Antiviral Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome: A Literature Review

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A B S T R A C T
Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is a delayed infrequent potentially life-threatening drug reaction. Fever, rash, lymphadenopathy, eosinophilia, and hepatic involvement are common features. Aromatic anticonvulsants and allopurinol are the most frequent causative agents. However, some cases of antivirals induced DRESS are available. In this review, we try to summarize studies of antiviral induced DRESS syndrome. The data were collected by searching PubMed, Science Direct, Google Scholar, Scopus, Cochrane database systematic reviews, and Islamic World Science Citation Center (ISC). The Keywords used as search terms were “DRESS syndrome”, “drug-induced hypersensitivity reaction (DIHS)”, “antiviral”, and names of various antiviral agents. Finally, a total of 28 relevant articles up to the date of publication were included for review. Totally, 30 cases of antiviral induced DRESS are reported. European registry on severe cutaneous adverse drug reactions (RegiSCAR) was the usual used clinical diagnostic criteria. Most of the reports were related to, telaprevir. Rash and fever actually occurred in a large number of these patients. Eosinophilia was the most reported hematologic involvement. Liver injury is the most defined type of organ damage. Most of the patients managed with systemic corticosteroids. The death occurred in 1 patient from liver decompensation. The reactivation various viruses especially HHV-6 is reported in 2 Cases. The latency period was between 10 and 330 days after drug administration. It is necessary to perform more studies, especially those focused on the association between DRESS syndrome and viral reactivation and also its effective management.

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Introduction
Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), and DIDMOHS (drug-induced delayed multiorgan hypersensitivity syndrome) (1) is a delayed potentially fatal multiorgan systemic idiosyncratic drug reaction characterized by skin rash, fever, enlarged lymph nodes, organ involvement (usually liver & kidneys), and leukocytosis with hypereosinophilia (2, 3). Aromatic anticonvulsant drugs (e.g., carbamazepine, phenytoin and phenobarbital) and allopurinol are the most common offending medications. However, various reports of DRESS induced by antimicrobial agents including antiviral medications are available (1, 2, 4, 5).

Fortunately, this reaction is usually reversible, with a low incidence of residual damage or mortality, in case of timely discontinuation of antibiotics and the use of topical or systemic corticosteroids (5, 6). However, many questions remain to be answered about the DRESS syndrome. In this review, we have collected available evidence on this syndrome, particularly in terms of its epidemiology, pathogenesis, risk factors, clinical manifestation and diagnosis, and management and above all, reports of DRESS syndrome with antiviral agents during last decades.
**Methods**

The data were collected by searching PubMed, ScienceDirect, Google Scholar, Scopus, Cochrane database systematic reviews, and Islamic World Science Citation Center (ISC). The Keywords used as search terms were “DRESS syndrome”, “drug-induced hypersensitivity reaction(DIHS)”, “antiviral”, “abacavir”, “tenofovir”, “raltegravir”, “dolutegravir”, “nevirapine”, “ribavirin”, “telaprevir”, “boceprevir”, “cidofovir”.

**Results**

By searching these databases, 60 articles were found, 28 of them were removed by reading abstract; 4 articles were not in English and were removed. Finally, a total of 28 relevant articles (30 cases of DRESS) up to the date of publication were included for review. The related articles are summarized in Table 2. All case reports and case-series on antiviral induced DRESS between 1998 and 2019 are included in this review. Most of the reports were related to, telaprevir and then nevirapine. The cases’ age range was from 11 months to 66 years and most of them were female. RegiSCAR criterion was the most common used diagnostic criteria in reviewed studies. The latency period between antiviral use onset and DRESS occurrence was between 10 and 330 days. Improving the clinical condition and laboratory parameters happened approximately in the first few days after antiviral discontinuation, in most of the patients and just 1 patient died from liver decompensation. So, immediate withdrawal of causative drug was the most important single measure in DRESS management and prescription of systemic corticosteroids (orally or parenterally) was also the standard of care. Supportive procedures are also helpful, including fluid and electrolyte management and antihistamines for cutaneous symptoms relief.

**Discussion**

In this review we tried to collect all available reported data on antiviral induced DRESS in case reports and case-series. It could be useful for the physicians and the pharmacists to know the most accused antivirals for this reaction, its most common characteristics and also the way to manage it appropriately. These are discussed in detail, below.

**Epidemiology & pathogenesis**

The prevalence of DHS ranges between 1 in 1000 and 1 in 10,000 exposures. It occurs more frequently in females (2-4). It is not well defined but likely is multifactorial. Exposure to a causative drug is necessary but not enough. It is proposed that a Gell and Coombs classification type IV reaction occurs in DRESS, in which cytokine release from activated T cells contributes to many of the clinical features (5). Actually, DRESS includes Th2-lymphocytes and CD8+ T cells. It is probable that Th2 cells induce type IVb hypersensitivity response affecting the skin, while CD8+ T cells cause damage to internal organs (7). Furthermore, a specific defect in the metabolism and detoxification of a drug can happen in phenotypic susceptible patients. Then the toxic metabolite acts as a hapten, initiating an immune response. In other words, genetic polymorphisms of these elimination mechanisms have been implicated in several skin drug reactions, like DRESS.

For example, Sulfonamide antibiotics are converted to reactive metabolites by slow acetylators patients, typically hydroxylamines and nitroso compounds, which can be cytotoxic. In patients with glutathione deficiency, detoxification of these toxic metabolites is not possible and can lead to DRESS syndrome (3, 8).

**Clinical manifestation**

Symptoms typically develop after 2 to 6 weeks of medication use. Reexposure to the same drug may cause symptoms even within 24 hours. The symptoms may last for weeks or even months after the medication discontinuation. The most common presentations are fever (between 38˚- 40˚C), malaise, pharyngitis, and cervical lymphadenopathy. A generalized exanthema’s morbilliform rash develops in 75% of cases, either with or soon after the fever. Skin presentations can be as exfoliative erythroderma, follicular or nonfollicular pustules, purpuric lesions or blisters, and tense bullae induced by dermal edema. Typically involved sites are the face, upper trunk, and extremities. Facial edema is also a common finding. Rash involving more than 50% of body surface area and/or 2 of the following: facial edema, scaling or purpura, infiltrated lesions are most suggestive of DRESS. Additionally, encephalitis, aseptic meningitis, myositis, bleeding, thyroiditis, respiratory distress syndrome, pericarditis, myocarditis, pneumonitis, colitis, pancreatitis, hypotension, interstitial nephritis, arthritis, arthralgia, and orchitis have been reported as organ involvements (9). Typically, organ involvement occurs 1-2 weeks after skin eruption. Elevated levels of liver transaminase, bilirubin, alkaline phosphatase, and prothrombin time are reported in about half of patients (1, 5). Fulminant hepatitis is the main cause of death associated with this syndrome, occurring in 5% to 10% of cases. Acute eosinophilic myocarditis is the most common form of cardiac involvement, and this can progress to acute necrotizing eosinophilic myocarditis (ANEM), presents with tachycardia, chest pain, and shortness of breath. It is important to recognize ANEM early, as it has a mortality of >50%, with an average survival of 3-4 days (10).

Renal involvement is usually asymptomatic, which occurs in 8-11% of patients with DRESS syndrome and is recognized by biochemical markers; serum creatinine or blood urine nitrogen. It is typically self-limiting but it can progress to severe interstitial nephritis in severe cases. The long-term sequelae of DRESS syndrome consist of autoimmune conditions such as type 1 diabetes and Grave’s disease, which can happen after months to years (10).
Finally, hematologic involvement includes thrombocytopenia, atypical lymphocytosis (40%), hypereosinophilia (90%), neutrophilia or neutropenia; and hemolytic anemia (1, 5, 7).

The mortality rate due to DRESS is reported between 10% and 30%, and it comes with lung and/or hepatic involvement and sometimes with bacterial ulcer lesions (11). It should be noted that antibiotic-induced DRESS is less severe than anticonvulsant-or allopurinol-induced DRESS (12-14).

**Diagnostic criteria**

Various criteria have been established for the identification of DRESS syndrome. The Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) has established 7 criteria for diagnosis of this syndrome: 1) maculopapular rash developing >3 weeks after initiating a limited number of drugs; 2) prolonged clinical symptoms; 3) fever; 4) leukocyte abnormalities (leukocytosis and/or atypical lymphocytosis and/or eosinophilia); 5) elevation of liver enzymes; 6) lymphadenopathy; and 7) reactivation of HHV-6 in the second to third week after the onset of symptoms. A probable diagnosis (atypical DRESS) requires the presence of 5 of these 7 criteria and a definitive diagnosis (typical DRESS) requires all 7 (15). The more specific cutaneous adverse reaction scale has been published as part of the European registry on severe cutaneous adverse drug reactions (RegiSCAR) which is based on registry data from cases of DRESS syndrome between 2002 and 2007 in the Netherlands, Italy, Israel, Germany, France, and Austria (16). The diagnosis is definite if more than 5 of the following 7 characteristics occurs: 1) skin eruption, 2) fever (>38°C), 3) lymph–adenopathy at least 2 sites, 4) involvement of at least 1 internal organ, 5) lymphocytosis (>4×10^3/μL) or lymphocytopenia (<1.5×10^3/μL), 6) blood eosinophilia (>10% or 700/μL), and 7) thrombocytopenia (<120×10^3/μL) (17). The diagnosis is probable and possible if the final score is 4-5 or 2-3, respectively (3).

This scoring system is based on registry data from cases of DRESS syndrome between 2002 and 2007 in the Netherlands, Italy, Israel, Germany, France, and Austria. Though the RegiSCAR score is helpful for diagnosis, it does not estimate causality (16). It has been designed to grade DRESS cases as “no,” “possible,” “probable,” or “definite” case (3). The Naranjo et al. scale is used for DRESS diagnosis in some reports, which classifies the probability that an adverse event is related to medication based on a list of weighted questions, which evaluate factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, serum drug levels, and previous patient experience with the medication, and classify adverse drug reactions into definite, probable, possible, and doubtful accordingly (18). There are some other clinical criteria that are summarized in Table 1 (5).

| Clinical criteria for DRESS syndrome | **Roujeau criteria (2005)** | Suspicion of drug reaction Eosinophilia of >1500/mL and/or atypical lymphocytes Failure of at least two organ systems with the skin being one of them |
|-------------------------------------|-------------------------------|---------------------------------------------------------------------------------|
| **DRESS syndrome**                  | **Bouquet and colleagues’ (1996)** | Cutaneous drug eruption, Hematologic abnormalities (eosinophilia of >1500/mL or atypical lymphocytes) Systemic involvement including adenopathies of a >2-cm diameter, interstitial nephritis, interstitial pneumonia, or carditis |
| **DIHS/DRESS**                      | **Kano and Shiohara(2006)** | Maculopapular rash starting no longer than 3 wks after starting one of a limited number of drugs, Prolonged clinical symptoms 2 wks after discontinuation of the causative drug, Fever higher than 38°C Liver or renal abnormalities Leukocyte abnormalities Lymphadenopathy HHV6 reactivation |

DIHS, drug-induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; HHV6, human herpesvirus 6.

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Table 1. Some clinical criteria for DRESS syndrome diagnosis.
Offending medications

Aromatic anticonvulsant drugs (e.g., carbamazepine, phenytoin and phenobarbital) and allopurinol have been described to be the most frequent causative agents. Antibiotics including sulfonamides, minocycline, trimethoprim and antiviral medications such as abacavir and nevirapine, dapsone, NSAIDs, angiotensin-converting enzyme inhibitors, beta-blockers, and lamotrigine also have been reported (1, 5, 29). There are reports of DRESS with various antiviral agents which are reviewed below.

Telaprevir

Dermatological side effects often exist during the treatment of hepatitis C (HCV), however, most are simply managed. In the trials on telaprevir (TVR), the severity of rash was classified as grade 1-3. Grade 1 (mild) reactions were localized skin eruptions with limited distribution, with or without associated pruritus; grade 2 (moderate), diffuse skin eruptions involving up to almost 50% of body surface area with or without superficial skin peeling, pruritus, or mucous membrane involvement with no ulceration; and grade 3 (severe), generalized rash involving either 50% or more of body surface area or rash appearance with bullae, purpura, vesicles, epidermal detachment, or superficial ulceration of mucous, atypical or typical target lesions. No telaprevir discontinuation is necessary for Grade 1 or 2 and grade 3 reactions could be managed appropriately with the prompt withdrawal of medication and topical corticosteroids (30). Moreover, severe skin involvement such as Stevens-Johnson syndrome and DRESS can happen, and if unrecognized or unmanaged can be fatal (31). In phases II and III trials three patients with suspected Stevens-Johnson syndrome and 11 patients (0.4%) with DRESS were reported (32). All treatment must be discontinued instantly, in these kinds of reactions (30). Two cases of TVR induced DRESS is reported by Mousa et al., This presentation happened later than previous reports that stated a usual presentation at 2-6 weeks and also a delayed resolution is reported despite the withdrawal of TVR (22). Risk factors for DRESS with TVR are White race, age above 45 years, body mass index below 30, and first HCV therapy (32).

Boceprevir

Boceprevir is one of the main treatments for HCV with high efficacy. It causes frequent cutaneous side effect even including DRESS (33).

Abacavir

Abacavir also is famous among nucleoside analog reverse-transcriptase inhibitors (NRTIs) for its hypersensitivity reactions. While the HLA-B5701 allele is severely related to this reaction, another pathogenic mechanism, irrespective of HLA-B5701 status should also be involved. So, severe drug reactions may still happen, even in a subject with a negative test for this haplotype or for the abacavir patch test or both of them (34).
Tenovir

Tenovir-induced DRESS is rarely reported. Aqtash et al., reported a patient that indicated DRESS secondary to tenovir. After its prompt withdrawal, the manifestation resolved within ten days (35).

Raltegravir

Raltegravir, another HIV-1 integrase strand transfer inhibitor, also induced DRESS syndrome in some patients. It is reported that patients of Hispanic or African ethnicity are more susceptible to this reaction which is consistent with the prevalence of the HLA-B*53/HLA-C*04 haplotype, which is common in people of African ethnicity (approximately 10%), less common in people of Hispanic ethnicity (approximately 3%), and rare in people of Caucasian or Asian ethnicity (<1%) (36).

Dolutegravir

Dolutegravir is increasingly used as a component of antiretroviral regimens in HIV positive patients. So, close post-marketing surveillance is necessary to detect potential cases of DRESS syndrome linked to this medication (37).

Nevirapine

Nevirapine a nonnucleoside reverse-transcriptase inhibitors (NNRTI) medication scarcely is used in HIV patients nowadays. Rash (16%), nausea and elevation of liver enzymes are the most commonly described adverse reaction in adults which usually do not require cessation of therapy (38). Lots of studies in recent years have described an increased association of DRESS syndrome with nevirapine, becoming the third leading cause. Even Meningoencephalitis could be a feature of DRESS syndrome with nevirapine (38).

Bourezane et al., and Fields et al., explained the first case of DRESS associated with nevirapine therapy that was successfully treated with intravenous methylprednisolone and intravenous immune globulin, respectively. However, most patients with nevirapine-related DRESS syndrome are treated with either intravenous dexamethasone (15-20 mg/ day) or oral prednisolone (0.5-0.7 mg/kg/day) for a mean duration of 49 days (39). Reexposure to the medication is usually followed by more severe hypersensitivity symptoms (40).

Cidofovir

There is also a report of DRESS with cidofovir in an infant. No massive organ involvement was found and it completely resolved after drug discontinuation (41). However, it is proposed that this patient possibly did not develop a DRESS but only a severe viral reactivation or “VRESS” (viral reactivation with eosinophilia and systemic symptoms). These reactivations are related to immunosuppression and probably also some genetic antecedents. Corticosteroids, intravenous gammaglobulins or antivirals are needed for VRESS management (42).

Management

The principal of DRESS syndrome management is an immediate withdrawal of causative drug and prescription of systemic corticosteroids (orally or parenterally) as the standard of care. But the efficacy of systemic corticosteroids is unclear and randomized clinical trials are lacking. Therefore further studies are needed to recommend specific treatment guidelines (43). However, experts recommend this measure for patients with life-threatening hepatitis, pneumonia, or nephritis (5). In patients without severe organ involvement, topical corticosteroids were preferred based on observational data (9). But most experts also favor steroid use even in these cases by relying on the fact that relapses of DRESS syndrome often occur after steroid tapering (6). They might inhibit eosinophilic accumulation, which is thought to account for organ involvement, perhaps by inhibiting the effect of IL-5 (44). Immunosuppressive therapy with agents such as cyclophosphamide or cyclosporine maybe even essential in steroid-resistant cases (45). In severe DRESS, plasma exchange or intravenous immunoglobulin has also been used, although data on this is limited (5). Supportive procedures are also helpful, including fluid and electrolyte management and antihistamines for cutaneous symptoms relief (5). N-acetylcysteine potentially deactivates drug-derived reactive metabolites responsible for protein adduct formation and specific T cell stimulation and restocks the glutathione stores to counterbalance oxidative stress (46). Gancyclovir has been recommended in patients with severe signs and the confirmation of a major viral reactivation of HHV-6 (47). Reexposure to suspected drugs is absolutely contraindicated after a diagnosis of DRESS. However, because of the nature of some infections like tuberculosis and the lack of proper therapeutic alternatives, a reintroduction could be acceptable in some cases (23).

Conclusion

In this review, all available reports of antiviral induced DRESS are collected. Totally 30 cases are found. Most of the reports are related to telaprevir. European registry on severe cutaneous adverse drug reactions (RegiSCAR) was the usual used clinical diagnostic criteria. Rash and fever actually occurred in a large number of these patients. Eosinophilia was the most reported hematologic involvement. Liver injury is the most defined type of organ damage. Renal involvement is usually mild and recovered after medication discontinuation without permanent sequelae. Most of the patients were managed with systemic corticosteroids including both oral and parenteral forms. The death occurred in 1 patient from liver decompensation. The reactivation various viruses especially HHV-6 is reported in 2 Cases. It is necessary to perform more studies, especially those focused on the association between DRESS syndrome and viral reactivation and also its effective management.
| Table 2. Summary of the published human studies on antiviral induced DRESS syndrome |
|----------------------------------|-----------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-----------------|
| **Study** | **Associated medication** | **Type of study** | **Age (year, month) / Sex** | **Diagnostic criteria** | **Clinical presentation** | **Latency period (day)** | **Eosinophilia (%)** | **Atypical lymphocytes** | **Other hematologic findings** | **Liver abnormalities** | **Renal impairment** | **Skin patch test or other tests result** | **The coincidence of viral infection** | **Management** | **Outcome** |
| 1 | Calza et al. (34) | Abacavir | Case report (41 y old male) | Naranjo criteria | Fever & chills, weight loss, and cutaneous eruption. Rash resolved with the discontinuation of the medication. | 300d |  |  |  |  |  | Skin patch test not performed | Negative CMV & EBV | Oral antihistamine | Within two days, the temperature became normal, whereas the skin rash evolved into a desquamative phase and disappeared completely 10 days later. |
| 2 | Almudimee-gh et al. (48) | Tenofovir | Case report (46 y old female) | RegiSCAR criteria score=5 “Probable” | Generalized skin rash and fever, exanthema with facial edema and oral mucosal erythema | 28d | Yes | Lymphocytosis |  |  |  |  | Reactivation of herpesvirus & CMV | Oral GCs | Valganciclovir | Rapid clinical and biological improvement |
| 3 | Aqtash et al. (35) | Tenofovir | Case report (65 y old male) | RegiSCAR criteria “probable” | Generalized skin rash, tongue swelling, and lip peeling, generalized maculopapular rash, erythematous but non-blanching | 60d | Yes |  |  |  |  |  |  | IV hydration | Oral GCs | His liver enzymes normalized. |
| 4 | Zhang et al. (49) | Raltegravir | Case report (64 y old female) | Generalized morbilliform exanthem, pruritus, pronounced facial edema, and edema, diffuse lymphadenopathy, but was afebrile | 42d | Yes (18%) | Leukocytosis | Rise of ALT, AST, ALP | Rise of TB, DB |  |  | Spongiotic dermatitis with eosinophilia | IV hydration | Oral antihistamine | Facial edema and exanthem improved significantly as did the rest of her symptoms. |
| 5 | Loulergue et al. (50) | Raltegravir | Case report (46 y old female) | Fever, abdominal pain, extensive skin rash, enlarged cervical lymph nodes, erythematous papulosquamous skin rash approximately 70% of the body | 60d |  |  |  |  |  |  |  |  |  |  | The fever and skin rash regressed over the course of 2 weeks, and liver function tests and serum creatinine returned to normal values over the course of 2 months. |
| 6 | Perry et al. (51) | Raltegravir | Case report (55 y old patient) | Generalized maculopapular rash, pruritus, malaise, and pyrexia | 28d | Yes |  |  |  |  |  |  |  | Compact orthokeratosis, mild diffuse spongiosis, with lymphocytic exocytosis with occasional neutrophils, focal eosinophilic exocytosis, rare individually dyskeratotic keratinocytes, mild superficial and mid-perivascular and interstitial lymphoid cell infiltrate with eosinophils, papillary dermal edema | Emollients |  | Rash improved over the subsequent two weeks. The eosinophil count is declining. |
| Case report | RegiSCAR criteria | Symptoms and findings | Outcome | Treatment | Notes |
|-------------|-------------------|----------------------|---------|-----------|-------|
| 7 | Yee et al. (52) | Rasgitavir | Score >5 | Fever, Cervical and submandibular lymphadenopathy, diffuse morbilliform rash with mucosal pruritis, facial edema, and edematos hands and feet, nephritis, hepatitis, rash, fever, tachycardia, hypotension, tachypnoea | Yes | Anemia, rise of ALT, AST, and hepatic failure | Oral antihistamines, Oral GCs | The patient’s rash, fever, and hepatitis completely resolved |
| 8 | Scaggs et al. (53) | Rasgitavir | “definite” | Fever, malaise, epistaxis, erythematous maculopapular rash, axillary and inguinal lymphadenopathy, hypereosinophilia | Yes (18.2%) | Rise of AST, ALP, GGT, and total bilirubin, and direct bilirubin, severe icterus, jaundice | Patch testing was negative for abacavir (a common cause of drug rash) | Systemic GCs (oral & parenteral) | The rash had resolved, the liver function had improved, and the coagulation panel had normalized. Her liver function normalised after 6 weeks of prednisone |
| 9 | Martin et al. (37) | Dolutegravir | Score =6 | Severe generalized uticarial rash, pyrexia, lymph node enlargement, painful oral ulceration, moderate renal failure, hypereosinophilia, atypical circulating lymphocytes | 35d | Mild transaminitis | Skin biopsy: infiltrates in the dermis with main eosinophils. | Parenteral and topical GCs | Transient improvement of the patient’s condition over the next 10 days. Relapse of rash and development of severe hepatic failure. Then after several weeks despite corticosteroid therapy, the patient died from liver decompensation |
| 10 | Bourezane et al. (54) | Nevirapine | Score =9 | Generalized maculopapular rash without mucosal involvement, and enlarged lymph nodes and hepatosplenomegaly | Yes (18%) | Rise of ALT, AST, ALP, and GGT, and mild proteinuria | Superficial dermal leukocytoclastic vasculitis and lichenoid reaction. | Parenteral GCs | The skin rash resolved completely with marked scaling, liver function values decreased within 3 days. Systemic manifestations resolved after 10 days. |
| 11 | Lanzafame et al. (58) | Nevirapine | Score =6 | Fever, diffuse maculopapular rash and impaired consciousness. | Yes (24.9%) | Rise of ALT, AST | Superficial dermal leukocytoclastic vasculitis and lichenoid reaction. | Parenteral GCs | After 2 days the clinical condition and laboratory parameters improved dramatically. |
| 12 | Santos et al. (40) | Nevirapine | Score =5 | Generalized fever, maculopapular rash, and intestinal pneumonitis. | Yes (31%) | Rise of ALT, AST | IVIG | Rash improved 24 hours after the IVIG infusion. |
| Case Report | Drug | Clinical Manifestations | Laboratory Findings | Treatment | Outcomes |
|-------------|------|------------------------|---------------------|-----------|----------|
| Breining et al. (55) | Nevirapine | High-grade fever, diffuse maculopapular, erythematous and prurigous exanthem with facial edema, diffuse lymphadenopathy | Yes | Hyperleukocytosis | Cytolytic hepatitis (jaundice) |
| Gill et al. (56) | Nevirapine | RegiSCAR criteria | Yes (60%) | Rise of ALT, AST, ALP | Oral GCs |
| Junior et al. (39) | Nevirapine | Fever, right hypochondrium pain, skin rash, myalgias and arthralgias, icterus, pallor, gradual onset of right hypochondrium pain | Yes | Rise of ALT, AST, ALP | Oral GCs |
| Raghukumar et al. (57) | Nevirapine | Fever, generalized maculopapular rash, and was found to have pallor, icterus, multiple cervical lymph nodes, and hepatosplenomegaly | Yes | Anemia | Oral GCs |
| Janocha-Litwin et al. (58) | Telaprevir | Fever, skin lesions, pruritus, lymphadenopathy, hepatic palmar erythema | Yes (31.9%) | Decreased haptoglobin and prothrombin time | Systemic GCs |
| Montaadiei et al. (59) | Telaprevir | Fever, maculopapular exanthem with edema of the face and the palms, malaise | Yes | Rise of ALT, AST | Topical and oral GCs |
| Case report | Telaprevir | RegiSCAR criteria | Fever, fatigue, anorexia, and chill | 96d | Yes (42%) | Rise of ALT, AST, and total bilirubin | Topical and systemic GCs (oral & parenteral) |
|-------------|------------|------------------|-----------------------------------|-----|----------|-----------------------------------|-----------------------------------------|
| 19          | Kesari et al. (60) | “definite” | Fever, chills, severe generalized plaque-like pruritic rash | 300d | Yes (22.1%) | Rise of AST | IV hydration |
|             |            | “probable” | Fever, chills, severe generalized plaque-like pruritic rash | 9d | No | No | Visiting in one week demonstrated significant improvement in the rash |

**Telaprevir**

| Case report | Telaprevir | RegiSCAR criteria | Fever, diffuse, generalized plaque-like pruritic rash | 330d | Yes | Rise of ALT, GGT, and total bilirubin | Topical and oral GCs |
|-------------|------------|------------------|-----------------------------------|------|-----|-----------------------------------|-----------------|
| 20          | González Quesada et al. (61) | “definite” | Fever, chills, severe generalized plaque-like pruritic rash | 330d | Yes | Rise of ALT, GGT, and total bilirubin | Topical and oral GCs |
|             |            | “probable” | Fever, chills, severe generalized plaque-like pruritic rash | 98d | Yes | Rise of ALT, GGT, and total bilirubin | Topical and oral GCs |

**Telaprevir**

| Case report | Telaprevir | RegiSCAR criteria | Fever, diffuse, generalized plaque-like pruritic rash | 84d | Yes (15%) | Thrombocytopenia | Rise of AST and total bilirubin | Topical GCs, Oral antihistamine, Magic mouthwash, Ranitidine |
|-------------|------------|------------------|-----------------------------------|------|----------|-----------------|---------------------------------|---------------------------------|
| 21          | Mousa et al. (22) | “definite” | Fever, diffuse, generalized plaque-like pruritic rash | 84d | Yes | Thrombocytopenia | Rise of AST and total bilirubin | Topical GCs, Oral antihistamine, Magic mouthwash, Ranitidine |
|             |            | “probable” | Fever, diffuse, generalized plaque-like pruritic rash | 84d | Yes | Thrombocytopenia | Rise of AST and total bilirubin | Topical GCs, Oral antihistamine, Magic mouthwash, Ranitidine |

**Telaprevir**

| Case report | Telaprevir | RegiSCAR criteria | Fever, diffuse, generalized plaque-like pruritic rash | 300d | Yes (19%) | Thrombocytopenia | Rise of AST and total bilirubin | Topical GCs, Oral antihistamine, IV fluids |
|-------------|------------|------------------|-----------------------------------|------|----------|-----------------|---------------------------------|---------------------------------|
| 21          | Mousa et al. (22) | “definite” | Fever, diffuse, generalized plaque-like pruritic rash | 300d | Yes | Thrombocytopenia | Rise of AST and total bilirubin | Topical GCs, Oral antihistamine, IV fluids |
|             |            | “probable” | Fever, diffuse, generalized plaque-like pruritic rash | 300d | Yes | Thrombocytopenia | Rise of AST and total bilirubin | Topical GCs, Oral antihistamine, IV fluids |

**Telaprevir**

| Case report | Telaprevir | RegiSCAR criteria | Fever, diffuse, generalized plaque-like pruritic rash | 56d | Yes (11%) | Leukopenia | Similar superficial perivascular dermatitis and interface dermatitis, as well as mild spongiosis and basal cell layer liquefaction. No eosinophils were seen. | Oral antihistamine, IV fluids |
|-------------|------------|------------------|-----------------------------------|-----|----------|--------|-------------------------------------------------|-----------------|
| 22          | Akar et al. (31) | “definite” | Fever, diffuse, generalized plaque-like pruritic rash | 56d | Yes | Leukopenia | Similar superficial perivascular dermatitis and interface dermatitis, as well as mild spongiosis and basal cell layer liquefaction. No eosinophils were seen. | Oral antihistamine, IV fluids |
|             |            | “probable” | Fever, diffuse, generalized plaque-like pruritic rash | 56d | Yes | Leukopenia | Similar superficial perivascular dermatitis and interface dermatitis, as well as mild spongiosis and basal cell layer liquefaction. No eosinophils were seen. | Oral antihistamine, IV fluids |

**Telaprevir**

| Case report | Telaprevir | RegiSCAR criteria | Fever, diffuse, generalized plaque-like pruritic rash | 56d | Yes | Leukopenia | Similar superficial perivascular dermatitis and interface dermatitis, as well as mild spongiosis and basal cell layer liquefaction. No eosinophils were seen. | Oral antihistamine, IV fluids |
|-------------|------------|------------------|-----------------------------------|-----|----------|--------|-------------------------------------------------|-----------------|
| 22          | Akar et al. (31) | “definite” | Fever, diffuse, generalized plaque-like pruritic rash | 56d | Yes | Leukopenia | Similar superficial perivascular dermatitis and interface dermatitis, as well as mild spongiosis and basal cell layer liquefaction. No eosinophils were seen. | Oral antihistamine, IV fluids |
|             |            | “probable” | Fever, diffuse, generalized plaque-like pruritic rash | 56d | Yes | Leukopenia | Similar superficial perivascular dermatitis and interface dermatitis, as well as mild spongiosis and basal cell layer liquefaction. No eosinophils were seen. | Oral antihistamine, IV fluids |
| Page | Author | Drug | Case report | RegiSCAR criteria | Description | Duration | Reaction | Topical & oral | Cutaneous and systemic symptoms | Antihistamine |
|------|--------|------|-------------|-------------------|-------------|----------|-----------|---------------|----------------|-----------------|
| 23   | Brocato et al. (62) | Telaprevir | Case report (61 y old female) | Fever, Vasculopulmonary injury: lesion, oropharyngeal mucosa hypoplasia, bilateral painful pharyngeal lymphadenopothy associated with pruritus, malaise and arthralgia | 21d | Yes (19.8%) | Yes | 2.2% | LFT anomalies | Rises of ALT, AST | Oral antihistamine |
| 24   | Shuster et al. (63) | Telaprevir | Case report (65y old female) | Fever, cervical lymphadenopathy, several intensely pruritic papules on her buttocks that spread rapidly | 21d | Yes | Severe anemia | Rise of ALT, AST | High potency topical GCs | Recovered within two weeks. |
| 25   | Kömür et al. (32) | Telaprevir | Case report (50 y old female) | Fever, Generalized pruritic maculopapular, facial edema | 42d | Yes (19.6%) | Leukopenia | Rise of ALT, AST, ALP | Systemic antihistamines | Fever was under control. |
| 26   | Cengiz et al. (30) | Telaprevir | Case report (65y old male) | Fever, Generalized pruritic maculopapular exanthema with facial edema, enlarged and painful inguinal lymph nodes, bilateral lower extremity edema, malaise, nausea, fatigue. | 330d | Yes (96.1%) | Rise of AST & GGT and total bilirubin | Superficial perivascular dermatitis, focal spongiosis in line with the literature | Topical and parenteral GCs | Fever was under control, systemic symptoms resolved. Cutaneous symptoms resolved completely subsequent to cessation of therapy. |
| 27   | Samain et al. (31) | Boceprevir | Case report (56y old female) | Fever, Generalized maculopapular exanthema with facial edema, lymphadenopathies, and alteration of the general state | 56d | Yes | Rise of GGT | Foci of spongiosis, keratinocyte necrosis, vascular alteration of the basal cell layer and perivascular inflammatory infiltrate composed of lymphocytes, many eosinophils and neutrophils | Topical GCs | Cutaneous and systemic symptoms disappeared within a few weeks. The eosinophilia persisted more than 7 weeks. |
| 28   | Descamps et al. (42) | Cidofovir | Case report (11 months-old infant) | Fever, Exfoliative erythroderma, periorbital and facial edema | 20d | Yes | Rise of GGT | Panniculitis | Parenteral GCs | Symptoms and peripheral blood eosinophilia only resolved on withdrawal of cidofovir. She recovered quickly. |

DRESS, drug rash with eosinophilia and systemic symptoms; HHV, human herpesvirus; EBV, Epstein-Barr virus; CMV, Cytomegalovirus; LFT, Liver function test; AST, Aspartate aminotransferase; ALT, Alanine transaminase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl transferase; SCr, Serum creatinine; PT, Prothrombin time; IV, Intravenous therapy; IVIG, Intravenous Immune Globulin; RegiSCAR, European registry on severe cutaneous adverse drug reactions; TB, Total bilirubin; DB, Direct bilirubin; TN, Intravenous therapy.
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