The First Clinical Study Using a New Biodegradable Implant for the Treatment of Lips, Wrinkles, and Folds

Michael Olenius, M.D.

Aesthetic Plastic Surgery 1998:22:97-101

Aesth. Plast. Surg. 22:97–101, 1998

Aesthetic Plastic Surgery

The First Clinical Study Using a New Biodegradable Implant for the Treatment of Lips, Wrinkles, and Folds

Michael Olenius, M.D.

Kirurg-Centrum, Stockholm, Sweden

Abstract. A new tissue augmentation product, made from hyaluronic acid, was clinically evaluated at three clinics in accordance with the new directive, EN 540, for medical implants. One hundred patients were fully assessed following treatments in 285 locations. The treatment was completed when the skin was levelled following one to two injections. At 6 months follow-up of all patients and at 12 months follow-up of a randomized group of the patients all showed that close to 60% of the effect was still there. No serious or permanent adverse events were noted.

Key words: Hyaluronic acid—Hyaluronan—Implant—Wrinkle—Bioimplant

The aging skin is a challenge to the aesthetic therapist. Following treatment with ointments, more profound wrinkles and folds need more effective correction through tissue augmentation. One such product has been used for more than a decade. It is based on bovine collagen and has been found to be sensitizing, short-lasting, and, in recent years, also a potential source for the transmittal of certain viral diseases.

To date, a wide variety of other materials have been used for repairing depressed contour deformities, e.g., teflon, silicone, gold, collagen, and most recently, cross-linked hylan, a rooster comb derivative of hyaluronic acid [1,2,4,5,7,8,13]. The commercial preparations of these materials have not appeared to have all the properties of an optimal substance, such as pronounced tissue augmentation, transparency, nontoxicity, a long-lasting effect, and biodegradability. Thus, a safe and long-lasting, yet degradable, implant is in great demand for use in the growing practice of tissue augmentation of the aging skin. Hyaluronic acid is a natural polymer with extraordinarily good biological compatibility. It is a constituent of all connective tissues in humans and most other vertebrates (1). However, the preparations available at present have proved to have some significant shortcomings. Most importantly, hyaluronic acid extracted from rooster combs has proved to be potentially sensitizing to some individuals if it is not highly purified [10,11]. Secondary, nonmodified preparations do not last for more than 2 days in the intradermal space in rabbits [9].

In contrast, stabilized hyaluronic acid is designed to elicit isovolemic degradation for at least a year (Restylane from Q-Med AB). The source of the raw material is nonanimal cells and it is therefore not associated with the safety drawbacks of rooster comb hyaluronic acid. The stabilized formulation is designed to give a long duration, while remaining biocompatible and injectable. Trials in several animal species indicate that a stabilized form of hyaluronic acid does not elicit humoral or cell-mediated immune reactions, and that it is noninflammatory, nontoxic, and not recognized as a foreign body in the tissue [3].

Objective

The primary objective of the study was to investigate the safety and efficacy of stabilized hyaluronic acid when injected intradermally to correct wrinkles and folds in the face. The secondary objective was to investigate device performance after implantation.

Correspondence to Dr. Michael Olenius, M.D., Kirurgcentrum, Olof Palmes g. 13 A, 111 37 Stockholm, Sweden.

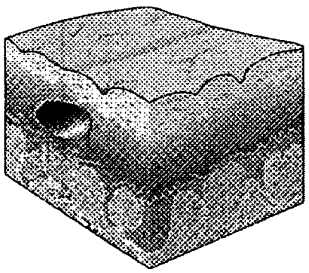

Fig. 1. The material should be injected intradermally.

Materials and Methods

Material and Injection Technique

Stabilized hyaluronic acid (Restylane) is a sterile, nonpyrogenic, viscoelastic implant material. It is a clear, colorless, and transparent gel packaged in a disposable syringe of 0.7 ml. It is produced by cross-linking approximately every 200th part of the glucoseaminoglucan molecule of hyaluronic acid under controlled conditions to yield a 2% gel. The resulting polymer is a molecular network that resides in the intercellular matrix of the skin for more than a year. In the present study, it was implanted through a 27–30 Gauge needle with the eye opening of the needle facing upward. The injections were done intradermally (Fig. 1) and string-wise while pulling the needle out of the site. To prevent the material from leaking out, the injection was stopped just before needle extraction. If the defect remained, then the same procedure was repeated with several punctures of the epidermis until the whole deformity was sufficiently treated. It was not possible to define the adequate amount of gel beforehand, but it was recommended that the physician did not overcorrect the defect.

Patients

One hundred thirteen patients (106 females and seven males) were recruited to the present study, each one receiving treatment in up to three sites. Wrinkles and folds to be included were limited to those, which historically are known to respond well to soft tissue augmentation, e.g., glabellar lines, nasolabial folds, mouth angle wrinkles, and other facial lines. A total of 285 sites were treated.

All patients were evaluated at week no. 0, 1, 12, and 26. Twenty patients were randomly selected to come back after 52 weeks for an additional assessment. If the result of the injection at week 1 was estimated to be poorer than an 80% correction, then a second "touch-up" injection was given at week 2. Such complementary treatment was considered appropriate in 66% of the sites.

At all visits, the patient was closely supervised for at least 30 min after the treatment. The physician especially checked for the occurrence of erythema, swelling, local pain, redness, itching, and tenderness. Any noticeable adverse event was carefully noted and followed up.

Evaluation

After visual examination of the treated area, the physician evaluated the degree of correction and improvement and marked the result on a visual analogue scale from 0 to 100%. Obviously, these estimates are subjective in nature. On the other hand, full correction meant that the treated area was on a level with the surrounding skin or on a level with treatment intent in the case of the lips, for example. In addition, any changes in the feeling, texture, and color of the treated area were evaluated and recorded at each visit. Both of these efficacy evaluations were also made by the patient using the same scales.

Results

Efficacy

Figure 2 shows the efficacy results as evaluated by the physicians and the patients in percentages (0–100%) of either correction or aesthetic improvement. The figure shows that the touch-up treatment at week 2 confirms the instructions in the protocol to make a close to 100% correction at that time point. At the remaining visits at weeks 12, 26, and 52, there were decreasing percentages of correction. Interestingly, after 1 year the results showed a 66% and 57% improvement, as assessed by the evaluator and the patient, respectively. Of all the 285 sites studied, 81% declined with time, whereas 5% were the same and 14% increased in size at least once. Treatment failures were those that showed a decline to less than 20% by week 12. In all, 1.5% of the treatments were reported as failures.

The three main parameters studied on all 285 sites were degree of correction, the physician's estimate of the degree of improvement, and the patient's assessment of the degree of improvement. These groups were never significantly different from each other at the same week.

Tables 1 and 2 show the results from the physicians, and the patients' evaluation of the feeling, texture, and color of the area. The only change that was due to the treatment was that the area was very similar to the surrounding skin at the start of the treatment, but that it became somewhat firmer after the injections (Fig. 3).

It is noteworthy that the feeling of the area tended toward normalization during the later evaluations, despite the fact that the degree of improvement was only somewhat reduced.

Safety

Besides a low frequency of injection-related adverse events, the study has not revealed any symptoms or reactions that indicate that the use of stabilized hyaluronic acid injections is associated with a risk to the patient. Injection-related adverse events that were clearly related

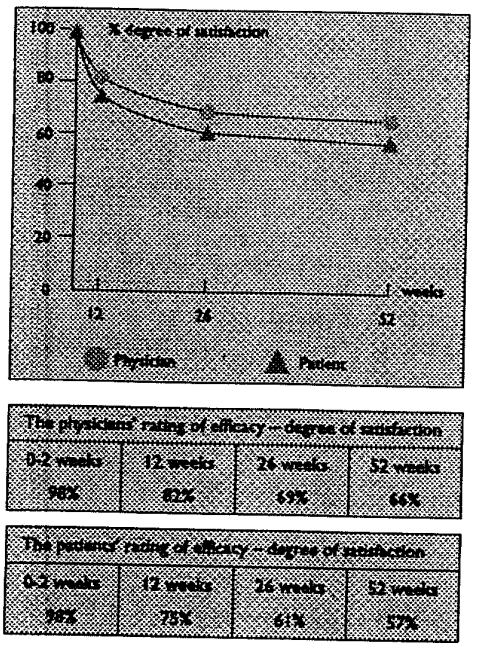

Fig. 2. The physicians' and the patients' rating of efficacy.

to the actual injection of the bulking agent were seen in about 8% of the sites and dissolved within the first week following the treatment (Table 3).

A few events were noted to occur during the follow-up, but were not associated with the device. These are listed in Table 4. No adverse events were found to be related to the actual implant.

Finally, a few events were noted that seemed to be associated with the technique used when injecting the device (Table 5). It is quite easy to obtain too superficial an implantation of the device with concomitant optical phenomena or to inject the material unevenly. It is also worth noting that a material that exhibits a long residence time in the skin is likewise a source of entrapment of mainly hemoglobin emanating from the small bleedings often found during the injections. This will show up as darker spots.

Discussion

Materials used for the purpose of implanatation in the dermal area of the skin have differed over the years. Due to the living nature of the skin, permanent implants have been shown to be less desirous. Corrections are some-

Table 1. Physicans' evaluations of area feeling, texture and color. (The figures denote the number of sites, expressed as a percentage)

	Area feels				Texture			Color		
	1	2	3	4	1	2	3	1	2	3
	looser	same	somewhat firmer	much firmer	rougher	the same	smoother	paler	same	darker
Week 0	4	91	4	0	*	97	*	*	98	*
Week 1	0	57	41	2	0	99	1	0	95	5
Week 2	0	42	51	6	0	98	2	0	98	2
Week 12	0	86	14	0	0	100	0	0	100	0
Week 26	0	87	10	2	0	100	0	0	99	1
Week 52	0	93	4	4	4	96	0	4	96	0

* = The scale at week 0 was 2-graded: "The same" or "Different."

Table 2. Patients' evaluations of area feeling, texture and color. The figures denote the number of sites, expressed as a percentage.

	Area feels				Texture			Color		
	1	2	3	4	1	2	3	1	2	3
	looser	same	somewhat firmer	much firmer	rougher	the same	smoother	paler	same	darker
Week 0	3	93	3	0	1	97	2	*	98	*
Week 1	0	55	44	1	4	94	2	0	94	6
Week 2	0	41	52	7	0	99	1	0	96	4
Week 12	0	71	28	1	0	98	2	0	97	3
Week 26	0	83	16	2	1	97	2	2	95	3
Week 52	0	90	5	0	0	100	0	0	100	0

* = The scale at week 0 was 2-graded: "The same" or "Different"

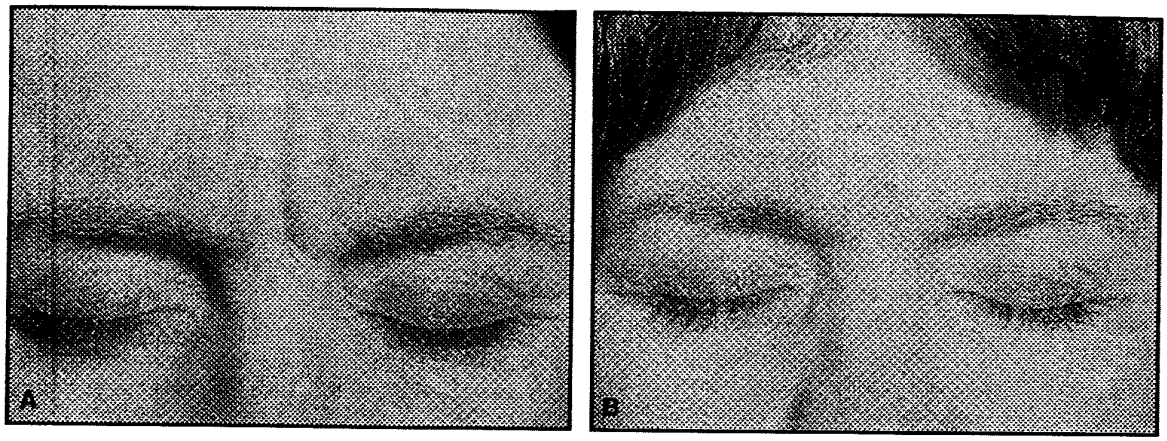

Fig. 3. Glabellar line before (**A**) and after (**B**) treatment with Restylane.

Table 3. Injection related adverse events commencing within one week after treatment (week 0, 1 and 2)

Adverse events	No. of sites (AR)	Frequency (No. of sites = 285)	Comments
Moderate redness, red spots, swollen	19	6.6 %	All sites back to normal within 1 week
Darker area	4	1.4 %	3 sites at week 1 1 site at week 2
Slight pain	1	0.4 %	1 site at week 1
Total	(13 AR)	8.4 %	No adverse event lasted longer than 1 week

Table 4. Adverse events probably not related to investigational product (week 12, 26, and 52)

Adverse events	No. of sites (AR)	Frequency (No. of sites = 285)	Comments
Tics	4	1.4 %	Also present prior to the treatment
Telangiectasia	2	0.7 %	At week 52 only
String	1	0.4 %	Lip augmentation, only at week 12 and not in contact with treated site
Acneiform spots	5	1.4 %	The reaction occured only at one follow-up visit per patient
Total	(12 AR)	3.9 %	

Table 5. Adverse events probably related to the handling of the investigational product (week 12, 26 and 52)

Adverse events	No. of sites (AR)	Frequency (No. of sites = 285)	Comments
Red spots	6	2.5 %	Too superficial injections making epidermis transparent
Darkness	5	1.8 %	Injection related haematoma
Bumps	2	0.7 %	Uneven injections
Total	(13 AR)	5.0 %	Conclusion: no AE reported is considered to be only device related

times moved out of the folded area, thus creating a lateral augmentation, which means the wrinkle is increased instead of being reduced. In recent years implant materials have also been found to migrate to the lung and the brain [12]. It is therefore advantageous to use degradable materials.

However, degradable materials are metabolized and may lead to inflammatory reactions as well as give rise to a foreign-body reaction or an immunological response, thus resulting in an autoimmune disease like the ones that were reported earlier from treatments with bovine collagen [6].

The material used in this study is based on hyaluronic acid, which has already been used in its native form as an implant for more than 20 years and in millions of individuals without causing adverse reactions. The critical elements in relation to hyaluronic acid are the source of the material and the method of stabilizing it to yield a long residence time in the skin.

The manufacturer of the presently evaluated material (Restylane) has chosen a nonanimal origin, thereby

avoiding any form of impurity that may stem from animals, as with hyaluronic acid from chickens.

The method of stabilizing hyaluronic acid in this case results in a very small modification of the natural hyaluronic acid molecule in the range of a mere 0.5%–1%. The long residence time is obtained through the formation of intermolecular bonds. This leads to an indefinitely large network that is only physically broken down to 100-μm fragments to allow the hyaluronic acid to be injected. The net result of this is a material that is essentially similar to and as well tolerated by cells and tissues as its unmodified native origin, but with a residence time that is at least 100 times as long.

Conclusion

Stabilized hyaluronic acid fulfilled the expectations of giving a safe and efficient tissue augmentation.

References

1. Balazs EA, Leshchiner EA; Hyaluronan, its cross-linked derivative—hylan—and their medical applications. In Inagaki H, Phillips GO (ed): *Cellulosics Utilization: Research and Rewards in Cellulosics.* Tokyo: Elsevier, Applied Science Publications, pp. 233–241, 1988
2. Burton JL, Cunliff WJ: The subcutaneous fat: oil granuloma. In Rook A, Wilkinson DB, Ebling FJG, Champion RH, Burton JL (eds): *Textbook of Dermatology* Oxford: Blackwell, 1986, pp. 1870–1871, 1986
3. Company Reports Q-Med Sweden, Seminariegatan 21, 752 28 Uppsala, Sweden
4. Donald PJ: Collagen grafts—here today gone tomorrow. Otolaryn—Head and Neck Surg., **95:**607–614, 1986
5. Fisher JC: Discussion of: DeLustro F., Smith STS, et al: Reaction to injectable collagen: Results in animal models and clinical use, (Plast. Reconstr. Surg. 79:581–592, 1987), Plast Reconstr Surg **79:**593–594, 1987
6. Jean Cukier MD, Richard A, Beauchamp MD, Joseph S, Spindler MD, Sarah Spindler MS, Carlos Lorenzo MD and David E: Trentham association between bovine collagen dermal implants and a dermatomyositis or a polymyositis-like syndrome, Ann Intern Med **118:**920–928, 1993
7. Knapp TR, Kaplan EN, Daniels J: Injectable collagen for soft tissue augmentation. Plast Reconstr Surg **60:**398, 1977
8. McPherson JM, Ledger PW, Sawamura S, Conti A, Wade S, Reihanian H and Wallance DG: The preparation and physio-chemical characterization of an injectable form of reconstituted glutaraldehyde cross linked, bovine corium collagen. J Biomed Mater **20:**79–82, 1986
9. Reed RK, Laurent UBG, Frazer JRE and Laurent TC: Removal rate of [^{3}H]hyaluronan injected subcutaneously in rabbits. Am J Physiol **259:**H532–H535, 1990
10. Richter AW: Non-immunogenicity of purified hyaluronic acid preparations tested by passive cutaneous anaphylaxis. Int Arch Allergy Appl Immunol **47:**211–217, 1974
11. Richter AW, Ryde EM and Zetterström EO: Non-immunogenicity of a purified sodium hyaluronic preparation in man. Int Arch Allergy Appl Immunol **59:**45–48, 1979
12. Ross A, Rames and Ian A Aaronson: Migration of polytef paste to the lung and brain following intravesical injection for the correction of reflux, Pediatr Surg Int **6:**239–240, 1991
13. Selmanowitz VJ, Orentreich N: Medical-grade fluid silicone: a monographic review. J Dermatol Surg Oncol **3:**597–611, 1977