutes of drug injection) are often triggered by IgE directed toward non-self peptide sequences, but are also non-IgE-mediated; mechanism of acute infusion reactions not entirely understood, possibly release of pro-inflammatory cytokines or complement activation may play a role Delayed reactions possibly triggered by IgG ADAs, which induce complement cascade via formation of immune complexes as well as Fc-IgG-mediated activation of neutrophils or rarely by T cells; occur within 6 hours and 14 days following application	Anaphylaxis, urticaria, acute infusion reactions, injection site reactions Delayed infusion reactions, serum sickness-like reaction, maculopapular exanthema, vasculitis, nephritis, thrombocytopenia
γ	Impaired function (immunodeficiency), cytokine or immune imbalance: biologics alter normally functioning immune system; the broader the physiological role of the effector molecule (i.e., TNF- α), the more heterogeneous effects can be observed when blocking them by biological agents	Infections, neoplasms, autoimmune and autoinflammatory diseases	
δ	Cross-reactivity: related to co-expression of molecular target on pathologic and normal tissues or to reaction of antibodies to molecules with similar structure	Acneiform eruptions in anti-EGFR treatments	
ϵ	Non-immunological side effects: are not predictable and are not related to mechanism of action of biological agent	Neuropsychiatric adverse events, aggravation of heart failure by TNF- α inhibitors, retinopathy	

ADAs = anti-drug antibodies, TNF = tumor necrosis factor, EGFR = epidermal growth factor receptor, Ig = immunoglobulin.

Table 4 | The Adverse Drug Reaction Probability Scale developed in 1991 by Naranjo et al. (6).

Question	Yes	No	Do not know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Total score: the reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less.

(patients with rheumatoid arthritis) (13–15). ISRs with ustekinumab occurred at similar or lower rates than placebo (1). In psoriatic patients treated with ixekizumab, ISRs were the third most common adverse event and were more common in patients weighing < 60 kg compared to those weighing ≥ 60 kg. In patients with psoriatic arthritis (PsA), however, this difference was observed in those weighing < 100 kg compared to heavier patients (17). ISRs were also common in patients treated with brodalumab (19). In one study, 0.7% and 0.5% of psoriatic patients treated with guselkumab reported ISRs through week 48 and week 156, respectively (20). The exact percentages of ISRs during secukinumab, risankizumab, and tildrakizumab treatment were not reported; however they were common with risankizumab treatment (18, 25, 26).

Type γ reactions

Skin infections

TNF-α is an acute-phase proinflammatory cytokine released by many inflammatory cells, including in response to various microorganisms. It is essential for an immune response against granulomatous infections (8). The risk of invasive fungal infections during treatment with TNF-α inhibitors increases with neutropenia, lymphopenia, associated diseases, and comorbidities such as diabetes mellitus and alcoholism and concomitant treatment with other immunomodulators (27). IL-17, another important cytokine in the psoriasis inflammatory pathway, is also important in mucocutaneous defense against fungal infections, most prominently *Candida albicans*, but also other fungi such as dermatophytes, *Malassezia* spp., and others. It prevents microbial dysbiosis through various mechanisms (28). Moreover, IL-23 also regulates defense against mucocutaneous fungal infections, most likely through both IL-17-dependent and -independent mechanisms (29). To sum up, blocking these cytokine pathways theoretically increases the risk of certain infections. Data from clinical trials and post-marketing studies are listed in the following paragraphs.

Skin and soft-tissue infections (abscess, paronychia, impetigo, cellulitis, necrotizing fasciitis, herpes zoster, or herpes simplex) and fungal infections are common to very common during thera-

py with TNF-α (Fig. 1) or IL-17 inhibitors, and they are uncommon during ustekinumab or anti-IL23 therapy with the exception of risankizumab, during therapy with which tinea infections commonly occur (7, 13–20, 25, 26) (Fig. 2). Molluscum contagiosum occurrence during infliximab therapy for psoriasis is mentioned in case reports; however, the authors also treated molluscum contagiosum in a patient on infliximab therapy, but a case report has not yet been published (9) (Fig. 3). Regarding the higher incidence of human papillomavirus infections in those treated with TNF-α inhibitors, the studies are contradictory (30).

Next, opportunistic infections, including *Candida*, *Pneumocystis*, coccidioidomycosis, histoplasmosis, and aspergillosis, are uncommon or rare during treatment with TNF-α inhibitors or ustekinumab (7, 13–16). Interestingly, the uncommon incidence of *Candida* spp. infections has also been reported in patients receiving anti-IL17 treatment, but it was higher compared to placebo: 1.4% and 0.6% of patients treated with ixekizumab 80 mg every 2 weeks or every 4 weeks versus 0.5% in a placebo group, and 3.55 per 100 patient years (PYs) versus 1 per 100 PYs in psoriatic patients on therapy with secukinumab 300 mg or placebo, respectively (11, 17–19). Moreover, oral candidiasis was the most common adverse effect of secukinumab in Japanese patients with psoriasis and PsA (31). When reported, candidiasis was mild or



Figure 1 | Recurrent furuncles and carbuncles in a patient treated with various TNF-α inhibitors, ustekinumab, and guselkumab.



Figure 2 | Tinea manuum in a patient on a therapy with IL-17 inhibitor secukinumab.



Figure 3 | Molluscum contagiosum on the right upper extremity in a patient treated with TNF-α inhibitor infliximab.

moderate in severity with response to topical therapy and without the need to discontinue biologics. Despite uncommon occurrence, examination of the skin for signs of fungal infection before the introduction of biologics and regular monitoring of such signs are recommended (11).

Finally, there is a 1.6- to 25.1-fold increased risk of tuberculosis by inhibiting TNF- α with biologics, especially adalimumab and infliximab. It is not specifically stated in the literature what percentage of tuberculosis cases are cutaneous mycobacterial infections (8). Reactivation of atypical mycobacterial infections during treatment with TNF- α inhibitors has also been reported in the literature (32).

Skin cancer

Numerous data suggest an increased incidence of skin cancer in patients with psoriasis compared to the general population because of either previous or concomitant treatment with psoralen and UVA (PUVA), broadband UVB, systemic immunosuppressants (i.e., cyclosporine or methotrexate), or the biologics themselves. However, the isolated impact of these is difficult to determine. As regards TNF- α inhibitors, phase IV observational studies have not shown an increased risk of skin cancer in dermatological patients, but other population-based studies found a higher incidence of basal cell carcinoma and squamous cell carcinoma. With ustekinumab, IL-12 and IL-23 probably have opposite effects in carcinogenesis. By blocking these targets, one would expect



Figure 4 | Penile squamous cell carcinoma in a patient treated with ustekinumab.

skin cancer not to occur more frequently, and this is confirmed by a number of placebo-controlled and post-marketing studies (11). TNF- α inhibitors and ustekinumab were evaluated together in a recent meta-analysis of patients with psoriasis or PsA, in which an incidence of keratinocyte cancer of 124.5 per 10,000 PYs and melanoma of 6.1 per 10,000 PYs was calculated (Fig. 4). This is much higher than the World Health Organization age-standardized world incidence of melanoma and non-melanoma skin cancer, which are 3.4 and 11 per 100,000 PYs, respectively (33). Next, in phase III trials of ixekizumab there were no statistically significant differences in the incidence of non-melanoma skin cancer between ixekizumab- and placebo-treated groups in a 60-week study period (34). Finally, there are no observational studies to monitor the incidence of skin cancer in patients treated with other IL-17 inhibitors or IL-23 inhibitors (33). Given the mixed findings, patients on biologic therapy should undergo routine skin check-ups before and during therapy with biologics, especially patients treated with TNF- α inhibitors and with a history of immunosuppressive or PUVA treatment (13, 16).

Finally, the rate of cutaneous lymphomas (primary cutaneous lymphomas and lymphomas with cutaneous involvement) seems to be higher in those treated with TNF- α inhibitors compared to the general population. This highlights the physiological role of TNF- α in innate immunity and anticancer survival (35). However, the actual role of TNF- α inhibitors in the development of cutaneous lymphomas is again difficult to assess because chronic inflammation and prior immunosuppressive therapy also increase the risk of lymphoproliferative diseases (9). This highlights the need for biopsy of all suspected lesions in patients with a history of treatment with TNF- α inhibitors (35).

Autoimmune and autoinflammatory disorders

Inhibition of target molecules in the inflammatory cascade of psoriasis can lead to the development of various autoimmune and autoinflammatory diseases, the pathophysiology of which has not yet been fully elucidated. However, the role of cytokine imbalance is anticipated, and the most commonly mentioned is the increase in interferon α concentration after TNF- α blockade. Biologics may suppress the Th1 immune response, and so the Th2-driven diseases can be prevailed (11, 36). Autoimmune and autoinflammatory disorders may also be a result of a shift in cutaneous immune response pattern, a spatial shift of activated immune cells to the skin, or an imbalance or dysfunction of regulatory T cells (37). Regarding IL-17a inhibitors, a possible explanation of their paradoxical adverse effects is the selective blockade of IL-17a, leading to overexpression of other IL-17 isoforms. In principle, immune imbalance syndromes are rare, and so it is most likely that patients' predisposition or their associated diseases also contribute to their development (36). This category is divided into paradoxical skin adverse effects and other autoimmune and autoinflammatory diseases.

Paradoxical skin adverse effects

Many so-called paradoxical skin adverse effects of biologics have been described in the literature, including psoriatic, eczematous, and granulomatous reactions, lichenoid eruptions, neutrophilic skin diseases, and hidradenitis suppurativa. They represent the appearance of those skin diseases that can otherwise be treated with the same biological agent (3). They almost certainly recur if

the same drug is restarted again, and they recur in 50% of patients if another drug from the same class of biologics is introduced (30). A new onset of psoriasis, a worsening of it, or an onset of a different morphology of psoriasis compared to the previous one has been described with all biologics for psoriasis except IL-23 inhibitors. They seem to be more common with TNF- α inhibitors and can occur at any time, but on average they recur after 14 months of treatment (11, 31, 36, 38). The most common subtypes are plaque psoriasis and palmoplantar pustular psoriasis (11).

Another paradoxical adverse effect is eczema or dermatitis; that is, atopic dermatitis, dyshidrotic eczema, nummular eczema and contact dermatitis (36). They occur uncommonly to rarely during treatment with certolizumab pegol, ustekinumab, secukinumab, and ixekizumab, whereas they were common during adalimumab and infliximab therapy (7, 13, 15–18).

Granulomatous reactions are next in the series of paradoxical adverse effects given the key role of TNF- α in the formation of granulomas (9). Cutaneous sarcoidosis with or without systemic involvement has been uncommonly to rarely reported during treatment with TNF- α inhibitors (7, 13–15). It can develop 1 month to 4 years after starting therapy (39, 40). Several cases of palisaded neutrophilic granulomatous dermatitis and granuloma annulare have been reported with TNF- α inhibitors prescribed because of rheumatoid arthritis or PsA (9). A case of granulomatous rosacea 4 weeks after initiating etanercept therapy for plaque psoriasis and PsA has also been published (41). Lesions of granulomatous reactions improved after withdrawal of offending biologics (9).

Isolated cases of lichenoid eruptions involving the skin, oral, genital mucosa, nails, and/or hair-follicles have been mentioned during therapy with TNF- α inhibitors (42).

Pyoderma gangrenosum can be paradoxically triggered by TNF- α inhibitors and has also been reported in a patient during therapy with secukinumab (23, 37). Moreover, case reports of microbial pustulosis of the folds in patients with inflammatory bowel disease on a therapy with adalimumab or infliximab have been published (43). Finally, Sweet syndrome has been mentioned with adalimumab (11).

The occurrence of hidradenitis suppurativa has been described in patients with rheumatoid arthritis, Crohn's disease or spondyloarthropathies during treatment with TNF- α inhibitors (37, 44).

Other autoimmune and autoinflammatory disorders

With negative antibody titers at baseline, antinuclear antibodies (ANA) are detected in up to 11%, 12%, 50 to 68%, and 17% of patients treated with etanercept, adalimumab, infliximab, and certolizumab pegol, respectively. These data were mostly obtained from patients with rheumatoid arthritis (4, 7, 13–15). Among patients treated with etanercept, infliximab, and certolizumab pegol, 3 to 15%, 17%, and 2%, respectively, developed new positive anti-double-stranded DNA antibodies compared to 0 to 3%, 0%, and 1% of those on placebo (7, 14, 15). Other autoantibodies are rarely reported (14). A possible explanation for the formation of autoantibodies is the increased concentration of antigens because of reduced phagocytosis and the absence of suppression of autoreactive B and T cells (9, 45). Nevertheless, drug-induced lupus and lupus-like syndrome develop uncommonly to rarely during TNF- α inhibitor therapy. More precisely, only two out of 3,441 patients treated with adalimumab and only 0.18% out of 11,000 patients treated with either infliximab or etanercept for rheumatic diseases developed it (7, 9, 13–15). There are also reports of lupus-like syn-

drome induction by ustekinumab and secukinumab (46). Drug-induced lupus can be manifested as systemic, subacute cutaneous, or discoid lupus erythematosus with the onset on average 14 to 16 months after starting therapy (9, 10). However, if symptoms suggestive of lupus-like syndrome occur and antibodies against double-stranded DNA are positive, discontinuation of therapy is required (4). After that, patients have improved (13). In addition to cutaneous lupus erythematosus, the possibility of triggering dermatomyositis and morphea by TNF- α inhibitors has also been described in the literature (7, 13–15).

Bullous dermatoses occur uncommonly to rarely with TNF- α inhibitors. There are case reports of bullous pemphigoid associated with adalimumab, IgA bullous dermatosis with infliximab and ustekinumab, and pemphigus foliaceus associated with infliximab (11).

Alopecia, histologically resembling either idiopathic psoriatic alopecia, alopecia areata, or both, is uncommon during certolizumab pegol therapy, whereas it occurs commonly during therapy with adalimumab or infliximab. Alopecia is mostly non-scarring. In a small case series, there was near complete hair regrowth 1 to 10 months after discontinuation of TNF- α inhibitors introduced because of inflammatory arthritis (47).

Behçet's disease has very rarely been reported in patients treated with secukinumab (23).

Type δ reactions

No skin adverse effects of biologics prescribed in patients with psoriasis are classified in this category.

Type ϵ reactions or non-immunological adverse effects

This subgroup lists various skin side effects that cannot be classified in any of the groups above. The mechanisms of their occurrence are not explained in detail. Pruritus is commonly present during therapy with TNF- α inhibitors, ustekinumab, and risankizumab (7, 13–16, 25). Hemorrhage and ecchymoses are uncommon during therapy with certolizumab pegol, but common during adalimumab or infliximab therapy (7, 13, 15). Thrombophlebitis is uncommon during therapy with certolizumab pegol and infliximab (7, 15). Livedo reticularis and teleangiectasia are rare during therapy with certolizumab pegol (15). Raynaud's phenomenon can be induced by certolizumab pegol and secukinumab (15, 18, 48). Onychoclasia and impaired healing are common during adalimumab therapy. Moreover, hyperhidrosis was common during adalimumab or infliximab treatment, and dry skin is commonly reported during infliximab treatment (7, 13). However, many skin adverse effects were mentioned only rarely in the literature; for example, night sweats and scars with adalimumab; seborrhea, hyperkeratosis, and abnormal skin pigmentation with infliximab; ulcers, photosensitivity, acne, skin discoloration, dry skin, nail disorders, and hair texture disorders with certolizumab pegol; embolia cutis medicamentosa, Grover's disease, and striae with etanercept; and, last but not least, erythema annulare centrifugum with ustekinumab (7, 13, 15, 16, 49, 50). Eosinophilic cellulitis (Wells' syndrome) has been reported in case reports of patients treated with adalimumab and etanercept (51, 52).

Conclusions

As biologic drugs have revolutionized the treatment of psoriasis

and other diseases, clinicians are also facing their adverse effects, which should not prevent future prescribing. Possible skin adverse effects are numerous, classified according to the expected mechanisms of action. Because many data about skin adverse effects during therapy with biologics derive from retrospective studies, case series, and case reports, the clinician must rule out other

potential causes for the observed side effects and be aware of potential biases. Further larger placebo-controlled studies are needed to clarify the exact mechanisms of occurrence of skin adverse effects of biologics registered by the EMA for moderate-to-severe plaque psoriasis and to provide guidelines for their management and prevention.

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