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REVIEW ARTICLE

Biological therapy in Psoriasis: An emphasis on its dermatologic adverse events

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Abstract

Objective: To report an overview of dermatologic adverse events (AEs) related to biologics used for psoriasis and compare common dermatologic AEs across different biologic classes.

Data Sources: A comprehensive search in MEDLINE via PubMed from inception through June 9, 2021, was conducted.

Study Selections: The selection process was performed independently by two reviewers. Studies were eligible if patients were diagnosed with plaque-type psoriasis, were treated with biologics, and had ≥ 1 dermatologic AE.

Results: A total of 1023 records were identified, and 127 studies were included. The incidence of dermatologic AEs was 4.17% for tumor necrosis factor-α (TNF-α) inhibitors, 9.49% for interleukin (IL)-12/23 inhibitor, 12.40% for IL-17 inhibitors, and 7.37% for IL-23 inhibitors. Biologic-related dermatological AEs can be classified into allergic skin reactions, inflammatory skin diseases, skin infections, skin neoplasms, and miscellaneous AEs. An evident class effect was observed. Skin neoplasms (1.45%), mainly nonmelanoma skin cancer (1.36%), predominated among TNF-α inhibitors. Allergic skin reactions (6.25%) were frequently reported with IL-12/23 inhibitor. During treatment with IL-17 inhibitors, skin infections (5.01%) were common, and the most common was driven by mucocutaneous candidiasis (4.85%). Inflammatory skin disease (2.32%), mainly eczematous eruptions (0.84%), dominated in IL-23 inhibitors.

Conclusions: A predominance of specific dermatologic AEs appears in distinct biologic classes due to their different specific targets of action. Further study is needed to understand the mechanisms of these potential AEs, which will help in their management.

Key words: Infliximab, adalimumab, etanercept, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, tildrakizumab, risankizumab, skin (cutaneous), safety, side effect, AE, ADR

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Introduction

Psoriasis is a chronic systemic immune-mediated skin disease affecting 0.09% to 5.1% of the general population.[1] Knowledge about the immunopathogenesis of psoriasis has transformed the therapeutic approach toward targeted therapy. Biologics, representing targeted therapy, refer to complex molecules including monoclonal antibodies and receptor fusion proteins that target specific parts of the immune responses. The targets of currently available biologics for the treatment of psoriasis are tumor necrosis factor-α (TNF-α), the interleukin 12 (IL-12)/T-helper 1 (Th1) pathway, and the IL-23/Th17 pathway, which play crucial roles in psoriasis pathogenesis.[2-4]

Currently, US Food and Drug Administration (FDA)-approved biologics for psoriasis (excluding biosimilars) are infliximab, adalimumab, etanercept, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab.[3,5] Most of these drugs showed excellent efficacy with an acceptable safety profile. However, the expanding use of biologics is inevitably accompanied by the emergence of new adverse events (AEs). Dermatologic AEs

have frequently been reported in studies and clinical experiences, posing a significant challenge for physicians. Due to their different targets of action, various dermatologic AEs have been observed across each biologic class.[3,4] This review aims to report an overview of dermatologic AEs related to biologics used for psoriasis and compare common dermatologic AEs across different biologic classes.

Methods

Literature search

A comprehensive search in MEDLINE via PubMed from inception through June 9, 2021, was conducted. The search terms included the following: "psoriasis," or "psoriatic," combined with either "skin," or "cutaneous," combined with either "safety," or "adverse," and one of the following: "infliximab," "adalimumab," "etanercept", "certolizumab," "ustekinumab," "secukinumab," "ixekizumab," "brodalumab," "bimekizumab," "guselkumab," "tildrakizumab," or "risankizumab".

The search terms aimed to include all dermatologic AEs related to FDA-approved biologics for patients with psoriasis. To be comprehensive, bimekizumab, an FDA approval-pending biologic for moderate-to-severe plaque psoriasis (as of July 2021), was also included in the present review.

Study selections

Study selections were performed independently by two reviewers. All references were screened to identify eligible studies. The language was limited to English. Studies were eligible if patients were diagnosed with plaque-type psoriasis, were treated with infliximab, adalimumab, etanercept, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, tildrakizumab, or risankizumab, and had ≥ 1 dermatologic AE. Patients diagnosed with other types of psoriasis without plaque-type psoriasis, treated with more than one biologic agent, treated with concurrent therapy, or treated with biosimilars were excluded. Pool analysis and subgroup analysis were also excluded. A flow diagram of the study selection process is shown in **Figure 1**.

Data analysis

Reported dermatologic AEs from all types of studies, including case series and case reports, were included to reflect all dermatologic AEs following the use of biologics, and are presented as the number of reported cases (N). In contrast, comparisons across biologic classes were performed using the rate of dermatologic AEs (%) calculated based on data from clinical and observational studies.

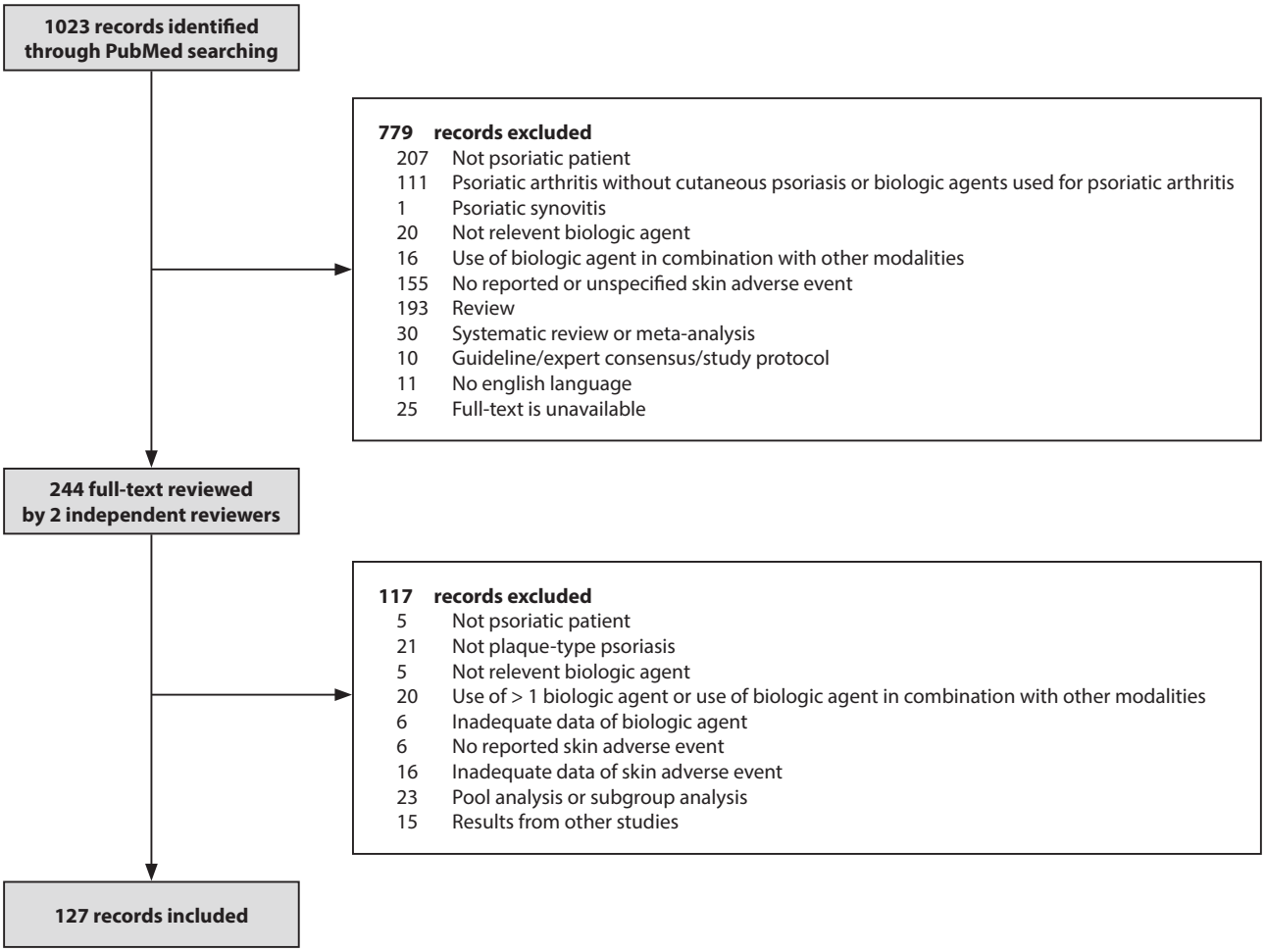

Figure 1. A flow diagram of study selection process.

Results

A total of 1023 records were identified from PubMed. After the papers were screened and reviewed, 127 eligible studies (41 clinical studies, 14 observational studies, 16 case series, and 56 case reports) were included. Of these studies, 76 were related to TNF-α inhibitors (25 infliximab, 25 adalimumab, 26 etanercept, and 0 certolizumab), 16 were related to IL-12/23 inhibitor (16 ustekinumab), 36 were related to IL-17 inhibitors (19 secukinumab, 8 ixekizumab, 5 brodalumab, and 4 bimekizumab), and 11 were related to IL-23 inhibitors (5 guselkumab, 3 tildrakizumab, 3 risankizumab). Regarding clinical and observational studies, the total number of studied patients was 671 for infliximab, 11,226 for adalimumab, 3,340 for etanercept, 4,614 for ustekinumab, 3,153 for secukinumab, 3,370 for ixekizumab, 2,620 for brodalumab, 1,011 for bimekizumab, 1,171 for guselkumab, 532 for tildrakizumab, and 930 for risankizumab. The details of all eligible studies are provided in **Supplementary Table 1**.

Review

The initiation of pathogenesis in psoriasis is triggered by predisposing genotype and external factors. These triggers disrupt keratinocytes, which then release self-deoxyribonucleic acid (DNA) and the antimicrobial peptide LL37 (cathelicidin). Self-DNA and pathogen-derived DNA bind with LL37 and form a complex that activates plasmacytoid dendritic cells (DCs). Plasmacytoid DCs release type 1 interferons (IFNs) and TNF-α, which promote myeloid DCs. Subsequently, the T-cell mediated immune response becomes greatly exaggerated resulting in the release of cytokines related to keratinocyte activation and proliferation, plus the recruitment and activation of further inflammatory cells. Currently available biologics aim to target specific parts of the immunopathogenesis of psoriasis. The target sites of biologics in psoriasis are illustrated in **Figure 2**.[2,4]

Dermatologic AEs observed during biologic treatment could be categorized into five groups: allergic skin reactions, inflammatory skin diseases, skin infections, skin neoplasms, and miscellaneous AEs. The highest incidence of dermatologic AEs was reported during IL-17 inhibitor treatment (12.40%), followed by IL-12/23 inhibitor (9.49%), IL-23 inhibitor (7.37%), and TNF-α inhibitor (4.17%) treatment. The dominances of dermatologic AEs across biologic classes varied, suggesting a class effect. Skin neoplasms, allergic skin reactions, skin infections, and inflammatory skin diseases predominated in TNF-α inhibitors, IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors, respectively (**Figure 3**). The three most common dermatologic AEs are ranked and illustrated by biologic class in **Figure 4**.

TNF-α inhibitors

TNF-α is a proinflammatory cytokine involved in various steps in the immunopathogenesis of psoriasis.[2]

Previous studies demonstrated an increased risk of nonmelanoma skin cancer (NMSC) in patients administered TNF-α inhibitors, while the risk of melanoma remained inconclusive.[6-8] The relative risk of NMSC is 2.02 in patients receiving TNF-α inhibitor treatment, the majority of which are basal cell carcinoma and squamous cell carcinoma.[9] Consistent with previous findings, our review observed a predominance of skin neoplasms in TNF-α inhibitors (1.45%), especially NMSCs (1.36%). Regarding the 231 reported NMSCs, 138 were observed in patients treated with adalimumab (**Table 1**). Similarly, the number of melanomas observed in patients treated with TNF-α inhibitors was higher than those treated with IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors. Since TNF-α regulates many facets of cell function, including proliferation, activation, differentiation, and apoptosis, blocking TNF-α may disturb the tumor suppression mechanism through the inhibition of TNF-α cytotoxic effects. Consequently, TNF-α inhibitors may induce rapid proliferation of epithelial tumors.[2,10] However, there are some limitations due to data on the risk of cancer from the included studies. Assuming that most of the patients with moderate-to-severe psoriasis encountered several immunosuppressive treatments before receiving TNF-α inhibitors, some were treated with psoralen and UVA (PUVA), which are associated with an increased NMSC risk,[11] it is difficult to conclude that NMSC is specifically attributable to biologic therapy alone.

Allergic skin reactions (1.24%) were also frequently reported in patients treated with TNF-α inhibitors which mainly contributed to injection site reactions (ISRs) (0.72%) and infusion reactions (0.43%) (**Table 1**). Factors associated with injection site pain and ISRs include pH, volume and excipients, temperature, and the injection process, while patient-related factors, such as low body weight, and female sex, can make an individual more susceptible.[12] Thoumaidou et al.,[13] reported high incidences of ISRs (> 5%) during etanercept and adalimumab treatment, which were higher than our findings. This could be explained by different patient conditions and numbers of patients. The incidence of infusion reactions following infliximab was 9.69%. The immediate infusion reactions to infliximab result from rapid infusion rate-related cytokine release from the local immune cells. A recent systematic review discussed primary prevention by a gradual increase in the infusion rate, co-administration of immunomodulators, and premedication with corticosteroids, antihistamines, and antipyretics, plus proposed a management algorithm for infusion reactions.[14]

Bacterial and viral infections were frequently observed during TNF-α inhibitor treatment. The rates of bacterial, viral, and fungal infections were 0.35%, 0.20%, and 0.09%, respectively. The blockade of TNF-α-mediated immune responses can interfere with innate and cell-mediated immune responses by suppressing IFN-γ effects, reducing T cell activity, and interfering with granuloma formation and stabilization.[15-17] TNF-α inhibitors are likely to increase the risk of all granulomatous infections, including tuberculosis and nontuberculous mycobacterial infections (NTMs). However, with the exception of tuberculosis, relatively little data has been published on this association.[18] In this review, cutaneous NTM was found in 2 patients (1 *Mycobacterium haemophilum* infection and 1 *Mycobacterium poriferae*) following infliximab and etanercept treatment.

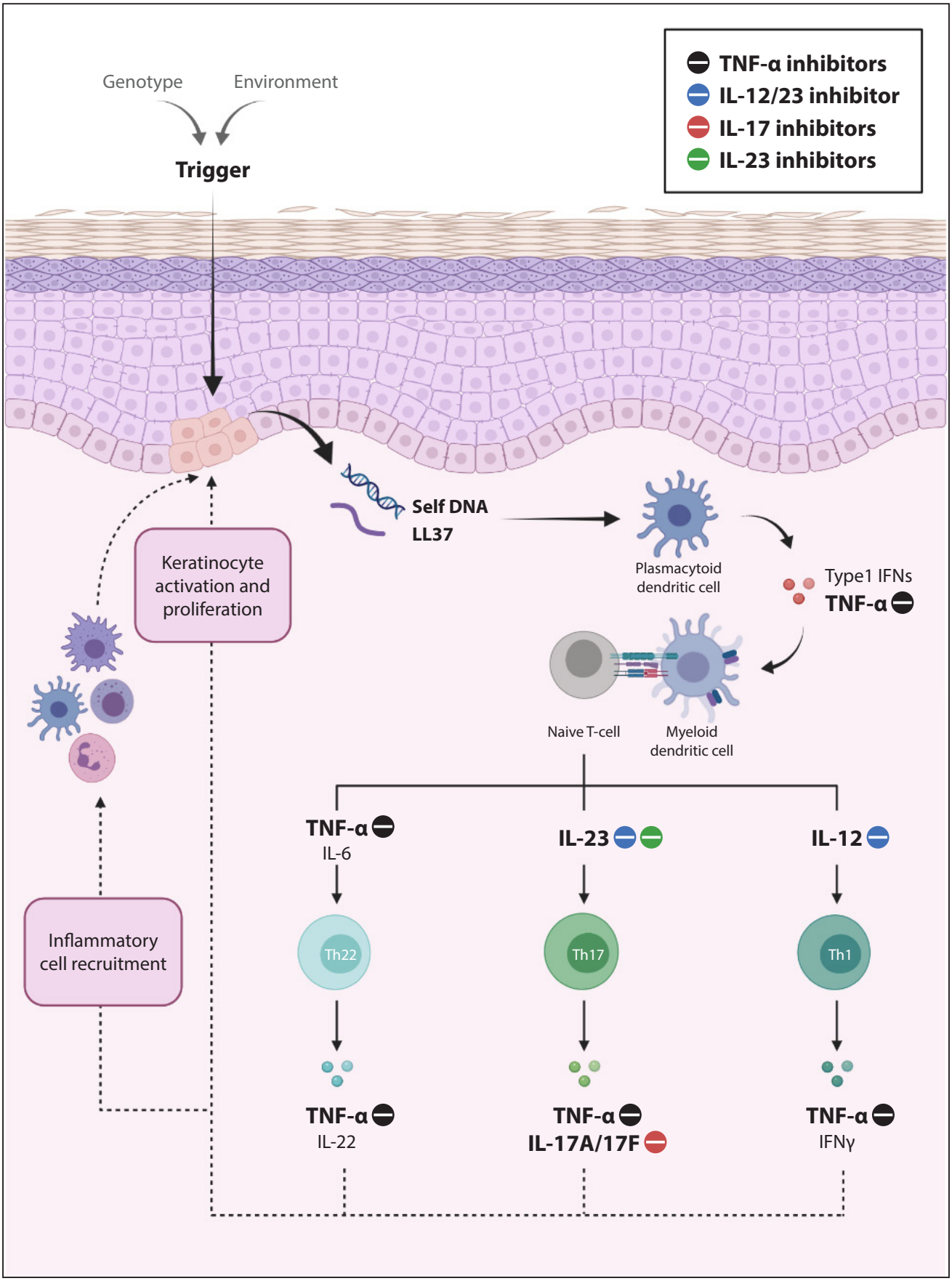

Figure 2. Target of biologics in the immunopathogenesis of psoriasis.
TNF-α inhibitors, IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors target specific parts of the immunopathogenesis of psoriasis.
DNA deoxyribonucleic acid; IFNs, interferons; IL, interleukin; TNF, tumor necrosis factor

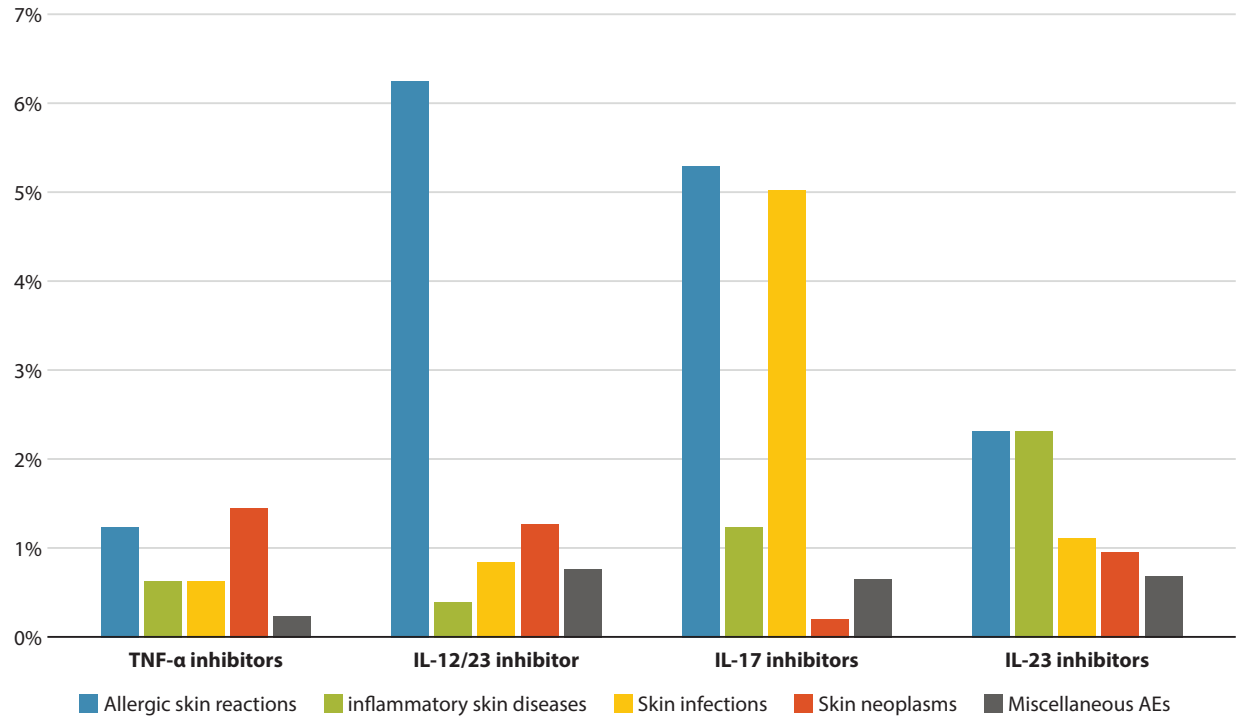

Figure 3. Overview of dermatologic adverse events by biologic class.
Bar graphs represent the rate of dermatologic adverse events (%) by biologic class based on data from clinical and observational studies.
AE, adverse event; IL, interleukin; TNF, tumor necrosis factor

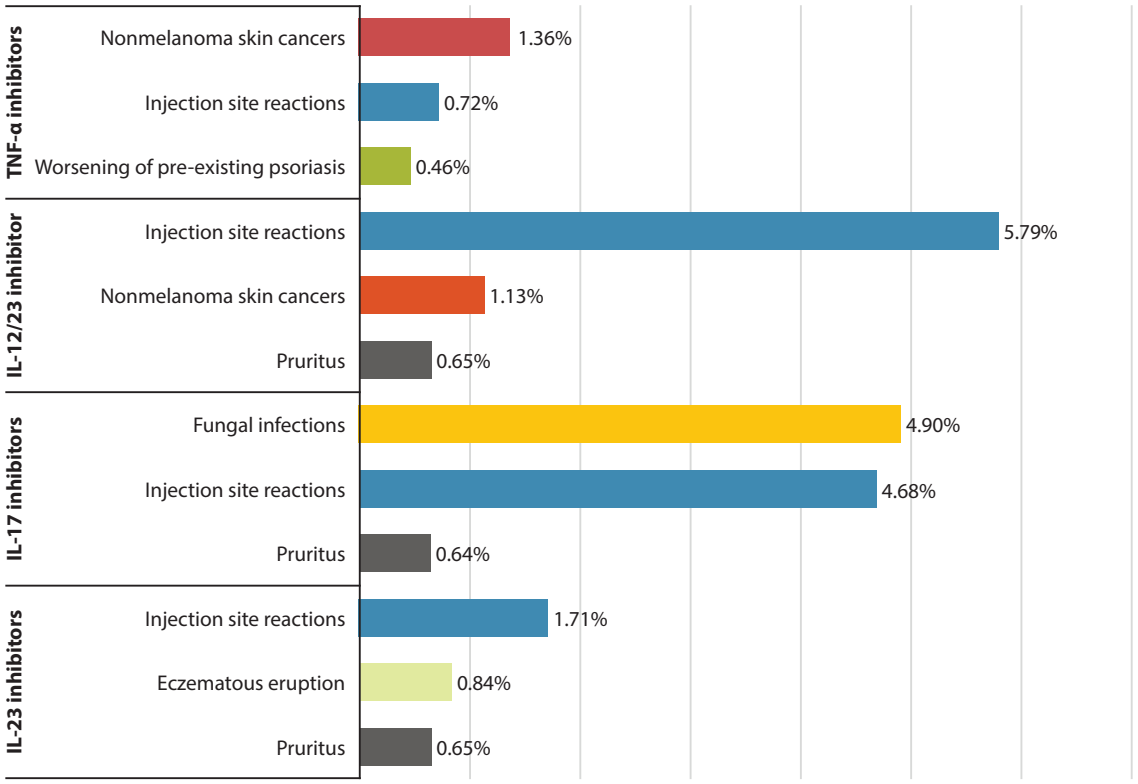

Figure 4. Three most common dermatologic adverse events by biologic class.
Bar graphs represent the rate of dermatologic adverse events (%) by biologic class based on data from clinical and observational studies.
IL, interleukin; TNF, tumor necrosis factor

Table 1. Summary of dermatologic adverse events during tumor necrosis factor-α inhibitors treatment.

	Infliximab		Adalimumab		Etanercept		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Allergic skin reactions								
Injection site reactions	2	(0.30)	39	(0.34)	71	(2.07)	112	(0.72)
Infusion reactions	65	(9.69)	0	(0.00)	0	(0.00)	65	(0.43)
Hypersensitivity reactions								
Non-anaphylactic reaction	5	(0.57)	6	(0.05)	0	(0.00)	11	(0.07)
Anaphylaxis	3	(0.45)	1	(0.01)	0	(0.00)	4	(0.03)
Nicolau syndrome	0	(0.00)	0	(0.00)	1	(0.00)	1	(0.00)
Inflammatory skin diseases								
Erythema	2	(0.30)	0	(0.00)	0	(0.00)	2	(0.01)
Maculopapular rash	0	(0.00)	2	(0.00)	0	(0.00)	2	(0.00)
Urticaria	11	(1.49)	2	(0.01)	1[a]	(0.00)	14	(0.07)
Intertriginous and flexural exanthema	1	(0.00)	0	(0.00)	0	(0.00)	1	(0.00)
Acute generalized skin eruption	0	(0.00)	2	(0.00)	1	(0.00)	3	(0.00)
Eczema								
Eczematous eruption	3	(0.45)	0	(0.00)	0	(0.00)	3	(0.02)
Contact dermatitis	3	(0.45)	0	(0.00)	0	(0.00)	3	(0.02)
Lichen simplex chronicus	1	(0.00)	0	(0.00)	0	(0.00)	1	(0.00)
Psoriasis								
Worsening of pre-existing psoriasis	10	(1.49)	50	(0.41)	14	(0.42)	74	(0.46)
Paradoxical psoriasis	3	(0.00)	6	(0.00)	2	(0.00)	11	(0.00)
Psoriasiform eruption	0	(0.00)	1	(0.00)	0	(0.00)	1	(0.00)
Other inflammatory skin diseases	5	(0.60)	3	(0.00)	7	(0.00)	15	(0.03)
Skin infections								
Fungal infections	6	(0.89)	8	(0.07)	2	(0.00)	16	(0.09)
Viral infections	15	(2.24)	0	(0.00)	16	(0.48)	31	(0.20)
Bacterial infections	9	(0.75)	27	(0.24)	24	(0.66)	60	(0.35)
Cutaneous leishmaniasis	1	(0.00)	0	(0.00)	0	(0.00)	1	(0.00)
Unspecified skin infection	1	(0.00)	0	(0.00)	0	(0.00)	1	(0.00)
Skin neoplasms								
Benign neoplasms/eruptive naevi/pseudolymphoma	3	(0.00)	2	(0.00)	1	(0.00)	6	(0.00)
Malignant neoplasms								
Nonmelanoma skin cancers	16	(0.60)	138	(1.20)	77	(2.04)	231	(1.36)
Melanoma	1	(0.15)	13	(0.11)	1	(0.00)	15	(0.09)

Table 1. (Continued)

	Infliximab		Adalimumab		Etanercept		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Miscellaneous								
Pruritus	22	(3.28)	0	(0.00)	0	(0.00)	22	(0.14)
Acne	3	(0.45)	0	(0.00)	9	(0.27)	12	(0.08)
Sarcoidosis	0	(0.00)	2	(0.00)	0	(0.00)	2	(0.00)
Pigmentary disorders	1[b]	(0.00)	1[c]	(0.00)	2[c]	(0.00)	4	(0.00)

The number of reported cases (N) was calculated based on data from all types of studies while the percentage (%) was calculated based on data from clinical and observational studies.
[a] 1 figurate urticaria[45]
[b] 1 vitiligo[25]
[c] 3 lentiginous hyperpigmentation[46,47]

Herpes zoster, herpes simplex, molluscum contagiosum, and skin papilloma were observed in patients treated with infliximab and etanercept (**Supplementary Table 2**). Hu et al.,[19] demonstrated that molluscum contagiosum attenuates TNF-α-mediated host immune killing mechanisms; therefore, receiving TNF-α inhibitors may compromise TNF-α-mediated antiviral defenses. In contrast, a recent meta-analysis of cohort studies showed no significantly increased risk of herpes zoster infection among psoriatic patients treated with infliximab, adalimumab, and etanercept.[20]

Inflammatory skin diseases that develop after treatment with TNF-α inhibitors have also been reported. Most of these cases were worsening of pre-existing psoriasis, paradoxical psoriasis, and psoriasiform eruption in 86 patients. There is a hypothesis that the blockage of TNF-α allows an increased and uncontrolled production of type 1 interferons (IFNs) by plasmacytoid DCs, which may induce and worsen psoriasiform lesions.[21] TNF-α inhibitors may also induce and worsen psoriatic skin lesions in approximately 0.6% to 5.3% of patients. Crohn's disease and rheumatoid arthritis were the most common underlying diseases, and they were also reported in patients with psoriasis and psoriatic arthritis. These paradoxical psoriatic eruptions sometimes manifest in initially unaffected skin and may exhibit a new or different morphology from their original presentation of psoriasis. For example, patients with a history of plaque or guttate psoriasis may develop pustular lesions after TNF-α inhibitor therapy.[21] The patients who discontinued TNF inhibitor therapy had the greatest resolution of symptoms (47.4%) compared with those who switched to a different TNF agent (36.7%) or continued therapy (32.9%).[22]

Two cases of sarcoidosis were reported during adalimumab treatment and 1 case of vitiligo developed after 14 weeks of infliximab therapy. These rare paradoxical skin reactions could be associated with the activation of specific autoreactive T-cells due to cytokine imbalance following TNF-α inhibitors.[23-25]

IL-12/23 inhibitor

Ustekinumab suppresses psoriasis through IL-12- and IL-23-mediated inflammation. Unlike TNF-α inhibitors, the target site of action (the subunit p40 of IL-12 and IL-23) is specific to the IL-12/Th1 pathway and IL-23/Th17 pathway.[4]

Comparing across biologic classes, the IL-12/23 inhibitor had the highest incidence of allergic skin reactions (6.25%) consisting of ISRs (5.79%) and non-anaphylactic reactions (0.46%) (**Table 2**). Our reported incidence of ISRs was higher than those previously reported (1–2%).[13] Interestingly, the incidence of ISRs during ustekinumab administration was the second highest among all included biologics, only lower than that of ixekizumab (9.38%), although ustekinumab is a fully human monoclonal antibody without a known allergenic potential vehicle component. Regarding the mechanism of action, ISRs can be divided into two groups: irritative reactions and allergic reactions to the ingredients or to the drug itself. It is plausible that the effect might be caused by irritative reactions. Causes of irritative reactions described in previous literature were inappropriate injection techniques, injection close to a blood vessel, the chemical and physical properties of the injected drug, and a reaction to the vehicle component.[3,13,26] However, the incidence rate of ISRs was known to be highest in TNF-alpha inhibitors which is inconsistent with our study. Further studies are needed to provide evidence of the incidence rate of ISRs.

Skin neoplasms (1.26%) were the second most frequently reported dermatologic AEs during ustekinumab treatment. NMSCs had a major contribution. The incidence of NMSCs in patients treated with ustekinumab ranked as the third highest rate following etanercept (2.04%) and adalimumab (1.20%). The most common type of NMSC was basal cell carcinoma (41 patients) followed by squamous cell carcinoma (12 patients), which corresponds to previous findings.[27] Nevertheless, ustekinumab administration was not associated with increased malignancy risk.[3,8,28]

Table 2. Summary of dermatologic adverse events during interleukin 12 and interleukin 23 inhibitor treatment.

	Ustekinumab	
	N	(%)
Allergic skin reactions		
Injection site reactions	267	(5.79)
Hypersensitivity reactions		
Non-anaphylactic reactions	22	(0.46)
Inflammatory skin diseases		
Erythema	4	(0.09)
Urticaria	5	(0.11)
Eczema		
Atopic-dermatitis-like eruption	2	(0.00)
Contact dermatitis	8	(0.17)
Psoriasis		
Worsening of pre-existing psoriasis	1[a]	(0.02)
Other inflammatory skin diseases	3	(0.00)
Skin infections		
Fungal infections	25	(0.52)
Bacterial infections	16	(0.33)
Cutaneous protothecosis	1	(0.00)
Skin neoplasms		
Benign neoplasms/eruptive naevi/pseudolymphoma	1	(0.00)
Malignant neoplasms		
Nonmelanoma skin cancers	55	(1.13)
Melanoma	6	(0.13)
Miscellaneous		
Pruritus	35	(0.76)
Frontal fibrosing alopecia	1	(0.00)
Cutaneous infarction	1	(0.00)

The number of reported cases (N) was calculated based on data from all types of studies while the percentage (%) was calculated based on data from clinical and observational studies.
[a] 1 pustular psoriasis.[48]

The rate of skin infections in patients treated with ustekinumab was 0.85%. No viral infection was reported. IL-12 and IL-23 are essential cytokines for immunity. IL-12 is responsible for the differentiation of naïve Th cells to Th1 cells, which initiates and expands inflammatory reactions. IL-23 acts early in the inflammatory cascade in response to microbial products and inflammatory cytokines and promotes Th17 differentiation. Th17 cells produce several proinflammatory cytokines and activate further downstream inflammatory responses. Hence, IL-23 is essential not only for early local immunity but also for innate and adaptive immune responses. Blockade of the cytokines IL-12 and IL-23 can disrupt the activation of immune and inflammatory reactions.[29] Therefore, skin infections following the use of ustekinumab could be postulated (details provided in **Supplementary Table 3**).

Reports of 2 atopic-dermatitis-like eruptions and 1 subacute cutaneous lupus erythematosus (SCLE) supported the possibility of Th1/Th2 imbalance following IL-12/23 inhibitor. The inhibition of IL-12 and IL-23 cytokines may shift T-cell differentiation toward the opposing Th2 pathway, resulting in exaggerated Th2 and Th22 cell responses. Consequently, atopic-dermatitis-like eruption, a Th2-mediated skin disease, can develop.[30-32] Tierney et al.,[33] proposed that redundant Th22 production causes increased TNF-α through IL-6, which can lead to several inflammatory and autoimmune diseases, including SCLE.

IL-17 inhibitors

The IL-17 family consists of 5 members (IL-17A to IL-17F). In psoriatic lesions, significant upregulation of IL-17A, C, and F was demonstrated. IL-17A and IL-17F, produced mainly by Th17 cells and other immune cells (e.g., neutrophils, mast cells, natural killer cells, and lymphoid tissue-inducer cells), stimulate keratinocytes to produce proinflammatory cytokines and chemokines. Due to its high biological activity, IL-17A is a key cytokine contributing to psoriasis pathogenesis.[34-36]

The early introduced IL-17 inhibitors secukinumab and ixekizumab selectively bind and neutralize IL-17A. Brodalumab interferes with IL-17 through IL-17 receptor A subunit (IL-17RA) blockade, which leads to the blockade of IL-17A, IL-17A/F, IL-17F, IL17-C, and IL-17E. The target sites of bimekizumab (FDA approval pending) are IL-17A and IL-17F.[4]

Allergic skin reactions, skin infections, and inflammatory skin diseases were commonly reported (**Figure 3**). Concerning allergic skin reactions, most of them were ISRs. In the present review, the highest incidence of reported ISRs was observed in patients treated with ixekizumab (9.38%) (**Table 3**). A previous study revealed that the highest incidence rate of ISRs was reported in etanercept (2.97–37%), followed by adalimumab (5–20%) and ixekizumab (13–17%). The mechanisms of injection site reactions following different biologics can be multifactorial, nonspecific, immunologic, and nonimmunologic factors, such as volume, temperature, pH, speed of injection, needle size, injection techniques, and location of surrounding blood vessels. A recent study reported that the reactions from ixekizumab were generally mild-to-moderate in severity, resolved spontaneously without concomitant treatment, and did not require treatment discontinuation.[13,26]

Table 3. Summary of dermatologic adverse events during interleukin 17 inhibitors treatment.

	Secukinumab		Ixekizumab		Brodalumab		Bimekizumab		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Allergic skin reactions										
Injection site reactions	11	(0.35)	316	(9.38)	145	(5.53)	3	(0.30)	475	(4.68)
Hypersensitivity reactions										
Non-anaphylactic reactions	12	(0.35)	47	(1.39)	2[a]	(0.08)	0	(0.00)	61	(0.59)
Anaphylaxis	1	(0.03)	0	(0.00)	1	(0.04)	0	(0.00)	2	(0.02)
Inflammatory skin diseases										
Papular rash	0	(0.00)	0	(0.00)	1	(0.04)	0	(0.00)	1	(0.01)
Pustular rash	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.10)	1	(0.01)
Urticaria	5	(0.16)	0	(0.00)	5	(0.19)	0	(0.00)	10	(0.10)
Dermatitis	4	(0.13)	0	(0.00)	0	(0.00)	0	(0.00)	4	(0.04)
Dermatitis acneiform	3	(0.10)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.03)
Photosensitive cutaneous eruption	0	(0.00)	1	(0.00)	0	(0.00)	0	(0.00)	1	(0.00)
Unspecified rash	3	(0.10)	0	(0.00)	0	(0.00)	0	(0.00)	3	(0.03)
Eczema										
Eczematous eruption	33	(1.05)	1	(0.03)	3	(0.11)	0	(0.00)	37	(0.36)
Atopic-dermatitis-like eruption	7	(0.19)	5	(0.15)	0	(0.00)	0	(0.00)	12	(0.11)
Contact dermatitis	12	(0.38)	0	(0.00)	1	(0.04)	0	(0.00)	13	(0.13)
Dyshidrotic eczema	1	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)	1	(0.00)
Psoriasis										
Worsening of pre-existing psoriasis	22	(0.70)	0	(0.00)	2[b]	(0.08)	12	(1.19)	36	(0.35)
Paradoxical psoriasis	1	(0.00)	0	(0.00)	2	(0.00)	0	(0.00)	3	(0.00)
Psoriasiform eruption	1	(0.03)	5	(0.12)	0	(0.00)	0	(0.00)	6	(0.05)
Other inflammatory skin diseases	3	(0.00)	0	(0.00)	1	(0.04)	1	(0.10)	5	(0.02)
Skin infections										
Fungal infections	91	(2.89)	78	(2.31)	161	(6.15)	168	(16.62)	498	(4.90)
Viral infections	0	(0.00)	2	(0.06)	1	(0.04)	0	(0.00)	3	(0.03)
Bacterial infections	2	(0.03)	0	(0.00)	9	(0.27)	0	(0.00)	11	(0.08)
Skin neoplasms										
Malignant neoplasms										
Nonmelanoma skin cancers	12	(0.32)	2	(0.06)	0	(0.00)	4	(0.40)	18	(0.16)
Melanoma	3	(0.10)	1	(0.03)	0	(0.00)	1	(0.10)	5	(0.05)
Miscellaneous										
Pruritus	59	(1.87)	0	(0.00)	6	(0.23)	0	(0.00)	65	(0.64)
Sarcoidosis	0	(0.00)	0	(0.00)	1	(0.04)	0	(0.00)	1	(0.01)

The number of reported cases (N) was calculated based on data from all types of studies while the percentage (%) was calculated based on data from clinical and observational studies.
DFSP, Dermatofibrosarcoma protuberans; LE, lupus erythematosus; SLE, Systematic lupus erythematosus
[a] 2 angioedema[49]
[b] 2 erythrodermic psoriasis[49]

The rate of skin infections (5.01%) was remarkably high among biologic classes, mainly driven by fungal infections (4.90%), followed by bacterial infections (0.08%). Fungal infections comprised 492 (4.85%) mucocutaneous candidiasis, 4 (0.04%) cutaneous dermatophytosis, and 2 (0.02%) unspecified fungal infections. Bacterial infections included furunculosis, abscess, erysipelas, cellulitis, and necrotizing fasciitis (**Supplementary Table 4**). In addition to its role in psoriasis immunopathogenesis, IL-17 acts as a proinflammatory cytokine during the innate and adaptive immune response against mucosal and cutaneous *Candida albicans* infection. Therefore, the blockade of IL-17 can lead to defects in local defensive mechanisms, resulting in increased susceptibility to Candida infection. Moreover, IL-17 is associated with humoral immunity by promoting B cell isotype switching and germinal center formation.[37,38] Consequently, various bacterial, viral, and fungal infections could occur following IL-17 inhibitor treatment. In this review, most infections following IL-17 inhibitors were mucocutaneous candidiasis (4.85%), followed by cellulitis (0.07%).[39,40] A higher rate of skin infections was observed in patients treated with bimekizumab (16.62%) and brodalumab (6.15%) which could be explained by the boarder effects of these 2 biologics on IL-17 members.

Eczematous and atopic-dermatitis-like eruptions were observed in 1.24%, 0.18%, and 0.11% of patients treated with secukinumab, ixekizumab, and brodalumab, respectively. The number of eczematous eruptions and atopic-dermatitis-like eruptions reported during IL-17 inhibitor treatment was higher than those during treatment with drugs from other biologic classes. Several theories have been proposed for this phenomenon. Immune or cytokine imbalance syndromes, or the type γ reaction described by Pichler,[41] could be used to clarify the occurrence of eczema. Under normal circumstances, the immune system and Th1/Th2 balance are well balanced. Thus, the blockade of IL-17, an effector cytokine of Th17, could shift toward a Th-2-dominated immune response that can present as eczematous eruptions or atopic-dermatitis-like eruptions in psoriatic patients treated with IL-17 inhibitors.[32] Furthermore, it has been hypothesized that a defect in host defenses against *Staphylococcus aureus* skin infection following IL-17 inhibitors may be involved since atopic eczema lesions are often infiltrated by *Staphylococcus aureus* colonization.[42] Regarding the findings of the present review, eczematous eruptions and atopic-dermatitis-like eruptions were more frequently observed in patients treated with secukinumab and ixekizumab than in those treated with brodalumab, which can be explained by the mechanism proposed by Caldarola G. et al.[43] Secukinumab and ixelizumab selectively block IL-17A, which might induce the overexpression of other IL-17 members. Increasing IL-17C levels could lead to overstimulation keratinocytes, which may be associated with Th2-driven inflammatory skin disease (i.e., atopic dermatitis).

Compared to other biologic classes, IL-17 inhibitors had the lowest incidence of skin neoplasms (0.21%). No definite evidence supported the increased malignancy risk associated with IL-17 inhibitors.[3]

IL-23 inhibitors

Recent knowledge from genetic analyses revealed that the IL-23/Th17 axis is the dominant pathogenic pathway for psoriasis.[2] Novel biologics, i.e., guselkumab, tildrakizumab, and risankizumab, were developed to target only the IL-23/Th17 axis via subunit p19 of IL-23. In contrast to ustekinumab, the IL-12/Th1 axis is not affected, which reduces some potential AEs.[3]

The overall number of dermatologic AEs in patients treated with IL-23 inhibitors was low compared to other biologic classes, which may be explained by the fact that IL-23 inhibitors are the most recent class of biologics. Allergic skin reactions (2.32%) and inflammatory skin diseases (2.32%) were the most common cutaneous adverse effects, followed by skin infections (1.10%) and skin neoplasms (0.95%) (**Figure 3**).

Comparing across biologic classes, the incidence of inflammatory skin diseases (2.32%) dominated in patients treated with IL-23 inhibitors, especially eczematous eruption (**Table 4**). As IL-23 is an upstream cytokine regulator in the IL-23/Th17 axis, the blockade of IL-23 leads to IL-17A and IL-17F suppression.[44] Therefore, the occurrence of eczematous eruption following IL-23 inhibitors could be explained by Th1/Th2 imbalance (as mentioned in the IL-17 inhibitor section).[32]

Despite an intact Th1 response, skin infections were reported in 1.10% of patients treated with IL-23 inhibitors (0.08% fungal infections, 0.53% viral infections, 0.46% bacterial infections, and 0.04% unspecified skin infections). It is difficult to describe any relevant information due to limited detailed data in the included studies.

The rate of skin neoplasms following IL-23 inhibitor treatment was 0.95%. Benign skin neoplasms were more frequently reported than malignant neoplasms (details provided in **Supplementary Table 5**); however, the relationship between IL-23 and benign skin neoplasms has not been elucidated. Regarding malignant neoplasms, a previous study by Ergen et al.,[27] reported malignancies in clinical trials of IL-12/23 and IL-23 inhibitors in patients with moderate-to-severe psoriasis receiving active treatment with IL-12/23 or IL-23 inhibitors and found that NMSCs were the most frequently reported malignancies. Furthermore, they reviewed the malignancy data from animal models of IL-23 deficiency and discovered conflicting data. More studies are needed to clarify this finding.

To the best of our knowledge, this review is the first to present an overview of dermatologic AEs related to FDA-approved and FDA approval-pending (as of July 2021) biologics used for moderate-to-severe psoriasis, as well as emerging dermatologic AEs, and compare those across different biologic classes by classifying the impacts into five groups, in addition to postulating the mechanism that may explain individual phenomena. Data were categorized per biologic group with the intention of facilitating use in clinical practice and to illustrate a class effect. However, our study contains some limitations. First, the reported dermatological AEs from case series and case reports were unable to be included in the incidence calculation, which may affect the incidence reported here. However, they were counted and presented as the number of cases (N) to obtain all reported dermatologic AEs.

Table 4. Summary of dermatologic adverse events during interleukin 23 inhibitors treatment.

	Guselkumab		Tildrakizumab		Risankizumab		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Allergic skin reactions								
Injection site reactions	35	(2.99)	8	(1.50)	2	(0.22)	45	(1.71)
Hypersensitivity reactions								
Non-anaphylactic reactions	0	(0.00)	3	(0.56)	13	(1.40)	16	(0.61)
Inflammatory skin diseases								
Papular rash	0	(0.00)	0	(0.00)	1	(0.11)	1	(0.04)
Urticaria	1	(0.09)	9	(1.69)	0	(0.00)	10	(0.38)
Heat rash	1	(0.09)	0	(0.00)	0	(0.00)	1	(0.04)
Dermatitis	2	(0.17)	0	(0.00)	0	(0.00)	2	(0.08)
Eczema								
Eczematous eruption	1	(0.09)	21	(3.95)	0	(0.00)	22	(0.84)
Contact dermatitis	0	(0.00)	10	(1.88)	5	(0.54)	15	(0.57)
Psoriasis								
Worsening of pre-existing psoriasis	1	(0.09)	8	(1.50)	1	(0.11)	2	(0.38)
Skin infections								
Fungal infections	1	(0.09)	0	(0.00)	1	(0.11)	2	(0.08)
Viral infections	1	(0.09)	10	(1.88)	3	(0.32)	14	(0.53)
Bacterial infections	5	(0.43)	4	(0.75)	3	(0.32)	12	(0.46)
Unspecified skin infection	1	(0.09)	0	(0.00)	0	(0.00)	1	(0.04)
Skin neoplasms								
Benign neoplasms/eruptive naevi/ pseudolymphoma	0	(0.00)	14	(2.63)	0	(0.00)	14	(0.53)
Malignant neoplasms								
Nonmelanoma skin cancers	2	(0.17)	0	(0.00)	8	(0.86)	10	(0.38)
Melanoma	0	(0.00)	1	(0.19)	0	(0.00)	1	(0.04)
Miscellaneous								
Pruritus	3	(0.26)	13	(2.44)	1	(0.11)	17	(0.65)
Lymphoedema	0	(0.00)	1	(0.19)	0	(0.00)	1	(0.04)

The number of reported cases (N) was calculated based on data from all types of studies while the percentage (%) was calculated based on data from clinical and observational studies.

In addition, unspecified/incomplete data regarding the type of biologic and dermatologic AEs can affect the incidence and the number of reported cases. A large number of dermatologic AEs were observed and expected to rise in response to an increase in use of biologics for the treatment of psoriasis. Future studies are required to evaluate the incidence rate, identify definite mechanisms, and examine factors associated with these dermatologic AEs to foster effective treatment of psoriasis.

Conclusions

Dermatologic AEs are commonly observed during biologic therapies in patients with psoriasis. Certain AEs dominated in specific biologic classes, suggesting a class effect. Identifying definite mechanisms of these potential AEs is challenging yet could provide tremendous assistance in guiding the appropriate selection of biologics for use in treating psoriatic patients.

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Conflict of interest

The authors declared no conflict-of-interest. Figure 2 was created with BioRender.com.

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Author contributions

- PP and PR analyzed and interpreted the data and were the major contributor in writing the manuscript.
- KN was the minor contributor in writing the manuscript.
- All authors reviewed and approved the final manuscript.

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