ADVERSE EFFECTS OF ANTIRETROVIRAL THERAPY ON ORAL TISSUES IN HIV POSITIVE INDIVIDUALS

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Abstract

Since AIDS was first recognized nearly 20 years ago, remarkable progress has been made in improving the quality and duration of life of HIV-infected persons. There has been extraordinary recent progress in developing therapies against HIV, particularly the highly active antiretroviral therapies (HAART), consisting of combinations of antiretroviral agents such as inhibitors of the HIV reverse transcriptases and proteases. Systemic and orofacial infections and other lesions have thereby been reduced and have extended life substantially. However, antiretroviral regimens are complicated and difficult for patients to follow, and they can have serious side effects, such as osteonecrosis and bone demineralization. This paper summarises some of the oral adverse effects of antiretroviral agents.

Key Words: Human Immunodeficiency virus (HIV), antiretroviral therapies, adverse effects

Introduction

Acquired Immunodeficiency syndrome (AIDS), caused by Human Immunodeficiency virus (HIV) is one of the most dreadful diseases affecting the mankind. Since the appearance of the first cases of contamination by the HIV virus, in the 1980s, there has been a continuous and progressive increase in the number of infected patients. HIV damages the immune system, especially the CD4+T lymphocytes, producing a profound immunological defect in the cell mediated immunereactivity, predisposing the individual to various opportunistic infections.[1]

More than 90% of HIV infected patients present with atleast one oral manifestation at some time during the course of the disease. Oral manifestations of HIV infection include oral candidiasis, oral hairy leukoplakia, Kaposi's sarcoma, herpes simplex, herpes zoster, periodontal disease and salivary gland disease. Salivary gland diseases include xerostomia, cysts and Sjogren's syndrome like condition with persistent glandular enlargement. Periodontal diseases include HIV associated gingivitis, linear gingival erythema, necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP).[2]

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. However, these advantages are accompanied with marked increase in the number of adverse drug reactions, some of which affect the orofacial region.[3]

Antiretroviral Drugs

Antiretroviral drugs used in HIV management fall into three major classes: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). A nucleotide reverse transcriptase inhibitor (NtRTI), tenofovir (Viread), and a newly approved fusion inhibitor, enfuvirtide (Fuzeon) also are available. The protease inhibitors have the most side effects and strictest dosing regimens.[4]

The antiretrovirals (ARVs) reduce viral load and increase CD4+ T cell count, thereby slowing disease progression and improving the patients' quality of life. Since the approval of AZT by the US FDA in 1987, it has been widely used for the treatment of Human immunodeficiency virus infection.[5]

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs block HIV reverse transcriptase activity by competing with natural substrates and being incorporated into viral DNA where they act as chain terminators in the synthesis of pro-viral nucleic acids. Zidovudine was the mainstay of anti-HIV therapy for several years (Kinloch-De Loes *et a.l,* 1995) but is now rarely used alone.[6]

The NRTIs often produce adverse effects and perhaps more significantly, resistance may arise (Stuyver *et al*., 1997).[7] Among the common effects of many are haematological toxicity, neurological toxicity including effects on memory, cognition, motor and peripheral nerve function, and enhanced risk of oral infection. (Bayard *et al*, 1992; Epstein and Scully, 1993).[8,9]

Effects of NRTIs on oral tissues

Drugs such as zidovudine may lead to bone marrow suppression which may predispose to ulcers. The use of NRTIs can also cause leukopenia, usually neutropenia, (Bayard *et al*., 1992) and may manifest with mouth ulcers.[8]

Oral ulceration is recorded particularly with zalcitabine (dideoxycytidine) which produces mouth ulcers in 3– 30% of patients (Adkins *et al*., 1997). [10] These ulcers resolve at the latest by the third week of therapy, or if the drug is withdrawn and they do not develop in patients given only low doses of zalcitabine (McNeely *et al*., 1989).[11]

Erythema multiforme (Creagh-Kirk *et al*., 1988) [12] and toxic epidermal necrolysis are especially well recognized in HIV disease, particularly as reactions to sulphonamides and to antiretroviral agents (Bayard *et al*., 1992).[8]
The use of zidovudine is related to occurrence of oral lichenoid reactions in HIV disease (Ficarra *et al*., 1993), [13] and there may be mucositis. Zidovudine can also induce mucocutaneous hyperpigmentation.[14]

Didanosine has also produced erythema multiforme and not unusually induces xerostomia. Xerostomia may be seen in up to one-third of patients taking didanosine.[14]

Non-nucleoside reverse transcriptase inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) directly bind to HIV reverse transcriptase to inhibit it. The group includes drugs like efavirenz, nevirapine and delavirdin (Drake, 2000). [15] NNRTIs suffer from similar disadvantages to NRTIs (Drake, 2000), especially rashes. Serious cutaneous manifestations such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with the nevirapine.[4]

Effects of NNRTIs on oral tissues

Orofacial adverse effects have only occasionally been recorded with NNRTIs. Nevirapine for example, has produced severe erythema multiforme type reactions (Wetterwald *et al*., 1999).[16]

Protease inhibitors

The protease inhibitors (PIs) competitively inhibit an HIV aspartyl protease without affecting the comparable human enzyme and induce a profound and sustained fall in HIV viral load and restore T cell counts.[14] 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.[3]

The most common adverse reaction of PIs is lipodystrophy syndrome, abnormal fat distribution, central adiposity, insulin resistance, hyperglycaemia and hyperlipidaemia. Cutaneous side effects include rashes.[3]

Severe hepatotoxicity (i.e., more than a fivefold increase from the upper limit of

normal in alanine transaminase or aspartate transaminase levels) can occur in patients treated with PIs.[4]

Effects of protease inhibitors on oral tissues

Taste abnormalities are common with protease inhibitors. Three of the protease inhibitors (indinavir, ritonavir, and saquinavir) were found to be predominantly bitter (with additional qualities of medicinal, metallic, astringent, sour, and burning). Ritonavir in particular can give rise to circumoral paraesthesia in over 25% of patients: about 10–20% of patients receiving protease inhibitors may develop abnormalities of taste (Temesgen and Wright, 1999).[17] Amprenavir can also produce significant paraesthesia.[14]

The protease inhibitor drugs can induce lipodystrophy leading to swelling in the parotid region attributed to parotid lipomatosis with dyslipidaemia and facial lipoatrophy (Olive *et al.*, 1998).[18]

Up to 7% of patients using protease inhibitors may have xerostomia and/or oral ulceration, and rare patients develop angioedema or erythema multiforme. [14] Indinavir can also produce cheilitis; study by Calista and Boschini (2000) showed cheilitis in 57% of the patients.[19]

Highly active antiretroviral therapies (HAART)

In recent years, Highly Active Antiretroviral Therapy (HAART) has become the management modality of choice in the management of HIV infection. HAART, consisting of 2 nucleotide analogues and a protease inhibitor (PI), is a currently recommended regimen for suppressing HIV replication and for restoring or preserving host immunity. HAART therapy has changed the quality and length of life for individuals with HIV infection.[20]

Recent studies have shown a decrease in the prevalence of the salivary gland disorder diffuse infiltrative lymphocytosis syndrome (DILS) (also referred to as Sjögren–like syndrome) that are unique to HIV-infected individuals.[20]

Effect of HAART on oral tissues

Since the introduction of antiretroviral drugs, particularly the highly active antiretroviral therapy (HAART), the prevalence of oral candidiasis in HIV-infected adults and children has decreased dramatically. Two potential mechanisms account for this finding, the immune reconstitution induced by HAART and an antifungal effect. HAART results in an increase in the levels of CD4+ T lymphocytes rescuing the immune system, while the protease inhibitors present in the drug cocktail could interfere with secreted aspartic proteinases (SAPs), the main proteases secreted by C. albicans, hampering its proliferation and pathogenicity.[21]

Conversely, oral and perioral adverse effects can arise and may sometimes result in patient non-adherence to anti-HIV therapy. The particular adverse effects depend on the agents used in HAART.[14]

Greenspan et al. (2001) in their study observed an increase in the incidence of oral warts on administration of HAART in HIV infected individuals. HAART is also associated with morbilliform exanthematous eruptions and mucosal pigmentation.[3]

Conclusion

The medical management of patients with HIV infection is challenging to physicians and other healthcare professionals. The advance and development of new HIV drugs and treatment strategies increase the risk of unusual adverse drug reactions. It is important to recognize the safety profile of these new treatments. The healthcare professionals who attend HIV-infected patients must have a profound knowledge of the safety profile of drugs.

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