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

| Generic                                        | Brand         | Indication                                                                 |
|------------------------------------------------|---------------|-----------------------------------------------------------------------------|
| 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                                      | Talinlar      | Cancers with \textit{BRAF} gene mutation                                    |
| Dimethyl fumarate                               | Tecfidera     | Multiple sclerosis                                                           |
| Dolutegravir                                    | Tivicay       | HIV                                                                         |
| Divalcarbazepine                                | Aptiom        | Partial-onset seizures                                                      |
| Flutemetamol                                    | Vizamyl       | Alzheimer disease                                                            |
| Fluticasone furoate and vilanterol              | Breo Elipta   | 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 |
| Iuliconazole                                    | 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                          |
| Osmipenene                                      | 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 \textit{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 |
| Cerditinib                                      | Zykadia       | Non-small cell lung cancer                                                   |
| Dalbavancin                                     | Dalvance      | Skin infections                                                              |
| Dapagliptin                                     | 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                                                       |
| Elsolusfase 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                                                            |
| Generic          | Brand      | Indication                                                                 |
|------------------|------------|-----------------------------------------------------------------------------|
| Miltefosine      | Impavido   | Leishmaniasis                                                               |
| Naloxegol        | Movantik   | Constipation that is caused by opioids                                       |
| Netupitant       | Akynezo    | Nausea and vomiting caused by chemotherapy                                   |
| Nintedanib       | Otev       | Idiopathic pulmonary fibrosis                                                |
| Nivolumab        | Opdivo     | Non-small cell lung cancer                                                  |
| Olaparib         | Lyparza    | 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                                                                   |
| Pifrenidone      | Esbriet    | Idiopathic pulmonary fibrosis                                                |
| Ramucirumab      | Cyramza    | Stomach cancer, colorectal cancer, or non-small cell lung cancer            |
| Siltuximab       | Sylvant    | Multicentric Castleman disease                                              |
| Suvorexant       | Belsomra   | Insomnia                                                                    |
| Tasmelteon       | Heltioz    | 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      | Cotelic    | 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                                                            |
| Filbanserin      | 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 |
| Lenvatinitib | 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

| Generic | Brand | Indication |
|---------|-------|------------|
| Atezolizumab | Tecentriq | Urothelial carcinoma |
| Bezlotoxumab | Ziplava | Clostridium difficile |
| Brivaracetam | Briviact | Partial-onset seizures |
| Crisaborole | Eurista | 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 |
| Liptegast ophthalmic solution | Xiidra | Dry eye disease |
| Lixisenatide | Adlyxin | Glycemic control (blood sugar levels) |
| Nusinersen | Spinraza | Spinal muscular atrophy |
| Obeticholic acid | Ocaliva | Chronic liver disease |
| Obinutuzumab | 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

| Generic | Brand | Indication |
|---------|-------|------------|
| Abaloparatide | Tymlos | Osteoporosis |
| Abemaciclib | Verzenio | Breast cancers |
| Acalabrutinib | Calquence | Mantle cell lymphoma |
| Angiotensin II | Giapreza | Septic or other distributive shock |
| Generic | Brand | Indication |
|---------|-------|------------|
| Avelumab | Bavencio | Merkel cell carcinoma |
| Benralizumab | Fasenra | Asthma |
| Benzimidazole | Benzimidazole | 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 | Hemintra | Hemophilia A |
| Enasidenib | Idhifa | Acute myeloid leukemia |
| Ertugliflozin | Steglatro | Type 2 diabetes mellitus |
| Etezolacetide | Parsabiv | Secondary hyperparathyroidism |
| Glecaprevir and pibrentasvir | Maviret | Hepatitis C virus |
| Guselkumab | Tremfya | Plaque psoriasis |
| Inotuzumab ozogamicin | Besponsa | Acute lymphoblastic leukemia |
| Latanoprostene bunod ophthalmic solution | Vyzulta | Open-angle glaucoma |
| Lzettermovir | 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 | Mepsevi | Mucopolysaccharidosis type VII also known as Sly syndrome |

2018

| Generic | Brand | Indication |
|---------|-------|------------|
| Amifampridine | Firdapse | Lambert–Eaton myasthenic syndrome |
| Apalutamide | Erleada | Prostate cancer |
| Avatrombopag | Doptelet | Thrombocytopenia |
| Baloxavir marboxil | Xofluza | Influenza |
| Generic Product                                      | Brand      | Indication                                                      |
|-----------------------------------------------------|------------|----------------------------------------------------------------|
| Baricitinib                                          | Olumiant   | Rheumatoid arthritis                                            |
| Bictegravir, emtricitabine, tenofovir alafenamide    | Biktarvy   | HIV                                                             |
| Binimetinib                                         | Mektovi    | Melanoma                                                        |
| Burosumab-twza                                       | Crysivita  | X-linked hypophosphatemia                                        |
| Calaspargase pegol-mknl                              | Asparlas   | Acute lymphoblastic leukemia                                     |
| Cannabidiol                                         | Epidiolex  | Epilepsy                                                        |
| Cemiplimab-rwlc                                      | Libtayo    | Squamous cell carcinoma                                         |
| Cenocepinib                                          | Oxervate   | Neurotrophic keratitis                                           |
| Daclominib                                          | Vizimpro   | Non-small-cell lung cancer                                      |
| Doravirine                                          | Pifeltro   | HIV                                                             |
| Duvelisib                                           | Copiktra   | Chronic lymphocytic leukemia                                     |
| Elagolox sodium                                      | Orilissa   | Endometriosis                                                    |
| Elapegademase-lvrl                                   | Revcovi    | Adenosine deaminase severe combined immunodeficiency            |
| Empalumab-lzsgemapalumab-lzsg                       | Gamifant   | Hemophagocytic lymphohistiocytosis                               |
| Encorafenib                                         | Braftovi   | Melanoma                                                        |
| Eravacycline                                         | Xerava     | Intra-abdominal infections                                       |
| Erenumab-aoee                                       | Aimovig    | Migraine                                                        |
| Fish oil triglycerides                               | Omegaven   | Parenteral nutrition                                             |
| Fosnetupitant and palonosetron                       | Akynezo    | Chemotherapy-induced nausea and vomiting                        |
| Fostamatinib                                         | Tavalisse  | Chronic immune thrombocytopenia                                  |
| Fremanezumab-vfrm                                    | Ajovy      | Migraine                                                        |
| Galncanomab-gnml                                     | Emality    | Migraine                                                        |
| Gilteritinib                                         | Xospata    | Acute myeloid leukemia                                           |
| Glasdegib                                           | Daurismo   | Acute myeloid leukemia                                           |
| Ibaltizumab-uiry                                     | 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                              | Lucemypa   | Opioid withdrawal                                                |
| Lorlatinib                                          | Lorbrena   | Non-small cell lung cancer                                       |
| Lusutrombopag                                        | Mulpleta   | Thrombocytopenia                                                 |
| Lutetium Lu 177 dotatat                              | Lutathera  | Gastroenteropancreatic neuroendocrine tumors                    |
| Migalastatin                                         | Galafold   | Fabry disease                                                    |
| Mogamulizumab-kpcc                                   | 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-pqppz                                      | Palynziq   | Phenylketonuria                                                  |
| Plazomicin                                           | Zemdri     | Complicated urinary tract infections                             |
| Prucalopride                                         | Motegrity  | Chronic idiopathic constipation                                  |
| Ravulizumab                                          | Ultomiris  | Paroxysmal nocturnal hemoglobinuria                              |
| Revefenacin                                          | Yupelri    | Chronic obstructive pulmonary disease                            |
| Rifampycin                                          | Aemcolo    | Travelers' diarrhea                                              |
| Saripycline                                          | Seyesara   | Acne vulgaris                                                    |
| Segesterone acetate and ethinyl estradiol vaginal system | Annovera | Contraception                                                    |
| Sodium zirconium cyclosilicate                       | Lokelma    | Hyperkalemia                                                     |
| Stiripentol                                          | Diacomit   | Dravet syndrome                                                  |
any cutaneous adverse events. 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
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.
| 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         | 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-aiyk    | 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

*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<sup>a</sup> | 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<sup>a</sup> | 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<sup>a</sup> | 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          |                                           |
| 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 sulphate      | 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<sup>a</sup> | 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 non-structural 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 |

<sup>a</sup> Includes Ivacaftor 125 mg.
| 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 maculo-papular rash            |
| Pirfenidone†    | 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                                                                 | Eczematous, maculopapular, and lichenoid (14.3%) |
| Simeprevir      | Olysio     | HCV        | Prevents viral maturation through inhibition of the NS3/4A protease | 2013          | 12                                                              |                                                                         | Photosensitivity                                    |                                           |
| 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

†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...
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 Selsepix (Uptravi®)

Selsepix is a medication used to treat pulmonary arterial hypertension that was approved in 2015. Selsepix is an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Rashes were seen in 11% of patients taking selsepix 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

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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;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.0000000000000332.
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-dcontinu es-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/dac liluzumab-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 (daciluzumab) 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 daciluzumab 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, Hijnjen 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, Haecck I, et al. Dupilumab facial redness: positive effect of itraconazole. JAAD Case Rep. 2019;5(10):888–91. https://doi.org/10.1016/j.jder.2019.07.020.
15. Bellhomme 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™ (ibaluzumab-uiyk) injection [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761065lbl.pdf. Accessed 22 Dec 2019.
17. US FDA. Sylvant (siliximab) [prescribing information]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125496s001lbl.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 siliximab (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.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/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-Esquerra P, Calderón-Moreno M, Morales-Cabeza C, Tornero-Molina P. Allergy to benznidazole: cross-reactivity with other nitrimentozades. J Allergy Clin Immunol Pract. 2017;5(3):827–8. https://doi.org/10.1016/j.ji mapi.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/civ990.
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. Drugs. 2018;78(1):123–30. https://doi.org/10.1055/s-0038-1680002.
30. Blatt A, Dimethyl fumarate: a review in moderate to severe plaque psoriasis. Drugs. 2018;78(1):123–30. https://doi.org/10.1055/s-0038-1680002.
31. EMC. Skilarence 120 mg gastro-resistant tablets: summary of product characteristics (SmPC). https://www.medicines.org.uk/emc/product/7480/smcp. 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.
Cutaneous Adverse Events in Newly Approved FDA Non-cancer Drugs: A Systematic Review

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.2015.55.3.241.

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/2018/209299s000lbl.pdf. Accessed 31 Dec 2019.

39. US FDA. Tavalisse™ (fostamatinib disodium hexahydrate) tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206619s000lbl.pdf. Accessed 31 Dec 2019.

40. US FDA. Cresemba (isavuconazonium sulfate) [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf. Accessed 31 Dec 2019.

41. US FDA. Press announcements. FDA approves Kalydeco to treat cystic fibrosis. https://web.archive.org/web/20160718174540/https://www.accessdata.fda.gov/ucm/cdms/groups/fdacomm/_documents/fda_docs/pressannouncements/ucm289633.htm. Accessed 31 Dec 2019.

42. US FDA. Orkambi® (lumacaftor/ivacaftor) tablets, for oral use. Orkambi® (lumacaftor/ivacaftor) oral granules [prescribing information]. Available from: https://pi.vrx.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. Ocalfa (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 Guillen B, Giaçaman MM, Valenzuela Oñate C, Magdaleno Tapijal J, Hernández Bel P, Pérez FA. Pirfenidone-induced photosensitivity confirmed by pathological phototest. Photodermat 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/2016/205123s012lbl.pdf. Accessed 31 Dec 2019.

54. Borgia F, Cacciola I, Filomia R, Vaccaro M, Squadrito G, Canavò 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/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.