

Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection

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HIV-infected patients have a higher risk of developing cutaneous reactions than the general population, which has a significant impact on patients' current and future care options. The severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage. HIV-infected patients just at the beginning of antiretroviral treatment can frequently show a wide variety of adverse drug effects such as drug rashes, hyperpigmentation, hair loss, hypersensitivity reactions, injection site reaction, urticarial reaction, erythema multiforme, toxic epidermal necrolysis or Stevens–Johnson syndrome. The early detection and treatment of cutaneous adverse drug reactions, plus identification of the causative agent, are essential to prevent the progression of the reaction, preventing additional exposures and ensuring the appropriate use of medications for the current condition and keeping in mind others, such as patient age. This article emphasizes the most common features of an antiretroviral drug-induced cutaneous reaction from protease inhibitors, non-nucleoside analogue reverse transcriptase inhibitors, fusion inhibitors, nucleoside reverse transcriptase inhibitors, integrase inhibitors and inhibitors of the CCR5 chemokine receptor, paying special attention to the newest drugs approved for the treatment of HIV infection, such as tipranavir, darunavir, etravirine, enfuvirtide, raltegravir and maraviroc.

Keywords: HIV, adverse drug reactions, skin, HAART

Introduction

The use of highly active antiretroviral therapy (HAART) has had an important impact on the course and treatment of disease and disease-related morbidity of HIV-infected patients, increasing their lifespan and quality of life.¹ However, these advantages have been accompanied with a marked increase in the number of adverse drug reactions, including minor and serious cutaneous adverse drug reactions.² In fact, within the first year of treatment, adverse drug reactions, and not treatment failure, are the most common reasons for the discontinuation of HAART among HIV-infected patients. Patients infected with HIV are highly susceptible to adverse dermatological reactions to specific medications. Up to 80% of HIV-infected patients experience adverse drug reactions at some point during their therapy, presumably as a result of immune dysregulation, altered drug metabolism and/or polypharmacy.³

HIV-infected patients have a higher risk of developing cutaneous reactions than the general population,⁴ which has a significant impact on patients' current and future care options. The severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage. HIV-infected patients at the beginning of the antiretroviral treatment can frequently show a

wide variety of adverse drug effects such as drug rashes, hyperpigmentation, hair loss, hypersensitivity reactions, injection site reaction, urticarial reaction, erythema multiforme, toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS). Cutaneous adverse drug reactions have been reported with all antiretroviral medications. Therefore, it is necessary to develop and get approval of novel antiretrovirals as soon as possible in order to avoid these cutaneous adverse reactions. However, at the moment, clinical trials have not given conclusive safety results. It is critical to be very cautious when implementing these agents into HIV treatment regimens. The information we have regarding these adverse drug reactions comes mainly from clinical practice. Data gathered regarding the safety of new antiretroviral drugs tested in even small populations will contribute to determine the role of these rapidly approved agents.

This article emphasizes the most common features of an antiretroviral drug-induced cutaneous reaction, especially for the newest drugs approved for the treatment of HIV infection. It is divided into two sections: the first section is about the most common dermatological drug reactions and the second about the antiretroviral drugs associated with a high incidence of cutaneous reactions, paying special attention to the drugs more commonly used and the newest ones (Table 1).

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Table 1. Most common adverse cutaneous reactions associated with the newest antiretroviral drugs

Class of drug	Adverse cutaneous reaction
Protease inhibitors	
lopinavir/ritonavir	maculopapular rash
amprenavir and fosamprenavir	skin rash
atazanavir	skin rash
tipranavir	skin rash
darunavir	maculopapular rash
Non-nucleoside analogue reverse transcriptase inhibitors	
efavirenz	skin rash and DRESS syndrome
etravirine	skin rash
Fusion inhibitors	
enfuvirtide	injection site reactions
Nucleoside reverse transcriptase inhibitors	
tenofovir	skin rash
abacavir	hypersensitivity reaction
emtricitabine	skin rash and skin discoloration
Integrase inhibitors	
raltegravir	skin rash and diaphoresis
Inhibitors of the CCR5 chemokine receptor	
maraviroc	pruritic rash

Common dermatological drug reactions in HIV-infected patients

Morbilliform exanthematous eruptions

The morbilliform eruption, often referred to as a maculopapular rash, is the most common type of reaction after HIV treatment. HIV-infected patients are more prone to drug-related rashes than the general population. This type of cutaneous drug reaction is usually observed secondary to HAART or treatment with an antibiotic such as amoxicillin, ampicillin, cephalosporins and sulphonamides. These are characterized by widespread pink-to-red blanchable macules and papules. These eruptions usually favour the trunk and proximal extremities and are accompanied by pruritus, which may be intense and uncomfortable.⁵ Morbilliform drug eruptions usually appear between 2 and 10 weeks after starting antiretroviral drug therapy. However, re-exposure to a previous offender can trigger the reaction in 1–2 days. A maculopapular drug eruption may take up to 2 weeks to resolve after discontinuation of the offending agent.⁶ A maculopapular drug eruption will occasionally evolve into exfoliative erythroderma.⁷ It is not definitively known whether maculopapular drug reactions may evolve into SJS or TEN.⁸ The presence of necrosis, ulcers, mucosal involvement, fever and signs of systemic involvement should alert the clinician to the presence of a severe bullous reaction.

Hyperpigmentation

Nail and skin hyperpigmentation have been reported in long-standing patients infected with HIV. Hyperpigmentation can also be shown as a manifestation of photosensitivity in HIV-infected patients. It has been observed either related to or independent of the HAART therapy. Therefore, in patients with HIV infection, it is difficult to distinguish the reason for the aetiology of

hyperpigmentation. These adverse effects resemble the dermatological effects of retinoids. Homologies between the amino acid sequences of retinoic acid-binding protein 1 and the catalytic site of HIV type-1 (HIV-1) proteases have been noted.⁹ Moreover, drug-induced nail pigmentation typically involves several nails and is usually reversible. However, it may take several years to recover melanin production by melanocytes of the nail matrix after drug withdrawal.¹⁰

Urticaria

Urticaria is characterized by transient swellings of the skin, which fluctuate over several hours. Deeper swellings of the subcutaneous and submucosal tissue are known as angio-oedema. Urticarial eruptions occur in a generalized fashion, but tend to occur more frequently in areas covered by clothing. The plaques, also known as wheals, hives or welts, result in a localized oedema of the dermis. They appear as white, oedematous zones that vary in size from a few millimetres up to centimetres. They are surrounded by erythema and are often accompanied by pruritus.¹¹ Urticaria may be classified as acute, chronic or physical. It is termed acute when the condition lasts from a few hours to a few weeks, as opposed to chronic urticaria, which may occur several times a week and last for at least 6 weeks.¹² Drugs may cause urticaria by different mechanisms. The most well-known mechanism is the allergic reaction mediated by immunoglobulin E antibodies, which induce acute generalized urticaria.

Treatment of urticaria induced by antiretroviral drugs includes discontinuation of the offending drug and treatment with systemic antihistamine therapy. If urticarial reaction is severe and unresponsive to antihistamines, the use of corticosteroids is recommended. Patients with severe discomfort due to pruritus could improve with low doses of doxepin, an antidepressant medication that blocks both H₁ and H₂ receptors.¹³

Stevens–Johnson syndrome/toxic epidermal necrolysis

SJS and TEN are rare and severe cutaneous reactions caused by antiretroviral agents. The prognosis of the reactions largely depends on the quality of their treatment. There is a controversy regarding the relationship between SJS and TEN,¹⁴ which are considered to be variants of the same disease process. However, the diagnosis of SJS or TEN can be made only when the skin eruption is at its final stage. TEN rapidly progresses to involve complete detachment of the epidermis involving >30% and up to 100% of the body surface, with a mortality rate of 25% to 75%.¹⁵ SJS manifests as two mucosal sites of involvement in conjunction with widespread skin lesions, which may either be target-shaped or consist of erythematous macules. The prodromal phase of the eruption is more intense than the one observed with erythema multiforme and includes fever, arthralgia, malaise, headache, vomiting, diarrhoea and myalgia. Lesions usually involve the eyes and mouth, and occasionally the upper airway, gastrointestinal tract, myocardium and/or kidneys. The pathogenesis of SJS has not been completely defined, although a cell-mediated immune response may be involved. Evidence also exists for an immune complex reaction as the primary aetiology.¹⁶ A diagnosis of SJS is made usually by clinical determination as a result of a biopsy, which confirms the findings and excludes other processes such as bullous fixed-drug eruption or staphylococcal-scalded syndrome. SJS is relatively rare, with approximately 1–7 cases per million persons reported each year.¹⁷ Drugs are the most common cause of SJS; more than 100 different agents have been reported to cause SJS.^{18,19} Nevirapine is the classic example of an HIV drug associated with SJS/TEN. TEN is a morbilliform eruption that occurs soon after drug administration, and it is accompanied by large erythematous and tender areas of the skin. Drugs play 80% to 90% of the role in the aetiology of TEN.²⁰ Correlation between the illness and the drug intake is based on the recognition that TEN usually develops 1–3 weeks after the administration of the offending drug. The clinical diagnosis is based on the presence of characteristic eruptions of erythematous confluent maculae and bullae, together with a positive Nikolsky's sign (detachment of epidermis from a finger with lateral pressure). Typical targetoid lesions develop on the face, neck and trunk and involve >30% of the body surface. Extensive mucosal erosion is also frequent. A skin biopsy can show a typical histomorphological picture of full-thickness epidermal necrosis, with only slightly altered underlying dermis; immunohistochemical analysis can confirm the diagnosis by excluding other cutaneous diseases that clinically mimic TEN.²¹ Prodromal symptoms are often severe and include nausea, vomiting, angina, high fever, malaise and painful skin. Complications of TEN include acute tubular necrosis, sepsis and acute respiratory failure requiring ventilatory support, gastrointestinal haemorrhage, ileal involvement, pancreatitis, conjunctivitis and keratitis. Sequelae include pathological scarring, disturbances in skin pigmentation, ocular diseases, heterotopic ossification and abnormal nail growth. Morbidity and mortality are high (25% to 50%), usually from fluid and electrolyte imbalances and secondary bacterial infections.²²

To date, there is no established treatment for SJS/TEN. Early withdrawal of the offending drug is essential. One study examined the result of discontinuing all potentially causative drugs at the first sign of a blister or erosion (typical of SJS or TEN) that was not explained by another cause. The difference in mortality

was 11% for early recognition and drug withdrawal versus 27% for late withdrawal (when the drugs had short elimination half-lives).²³ Symptomatic treatment is necessary and consists of local management, maintenance of fluid and electrolyte balance, nutritional support and systemic treatments that aim to stop the progression of the skin disease. Several therapies have been proposed for TEN, with contradictory results. In fact, mortality ranges from 10% to 40% in the literature, and the heterogeneity of the treatment seems to reflect that they are only partially efficacious. In the early stages of TEN, systemic administration of short courses of corticosteroids has been proposed, but its effectiveness has never been demonstrated in controlled trials.²⁴ Currently, the best results have been obtained with the use of intravenous immunoglobulin. Evidence for a possible effective treatment of TEN with intravenous immunoglobulin came from laboratory data, demonstrating that the sudden and widespread apoptosis of epidermal cells in TEN is related to the up-regulation of a protein called Fas ligand on the membrane of keratinocytes.²⁵ However, several studies did not show a significant improvement in mortality for TEN patients treated with intravenous immunoglobulin and may indicate a potential detriment in their use, especially in elderly patients and in those with impaired renal function.^{26,27} Otherwise, the multicentre retrospective analysis of 48 consecutive cases reported an improvement in the survival of patients treated with intravenous immunoglobulin, recommending early treatment at a total dose of 3 g/kg over 3 consecutive days.²⁸

Drug hypersensitivity syndrome (DHS)

DHS is an acronym of the DRESS syndrome (drug rash with eosinophilia and systemic symptoms). It occurs between 1 and 6 weeks after the initiation of drug therapy. This syndrome is characterized by exfoliative dermatitis, fever and potentially life-threatening damage (hepatitis, nephritis and pneumonitis). Eosinophilia is also common and corresponds to the most characteristic analytical feature of this syndrome. Visceral involvement in DHS can include the kidneys, liver, heart, lung, thyroid and brain.²⁹ The cutaneous eruption in DHS often progresses from a macular erythema, which starts on the face, upper trunk and upper extremities, to a dusky reddish and confluent papular rash that is pruritic and can often desquamate. The face, upper trunk and extremities are initially involved.³⁰ Oedema is a hallmark of DRESS, particularly in a facial distribution.³¹ In contrast to SJS and TEN, involvement of the mucous membranes is rare. This condition must be recognized early in order to immediately stop the suspected drugs, but this is not always sufficient to achieve a full recovery. Topical high-potency corticosteroids can be helpful in treating cutaneous lesions. Systemic corticosteroids are usually required for a full recovery.³² Abacavir is the classic example of an HIV drug associated with DHS.

Cutaneous adverse drug reaction associated with the newest antiretroviral drugs*Protease inhibitors (PIs)*

PIs have a potent activity against HIV, and treatment with these agents has been shown to reduce the incidence of mortality in

HIV-infected patients. However, side effects associated with this drug often limit its long-term tolerability. The most common adverse reaction of PIs is lipodystrophy syndrome, abnormal fat distribution, central adiposity, insulin resistance, hyperglycaemia and hyperlipidaemia. Moreover, cutaneous side effects are well described for many PIs. The rate of rash in patients treated with a PI has been recently estimated as around 5%.³³ PIs include indinavir, ritonavir, nelfinavir, lopinavir, amprenavir, fosamprenavir, atazanavir, tipranavir and darunavir. Only adverse cutaneous effects associated with the most recently approved PIs will be discussed in this article.

Lopinavir/ritonavir

Excellent therapeutic efficacy has been documented by multiple clinical trials for the treatment of antiretroviral-naïve and -experienced patients with lopinavir/ritonavir. The main side effects associated with lopinavir/ritonavir are gastrointestinal disturbances and elevations of serum lipids.³⁴ Lopinavir/ritonavir has been implicated in a wide range of early skin adverse reactions. Its rate of maculopapular rash was estimated to be 2% to 4%.³⁵ These cutaneous changes are not related to the number of CD4⁺ lymphocytes, viral load or clinical stage of the HIV disease.³⁶ In contrast, a case of acute generalized exanthematous pustulosis induced by prophylaxis with lopinavir/ritonavir was reported.³⁷ Lopinavir/ritonavir therapy was also associated once with a multi-organ hypersensitivity reaction in an HIV patient.³⁸ The manufacturer of lopinavir/ritonavir suggests that hair loss occurred in only 0.01% of the patients treated.³⁹ Nevertheless, recently many cases of hair loss and alopecia induced by lopinavir/ritonavir have been reported.^{40–42} Hair loss and alopecia are possible adverse events in HIV-infected patients treated with a PI, particularly indinavir. The exact mechanism of indinavir-induced retinoid-like effects is unclear. Hypotheses regarding pathogenesis include interference with retinoid metabolism due to an enhancement of the retinoic acid-signalling pathway,⁴³ an increase in the synthesis of retinoic acid or a cytochrome P450-mediated decrease in the oxidative metabolism of retinoic acid.⁴⁴ The HIV PIs ritonavir, indinavir, saquinavir and nelfinavir heightened the activity of retinal dehydrogenase—a key enzyme involved in retinoic acid synthesis—by 24%, 17%, 17% and 10%, respectively.⁴⁵

Amprenavir and fosamprenavir

Amprenavir is a PI approved for the treatment of HIV infection in combination with other antiretroviral agents in treatment-naïve and -experienced patients. The safety profile of amprenavir alone or in combination with other antiretrovirals was examined in a study of over 1330 patients in 30 Phase I to III clinical trials, and the results show that ~3% of the patients chose to discontinue treatment because of severe or life-threatening rash. Most adverse events in two Phase III trials occurred in the range of 2–21 days.⁴⁶ However, it has been described as a successful desensitization to amprenavir after the occurrence of a maculopapular exanthema in an HIV-infected patient with late-stage disease. Desensitization may allow continuing amprenavir treatment without recurrence of rash for 19 months of follow-up.⁴⁷

Fosamprenavir is the prodrug of amprenavir. It was synthesized to enhance oral bioavailability of amprenavir, thus allowing a reduction in the pill burden and offering the potential

for improving patient compliance. Skin rash was reported in 19% of treatment-naïve and -experienced patients treated with fosamprenavir, but no causal relationship was found between the two. Pruritus was reported in <1% of the patients. Moderate-to-severe drug-related skin rash was reported in 3% to 8% of the patients and led to treatment discontinuation in <1% of the subjects. Mild-to-moderate maculopapular rashes were typically observed within the first 2 weeks of treatment, but did not require discontinuation of the treatment.^{48,49} One case of SJS was reported during Phase III clinical trials.⁵⁰ Therefore, fosamprenavir should be discontinued in cases of severe or life-threatening rashes or in patients exhibiting systemic systems in addition to a rash. Both fosamprenavir and amprenavir contain a sulphonamide moiety; therefore, these medications should be used with caution in patients with known sulphonamide allergy.⁵¹

Atazanavir

Atazanavir is a once-daily PI. This antiretroviral can be used alone for treating antiretroviral-naïve patients or in conjunction with ritonavir for treating antiretroviral-experienced patients. Atazanavir, in contrast to other PIs and efavirenz, does not have any adverse effect on lipid profile.⁵² The predominant cutaneous findings of atazanavir are skin, hair and nail reactions. A mild rash has been described in HIV-infected patients treated with atazanavir with an incidence of 6%.⁵³ In other clinical trials, the onset of rash generally was 8 weeks after the initiation of atazanavir, and its duration was 1.3 weeks. Rashes were usually mild-to-moderate maculopapular skin eruptions. Recently, three cases of skin rash associated with atazanavir have been described; however, these were the only three cutaneous adverse reactions observed among 323 patients treated with atazanavir. In only one case, the rash was sufficiently severe to induce treatment withdrawal.⁵⁴ Reports of SJS and erythema multiforme have also been reported, but the discontinuation rate due to severe skin reactions in these trials was only 0.4%.⁵⁵

Tipranavir

In June 2005, tipranavir, a non-peptidomimetic PI, was approved by the Food and Drug Administration for use in combination with ritonavir for treatment-experienced HIV-infected patients harbouring PI-resistant virus. Rash is the most common cutaneous side effect associated with tipranavir. During clinical trials, rash was reported in 10% of the female and in 8% of the male patients receiving tipranavir/ritonavir, leading to drug discontinuation in 0.5% of the patients. Generally, rash onset was 53 days after treatment, and the median duration was 22 days. Rash was generally mild to moderate in severity and included urticarial rash, maculopapular rash and possible photosensitivity. Furthermore, in some cases, it was accompanied by joint pain or stiffness, throat tightness or generalized pruritus.⁵⁶ Because tipranavir contains a sulphonamide moiety, it may be that rash occurs in patients allergic to sulfa-containing drugs.⁵⁶ Sulphonamide allergy is not an absolute contraindication in these patients, but it should be used very cautiously. Rash was reported in 8% to 14% of the patients during Phase II clinical trials and in 2% of those in the RESIST studies.^{57,58} A drug-interaction trial between tipranavir/ritonavir and ethinyl estradiol found that women taking concomitantly ethinyl estradiol had an increased risk of non-serious rash.⁵⁶

Therefore, women taking hormone replacement therapy or oral contraceptives may have a higher risk of developing rash than men. During two 48 week, randomized, controlled clinical trials, moderate-to-severe rash was reported in 3.1% of the patients receiving tipranavir/ritonavir 500 mg/200 mg twice daily compared with 3.8% of the patients receiving another comparable PI such as lopinavir/ritonavir, indinavir/ritonavir, saquinavir/ritonavir and amprenavir/ritonavir.⁵⁶

Darunavir

Darunavir is a peptidomimetic PI that has been recently approved in several countries, including the USA and all those in the European Union, for treatment-experienced patients with HIV-1 infection. For HIV-1-infected patients with limited or no treatment experience, this drug is currently under evaluation.⁵⁹ Information on cutaneous adverse reactions to this PI is currently limited to clinical trial reports because of its short commercial life. In clinical trials, self-limiting, maculopapular rashes were generally of mild-to-moderate severity. Rashes of all grades, with uncertain causality, occurred in ~7% of the patients. The rate of discontinuation of the patients included in these clinical trials due to rash was 0.3%.⁵⁹ In the TITAN trial, rash was reported in 16.1% of the darunavir/ritonavir and 6.7% of the buprenavir/ritonavir recipients.⁶⁰ A severe skin rash including erythema multiforme and SJS has also been reported during clinical trials.⁵⁹

Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)

NNRTIs are potent antiretrovirals that were introduced in 1996 for the treatment of HIV infection. These classes of drugs have two advantages: they increase the adherence to the HAART and delay the use of PIs. Cutaneous problems (rash) and hepatotoxicity are the main side effects induced by NNRTI. An important factor in an NNRTI rash is previous history of adverse cutaneous reactions. A retrospective history showed that patients with a history of sulfa rash were more likely to develop NNRTI rash than those who had taken sulphonamide class drugs but had not experienced a rash.⁶¹ NNRTIs include delavirdine, nevirapine, efavirenz and etravirine. In clinical practice, general cutaneous reactions appear to be less common with efavirenz than with delavirdine or nevirapine.⁶² Furthermore, due to somewhat dissimilar structures, skin rashes occurring during therapy with delavirdine or nevirapine may not recur with subsequent administration of efavirenz.⁶³ In this article, only cutaneous side effects associated with the most recently approved NNRTIs will be discussed.

Efavirenz

Efavirenz skin rashes are generally a mild-to-moderate diffuse maculopapular skin eruption or pruritic erythema. New onset rash was reported in 26% of the efavirenz-treated patients compared with 17% of the patients in control groups. The onset of rash was generally 11 days after starting treatment in adults with a median duration of 16 days.⁶⁴ Occasionally, it could develop as vesicles, moist desquamations and/or mouth ulcerations.⁶⁵ It has also been shown that efavirenz could induce photosensitive drug eruptions. In all cases, the photosensitivity developed ~2 months after starting administration of efavirenz and the rash appeared only in

the sun-exposed areas.^{66–68} Moreover, there are some papers reporting cases of cutaneous leucocytoclastic vasculitis associated with efavirenz treatment.⁶⁹ However, efavirenz has been implicated in SJS,⁷⁰ although only with an incidence of 0.14% in all studies and expanded access.⁷¹ Efavirenz treatment related to immune hypersensitivity reaction is rare. Behrens *et al.*⁷² reported severe pulmonary hypersensitivity, maculopapular pruritic rash, myalgia and fever for 10 days after the initiation of efavirenz treatment. The event immediately resolved upon discontinuation of efavirenz and treatment with corticosteroids. Rechallenge with efavirenz led to a generalized erythema with fever and mucosal involvement.⁷² DRESS syndrome was reported in association with efavirenz 20 days after starting efavirenz, lamivudine and stavudine. All drugs were discontinued, and an intravenous steroid therapy was started. The patient was also rechallenged with lamivudine, stavudine and nelfinavir, but not with efavirenz, without recurrence.⁷³ Foti and Piatt⁷⁴ described the successful use of prednisone at a dose of 1 mg/kg every other day for 2 weeks to treat hypersensitivity caused by efavirenz in a paediatric patient. Not-DRESS syndrome, which consists of acute hypersensitivity syndrome with severe hepatitis, pneumonitis and interstitial nephritis, has been related to efavirenz administration. This case report stated that the absence of skin changes and eosinophilia does not exclude the development of a hypersensitivity syndrome related to efavirenz therapy.⁷⁵ Leung *et al.*⁷⁶ reported a case of the hypersensitivity syndrome in a patient initiated on efavirenz therapy. Eleven days after starting the therapy with tenofovir, emtricitabine and efavirenz, the patient developed a hypersensitivity reaction manifested by rash and fever preceding severe drug-induced hepatitis. Hepatitis resolved with discontinuation of the HAART. The patient was rechallenged with tenofovir and emtricitabine 1 year later; no adverse reactions occurred.⁷⁶ Phillips *et al.*⁷⁷ described a patient with efavirenz-induced hypersensitivity syndrome reaction, who was successfully desensitized to efavirenz. Recently, Vitezica *et al.*⁷⁸ studied the possible relationship between cutaneous hypersensitivity induced by nevirapine and efavirenz and an HLA-DRB101 allele in a French cohort of HIV-infected patients. Rashes associated with nevirapine or efavirenz administration were significantly associated with the HLA-DRB101 allele. The results of this study suggest that the HLA-DRB101 allele plays an important role in the susceptibility to cutaneous reactions associated with nevirapine and efavirenz in HIV-infected patients.⁷⁸

Etravirine

Etravirine is one of the newest antiretroviral medications available for the treatment of HIV infection in 2008. In treatment-experienced patients with NNRTI resistance, treatment with etravirine achieved better virological suppression at week 24 than placebo. The vast majority of skin reactions is described in clinical trials. Rash of any type was one of the most commonly reported adverse events occurring in 16.9% of the etravirine-treated patients compared with 9.3% in placebo, according to pooled data from two randomized, double-blind, placebo-controlled, Phase III clinical trials of HIV-1-infected patients.^{79,80}

Most rashes were described as erythematous or maculopapular and were of mild or moderate severity. They tended to occur within the first few weeks of treatment and resolved with continued treatment. In the etravirine group, women have been reported to be more prone to develop rash than men. Severe and

potentially life-threatening skin reactions including hypersensitivity reaction, SJS and erythema multiforme were reported in <0.1% of the etravirine-treated patients during clinical trials of HIV-1-infected patients. If severe rash occurs, etravirine therapy should be discontinued and appropriate treatment initiated.⁸¹

Fusion inhibitors, e.g. enfuvirtide

Enfuvirtide was the first of a class of antiretroviral medications called fusion inhibitors. It is administered via subcutaneous injections twice a day. The majority of cutaneous side effects are related to the subcutaneous administration route, such as injection site reactions, which include erythema, induration nodules, discomfort, pruritus and pain. In two 48 week Phase III trials, 98.3% had at least one injection site reaction during the first week of enfuvirtide treatment. In most patients, the reaction appears during the first week of treatment. These reactions were reported as mildly or moderately painful, but usual activities were not affected. However, few patients had infections at the injection site; 8.7% required analgesics, or reported limits in usual activities. Finally, only 4.4% of the patients in the randomized enfuvirtide group discontinued treatment due to injection site reaction.^{82,83} After a rather long period of treatment with enfuvirtide, cutaneous reactions comprised a variety of features, ranging from a transient acute pattern to scleroderma-like lesions.⁸⁴ Shalit *et al.*⁸⁵ studied the tolerability after administration of enfuvirtide with a thin-walled needle. This study concluded that 87% of the patients reported injection site reactions; 59% and 28% reported worst pain/discomfort grade ≤ 1 and grade ≥ 2 , respectively, and none were considered serious.⁸⁵ Many recommendations such as post-injection massage, rotating injection sites and avoiding existing injection site reaction were proposed in order to decrease the injection site reaction.⁸⁶ The more important strategies to improve patient satisfaction and to lessen adverse events were attempted by administering enfuvirtide via a needle-free, gas-powered injection system (Biojector). Still given twice a day, this type of injection led to plasma concentrations similar to those shown with standard subcutaneous needle injections and had a significant reduction in the injection site reaction scores.⁸⁷ Hypersensitivity reaction, as a consequence of enfuvirtide treatment, has an incidence rate of <1% of patients in clinical trials;⁸⁸ these patients present combinations of rash, fever, nausea, vomiting, chills, rigors, hypotension and elevated liver enzyme levels. Case reports described some successful desensitization protocols in patients who had experienced a hypersensitivity reaction to enfuvirtide.^{89–91}

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs were the first medication approved for the treatment of HIV. Class-wide side effects include lactic acidosis, hepatic steatosis and lipodystrophy.⁹² Currently, the nucleoside analogues used comprise zidovudine, didanosine, lamivudine, stavudine, tenofovir, abacavir and emtricitabine.

Tenofovir

Tenofovir disoproxil fumarate is a nucleotide analogue similar to adefovir and cidofovir. Rash, including pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash, has been reported in 5% to 7% of the patients treated with tenofovir.

In a double-blind study, in HIV treatment-naïve patients, rash occurred in 18% of the patients who received treatment with tenofovir.⁹³ A case of lichenoid eruption with eosinophilia associated with tenofovir therapy was described.⁹⁴ A tenofovir hypersensitivity syndrome, consisting mainly of a maculopapular rash on the face, extremities and trunk, has been reported in nine HIV-infected patients.⁹⁵

Abacavir

Abacavir is an NRTI approved for use as part of a combination antiretroviral therapy. It is available as a single entity formulation or as a fixed-dose combination with lamivudine and with lamivudine/zidovudine.⁹⁶ The most significant skin reaction associated with abacavir is hypersensitivity reaction. It has been reported to occur in patients, ranging from 2.3% to 9%.⁹⁷ Abacavir hypersensitivity is a reversible, life-threatening, immune-mediated systemic reaction that generally occurs within the first 6 weeks of exposure to the drug.⁹⁸ Symptoms most commonly associated with a hypersensitivity reaction are fever (80%), rash (70%), gastrointestinal effects (50%), lethargy or malaise (40% to 60%) and upper or lower respiratory effects (18% to 30%). The clinical classification of abacavir hypersensitivity includes at least two of the following symptoms: fever, rash, nausea, vomiting, headache, respiratory and gastrointestinal symptoms, lethargy, myalgia or arthralgia occurring <6 weeks after exposure and resolving within 72 h of withdrawal of the drug.⁹⁹ Overall, 98% of the cases included either fever or rash or both.¹⁰⁰ Rash was described as maculopapular or urticarial rash and generally was mild or moderate in severity. In addition, numerous laboratory abnormalities were reported, including lymphopenia, leucopenia, thrombocytopenia and elevated transaminase levels. Rechallenge with abacavir following a hypersensitivity reaction is contraindicated. Fatal hypotension has occurred in patients who have been rechallenged following a hypersensitivity reaction to abacavir. Case reports of anaphylactic-like or other severe reactions within hours of re-exposure have been reported.¹⁰¹ Once the hypersensitivity syndrome reaction has been diagnosed, abacavir therapy should be discontinued immediately and permanently. Upon withdrawal of the drug, symptoms could start to resolve within 24–72 h without the need for supportive medical intervention. If supportive therapy is warranted due to severe gastrointestinal losses or dehydration, intravenous hydration and antipyretics can be offered. Antiemetics and analgesics may be useful for short-term use. Corticosteroids, given prophylactically, do not appear to reduce the severity or frequency of the abacavir hypersensitivity syndrome and actually only delay the onset of symptoms.¹⁰² A hypersensitivity reaction to abacavir is strongly associated with the presence of the *HLA-B*5701* allele. In this regard, clinical trials have been developed to assess the utility of prospective screening for the presence of the *HLA-B*5701* allele in patients prior to their first exposure to abacavir.^{103,104} Rauch *et al.*¹⁰³ evaluated a cohort of patients who were prospectively screened for *HLA-B*5701*. In this prospective study, there were no cases of abacavir hypersensitivity among 148 *HLA-B*5701*-negative patients treated with abacavir. Prospective screening for *HLA-B*5701* resulted in a decrease in the incidence of abacavir hypersensitivity syndrome reaction to 2% compared with 8% prior to genetic screening, indicating the benefit of *HLA-B*5701* screening in reducing false-positive clinical diagnosis.¹⁰³ Similar results have been shown in France, with a decrease in the incidence of abacavir hypersensitivity from 12% to <0.5%

when routine genetic screening for *HLA-B*5701* was employed in abacavir-naïve patients. The rate of unwarranted interruptions of abacavir therapy decreased from 10.2% to 0.73%.¹⁰⁴ A large randomized trial provides definitive data regarding the clinical usefulness of prospective screening for *HLA-B*5701* on the incidence of the abacavir hypersensitivity syndrome reaction. This study demonstrated that *HLA-B*5701* screening reduced the risk of hypersensitivity reaction to abacavir. Predominantly in Caucasian populations, 94% of the patients do not carry the *HLA-B*5701* allele and are at low risk for a hypersensitivity reaction to abacavir. These findings support the potential for a widespread implementation of *HLA-B*5701* screening into routine clinical practice to decrease the incidence of a hypersensitivity syndrome reaction.¹⁰⁵ This screening will set an important precedent for the use of genetic testing to improve drug safety.

Suspected cases of SJS have been observed during clinical practice.¹⁰⁶ Abacavir should not be re-started in patients who develop SJS because of the possibility that the event was a hypersensitivity reaction rather than SJS.¹⁰⁷ TEN has been reported in association with abacavir therapy.¹⁰⁸

Emtricitabine

Emtricitabine is a once-daily NRTI used to prevent the replication of HIV and hepatitis B virus. Emtricitabine is structurally similar to lamivudine, differing only in the addition of fluorine. Minor emtricitabine intolerance in treatment-stable patients who switched from lamivudine to emtricitabine was described.¹⁰⁹ The most commonly reported adverse events in emtricitabine clinical trials were headache, nausea, diarrhoea and skin rashes. In the two pivotal studies, skin rash, including pruritus, maculopapular rash, urticaria, vesiculobullous rash and pustular rash, was observed in 17% to 30% of the patients.^{110,111} These cutaneous adverse reactions were generally of mild or moderate intensity; only 1% of the patients discontinued treatment because of rash.¹¹²

Skin discoloration, which is typically reported as hyperpigmentation, usually affects either the palms of the hands or the soles of the feet and was observed in 10 (3.5%), 14 (6%) and 5 (2%) emtricitabine recipients with an overall incidence of 3.4%. Five patients (17%) of these 29 reported skin discoloration events, which resolved during continued treatment with emtricitabine.¹¹³ In contrast to abacavir, it is almost exclusive to patients of African origin.¹¹⁴ However, no patient, regardless of race, perceived this benign event as a significant disability and none discontinued treatment as a result of hyperpigmentation.¹¹³ Hyperpigmentation occurs more frequently in children, with a frequency of 32%.¹¹²

Integrase inhibitors, e.g. raltegravir

Raltegravir is the first in a new class of orally administered HIV-1 integrase inhibitors. It selectively inhibits the strand transfer activity of HIV-1 and its integration into human DNA. As a new class drug, information is only available from clinical trials.

We can conclude from these studies that the possible adverse effects caused by raltegravir are diaphoresis (reported in 4% of the patients, range 200–600 mg) in a multicentre, double-blind, randomized, placebo-controlled study of 35 HIV-infected treatment-naïve patients¹¹⁵ and pruritus in 2.3% to 6.7% patients who received raltegravir at different doses (range 200–600 mg) in a Phase II, double-blind, randomized, placebo-controlled,

24 week trial. The majority of the rash events in raltegravir-treated subjects were mild to moderate in intensity, and no study discontinuations were reported in the Phase II and III development programmes due to rash. A clear pattern of rash has not been established, and many of the rash events have been confounded by use of concomitant medications associated with rash, such as darunavir, abacavir and delavirdine. All patients received treatment twice a day. In addition, all patients received an optimized background antiviral regimen.^{116–118} Based on the pooled data from clinical trials, hypersensitivity occurred in two treatment-experienced HIV-1-infected patients receiving raltegravir 400 mg twice a day in combination with optimized background therapy.¹¹⁹

Inhibitors of the CCR5 chemokine receptor, e.g. maraviroc

Maraviroc is a specific, slowly reversible, non-competitive, small-molecule antagonist of the CCR5 chemokine receptor. It is the first CCR5 co-receptor antagonist approved. Cutaneous adverse events associated with maraviroc are limited to the safety data from the MOTIVATE-1 and -2 trials.^{120,121} Incidence of pruritus and vascular hypertensive disorders also occurred in 3.8% of the patients receiving maraviroc in clinical trials. Pruritic rash may precede the development of hepatotoxicity; therefore, patients with signs or symptoms of an allergic reaction (rash, eosinophilia and elevated IgE) should be evaluated to evidence hepatotoxicity.¹²²

Conclusions

The medical management of patients with HIV infection is challenging to physicians and other healthcare professionals who are not familiar with the use of antiretroviral agents. The advance and development of new HIV drugs and treatment strategies increase the risk of unusual adverse drug reactions associated with HAART. It is important to recognize the safety profile of these new treatments. Skin toxicities are common complications of HIV infection, and this is a significant risk factor for adverse drug reactions. In HIV-infected patients, there is a high prevalence of severe bullous and hypersensitivity reactions induced by antiretroviral therapy. Furthermore, HIV-infected patients may have recurrent cutaneous reactions from other medications such as antibiotics, non-steroidal anti-inflammatory drugs and antituberculosis agents. Withdrawal of the suspected drug is essential for prognosis. The rapid detection and treatment of cutaneous adverse drug reactions, plus identification of the causative agent, are essential for preventing the progression of the reaction, preventing additional exposures and ensuring the appropriate use of medications for the current condition and for other conditions, such patient age. It is also important to perform a causality assessment of the suspected drug reaction in order to determine whether drug discontinuation is mandatory, as well as to put emphasis on patient education in order to avoid the development of skin toxicities in the future.

To sum up, healthcare professionals who attend HIV-infected patients must have a profound knowledge of the safety profile of drugs, especially those related to possible cutaneous adverse reactions induced by newly developed drugs.

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