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

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ABSTRACT

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.

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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+ 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 exanthemata'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 (>4×103/μL) or lymphocytopenia (<1.5×103/μL), 6) blood eosinophilia (>10% or 700/μL), and 7) thrombocytopenia (<120×103/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, drug serum 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).

Table 1. Some clinical criteria for DRESS syndrome diagnosis.

Clinical criteria for DRESS syndrome		
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.

Besides the various diagnostic criteria, there some other accessory tools for its confirmation. The lymphocyte transformation test (LTT) helped to detect the drugs involved in DRESS and has a general sensitivity in the range of 60-70% and a general specificity of at least 85% (19). The epicutaneous test is useful in the diagnosis of delayed T-cell lymphocyte-mediated drug hypersensitivity and it is positive in 64% of DRESS syndrome cases (20). Immunobiologic tests, especially the enzyme-linked immunospot (ELISPOT) assay could be beneficial to detect circulating drug-specific T cells and diagnose the culprit drug, in patients with DRESS syndrome (21).

Skin biopsy demonstrates nonspecific findings as lymphocytic infiltrate on the papillary dermis, which contains eosinophils and is denser than in other drug reactions (6, 22). The sensitivity of patch testing in DRESS was about 57% at 72-hour reading. According to the proposed guidelines for performing patch tests in skin adverse drug reactions, the test must be done 6 months after complete healing of DRESS under the close follow-up to optimize the management of disease relapse during the test (21, 23). Intradermal test (IDT) also is known to be a sensitive, useful, and safe method for identifying drug-induced DRESS. It is somewhat more sensitive than patch testing (24).

Risk factors

In lots of previous reports, DRESS occurrence might be associated with the human herpesvirus (HHV)-6 & 7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) reactivation (3, 25). HHV-6 is the most reported one (26). The viral-specific and non-specific CD8+ and CD4+ T cells proliferation and cytokine release may be stimulated by these viruses, which are believed to be the cause of hypersensitivity reactions to previously tolerated drugs (27). It is also mentioned that because of a reduced level of glutathione, selenium and other antioxidants, patients with human immunodeficiency virus are at higher susceptibility to toxic drug metabolites. The changes in both TH1 and TH2 cytokine production and transient increase in the level of interleukin 5 has been proven early in the disease process in some patients, which contributes to the eosinophilia (1).Besides, specific genetic polymorphisms present in some ethnicities may have a role in DRESS. In a 7-year prospective study of drug hypersensitivity syndrome, it was more prevalent in patients of Afro-Caribbean descent (8). Moreover, the first degree relatives of the patient who experienced DRESS should also be warned about its possibility (7, 28). In certain populations, susceptibility to drug hypersensitivity has also been related to specific HLA haplotypes, including HLAB* 1502 and HLA-B*5801 (29).

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).

Tenofovir

Tenofovir-induced DRESS is rarely reported. Aqtash et al., reported a patient that indicated DRESS secondary to tenofovir. 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	The latency period (day)	Eosinophilia (%)	Atypical lymphocytes	Other hematologic findings	Liver abnormalities	Renal impairment	A skin biopsy or other tests result	The coincidence of viral infection	Management	Outcome
1	Calza et al. (34)	Abacavir	Case report (41y old male)	Naranjo criteria	Fever & chills, weakness, and reduced appetite, generalized rash on the face, trunk and arms, characterized by multiple maculopapular and orticarioid lesions and was associated with severe exanthema including painful mucosal ulcerations of the oropharynx.	300d						Skin patch test not performed	Negative CMV & EBV	Oral antihistamine Oral GCs	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 (46y old female)	RegiSCAR criteria score=5 "Probable"	Fever, exanthema with facial edema and oral mucosal	28d	Yes		Lymphocytosis	cytolytic hepatitis			Reactivation of herpesvi-rus & CMV	Oral GCs Valganciclovir	Rapid clinical and biological improvement
3	Aqtash et al. (35)	Tenofovir	Case report (65y old male)	RegiSCAR criteria "probable"	Generalized skin rash, tongue swelling, and lip peeling, generalized maculopapular rash erythematous but non-blanching	60d	Yes			Rise of ALT,AST,ALP	Rise of TB,DB	Spongiotic dermatitis with eosinophilia		IV hydration Oral GCs	His liver enzymes normalized.
4	Zhang et al. (49)	Raltegravir	Case report (64y old female)		Generalized morbilliform exanthem, pruritus, pronounced facial erythema, and edema, diffuse lymphadenopathy, but was afebrile	42d	Yes (18%)		Leukocytosis	Rise of ALT, AST				Topical and Parenteral GCs IV antihistamine	Facial edema and erythema improved significantly as did the rest of her exanthema.
5	Loulergue et al. (50)	Raltegravir	Case report (46y old female)		Fever, abdominal pain, extensive skin rash, enlarged cervical lymph nodes, erythematous-papulous skin rash approximately 70% of the body	60d				Rise of LFT, ALP & total bilirubin Mild icterus	Rise of SCr				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 (55y old patient)		Generalized maculopapular rash, pruritus, malaise, and pyrexia	28d	Yes			Rise of ALT, ALP, and GGT Decrease of Albumin		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 Topical and oral GCs	Rash improved over the subsequent two weeks. The eosinophil count is declining.

7	Yee et al. (52)	Raltegravir	Case report (18y old female)	RegiSCAR criteria Score >5	Fever, Cervical and submandibular lymphadenopathy, diffuse morbilliform rash, generalized pruritus, facial edema, and edematous hands and feet, tachycardia, hypotension tachypnoea	42d	Yes		Anemia	Rise of ALT, AST Hepatitis				Oral antihistamine Oral GCs	The patient's rash, fever, and hepatitis completely resolved
8	Scaggs et al. (53)	Raltegravir	Case report (10y old girl)	RegiSCAR criteria score=6 "definite" Japanese consensus group score=6	Fever, malaise, epistaxis, erythematous maculopapular rash, axillary and inguinal lymphadenopathy, hepatomegaly	10d	Yes (18.2%)			Rise of AST, ALP, GGT, and total bilirubin, and direct bilirubin scleral icterus, jaundice	Rise of SCr	Patch testing was negative for abacavir (a common cause of dress)		Systemic GCs (oral & parenteral)	The rash had resolved, the liver function had improved, and the coagulation the panel had normalized. Her liver function normalized after 6 weeks of prednisone
9	Martin et al. (37)	Dolutegravir	Case report (59y old male)	RegiSCAR criteria system=9 "definite"	Severe generalized urticarial 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 ten 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	Case report (32y old man)		Generalized maculopapular rash without mucosal involvement, and enlarged lymph nodes and hepatosplenomegaly painful palmoplantar erythema.		Yes (18%)			Rise of ALT, AST, ALP, and GGT Decrease in PT	Mild proteinuria (57 %)	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. (38)	Nevirapine	Case report (35y old male)		Fever, diffuse maculopapular rash and impaired consciousness.		Yes (24.9%)			Rise of ALT, AST				GCs	After 2 d the clinical condition and laboratory parameters improved dramatically.
12	Santos et al. (40)	Nevirapine	Case report (12y old female)	Naranjo criteria	Generalized fever, maculopapular rash, and interstitial pneumonitis.	56d	Yes (31%)			Rise of ALT, AST				IVIG	Rash improved 24 hours after the IVIG infusion.

13	Breining et al. (55)	Nevirapine	Case report (25y old female)		High-grade fever, diffuse maculopapular, erythematous and pruriginous exanthema with facial edema, diffused lymphadenopathy	20d	Yes		Hyperleukocytosis	Cytolytic hepatitis (painful hepatomegaly) jaundice	Rise of ALT			Oral GCs	The eruption and the fever disappeared within 5 days and the cytolysis decreased progressively reaching ALT=3 N after 1 month.
14	Gill et al. (56)	Nevirapine	Case report (41y old patient)	RegiSCAR criteria	High-grade fever and a skin rash which was erythematous, maculopapular, pruritic involved the neck and all four limbs	21d	Yes (60%)			Rise of ALT, AST Hepatomegaly				Oral GCs	Fever subsided after stopping nevirapine but his rash worsened for the initial 4–5 days and became more confluent. The treatment was continued and he responded after 6 days and improved symptomatically thereafter.
15	Junior et al. (39)	Nevirapine	Case report (47y old female)		Fever, right hypochondrium pain, skin rash, myalgias and arthralgias, holuria, pruritus, gradual onset of right hypochondrium pain.	20d		Yes		Rise of ALT, AST, ALP, and GGT Jaundice				Parenteral GCs	She was recovered sufficiently to be safely discharged from the hospital.
16	Reghukumar et al. (57)	Nevirapine	Case report (45y old male)		Fever, generalized maculopapular pruritic rash and was found to have pallor, icterus, multiple cervical lymph nodes, and hepatosplenomegaly	14d	Yes		Anemia (The direct Coombs test was positive)	Hepatospl enomegaly Progressive anemia (Direct Coombs test was positive) due to Autoimmune hemolytic anemia	Indirect hyperbilirubinemia with transaminitis and interstitial nephritis.	Peripheral smear was suggestive of extravascular hemolysis.		GCs	Significant improvement in the patient
17	Janocha-Litwin et al. (58)	Ribavirinl/ Telaprevir	Case report (52y old male)		Fever, skin lesions, pruritus, lymphadenopathy, hepatic palmar erythema		Yes (31.9%)		Thrombocytopenia	Decreased Albumin and prothrombin time symptoms of active liver disease, cirrhotic liver without focal lesions hepatosplenomegaly				Systemic GCs (oral & parenteral) moisturizing ointments	Resolution of skin lesions, pruritus, lymphadenopathy
18	Montaudié et al. (59)	Telaprevir	Case report (57y old female)		Fever, maculopapular exanthema with edema of the face and the palms, malaise	84d	Yes			Rise of ALT, AST		Keratinocyte necrosis, vacuolar alteration of the basal cell layer and a mild dermal perivascular inflammatory infiltrates, mainly lymphocytic, without eosinophils.		Topical and oral GCs	Cutaneous and systemic symptoms disappeared within 1month with a normalization of the LFT values

19	Kesar et al. (60)	Telaprevir	Case report (60y old male)	RegiSCAR criteria "definite"	Fever, severe fatigue, anorexia, and chill	98d	Yes (42%)			Rise of ALT, AST, and total bilirubin				Topical and systemic GCs (oral & parenteral) oral & IV antihistamine	
			Case report (62y old male)	RegiSCAR criteria "probable"	Fever, chills, severe generalized plaque-like pruritic rash	330d	Yes (22.1%)			Rise of AST				IV hydration Oral antihistamine Oral and topical GCs	Visiting in one week demonstrated significant improvement in the rash
20	González Quesada et al. (61)	Telaprevir	Case report (52y old female)		Generalized pruritic,	77d	Yes		Anemia	Rise of ALT, GGT	Rise of SCr			Topical and oral GCs	Cutaneous and systemic symptoms improved in 14d and disappeared com-pletely in a month.
21	Mousa et al (22)	Telaprevir	Case report (65y old female)	RegiSCAR criteria (8 points) "definite" Naranjo criteria (6 points) "probable"	Fever, diffuse generalized maculopapular eczematous rash, facial edema, lymphadenopathy	84d	Yes (15%)		Thrombocytopenia	Rise of AST and total bilirubin	Rise of SCr	Superficial perivascular dermatitis and focal interface dermatitis. The perivascular inflammation is predominantly lymphocytic and includes rare eosinophils		Topical GCs Oral antihistamine Magic mouthwash Ranitidine.	Rapid resolution of the fever and swelling with gradual improvement of the skin rash, significant improvement in the rash, kidney function returning to baseline
			Case report (51y old male)	RegiSCAR criteria (8 points) "definite" Naranjo criteria (7 points) "probable"	Fever, a diffuse pruritic maculopapular Rash, lymphadenopathy, facial edema, oral mucosal ulcers, atrial fibrillation	300d	Yes (19%)	Yes	Thrombocytopenia	Rise of AST and total bilirubin	Rise of SCr	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	His skin rash improved significantly and the other symptoms resolved during his hospital stay
22	Akar et al. (31)	Telaprevir	Case report (48y old female)	Naranjo criteria (7points) "probable" RegiSCAR criteria (6 points) "definite"	Fever, Severe generalized plaque-like pruritic rash, diarrhea (co-occurrence with salmonella infection)	56d	Yes (11%)		Leukopenia severe anemia			Punch biopsy of the skin: superficial perivascular dermatitis		Topical GCs, moisturizer, oral H1, and H2 receptor blockers.	Resolution of rash and symptoms

23	Broccolo et al. (62)	Telaprevir	Case report (51y old female)	RegiSCAR criteria	Fever, Maculopapular itchy lesions, oropharyngeal mucosa hyperemia, bilateral painful axillary lymphadenopathies associated with pruritus, malaise and arthralgia	21d	Yes (19.8%)	Yes	Lymphocytope-nia(7.2 %)	Liver abnormalities		Dermal perivascular inflammatory infiltrate, composed of lymphocytes and histiocytes with scattered eosinophils in the dermis, consistent with a drug reaction.	Reactivation of HHV-6 Positive Abs for CMV, EBV, adeno-virus	Topical & oral GCs Antihistamine	Cutaneous and systemic symptoms improved in a few days, whereas the blood cells the count returned to normal within two weeks.
24	Shuster et al. (63)	Telaprevir	Case report (50y 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 oral antihista-mine	Recovered within two weeks. Her cutaneous eruption and eosin-ophilia resolved and her liver function tests returned to baseline over the next two weeks.
25	Kömür et al. (32)	Telaprevir	Case report (66y old female)		Fever, Generalized pruritic maculopapular, facial edema	42d	Yes (19.6%)		Leukopenia	Rise of ALT, AST, ALP				Systemic antihistamines Topical GCs	Fever was under control Systemic symptoms resolved. Cutaneous symptoms resolved completely subsequent to cessation of therapy
26	Cengiz et al. (30)	Telaprevir	Case report (64y old male)	RegiSCAR criteria (9 points) "definite" Naranjo criteria score (7 points) "probable"	Fever, generalized, pruritic maculo-papular exanthema with facial edema, enlarged axillary and 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 liter-ature.	EBV Ig M, CMV IgM, and HHV 6 IgM antibodies were negative	Topical and parenteral GCs Oral antihistamine	In two days fever was under control and eosinophilia was improved, the cutaneous rash was completely resolved in two weeks, as well
27	Samain et al. (33)	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, vacuolar alteration of the basal cell layer and perivascular inflammatory infiltrate composed of lymphocytic, many eosinophilia 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 Maybe VRESS	Case report (11-months-old infant)		Fever, Exfoliative erythroderma, periorbital and facial edema	20d	Yes							Parenteral GCs Cyclosporine	ymptoms 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; GCs, Glucocorticoids are a class of corticosteroids; IVIG, Intravenous Immune Globulin; RegiSCAR, European registry on severe cutaneous adverse drug reactions; TB, total bilirubin; DB, Direct bilirubin; IV, Intravenous therapy

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