Drugs in R&D (2020) 20:171–187
https://doi.org/10.1007/s40268-020-00311-6

REVIEW ARTICLE

Cutaneous Adverse Events in Newly Approved FDA Non-cancer Drugs: A Systematic Review

Paul C. Macklis[1] · Brittany Dulmage[1] · Brady Evans[1] · Misha Rosenbach[2] · Johann E. Gudjonsson[3] · Benjamin H. Kaffenberger[1]

Published online: 17 June 2020

Abstract
The prevalence of cutaneous adverse events attributable to newly approved anti-cancer drugs has been well reviewed in the dermatologic literature. In contrast, over 75% of US Food and Drug Administration approvals in the past 5 years have been for non-cancer drugs and indications. This represents multiple other categories of approved medications associated with cutaneous adverse reactions. To investigate the cutaneous adverse events associated with these potentially neglected medications, a systematic review was conducted. Two hundred and forty-one medications approved by the Food and Drug Administration between 2013 and 2018 were reviewed and 180 non-oncologic drugs were identified. The prescribing information for each medication was reviewed for the presence of cutaneous adverse events and a supplemental literature search was performed to better characterize any adverse events outlined within the prescribing information. Most reactions were classified as morbilliform, macular, popular, or maculopapular. Fortunately, only a few severe cutaneous adverse reactions were reported, namely in benznidazole, cannabidiol, and sofosbuvir. This review summarizes available data drawn from clinical trials and case reports involving cutaneous adverse events from the 21 non-oncologic medications associated with cutaneous adverse events.

Key Points

One hundred and eighty non-oncologic medications received US Food and Drug Administration approval between 2013 and 2018.

Twenty-one of these medications were associated with cutaneous adverse events from mild rashes to severe reactions including Stevens–Johnson syndrome.

Clinicians should consider these newly approved medications when managing cutaneous pathologies.

1 Introduction

In the past 5 years, over 40 new medications or new indications have been approved yearly by the US Food and Drug Administration (FDA), presenting a formidable task for dermatologists to remain current with dermatologic adverse events of these newly FDA-approved therapies. Fortunately, numerous reviews have highlighted adverse events among new therapies with cancer indications [1–3]. However, that represents fewer than 25% of all new approvals or new indications. This article reviews the adverse cutaneous side effects of all non-cancer FDA-approved medications released between 2013 and 2018.

2 Methodology

Drugs approved by the FDA between 2013 and 2018 were systematically reviewed directly from the FDA website's database, and a list of the 241 medications and their approved indications was created (Table 1). Subsequently, 61 medications with cancer indications were removed. Then, the prescribing information package inserts for the remaining 180 drugs were reviewed and evaluated for mention of

✉ Benjamin H. Kaffenberger
Benjamin.Kaffenberger@osumc.edu

[1] Division of Dermatology, Department of Internal Medicine, The Ohio State University Wexner Medical Center, 2012 Kenny Road, Rm 232, Columbus, OH 43212, USA

[2] Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[3] Department of Dermatology, University of Michigan Medical School, Ann Arbor, MI, USA

Table 1 All medications approved by the US Food and Drug Administration between 2013 and 2018

Generic	Brand	Indication
2013		
Afatinib	Gilotrif	Non-small cell lung cancer
Alogliptin	Nesina	Type 2 diabetes mellitus
Canagliflozin	Invokana	Type 2 diabetes mellitus
Conjugated estrogens and bazedoxifene	Duavee	Menopause
Dabrafenib	Tafinlar	Cancers with *BRAF* gene mutation
Dimethyl fumarate	Tecfidera	Multiple sclerosis
Dolutegravir	Tivicay	HIV
Eslicarbazepine	Aptiom	Partial-onset seizures
Flutemetamol	Vizamyl	Alzheimer disease
Fluticasone furoate and vilanterol	Breo Ellipta	Chronic obstructive pulmonary disease
Gadoteric acid	Dotarem	Gadolinium-based contrast agent used with MRI
Ibrutinib	Imbruvica	Mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenstrom macroglobulinemia
luliconazole	Luzu	Tinea pedis, tinea cruris, and tinea corporis
Macitentan	Opsumit	Pulmonary arterial hypertension
Mipomersen	Kynamro	Familial hypercholesterolemia
Obinutuzumab	Gazyva	Chronic lymphocytic leukemia and follicular lymphoma
Ospemifene	Osphena	Painful intercourse and vaginal dryness
Pomalidomide	Pomalyst	Multiple myeloma
Radium-223	Xofigo	Prostate cancer
Riociguat	Adempas	Chronic thromboembolic pulmonary hypertension
Simeprevir	Olysio	Hepatitis C virus
Sofosbuvir	Sovaldi	Hepatitis C virus
Technetium Tc 99 m tilmanocept	Lymphoseek	Lymphatic mapping in patients with solid tumors
Trametinib	Mekinist	Cancer in people who have a '*BRAF*' gene mutation
Trastuzumab emtansine	Kadcyla	HER2-positive breast cancer
Umeclidinium bromide	Anoro Ellipta	Chronic obstructive pulmonary disease
Vortioxetine	Brintellix	Major depression
2014		
Albiglutide	Tanzeum	Type 2 diabetes mellitus
Apremilast	Otezla	Arthritis
Belinostat	Beleodaq	Peripheral T-cell lymphoma
Blinatumomab	Blincyto	Acute lymphoblastic leukemia
Ceftolozane	Zerbaxa	Complicated intra-abdominal infections and complicated urinary tract infections
Ceritinib	Zykadia	Non-small cell lung cancer
Dalbavancin	Dalvance	Skin infections
Dapagliflozin	Farxiga	Type 2 diabetes mellitus
Dasabuvir	Viekira Pak	Hepatitis C virus
Droxidopa	Northera	Dizziness or a light-headed feeling
Dulaglutide	Trulicity	Type 2 diabetes mellitus
Efinaconazole	Jublia	Onychomycosis
Eliglustat	Cerdelga	Type 1 Gaucher disease
Elosulfase alfa	Vimzim	Mucopolysaccharidosis IV type A
Empagliflozin	Jardiance	Type 2 diabetes mellitus
Finafloxacin	Xtoro	Acute otitis externa
Idelalisib	Zydelig	Chronic lymphocytic leukemia
Ledipasvir	Harvoni	Hepatitis C virus
Metreleptin	Myalept	Leptin deficiency

Table 1 (continued)

Generic	Brand	Indication
Miltefosine	Impavido	Leishmaniasis
Naloxegol	Movantik	Constipation that is caused by opioids
Netupitant	Akynzeo	Nausea and vomiting caused by chemotherapy
Nintedanib	Ofev	Idiopathic pulmonary fibrosis
Nivolumab	Opdivo	Non-small cell lung cancer
Olaparib	Lymparza	Ovarian cancer
Olodaterol	Striverdi Respimat	Chronic obstructive pulmonary disease
Ombitasvir	Viekira Pak	Hepatitis C virus
Oritavancin	Orbactiv	Bacterial skin and skin structure infections
Paritaprevir	Viekira Pak	Hepatitis C virus
Peginterferon beta-1a	Plegridy	Relapsing forms of multiple sclerosis
Pembrolizumab	Keytruda	Melanoma
Peramivir	Rapivab	Influenza
Pirfenidone	Esbriet	Idiopathic pulmonary fibrosis
Ramucirumab	Cyramza	Stomach cancer, colorectal cancer, or non-small cell lung cancer
Siltuximab	Sylvant	Multicentric Castleman disease
Suvorexant	Belsomra	Insomnia
Tasimelteon	Hetlioz	Non-24-h sleep–wake disorder
Tavaborole	Kerydin	Onychomycosis
Tazobactam	Zerbaxa	Drug-resistant bacteria
Tedizolid	Sivextro	MRSA infections
Vedolizumab	Entyvio	Ulcerative colitis and Crohn disease
Vorapaxar	Zontivity	Lower the risk of stroke or serious heart problems
2015		
Alectinib	Alecensa	Anaplastic lymphoma kinase-positive lung cancer
Alirocumab	Praluent	High cholesterol
Aripiprazole lauroxil	Aristada	Schizophrenia
Asfotase alfa	Strensiq	Perinatal, infantile, and juvenile-onset hypophosphatasia
Brexpiprazole	Rexulti	Schizophrenia
Cangrelor	Kengreal	Prevent the formation of harmful blood clots
Cariprazine	Vraylar	schizophrenia
Ceftazidime-avibactam	Avycaz	Complicated intra-abdominal infections
Cholic acid	Cholbam	Bile acid synthesis disorders
Cobimetinib	Cotellic	Melanoma
Daclatasvir	Daklinza	Hepatitis C virus
Daratumumab	Darzalex	Multiple myeloma
Deoxycholic acid	Kybella	Moderate-to-severe fat below the chin
Dinutuximab	Unituxin	Neuroblastoma
Edoxaban	Savaysa	Stroke and dangerous blood clots
Elotuzumab	Empliciti	Multiple myeloma
Eluxadoline	Viberzi	Irritable bowel syndrome with diarrhea
Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	Genvoya	HIV
Evolocumab	Repatha	High cholesterol
Flibanserin	Addyi	Generalized hypoactive sexual desire disorder
Idarucizumab	Praxbind	Reverse Pradaxa's blood-thinning effects
Insulin degludec injection	Tresiba	Diabetes mellitus
Isavuconazonium sulfate	Cresemba	Invasive aspergillosis and invasive mucormycosis
Ivabradine	Corlanor	Heart failure

Table 1 (continued)

Generic	Brand	Indication
Ixazomib	Ninlaro	Multiple myeloma
Lenvatinib	Lenvima	Differentiated thyroid cancer
Lesinurad	Zurampic	Gout
Lumacaftor 200 mg/ivacaftor 125 mg	Orkambi	Cystic fibrosis
Mepolizumab	Nucala	Asthma
Necitumumab	Portrazza	Squamous non-small cell lung cancer
Osimertinib	Tagrisso	Non-small cell lung cancer
Palbociclib	Ibrance	Breast cancer
Panobinostat	Farydak	Multiple myeloma
Parathyroid hormone	Natpara	Hypocalcemia
Patiromer for oral suspension	Veltassa	Hyperkalemia
Rolapitant	Varubi	Delayed-phase chemotherapy-induced nausea and vomiting
Sacubitril/valsartan	Entresto	Heart failure
Sebelipase alfa	Kanuma	Lysosomal acid lipase deficiency
Secukinumab	Cosentyx	Plaque psoriasis
Selexipag	Uptravi	Pulmonary arterial hypertension
Sonidegib	Odomzo	Basal cell carcinoma
Sugammadex	Bridion	Reverse effects of neuromuscular blocking drugs
Trabectedin	Yondelis	Soft-tissue sarcomas
Trifluridine and tipiracil	Lonsurf	Colorectal cancer
Uridine triacetate	Xuriden	Hereditary orotic aciduria
2016		
Atezolizumab	Tecentriq	Urothelial carcinoma
Bezlotoxumab	Zinplava	*Clostridium difficile*
Brivaracetam	Briviact	Partial-onset seizures
Crisaborole	Eucrisa	Mild-to-moderate eczema
Daclizumab	Zinbryta	Multiple sclerosis
Defibrotide sodium	Defitelio	Hepatic veno-occlusive disease
Elbasvir and grazoprevir	Zepatier	Hepatitis C virus
Eteplirsen	Exondys 51	Duchenne muscular dystrophy
Fluciclovine F 18	Axumin	Prostate cancer
Gallium Ga 68 dotatate	NETSPOT	Neuroendocrine tumors
Ixekizumab	Taltz	Plaque psoriasis
Lifitegrast ophthalmic solution	Xiidra	Dry eye disease
Lixisenatide	Adlyxin	Glycemic control (blood sugar levels)
Nusinersen	Spinraza	Spinal muscular atrophy
Obeticholic acid	Ocaliva	Chronic liver disease
Obiltoxaximab	Anthim	Anthrax
Olaratumab	Lartruvo	Soft-tissue sarcoma
Pimavanserin	Nuplazid	Hallucinations and delusions associated with Parkinson disease
Reslizumab	Cinqair	Asthma
Rucaparib	Rubraca	Ovarian cancer
Sofosbuvir and velpatasvir	Epclusa	Hepatitis C virus
Venetoclax	Venclexta	Chronic lymphocytic leukemia
2017		
Abaloparatide	Tymlos	Osteoporosis
Abemaciclib	Verzenio	Breast cancers
Acalabrutinib	Calquence	Mantle cell lymphoma
Angiotensin II	Giapreza	Septic or other distributive shock

Table 1 (continued)

Generic	Brand	Indication
Avelumab	Bavencio	Merkel cell carcinoma
Benralizumab	Fasenra	Asthma
Benznidazole	Benznidazole	Chagas disease
Betrixaban	Bevyxxa	Venous thromboembolism
Brigatinib	Alunbrig	Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer
Brodalumab	Siliq	Moderate-to-severe plaque psoriasis
Cerliponase alfa	Brineura	Batten disease
Copanlisib	Aliqopa	Relapsed follicular lymphoma
Deflazacort	Emflaza	Duchenne muscular dystrophy
Delafloxacin	Baxdela	Bacterial skin infections
Deutetrabenazine	Austedo	Chorea from Huntington disease
Dupilumab	Dupixent	Eczema
Durvalumab	Imfinzi	Urothelial carcinoma
Edaravone	Radicava	Amyotrophic lateral sclerosis
Emicizumab	Hemlibra	Hemophilia A
Enasidenib	Idhifa	Acute myeloid leukemia
Ertugliflozin	Steglatro	Type 2 diabetes mellitus
Etelcalcetide	Parsabiv	Secondary hyperparathyroidism
Glecaprevir and pibrentasvir	Mavyret	Hepatitis C virus
Guselkumab	Tremfya	Plaque psoriasis
Inotuzumab ozogamicin	Besponsa	Acute lymphoblastic leukemia
Latanoprostene bunod ophthalmic solution	Vyzulta	Open-angle glaucoma
Lzetermovir	Prevymis	Prevent infection after bone marrow transplant
Macimorelin acetate	Macrilen	Growth hormone deficiency
Meropenem and vaborbactam	Vabomere	Complicated urinary tract infections
Midostaurin	Rydapt	Acute myeloid leukemia
Naldemedine	Symproic	Opioid-induced constipation
Neratinib maleate	Nerlynx	Breast cancer
Netarsudil	Rhopressa	Glaucoma
Niraparib	Zejula	Epithelial ovarian, fallopian tube, or primary peritoneal cancers
Ocrelizumab	Ocrevus	Relapsing and primary progressive forms of multiple sclerosis
Ozenoxacin	Xepi	Impetigo
Plecanatide	Trulance	Chronic idiopathic constipation
Ribociclib	Kisqali	Breast cancer
Safinamide	Xadago	Parkinson disease
Sarilumab	Kevzara	Rheumatoid arthritis
Secnidazole	Solosec	Bacterial vaginosis
Semaglutide	Ozempic	Type 2 diabetes mellitus
Sofosbuvir, velpatasvir, and voxilaprevir	Vosevi	Hepatitis C virus
Telotristat ethyl	Xermelo	Carcinoid syndrome diarrhea
Valbenazine	Ingrezza	Tardive dyskinesia
Vestronidase alfa-vjbk	Mepsevii	Mucopolysaccharidosis type VII also known as Sly syndrome
2018		
Amifampridine	Firdapse	Lambert–Eaton myasthenic syndrome
Apalutamide	Erleada	Prostate cancer
Avatrombopag	Doptelet	Thrombocytopenia
Baloxavir marboxil	Xofluza	Influenza

Table 1 (continued)

Generic	Brand	Indication
Baricitinib	Olumiant	Rheumatoid arthritis
Bictegravir, embitcitabine, tenofovir alafenamide	Biktarvy	HIV
Binimetinib	Mektovi	Melanoma
Burosumab-twza	Crysvita	X-linked hypophosphatemia
Calaspargase pegol-mknl	Asparlas	Acute lymphoblastic leukemia
Cannabidiol	Epidioloex	Epilepsy
Cemiplimab-rwlc	Libtayo	Squamous cell carcinoma
Cenegermin-bkbj	Oxervate	Neurotrophic keratitis
Dacomitinib	Vizimpro	Non-small-cell lung cancer
Doravirine	Pifeltro	HIV
Duvelisib	Copiktra	Chronic lymphocytic leukemia
Elagolix sodium	Orilissa	Endometriosis
Elapegademase-lvlr	Revcovi	Adenosine deaminase severe combined immunodeficiency
Emapalumab-lzsgemapalumab-lzsg	Gamifant	Hemophagocytic lymphohistiocytosis
Encorafenib	Braftovi	Melanoma
Eravacycline	Xerava	Intra-abdominal infections
Erenumab-aooe	Aimovig	Migraine
Fish oil triglycerides	Omegaven	Parenteral nutrition
Fosnetupitant and palonosetron	Akynzeo	Chemotherapy-induced nausea and vomiting
Fostamatinib	Tavalisse	Chronic immune thrombocytopenia
Fremanezumab-vfrm	Ajovy	Migraine
Galcanezumab-gnlm	Emgality	Migraine
Gilteritinib	Xospata	Acute myeloid leukemia
Glasdegib	Daurismo	Acute myeloid leukemia
Ibalizumab-uiyk	Trogarzo	HIV
Inotersen	Tegsedi	Polyneuropathy of hereditary transthyretin-mediated amyloidosis
Ivosidenib	Tibsovo	Acute myeloid leukemia
Lanadelumab	Takhzyro	Hereditary angioedema
Larotrectinib	Vitrakvi	Cancers with a specific biomarker
Lofexidine hydrochloride	Lucemyra	Opioid withdrawal
Lorlatinib	Lorbrena	Non-small cell lung cancer
Lusutrombopag	Mulpleta	Thrombocytopenia
Lutetium Lu 177 dotatate	Lutathera	Gastroenteropancreatic neuroendocrine tumors
Migalastat	Galafold	Fabry disease
Mogamulizumab-kpkc	Poteligeo	Non-Hodgkin lymphoma
Moxetumomab pasudotox-tdfk	Lumoxiti	Hairy cell leukemia
Moxidectin	Moxidectin	Onchocerciasis
Omadacycline	Nuzyra	Bacterial pneumonia and skin infections
Patisiran	Onpattro	Hereditary transthyretin-mediated amyloidosis
Pegvaliase-pqpz	Palynziq	Phenylketonuria
Plazomicin	Zemdri	Complicated urinary tract infections
Prucalopride	Motegrity	Chronic idiopathic constipation
Ravulizumab	Ultomiris	Paroxysmal nocturnal hemoglobinuria
Revefenacin	Yupelri	Chronic obstructive pulmonary disease
Rifamycin	Aemcolo	Travelers' diarrhea
Sarecycline	Seysara	Acne vulgaris
Segesterone acetate and ethinyl estradiol vaginal system	Annovera	Contraception
Sodium zirconium cyclosilicate	Lokelma	Hyperkalemia
Stiripentol	Diacomit	Dravet syndrome

Table 1 (continued)

Generic	Brand	Indication
Tafenoquine	Krintafel	*Plasmodium vivax* malaria
Tagraxofusp-erzs	Elzonris	Blastic plasmacytoid dendritic cell neoplasm
Talazoparib	Talzenna	Patients with breast cancer with a germline *BRCA* mutation
Tecovirimat	TPOXX	Smallpox
Tezacaftor; ivacaftor	Symdeko	Cystic fibrosis
Tildrakizumab	Ilumya	Plaque psoriasis

HER2 human epidermal growth factor receptor 2, *HIV* human immunodeficiency virus, *MRI* magnetic resonance imaging, *MRSA* methicillin-resistant *Staphylococcus aureus*

any cutaneous adverse reactions. Medications that produced cutaneous adverse events other than injection-site reactions in more than 5% of patients from pivotal clinical trials or the package insert were included in the study, resulting in the ultimate inclusion of 21 medications (Fig. 1). Subsequently, a supplemental literature review was performed using the PubMed search engine and MEDLINE database to better characterize the rash using the search terms: "Drug Name", AND rash, OR cutaneous, OR dermatitis. The relevant articles were evaluated and any mention of an adverse cutaneous event was extracted and summarized. Of note, the literature review conducted for this study included an emphasis on rashes rather than subjective complaints such as pruritus. References from the articles were cross-checked and additional articles were added if not found in the search strategy.

3 Systematic Review of Drug-Related Cutaneous Adverse Events

Table 2 reviews monoclonal antibody medications approved between 2013 and 2018 with reported adverse cutaneous events in greater than 5% of patients. Table 3 reviews small-molecule medications approved between 2013 and 2018 that reported adverse cutaneous events in greater than 5% of patients.

3.1 Monoclonal Antibodies

3.1.1 Daclizumab (Zinbryta)

Daclizumab was previously approved in 1997 under the brand name Zenapax to prevent organ rejection in de novo allogenic renal transplant recipients [4]. This form of daclizumab was associated with the development of acne seen in 8.9% of patients taking daclizumab vs 7.2% of patients using placebo [4]. However, this form of daclizumab was ultimately discontinued in 2009 because of diminishing market demand rather than safety concerns [5]. In 2016, daclizumab was approved for the treatment of multiple sclerosis. However, daclizumab was voluntarily removed from the market owing to reports of encephalitis associated with its use [6].

Daclizumab binds to CD25, a high-affinity interleukin (IL)-2 receptor subunit on T cells, to prevent IL-2-mediated T-cell activation in patients with multiple sclerosis [7]. Rashes were seen in 7% of patients taking daclizumab during clinical trials vs 3% of patients taking placebo. Details of the clinical trial indicate that the observed rash was described as an erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash [8]. Additional details are limited; however, a supplementary case series also demonstrated an urticarial papulovesicular rash occurring roughly 3 months after discontinuation of daclizumab [9]. While this drug is immunosuppressive, it is possible that a wide variety of morbilliform hypersensitivity reactions may be seen due to an additional loss or delayed loss of immune tolerance from an off-target decrease in T-regulatory cells also displaying the CD25 antigen [7].

3.1.2 Dupilumab (Dupixent®)

Dupilumab, approved in 2017, is a medication used to treat eczema. It inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. While the clinical trials did not reveal any novel cutaneous adverse events apart from injection-site reactions, which were seen in 10% of patients taking dupilumab compared with 6% of patients taking placebo [10], a recent case series describes a paradoxical head and neck erythema in seven patients after taking dupilumab for 10–39 weeks [11]. Both clinical and histopathological findings suggested that these were drug-induced skin reactions. A multi-institution retrospective medical record review revealed that dupilumab-induced facial redness was seen in approximately 10% of patients treated with dupilumab in daily practice [12]. A French national retrospective study found that approximately 4% of patients taking dupilumab developed head and neck dermatitis [13]. A recent case

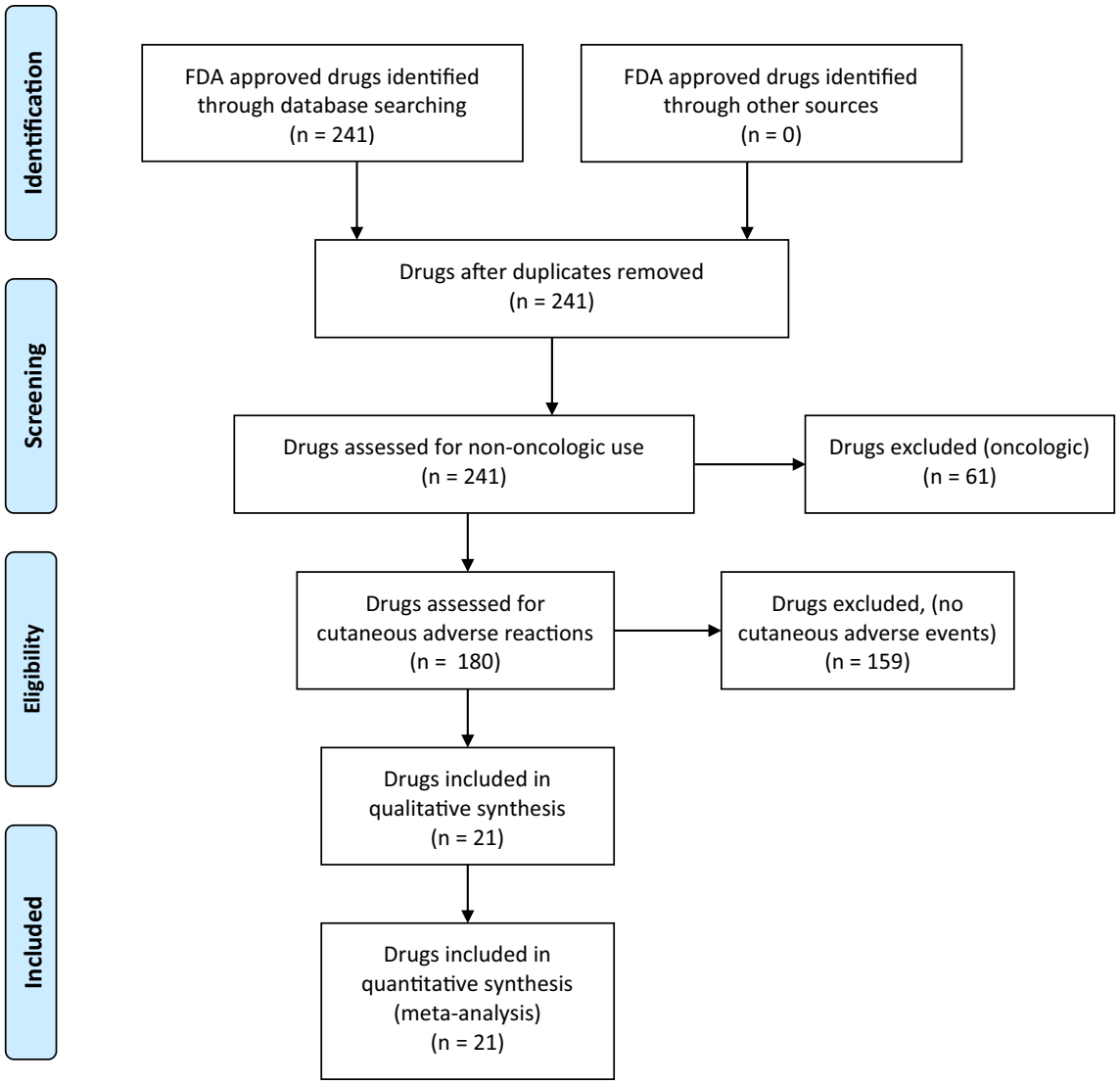

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram detailing the systematic review process. *FDA* US Food and Drug Administration

report has suggested that this dupilumab-induced facial redness is attributable to hypersensitivity to *Malassezia* species and advocates for the use of oral itraconazole in the management of this symptom [14]. Yet another case report describes systemic sarcoid-like granulomatosis occurring 4 months after initiation of dupilumab therapy [15].

3.1.3 Ibalizumab-uiyk (Trogarzo®)

Ibalizumab-uiyk was approved in 2018 for the treatment of human immunodeficiency virus. It is a fusion inhibitor, blocking the human immunodeficiency virus-1 virus from infecting CD4+ T cells by binding to domain 2 of CD4. This interferes with post-attachment steps required for the entry of human immunodeficiency virus-1 particles into host cells, thus preventing the viral transmission that occurs via cell–cell fusion. Rashes were seen in 5% of patients taking ibalizumab-uiyk during clinical trials and were described as a rash, erythematous rash, generalized rash, macular rash, maculopapular rash, and papular rash [16]. Supplemental case reports have not been published to further describe the skin adverse events.

3.1.4 Siltuximab (Sylvant®)

Approved in 2014, siltuximab is a medication used to treat multicentric Castleman disease. It binds to IL-6, thereby preventing its association with both soluble and membrane-bound IL-6 receptors. Rashes were seen in 28% of patients taking siltuximab during clinical trials vs 12% of patients

Table 2 Monoclonal antibody drugs approved by the US Food and Drug Administration between 2013 and 2018 known to cause adverse cutaneous events in more than 5% of patients

Drug name	Brand name	Indication	Mechanism	Year approved	% of patients who developed a rash with this drug during a pivotal clinical trial	% of patients who developed a rash while taking a placebo	Rash description (clinical trial)	Rash description (supplemental case report)
Daclizumab[a]	Zinbryta	Multiple sclerosis (kidney transplant rejection prevention)	Binds to CD25, a high-affinity IL-2 receptor subunit on T cells	2016 (1997)	7	3	Erythematous, exfoliative, macular, maculopapular, papular, pruritic, and vesicular	Urticarial, papulovesicular, acne
Dupilumab	Dupixent	Eczema	Antagonizes IL-4 and IL-13 receptors	2017				Head and neck erythema, dermatitis, granulomatosis
Ibalizumab-uiyk	Trogarzo	HIV	Prevents viral fusion	2018	5		Erythematous, generalized, macular, maculopapular, papular	
Siltuximab	Sylvant	Multicentric Castleman disease	Binds to IL-6	2014	28	12	Generalized, maculopapular, popular, and pruritic	Rash

HIV human immunodeficiency virus, *IL* interleukin

[a]Indicates that the drug has been either previously approved (either in the USA or abroad), or approved abroad for an alternative indication. Parentheses indicate the associated indications and dates for this alternative approval

Table 3 Small-molecule drugs approved by the US Food and Drug Administration between 2013 and 2018 known to cause adverse cutaneous events in more than 5% of patients

Drug name	Brand name	Indication	Mechanism	Year approved	% patients who developed a rash during a pivotal clinical trial	% patients who developed a rash on placebo during a pivotal clinical trial	Rash description (clinical trial)	Rash description (supplemental case report)
Benznidazole[a]	Benznidazole	Chagas disease	Unknown	2017 (1970s)	16	0	Rash	Rash, skin eruptions, hypersensitivity dermatitis, drug eruption, AGEP, DRESS syndrome, SJS/TEN, classic generalized morbilliform eruption, skin peeling
Cannabidiol	Epidiolex	Epilepsy	Unknown	2018	13	3	Rash	Diffuse, erythematous, pustular rash of the bilateral arms, axillae, buttocks, and groin
Dasabuvir	Viekira Pak	HCV	Inhibits NS5B palm polymerase, preventing viral replication	2014	16	9	Pruritus, erythema, eczema, maculopapular, macular, dermatitis, papular, skin exfoliation, pruritic, erythematous, generalized, dermatitis allergic, dermatitis contact, exfoliative, dermatitis, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria	Generalized maculopapular rash
Dimethyl fumarate[a]	Tecfidera	Multiple sclerosis (psoriasis)	Activates the nuclear erythroid 2-related factor 2 transcriptional pathway	2013 (2017)	8	3	Rash	EN, rash, and pruritus in children
Edaravone[a]	Radicava	ALS (ischemic stroke)	Free radical scavenger	2017 (2009)	8	5	Dermatitis, eczema	
Fish oil triglycerides	Omegaven	Parenteral nutrition-associated cholestasis	Source of calories and essential fatty acids	2018	8		Rash	
Fostamatinib	Tavalisse	ITP	Inhibits spleen tyrosine kinase (SYK)	2018	9	2	Erythematous and macular	

Table 3 (continued)

Drug name	Brand name	Indication	Mechanism	Year approved	% patients who developed a rash during a pivotal clinical trial	% patients who developed a rash on placebo during a pivotal clinical trial	Rash description (clinical trial)	Rash description (supplemental case report)
Isavuconazonium sulfate	Cresemba	Invasive mucormycosis	Prevents ergosterol synthesis by inhibition of lanosterol 14-alpha-demethylase	2015	8.6	13.9 (voriconazole, not placebo)	Pruritus	
Lumacaftor 200 mg[a]/ Ivacaftor 125 mg	Orkambi	Cystic fibrosis	Lumacaftor: increases the amount of CFTR at the cell surface Ivacaftor: enhances the CFTR protein's function	2015 (2012)	7	2	Rash	Rash
Moxidectin	Moxidectin	Onchocerciasis due to *Onchocerca volvulus*	Binds to GluCl channels, GABA receptors, and/or ABC transporters	2018	37	21 (ivermectin, not placebo)	Papular, urticaria	Pruritus and rash
Obeticholic acid	Ocaliva	Chronic liver disease	Agonist for FXR; a regulator of bile acid, inflammatory, fibrotic, and metabolic pathways	2016	10	8	Urticaria, macular, papular, maculopapular, heat rash, cholinergic urticaria	
Ombitasvir	Viekira Pak	HCV	Inhibits HCV nonstructural protein 5A	2014	16	9	Pruritus, erythema, eczema, maculopapular, macular, dermatitis, papular, skin exfoliation, pruritic, erythematous, generalized, dermatitis allergic, dermatitis contact, exfoliative, dermatitis, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria	Generalized maculopapular rash

Table 3 (continued)

Drug name	Brand name	Indication	Mechanism	Year approved	% patients who developed a rash during a pivotal clinical trial	% patients who developed a rash on placebo during a pivotal clinical trial	Rash description (clinical trial)	Rash description (supplemental case report)
Paritaprevir	Viekira Pak	HCV	Inhibits HCV NS3/4A serine protease, thereby preventing viral replication	2014	16	9	Pruritus, erythema, eczema, maculopapular, macular, dermatitis, papular, skin exfoliation, pruritic, erythematous, generalized, dermatitis allergic, dermatitis contact, exfoliative, dermatitis, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria	Generalized maculopapular rash
Pirfenidone[a]	Esbriet	Idiopathic pulmonary fibrosis	Inhibits TGF-beta production and response, thereby reducing collagen production	2014 (2011)	30	10	Rash	Erythematous rash with edema, photosensitivity reaction (acute dermatitis with focal presence of necrotic keratinocytes)
Selexipag	Uptravi	Pulmonary arterial hypertension	Oral prostacyclin receptor agonist	2015	11	8	Rash	
Simeprevir	Olysio	HCV	Prevents viral maturation through inhibition of the NS3/4A protease	2013	12		Photosensitivity	Eczematous, maculopapular, and lichenoid (14.3%)
Sofosbuvir	Sovaldi	HCV	Inhibits NS5B, thereby inhibiting HCV RNA synthesis	2013	8		Pruritus	SJS

AGEP acute generalized exanthematous pustulosis, *ALS* amyotrophic lateral sclerosis, *CFTR* cystic fibrosis transmembrane conductance regulator, *DRESS* Drug Rash with Eosinophilia and Systemic Symptoms syndrome, *EN* erythema nodosum, *FXR* farnesoid X receptor, *HCV* hepatitis C virus, *ITP* immune thrombocytopenic purpura, *SJS/TEN* Stevens–Johnson syndrome/toxic epidermal necrolysis, *TGF* transforming growth factor

[a]Drug has been either previously approved (either in the USA or abroad), or approved abroad for an alternative indication. Parentheses indicate the associated indications and dates for this alternative approval

taking placebo. Details of the clinical trial indicate that the observed rash was described as generalized, maculopapular, papular, or pruritic [17]. A phase II, open-label multicenter study also noted rash as a side effect for 42% of patients taking siltuximab [18]. Additional case reports have not been published to supplement the clinical trial data.

3.2 Small-Molecule Medications

3.2.1 Benznidazole

Benznidazole, a nitroimidazole, was approved by the FDA in 2017 for the treatment of Chagas disease in children up to age 12 years. However, it has been utilized since the 1970s in Latin America [19], and has been available to clinicians in the USA through the Centers for Disease Control and Prevention since 2011 [20]. Its mechanism of action is unknown. Rashes were seen in 16% of patients taking benznidazole during clinical trials vs 0% of patients taking placebo [21]. The clinical trial did not offer further characterization of the rash.

A prospective descriptive study examining the effects of benznidazole treatment also describes an associated rash in 31.3% of patients and skin peeling in 25% of patients. In 15.6% of the patients, the rash was classified as skin eruptions that culminated in discontinuation of the drug [22]. Severe cutaneous adverse reactions such as acute generalized exanthematous pustulosis [23] and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) [24] have also been reported.

A prospective study found that dermatitis due to hypersensitivity was seen in 32.4% of patients taking benznidazole [25], and a supplemental case series describes the induced rash as a classic generalized morbilliform eruption, suggesting that patch testing may be beneficial in the confirmation of hypersensitivity reactions to benznidazole given its necessity in trypanosomiasis [26]. Interestingly, another nitroimidazole drug, metronidazole, has been reported to be a cross-reactor in several cases [26]. Additionally, a prospective observational study describes a drug eruption occurring in 38.5% of patients taking benznidazole [27].

3.2.2 Cannabidiol (Epidiolex®)

Cannabidiol oral solution was approved in 2018 to treat seizures associated with Lennox–Gastaut syndrome and Dravet syndrome. Its mechanism of action is unknown. Rashes were seen in 13% of patients taking cannabidiol during clinical trials vs 3% of patients taking placebo [28]. The clinical trial did not elaborate on the exact nature of the rash, but a case report describes an instance of acute generalized exanthematous pustulosis 48 h after self-medicating with over-the-counter oral cannabidiol for hypertension [29].

3.2.3 Dimethyl Fumarate (Tecfidera®)

Approved in 2013, dimethyl fumarate is a medication used to treat multiple sclerosis. It has also been approved to treat psoriasis in Europe [30], receiving approval from the European Medicines Agency in 2017 under the brand name Skilarence® [31]. Its mechanism of action is thought to involve activation of the nuclear erythroid 2-related factor 2 (nuclear factor erythroid-derived 2-like 2; Nrf2) transcriptional pathway. Rashes were seen in 8% of patients taking dimethyl fumarate during clinical trials vs 3% of patients taking placebo but did not result in treatment discontinuation [32]. Details of the clinical trial indicate that the observed rash was described as simply a rash. However, flushing was also noted in 40% of patients taking dimethyl fumarate vs 6% of patients taking placebo. It is believed that the flushing reaction described is most likely prostaglandin mediated and may be less visible or likely to develop in non-white populations [33]. A case report details an instance of erythema nodosum occurring in a woman after 6 years of dimethyl fumarate treatment [34]. Additional clinical trials have shown high rates of rashes (23%) and pruritus (8%) in children [35].

3.2.4 Edaravone (Radicava®)

Edaravone is a medication used to treat amyotrophic lateral sclerosis that was approved in 2017. Edaravone has also been approved for the treatment of acute ischemic stroke in Japan since 2009 [36]. It is believed to act as a free radical scavenger, thereby preventing oxidative stress damage to neurons. Rashes were seen in 8% of patients taking edaravone during clinical trials vs 5% of patients taking placebo [37]. Details of the clinical trial indicate that the observed rash was described as dermatitis or eczema.

3.2.5 Fish Oil Triglycerides (Omegaven)

Fish oil triglycerides as an injectable emulsion are used to treat parenteral nutrition-associated cholestasis. They were approved by the FDA in 2018 and act by providing a biologically utilizable source of calories and essential fatty acids. Rashes were seen in 8% of patients taking fish oil triglycerides during clinical trials [38]. The clinical trial did not elaborate on the exact nature of the rash and no specific case reports were found to offer further clarification.

3.2.6 Fostamatinib (Tavalisse®)

Approved in 2018, fostamatinib is a medication used to treat immune thrombocytopenic purpura. Its mechanism of action involves inhibition of spleen tyrosine kinase (SYK). Rashes were seen in 9% of patients taking fostamatinib during clinical trials vs 2% of patients taking placebo. Details of the clinical trial indicate that the observed rash was described as a rash, with erythematous and macular features, suggesting a morbilliform reaction [39].

3.2.7 Isavuconazonium Sulfate (Cresemba®)

Isavuconazonium sulfate is a triazole antifungal medication used to treat invasive mucormycosis that was approved in 2015. Its mechanism of action involves inhibition of ergosterol synthesis by inhibiting the cytochrome P450-dependent enzyme, lanosterol 14-alpha-demethylase. Rashes were seen in 8.6% of patients taking isavuconazonium sulfate vs 13.9% of patients taking voriconazole [40]. Details of the clinical trial indicate that the observed rash was pruritic but without other descriptors. Given the active comparator had a higher rate of cutaneous disease, it is possible that a rash while taking isavuconazonium may be attributable to the high acuity of the treated infection, polypharmacy, or the overall complexity of treated patients who are often immunocompromised rather than the drug itself.

3.2.8 Lumacaftor 200 mg/Ivacaftor 125 mg (Orkambi®)

Lumacaftor 200 mg/ivacaftor 125 mg, approved in 2015, is a medication used to treat cystic fibrosis in children. This medication utilizes two active ingredients: lumacaftor and ivacaftor. While lumacaftor increases the amount of protein at the cell surface by targeting the defective F508del cystic fibrosis transmembrane conductance regulator protein, ivacaftor (which was approved by the FDA to treat cystic fibrosis in 2012 under the brand name Kalydeco®) [41] enhances the cystic fibrosis transmembrane conductance regulator protein's function once it reaches the cell surface. Rashes were seen in 7% of patients taking lumacaftor 200 mg/ivacaftor 125 mg during clinical trials vs 2% of patients taking placebo [42]. The clinical trial did not offer a description of the rash. An article detailing the phase III clinical trial for this medication also comments on the presence of a rash in one patient that resulted in discontinuation of the medication [43]. However, this article did not offer any further clarification regarding the nature of the rash.

3.2.9 Moxidectin

Moxidectin, approved in 2018, is a medication used to treat onchocerciasis due to *Onchocerca volvulus*. It binds to glutamate-gated chloride channels, gamma-aminobutyric acid receptors, and/or ATP-binding cassette transporters. Rashes were seen in 37% of patients taking moxidectin during clinical trials vs 21% of patients taking ivermectin. Details of the clinical trial indicate that the observed rash was described as a papular or urticarial [44]. A randomized controlled trial comparing moxidectin to ivermectin found that statistically significant higher percentages of participants treated with moxidectin experienced pruritus (87% vs 56%) and rash (63% vs 42%) [45]. The study did not offer further characterization of the rash.

3.2.10 Obeticholic Acid (Ocaliva®)

Approved in 2016, obeticholic acid is a medication used to treat chronic liver disease. It is an agonist for farnesoid X receptor, a nuclear receptor expressed in the liver and intestine that regulates bile acid and inflammatory, fibrotic, and metabolic pathways. Rashes were seen in 10% of patients taking obeticholic acid during clinical trials vs 8% of patients taking placebo [46]. Details of the clinical trial indicate that the observed rash was described as urticarial, macular, papular, maculo-papular, heat rash, and cholinergic urticaria.

3.2.11 Ombitasvir, Dasabuvir, and Paritaprevir (Viekira Pak®)

Ombitasvir, dasabuvir, and paritaprevir are three medications that were approved by the FDA in 2014 to treat hepatitis C virus (HCV). They are used as a combination drug, along with ritonavir, in the commercial formulation "Viekira Pak®". Ombitasvir is an inhibitor of the HCV non-structural protein 5A. Dasabuvir inhibits the action of NS5B palm polymerase, effectively terminating RNA polymerization and stopping the replication of the HCV's genome. Paritaprevir prevents HCV replication by inhibiting the HCV's NS3/4A serine protease. Rashes were seen in 16% of patients taking the combination of ombitasvir, dasabuvir, paritaprevir, and ritonavir vs 9% of patients taking placebo during clinical trials [47]. Details of the clinical trial indicate that the observed rash was described as eczematous, maculo-papular, macular, dermatitis, papular, pruritic, erythematous, generalized, allergic dermatitis, contact dermatitis, exfoliative, dermatitis, photosensitivity reaction, psoriasis, ulcers, and urticarial. A case report describes the development of a generalized maculopapular rash appearing 2 weeks after starting this antiviral treatment [48].

3.2.12 Pirfenidone (Esbriet®)

Approved in 2014, pirfenidone is a medication used to treat idiopathic pulmonary fibrosis; an indication for which it was

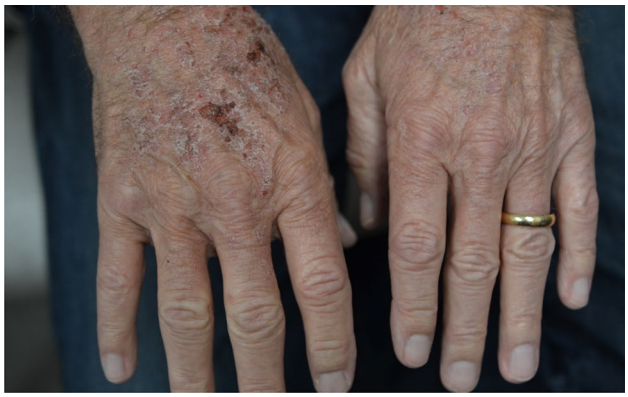

Fig. 2 Pirfenidone phototoxic drug eruption

approved in 2011 by the European Medicines Agency [49]. It reduces fibroblast proliferation by inhibiting the production of transforming growth factor-beta and reducing the collagen production stimulated by transforming growth factor-beta. Rashes were seen in 30% of patients taking pirfenidone during clinical trials vs 10% of patients taking placebo [50]. The clinical trial did not offer greater description of the rash, but a case report described the rash as erythematous with edema and noted that it occurred in 32% of patients taking pirfenidone vs 12% of patients taking placebo. A photosensitivity reaction (Fig. 2) was also noted in 12% of patients taking pirfenidone vs 2% of patients taking placebo, which was characterized histopathologically as acute dermatitis with focal presence of necrotic keratinocytes [51].

3.2.13 Selexipag (Uptravi®)

Selexipag is a medication used to treat pulmonary arterial hypertension that was approved in 2015. Selexipag is an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Rashes were seen in 11% of patients taking selexipag during clinical trials vs 8% of patients taking placebo [52]. The clinical trial described the cutaneous adverse reaction as simply a rash and no case reports offering further clarification were identified.

3.2.14 Simeprevir (Olysio®)

Simeprevir, approved in 2013, is a medication used to treat HCV. It prevents viral maturation through inhibition of the NS3/4A protease. Rashes were seen in 12% of patients taking simeprevir during clinical trials [53]. The clinical trial described the reaction as a rash that included photosensitivity. A retrospective case series reports that patients taking simeprevir experienced rashes described as eczematous (28.6%), maculopapular (57.1%), and lichenoid (14.3%) [54].

3.2.15 Sofosbuvir (Sovaldi®)

Sofosbuvir was approved in 2013 as a medication to treat HCV. Sofosbuvir inhibits the HCV NS5B protein, thereby inhibiting viral RNA synthesis. Rashes were seen in 8% of patients taking sofosbuvir during clinical trials [55]. Details of the clinical trial indicate that the observed rash was described as a rash and pruritus. A case report detailed an instance of Stevens–Johnson syndrome 10 days after initiating sofosbuvir therapy [56].

4 Conclusions

Of the 241 medications approved by the FDA between 2013 and 2018, 21 of the non-chemotherapeutic agents were associated with a prominent rate of cutaneous adverse events. Most reactions were classified as morbilliform, macular, popular, or maculopapular. This study was largely limited by the frequently vague and non-specific rash reporting found in the medication package inserts as well as the available case reports. Notably, the lack of specificity in the FDA package inserts highlights the importance of dermatologists reporting adverse events during clinical trials and post-marketing surveillance. Trials should consider engaging with dermatology experts to provide more granular detail of drug reactions when skin toxicities appear common. Fortunately, only a few severe cutaneous adverse reactions have been reported, namely in benznidazole, cannabidiol, and sofosbuvir. When suspicious, careful history taking of any additions or changes to a patient's medication regimen is an important component of the dermatology assessment. Familiarization with these new therapeutics including understanding their indications and who may be treated should help dermatologists and referring physicians to recognize drug reactions early.

Compliance with Ethical Standards

Funding No funding was received for the preparation of this article.

Conflict of interest Benjamin H. Kaffenberger is an investigator and funded by the Dermatology Foundation in the investigation of drug eruptions. Paul C. Macklis, Brittany Dulmage, Brady Evans, Misha Rosenbach, and Johann E. Gudjonsson have no conflicts of interest that are directly relevant to the content of this article.

References

1. Biswal SG, Mehta RD. Cutaneous adverse reactions of chemotherapy in cancer patients: a clinicoepidemiological study. Indian J Dermatol. 2018;63(1):41–6. https://doi.org/10.4103/ijd.IJD_65_17.
2. Ng CY, Chen C-B, Wu M-Y, et al. Anticancer drugs induced severe adverse cutaneous drug reactions: an updated review on the risks associated with anticancer targeted therapy or immunotherapies. J Immunol Res. 2018;17(2018):5376476.
3. Rosen AC, Balagula Y, Raisch DW, et al. Life-threatening dermatologic adverse events in oncology. Anticancer Drugs. 2014;25(2):225–34. https://doi.org/10.1097/CAD.0000000000000032.
4. EMA. Zenapax [prescribing information]. https://www.ema.europa.eu/en/documents/product-information/zenapax-epar-product-information_en.pdf. Accessed 12 May 2020.
5. MPR. Roche discontinues Zenapax injection. Published 22 December, 2009. https://www.empr.com/home/news/roche-discontinues-zenapax-injection/. Accessed 12 May 2020.
6. GOV.UK. Daclizumab beta (Zinbryta▼): risk of immune-mediated encephalitis: some cases several months after stopping treatment. https://www.gov.uk/drug-safety-update/daclizumab-beta-zinbryta-risk-of-immune-mediated-encephalitis-some-cases-several-months-after-stopping-treatment. Accessed 12 May 2020.
7. Huss DJ, Mehta DS, Sharma A, et al. In vivo maintenance of human regulatory T cells during CD25 blockade. J Immunol. 2015;194(1):84–92. https://doi.org/10.4049/jimmunol.1402140.
8. US FDA. Zinbryta (daclizumab) injection, for subcutaneous use [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761029s007lbl.pdf. Accessed 22 Dec 2019.
9. Lockhart A, Kirby B, McGuigan C. Rash developing after cessation of daclizumab for relapsing remitting MS; a case series. Mult Scler Relat Disord. 2019;35:239–40. https://doi.org/10.1016/j.msard.2019.08.008.
10. US FDA. Dupixent (dupilumab) injection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf. Accessed 22 Jan 2020.
11. de Wijs LEM, Nguyen NT, Kunkeler ACM, Nijsten T, Damman J, Hijnen DJ. Clinical and histopathological characterization of paradoxical head and neck erythema in patients with atopic dermatitis treated with dupilumab: a case series. Br J Dermatol. 2019. https://doi.org/10.1111/bjd.18730.
12. Waldman RA, DeWane ME, Sloan B, Grant-Kels JM. Characterizing dupilumab facial redness: a multi-institution retrospective medical record review. J Am Acad Dermatol. 2020;82(1):230–2. https://doi.org/10.1016/j.jaad.2019.06.026.
13. Soria A, Du-Thanh A, Seneschal J, Jachiet M, Staumont-Sallé D, Barbarot S. Development or exacerbation of head and neck dermatitis in patients treated for atopic dermatitis with dupilumab. JAMA Dermatol. 2019;155(11):1312–5. https://doi.org/10.1001/jamadermatol.2019.2613.
14. de Beer FSA, Bakker DS, Haeck I, et al. Dupilumab facial redness: positive effect of itraconazole. JAAD Case Rep. 2019;5(10):888–91. https://doi.org/10.1016/j.jdcr.2019.07.020.
15. Belhomme N, Gaignon T, Jouneau S, et al. Drug-induced granulomatosis: is dupilumab the new kid on the block? J Eur Acad Dermatol Venereol. 2020. https://doi.org/10.1111/jdv.16218.
16. US FDA. Trogarzo™ (ibalizumab-uiyk) injection [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761065lbl.pdf. Accessed 22 Dec 2019.
17. US FDA. Sylvant (siltuximab) [prescribing information]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125496s000lbl.pdf. Accessed 23 Dec 2019.
18. van Rhee F, Casper C, Voorhees PM, et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. Oncotarget. 2015;6(30):30408–199.
19. CDC. Chagas disease: what US clinicians need to know. https://www.cdc.gov/parasites/cme/chagas/lesson_3/20.html. Accessed 12 May 2020.
20. Infectious Disease Advisor. CDC advises that benznidazole now only available through drug company. Published 27 August, 2018. Available from: https://www.infectiousdiseaseadvisor.com/home/topics/vector-borne-illnesses/cdc-advises-that-benznidazole-now-only-available-through-drug-company/. Accessed 12 May 2020.
21. US FDA. Benznidazole tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209570lbl.pdf. Accessed 31 Dec 2019.
22. de Pontes VMO, de Souza Júnior AS, da Cruz FMT, et al. Adverse reactions in Chagas disease patients treated with benznidazole, in the State of Ceará [in Portuguese]. Rev Soc Bras Med Trop. 2010;43(2):182–7. https://doi.org/10.1590/s0037-86822010000200015.
23. ScienceDirect. Acute generalized exanthematous pustulosis due to benznidazole. https://www.sciencedirect.com/science/article/abs/pii/S2213219814003833?via%3Dihub. Accessed 10 Jan 2020.
24. González-Ramos J, Noguera-Morel L, Tong HY, et al. Two cases of overlap severe cutaneous adverse reactions to benznidazole treatment for asymptomatic Chagas disease in a nonendemic country. Br J Dermatol. 2016;175(3):604–7. https://doi.org/10.1111/bjd.14451.
25. Carrilero B, Murcia L, Martinez-Lage L, Segovia M. Side effects of benznidazole treatment in a cohort of patients with Chagas disease in non-endemic country. Rev Esp Quimioter. 2011;24(3):123–6.
26. Noguerado-Mellado B, Rojas-Pérez-Ezquerra P, Calderón-Moreno M, Morales-Cabeza C, Tornero-Molina P. Allergy to benznidazole: cross-reactivity with other nitroimidazoles. J Allergy Clin Immunol Pract. 2017;5(3):827–8. https://doi.org/10.1016/j.jaip.2016.09.047.
27. Salvador F, Sánchez-Montalvá A, Martínez-Gallo M, et al. Evaluation of cytokine profile and HLA association in benznidazole related cutaneous reactions in patients with Chagas disease. Clin Infect Dis. 2015;61(11):1688–94. https://doi.org/10.1093/cid/civ690.
28. US FDA. Epidiolex® (cannabidiol) oral solution [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf. Accessed 27 Dec 2019.
29. Pettit C, Massick S, Bechtel M. Cannabidiol-induced acute generalized exanthematous pustulosis. Dermatitis. 2018;29(6):345–6. https://doi.org/10.1097/DER.0000000000000422.
30. Blair HA. Dimethyl fumarate: a review in moderate to severe plaque psoriasis. Drugs. 2018;78(1):123–30. https://doi.org/10.1007/s40265-017-0854-6.
31. EMC. Skilarence 120 mg gastro-resistant tablets: summary of product characteristics (SmPC). https://www.medicines.org.uk/emc/product/7480/smpc. Accessed 12 May 2020.
32. US FDA. Tecfidera® (dimethyl fumarate) delayed-release capsules, for oral use [prescribing information]. https://www.tecfidera.com/content/dam/commercial/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf. Accessed 31 Dec 2019.

33. Ochi H, Niino M, Onizuka Y, et al. 72-week safety and tolerability of dimethyl fumarate in Japanese patients with relapsing-remitting multiple sclerosis: analysis of the randomised, double blind, placebo-controlled, phase III APEX study and its open-label extension. Adv Ther. 2018;35(10):1598–611. https://doi.org/10.1007/s12325-018-0788-8.
34. Algahtani H, Shirah B, Marghalani S, Algarni A. Erythema nodosum in a patient with multiple sclerosis on dimethyl fumarate. Mult Scler Relat Disord. 2019;28:155–8. https://doi.org/10.1016/j.msard.2018.12.032.
35. Makhani N, Schreiner T. Oral dimethyl fumarate in children with multiple sclerosis: a dual-center study. Pediatr Neurol. 2016;57:101–4. https://doi.org/10.1016/j.pediatrneurol.2016.01.010.
36. Miyahi Y, Yoshimura S, Sakai N, et al. Effect of edaravone on favorable outcome in patients with acute cerebral large vessel occlusion: subanalysis of RESCUE-Japan Registry. Neurol Med Chir (Tokyo). 2015;55(3):241–7. https://doi.org/10.2176/nmc.ra.2014-0219.
37. US FDA. Radicava (edaravone injection), for intravenous use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209176lbl.pdf. Accessed 31 Dec 2019.
38. US FDA. Omegaven (fish oil triglycerides) injectable emulsion [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/0210589s000lbledt.pdf. Accessed 27 Dec 2019.
39. US FDA. Tavalisse™ (fostamatinib disodium hexahydrate) tablets, for oral use [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209299lbl.pdf. Accessed 23 Dec 2019.
40. US FDA. Cresemba (isavuconazonium sulfate) [prescribing information]. https://www.astellas.us/docs/cresemba.pdf. Accessed 31 Dec 2019.
41. US FDA. Press announcements. FDA approves Kalydeco to treat rare form of cystic fibrosis. https://web.archive.org/web/20160318062836/https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm. Accessed 12 May 2020.
42. US FDA. Orkambi® (lumacaftor/ivacaftor) tablets, for oral use Orkambi® (lumacaftor/ivacaftor) oral granules [prescribing information]. Available from: https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf. Accessed 31 Dec 2019.
43. Milla CE, Ratjen F, Marigowda G, et al. Lumacaftor/ivacaftor in patients aged 6–11 years with cystic fibrosis and homozygous for F508del-CFTR. Am J Respir Crit Care Med. 2017;195(7):912–20. https://doi.org/10.1164/rccm.201608-1754OC.
44. US FDA. Moxidectin [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf. Accessed 23 Dec 2019.
45. Awadzi K, Opoku NO, Attah SK, Lazdins-Helds J, Kuesel AC. A randomized, single-ascending-dose, ivermectin-controlled, double-blind study of moxidectin in Onchocerca volvulus infection. PLoS Negl Trop Dis. 2014;8(6):e2953. https://doi.org/10.1371/journal.pntd.0002953.
46. US FDA. Ocaliva (obeticholic acid) tablets, for oral use [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207999s000lbl.pdf. Accessed 31 Dec 2019.
47. US FDA. Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf. Accessed 31 Dec 2019.
48. Navarro-Triviño FJ, Muñoz-Medina L, Navarro-Navarro I, Ruiz-Villaverde R. Cutaneous eruptions by new therapies against hepatitis C virus infection: not as common as we presumed. Int J Dermatol. 2018;57(4):493–4. https://doi.org/10.1111/ijd.13882.
49. Genentech. Esbriet® (pirfenidone): information for patients. https://www.gene.com/patients/medicines/esbriet. Accessed 12 May 2020.
50. Genentech. Esbriet® (pirfenidone) capsules and film-coated tablets, for oral use [prescribing information]. https://www.gene.com/download/pdf/esbriet_prescribing.pdf. Accessed 31 Dec 2019.
51. Ferrer Guillén B, Giácaman MM, Valenzuela Oñate C, Magdaleno Tapial J, Hernández Bel P, Pérez FA. Pirfenidone-induced photosensitivity confirmed by pathological phototest. Photodiagn Photodyn Ther. 2019;25:103–5. https://doi.org/10.1016/j.pdpdt.2018.11.015.
52. US FDA. Uptravi® (selexipag) tablets, for oral use [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207947s000lbl.pdf. Accessed 31 Dec 2019.
53. US FDA. Olysio (simeprevir) capsules, for oral use [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205123s012lbl.pdf. Accessed 31 Dec 2019.
54. Borgia F, Cacciola I, Filomia R, Vaccaro M, Squadrito G, Cannavò SP. Mucocutaneous toxicity during simeprevir treatment for hepatitis C: a single institution, retrospective case series. Br J Clin Pharmacol. 2017;83(5):1152–4. https://doi.org/10.1111/bcp.13221.
55. US FDA. Sovaldi® (sofosbuvir) tablets, for oral use [prescribing information]. https://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf. Accessed 31 Dec 2019.
56. Verma N, Singh S, Sawatkar G, Singh V. Sofosbuvir induced Steven Johnson syndrome in a patient with hepatitis C virus-related cirrhosis. Hepatol Commun. 2018;2(1):16–20. https://doi.org/10.1002/hep4.1126.