Four-Year Follow-Up of Polyalkylimide Gel Use for the Treatment of HIV-Associated Lipoatrophy

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Purpose: To evaluate polyalkylamide gel (PAIG) use in treating HIV-associated facial lipoatrophy (FLA) 4 years after its injection in an open-label, randomized controlled trial (RCT). **Methods**: Five patients were treated with PAIG in a pilot study, and 31 patients were subsequently enrolled in the RCT of immediate or delayed (12 weeks later) PAIG injections. Endpoints included proportion of participants with complications; changes in FLA severity score (FLSS); and quality of life (QoL), depression, anxiety, and satisfaction scores. Infections were classified as "confirmed" if purulent material was extracted and/or an organism cultured. Infections were classified as "possible" if only clinical signs were present without purulent discharge or microbiologic confirmation. **Results:** Year 4 results were available for 5 pilot and 27 full-scale study participants. Delayed complications included 5 confirmed infections (15.6%), 3 possible infections (9.4%), nodules (25%), and bleeding (3%). No significant changes were observed between years 2 to 4 in patient-graded FLSS, QoL, depression, and anxiety scores. Whereas 94% of participants were satisfied with their overall treatment, only 69% were satisfied with PAIG treatment specifically. **Conclusion:** Even though PAIG treatment was associated with delayed complications including high rates of infection and nodules, most patients were satisfied with the treatment. **Key words:** *Bio-Alcamid, delayed adverse events, facial lipoatrophy, HIV, infection, polyalkylimide gel*

Facial lipoatrophy (FLA) remains one of the most distressing complications of antiretroviral therapy (ART) for patients infected with HIV.[1–3] The iatrogenic depletion in facial fat can be highly stigmatizing for patients, can lead to poor self-esteem and depression, and may subsequently negatively affect ART adherence.[1–4] Because effective medical therapies for reversing FLA have been lacking, emphasis has been placed on correction of FLA using facial fillers.[5–7] The 2 most commonly used facial fillers for the treatment of HIV-associated FLA are poly-L-lactic acid (PLA) (New-Fill; Biotech Industry SA, Luxembourg)[8,9] and polyalkylimide gel (PAIG) (Bio-Alcamid; Polymekon, Biotech Industrie, Milan, Italy).[10–12] PAIG possesses several properties that may be advantageous relative to other products, including the requirement of only a single course of treatment; PAIG yields results that are permanent, but removal is easy should such need subsequently arise.[13] It is a nonbiodegradable, nonallergenic, nontoxic polymer composed of 96% nonpyrogenic water and 4% polyalkylimide. To date, it has been shown to be safe and effective in the treatment of HIV-associated FLA.[10,11,13]

We previously reported the week 48 and 96 results of a randomized, open-label study of PAIG for the correction of FLA in 31 HIV-positive patients.[14,15] The results of the study demonstrated that treatment with PAIG was safe and effective at both time points, resulting in sustained reductions in the severity of FLA and improvements in patient QoL,

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anxiety, and depression scores that were measured using validated instruments.[14,15] However, publication of several cases of delayed adverse events associated with PAIG have called the long-term safety of this product into question.[16–28] Most notably, several centers have described infectious complications such as cellulitis and abscess formation following the prolonged use of PAIG for HIV-associated FLA.[16–29] Given the ramifications of delayed infectious complications on the sustained use of PAIG, we sought to explore the occurrence of such events in a group of treated patients who participated in a randomized controlled trial (RCT). In this report, we present the 4-year follow-up data of the 31 patients enrolled in the open-label RCT, along with 5 patients who were previously enrolled in a pilot study.[30]

METHODS

Study Population and Design

Details of the study methodology have been previously described.[14] Briefly, 31 HIV-positive individuals with FLA were enrolled from April to September 2005 and were randomly assigned to receive either immediate (weeks 0 and 6; n = 16) or delayed (weeks 12 and 18; n = 15) PAIG injections administered into the subcutaneous plane using aseptic technique. Additional injections ("touch-ups") were arranged if the treating surgeon deemed the initial level of correction less than optimal. Injection techniques employed in this study were previously described.[14] An additional 5 patients were enrolled in a pilot study in November 2004 prior to launching the full-scale study.[30] All pilot and full-scale study participants had FLA confirmed by physician assessment, were 18 years of age or older, had received no prior corrective therapy for FLA, and provided written informed consent prior to participation in the study. The original study protocol and subsequent amendment for a 4-year follow-up visit were approved by an independent research ethics board.

Assessments

The long-term safety of the PAIG was assessed by asking participants whether they experienced the following complications: pain, swelling, redness, bruising, nodules, bleeding, necrosis, and infection. Infections were classified as "confirmed" if purulent material was extracted and/or an organism cultured. Infections were classified as "possible" if only clinical signs were present, including erythema, edema, and pain, without purulent discharge or microbiologic confirmation. In cases where complications were described, additional questions were asked about the timing of their onset relative to the initial injection, peak severity based on a visual analogue scale of 0 to 10, and duration. Additional questions were asked regarding potential precipitating factors and management of the complications. Other outcome measures included the FLA severity scores (FLSS) using the 5-point Carruthers scale and QoL, depression, and anxiety scores using validated surveys.[31–34] The FLSS is a validated 4-point grading scale of FLA ranging from 1 (*mild FLA*) to 4 (*severe FLA*).[31] Grade 0 was used to represent the condition of no FLA.[14] Quality of life and depression were assessed using the Medical Outcomes Study HIV Health Survey (MOS-HIV), the Hospital Anxiety and Depression Scale (HADS), and the slightly modified Dermatology Quality of Life Survey (sDQLS); these have all been validated and previously described.[32–34] Satisfaction with treatment was assessed by asking patients the following questions: "Overall, how satisfied are you with the treatment you received?" (ie, overall treatment) and "Overall, how satisfied are you with the Bio-Alcamid injections?" (ie, PAIG treatment specifically). For these questions, participants could answer on a 5-point Likert scale that included the following options: very unsatisfied, unsatisfied, neither unsatisfied or satisfied, satisfied, and very satisfied. A final binary question was asked about whether they would recommend treatment with PAIG injections.

Statistical Analysis

Demographics and adverse events were summarized using frequencies and proportions for categorical variables and median and interquartile range (IQR) for continuous variables such as duration and severity. Differences in FLSS and QoL scores between the pilot, immediate, and delayed treatment groups were evaluated using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The comparisons of change in results from baseline to year 4 and from year 2 to 4 and for the pilot, immediate, and delayed treatment groups and entire group as a whole were

carried out using the Wilcoxon sign rank test. The satisfaction questions were dichotomized and summarized using proportions for the pilot and full-scale RCT participants separately as well as for the combined group as a whole; comparisons were made using the chi-square test.

RESULTS

Baseline Characteristics

Thirty of the 31 patients enrolled in the full-scale study were male, and the median age of the cohort was 48 years (IQR, 45–55), whereas all 5 patients in the pilot study were male with a median age of 45 years (IQR, 43–46). At baseline, the 31 patients in the full-scale study had a median physician FLSS of 2 (IQR, 1–3) and 23 (74%) of them had moderate to severe FLA (ie, grade 2–4). All 5 patients in the pilot study had moderate to severe FLA with a median physician FLSS of 4 (IQR, 3–4). The additional baseline characteristics for the participants are summarized in **Table 1**. Four participants were lost to follow-up, and subsequent results report on the remaining 32 participants.

Safety

The delayed adverse events through 4 years of follow-up for the pilot and full-scale studies are

Table 1. Participant demographics[a]

Variable	Pilot treatment (n = 5)	Immediate treatment (n = 16)	Delayed treatment (n = 15)
Median age, years (IQR)	45 (43–46)	47 (43–52)	51 (46–55)
Male	5 (100%)	15 (94%)	15 (100%)
Median years with HIV diagnosis (IQR)	12 (10–15)	16 (13–17)	16 (13–17)
Race			
Caucasian	5 (100%)	16 (100%)	13 (87%)
Black	0 (0%)	0	1 (7%)
Asian	0 (0%)	0	1 (7%)
Median years ever on ART (IQR)	9 (9–15)	12 (10–15)	11 (8–15)
On prior d4T or ddI	5 (100%)	14 (93%)	14 (93%)
Median years on d4T or ddI (IQR)	5.50 (2.55–9.96)	2.97 (1.11–4.57)	4.01 (2.34–5.30)
Still on d4T or ddI	0 (0%)	2 (13%)	3 (20%)
Median viral load at study entry, $\log_{10}$ copies/mL (IQR)	1.69 (1.69–2.78)	1.69 (1.69–2.54)	1.69 (1.69–1.71)
Median CD4+ cell count at study entry, cells/μL (IQR)	390 (325–510)	500 (380–590)	480 (260–590)
Grade of facial lipoatrophy using Carruther's Scale			
Grade 1	0 (0%)	2 (13%)	6 (40%)
Grade 2	1 (20%)	8 (50%)	4 (27%)
Grade 3	1 (20%)	5 (31%)	3 (20%)
Grade 4	3 (60%)	1 (6%)	2 (13%)
Median three physicians' score (IQR)	4 (3–4)	2 (2–3)	2 (1–3)

Note: Immediate and Delayed treatment groups were part of full-scaled open-labeled randomized study. Values given are n (%), unless otherwise indicated. ART = antiretroviral therapy; d4T = stavudine; ddI = didanosine; IQR = interquartile range.

[a]For more detailed study population demographics, see prior publications.[14,15,30]

summarized in **Table 2A**, for the 32 participants with 4-year follow-up. Many adverse events occurred immediately after the injection and were mostly mild and transient, resolving after a median of 3 days (IQR, 2–5), and they are described in earlier publications.[14] The most significant delayed adverse events reported were infections and nodules. There were 5 confirmed infections (15.6%) with a median time of occurrence of 2.8 years (IQR, 2.5–3.5) from baseline PAIG injection; the duration between onset and resolution was 30 days (IQR, 30–60). Four patients with confirmed infections had organisms cultured from suctioned material (3 with purulent material and 1 with serous material). Three additional participants described possible infections (9.4%), with a median time of occurrence of 3.7 years (IQR, 1.5–4.4) from baseline PAIG injection and a duration between onset and resolution of 10 days (IQR, 4–30). All participants with confirmed and possible infections described localized edema, pain, and erythema. Infection-related risk factors, precipitating events, and management are detailed in **Table 2B**. All patients

Table 2A. Reported injection-related adverse events from the pilot study and full-scale study

					All participants (n = 32)		
Adverse events	Pilot study (n = 5)	Immediate (n = 14)	Delayed (n = 13)	Total no. of events	Time since treatment, years *M* (IQR)	Peak severity *M* (IQR)	Duration in days *M* (IQR)
Injection-related adverse events							
Pain	4 (80%)	1 (7%)	3 (23%)	8 (25%)	2.8 (1.8–3.7)	10 (8–10)	7 (4–30)
Edema (swelling)	4 (80%)	1 (7%)	3 (23%)	8 (25%)	3.2 (2.5–3.7)	10 (7–10)	18 (10–30)
Erythema (redness)	4 (80%)	1 (7%)	3 (23%)	8 (25%)	2.6 (2.1–3.1)	7 (5–9)	5 (4–7)
Bruise	1 (20%)	0	0	1 (3%)	–	–	–
Nodules	0	3 (21%)	5 (38%)	8 (25%)	–	6 (5–7)	[a]
Bleeding	1 (20%)	0	0	1 (3%)	–	–	–
Necrotic	0	0	0	0			
Confirmed infection	4 (80%)	0	1 (8%)	5 (16%)	2.8 (2.5–3.5)	10 (9–10)	30 (30–60)
Possible infection	0	1 (7%)	2 (15%)	3 (9%)	3.7 (1.5–4.4)	8 (8–9)	10 (4–30)

Table 2B. Treatment of delayed infections and risk factors from the pilot study and full-scale study

	Pilot (n = 5)	Immediate (n = 14)	Delayed (n = 13)	Total no. of events
Management of infections				
Oral antibiotics[b]	4 (80%)	1 (7%)	3 (23%)	8 (25%)
IV antibiotics[b]	1 (20%)	0	1 (8%)	2 (6%)
Anti-inflammatories	3 (60%)	0	0	3 (9%)
Drainage of purulent material	3 (60%)	0	1 (8%)	4 (13%)
Organism isolated[c]	3 (60%)	0 (0%)	1 (8%)	4 (13%)

(Continued)

Table 2B. *Continued*

	Pilot (n = 5)	Immediate (n = 14)	Delayed (n = 13)	Total no. of events
Removal of product				
Confirmed infection	4 (80%)	0	1 (8%)	5 (16%)
Possible infection	0	0	1 (8%)	1 (3%)
No infection	0	0	0	0
Visit to emergency department	2 (40%)	0	1 (8%)	3 (9%)
Admission into hospital	1 (20%)	0 (0%)	1 (8%)	2 (6%)
Full resolution of confirmed and possible infections	4 (80%)	1 (7%)	3 (23%)	8 (25%)
Precipitating events				
Prior dental procedure				
Confirmed infection	4 (80%)	0	1 (8%)	5 (16%)
Possible infection	0	0	1 (8%)	1 (3%)
No infection	0	8 (57%)	8 (62%)	16 (50%)
Trauma to area	0	1 (7%)	0	1 (3%)
Hospitalization prior to infection	1 (20%)	1 (7%)	0	2 (6%)
Risk factors to infections				
Diabetes	1 (20%)	2 (14%)	2 (15%)	5 (16%)
Chronic renal failure	0	0	0	0
Smoker	0	2 (14%)	4 (31%)	6 (19%)
On prednisone or steroid	2 (40%)	2 (14%)	2 (15%)	6 (19%)

Note: IV = intravenous; IQR = interquartile range.

[a]Ongoing event (or duration of event greater than 1 year).

[b]Oral antibiotics used included cephalexin in 2 cases; penicillin, clindamycin and cephalexin combined and ciprofloxacin in 1 case each; and 3 with unspecified antibiotic. Specific IV antibiotics were unspecified in all cases. Antibiotics used were self-reported, not confirmed in chart.

[c]Organisms isolated included *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, and *Enterobacter cloacae* in 1 case each; 1 case had an unspecified organism. The 3 confirmed organisms were confirmed in hospital chart.

with confirmed infections had dental procedures including routine dental cleaning prior to developing an infection, compared to 63% who did not have confirmed infection (P = .16) (**Table 3**). For the 3 patients with possible infections, 1 had prior dental procedures (33%). In comparison to participants with no infection, those with confirmed or possible infections had an odds ratio of 1.5 (95% CI, 0.2–9.2; P = .99) for prior dental procedures. The only other covariate associated with infection, both confirmed and confirmed/possible, was more severe FLA grade (**Table 3**). Additional delayed complications observed in patients included nodules (n = 8; 25%, all the nodules were ongoing) and bleeding (n = 1; 3%). There were no correlates of nodules (data not shown). There were no cases of necrosis.

Efficacy

The 4-year efficacy results of the study are summarized in **Table 4**. An analysis for the entire

Table 3. Association between demographic and clinical variables and confirmed/possible infection

Variable	No infection (n = 24)	Confirmed infection (n = 5)	P^a	Confirmed/ possible infection (n = 8)	P^b
Age, years[c]	48 (44–55)	46 (45–52)		46 (43–54)	.56
FLSS			.05		.02
Grade 1 & 2	17 (71%)	1 (20%)		2 (25%)	
Grade 3 & 4	7 (29%)	4 (80%)		6 (75%)	
ART duration, years[c]	12 (9–15)	9 (8–9)	.35	9 (8–14)	.50
d4T/ddI duration, years[c]	4 (1–5)	4 (3–6)	.71	4 (2–7)	.75
Viral load at study entry, $\log_{10}$ copies/mL[c]	1.69 (1.69–2.65)	1.69 (1.69–1.71)	.84	1.69 (1.69–1.75)	.91
CD4 count at study entry, cells/μL[c]	490 (350–585)	510 (325–610)	.92	515 (318–630)	.73
Prior dental procedure	16 (75%)	5 (100%)	.10	6 (75%)	.66

Note: FLSS = facial lipoatrophy severity scores; ART = antiretroviral treatment; d4T = stavudine; ddI = didanosine.

[a]Comparison of confirmed infection versus no infection using chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

[b]Comparison of confirmed/possible infection versus no infection using chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

[c]Median (interquartile range).

Table 4. Four-year report of facial lipoatrophy severity scores (FLSS) and quality of life scores

	Pilot group (n = 5)	Immediate treatment (n = 14)	Delayed treatment (n = 13)	Entire cohort (n = 32)	P^a
Physician's grade[b]	1 (1–1)	1 (0–1)	1 (1–1)	1 (1–1)	.69
Patient's grade	0 (0–1)	1 (0–1)	1 (1–2)	1 (0–1)	.04
MOS-HIV					
Quality of life	50 (25–50)	75 (50–75)	63 (50–75)	75 (50–75)	.08
Physical health summary score	293 (213–332)	465 (405–560)	312 (275–527)	418 (290–543)	.03
Mental health summary score	375 (225–407)	543 (492–615)	448 (372–592)	505 (375–589)	.08
HADS					
Depression	13 (10–14)	7 (5–9)	7 (6–11)	7 (5–12)	.08
Anxiety	9 (8–14)	8 (5–10)	9 (8–10)	9 (6–10)	.54
sDQLS	1 (0–2)	1 (0–1)	1 (0–3)	1 (0–3)	.80

Note: Values given are median (interquartile range). MOS-HIV = Medical Outcomes Study HIV Health Survey; HADS = Hospital Anxiety Depression Scale; sDQLS = slightly modified Dermatology Quality of Life Survey (sDQLS).

[a]Kruskal-Wallis test.

[b]Average of three physicians' scores.

group as a single cohort was also conducted assessing the change from baseline to year 4, as most efficacy endpoints showed no difference between the groups. Physician and patient FLSS scores both changed by a median of –2 (IQR, –2, –1) ($P < .001$) and –1 (–3, –1) ($P < .001$) from baseline to year 4, respectively. Changes in QoL and physical health domains of the MOS-HIV scale at year 4 relative to baseline were not significantly different. Improvements were observed for the mental health domain ($P = .02$), sDQLS ($P < .001$) and in both the depression ($P < .001$) and anxiety ($P < .001$) portions of the HADS scale from baseline to year 4.

Because our last follow-up report was at 2 years from baseline, a comparison of outcome measures between years 2 and 4 was performed (**Table 5**). There were 2 patients from the pilot group and 1 patient from the full-scale immediate group who received additional touch-up injections of PAIG between years 2 and 4. While there were no significant changes observed in median patient-graded FLSS, MOS-HIV QoL, sDQLS, physical and mental health summary scores, or depression and anxiety scores between years 2 to 4 of follow-up, a significant difference in median physician FLSS score was observed during this time frame (1; IQR, 0–1; $P < .001$).

Satisfaction

The answers to the satisfaction questions separated by group are presented in **Table 5**. The proportion of the overall patients responding that they were satisfied or very satisfied with their overall treatment and treatment with PAIG specifically was 94% and 69%, respectively (**Table 6**). Seventy-eight percent of patients would recommend treatment with PAIG injections (**Table 6**).

Table 5. Changes in facial lipoatrophy severity and quality of life scores from 2 to 4 years

	Pilot group (n = 5)	Immediate treatment (n = 14)	Delayed treatment (n = 13)	P^a	Entire cohort (n = 32)	P^b
Physician's grade[c]	1 (0, 1)	1 (0, 1)	0 (0, 1)	.07	1 (0, 1)	<.001
Patient's grade	0 (0, 1)	0 (–1, 0)	0 (0, 1)	.37	0 (0, 1)	.43
MOS-HIV						
Quality of life	–25 (–25, 0)	0 (–25, 0)	0 (–25, 0)	.60	0 (–25, 0)	.27
Physical health summary score	–103 (–155, –66)	23 (0, 50)	2 (–38, 25)	.02	3 (–42, 37)	.68
Mental health summary score	–101 (–216, –51)	3 (–62, 58)	–1 (–91, 32)	.08	–5 (–91, 32)	.14
HADS						
Depression	3 (2, 7)	0 (–1, 2)	1 (–2, 3)	.10	0 (–1, 3)	.11
Anxiety	1 (–2, 4)	–2 (–3, 2)	0 (–3, 1)	.77	0 (–3, 2)	.46
sDQLS	0 (0, 2)	0 (0, 1)	0 (–2, 1)	.64	0 (–1, 1)	.94

Note: Values given are median (interquartile range). MOS-HIV = Medical Outcomes Study HIV Health Survey; HADS = Hospital Anxiety Depression Scale; sDQLS = slightly modified Dermatology Quality of Life Survey (sDQLS).

[a]Kruskal-Wallis test.

[b]Wilcoxon signed rank test.

[c]Average of three physicians' scores.

Table 6. Satisfaction with treatment at year 4

	Pilot study (n = 5)	Full-scale study (n = 27)	*P*	Combined full-scale and pilot study (n = 32)
Satisfied with overall treatment			.17	
Very unsatisfied/unsatisfied	0	0		0
Neither	1 (20%)	1 (4%)		2 (6%)
Very satisfied/satisfied	4 (80%)	26 (96%)		30 (94%)
Satisfied with Bio-Alcamid injections			.57	
Very unsatisfied/unsatisfied	1 (20%)	4 (15%)		5 (16%)
Neither	0 (0%)	5 (19%)		5 (16%)
Very satisfied/satisfied	4 (80%)	18 (67%)		22 (69%)
Would recommend Bio-Alcamid treatment	3 (60%)	22 (81%)	.29	25 (78%)

DISCUSSION

The results of our study provide the first evidence of delayed complications associated with PAIG originating from a controlled clinical trial with sufficient follow-up for an assessment of the product safety.[16–29] One of our most important findings is the report on delayed adverse events, including confirmed infections at a rate of 15.6% approximately 2.5 years on average from baseline injection that lasted a total of 30 days. Furthermore, an additional 9.4% of participants described a clinical picture consistent with possible infection. As all the possible infections presented with pain, edema, and erythema, it is possible that they were inflammatory reactions rather than infections. It is important to note that all cases of infection resolved after the administration of antibiotics (confirmed and possible), and most required surgical removal of the PAIG (100% for confirmed infections, 33% for possible infections). Because all the patients who experienced a confirmed infection did so following dental procedures, clinicians may consider providing antibiotic prophylaxis to patients with PAIG implants prior to dental procedures. The other clinical variable associated with infection was severity of FLA; this would be an important counseling point for patients with grade 3 or 4 FLA considering treatment with PAIG. The other significant delayed complications were nodules and bleeding at rates of 25% and 3%, respectively.

We were reassured that efficacy was in general no different between years 2 to 4 following PAIG injection. Perhaps most importantly, there was no difference in patient-graded FLSS, MOS-HIV QoL, physical and mental health summary scores, and depression and anxiety scores during this interval. We were also reassured to find that 94% of patients were satisfied with their overall treatment; however, fewer were satisfied with the PAIG specifically. Furthermore, 78% of participants stated that they would recommend treatment with PAIG, suggesting that PAIG may still have a role in the treatment of HIV-associated FLA. Our satisfaction results are important to interpret in the context of the history of release and availability of dermal fillers in Canada. PAIG was the first filler available for use of FLA in Canada in 2005 and was welcomed by members of the HIV-positive community who suffered from severe pathologic facial dysmorphias.

Our study has several limitations, some of which have been presented in previous publications.[14,15] The main limitation for this analysis is the subjective ascertainment and lack of objective definition of complications. Defining infections objectively posed particular difficulty. The 2 clinical factors supporting the diagnosis of the 5 identified cases of "confirmed" infections were the presence of purulent material and the microbiologic confirmation of an infectious organism. On the other hand, while the "possible" infections clinically presented in a

similar fashion with erythema, edema, and pain, the lack of the 2 confirming clinical factors prevented classification of these cases as "confirmed." Some experts may propose that the possible infections we have reported are cases of inflammation. From a clinical standpoint, whether caused by infection or inflammation, the symptoms were considered severe by the patients, lasted for an extended period of time, and were often treated with antibiotics and surgical management. A further limitation is that data on other important complications were not gathered including mitigation and ridging.

In summary, while we found that treatment of HIV-associated FLA with PAIG in our study population resulted in long-term sustained physical efficacy (as defined using the physician- and patient-scored FLSS and mental efficacy using QoL, anxiety and depression instruments), delayed complications were common and severe. The most significant complication was infection occurring in 1 in 7 to 1 in 4 of our population after a median of 2.5 years. This may represent early signs of significant rates of long-term complications in our population. We are concerned that the proportion of patients with infection may increase with time as described by others.[16–29] For this reason, we have decided to continue the follow-up of our study with additional visits at 7 and 10 years after PAIG injection. Also, because all of the "confirmed" infections occurred following a dental procedure, clinicians may wish to consider providing antibiotic prophylaxis to patients with PAIG implants prior to such procedures. Such antibiotic prophylaxis should cover skin and oral flora such as amoxicillin/clavulanic acid or clindamycin. Another consideration would be to use cephalexin or amoxicillin, which are the antibiotics recommended for patients with prosthetic point replacements.[35,36] This recommendation merits further investigation and discussion.

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