



Treatment of facial lipoatrophy with injections of polyactic acid in HIV-infected patients: results from a cohort of 94 patients

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Abstract

Background Polyactic acid (PLA), has been used for the treatment of facial lipoatrophy due to HAART for several years. However, the long term efficacy of this treatment is not well established.

Method : Patients with a sustained count of HIV infection (CD4 count > 200/mm³ and plasma viral load < 20,000 copies/ml for at least 3 months) were injected with PLA in the derm of both cheeks. Injections of PLA mixed with xylocaine were done every 15 days. Efficacy of the treatment was assessed using a standardized quality of life questionnaire (QoL), an analogic visual scale satisfaction index (AVSSI) (graded 1/10 to 10/10) and tridimensional photographs of the face for 50 patients. After superimposition, these photographs were analyzed by a software calculating the maximal thickness increase at the site of injections. The safety of the treatment was assessed at each visit.

Results : Ninety four patients (88 males, 6 females) received PLA injections. Mean age was 43 years (30-64). CDC clinical stages were A in 90 % of cases, B in 6 % and C in 4 %. All patients, but 4, were under HAART (DTT containing regimen in 40 % patients). Median CD4 count was 500/mm³. Plasma HIV RNA was below 200 copies/ml in 71 % of cases. Median follow-up was 12 months. Median number of injections per patient was 5 and median injected volume was 2.5 ml per cheek. Median AVSSI increased from 3.4 (baseline) to 6.8 after the completion of the procedure and was maintained, 7.5 months later, at 7. No significant variation of QoL was noted. Median dermal thickness increase in both cheeks was 2 mm after 2 injections, and 2.3 when measured 7 months after the last injection. Seven patients experienced a malaise after the first injection. Grade 1 or 2 pain was noted in 80 % of patients. Non inflammatory small nodules in the injected area were detected in 12 patients (11.7 %). Minor bleeding was noted in 4 patients. In one patient the treatment was stopped after the first injection because of an anaphylactic reaction, possibly related to the injection. No specific treatment was required.

Conclusion : After a mean follow-up of 12 months in 94 patients, intradermal injections of PLA appeared to be safe with a long lasting increase in AVSSI.

Introduction

Changes in fat distribution has emerged as a frequent complication of HAART. Today, treatment of facial atrophy consists in either plastic surgery or filling with synthetic compounds. The incoercity of polyactic acid (Newfill®), the absence of severe reported side-effects, its biocompatibility and biodegradability, makes this filling component an attractive option for the treatment of HIV-associated lipoatrophy of the face. The main objective of this work was to evaluate the safety and the long-term efficacy of intradermal injections of polyactic acid (Newfill®), in the treatment of facial lipoatrophy in HIV-infected patients.

Patients and Methods

Inclusion criteria

- HIV-infected patients with facial lipoatrophy as judged by the patient himself and by the physician
- Age 18 to 65 years
- CD4 > 200/mm³ and plasma HIV viral load < 20,000 copies/ml for at least 3 months
- Stable antiretroviral therapy for at least 3 months

Exclusion criteria

- Quick's time < 70 s, Kaolin activated clotting time > 1.5 fold normal range
- Platelet count < 80,000/mm³, Ivy bleeding time > 4 minutes and 30 seconds
- Concomitant therapy with non steroid anti-inflammatory or acetyl salicylic acid
- Skin abnormalities of the face (severe acne, Kaposi sarcoma, herpetic infection...)
- Pregnancy or breast feeding
- Acute opportunistic infection, a major or unstable intercurrent illness

Injection

All patients had a screening visit with the dermatologist practicing the injections. All details about the treatment procedure were provided to the patients. All patients entering the treatment procedure were offered a psychological support by a psychologist, during all the therapy and the follow-up.

Both cheeks were injected at each visit, every 15 days, by the same dermatologist. Polyactic acid (Newfill®) was mixed with adrenaline-free lidocaine, using 18 G x 1/2 needles. Proportions of the mixture were ¾ polyactic acid and ¼ lidocaine. The mixture was then divided in 4 separated 1 ml syringes and injected in the median derm of the cheek, using 26 G x ½ needles, after cleaning the derm with povidone-iodine. Patients were lying during all the procedure. At each visit, a total quantity of 3 ml (0.15 g) of polyactic acid per cheek was injected in multiple sites. Then ice was applied on the treated cheek for ten minutes. After injection, a prolonged massage of the face was done to avoid the development of dermal nodules at the site of injection.

Efficacy of the treatment was assessed throughout the treatment procedure, at the end of the treatment and during follow-up:

The primary efficacy endpoint of the study was the proportion of patients with an increased AVSSI (Analogic Visual Scale Satisfaction Index) score as compared to baseline.

The question patients had to answer to was : "What is your satisfaction about the aspect of your face, in relation with the lipoatrophy". Using the scale, patients satisfaction was determined by a number, comprised between 0 (total dissatisfaction) to 10 (total satisfaction).

Secondary endpoints were:

- A gain in dermal thickness of at least 2 mm assessed by tridimensional photographs. These photographs were analyzed by a digital surface photometry software (3DMD LLC®, London, England) calculating the thickness of the derm at the site of injection.
- An increase of Mental and Physical Component Summary scores. A standardized questionnaire evaluating quality of life (QoL) (MOS SF-36) was filled by the patient. The mental and physical component summary scores (MCS and PCS respectively) (minimum 0, maximum 100) of the MOS SF-36 were analysed and compared to baseline values.
- The correct ordering of digital photographs. Photographs were blindly ordered by two independent observers as "before and after treatment".

Tolerance of the treatment was assessed, at each visit, through a thorough questioning and clinical examination. Severity of adverse-events was graded according to the ANRS grading scale.

Results

Ninety-four patients received at least one injection of polyactic acid.

Table 1: Demographics and baseline characteristics of the patients

| Item | N (%) |
|--------------------------------------|--------------|
| Male (n) | 88 (94 %) |
| Age (years), median (min ; max) | 44 (30 ; 64) |
| HIV risk factors | |
| Homosexual | 54 (57 %) |
| Heterosexual | 18 (19 %) |
| Intravenous drug user | 8 (9 %) |
| Unknown | 14 (15 %) |
| Ethnicity | |
| Caucasian | 87 (93 %) |
| Black | 6 (6 %) |
| Asiatic | 1 (1 %) |
| CDC clinical stage | |
| A | 85 (90 %) |
| B | 6 (6 %) |
| C | 3 (3 %) |
| Median CD4 (cells/100) (min ; max) | 500 (98;650) |
| Plasma HIV RNA level < 200 copies/ml | 67 (71 %) |
| Treatment regimen | |
| HAART with NRTI only | 5 (5 %) |
| HAART with PI | 51 (54 %) |
| HAART with NNRTI | 38 (40 %) |
| No treatment | 4 (4 %) |
| DTT-containing regimen | 38 (42 %) |
| Severity of lipoatrophy*, n (%) | |
| Light | 34 (36%) |
| Moderate | 40 (43%) |
| Severe | 20 (21%) |

Legend: NRTI : nucleoside reverse transcriptase inhibitor
NNRTI : non nucleoside reverse transcriptase inhibitor
PI : protease inhibitor. *: as classified by the clinician (adapted from James et al Dermatol Surg 2002)

Polyactic acid injections

- Median number of injections per patient was 5 (1; 7)
- Median injected volume of polyactic acid mixed with xylocaine per cheek was 2.46 ml (1.00; 3.55) and 2.40 ml (1.00, 3.76) for right and left cheek respectively.
- Injections in temples were also required in 39 patients (41%).

Table 2: Adverse events

| Adverse events | N (percent) |
|--|-------------|
| Post injection oedema | 94 (100%) |
| Pain during injection | 72 (77%) |
| grade 1* | 46 (49%) |
| grade 2** | 25 (27%) |
| grade 3 | 1 (1%) |
| grade 4 | 0 |
| Post injection non inflammatory nodules | 12 (13%) |
| Vagal hypertonia during injection | 7 (7.5%) |
| Ecchymosis or bleeding at the injection site | 4 (4%) |
| Anaphylactic reaction | 1 (1%) |
| Central facial palsy | 1 (1%) |
| Post injection inflammatory nodules | 1 (1%) |

*Grade 1: slight pain requiring no treatment

**Grade 2: Moderate pain which could require level 1 analgesics

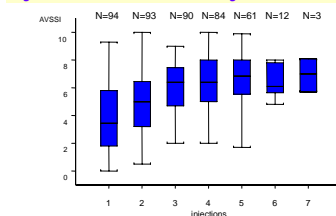
Table 3: Primary efficacy endpoint: AVSSI score

| Evaluation criteria | Baseline | End of treatment | Last follow-up visit |
|-----------------------------|----------------------------|------------------|------------------------------------|
| | (n = 94) | (n = 93) | (n = 87) |
| | (After 5 ± 0.9 injections) | | (7.5 ± 4.8 months after treatment) |
| • AVSSI (0-10) | 3.4 | 6.8 | 7 |
| median (min;max) | (0 ; 9.3) | (1.7 ; 9.9)* | (1.8 ; 9.5)* |
| • Success rate ^b | - | 87% (82/94) | 73.5% (69/94) |

*AVSSI : analogic visual satisfaction score index. **: success rate defined as percentage of patients whose AVSSI score were greater than baseline values or (last follow-up patients and missing data were considered as failure);

***: p<.0001 versus baseline;

Figure 1: median AVSSI score during treatment



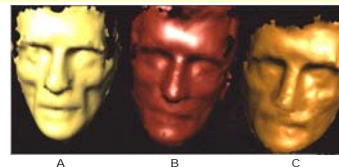
Box plots indicate the 1st and 3rd quartile and also the minimal and maximal values of AVSSI at each injection.

Table 4: secondary efficacy endpoints

| Evaluation criteria | Baseline | End of treatment | Last follow-up visit | |
|---|--------------------|--------------------|----------------------|----------------------|
| | (n = 89) | (n = 90) | (n = 87) | (n = 87) |
| Quality of life (SF-36) scores | | | | |
| median (min-max): | | | | |
| - Mental component summary score | 42.9 (17.9 ; 65.6) | 44.8 (17.5 ; 63.5) | 41.6 (17.5 ; 63.5) | 41.6 (17.5 ; 63.5) |
| - Physical component summary score | 53.7 (28.8 ; 65.6) | 52.8 (28.9 ; 63.5) | 51.9 (28.9 ; 64.5) | 51.9 (28.9 ; 64.5) |
| | | Observer A | Observer B | Observer A |
| | | (n = 83) | (n = 83) | (n = 72) |
| Blinded digital photographs ordering | | | | |
| Success rate ^a | 50% (53/94) | 59% (55/94) | 52% (49/94) | 59% (55/94) |
| (Kappa) | (0.26) | (0.26) | (0.38) | (0.38) |
| | | After 2 injections | | Last follow-up visit |
| | | Right cheek | Left cheek | Right cheek |
| | | (n = 49) | (n = 49) | (n = 36) |
| 3-D photographs of the face (gain in dermal thickness (mm)) | | | | |
| median | 1.9 | 1.9 | 2.4 | 2.2 |
| (min-max) | (0.5 ; 4.7)* | (0.4 ; 5.5)* | (0.7 ; 6.1)* | (0.9 ; 5.0)* |
| Success rate ^a | 44% (22/50) | 46% (23/50) | 44% (22/50) | 48% (24/50) |

*: success rate defined as percentage of patients whose Digital Photographs ordering was correct or whose increase in dermal thickness was greater or equal to 2 mm (last follow-up patients and missing data were considered as failure); **: increase in thickness is compared with the photography taken before the first injection; ***: p<.0001 versus baseline

Figure 2: 3D Photographs of a patient before treatment (A), 2 months (B) and 6 months (C) after treatment



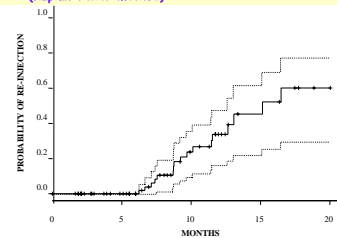
Discussion

If success is defined as an increase of AVSSI score as compared to baseline, then success rate was 87% at the end of treatment and 73.5% at the last follow-up visit. These good results should be, however, counterbalanced by the analysis of secondary endpoints.

Indeed measurement of quality of life showed no change throughout the treatment. Results of the blinded re-ordering of Digital Photographs showed at best a success rate of 59%, but with low correlation factor between both observers (Kappa score < 0.3). Success rate with 3D photographs was only 48%.

Finally, the probability of reinjection of polyactic acid estimated by Kaplan-Meier method was 45.3% fifteen months after the end of the treatment (figure 3).

Figure 3: Estimated probability of PLA reinjection during follow-up (Kaplan-Meier method)



Conclusions

- Treatment of HIV-associated lipoatrophy of the face with intradermal injections of polyactic acid (Newfill®) is a safe procedure.
- Eighty-seven percent of patients increased AVSSI score at the end of treatment.
- The real benefit of this procedure is however difficult to assess and its beneficial effect decrease with time.

