Infectious Complications of Bio-Alcamid Filler Used for HIV-Related Facial Lipoatrophy

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Background. Human immunodeficiency virus (HIV)–related facial lipoatrophy is a devastating adverse effect of antiretroviral therapy. At this time, the most viable treatment option is cosmetic surgery with synthetic fillers. Bio-Alcamid has many advantages over other fillers, and has become widely used. The objective of this study was to determine the incidence rate of infectious complications associated with Bio-Alcamid facial filler in patients with HIV-related facial lipoatrophy (FLA).

Methods. This retrospective study identified patients who had received treatment with Bio-Alcamid, and reviewed their long-term outcomes.

Results. Two hundred sixty-seven patients with Bio-Alcamid were reviewed. Infectious complications were documented in 56 (19%) patients. The incidence rate of infection was 0.07 per patient-year of follow-up. Among patients with infections, the median time from first Bio-Alcamid treatment to infection was 32 months (interquartile range, 21–42). We did not find an association between the development of infection and the level of immune suppression by HIV. Surgical drainage in addition to antibiotics was required for the majority of patients. Potential risk factors for infection include severity of FLA and a preceding history of facial manipulation, including Bio-Alcamid touch-up treatments, cosmetic surgery, facial trauma, and dental work.

Conclusions. Bio-Alcamid treatment of HIV-related FLA was associated with a high rate of infectious complications, often presenting years after treatment. Antibiotic prophylaxis should be considered in patients with Bio-Alcamid prior to dental work or facial manipulation.

INTRODUCTION

Lipodystrophy syndrome, first described in 1998 [1], is a particularly distressing adverse effect attributed to combination antiretroviral therapy (cART). The prevalence varies between studies but is estimated to impact more than half of cART-treated patients [2]. Facial lipoatrophy (FLA) is an especially devastating manifestation characterized by depletion of buccal and temporal fat. The presence of FLA can result in stigmatization, depression, forced disclosure of human immunodeficiency virus (HIV) serostatus, and reduced adherence or even discontinuation of cART [3, 4].

Pharmacological management of FLA is limited and inadequate. Antiretroviral switch therapy studies from a thymidine analogue have shown minor limb fat gains with prolonged time but has minimal to no effect on the face [5–7]. Other strategies for the management of lipodystrophy, such as recombinant human growth hormone–releasing hormone and thiazolidinediones, have not demonstrated significant improvement in FLA [8–10]. Consequently, surgical correction of facial lipoatrophy has become the mainstay of treatment. Surgical approaches have included autologous fat transplantation, and implantation of facial fillers that are either nonpermanent (hyaluronic acid, poly-L-lactic acid [PLA], hydroxyapatites) or permanent (silicon oil, polymethylmethacrylate [PMMA], polyacrylamide hydrogel [PAAG], and polyalkylimide) [11].

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Polyalkylimide (Bio-Alcamid) is a nonreabsorbable polymer derived from acrylic acid. Once injected, it induces host tissue to form a fibrous capsule around the deposit, which can theoretically be removed in its entirety years after implantation [12]. Another advantage is that it can be injected in large volumes in 1 session with minimal need for subsequent injections. Bio-Alcamid had been used extensively in Europe and Mexico and was approved for use in Canada in 2002 for use in HIV-associated facial lipoatrophy. The benefits and safety of Bio-Alcamid were demonstrated in a multicentre (n = 2000) European study of healthy patients treated for a variety of aesthetic defects with excellent cosmetic results and no significant adverse events during a short period of follow-up [13]. The benefits of Bio-Alcamid have subsequently been shown in several other studies, which have included patients with HIV-related FLA. [14–19]. In addition to cosmetic satisfaction, use of this product has also been shown to increase quality of life in patients with HIV-related FLA [20, 21]. Adverse effects associated with Bio-Alcamid have been presented in a small number of reports (including both HIV and non-HIV patients), which have included migration, hardening, inflammatory reactions, granuloma formation, and infections [22–26]. Although an initial favorable experience with Bio-Alcamid was reported by 1 group [24], a subsequent publication of the extended follow-up of their patients noting several complications led them to discontinue its use [25]. In a retrospective evaluation conducted by the Dutch Society of Cosmetic Medicine, 40 physicians were surveyed regarding their experiences with Bio-Alcamid [26]. Of a total of 4738 treatments, 154 complications were reported. The most common complication was inflammation, and others included hardening and migration of the product. This study found a higher incidence of inflammation among the HIV patients; however, it could not be determined whether this was significant. These reports show similar clinical presentation and progression of infection in both HIV and non-HIV patients; however, due to limited data, it is difficult to assess for any significant differences.

In Toronto, Canada, we noticed a series of patients presenting with infections of the implant many years after Bio-Alcamid treatments and sought to investigate this further. The objective of this study was to determine the incidence and nature of infectious complications associated with Bio-Alcamid, and outcomes of therapy.

METHODS

Study Design

This study is a retrospective evaluation of patients who were treated with Bio-Alcamid for HIV-related facial lipoatrophy. Sources of patient data were plastic surgery and HIV clinics and emergency room visits or hospitalizations in the Toronto area. Four plastic surgery clinics in Toronto provide Bio-Alcamid treatments, 1 of which did not participate in this study due to administrative constraints. HIV clinics were identified by the referring physician's name in the surgical charts, and all HIV clinics that were approached participated in the study. Patients treated with Bio-Alcamid between 2004 and 2010 were identified, and a review was performed for long-term outcomes. Ethics approval was obtained from the University Health Network ethics review board. Individual patient consent was not obtained as this retrospective study involved minimal risk to the patient and did not adversely affect their rights and welfare, and patient identifiers were not collected.

Definitions

The primary outcome of this study is the incidence of infectious complications of Bio-Alcamid used for HIV-associated FLA. Infections were categorized as: definite (if there was a typical clinical presentation [swelling, erythema, pain, purulence, fever] and microbiological confirmation from aspirated material) or probable (those with typical clinical presentations but cultures were negative, not performed, or results not documented). Primary infections were defined as the initial presentation or infection in a different location from a previous infection. Recurrent infections were defined as repeat presentation with symptoms of infection in the same location after resolution of previous infection and cessation of antibiotic therapy. These could not be differentiated into relapse versus reinfection.

Statistical Analysis

The incidence of primary infections was calculated as the number of infections per patient-year of follow-up. Descriptive statistics were used to compare demographic and clinical characteristics of patients who developed infections to those who did not. Percentages and frequencies were used to summarize categorical variables, and medians and interquartile ranges were used to summarize continuous variables. Categorical and continuous variables were compared between groups with and without infections using χ^2 tests and Wilcoxon rank-sum tests, respectively. The Kaplan-Meier method was used to describe the probability of development of primary infection by the duration of time since initial procedure. Univariate and multivariable logistic regression models were performed to analyze factors associated with infection.

RESULTS

Patient Characteristics and Surgical Data

We identified a total of 292 patients treated with Bio-Alcamid for HIV-associated facial lipoatrophy in Toronto between January 2004 and March 2010. Twenty-five of them were excluded from the study as they were from out of country and had no further documented follow-up after their first

Table 1. Patient Characteristics at Time of First Bio-Alcamid Treatment[a]

Characteristic	N[b]	Patients Who Developed An Infection (N = 56) Median (IQR)/Count (%)	N[b]	Patients Without Infection (N = 211) Median (IQR)/Count (%)	*P* value
Demographics					
Age	53	48 (42–54)	205	49 (44–54)	.35
Male	55	53 (96%)	203	198 (98%)	.64
Clinical					
Years of HIV	36	16 (12–18)	101	15 (11–17)	.35
Viral load <50 copies/mL	37	34 (92%)	101	79 (78%)	.08
$CD4^+$ count (cells/mm^3)	35	500 (310–650)	101	470 (350–640)	.87
On antiretrovirals	56	56 (100%)	211	208 (99%)	>.99
Bio-Alcamid treatment					
Date of first treatment	*55*	Sep 05 (Apr 05–Jun 06)	211	May 06 (Sep 05–Mar 07)	<.001
Months of follow-up	55	63 (29–72)	206	21 (6–61)	<.001
Number of injections	44	4 (2–4)	198	4 (2–4)	.90
Injection volume (mL)	47	15 (10–17)	202	10 (9–15)	.01
Antibiotic prophylaxis	53	53 (100%)	210	210 (100%)	…
Touchups	50	41 (82%)	201	109 (54%)	.0003

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

[a] Categorical and continuous variables were compared using χ^2 tests and Wilcoxon rank-sum tests, respectively.

[b] N indicates the number of patients for whom the information was available.

treatment. Among the remaining 267 patients, the median follow-up was 30 months (interquartile range [IQR], 8–65). Demographic data and details of the Bio-Alcamid treatment are presented in Table 1 by whether or not the patient experienced an infectious outcome.

Infectious Complications

Of the 267 patients treated with Bio-Alcamid, 56 (19%) were documented to have developed infections associated with the implant. Of these 56 patients with primary infections, 17 patients had 1 or more recurrences or relapses at the same site, and 1 patient developed a new infection on the opposite side of his face. Thus, overall, there were 57 primary infections (n = 16 definite) and 21 recurrent infections (n = 5 definite), for a total of 78 infections. The incidence rate (95% confidence interval [CI]) for total infections was 0.10 (.08, .13) per patient-year of follow-up. The rate of primary infections was 0.07 (.06, .09), comprising a definite rate of 0.02 (.01, .03) and a probable rate of 0.05 (.04, .07) per patient-year of follow-up.

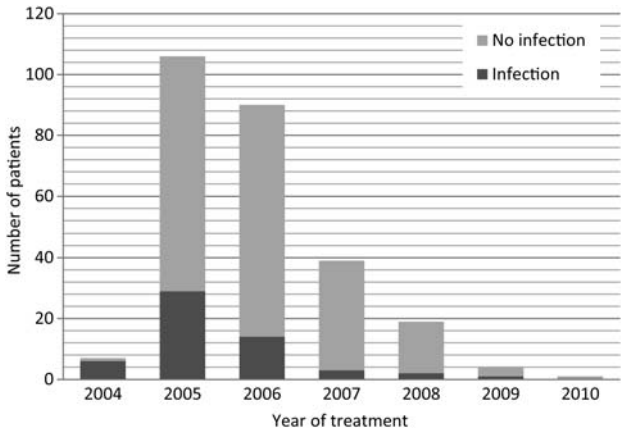

Figure 1. Year of first Bio-Alcamid treatment showing numbers of patients who developed infection.

Figure 1 shows the numbers of patients who developed infections by the year of first Bio-Alcamid treatment. A higher proportion of patients treated in 2004 or 2005 had infections (31%) than patients treated in 2006 or later (7.5%; *P* = .0007). Among patients who experienced an infection, the median time to presentation of primary infection was 32 months (IQR 21–42) from the first Bio-Alcamid treatment. A Kaplan-Meier curve of time to first primary infection is shown in Figure 2. The probability of developing an infection by 38 months after the first Bio-Alcamid treatment was 25%.

Thirty-six patients with infections, (n = 13 definite, n = 23 probable) had detailed data available for analysis, which is summarized in Table 2. The most commonly isolated organisms were methicillin-sensitive *Staphylococcus aureus* and *Streptococcus* species. Other organisms identified included methicillin-resistant *S. aureus*, *Enterobacter* species, and *Propionibacterium* species. Of the patients with recurrent infection, 2 patients had 2 recurrences and 1 had 3 recurrences.

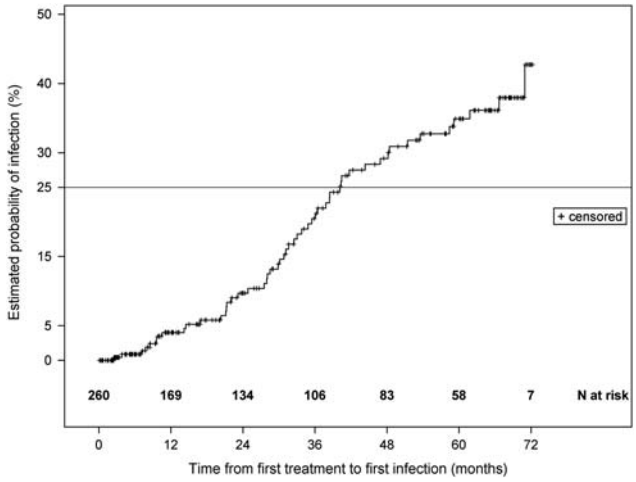

Figure 2. Kaplan-Meier curve of time to first infectious complication.

Table 2. Characteristics of Infections[a]

Characteristic	Median (IQR) or N (%)
Time from first treatment to first infection (months)	37.5 (28.0–48.0)
Organism	
Staphylococcus aureus	8 (22%)
Streptococcus species	2 (6%)
Commensal flora	2 (6%)
Other	3 (8%)
Culture negative	5 (14%)
Not documented	16 (44%)
Surgical intervention[b]	
None	7 (19%)
Debridement	3 (8%)
Aspiration	9 (25%)
Incision and drainage	17 (47%)
Partial removal	15 (42%)
Complete removal	4 (11%)
Duration of antibiotics (weeks)	3.0 (1.5–5.0)
Relevant circumstances[c]	
Dental work	11 (31%)
Cosmetic surgery	3 (8%)
Other	6 (7%)
None	18 (50%)
Recurrence/relapse[d]	17 (47%)
Time from first infection to first recurrence (months)	5.5 (2.0–13.0)
$CD4^+$ count at time of infection (cells/mm^3)	500 (346–760)

Abbreviation: IQR, interquartile range.

[a] Data are for 36 out of 56 patients with infections.

[b] Some patients received more than 1 intervention.

[c] Within 1 month prior to infection. Some patients had more than 1 relevant circumstance.

[d] Patients with at least 1 recurrence/relapse.

Three patients grew the same organism on recurrent infection; there were no patients for whom a recurrent infection grew a different organism from the preceding occurrence(s). Four patients were undergoing treatment for infection at the time of study completion. Prior to development of the infection, 17 patients had facial manipulation within the vicinity of the Bio-Alcamid implant within the previous month. The most common circumstance prior to infection was dental work. Results of univariate and multivariable logistic regression models of factors associated with infection are shown in Table 3. Patients were approximately 2.5 times more likely to have an infection if they ever had a touch-up treatment. After adjusting for age, those treated in later years were less likely to develop infection compared to those treated in 2004 or 2005.

DISCUSSION

The use of fillers in cosmetic surgery is extensive, with increasing numbers of treatments performed each year. Legislation and approval of cosmetic fillers may not be accompanied by long-term follow-up data on their risks and benefits, and may be lacking for certain patient groups. Cosmetic surgery, particularly facial fillers, is the only viable option at this time for the treatment of HIV-related facial lipoatrophy. However, in this study we found an unacceptably high rate of infectious complications with the use of Bio-Alcamid for HIV-related FLA.

Other techniques have been used in HIV-related FLA, none of which have been found to be ideal. Autologous fat transfer is performed by harvesting fatty tissue from the abdomen or dorsocervical fat regions and placing it in the area of facial atrophy. Transferred fat often continues to atrophy, and benefits last for only 6–12 months [11]. PLA and hyaluronic acid fillers involve multiple injections over a period of weeks and the material gradually degrades over months, necessitating retreatment [27–31]. A major adverse cosmetic event reported has been the development of subcutaneous nodules [27, 28]. PMMA fillers have the advantage of more permanent effects; however, granulomas have been consistently reported [32]. The permanent filler PAAG has shown a significant long-lasting benefit; however, this product requires multiple small injections over a long period of time, and infectious complications have been reported [33–35].

Bio-Alcamid appeared to be an ideal choice as it is permanent, and enables a larger injection volume and significantly lower number of treatments. Although it has been used extensively in Europe and America, there is little long-term safety data and emerging reports describing late-appearing infections and other complications [22–26]. There have been no systematic studies assessing long-term complication rates, especially those of infection.

Table 3. Univariate and Multivariable Logistic Regression Models on Factors Associated With Infection

	Univariate Model		Multivariable Model	
Effect	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at first treatment (per 10 years)	0.91 (.60, 1.38)	.65	0.88 (.55, 1.39)	.58
Year of first treatment				
>2006	0.23 (.09, .60)	.002	0.33 (.11, .96)	.04
2006	0.41 (.20, .82)	.01	0.57 (.26, 1.28)	.17
≤2005	1.00	–	1.00	…
No. of injections at first treatment	1.03 (.83, 1.27)	.79	…	…
Injection volume (cc) at first treatment	1.00 (0.99, 1.02)	.53	…	…
Having touch-up treatments	3.85 (1.77, 8.33)	.0006	2.62 (1.12, 6.15)	.03

Abbreviations: OR, odds ratio; CI, confidence interval.

Prompted by a few isolated cases of late-occurring infections, we retrospectively assessed 267 patients treated with Bio-Alcamid for HIV facial lipoatrophy, of whom 19% developed an infectious complication. The rate of primary infection was 0.07 per patient-year of follow-up, of which the rate of infection with microbiologic confirmation was 0.02. Both of these figures are likely underestimates because patients with infections are more likely to present to the emergency room or their primary care physician. Patients or treating physicians may have been unaware of the potential link of infection to the filler. In addition, it is possible that some patients with infections presented to alternate clinics and were not captured in this analysis. One other cosmetic surgery clinic in Toronto provides Bio-Alcamid treatments, but did not participate in this study. However, this clinic does not receive a significant number of referrals from HIV clinics in Toronto, so exclusion of this clinic would not likely have affected our results. Details on the clinical signs and symptoms were often limited in the surgeons' charts, and many cases could not be differentiated between infection and inflammation—to be conservative, these were not included as probable cases. Long-term follow-up was often incomplete.

Patient demographics and clinical characteristics were not significantly different between those who developed infection and those who did not. The majority of patients were male, had a median duration of 15 years of HIV infection, and were virologically well controlled at the time of treatment. It would appear unlikely that development of infection is related to level of immune suppression by HIV. Patients treated with Bio-Alcamid more recently were less likely to develop an infection. It is possible that infections were less likely as the surgeons gained experience and improved their technique, resulting in fewer injections and touch-up treatments, improved aseptic technique, improved access to the subcutaneous space, and less manipulation during treatment.

All of the manufacturer recommendations were followed by surgeons, and as such, in the absence of allergy, all patients received the same antibiotic prophylaxis (cephalexin 500 mg 4 times/day for 5 days) at the time of injections. As the majority of infections presented late (after 3 or more years), they are unlikely to be related to contamination during the operative procedure itself. The patients who developed infections had a significantly larger volume of filler instilled during their first treatment compared to those who did not develop infection. The need for use of a larger volume would imply a more severe degree of facial lipoatrophy. As facial lipoatrophy results in significant loss of the subcutaneous adipose tissue, the injection of large volumes of filler into this severely diminished space may be quite difficult and may result in leaving very little tissue between the filler and the external skin or the buccal mucosa of the oral cavity. The implant may then be vulnerable to contamination by skin or oral flora, especially with trauma and particularly as further subcutaneous fat is lost secondary to ongoing FLA or aging. This may in part explain the late onset of the complications. In addition, patients who had received touch-ups were 2.5 times more likely to develop infection. Thus, the risk of infection may be further increased not only for those with more severe FLA, but also for those requiring additional manipulation within the vicinity of the filler.

Facial manipulation or trauma within the vicinity of Bio-Alcamid is potentially a risk factor for the development of infection. One-third of patients had dental work in the month prior to development of infection. Symptoms presenting after facial manipulation could potentially be secondary to postprocedural swelling. A distinction was made between infection and postprocedural swelling if there were positive cultures, symptoms recurred after resolution, or symptoms were severe and resolved with the initiation of antibiotics. A previous study has also reported the onset of infection triggered by additional procedures near the site of Bio-Alcamid [36]. Procedures in the vicinity of

Bio-Alcamid can potentially puncture the subcutaneous space and contaminate the filler with oral or skin microorganisms. A role for biofilm has been hypothesized as a contributor to late-onset infections, inflammation, and granuloma formation associated with dermal fillers [37, 38]. There is little known as to the stability of Bio-Alcamid over the long term, and whether breakdown of the material could lead to complications.

Medical management alone did not appear to be sufficient as the majority of patients received surgical intervention and many required hospitalization. As many treating physicians were not aware of the presence of facial fillers or their potential complications, some of these infections were mistaken to be dental or soft-tissue infections, thus delaying definitive surgical management. The excision of Bio-Alcamid was technically difficult and often incomplete. The capsule could not be easily punctured and aspirated as a whole as described by the manufacturer. Retained product could serve as a source of recurrent infection and relapse. Although the majority did have resolution of the infection, median follow-up of patients with infection was 63 months, and it remains unclear what proportion will have further recurrences with time. Surgical incision and drainage is invasive, and especially undesirable on the face due to potential scarring. A large-needle aspiration technique has been developed and incorporated into managing these infections in Toronto [39].

We feel that the infectious complications rate associated with Bio-Alcamid observed in this study was unacceptably high. Whether the risk of this complication is increased in HIV is unclear, but we did not find higher rates in those with lower $CD4^+$ lymphocyte cell counts or uncontrolled HIV viremia. A limitation of this study is the lack of a control group. To our knowledge, there are no randomized trials comparing Bio-Alcamid to other facial fillers for the treatment of HIV-related FLA. Even in the context of a randomized trial, follow-up does not usually extend beyond 2 years. Since the median time to infection was 32 months among patients developing infections, the majority of these infections would not have been documented within a randomized-trial setting. Observational cohort data such as ours provide invaluable information on treatment outcomes in the clinical setting.

As there is no other permanent, high-volume facial filler that requires such few treatments as Bio-Alcamid, it continues to be used to fix severe soft tissue deficits such as facial lipoatrophy. It is important that physicians recognize the high rate of infectious complications associated with this product such that risks and benefits can be discussed with patients prior to this procedure. It is also imperative to recognize these infections immediately at presentation and refer them appropriately for medical and surgical management. Patients with Bio-Alcamid should also be counseled regarding manipulation of the face near the site of Bio-Alcamid, especially with procedures such as dental work. We feel strongly that antibiotic prophylaxis be considered prior to any facial manipulation in the vicinity of the filler.

CONCLUSION

Bio-Alcamid treatment for HIV-related facial lipoatrophy was associated with a high rate of infectious complications, often presenting years after treatment. Facial manipulation, especially dental work and more extensive lipoatrophy, seems to contribute to development of infection. Patients should be counseled regarding the risks and long-term adverse effects of Bio-Alcamid. Consideration should be given to antibiotic prophylaxis prior to dental work or other facial manipulation in patients who have been treated with Bio-Alcamid.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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