Sculptra™: A Novel Treatment Approach for HIV-Associated Facial Lipoatrophy

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INTRODUCTION

Human immunodeficiency virus (HIV) infection affects approximately one million persons in the U.S. alone. Along with recent advances in HIV treatment options, especially over the past decade, dramatic reductions in HIV-associated morbidity and mortality have been observed. As a result of an increase in life expectancy, however, the severity of side effects from these treatment options has increased drastically as well.

The most typical change observed is lipodystrophy syndrome, which to date has increased significantly among this patient population. HIV-infected patients present with unusual changes in the distribution of body fat. An increased amount of fat can be seen in various areas of the body, such as the stomach, neck, and breast tissue, with fat loss sometimes observed in the face, arms, legs, and buttocks. Although these changes in body fat have been associated with highly active antiretroviral therapy (HAART), they are not attributed solely to HAART. Other risk factors that tend to potentiate the development of lipoatrophy are depicted in Table 1.

Facial lipoatrophy, also known as “facial wasting,” has become more prevalent since the advent of HAART. Facial lipoatrophy is manifested by subcutaneous fat loss in the face, which most commonly presents as sunken cheeks, temples, and eyes. Among the available drug therapies, protease inhibitor (PI)-based therapy and nucleoside reverse transcriptase inhibitor (NRTI)-based HAART were most often associated with these side effects. The exact mechanism of how fat loss occurs remains to be discovered, but some investigators suspect mitochondrial toxicity as an etiological factor.

Although facial lipoatrophy might seem to be a “cosmetic” issue for many people who have not encountered it before, this condition has been associated with a high degree of psychological morbidity, including depression and anxiety, and has even led to inappropriate discontinuation of HAART. Stopping therapy can lead to an increase in opportunistic infections and death associated with acquired immunodeficiency syndrome (AIDS).

Current treatment options for patients with lipodystrophy have included switching from a PI-based or NRTI-based regimen (especially d4T, stavudine [Zerit®; Bristol-Myers Squibb Oncology]) with other “d” drugs like ddI and ddC) to a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; implants; and plastic surgery. Until recently, there were no treatment options for HIV-associated lipoatrophy. On August 3, 2004, the U.S. Food and Drug Administration (FDA) approved the first device for facial lipoatrophy in HIV-positive patients. Sculptra™ (Demik Laboratories/Aventis) is an injectable filler that is indicated for correcting facial lipoatrophy in HIV-positive patients. This product was initially approved in Europe in 1999 under the trade name New-Fill® and has been used for the cosmetic correction of scars and wrinkles.

PRODUCT DESCRIPTION AND PHARMACOKINETICS

Sculptra™ is an injectable implant that contains microparticles of poly-L-lactic acid (PLLA). It is a biodegradable, biocompatible, and immunologically inert synthetic polymer derived from the alpha-hydroxy acid family.

Sculptra™ is available as a lyophilized, sterile, freeze-dried preparation for injection in a clear glass vial. The preparation is reconstituted with 3 to 5 ml of Sterile Water for Injection (USP) and is then injected by a trained health care professional into the deep dermis layer or the subcutaneous layer of the skin only. The final composition consists of PLLA, sodium carboxymethylcellulose (USP), nonpyrogenic mannitol (USP), and the Sterile Water.

Table 1 Non-Drug Risk Factors in the Development of Lipoatrophy*

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<th>Factor</th>
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<tr>
<td>Caucasian race</td>
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<td>Family history of diabetes</td>
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<tr>
<td>Low body mass</td>
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<tr>
<td>High viral load and rapid increase in number of T cells after initiation of highly active antiretroviral therapy</td>
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* Lipoatrophy is multifactorial and is not attributed to one single condition. It can lead to serious heart disease, diabetes, and pancreatitis.
These injections gradually improve the appearance of skin folds and sunken areas by significantly increasing skin thickness. In clinical trials, the results of Sculptra use lasted for up to two years after the first treatment session.

**ADMINISTRATION**

Only health care providers who are fully trained and familiar with Sculptra should administer it. These professionals should be aware of the correction of volume deficiencies needed for each individual patient with HIV infection, and they must also be registered with Derml Laboratories to be able to order and give the injections.

The number of injection sessions needed differs for each patient, depending on the degree of severity of the lipoatrophy. Previous studies have noted three to five injection sessions per patient, given at two-week intervals.

**CLINICAL TRIALS**

The efficacy and safety of Sculptra have been demonstrated in two clinical trials.

**The VEGA Study**

The VEGA Study was a 96-week, open-label, non-control, single-center study in Paris, France, that evaluated the efficacy, safety, and durability of facial injections of New-Fill in HIV-infected patients with lipoatrophy. Of the 50 patients who were enrolled in this study, 49 (98%) were men and 42 (84%) were white.

To be included in the trial, patients had to be at least 18 years of age and had to have severe lipoatrophy, defined as thickness of fat tissue in the nasogenian area less than 2 mm, as measured by ultrasonography. The study participants also had to have received at least three years of antiretroviral therapy, with stable plasma HIV-1 RNA levels below 5,000 copies/ml within the three months of their enrollment into the study.

Patients were excluded from the study if they had any facial skin disease, if they had received a facial implant within the previous six months, or if they were currently receiving interferon or cytokine therapy. The average age of the participants was 45.9 years.

The participants received four to five sets of New-Fill injections every two weeks into and around the deep dermis of the atrophied area in each cheek. At weeks 0, 6, 24, 48, 72, and 96, they were evaluated by clinical examination, facial ultrasonography, and photographs. The Visual Analogue Scale (VAS) was used to assess the patients’ quality of life, and data were collected at weeks 0, 12, 24, 48, 72, and 96. The fifth set of injections was given only to patients whose facial total cutaneous thickness (TCT) was less than 8 mm at the sixth week.

The primary endpoint evaluated in this study was the proportion of responders, defined as patients with a TCT greater than 10 mm, measured at the nasogenian fold, at week 24. The proportion of patients with a TCT of at least 10 mm at week 24 was 41% (95% confidence interval [CI] 27–56 mm; P < .001). The median increases in TCT from baseline were also statistically significant at all time points from baseline. These values are shown in Table 2.

Quality-of-life measurements were obtained from 44 patients. These figures progressively increased from the baseline evaluation up until week 48 (+0.8, –3.9 to +10.0; P = .021).

No serious adverse drug events (ADEs) were reported during the trial, and no patients withdrew from the study because of side effects. The most common side effects noted were minimal, localized edema at the injection site; ecchymosis; and palpable, invisible subcutaneous micronodules, which resolved spontaneously.

The viral load and CD4+ cell count remained stable throughout the study period. No AIDS-defining event occurred during the trial.

**The Chelsea and Westminster Hospital Study**

A 24-week, randomized, open-label, single-center, non-control trial in London, UK, enrolled HIV-positive patients with facial lipoatrophy. The patients were randomly assigned to one of two study arms. Patients in the “immediate-treatment” arm received New-Fill injections bilaterally overlaying the buccal fat pads on day one and then two and four weeks later. Patients in the “delayed-treatment” arm received injections at weeks 12, 14, and 16.

This study was designed to evaluate the association between treatment and improvement in both subjective and objective outcomes. Lipoatrophy was defined by patient-agreed and physician-agreed changes. Ultrasound measurements and photographic assessments were performed. Patients also filled out the Hospital Anxiety and Depression Scale (HADS) at each visit.

Of the 30 patients who were enrolled in this study, 28 (93%) were men. The mean age of the patients was 41 (range, 32–60 years); 72% of the patients were white. Protease inhibitors were used for an average of 43.7 months (range, 21.5–58.8 months); NRTIs were used for an average of 79.4 months (range, 55–118.3 months).

Patients were excluded from the study if they were receiving anticoagulant therapy or if they had a prior history of facial surgical or cosmetic interventions for their facial lipoatrophy.

All patients underwent three sessions of New-Fill® injections into their cheeks and nasolabial areas. At week 12, there was a statistically significant difference in mean increases in dermal thickness between the two groups. The immediate-treatment arm noted an average increase of 4 to 5 mm, but no change was...
observed in the delayed-treatment arm ($P < .001$). At the end of the study, however, there were no differences in dermal thickness between the two groups.

During the study, anxiety and depression declined in both groups. Anxiety scores tended to show a difference between the two treatment arms at week 12, which was the point at which the second arm underwent the initiation of injections. No significant changes in viral load, CD4+ count, or blood parameters occurred during the trial.

### ADVERSE DRUG REACTIONS

Data on the ADEs resulting from Sculptra™ injections have been compiled from four clinical trials. Table 3 summarizes the most common ADEs that have been reported.

The results from the APEX-002 Study and the Blue Pacific Study (Aesthetic Medical Group) in Hermosa Beach, California, which are still ongoing, are provided for safety information only. These two, single-center, open-label, 12-month studies each enrolled 99 HIV-positive patients between ages 31 and 65 years with facial lipoatrophy. Most of these patients were white men, as in the previous trials.

### DRUG INTERACTIONS

Although no significant drug interactions have been reported with the use of Sculptra™, caution is warranted for patients who are also receiving anticoagulant agents because they may be at an increased risk of hematoma formation or localized bleeding at the injection site.

### CONTRAINDICATIONS

The available evidence indicates that Sculptra™ is relatively safe. It is contraindicated only for individuals with a known hypersensitivity to any of the components of the product.

### WARNINGS AND PRECAUTIONS

Health care providers should consider the following facts before administering Sculptra™:

1. The product’s long-term safety and effectiveness for more than two years have not been established. The manufacturer is conducting a post-approval study to evaluate the product’s safety and efficacy beyond two years.

2. Sculptra™ should be used only in the deep dermis and subcutaneous layers of the skin. Superficial skin injections should be avoided.

3. Health care providers must take special care when injecting Sculptra™ into areas of thin skin.

4. The safety and efficacy of Sculptra™ in the periorbital area have not been confirmed.

5. As with all transcutaneous procedures, there is a risk of infection with injections. Standard precautions for injection should always be followed.

6. Health care providers should be aware of the risk of hematoma or local-
ized injection-site bleeding if patients are receiving anticoagulant therapy.

7. Because there is a potential for contact with a patient’s body fluids, universal precautions are warranted. The use of aseptic technique is a necessity.

8. The product’s safety for use in pregnant women, in breast-feeding women, and in patients younger than 18 years of age has not been established.

9. Data are limited in terms of the use of Sculptra™ in women, in non-whites, and in patients with increased susceptibility to keloid formation and hypertrophic scarring. Dermik plans to conduct a post-approval study in these patients, who have not been not adequately represented in previous studies.

**PATIENT COUNSELING**

Following injection sessions with Sculptra™, patients should be given the following guidance:

1. An ice pack can be applied to the treatment area within the first 24 hours in order to reduce swelling. The ice should not be applied directly to the skin.

2. Patients should massage the treatment area daily for several days after an injection session to ensure more even distribution of the product.

3. Redness, swelling, or bruising may occur, but these effects usually resolve within hours to one week. Hematoma formation, if any, might take up to two weeks to resolve. Most small papules that develop in the treated area are usually invisible and asymptomatic. If any of these effects last longer than expected or if they appear to worsen, patients should be advised to report these findings to their health care providers immediately.

4. If there are no complications, such as open wounds, bleeding, redness, or swelling, patients may apply makeup a few hours after the injection session.

5. Patients should minimize their exposure to the excessive sun or ultraviolet lamps until any resulting swelling or redness has resolved.

6. Patients should be informed that it takes a few weeks for Sculptra™ to demonstrate its effects.

7. Patients may experience an initial facial swelling. When the swelling subsides and the original depressions...
reappear, they might think that the injections are not working. Patients should be advised that this effect is normal and that it will take a few weeks before the results of Sculptra™ become apparent.

PHARMACOECONOMICS

As with any pharmaceutical product, cost may be a concern for many patients and health care professionals who will be considering this device. Unfortunately, cost information regarding Sculptra™ is available only to health care providers who are registered with Dermik Laboratories to administer the injections. Therefore, we cannot make a cost comparison between this treatment option and others at this time.

OTHER TREATMENT OPTIONS

Alternative treatment options for patients with facial lipoatrophy are presented in Table 4 on page 213. Because some of the procedures listed are highly individualized, patients and their health care providers should be encouraged to discuss those strategies that would be most appropriate.

CONCLUSION

Although HIV infection is becoming more manageable for many patients and clinicians, the complications from antiretroviral therapy have become more difficult to manage. Unfortunately, facial lipoatrophy is the most difficult manifestation to correct. It remains a major concern among HIV-infected patients, because it can be psychologically and socially stigmatizing. Consequently, patients frequently request available treatments to correct this disorder.

It is vital that these patients not discontinue HAART. Discussing the problem with a health care professional is essential, because sometimes other factors contribute to the development of lipoatrophy.

Sculpta™ appears to be a safe, effective, and viable alternative for patients with HIV-associated facial lipoatrophy, especially for those who cannot switch their antiretroviral treatment regimens or who do not wish to undergo painful reconstructive procedures. Because the cost of many of the alternative procedures can be quite high, patients who are considering Sculptra™ injections should be encouraged to discuss all of the available choices with their physicians.

REFERENCES