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ALLERGIC SKIN DISEASES (L FONACIER, SECTION EDITOR)

Cutaneous Manifestations of Reactions to Biologics

Iris M. Otani[1] · Amy S. Levin[2] · Aleena Banerji[2]

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Abstract

Purpose of Review The goal of this paper is to review the major adverse cutaneous reactions that have been reported to the most commonly used biologics.

Recent Findings Anti-TNF agents and immune checkpoint inhibitors have significant, immune-mediated cutaneous manifestations that can necessitate discontinuation. Anti-TNF agents, IL-6 inhibitors, and IL-12/23 inhibitors can paradoxically cause psoriasis flares or unmask previously undiagnosed psoriasis. IL-17 inhibitors are unique in increasing risk for *Candida* infections. Benign injection site reactions, non-specific rash, cellulitis, and hypersensitivity reactions are relatively common adverse events.

Summary A wide variety of cutaneous reactions caused by biologics have been reported, ranging from benign injection site reactions to life-threatening cutaneous reactions necessitating discontinuation of the implicated biologic agent.

Keywords Cutaneous reactions · Biologics · Biological therapies · Anti-TNF agents · IL-6 inhibitors · IL-12/23 inhibitors

Abbreviations

TNF	Tumor necrosis factor
IBD	Inflammatory bowel disease
ISRs	Injection site reactions
CAPS	Cryopyrin-associated periodic syndromes
FMF	Familial Mediterranean fever
TRAPS	TNF receptor-1-associated periodic syndrome
HSRs	Hypersensitivity reactions
SLE	Systemic lupus erythematosus
irAEs	Immune-related adverse effects
TNF-α inhibitors	
IL-1 inhibitors	
IL-6 inhibitors	
B-cell depletion	
IL-12/23 inhibitors	
IL-17 inhibitors	
Immune checkpoint inhibitors	
IL-4/13 inhibitors	
IL-5 inhibitors	
JAK3 inhibitor	
Costimulation blockade	
Integrin receptor antagonists	

Summary

Introduction

Biological therapies are therapies that target the immune system to treat disease. As such, they can lead to a wide variety of unique immunological cutaneous manifestations. Common biologic therapies include interferons and recombinant interleukins, colony-stimulating factors, anti-cytokines, and targeted monoclonal antibodies. This review will focus on cutaneous adverse reactions of biologic agents used for the treatment of allergic disease, autoimmune disease, malignancy, and inflammatory bowel disease (see Table 1).

This article is part of the Topical Collection on *Allergic Skin Diseases*

✉ Iris M. Otani
iris.otani@ucsf.edu

[1] Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California San Francisco, San Francisco, CA, USA

[2] Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Table 1 Biologics reported to cause cutaneous manifestations

Drug class	Generic name	Brand name	Target	Mechanism	Administration	FDA-approved uses	Reference	Reported adverse cutaneous manifestations
TNF-α inhibitors	Infliximab	Remicade	TNFα	Binds soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors	Intravenous	Crohn's disease Ulcerative colitis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Plaque psoriasis	[1]	Skin infections (bacterial, fungal, viral) Psoriasis Eczema Actinic keratosis Skin cancer
	Etanercept	Enbrel	TNFα	Inhibits binding of TNFα and TNFβ to cell surface TNF receptors	Subcutaneous	Rheumatoid arthritis Polyarticular juvenile idiopathic arthritis Psoriatic arthritis Ankylosing Spondylitis Plaque psoriasis	[2]	Lupus/lupus-like syndromes Vasculitis Bullous pemphigoid Linear IgA bullous dermatosis
	Adalimumab	Humira	TNFα	Binds TNFα specifically and blocks interaction with cell surface TNF receptors; lyses surface TNF expressing cells	Subcutaneous	Rheumatoid arthritis Juvenile idiopathic arthritis Psoriatic arthritis Ankylosing spondylitis Crohn's disease Ulcerative colitis Plaque psoriasis Hideradenitis suppurativa Uveitis	[3]	Neutrophilic eccrine hidradenitis Sweet's syndrome Folliculitis and palmoplantar pustulosis Interface dermatitis Morphea Wells' syndrome Injection site reactions with subcutaneous administration Infusion reactions with intravenous infliximab
	Certolizumab	Cimzia	TNFα	Binds TNFα specifically and blocks interaction with cell surface TNF receptors	Subcutaneous	Crohn's disease Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis	[4]	
	Golimumab	Simponi	TNFα	Binds soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors	Subcutaneous	Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Ulcerative Colitis	[5]	Delayed serum sickness-like illness with intravenous infliximab
IL-1 inhibitors	Anakinra	Kineret	IL-1	Competitively inhibits IL-1 binding to IL-1 type I receptor	Subcutaneous	Rheumatoid arthritis Cryopyrin-Associated periodic syndromes (CAPS)	[6]	Injection site reactions Non-specific rash Cellulitis Herpes zoster
	Rilonacept	Arcalyst	IL-1	Acts as soluble decoy receptor that binds IL-1β to prevent IL-1β from beinding to cell surface receptors; also binds IL-1α and IL-1 receptor antagonist with lower affinity	Subcutaneous	CAPS --Familial cold auto-inflammatory syndrome (FCAS) --Muckle-Wells syndrome (MWS)	[7]	Injection site reactions Non-specific rash
	Canakinumab	Ilaris	IL-1	Binds IL-1β and prevents IL-1β from binding to IL-1 receptors; does not bind	Subcutaneous	CAPS -- FCAS --MWS	[8]	Non-specific rash

Table 1 (continued)

Drug class	Generic name	Brand name	Target	Mechanism	Administration	FDA-approved uses	Reference	Reported adverse cutaneous manifestations
				IL-1α or IL-1 receptor antagonist		Tumor necrosis factor receptor associated periodic syndrome (TRAPS) Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) Familial Mediterranean fever (FMF) Systemic juvenile idiopathic arthritis		
IL-6 inhibitors	Tocilizumab	Actemra	IL-6	Binds soluble and membrane-bound IL-6 receptors and inhibits signaling through these receptors	Subcutaneous Intravenous	Rheumatoid arthritis Giant cell arteritis Polyarticular juvenile Idiopathic arthritis Systemic juvenile Idiopathic arthritis Cytokine release syndrome	[9]	Injection site reactions with subcutaneous administration Systemic sclerosis Skin ulcer Psoriasis Hypersensitivity reactions
	Siltuximab	Sylvant	IL-6	Binds IL-6 and prevents IL-5 from binding to soluble and membrane-bound IL-6 receptors	Intravenous	Multicentric Castleman's disease who are HIV and HHV-8 negative	[10]	Pruritus Non-specific rash Cellulitis Eczema Psoriasis Xeroderma Hyperpigmentation
B-cell depletion	Rituximab	Rituxan	CD20	Binds CD20 and mediates B-cell lysis	Subcutaneous Intravenous	Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Rheumatoid arthritis Granulomatosis with polyangiitis Microscopic polyangiitis	[11]	Infusion reactions Delayed serum sickness Delayed urticaria/angioedema Sweet's syndrome Injection site reactions with subcutaneous administration
	Belimumab	Benlysta	BLyS	Binds B-lymphocyte stimulator (BLyS) and prevents BLyS from binding B cells, thereby reducing B cell survival	Subcutaneous Intravenous	Systemic lupus erythematosus	[12]	Skin infections Injection site reactions with subcutaneous administration Folliculitis Temporary mild hair loss
IL-12/23 inhibitors	Ustekinumab	Stelara	IL-12/23	Binds to p40 protein shared by IL-12 and IL-23	Subcutaneous Intravenous	Plaque psoriasis (moderate to severe) Psoriatic arthritis (active)	[13]	Psoriasis/psoriatic arthritis flares Alopecia areata

Table 1 (continued)

Drug class	Generic name	Brand name	Target	Mechanism	Administration	FDA-approved uses	Reference	Reported adverse cutaneous manifestations
						Crohn's disease (moderate to severe)		Linear IgA bullous dermatosis Eczematous drug reaction Lymphomatoid drug reaction
IL-17 inhibitors	Secukinumab	Cosentyx	IL-17	Binds IL-17A and prevents IL-17A from binding to IL-17 receptor	Subcutaneous	Plaque psoriasis (moderate to severe) Psoriatic arthritis (active) Ankylosing spondylitis (active)	[14]	Injection site reactions Increased risk for Candida infections
	Ixekizumab	Taltz	IL-17	Binds IL-17A and prevents IL-17A from binding to IL-17 receptor	Subcutaneous	Plaque psoriasis (moderate to severe)	[15]	
	Brodalumab	Siliq	IL-17RA	Binds IL-17 receptor A (IL-17RA) and prevents IL-17RA from binding IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer, and IL-25	Subcutaneous	Plaque psoriasis (moderate to severe)	[16]	
Immune Checkpoint Inhibitors	Nivolumab	Opdivo	PD-1	Binds to PD-1 receptor and prevents binding of PD-1 to PD-L1 and PD-L2 ligands	Intravenous	Unresectable or metastatic melanoma Metastatic non-small cell lung cancer Advanced renal cell carcinoma Classical Hodgkin lymphoma Recurrent or metastatic squamous cell carcinoma of the head and neck	[17]	Cutaneous immune-related adverse effects Pruritus Maculopapular rash Stevens-Johnson syndrome Vitiligo
	Pembrolizumab	Keytruda	PD-1	Binds to PD-1 receptor and prevents binding of PD-1 to PD-L1 and PD-L2 ligands	Intravenous	Unresectable or metastatic melanoma Metastatic non-small cell lung cancer with high PD-L1 expression Metastatic non-small cell lung cancer with PD-L1 expression Recurrent or metastatic squamous cell carcinoma of the head and neck	[18]	
	Avelumab	Bavencio	PD-L1	Binds PD-L1 and blocks binding of PD-L1 to PD-1 and B7.1/CD80	Intravenous	Metastatic Merkel cell carcinoma (age 12 years and older)	[19]	
	Atezolizumab	Tecentriq	PD-L1		Intravenous		[20]	

Table 1 (continued)

Drug class	Generic name	Brand name	Target	Mechanism	Administration	FDA-approved uses	Reference	Reported adverse cutaneous manifestations
				Binds PD-L1 and blocks binding of PD-L1 to PD-1 and B7.1/CD80		Locally advanced or metastatic urothelial carcinoma		
	Durvalumab	Imfinzi	PD-L1	Binds PD-L1 and blocks binding of PD-L1 to PD-1 and B7.1/CD80	Intravenous	Locally advanced or metastatic urothelial carcinoma	[21]	
	Ipilimumab	Yervoy	CTLA-4	Binds CTLA-4 and blocks binding of CTLA-4 to B7.1/CD80 and B7.2/CD86	Intravenous	Unresectable or metastatic melanoma Cutaneous melanoma with involvement of regional lymph nodes	[22]	
IL-4/13 inhibitors	Dupilumab	Dupixent	IL-4Rα	Binds IL-4Rα shared by IL-4 and IL-13 receptor and prevents IL-4 and IL-13 signaling	Subcutaneous	Atopic dermatitis (moderate to severe)	[23]	Injection site reactions
IL-5 inhibitors	Mepolizumab	Nucala	IL-5	Binds IL-5 and prevents binding of IL-5 to the IL-5 receptor α chain	Subcutaneous	Severe eosinophilic asthma (age 12 years and older) Has also been investigated but not FDA-approved for atopic dermatitis, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and nasal polyposis	[24–32]	Injection site reactions
	Reslizumab	Cinqair	IL-5	Binds IL-5 and prevents binding of IL-5 to the IL-5 receptor α chain	Intravenous	Severe eosinophilic asthma (age 18 years and older)	[33]	
JAK-3 inhibitor	Tofacitinib	Xeljanz	JAK	Inhibits Janus Kinase (JAK) JAK-3, which associates with the ϑc chain, a subunit of receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21	Oral	Rheumatoid arthritis Under investigation but not FDA-approved for psoriasis, alopecia areata, and inflamatory bowel disease	[34–38]	Acne Non-specific rash
Costimulation blockade Integrin receptor antagonists	Abatacept	Orencia	CD80/CD86	Binds B7.1/CD80 and B7.2/CD86, blocking their interaction with CD28 and inhibiting the costimulatory signal needed for full activation of T cells	Subcutaneous Intravenous	Adult rheumatoid arthritis Juvenile idiopathic arthritis Adult psoriatic arthritis Limitations: should not be giving with TNF-α inhibitors	[39–44]	Hypersensitivity reactions
	Natalizumab	Tysabri	α4-subunit	Binds α4-subunit of α4β1 and α4β7 integrins on cell surfaces of leukocytes excluding neutrophils,	Intravenous	Multiple sclerosis Crohn's disease Limitations: should not be given with	[45, 46]	Hypersensitivity reactions

Table 1 (continued)

Drug class	Generic name	Brand name	Target	Mechanism	Administration	FDA-approved uses	Reference	Reported adverse cutaneous manifestations
	Vedolizumab	Entyvio	α4β7	inhibiting α4-mediated leukocyte adhesion Binds α4β7 and blocks α4β7 interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), inhibiting memory T-cell migration into inflamed gastrointestinal tissue	Intravenous	immunosuppressants or TNF-α inhibitors Ulcerative colitis Crohn's disease	[47–52]	

TNF-α Inhibitors (tumor necrosis factor-α Inhibitors)

- Infliximab [1]
- Etanercept [2]
- Adalimumab [3]
- Certolizumab [4]
- Golimumab [5]

TNF-α inhibitors can cause a variety of cutaneous manifestations. Younger age at anti-TNF therapy initiation and Crohn's disease have been associated with increased risk of cutaneous manifestations [53•].

A study of 583 patients with IBD (inflammatory bowel disease) treated with anti-TNF therapy over a 14-year period found that 20.5% [120/583] of patients had dermatologic reactions [53•]. The most common were skin infections (11.6% [68/583]) and psoriatic lesions (10.1% [59/583]) [53•].

Skin infections were most commonly bacterial (50% [54 of 90 infections]) and fungal (24.5% [22/90]) [53•]. Viral herpes zoster infection has also been reported in 1.3% [22/1220] of patients receiving anti-TNF therapy (11 with adalimumab, 4 with etanercept, and 4 with infliximab) [54]. Patients treated with adalimumab (odds ratio 3.25) and infliximab (odds ratio 3.94) appear to be at increased risk for herpes zoster infections compared to etanercept (odds ratio of 1) [55].

Although anti-TNF therapy is a treatment for psoriasis, it can paradoxically induce new-onset psoriasis or worsen pre-existing psoriasis [56–59, 60•]. One review found 216 published cases of new-onset psoriasis (102 biopsy-proven) attributed to TNF-α inhibitors [60•]. Lesions started after an average of 14 months on anti-TNF therapy (range 1–120 months). The most common lesions were plaque psoriasis (44.8% [90/201] and palmoplantar pustular psoriasis (36.3% [73/201]). Generalized pustular psoriasis, psoriasiform dermatitis, scalp involvement with alopecia, guttate psoriasis, inverse psoriasis, and follicular psoriasis occurred less frequently. Lesions were found on the extremities (including palms and soles), trunk, face, axillae, groin, and scalp. Topical steroids were the most common treatment (76.5% [156/204]). Other treatments included vitamin D analogs, phototherapy, methotrexate, acitretin, cyclosporine, or coal tar. Psoriasis resolution occurred most frequently after stopping anti-TNF therapy (47.7% [31/65]), although it did also occur after switching to a different anti-TNF agent (36.7% [18/49]) and in some cases despite continuing the same anti-TNF agent (32.9% [27/82]).

The study of 583 IBD patients treated with anti-TNF therapy also reported eczema (2.2% [16/583]), actinic keratosis

(0.5% [3/583]), skin cancer including melanoma (0.9% [5/583]), and lupus (0.3% [2/583]) [53•]. Nested case-control studies found that use of anti-TNF therapy is associated with increased melanoma risk in IBD patients (OR 1.88) [61]. Lupus-like syndromes with photosensitivity, butterfly or maculopapular rash, and alopecia reportedly occur in 0.1–0.8% of patients on anti-TNF therapy [exact numbers not reported] [62]. Lesions generally appear at a mean of 11.6 months into treatment, most commonly with etanercept or infliximab (although cases have been reported with golimumab) [63].

Anti-TNF therapy has been associated with a number of autoimmune cutaneous manifestations. Two of the most common cutaneous autoimmune conditions, psoriasis and lupus, have already been described above [60•, 62]. A case series of 8 patients who developed vasculitis attributed to anti-TNF therapy (infliximab, etanercept, adalimumab) reported that cutaneous manifestations occurred in 63% [5/8] of these patients, with palpable purpura occurring in 80% [4/5] along with ulcers and erythematous blisters [64]. Vasculitis improved with discontinuation of anti-TNF therapy, as well as initiation of prednisone and other immunosuppressive agents (mycophenolate mofetil, hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide, or rituximab) [64]. There are several case reports of dermatomyositis induced by anti-TNF therapy (etanercept, adalimumab) that improved after discontinuation of anti-TNF therapy [65].

Autoimmune bullous disorders have been identified as treatment side effects of anti-TNF therapy. Bullous pemphigoid has been associated with adalimumab and pemphigus foliaceus has been associated with infliximab [66]. Infliximab has been reported as a trigger of linear IgA bullous dermatosis in case reports [67, 68]. Isolated cases of neutrophilic eccrine hidradenitis, Sweet's syndrome, pustular conditions (folliculitis and palmoplantar pustulosis), and interface dermatitis similar to erythema multiforme were identified by skin biopsy in patients on anti-TNF therapy (infliximab, etanercept, adalimumab) [69]. These conditions partially or completely improved after stopping the culprit drug, switching to a different anti-TNF agent, and/or treatment with steroids [69].

Case reports of morphea (localized scleroderma lesion) with adalimumab use [70] and Wells' syndrome (eosinophilic cellulitis characterized by pruritic plaques with eosinophilic infiltrate) with infliximab [71], adalimumab [72], and etanercept [73] have been reported (one case report each).

Injection site reactions during the first months of treatment with subcutaneous TNF-α inhibitors (etanercept, adalimumab, golimumab, certolizumab), and acute infusion reactions and delayed serum sickness-like illness caused by intravenous infliximab have also been reported [74, 75]. Infliximab administered intravenously has a reported acute infusion reaction rate of 5.8% [258/4448] [74]. Infusion reactions typically occur during the first 2 h after infusion but can occur up to 24 h after [75]. Cutaneous manifestations (pruritus, flushing, urticaria, and rash) reportedly occur in 21.1% [54/258] of acute infusion reactions [74, 75]. Infliximab can also cause delayed serum sickness-like illness 1–14 days after infusion with a reported rate of 0.9% [37/4448] [74, 75]. Cutaneous manifestations (rash, pruritus) were present in 24.4% [9/37] of these delayed reactions [74].

IL-1 Inhibitors

- Anakinra [6]
- Rilonacept [7]
- Canakinumab [8]

Anakinra

Local ISRs (injection site reactions) are the most frequent cutaneous manifestation of anakinra. Most ISRs occur during the first month of treatment and resolve within 7 days (range 1 to 74 days) [76, 77]. ISRs have been reported to occur at a wide range of rates: 31 [4/13] to 95% [20/21] in patients with refractory pericarditis [76, 78], 15 [6/41] to 67% [8/12] in patients with adult onset Still's disease [79, 80], and 5% [1/20] in patients with hidradenitis suppurativa [81].

Rash (further description not provided in original report) has necessitated discontinuation of anakinra in 5% [2/41] patients with adult-onset Still's disease [79]. Infections have also been reported: cellulitis in 5% [2/43] patients with CAPS (cryopyrin-associated periodic syndrome) [77] and two cases of herpes zoster (one in a patient with refractory pericarditis and another in a patient with adult-onset Still's disease) [77, 79].

Rilonacept

Local ISRs (injection site reactions) are the most frequent cutaneous manifestation of rilonacept [82]. ISRs have been attributed as the primary reason for rilonacept withdrawal [82]. ISRs are reported at a higher frequency in patients with gout treated with rilonacept (15% [150/985]) compared to placebo (3% [11/330]) [82]. Similarly, in a randomized alternating trial of rilonacept and placebo administered to 12 patients with colchicine-resistant or colchicine-intolerant FMF (familial Mediterranean fever), ISRs occurred in four study subjects treated with rilonacept only, three treated with rilonacept and placebo, and two treated with placebo only [83]. ISRs were also the most common adverse event in a prospective open-label extension study of rilonacept for

CAPS treatment [84]. Erythema occurred in 32% [32/101] of patients, pruritus in 13% [13/101], bruising in 12% [12/101], swelling in 11% [11/101], and irritation in 7% [7/101] [84].

Other cutaneous manifestations have been reported, but with less detail. One patient with gout treated with rilonacept in a phase 3 study had a "drug eruption" that was not described further [82]. Skin and subcutaneous tissue disorders were also reported in the phase 3 study (7% [66/985], for rilonacept compared to 5% [17/330] for placebo) but were not described in additional detail [82].

Canakinumab

Canakinumab has been associated with rash in 15% [3/20] of patients with TRAPS (TNF receptor-1 associated periodic syndrome) [85], skin and subcutaneous tissue disorders not described in additional detail in 4% [3/68] patients with CAPS [86], and ISRs in 15% [2/13] of patients with colchicine-resistant FMF [87].

IL-6 Inhibitors

- Tocilizumab [9]
- Siltuximab [10]

Tocilizumab

ISRs occur at a higher rate with tocilizumab compared to placebo in both patients with giant-cell arteritis (9% [14/149] with tocilizumab and 6% [6/101] with placebo) [88] and systemic sclerosis (5% [2/43] with tocilizumab and 2% [1/44] with placebo) [89]. In patients with systemic sclerosis, skin ulcer (2% [1/43]) and unspecified skin or subcutaneous tissue disorder (2% [1/43]) were also reported with tociluzimab but not with placebo [89].

Two cases of psoriasis induction attributed to tocilizumab therapy have been reported in patients with rheumatoid arthritis [90, 91]. Discontinuation of tocilizumab along with topical corticosteroids has been effective at treating tocilizumab-induced psoriasis [90]. A case of acute generalized exanthematous pustulosis in a patient treated with tocilizumab has also been reported [92].

Cutaneous manifestations can also occur as part of tocilizumab-induced HSRs (hypersensitivity reactions). Two studies found that 2% [5/243] of patients and 7% [5/72] of patients with rheumatoid arthritis or adult-onset Still's disease suffered immediate HSRs within 20–30 min of receiving a tocilizumab infusion [93, 94]. Out of the ten patients with tocilizumab-induced HSRs, nine had received tocilizumab at least one time prior to their reaction, although one patient experienced a reaction after the first lifetime infusion [93, 94].

In the study reporting tocilizumab-induced HSRs in 7% [5/72] of patients with rheumatoid arthritis or adult-onset Still's disease, four of the five patients experienced anaphylaxis with 75% [3/4] experiencing visible cutaneous manifestations of either rash of urticaria, and 25% [1/4] experiencing pruritus [93]. The three patients with anaphylaxis and visible cutaneous involvement had negative skin prick but positive intradermal testing, whereas the remaining two patients (one with anaphylaxis without visible cutaneous involvement and one with pruritus only) had negative skin prick and intradermal testing [93].

Siltuximab

Pruritus and skin rash are the most frequent cutaneous manifestations of siltuximab. In a phase II, placebo-controlled trial of 79 patients with multicentric Castleman disease, pruritus occurred in 42% [22/53] of patients with multicentric Castleman disease on siltuximab compared to 12% [3/26] on placebo [95]. In the same trial, maculopapular skin rash occurred in 34% [18/53] patients with multicentric Castleman disease on siltuximab compared to 12% [3/26] on placebo [95].

Cellulitis has been reported in 11% [2/19] patients with multicentric Castleman disease [95]. Eczema, psoriasis, xeroderma, and hyperpigmentation can also occur [96]. All four of these reactions were reported in 4% [2/53] patients with multicentric Castleman disease on siltuximab compared to 0% [0/26] on placebo [96].

B-Cell Depletion

- Rituximab [11]
- Belimumab [12]

Rituximab

Cutaneous manifestations occur during rituximab-induced infusion reactions at reported rates of 63 [42/67] to 64% [16/25] [11, 97, 98•]. In one study of 67 patients with rituximab infusion reactions, the most common cutaneous manifestation was generalized pruritus (45% [30/67]), followed by flushing (21% [14/67]), hives (16% [11/67]), and rash (9% [6/67]) [98•]. Transient skin rash has been reported in 4% [11/248] of patients with immune thrombocytopenia [99], and 2% [3/122] of patients with idiopathic thrombocytopenic purpura who received rituximab [100].

Delayed cutaneous reactions (cutaneous manifestations of serum sickness, and delayed urticaria / angioedema) also occur with rituximab [97, 101]. Most cases of rituximab-induced

serum sickness occur within 6 days of the first cycle, with rash reportedly occurring in 70% [23/33] of cases [101].

One case of Sweet's Syndrome has been reported with rituximab use [102].

Cutaneous reactions related to route of administration are reported more frequently with the subcutaneous route of administration [101]. In a randomized control trial of 176 patients with chronic lymphocytic leukemia receiving either subcutaneous or intravenous rituximab, subcutaneous injections were associated with injection-site erythema in 26% [22/85] of patients, injection-site swelling in 5% [4/85], erythema in 15% [13/85], rash in 12% [10/85], and pruritus in 8% [7/85] [101]. In contrast, intravenous injections were associated with no cases of injection-site erythema, injection-site swelling in 1% [1/89] of patients, erythema in 7% [6/89], rash in 10% [9/89], and pruritus in 4% [4/89] [101].

Belimumab

Skin infections have been reported in 5% [9/188] of patients with SLE (systemic lupus erythematosus) [103]. In a randomized placebo-controlled trial investigating belimumab as a therapy for SLE ISRs occurred more frequently with belimumab (6% [34/556]) compared to placebo (3% [7/280]) [104]. Herpes zoster/simplex have been reported as well [103], although they occurred with greater frequency in the placebo group (3% [18/556] in the belimumab group compared to 5% [13/280] in the placebo group) [104].

Belimumab-induced HSRs have been reported at rates of 1% [3/283] to 3% [5/188] to 7% [38/556] [103–105]. However, in the randomized placebo-controlled trial investigating belimumab as a therapy for SLE, HSRs were reported with an even higher frequency of 9% [25/280] in the placebo group) [104].

Folliculitis/rash has been reported in 3% [5/188] of patients with SLE, and temporary mild hair loss has been reported in 2% [4/188] [103].

IL-12/23 Inhibitors

- Ustekinumab [13]

Significant cutaneous manifestations have not been observed for ustekinumab [106, 107]. ISRs have been reported, but at similar or lower rates than placebo (2% [17/706] with ustekinumab versus 2% [17/819] with placebo in a phase II trial [107], and nine patients with ustekinumab versus ten patients with placebo in a phase III trial) [107, 108]. ISRs were all mild, and none resulted in discontinuation of assigned treatment [107, 108].

Concern has been raised regarding the possibility that non-melanoma skin cancers could develop due to inhibition of IL-12, a cytokine that has been associated with potential carcinogenicity risks. IL-12 has anti-tumor activity in mouse models [109] and IL-12-deficient mice are prone to tumor development [110]. However, ustekinumab also inhibits IL-23, and absence of IL-23 is associated with protection against carcinogenesis [111]. Indeed, clinical data has not shown an observed risk for non-melanoma skin cancers in patients treated with ustekinumab [112].

In a phase II trial, non-melanoma skin cancer (one basal-cell skin cancer and one squamous-cell skin cancer) was observed in two patients on ustekinumab, versus one case of basal cell skin cancer in a patient on placebo [107]. A French pharmacovigilance review of 91 reports and 100 serious adverse effects reported six skin cancers (three cases of basal cell carcinoma and three melanomas) between 2009 and 2013 [113]. However, in two phase III trials with placebo-controlled phases, crossover phases, and redosing/maintenance/withdrawal phases, rates of cutaneous cancers (type not specified in the study reports) were similar between patients receiving different combinations and dosings of ustekinumab and/or placebo [114, 115].

There is also no significant risk observed for cutaneous cancers during long-term follow-up. Two-year follow-up of patients in phase II and phase III trials investigating ustekinumab for psoriatic arthritis did not show significant differences in rates of non-melanoma skin cancer per 100 patient-years between placebo (0), ustekinumab 45 mg (0), and ustekinumab 90 mg (0.64) [112]. Pooled safety data from one phase 2 and three phase 3 trials (PHOENIX 1, PHOENIX 2, and ACCEPT) of 1247 patients treated for ≥ 2 years with ustekinumab did not have any reports of non-melanoma skin cancers [116•]. There were two reports of melanoma skin cancers that were not graded as serious (clarification regarding stage was not provided in the study report) [116•]. A 5-year follow-up study of the PHOENIX 2 clinical trial showed year-to-year variability without any increase over time for rates of non-melanoma skin cancers, with 0.57 per 100 patient-years for ustekinumab 45 mg ($n = 606$) and 0.32 patient-years for ustekinumab 90 mg ($n = 809$) [117•]. Analysis of 3117 patients with moderate-to-severe psoriasis who received more than one dose of ustekinumab, with 1482 patients receiving ustekinumab for ≥ 4 years, did not show significant differences in rates of non-melanoma skin care per 100 patient-years between ustekinumab 45 mg (0.64) and 90 mg (0.44) [118•]. The 47 patients who had non-melanoma skin cancers had basal cell carcinoma ($n = 40$) and squamous cell carcinoma ($n = 10$) (three patients had both basal cell and squamous cell carcinoma) [118•].

Flares of psoriasis and unmasking of psoriatic arthritis in patients previously diagnosed with plaque psoriasis have been reported, with one French pharmacovigilance study reporting that psoriasis flare-ups or inefficacy accounted for 10% [exact

numbers not reported] adverse effects reported between 2009 and 2013 [113, 119, 120].

Isolated cases of alopecia areata [121], linear IgA bullous dermatosis [122], eczematous drug reaction [123], and lymphomatoid drug reaction [124] have also been reported in the literature.

IL-17 Inhibitors

- Secukinumab [14]
- Ixekizumab [15]
- Brodalumab [16]

In pooled efficacy and safety data from three major phase III trials investigating ixekizumab as a treatment for plaque psoriasis (UNCOVER-1, UNCOVER-2, UNCOVER-3), adverse events occurred in similar proportions in patients on ixekizumab 80 mg every 2 weeks (54.8%), ixekizumab 80 mg every 4 weeks (58.8%), and placebo (46.8%) [exact numbers not reported] [125•]. ISRs were listed as the third most commonly reported adverse event (with nasopharyngitis and upper respiratory infections being the first two most common), although exact numbers were not provided [126–128]. Serious adverse events also occurred in similar proportions in patients on ixekizumab 80 mg every 2 weeks (1.7%), ixekizumab 80 mg every 4 weeks (2.2%), and placebo (1.5%), with the most common serious adverse event being cellulitis in patients on ixekizumab [exact numbers not reported] [128].

One concern for IL-17 inhibitor therapy is the possibility for increased *Candida* infections of the skin and mucosa, as IL-17 is an important cytokine in immunity against *Candida albicans* [129]. Reported rates of candidiasis have been higher in patients who received ixekizumab compared to placebo [130]. In pooled safety data from UNCOVER-1, UNCOVER-2, and UNCOVER-3, *Candida* infections were seen in similar but higher proportions in patients on ixekizumab 80 mg every 2 weks (1.4%) and ixekizumab 80 mg every 4 weeks (0.6%) compared to placebo (0.5%) [exact numbers not reported] [125•]. *Candida* skin-specific infections were seen in only three patients, two patients on ixekizumab every 2 weeks (0.3% [2/734]) and one patient on placebo (0.3% [1/360]) [127]. Of note, one of the patients on ixekizumab developed a persistent *Candida* skin infection that was resistant to multiple topical agents (clotrimazole for about 1 month, isoconazole/diflucortolone for 2 weeks, further treatments not reported) [127].

Candida infections occur more frequently in patients who receive brodalumab compared to both ustekinumab and placebo [131]. Among patients randomized to receive brodalumab 210 or 140 mg every 2 weeks, ustekinumab dosed per label, or placebo, *Candida* infections (site not specified) occurred more frequently in patients who received either brodalumab 210 mg (1.5% [18/1234]) or 140 mg (0.9% [11/1233]) every 2 weeks compared to both ustekinumab (0.5% [3/613]) and placebo (0.5% [3/622]) [131]. All *Candida* infections were mild or moderate [131]. None of the *Candida* infections were systemic [131].

Localized mucosal and cutaneous *Candida* infections have also been reported with secukinumab therapy. Among 676 patients randomized to secukinumab 300 mg or ustekinumab dosed per label, 12 (1.8% [12/676]) patients developed localized mucosal or cutaneous *Candida* infections. Although the distribution of adverse events were not reported to maintain blinding until after the final database lock, presumably a number of these infections occurred in the secukinumab group, given prior study data described above [132].

These data suggest that *Candida* infections are indeed a significant side effect of anti-IL-17 therapy, and it is recommended that patients on anti-IL-17 therapy are monitored regularly for skin and mucosal *Candida* infections [130].

Immune Checkpoint Inhibitors (ICIs)

- Nivolumab [17]
- Pembrolizumab [18]
- Avelumab [19]
- Atezolizumab [20]
- Durvalumab [21]
- Ipilimumab [22]

Immune checkpoint inhibitors are associated with unique irAEs (immune-related adverse effects). Skin irAEs include a maculopapular rash that can be pruritic, pruritus without skin lesions, alopecia, and vitiligo [133]. The most common irAE overall is rash and/or pruritus [134]. Other common irAEs are colitis, hepatitis, endocrinopathies, and pneumonitis [134].

A 2017 meta-analysis of 6938 patients in 26 CTLA-4, 17 PD-1, 3 combined CTLA-4 and PD-1, and 2 PD-L1 trials showed that cutaneous irAEs were more frequent with CTLA-4 mAbs compared to PD-1 mAbs (OR 2.0, 95% CI 1.8–2.3) [135•]. Rash/pruritus occurs in approximately 43% [1089/2520] of patients treated with the anti-CTL-4 mAb, ipilimumab, with 1.5% [38/2520] of these patients developing skin irAEs grade ≥ 3 [135•]. The proportion of patients who developed rash or pruritus (both all grades and grade ≥ 3) was smaller with anti-PD-L1 compared to anti-PD-1, although statistical comparisons were not possible due to the small number of PD-L1 studies [135•]. This supports the thought that anti-PD-L1 causes fewer irAEs due to preservation of PD-L2 binding [135•]. However, further investigation is needed regarding this hypothesis, as another study specifically comparing anti-PD-1 to anti-PD-L1 therapy reported an overall incidence of

4% [210/4793] for any grade rash irAE with anti-PD-L1 and 16% [224/1414] with anti-PD-L1 therapy [136].

In the anti-PD-1 trials [melanoma ($n = 2048$), non-small-cell lung cancer ($n = 1030$) and renal cell carcinoma ($n = 573$)], the highest frequency of cutaneous irAEs were observed in melanoma patients [135•]. However, non-melanoma patients still develop severe, life-threatening irAEs, making monitoring for irAEs essential regardless of the treatment indication [137]. An earlier meta-analysis from 2013 investigating the risk of rash among patients receiving anti-CTLA-4, ipilimumab, did not find a statistically significant difference in the risk of rash based on the dose or underlying tumor [138].

In the 2017 meta-analysis, pruritus was observed in 14% [571/4077] of patients on anti-PD-1 therapy, 5.1% [14/275] on anti-PD-L1 therapy, and 21.8% [549/2520] on anti-CTLA-4 therapy [135•]. The majority of pruritus cases were grade 1 or grade 2, as grade ≥ 3 pruritus was only observed in 0.1% [4/4077] of the patients on anti-PD-1 therapy, 0.0% [0/275] on anti-PD-L1 therapy, and 0.4% [10/2520] on anti-CTLA-4 therapy [135•]. Rash was observed in 12.2% [497/4077] of patients on anti-PD-1 therapy, 5.5% [15/275] on anti-PD-L1 therapy, and 21.4% [539/2520] on anti-CTLA-4 therapy [135•]. As with pruritus, the majority of rash cases were grade 1 or grade 2, as grade ≥ 3 pruritus was only observed in 0.3% [12/4077] of patients on anti-PD-1 therapy, 0.0% [0/275] on anti-PD-L1 therapy, and 1.1% [28/2520] on anti-CTLA-4 therapy [135•]. Vitiligo was observed in 4.0% [163/4077] of patients on anti-PD-1 therapy, 0.0% [0/275] on anti-PD-L1 therapy, and 1.1% [28/2520] on anti-CTLA-4 therapy [135•]. All vitiligo cases were grade 1 or grade 2 [135•].

Combining anti-PD-1 (nivolumab) with anti-CTLA-4 (ipilimumab) appears to compound the risk for irAEs. In a randomized, double-blind, phase 3 study comparing nivolumab alone to nivolumab plus ipilmumab to ipilimumab alone in patients with metastatic melanoma, rash/pruritus occurred in 45% [140/313] of patients on nivolumab alone, 74% [230/313] on nivolumab plus ipilimumab, and 68% [212/313] on ipilimumab alone [139].

The irAEs of rash/pruritus begin within the first 2 weeks of therapy [140]. Epidermal spongiosis and perivascular CD4(+) T-cell infiltrates with eosinophils can be seen on skin biopsies of rash [133]. A dermatology consult is recommended for all cases [136].

Therapy with ICIs can be continued despite grade 1 skin irAEs [140]. Holding a scheduled ICI dose can be considered for grade 2 skin irAEs until symptom improvement [141]. The initial treatment approach is supportive [140]. Topical corticosteroid creams of medium to high potency can be applied to a visible rash [134, 136, 141]. Topical corticosteroids can also be used to relief pruritus, in addition to cold compresses, oatmeal baths, and oral anti-histamines [136, 140, 141]. Oral aprepitant has been used for resistant pruritus [134]. If skin irAEs do not improve despite 12 weeks of supportive management, ICIs should be discontinued due to the possibility of the irAE worsening [140].

Grade 3 rashes should be treated with oral corticosteroids (prednisone 1 mg/kg daily or an alternative corticosteroid at an equivalent dose) and ICI therapy should be held until irAE symptoms improve to baseline or grade 1 or lower [136, 140, 141]. Infliximab, mycophenolate mofetil, and cyclophosphamide can be considered for grade 3 rashes that do not respond to oral corticosteroids [140].

ICIs should be discontinued for grade 4 skin irAEs because they can be life-threatening [136, 140, 141]. For example, in one trial of ipilimumab, 13 cases (2.41% [13/540]) of severe, life-threatening immune-related dermatitis (Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash with full thickness dermal ulceration or necrosis, bullae, or hemorrhage) were reported [22]. One (0.2% [1/540]) case was fatal and one (0.2% [1/540]) case required hospitalization. One patient died due to toxic epidermal necrolysis and one patient required hospitalization. In addition to discontinuing ICI therapy, patients should be treated with prednisone 1–2 mg/kg daily, methylprednisolone 1–4 mg/kg daily, or equivalent tapered over at least 30 days [136, 141]. Hospitalization, intravenous fluids, and electrolyte replacement should also be considered in appropriate cases [141].

Vitiligo occurs 3 or more weeks after starting ICI therapy [140]. It occurs more frequently over upper extremities [140] and occurs more often with anti-PD-1 agents (pembrolizumab: 10% [56/555]) compared with anti-CTLA-4 (ipilimumab: 2% [4/256]) [142]. There is no definitive treatment for vitiligo that occurs as an irAE [140].

Interestingly, rash/pruritus/vitiligo irAEs may be associated with a favorable treatment benefit, although further studies are needed to determine the validity of this association. Vitiligo was associated with progression-free survival and overall survival in patients with stage III-IV melanoma treated with immunotherapy (including general immune stimulation, vaccine therapy, ICI, and adoptive transfer) [143]. Rash/pruritus/vitiligo irAEs in patients treated with pembrolizumab therapy (66 patients treated for melanoma, 15 patients treated for lung cancer, 1 patient treated for prostate cancer, 1 patient treated for Merkel cell carcinoma) were associated with significantly longer progression-free intervals compared with patients who did not develop cutaneous irAEs [144]. There was a higher occurrence of vitiligo (71% [12/17] versus 28% [14/50], $p = 0.002$) in patients with complete or partial response to treatment compared to patients without response [145].

In addition to the previously mentioned irAEs, there has been one case reported of bullous pemphigoid with pembrolizumab [146], one case reported of Sweet's syndrome

with ipilimumab [147], and three cases reported of lichenoid dermatitis with an anti-PD-1 with pembrolizumab [148].

IL-4/13 Inhibitors

- Dupilumab [23]

ISRs are the main reported cutaneous adverse event for dupilumab. In clinical trials, ISRs were consistently reported at a higher frequency in patients with moderate-to-severe atopic dermatitis, nasal polyposis, and uncontrolled persistent asthma [149–153]. ISRs occurred in 7 [22/318]–40% [12/30] of patients treated with dupilumab compared to 3 [2/61]–13% [21/158] of patients treated with placebo [150–153]. In atopic dermatitis trials, skin infections and atopic dermatitis exacerbations were reported at a higher frequency in patients treated with placebo (skin infections, 8 [5/61]–8% [56/315] with placebo compared to 7 [21/318]–9% [38/425] with dupilumab; atopic dermatitis exacerbations, 18 [11/61]–46% [144/315] with placebo compared to 17% [54/318 and 72/42] with dupilumab) [150, 153]. Skin infections and atopic dermatitis exacerbations are reported only in dupilumab clinical trials for atopic dermatitis and reflect the disease course and not the effects of dupilumab. Indeed, the frequencies are lower with dupilumab, indicating that dupilumab is decreasing the occurrence of these adverse events by effectively treating atopic dermatitis.

IL-5 Inhibitors

- Mepolizumab [24–32]
- Reslizumab [33]

No serious adverse event has been reported with any anti-IL-5 treatment, including mepolizumab and reslizumab [154]. ISRs have been reported with mepolizumab, which is administered subcutaneously [154]. The only cutaneous adverse event reported in the DREAM, MENSA, SIRIUS, and COSMOS asthma trials were ISRs [155]. Pooled data showed that 5% [55/1105] patients on mepolizumab reported ISRs versus 2% [8/257] on placebo [155]. Injection-site reactions were also the only cutaneous adverse event observed in a trial comparing mepolizumab to placebo for eosinophilic granulomatosis with polyangiitis [30]. Injection-site reactions were reported in 15% [10/68] on mepolizumab versus 13% [9/68] on placebo [30].

JAK-3 Inhibitor

- Tofacitinib [34–38]

The only cutaneous adverse events observed with tofacitinib were acne in up to 16.8% [18/107] of patients and non-specific rash in up to 11.3% [12/106] of patients exposed to tofacitinib in clinical trials [156, 157].

Costimulation Blockade

- Abatacept [39–44]

Anaphylaxis or anaphylactoid reactions can occur during or after an infusion and can be life-threatening. There were two cases (< 0.1% [2/2688]) of anaphylaxis or anaphylactoid reactions in clinical trials with adult rheumatoid arthritis patients treated with intravenous abatacept [39]. Other reactions potentially associated with drug hypersensitivity, such as hypotension, urticaria, and dyspnea, each occurred in < 0.9% [exact numbers not reported] of patients [39]. Otherwise, headache, upper respiratory tract infection, nasopharyngitis, and nausea were the most commonly reported adverse events without any reported cutaneous manifestations in the adult rheumatoid arthritis clinical studies [39].

In the published literature, there is one case report each of erythema elevatum diutinum [158] and neutrophilic dermatosis [159], and several cases of psoriasiform reactions [45, 160, 161].

Integrin Receptor Antagonists

- Natalizumab [45, 46]
- Vedolizumab [47–52]

Natalizumab

Cutaneous manifestations can occur as part of natalizumab-induced HSRs. An early pivotal clinical trial reported that 25 patients receiving natalizumab had a total of 27 HSRs including urticaria ($n = 12$), allergic dermatitis ($n = 1$), and anaphylactic or anaphylactoid reactions (urticaria plus other signs, $n = 5$) [162]. In an observational, prospective study of 30 adult multiple sclerosis patients treated with natalizumab, two patients (6.7% [2/30]) developed severe anaphylactic shock and one patient (3.3% [1/30]) developed urticaria [163]. Interestingly, in a separate trial in 79 adult patients with active Crohn's disease despite ongoing infliximab treatment, there were no reported HSRs [49].

Vedolizumab

There are no cutaneous manifestations related to vedolizumab reported in the recent literature. In a large trial of vedolizumab for Crohn's disease patients ($n = 845$), there was one patient that developed an infusion-related HSR [50].

Conclusions

A wide variety of cutaneous reactions caused by biologics have been reported, ranging from benign injection site reactions to life-threatening cutaneous reactions necessitating discontinuation of the implicated biologic agent. Benign injection site reactions, non-specific rash, cellulitis, and hypersensitivity reactions are relatively common adverse events. Anti-TNF agents, IL-6 inhibitors, and IL-12/23 inhibitors can paradoxically cause psoriasis flares or unmask previously undiagnosed psoriasis. IL-17 inhibitors are unique in increasing risk for *Candida* infections. Anti-TNF agents and immune checkpoint inhibitors have significant, immune-mediated cutaneous manifestations that can necessitate discontinuation. Interestingly, rash/pruritus/vitiligo irAEs may be associated with a favorable treatment benefit in patients with malignancy treated with immune checkpoint inhibitors.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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