HIV-Related Lipodystrophy and Facial Lipoatrophy: The Role of Restylane SubQ in Reversing Facial Wasting

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HIV-associated lipodystrophy syndrome affects approximately 50% of HIV-positive patients, particularly those receiving antiretroviral therapy based on nucleoside reverse transcriptase inhibitors and protease inhibitors. Growing evidence suggests that certain antiretroviral drugs may precipitate or exacerbate lipoatrophy and associated metabolic abnormalities, and this is an important consideration when selecting appropriate treatment regimens. However, because of problems of cross-resistance among antiretroviral drug classes and other treatment-related toxicities, it is likely that, at some stage, the HIV-infected patient will have to take drugs that confer a risk of development of lipodystrophy syndrome.

Combination therapy for HIV, known as highly active antiretroviral therapy (HAART), has dramatically altered the prognosis for the HIV-infected individual. With optimal use of HAART, which includes regular monitoring of viral load, viral resistance, and compliance with medication, HIV infection has changed from being a fatal disease to a lifelong infection. However, HAART-related lipodystrophy syndrome, and especially facial lipoatrophy, is of great concern for patients and physicians involved in HIV care. For the patient, facial lipoatrophy is a major stigma that affects self-esteem and social interaction, and in some cases, it is a cause of noncompliance with HAART.

Accordingly, many treatment-experienced HIV patients are requesting, and being treated with, various dermal fillers for cosmetic correction of facial lipoatrophy. Prior to the introduction of HAART, when life expectancy for the HIV-infected individual was severely limited, permanent fillers were widely used for this purpose. Because these products remain in situ indefinitely and the facial soft tissues change over time, the permanent fillers are no longer a satisfactory treatment option. Now that HIV infection has been transformed into a chronic but not necessarily life-threatening disease, there is an urgent need for a safe, biodegradable, and biocompatible alternative dermal filler for treating HIV-associated facial lipoatrophy.

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Following the introduction of highly active antiretroviral therapy (HAART) in 1996, the prognosis for patients infected with human immunodeficiency virus (HIV) has changed dramatically. Whereas patients could previously expect to live for another 10 to 15 years after being diagnosed with acquired immune deficiency syndrome (AIDS), they now face the prospect of coping with a life-long infection that requires continuous antiretroviral therapy but does not necessarily shorten their survival. However, antiretroviral therapy must be taken on a regular basis, with strict attention to the recommended treatment schedule. Poor adherence to HAART is likely to result in suboptimal virologic suppression and, consequently, to promote the development of drug-resistant viral strains.

Not only can the consequences of poor compliance with antiretroviral therapy be devastating, the medication itself causes severe symptomatic and metabolic side effects in many patients. For the HIV-infected patient receiving HAART, one of the more dreaded sequelae is lipoatrophy of the face—perhaps the most obvious outward sign of HIV infection. This condition is distressing to the patient and, in many cases, leads to low self-esteem, depression, and social withdrawal.[1] Studies suggest a strong causal relationship between the use of protease inhibitors and certain nucleoside analogues (most notably stavudine and didanosine) and the development of facial lipoatrophy.[2,3]

Facial lipoatrophy is only one of several clinical manifestations of the metabolic changes associated with HAART, which collectively make up the lipodystrophy syndrome. This comprises dyslipidemia, insulin resistance, and abnormal glucose homeostasis, as well as altered fat distribution—loss of subcutaneous fat in the

face, limbs and buttocks, and relative accumulation of fat in the abdomen and dorso-cervical fat pad (the so-called "buffalo hump").[4] Although there is an initial increase in fat deposits in the limbs during the first few months of HAART in antiretroviral-naïve patients, this is followed by a progressive decrease over the long term.[3,5]

Abnormalities of body-fat composition have been reported in 40% to 50% of ambulatory HIV-infected patients.[6-8] Estimates of the prevalence of lipodystrophy syndrome are more variable, ranging from 10% to more than 80% in cross-sectional studies.[9,10] Facial lipoatrophy rates may be even higher, depending on the sex and age of the patient population and the type and duration of antiretroviral therapy.

Pathogenesis of Facial Lipoatrophy

The type and duration of HAART strongly influence the severity of facial lipoatrophy in HIV-infected patients, with protease inhibitor/nucleoside reverse-transcriptase inhibitor combinations producing the most pronounced changes.

Protease inhibitors can inhibit lipogenesis and adipocyte differentiation,[11] stimulate lipolysis,[12] and impair expression of the adipogenic factor sterol regulatory element-binding protein-1 (SREBP1).[13] Nucleoside-induced lipoatrophy may be partly due to mitochondrial injury resulting from inhibition of mitochondrial DNA polymerase gamma within the adipocyte[14] and depletion of mitochondrial DNA,[15] although the exact mechanisms underlying this effect remain unclear.

Combinations of nucleoside analogues and protease inhibitors also exert synergistic inhibitory effects on adipocyte differentiation and adipogenesis, both in vitro and in vivo.[16] The possible mechanisms underlying the lipoatrophy syndrome have recently been comprehensively reviewed.[17]

Assessment of Lipodystrophy

Peripheral fat loss in HIV-infected patients has been evaluated in several studies.[3,5] Visceral fat accumulation can be assessed by computed tomography, but since this procedure involves exposure to ionizing radiation, it should not be used without good reason. To date, there are no validated techniques for assessing the severity of facial lipoatrophy, although ultrasonography has been used successfully for this purpose.[18]

A system for classifying the severity of facial lipoatrophy, based on a 4-grade rating scale, has been proposed.[2] According to this system, facial lipoatrophy is graded as follows:

- Grade 1 – mild and localized facial lipoatrophy, with near-normal facial appearance.
- Grade 2 – deeper and longer central cheek atrophy, with early signs of the facial muscles (especially zygomaticus major) showing through the skin.
- Grade 3 – even deeper and wider areas of atrophy, with the muscles clearly showing through the skin.
- Grade 4 – atrophy covering a wide area and extending towards the orbit; the facial skin lies directly on the muscles and bone structures over wide areas.

Treatment Options

Although there are a number of treatment options for the patient with facial lipoatrophy, the physician's first priority should be to prevent development of this condition by selecting an appropriate antiretroviral drug regimen. With the expanding choice of drugs available for initiating HAART, the goal of averting facial lipoatrophy has now become more feasible. However, because of the problem of poor patient compliance with HAART and the potential risk of viral resistance to first-line therapy, situations will continue to arise whereby patients are necessarily placed on antiretroviral therapies that increase the risk of lipoatrophy.

For the patient showing early signs of facial lipoatrophy, modification of existing antiretroviral therapy—usually by replacing stavudine or zidovudine with a less toxic agent such as abacavir—is one possible option.[19] Another approach is to increase the volume of facial subcutaneous tissue through pharmacological means. This involves the use of glitazones—ligands for the transcription factor peroxisome proliferator-activated receptor gamma, which is essential for adipocyte differentiation. In patients with type 2 diabetes, rosiglitazone has been shown to increase body fat mass (predominantly in the subcutaneous compartment) by ~4 kg over a 12-week treatment period.[20] This effect is accompanied by an improvement in insulin sensitivity, but these benefits are partly offset by a significant elevation of plasma lipids. For this reason, use of glitazones for treatment of HAART-associated lipoatrophy cannot be recommended outside the clinical trial setting.

Dermal fillers

An alternative approach to the treatment of facial lipoatrophy is the use of dermal fillers to restore lost facial volume. During the last decade, dermal fillers (both degradable and nondegradable varieties) have been widely used for correction of age-related wrinkles and restoration of lost facial volume. The first fillers to be launched on the market more than 20 years ago were collagens of

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