Acta Derm Venereol 2003; 83: 1–9

Taylor&Francis
healthsciences

REVIEW ARTICLE

Severe Cutaneous Reactions Associated with the Use of Human Immunodeficiency Virus Medications

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Patients infected with human immunodeficiency virus are highly susceptible to adverse dermatological reactions to specific medications. Severe cutaneous conditions such as Stevens-Johnson syndrome and toxic epidermal necrolysis are associated with high morbidity and, notably for toxic epidermal necrolysis, high mortality. Although overall mortality from human immunodeficiency virus has dramatically declined owing to highly active antiretroviral therapy, these antiretroviral regimens have been associated with a wide spectrum of severe cutaneous reactions. We reviewed case reports and clinical trials in the English literature on Medline® (1966 to 2001) and Aidsline® (1980 to 2000) to determine the prevalence of Stevens-Johnson syndrome and toxic epidermal necrolysis attributable to the current FDA approved antiretroviral medications. We identified a total of approximately 50 patients who had Stevens-Johnson syndrome and/or toxic epidermal necrolysis associated with the use of 5 antiretroviral medications: 2 nucleoside reverse transcriptase inhibitors, zidovudine (2 patients) and didanosine (1 patient); 1 non-nucleoside reverse transcriptase inhibitor, nevirapine (42 patients); and 2 protease inhibitors, indinavir (1 patient) and amprenavir (an unspecified number within the 1% of over 1400 patients experiencing severe life-threatening reactions). Of the reports that specified the onset time of adverse reaction after initiation of treatment, 86% (19/22) of patients experienced reactions within 4 weeks. Ten of the approximately 50 patients were diagnosed with Stevens-Johnson syndrome or toxic epidermal necrolysis, due to specific antiretroviral medication, or a combination of medications identified by either resolution upon withdrawal, consistent biopsy findings or a positive rechallenge. The remainder of the identified patients were reported in articles lacking data regarding drug administration, reaction history or other details.

(Accepted September 2, 2002.)

Acta Derm Venereol 2003; 83: 1–9.

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Patients infected with human immunodeficiency virus (HIV) are highly susceptible to adverse dermatologic reactions to specific medications (1–6). Acquired immune deficiency syndrome (AIDS) patients have up to 15 times higher visit rates for common infectious and inflammatory skin conditions (3) and up to a 1000-fold higher risk of developing severe cutaneous reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) compared to the general population (7), estimated at 1.0 to 6 and 0.4 to 1.4 cases per one million inhabitants, respectively (7–12). SJS and TEN share multiple clinical and histopathological characteristics involving mucocutaneous and non-cutaneous derangements affecting ocular, respiratory, gastrointestinal, renal and haematologic systems (13–15). Mortality for SJS and TEN has been estimated between 1% and 5% (8, 10, 16, 17) and 10.3% and 70% (18), respectively. These diseases differ primarily in their extent of epidermal detachment (19), but are considered to exist within the same disease spectrum, both essentially drug-induced cutaneous eruptions (20), although there is a less clear association of drugs to SJS (13). Furthermore, there is recent evidence that SJS in the paediatric population is triggered predominantly by infection (21).

Although AIDS patients with TEN do not exhibit a significantly worse outcome (5, 22), they are more likely to use some of the drugs most frequently responsible for inducing SJS and TEN in immunocompetent individuals. The associated relative risks (RR) for the notable TEN and SJS provoking medications which include sulfonamides (RR 172), aromatic anti-convulsants, such as carbamazepine (RR 90), phenobarbital (RR 45) and phenytoin (RR 53), and allopurinol (RR 52) (23). More controversial is whether non-sulfonamide antibiotics like aminopenicillins, quinolones, cephalosporins and non-steroidal anti-inflammatory drugs are associated with these conditions (23). The leading culprit of SJS and TEN in HIV-infected patients are the sulfa drugs used as treatment or prophylaxis against toxoplasmosis and *Pneumocystis carinii* pneumonia (5). Moreover, sulfonamides have been associated with approximately one-third of TEN cases in the general population (14). The risk of

 ISSN 0001-5555

trimethoprim/sulfamethoxazole (TMP-SMX) attributed TEN/SJS or erythema multiforme in the general population is 26 in 1,000,000 (9). In contrast, the risk of TEN related to TMP/SMX is 980 out of 1,000,000 AIDS patients (2).

There are several mechanisms proposed to explain the increased risk of adverse cutaneous reactions in HIV patients, including the following: greater medication use in these patients relative to the general population (4); the use of high dosage therapy as "standard", such as in PCP and toxoplasmosis prophylaxis or treatment, although TMP/SMX at normal doses also produces TEN/SJS (2); genetic predisposition (24); infections from toxoplasmosis (4) or viruses (i.e. HIV, Epstein-Barr virus or cytomegalovirus) (3, 25, 26); apoptosis (27–29); and aberrant patterns of production and/or detoxification of drug metabolites, including the slow acetylation and decreased antioxidant levels observed in HIV-infected patients (2, 26, 30). Regardless of the aetiology, most likely multifactorial, these severe reactions are believed to be immune-mediated, a result of either immune-complex or cell-mediated immune destruction of mucocutaneous tissue. It is hypothesized that an immune response to metabolites acting as haptens adhering to epidermal cells triggers a cascade of events resulting in a lymphocytotoxic reaction involving CD4 T-lymphocytes, macrophages and activated CD8 T cells (31, 32). Although reports demonstrate associations between low T4 counts and the occurrence of rash in HIV infection (33, 34), neither a direct relationship is confirmed nor has the risk of adverse drug reactions and HIV progression been delineated (3).

During the period before 1981 to the end of 1999, approximately 725,000 cases of AIDS and over 425,000 deaths have been reported to the Center for Disease Control (35). With the introduction of highly active antiretroviral therapy (HAART), usually a combination of one or more nucleoside reverse transcriptase inhibitors (NRTI) and a protease inhibitor (PI), overall mortality from HIV has dramatically declined (36, 37), clearly related to the distribution, understanding and development of new antiretroviral medication and regimens. Concomitant with the prolonged suppression of viral replication is the improved quality of life and significantly decreased morbidity and incidence of opportunistic infection (37–41).

Between 1987 and 1999, 15 antiretroviral medications were licensed, 4 between 1987 and 1994, and an additional 11 between 1995 and 2000 (Table I). Currently, the International AIDS Society–USA panel, an international group of HIV experts, suggests one or two potent PIs with two NRTIs (42). The Department of Health and Human Services strongly recommends an initial antiretroviral regimen consisting of two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or one PI, or as an alternative, two NRTI plus one NRTI or NNRTI, or one or two PIs (43). Initial choice of antiviral combinations must be agreed upon after discussion with the patient and consideration about ease of administration, potency, resistance and toxicity.

Table I. *Current antiretroviral medications (abbreviation and/or trade name)*

Drug name	Year licensed	Manufacturer
Nucleoside reverse transcriptase inhibitors		
Zidovudine (AZT or Retrovir®)	1987	Glaxo Wellcome
Didanosine (ddI or Videx®)	1991	Bristol-Myers Squibb
Zalcitabine (ddc or Hivid®)	1992	Hoffman La Roche
Stavudine (d4T or Zerit®)	1994	Bristol-Myers Squibb
Lamivudine (3TC or Epivir®)	1995	Glaxo Wellcome
Abacavir (Ziagen®)	1998	Glaxo Wellcome
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine (Viramune®)	1996	Boehringer Ingelheim
Delavirdine (Rescriptor®)	1997	Agouron Pharmaceuticals
Efavirenz (Sustiva®)	1998	DuPont Pharmaceuticals
Protease inhibitors		
Saquinavir (Invirase®)	1995	Hoffman La Roche
(Fortovase®)	1997	Hoffman La Roche
Indinavir sulfate (Crixivan®)	1996	Merck and Company
Ritonavir (Norvir®)	1996	Abbott Laboratories
Nelfinavir (Viracept®)	1997	Agouron
Pharmaceuticals		
Amprenavir (Agenerase®)	1999	Glaxo Wellcome
Lopinavir(Kaletra®*, a combination with ritonavir)	2000	Abbott Laboratories

Given the nature of HAART (use of at least three antiretroviral medications) and concomitant use of medications such as sulfonamides and anticonvulsants associated with severe cutaneous reactions, it is often a challenge for clinicians to ascertain the specific medication inducing an adverse cutaneous reaction in the HIV patient. In some reports, identification of the single culprit drug is indeterminable (such as when a combination of antiretrovirals suspected of causing the reaction is discontinued and the individual drugs are never reinitiated). Yet in a majority of cases identification of the single culprit drug is made by either documentation of the temporal sequence between drug use and reaction, or when withdrawal or reintroduction results in cessation or onset of the cutaneous reaction, respectively.

Antiretroviral medications have been associated with a wide spectrum of dermatologic conditions (41,

44 – 61), including, but not limited to the following: diffuse pruritic maculopapular eruptions, erythroderma, generalized urticaria, acute generalized exanthematous pustulosis (AGEP), oedema, anaphylaxis with generalized erythema and other hypersensitivity syndromes including drug rash with eosinophilia and systemic symptoms (DRESS), oedema and pruritus, cutaneous leucocclastic vasculitis, alopecia, psoriasis, pyogenic granuloma, xerosis and dry lips, mucositis and hyperhidrosis. We reviewed case reports and clinical trials in the English literature on Medline® (1966 to September 2001) and Aidsline® (1980 to June 2000) in order to determine the prevalence of SJS and TEN attributable to the currently FDA approved antiretroviral medication.

METHODS

In our search of the literature, the following keywords were used to identify all of the appropriate published references: Stevens-Johnson Syndrome; toxic epidermal necrolysis; epidermal necrolysis, toxic; drug eruption; skin eruption; severe rash; adverse cutaneous reactions; drug hypersensitivity; anti-HIV agents, anti-viral agents; anti-retrovirals; and HAART. The previous search results were combined with the generic drug name for each antiretroviral medication. There were two exceptions to this method. Personal communications to Glaxo Wellcome were made to elucidate the number of SJS cases highlighted non-specifically in the label insert of amprenavir, which was cited by Fung et al. (62, 63). In the case of the newest protease inhibitor, the experimental name ABT-378, which is a combination of lopinavir and ritonavir (marketed by Abbott Laboratories as Kaletra®), was used as a key word in the literature search because of no attainable search results using the generic name, lopinavir. Criteria for inclusion of reports included clinical and/or histological diagnosis, or strong suspicion of TEN/SJS by the reporting investigators.

Identification of some patients with SJS or TEN was made conclusively from those reports which demonstrated resolution upon withdrawal, consistent biopsy findings or a positive rechallenge in the affected patients. At times, treatment with a combination of antiretroviral medications, rather than a specific medication only, was the explanation for the subsequent cutaneous reaction. The assumption that a specific medication within a drug combination resulted in the reaction was made only when there was previous evidence of such an association.

In the rest of the patients identified to have SJS or TEN due to antiretroviral medication, a temporal relationship between drug initiation and onset of adverse reaction, or simply a mention of the reaction associated with the medication by the reporting authors was used to identify the culprit drug or drug combinations.

Other severe systemic and cutaneous reactions associated with the use of antiretroviral medication (i.e. severe (grade 3) or life-threatening (grade 4) rash, acute generalized exanthematous pustulosis (AGEP), hypersensitivity syndrome (HSS), also known as drug rash with eosinophilia and systemic symptoms (DRESS), anaphylaxis or others) were excluded from this study. Grade 3 or 4 rashes, or other adverse effects, were included in this review when these reactions were observed in the same paper reporting SJS/TEN.

RESULTS

After the literature review, only five drugs were identified to induce SJS or TEN alone or in combination with other medications at the time of this report. Table II summarizes the findings.

Nucleoside reverse transcriptase inhibitors

Zidovudine. Murri et al. (64) reported the first case of zidovudine-associated TEN. On initial presentation, a 42-year-old man with HIV presented with fever, orocutaneous ulcerations and lesional histologic findings consistent with erythema multiforme. The patient was treated with zidovudine for one month prior to admission as well as acyclovir, spironolactone, folinic acid, vitamin B complex and dapsone/pyrimethamine, because of a previous rash secondary to co-trimoxazole treatment. Gradual improvement of the patient's condition occurred after discontinuation of the dapsone/pyrimethamine and zidovudine, along with a course of antibiotics and methylprednisolone. Zidovudine was restarted 14 days after admission along with aerosolized pentamidine for PCP prophylaxis, with the belief that EM was attributed to sulfonamide treatment. Two days later, the patient presented with fever, fatigue, de-epithelialization of the feet and mucosal ulceration. After discontinuation of all medications, he subsequently developed massive orocutaneous tissue loss (>75% body surface area, BSA) and histologic and clinical findings consistent with TEN. Despite improvement after 10 days of steroid and pefloxacin therapy, the patient eventually succumbed to *S. aureus* sepsis.

One episode of non-fatal SJS associated with rhabdomyolysis was observed in one of five HIV-infected patients[a], four of whom had rash, receiving treatment consisting of zidovudine with AS-101, an immunostimulatory synthetic organotellurium compound (65, 66). There was no conclusive evidence or discussion to implicate whether specifically zidovudine or AS-101 was associated with the severe reaction, which occurred within one week of three doses of AS-101 and daily zidovudine.

Didanosine. Parneix-Spake et al. (67) reported the case of a 35-year-old HIV-positive man with a biopsy and clinical signs suggestive of SJS, including fever, diffuse erythematous and papular eruption that were occasionally purpuric, erosions of his mouth, genitalia and right superficial keratitis. The patient recently discontinued ofloxacin 10 days before development of cutaneous symptoms, but was on several other medications including clindamycin, pyrimethamine, itraconazole, valproic acid and aerosolized pentamide concurrently with didanosine. Results of a French adverse drug monitoring algorithm considered the

Table II. *Summary of antiretroviral medication induced Stevens-Johnson syndrome or toxic epidermal necrolysis in HIV/AIDS patients*

Medication(s) (mg/day)*	No. of Patient(s)	Reaction	Onset of reaction	Means of attributing reaction to medication	Reference
Zidovudine (500)	1	Death due to TEN	2 days	Blinded rechallenge	64
Zidovudine (1200)/AS-101 -(3 mg/m^2 tiw)	1 of 5	SJS	One week	N/A	a
Didanosine (400)	1	SJS	21 days	Resolution with withdrawal	67
Nevirapine (200)/Zidovudine -(600)/Lamivudine (300)	1	SJS	10 days	Resolution after withdrawal	69
Nevirapine (N/A)	19	SJS	N/A	N/A	69
Nevirapine§†	9 of 2861	SJS	Within one month for 8 of 9 patients	N/A	68
Nevirapine§§ (N/A)	1 of 50,000	Death due to SJS	N/A	N/A	68
Nevirapine§§ (N/A)	1 of 50,000	Death due to TEN	N/A	N/A	68
Nevirapine (N/A)	3	SJS	N/A	N/A	b
Nevirapine** or Placebo/Zidovudine -(600)/Didanosine (400)	2 of 199	SJS (probable in one)	Within 4 weeks	Resolution after withdrawal	73
Nevirapine†††∞	2 of 49	SJS	Within 10 to 30 days	Resolution with withdrawal	81
Nevirapine (200)/Ritonavir (N/A)/Zidovudine (N/A)	1	Overlap SJS/TEN	13 d	Resolution with withdrawal and biopsy	75
Nevirapine**/Abacavir (N/A)††	1	Overlap SJS/TEN	25 d	Resolution with withdrawal and biopsy	75
Nevirapine (N/A)/Abacavir -(N/A)/Didanosine (N/A)***	1	SJS/TEN	33 d	N/A	74
Indinavir (N/A)/Stavudine -(N/A)/Lamivudine (N/A)§§§	1	SJS	Within 2 weeks	Resolution with withdrawal	83
Amprenavir (N/A)§§	13 of 1330	Severe cutaneous reactions (incl SJS)	N/A	N/A	Package Insert, 83

*Unless otherwise specified.
§A majority of patients received 200 mg/day for 2 weeks and 400 mg/day thereafter alone or in combination with other antiretrovirals.
†TMP/SMX taken by 6 of the 9 patients; the other 3 were using dapsone and rifampin.
**200 mg/day for 2 weeks followed by 400 mg/day thereafter.
§§Alone or in combination with other antiretrovirals.
††Patient also receiving long-term zidovudine, zalcitabine, nelfinavir, TMP/SMX and azithromycin.
∞Both patients with SJS received a β-lactam antibiotic during the nevirapine induction phase; one started with 400 mg/day. All other patients received 200 mg/day for 2 weeks followed by 400 mg/day thereafter.
***Patient also receiving TMP/SMX, fluconazole, and amitriptyline.
§§§Patient also receiving glipizide.
†††Other antiretroviral medication as part of a triple combination not specified.
[a]Falloon J, Ogata-Arakaki D, Baseler M, Davey R, Polis M, Kovacs J, et al. Therapy of HIV infection with AS-101 and zidovudine. Proceedings of the 6th International Conference on AIDS; 1990 June 20–23; San Francisco, USA. 6:209 (abstract no. S.B.492).
[b]Brantsma A. Proceedings of the 9th Annual Conference Australas Society HIV Medicine 1997; 9:143 (poster no. P52).

ofloxacin and other medications as probably excluded and doubtful, respectively. The didanosine, started 21 days prior to the severe reaction, was considered as probable according to the algorithm. Furthermore, resolution of the reaction occurred with withdrawal of the didanosine. There have been no other reported cases of SJS in the literature prior to this report (67).

Non-nucleoside reverse transcriptase inhibitors

Nevirapine. SJS or TEN has been reported to occur in 0.3% of patients taking nevirapine within the first 4–6 weeks of treatment (68, 69). Warren et al. cited a 1% risk of nevirapine-related TEN or SJS (70, 71). Moreover, in a randomized, controlled study reported by Carr et al. (72), a description suggestive of SJS (''significant constitutional symptoms and oral ulceration'') occurred in 2 of 49 patients receiving zidovudine or zidovudine with nevirapine. Unfortunately, it was not specified whether it was only those patients receiving the nevirapine who developed the symptoms. In addition, the authors of the trial did not specifically diagnose the reactions as SJS.

Warren et al. (70) reported a case of SJS in a 31-year-old man with HIV after using nevirapine, zidovudine and lamivudine. After 10 days of taking the combination,

the patient, who was not taking any other medication, nor had a history of drug allergy, developed fever, tender ulcers and haemorrhage on his lip and mouth, limbic subconjunctival haemorrhage, conjunctivitis, photophobia and erythematous target-like lesions on his trunk and extremities. The patient's lesions and condition began to improve 2 days after discontinuation of the antiretrovirals and initiation of supportive care with IV hydration and nutrition, along with antihistamines and analgesics. Rechallenge was not performed. Nevirapine was implicated in the reaction because of 19 previously reported cases of SJS to the FDA, and its association with 3 deaths (71). In contrast, there have been no reports of SJS/TEN attributable to lamivudine since its release in 1995, and only one report of zidovudine-induced TEN previously described (64).

Pollard et al. (68) reviewed the safety profile of nevirapine obtained from prospective, controlled and uncontrolled, multidose, clinical adult and paediatric trials conducted in the US and abroad by Boehringer-Ingelheim Pharmaceutical, Inc. (Ridgefield, Connecticut) and the AIDS Clinical Trials Group (ACTG). Detailed safety data were available for 906 adults (from pooled data) and 486 pediatric patients taking nevirapine. The most common drug-related adverse event was rash of any severity, seen in 19.8% of the 906 adult patients. Analysis of 4 controlled adult trials, totaling 658 patients (350 nevirapine treated), revealed a 16% incidence of rash attributable to nevirapine based on the difference between rash in the treatment group (35%) compared with the control group (19%). Severe rash was seen in 6.6% (23/350) of the nevirapine-treated group compared to 1.3% (4/308) of the controls. Positive rechallenge occurred in 57.1% (8/14). A majority of rash occurred within the first 6 weeks in both the nevirapine and control groups. It should be noted that in the clinical trials included in the analysis by Pollard and colleagues (68), treatment consisted of nevirapine monotherapy and in combination with other antiretrovirals. In two pooled paediatric trials, 24% of 37 patients experienced rash of any causality. The incidence of serious rash in paediatric patients receiving nevirapine/zidovudine/didanosine or nevirapine/didanosine judged as "possibly related to nevirapine", occurred in only 9 of 305 (3%) versus 1 of 126 (0.8%) controls taking zidovudine/didanosine from a trial that only reported serious adverse events (68). Eight of the 9 patients with the severe rash developed the reaction within 6 weeks.

In 2861 (2520 adults and 341 paediatric) patients receiving nevirapine in controlled and uncontrolled multidose clinical trials, 9 patients (7 adult and 2 paediatric) developed SJS or SJS/TEN overlap, an incidence of 0.3%, which is the source already cited by Barner & Myers (68, 71). Eight of the 9 patients developed the cutaneous reactions within 1 month (68). Two patients developed SJS/TEN overlap. Trimethoprim/sulfamethoxazole was taken concomitantly by 6 of the 9, and 1 of the other 3 patients was using dapsone and rifampin.

As previously mentioned, there have been only three deaths due to nevirapine between August 1996 and July 1998 based on prescription data from approximately 50,000 patients receiving nevirapine (marketed as Viramune® by Roxane Laboratories, Inc., Columbus, OH) (68). One death was attributable to TEN, 1 from SJS, and 1 from liver failure. The patients cited who died with TEN reportedly increased the nevirapine dose despite rash, contrary to the recommendations for rash management by the manufacturer. This includes a 2-week lead-in dose of 200 mg per day (induction phase) followed by 200 mg twice a day thereafter; the avoidance of increasing drug dosage in the face of rash during the lead-in period; and permanent discontinuation without re-challenge of the medication when severe rash or rash with constitutional symptoms develop (69).

In a randomized, double-blind, placebo-controlled trial by D'Aquila et al. (73) looking at a combination of nevirapine or placebo with zidovudine and didanosine, severe rash occurred in 17 of 199 patients (9%) in the triple therapy group (with nevirapine) versus 3 patients of 199 (2%) receiving double therapy (non-nevirapine). Rash graded as severe or potentially life-threatening occurred in 6 patients from the triple therapy group, and 1 from the double therapy group. Life-threatening diffuse maculopapular rash with oral ulceration was observed in four of the patients who received the triple therapy. Furthermore, from the triple therapy group, SJS was diagnosed in 1 and considered probable in a second patient; a third was treated presumptively to prevent it. All cutaneous reactions occurred within 4 weeks of therapy but resolved with drug withdrawal.

Descamps et al. (74) reported a case of SJS/TEN thought to be associated with the use of nevirapine taken with abacavir and didanosine. Cotrimaxazole (TMP/SMX) was initiated 43 days prior to antiretroviral treatment and amitriptyline with fluconazole months before that. The patient developed 20% epidermal detachment, diffuse blistering on his palms, soles, extremities and face, atypical targetoid lesions, conjunctivitis, multiple bullae and lip and oropharyngeal erosions. Neither the drug dosages nor the outcome of withdrawing all medications were specified. Nevirapine was the agent suspected of causing TEN because of the previously described association with TEN. Although nevirapine is the most probable agent to have caused this patient's TEN, the authors do not discuss the rare but nevertheless likely probability that didanosine, which is associated with one case of SJS, or abacavir,

a relatively new NRTI, may have been responsible for the development of the patient's reaction. Furthermore, abacavir is known to cause severe hypersensitivity reactions, associated with fever, nausea, myalgia, gastrointestinal and respiratory symptoms, and rash, in 3% in early phase I/II and subsequent clinical trials (75–77). There have been three deaths reported due to severe hypersensitivity from abacavir (78). In fact, a recent review outlines a management protocol for the abacavir-related allergic reactions (79).

Two cases of SJS/TEN overlap (epidermal detachment between 10% and 30%) in HIV-positive individuals were reported by Wetterwald et al. (75), who also suspected nevirapine with producing the reaction. The first patient developed dysphagia, fever, generalized cutaneous eruption of 50% BSA, epidermal detachment of 20% BSA, and full-thickness epidermal necrosis typical of TEN 13 days after initiating therapy with nevirapine, zidovudine and ritonavir. The patient's condition resolved 2 weeks after all drugs were withdrawn. Zidovudine was previously administered without incident and ritonavir re-challenge was negative. The second patient was already on long-term therapy with multiple medications, including the TMP-SMX, as well as zalcitabine, zidovudine, nelfinavir and azithromycin. However, 13–19% BSA epidermal detachment, high fevers, erosions of oral and genital mucosa and full-thickness epidermal necrosis occurred 25 days after beginning nevirapine and abacavir. The patient recovered 1 month after all medications, except for TMP/SMX and azithromycin, were discontinued.

Nevirapine was again associated with causing TEN with concomitant use of two protease inhibitors in a report by Phan et al. (80). The authors highlight rapid and successful resolution of the TEN, which involved approximately 50% BSA, mucosal erosions at multiple sites and a positive Nikolsky's sign, within 48 h of administration of intravenous gammaglobulin.

Rey and colleagues (81) reported 2 cases of SJS occurring in a retrospective study investigating the use of prednisolone in 27 of 49 patients receiving a triple antiretroviral regimen in an effort to reduce nevirapine rash. Overall, 8 of 27 patients (30%) who were receiving nevirapine and prednisolone during the lead-in period experienced rash, versus 2 of the 21 (9.5%) patients without the prednisolone. These data are in contrast to the reduced risk of rash seen in a study using prednisone during the nevirapine induction phase (82). One of the patients who had SJS started the nevirapine at full dose (400 mg/d) despite instructions to take 200 mg/d for 2 weeks. The other patient received a β-lactam antibiotic during the 2-week induction phase. Both cutaneous events resolved favourably after discontinuation of the nevirapine. Although the other antiviral drugs of the triple combination were not specified, nevirapine's association with SJS in other reports and especially the favourable outcome after discontinuation of the drug, make it most suspect.

Protease inhibitors

Indinavir. The first reported case of SJS resulting from protease inhibitors involved a clinically healthy HIV-infected 41-year-old male taking indinavir (83). Three days after taking indinavir, stavudine and lamivudine, the patient developed a diffuse non-pruritic exanthem over his neck, trunk and extremities, and a painful exfoliating eruption in his oral cavity and lips. Despite the symptoms, the patient continued the medications over the next 2 weeks, which progressed to include fever, weight loss, extensive mucositis, exfoliation and ulceration of the mucous membranes accompanied by discrete ovoid and round maculopapular rash involving the trunk and proximal limbs. Most signs and symptoms resolved after discontinuation of the medications, and never reappeared after stavudine, lamivudine and saquinavir (in place of indinavir) were reinitiated.

Amprenavir. Amprenavir is the relatively new protease inhibitor in the arsenal of antiretroviral medications. SJS has been reported to occur in only a few of the 1% of patients experiencing life-threatening cutaneous reactions from over 1400 patients taking the drug in multiple clinical trials (personal communications, Glaxo Wellcome). In a review of the safety profile of amprenavir alone or in combination with other antiretrovirals of over 1330 patients in 30 Phase I to III clinical trials (84), 3% of patients chose to discontinue treatment because of severe or life-threatening (grade 3 or 4) rash, the nature of which was not specified. Most adverse events in 2 Phase III trials occurred in the range of 2–21 days, but the time course of rash specifically was not highlighted.

CONCLUSIONS

Although severe cutaneous reactions to HIV medication are relatively rare, it is expected that cases will continue to be reported given the extensive use of HAART and the continued development of new antiretroviral medication. As suggested by other authors (85), future studies of antiretroviral medications should seek to highlight the potential side effects in addition to the benefits of HAART. Physicians and other health professionals must be aware of the related complications and risks attributable to HIV medications in the immunocompromised, many of whom are already at risk for the development of non-iatrogenic cutaneous reactions (86). Although previous investigators have highlighted therapeutic initiatives to manage SJS/TEN, including corticosteroids, immunosuppressives, anti-cytokines, immunoglobulins, antibiotics, plasmapheresis and epidermal (87–94), definitive treatment

remains controversial. Continued studies are needed to establish an efficacious protocol to manage these rare, morbid and sometimes fatal cutaneous diseases.

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