

Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA

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Marc-Antoine Valantin a,b; Camille Aubron-Olivier a; Jade Ghosn a; Elisabeth Laglenne c; Michelle Pauchard a; Hélène Schoen a; Raymond Bousquet a; Philippe Katz d; Dominique Costagliola b; Christine Katlama a,b

From the aDépartement des Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, BINSERM 0214 Université Pierre et Marie CURIE, Paris, France, cBiotech Industries SA, Luxembourg, and d7 rue Théodore de Banville 75017 Paris, France.

ABSTRACT

Background: In the absence of currently available therapy to manage facial lipoatrophy, strategies used to compensate for facial fat loss warrant clinical evaluation.

Methods: The goal of this open-label, single-arm, pilot study was to evaluate the efficacy and safety of facial injections of poly-L-lactic acid (PLA) (New-Fill) in HIV-infected patients with severe facial lipoatrophy. Patients received four sets of injection at day 0 and then every 2 weeks for 6 weeks. Patients were evaluated by clinical examination, facial ultrasonography, and photography at screening and at weeks 6, 24, 48, 72, and 96.

Results: Fifty patients were enrolled. At entry, the median facial fat thickness was equal to zero (range, 0.0-2.1 mm). The median total cutaneous thickness (TCT) increased significantly from baseline: +5.1 mm (range, 2.2-8.6 mm) at week 6, +6.4 mm (range, 3.1-9.1 mm) at week 24, +7.2 mm (range, 4.2-9.6 mm) at week 48, +7.2 mm (range, 3.5-9.6 mm) at week 72 and +6.8 mm (range, 3.9-10.1 mm) at week 96 ($P < 0.001$). The proportion of patients with TCT > 10 mm was observed in 19% at week 6, 41% at week 24, 61% at week 48, 52% at week 72 and 43% at week 96. In 22 (44%) patients, palpable but non-visible subcutaneous micronodules were observed with a spontaneous resolution in six patients at week 96.

Conclusion: The benefit of PLA for the correction of the facial lipoatrophy in HIV-infected patients was clearly demonstrated, with an evident aesthetic and quality of life improvement. The efficacy, safety profile, and the simplicity of the injection schedule of PLA make this filling material a potentially attractive treatment.

Introduction

The introduction of highly active antiretroviral therapy (HAART) has profoundly changed the clinical prognosis of HIV-infected patients with a drastic reduction in associated mortality and morbidity. However, this outcome has been tempered by the recognition that an HIV-associated lipodystrophy syndrome is a significant complication associated with antiretroviral therapy. Several features of this lipodystrophy syndrome, such as lipoatrophy, are now well recognized. Facial lipoatrophy is undoubtedly the most frequent and distressing sign for patients receiving anti-HIV therapy with good virologic and immunologic status. Treatment-related lipoatrophy has been cited as a reason to delay the initiation of antiretroviral therapy and has been reported to contribute to a reduction in patient adherence to therapy.

Despite some progress in the understanding of this syndrome in which both nucleoside analogues and protease inhibitors appear to be major causative factors, there remains no proven strategy to effectively manage many of the attendant complications, including potentially disfiguring facial lipoatrophy. As a result, symptomatic strategies used to compensate for facial fat loss warrant clinical evaluation. Poly-L-lactic acid (PLA) is a biocompatible and immunologically inert synthetic polymer which belongs to the class of resorbable biomaterials.

This product has been safely used in a variety of orthopedic and maxillofacial applications since the mid-1990s and was approved in Europe in 1999 for the cosmetic correction of scars and wrinkles. The goal of this study was to evaluate the efficacy and safety of facial injections of PLA in HIV-infected patients with severe facial lipoatrophy.

Methods

This study was an open-label, single-arm, pilot study to evaluate the efficacy, safety, and the durability of PLA in the correction of facial lipoatrophy in HIV-infected patients over 96 weeks.

Study population

HIV-infected patients older than 18 years were eligible for inclusion if they had severe lipoatrophy defined as a thickness of fat tissue in the nasogenian area less than 2 mm as measured by ultrasonography. Patients had to have received antiretroviral therapy for more than 3 years, with stable plasma HIV-1 RNA levels < 5000 copies/ml in the last 3 months. Patients with any facial skin disease, facial implant in the last 6 months, or current interferon or cytokine therapy were not eligible. The study protocol was approved by the institutional review board of the Pitié-Salpêtrière Hospital. All patients provided written, informed consent.

Study treatment

Patients received poly-L-lactic acid (New-Fill, Biotech industries SA, Luxembourg) for 6 weeks, administered as a set of injections given every 2 weeks: at day 0 and at weeks 2, 4, and 6. At each clinic visit, patients received several injections into and around the deep dermis of the atrophied area in each cheek. Before injection, the suspension was reconstituted from sterile dry powder of 0.15 g of poly-L-lactic acid (1 vial of New-Fill) by the addition of 3-4 ml of water for Injections BP. As PLA injections might be painful, 1 cc of lidocaine was injected locally. The injected quantity of PLA depended of the severity of skin depression. At each visit, a maximum of 4 ml of PLA was injected into each cheek. At

the end of each set, the cheeks were thoroughly massaged to ensure better distribution of the injected solution. Throughout the study, all injections were performed by the same trained dermatologist.

Follow-up

Patients were evaluated by clinical examination, facial ultrasonography, and photographs at screening and at weeks 6, 24, 48, 72, and 96. Patient quality of life (QOL) was measured by visual analogue scale and collected at screening, week 12, 24, 48, 72 and 96. Following the ultrasound evaluation performed at week 6, a fifth set of injections of PLA could be performed if the facial total cutaneous thickness (TCT) was < 8 mm. Injections were discontinued if any severe or moderate reaction developed following injection.

Radiologic assessment

Ultrasonographic and colour Doppler evaluation to quantify the dermal, epidermal and fat thickness were performed by the same trained radiologist using a digital multi-frequencies 7.5-13 MHz transducer and a 7 MHz color Doppler (Logiq 7, General Electric, West Milwaukee, Wisconsin, USA). All the ultrasonographic examinations were recorded. Measurements were performed in the nasogenian area located below the malar bone, ahead of the masseter. The temporal region was limited by the zygomatic apophysis and the orbital arcade. The change in TCT between the skin and the epidermis was measured by the study radiologist, and local reactions at the injection site were noted.

Criteria for evaluation

The primary end point was the proportion of responders, defined as patients with a TCT > 10 mm, measured at the nasogenian fold, at week 24. In the absence of standard values for facial thickness measured by ultrasonography, this value of 10 mm was chosen arbitrarily as a median range in few non-HIV infected individuals. For each patient, the TCT measurements were summarized by the mean of two values, one minimal and one maximal for each cheek.

Secondary end points included the change in TCT and QOL from baseline at weeks 6, 12, 24, 48, 72, and 96; the proportion of responders at weeks 6, 24, 48, 72, and 96; and the patient tolerability. Median and ranges were reported for TCT and QOL changes over time.

Sample size

The sample size was chosen to allow a 90% power to determine the percentage of responders with a precision of 20%, assuming a response rate of 80% with a type 1 error of 0.05. Therefore, 50 patients should be enrolled.

Results

Fifty patients were enrolled between June 2000 and February 2001 and included in the study analysis. Baseline characteristics listed below in Table 1. All patients had severe facial lipoatrophy with a median facial fat thickness equal to zero (0.0-2.1 mm) and a median TCT of 2.9 mm (range, 2.0-5.5 mm). They had been on antiretroviral therapy for a median duration of 8.6 years. In addition to facial atrophy, most patients had evidence of abnormal fat redistribution elsewhere in the body. All 50 patients received PLA injections. Overall, 26 patients had received four sets of injections and 20 patients had received five sets of injections. Four patients with sufficient dermal thickness correction had received three sets.

Table 1. Baseline Characteristics

Male sex; 98%
Age: 46
AIDS: 46%
HIV RNA: 2.3 log
HIV RNA <5000 c/ml: 92%
CD4 cells: 396
Duration of ART: 8.6 yrs
Number of ART regimens: 8
Number of drugs in current regimen: 3
Sunken cheek: 100%
Leg fat loss: 86%
Arm fat loss: 44%
Dorsocervical fat pad: 0
Breast enlargement: 20%
Waist enlargement: 30%
Adipose tissue thickness on the both cheeks: 0.0 mm (0.0-2.1)
Total cutaneous tissue thickness on the both cheeks: 2.9 mm (2-5.5)
Visual analogue scale for well being: 6.4

Ultrasound evaluations were performed in all patients at each time point except for two patients at week 6, one patient at week 24, one at week 48 and two patients at week 72. At week 96, three patients were not evaluated and five patients have not reached the 96-week follow-up.

The proportion of patients with a TCT of at least 10 mm was 19% at week 6 (95% CI, 9-33 mm), 41% at week 24 (95% CI, 27-56 mm) (the study's primary end point), 61% at week 48 (95% CI, 46-75 mm), 52% at week 72 (95% CI, 37-67 mm) and 43% at week 96 (95% CI, 28-59 mm). The median increases in TCT from baseline were significant ($P < 0.001$) at all these time points, with increases of +5.1 mm (range, 2.2-8.6 mm) at week 6, +6.4 mm (range, 3.1-9.1 mm) at week 24, +7.2 mm (range, 4.2-9.6 mm) at week 48, +7.2 mm (range, 3.5-9.6 mm) at week 72 and +6.8 mm (range, 3.9-10.1 mm) at week 96.

QOL were obtained from 44 patients and progressively increased between baseline and week 48 with a median change from baseline of +0.3 (range, -2.9 to +10.0) at week 12 ($P = 0.165$), +0.8 (range, -3.9 to +10.0) at week 24 ($P = 0.015$), +0.8 (-2.9 to +10.0) at week 48 ($P = 0.021$), +0.4 (-3.3 to +10.0) at week 72 ($P = 0.209$) and +0.4 (-3.9 to +10.0) at week 96 ($P = 0.120$).

No serious adverse events were observed during the study, and no patient interrupted PLA injections due to side effects. Minimal and localized oedema at the injection site was seen in most patients, which spontaneously resolved within 24-48 h. Fifteen patients developed minimal ecchymosis following injection, which also resolved spontaneously within 2-3 days. In 22 (44%) patients, palpable but non-visible subcutaneous micronodules were observed with a spontaneous resolution in six patients at week 96.

Over the course of the study, viral load and CD4 cell count remained stable with 90% of patients maintaining their plasma HIV RNA levels < 5000 copies/ml through 96 weeks. In three patients, the antiretroviral regimen was temporarily discontinued and resumed without

modification. In 13 patients, stavudine was switched to other nucleoside reverse transcriptase inhibitors with a median delay of 9.5 months (range, 4.7-23 months); from initiation of injections (in three patients because of lipoatrophy, in four because of inefficacy, in five because of other toxicities, and in one patients for personal reasons) while two patients started stavudine. No AIDS-defining event was recorded in the study.

Discussion by authors

The results of this open-label, noncomparative pilot study showed that the use of facial implants with polylactic acid (New-Fill) can produce significant improvement in the restoration of facial fat thickness and appearance in treatment-experienced HIV-infected patients with severe facial fat loss. Although there were no measurements of patients' facial thickness prior to initiation of antiretroviral therapy, one might reasonably assume that patients with a median 0 mm of facial fat thickness had very severe fat loss after initiating antiretroviral therapy. Our data demonstrate clearly the correction of facial lipoatrophy with a significant increase in dermal thickness at week 6, which progressively improved until week 48 (threefold increase from baseline) and was sustained at 72 and 96 weeks, for which the results were similar to those of 24 weeks.

We consider these results to be clinically relevant. Aesthetic improvement was clearly observed, accompanied by a significant increase in patient quality of life scores between baseline and week 48.

The progressive increase of dermal thickness surrounding PLA injection site (up to week 48) is consistent with the mechanism of action of such bioactive resorbable material; that is, a local reaction is induced, followed by a progressive increase in collagen deposition during which the bioactive material is degraded and safely undergoes resorption.

During the course of the study, some patients stopped taking stavudine. Taking into account the slow reversibility of the subcutaneous fat loss after replacing stavudine or zidovudine as demonstrated by A. Carr, we think that this is unlikely to have affected the results of the study. In addition, no increase in the subcutaneous fat tissue was observed in any patient (data not shown) making unlikely the role of a change in the antiretroviral therapy in the observed results.

In the context of this severe morphologic syndrome and with psychological consequences for most affected patients, use of a placebo or untreated control group was not acceptable. Therefore, a pilot study with quantitative measurements of facial thickness with long-term follow-up was chosen. To maximize homogeneity and reproducibility of the quantitative measurements (using ultrasonography), only one digital multifrequency transducer with the same operator was used for all measurements throughout the study period.

Despite biodegradable materials being widely available for use in corrective and cosmetic procedures, there are no substantial data based on quantitative measurement available in the literature to evaluate similar interventions in the treatment of HIV-associated lipoatrophy. Two previous, pilot studies with a follow up of 24 weeks have suggested the efficacy of PLA to improve facial lipoatrophy. Other therapeutic approaches to correct fat loss in HIV-associated lipoatrophy have also been reported in different studies. The use of hyaluronic acid injections has been associated with a rapid decline in the degree of correction and loss of aesthetic improvement following administration. Studies of autologous fat transplantation

injections to correct deep subcutaneous tissue losses have shown absorption of the transplanted fat with a graft survival rate of 40-60% at 1 year after treatment. The durability of autologous fat transplantation depends on several factors, including the harvesting and grafting technique, quality of transplanted tissue, and vascularity of the recipient site, and the results appear to be highly dependent on the surgeon's level of training. In addition, this approach requires the use of general anaesthesia and prolonged hospitalization. In contrast, our findings suggest that PLA implants have little impact on the daily activities of treated patients since the procedure can be performed on an outpatient basis without any need for recovery time. Furthermore, the simplicity of the procedure should lead to the rapid training of dermatologists or cosmetic surgeons.

Despite the total injected dose of PLA acid in this study being higher than that used in the treatment of wrinkles and scars, no serious adverse event was observed during the study. The most frequent event was palpable persistent, non-visible subcutaneous micronodules which did not bother the patients.

In the absence of an aetiological treatment (i.e., treating the underlying cause) and since other treatment approaches, such as modification of the patient's antiretroviral regimen or use of insulin-sensitizing agents or growth hormone have failed to show clinically significant changes in facial lipoatrophy, the use of biodegradable materials to improve physical appearance represents significant progress in therapeutic management of HIV-related lipoatrophy. Furthermore this data provided a basis for health insurances to consider the reimbursement of such therapy in patients with severe lipoatrophy.

In summary, this study demonstrated the benefit of PLA injections to correct facial lipoatrophy in HIV-infected patients-an important finding due to the absence of any currently available strategy to manage this complication. The efficacy, safety profile, and the simplicity of the injection schedule associated with the use of PLA make this filling material a potentially attractive treatment that may help alleviate the psychological and social consequences of facial lipoatrophy in affected HIV-infected patients.