
Artecoll: The Arizona Experience and Lessons Learned

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BACKGROUND. Artefill is one of several new materials being introduced to the US market as a soft tissue augmenting agent.

OBJECTIVE. The objectives were to evaluate the safety and efficacy of injecting Artecoll (Rofil Medical International Breda, the Netherlands) in facial wrinkles compared with injecting Zyderm or Zylplast (INAMED, Santa Barbara, CA, USA) and discuss the practical lessons learned.

METHODS. Thirty-eight patients were randomly selected to receive Artecoll or Zyderm/Zylplast into facial defects. Wrinkles were evaluated by the treating physician, the subject, and masked physician evaluators. Similar evaluations were performed on several collagen patients crossing over to Artecoll. Adverse reactions were recorded.

DRS. THALER AND UBOGY MOST RECENTLY ACQUIRED A FINANCIAL INTEREST IN ARTES MEDICAL, INC., WHICH WILL PRODUCE ARTEFILL.

IN THE last several years, there has been an explosion in the development of new soft tissue implants. This intensified search for the “perfect” implant seems to have coincided with the demise of silicone as a viable alternative for an injectable filler material.

Artecoll is one of the more novel injectable tissue augmenting agents to appear. Rofil Medical International (RMI) manufactures it in the Netherlands, and its use has been approved in several South American, Middle Eastern, Asian, and European countries since 1994, in Canada since 1998, and in Mexico since 1999. The company holding the patents and an investigational device exemption and conducting the US Food and Drug Administration (FDA) studies in the United States is Artes Medical, Inc. based in San Diego, California. Open-label studies for safety commenced November 1997 at five centers (including Arizona), and the pivotal double-masked study to determine safety and efficacy commenced June 1999 at eight centers (including Arizona) across the United States. On February 28, 2003, an FDA advisory committee voted in favor of final approval of this agent, which will be marketed in the United States as “Artefill™.” Artes Medical, Inc. received an approvable letter from the FDA on January 16, 2004, on the condition that Artefill will be produced in San Diego.

RESULTS. All evaluators felt Artecoll to be superior to collagen in all treated areas except for the glabella and upper lip lines. In these areas, differentiation by photographs between the two products became more difficult for the masked evaluators. The adverse side effects of Artecoll were almost equal with those of collagen, but most were of minimal consequence. Three patients developed persistent nodules (all in perioral sites), which were treatable with intralesional steroids.

CONCLUSION. Artecoll treatment of wrinkles and folds was found to be effective, long lasting, safe, and associated with a high percentage of patient acceptance. There is a learning curve in injecting this thicker, more permanent product.

Artecoll/Artefill is an alloplastic material composed of polymethylmethacrylate (PMMA) microspheres suspended in a mixture of 3.5% bovine collagen (atelo-collagen), 0.3% lidocaine, and 0.3% sodium chloride in a phosphate buffer set to pH 7.3. The microspheres comprise 20% of the mixture and the collagen 80%. At the time of the trial, the collagen was still made from the hide of calves from a closed herd in Germany fed solely milk and grass.¹ Atelo-collagen has three separate helical alpha chains wrapping to form a three-stranded helix. Amino acid analysis shows that atelocollagen is composed of type I collagen only, as opposed to Zyderm, which is composed of 95 to 98% type I with the remainder composed of type III collagen. It is processed with pepsin to remove the allergenic peptide ends like Zyderm. To reduce any possibility of bovine spongiform encephalopathy (BSE), the collagen is processed with 1 N sodium hydroxide for 1 hour at 20°C, which is internationally recognized for inactivating BSE and many other viruses.¹ Allergic reactions are much lower with atelo-collagen than with Zyderm (0.1% vs 3%).²

The collagen is rapidly broken down by collagenases and phagocytized by macrophages within 1 to 4 months like Zyderm, and during the same period of time, the microspheres become encapsulated, as seen with breast implants or pacemakers, with collagen fibers secreted by the body’s own fibroblasts.³ Encapsulation seems to prevent late dislocation and reduce granuloma formation and type IV allergy (fluid silicone, in contrast, evokes very little encapsulation).³ The amount of connective tissue reaction depends on the individual capacity to react to the microspheres (younger individuals have a greater response

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than do the elderly). In general, however, it appears to be closely related to the volume of collagen in the Artecoll of 80%.¹ The issue of migration of the microspheres to the lymph nodes and distant sites as in silicone has been looked at in animal and human tissue specimens and has never been detected.³ The reason is that migration is possible only if the foreign body is phagocytized or small enough to enter the lymphatic system. Many studies have shown that the 30- to 40-micron spherules are not phagocytized.^{4,5}

The basic science, animal, and initial clinical investigations with this product were performed by G. Lemperle and colleagues, a plastic surgeon at the University of Frankfurt in Germany.⁶ After observing the temporary nature of Zyderm and other filler agents in the skin in the early 1980s, they posited that it would be necessary to have an alloplastic material that would not be metabolized by the body if a "permanent" implant were to be achieved.¹ After studying different materials in rats, he found that PMMA stimulated macrophages the least in forming an early foreign body reaction. PMMA is commonly known as Plexiglas or Lucite. First synthesized in 1902 by O. Roehm,⁷ it was patented in 1928³ and has since been used widely in medicine and dentistry. Neurosurgeons and orthopedic surgeons use it in bone cement, dentists use it in dental implants, ophthalmologists replace cataracts with ocular PMMA lenses, plastic surgeons use it to correct bony facial deformities, cardiologists have pacemaker cases made of PMMA, and PMMA chains containing gentamicin have been used in the treatment of osteomyelitis and deeply infected wounds since 1974.⁶ It is chemically inert and stable for decades after implantation.³ Because polymerization of the microspheres approaches 100%, a toxic or allergic effect of residual monomers is unlikely. Even in hip or knee arthroplasties, the concentration of monomers is far greater with bone cement without any detectable harm. There have also been no reports of pernicious side effects, such as carcinoma, arising from years of use in orthopedics.

An initial product, called Arteplast, as well as other precursor products, was injected from 1989 to 1994.⁸ However, these initial products had an unacceptable rate of foreign body granulomas of close to 2.5%.² Foreign body giant cells are an agglomeration of "frustrated macrophages"¹ that cannot achieve proper phagocytosis of microscopic particles owing to their shape and size.^{9,10} Edges and corners of rough, irregularly shaped surfaces on particles accumulate surface charges and stimulate macrophages and giant cell formation.¹⁰⁻¹² It was found by scanning electron microscopy after dry sieving the larger 32- to 40-micron microspheres of Arteplast that smaller particles of 1 to 5 microns were attached. It was felt that these smaller particles were stimulating macrophages; thus, in 1994, manufacturing techniques were changed to include an ultrasonic bath and wet sieving through a

metallic grid to eliminate any surface charge. This treatment resulted in microspheres of uniform size and smooth surfaces.^{1,2} Experience worldwide now is with over 250,000 patients with this new Artecoll product, and foreign body granulomas are seen in only 0.01% of patients. The Canadian distributor of Artecoll, Canderm in Montreal, Quebec, has received reports on 12 patients with true foreign body granulomas among approximately 50,000 (0.024%) treated patients since 1998 (personal communication, Canderm, July 2005). Patients who have developed granulomas responded well to intralesional steroid crystals, such as triamcinolone or betamethasone.^{1,2}

The precursor products occasionally had a greater visibility through the skin resulting from intradermal placement. This was resolved by changing the technique to deep dermal implantation. With these changes, the final Artecoll product is very biocompatible and cosmetically acceptable: over 90% of patients injected were satisfied with their results in a European study.¹

In this article, we report the results and the adverse effects we have had in Arizona with this new, improved Artecoll compared with Zyderm/Zyplast collagen. We discuss our personal and our patient's masked evaluation of the product. In addition, masked observers were chosen to evaluate the results from our standardized photographs. Of note is that our study was part of the multicenter double-masked FDA trial reported recently.¹³

Materials and Methods

The institutional review board at Desert Samaritan Hospital approved the study protocol. Artecoll was obtained from Artes Medical, Inc. Zyderm II and Zyplast were also obtained from this source.

Study subjects were entered if they needed volume correction in the glabella, nasolabial folds, vertical upper lip lines, or mouth corners and if they met certain acceptance criteria. These criteria were that they (1) were 18 years of age or older, of either sex; (2) had realistic expectations of benefit from the procedure, that they will not look younger after the treatment, and that Artecoll treatment will not replace a face-lift, eyelid surgery, laser treatment, chemical peel, or dermabrasion; and (3) were willing to give informed consent. Exclusion criteria are listed in Table 1, but, in practice, there are few absolute contraindications to Artecoll/Artefill (except collagen and lidocaine allergy and perhaps keloid formers) because this agent does nothing more than stimulate granulation tissue formation (ie, wound healing), which occurs even in immunosuppressed patients. Subjects who voluntarily withdrew from the study at any time or elected alternative treatments or additional treatments during the follow-up period were evaluated as a treatment failure. If they did not return for two consecutive follow-up sessions, they were considered lost to follow-up.

Table 1. Exclusion Criteria

Pregnancy
Wrinkle treatment within 6 mo
Additional wrinkle treatment during trial
Ultraviolet light therapy
Chemotherapy or steroids within 3 mo
Anticoagulation medication
Autoimmune disorders
Atrophic skin diseases
Very thin and flaccid facial skin
Susceptibility to keloids
Lidocaine hypersensitivity
History of severe allergies
Allergy to collagen or beef
Positive skin test to collagen
Elevated serum immunoglobulin G levels to bovine collagen

On meeting the above criteria for inclusion and withdrawal, the patient was randomized by an off-site computer at Artes Medical into one of the two treatment groups of Zyderm/Zyplast or Artecoll. One month prior to treatment, a blood sample for anti-bovine collagen serum immunoglobulin G (IgG) was drawn followed by the administration of 0.1 cc of a skin test to Zyderm or atelocollagen depending on the subject's randomized assignment. The skin test was applied intradermally into the forearm and checked within 1 month. The IgG level was checked 1 month after subjects were treated (and repeated every few months if elevated). Four facial areas (glabella, nasolabial fold, radial upper lip lines, and mouth corners) were divided into right and center or left sides, giving eight possible discrete locations for treatment for an individual patient (a center glabellar fold or lip line was included on the left side). The areas treated were selected and identified by the patient prior to photographs and implantation. Treatments were performed at times 0, 2 weeks, and 4 weeks, with no limits on the volume of Artecoll or collagen injected. All patients were injected three times in this study with both products. Crossover patients were treated with Artecoll at the end of 6 months after collagen injections were finished and treated similarly. Topical anesthesia with EMLA or nerve blocks implementing 1% lidocaine with epinephrine was occasionally required for patients receiving either implants. For patient's "blindness," all syringes were masked with opaque adhesive tape. The investigator injecting the material recognized the content of the syringe by its shape and easier or more difficult extrudability. Artecoll is three times more viscous than Zyplast or Zyderm.² The masked evaluators were blinded in their evaluations as they evaluated the subjects' photographs.

Technique of Implantation

Material was implanted using either a 27-gauge needle for Artecoll or a 30-gauge needle for Zyderm. Artecoll was

injected strictly deep dermally, that is, at a location just above where it feels that the needle loses resistance. Zyderm II was injected intradermally in the glabella to avoid superficial necrosis and in the potential space under the vermilion border. Zyplast was injected in all other areas. Artecoll was injected using the multiple tunneling technique and injecting with constant pressure while withdrawing the needle, and Zyderm/Zyplast was injected in the same fashion as published by Klein.¹⁴ At the end of each injection, the implant was palpated and slight pressure was applied to smooth any irregularities. The glabellar folds were injected in a superior direction to avoid material producing a lump at the medial orbital rim. The nasolabial folds were supported with several bands parallel and medial to the fold and in the upper triangular portion adjacent to the ala. The upper lip lines were corrected by first injecting the entire white roll of the lip in its easily accessible subdermal space. From the vermilion border, each radial line was addressed by using a criss-cross technique, progressing in a superior direction. Proceeding in this manner averted a washboard effect and excessive material being deposited in the vermilion. Marionette lines were corrected by first augmenting the white roll about 1 cm in length from the oral commissure. The fold was then corrected beginning caudally and then proceeding in a criss-cross manner going toward and around the commissure in an attempt to elongate the lower lip and elevate the corner of the mouth. At the glabella and radial lip lines, this investigator tended to overcorrect slightly to the point of palpating a slight elevation, whereas the mouth corners and nasolabial folds were injected to a visible 100% correction.

Photographs were taken with a Yashica Dental Eye (Kyocera Optics, Inc., Denville, NJ, USA) using standardized settings of f16, a focus from lens to facial fold of 25.5 cm (10 inches), and a ring flash setting at "2." Identical film lots of Kodak 100 film supplied by the company monitoring the study (Paxmed International, San Diego, CA, USA) were used. Prints of 4 × 6 inches gave an enlargement of the fold of 1:2. Photographs were taken at baseline, 1 month, 3 months, 6 months, and, if Artecoll was administered, 12 months post-treatment. At each of these follow-up sessions, the physician and patient evaluated the success of the implantation comparing the deepest part of the wrinkle or the deepest wrinkle or fold in the area. If it is a fold that previously had a wrinkle and now did not have one, it was judged as fully corrected. Folds or wrinkles located centrally in an area were assigned to the left side. In a similar fashion, ratings were also conducted in a randomized manner by three independent masked observers but using only subject photographs. The raters were not informed of the treatment group or evaluation period for any photograph. Patients were unmasked at 6 months after the last treatment session, and 14 of the patients who had received collagen were crossed over to

additional Artecoll treatment. The masked observers were continued blinded to this crossover to better compare the results of the two products.

The rating system used by the physician and masked observer was based on a novel 6-point scale developed by Lemperle and colleagues called the Wrinkle Assessment Scale (WAS) (Table 2).¹⁵ It was specific for folds and lines as opposed to the 9-point scoring system of Fitzpatrick and colleagues¹⁶ and proved to be a valid measuring tool for the purposes of this study. The WAS is used "live" in direct comparison with the fold in the patient's face or indirectly comparing a patient's photograph with the pictures of the scale. We compared the deepest depth of the fold or furrow, not its length. If in doubt regarding its classification, we interpolated to the nearest 0.5 unit (eg, 3.5). In all folds, however, especially in the nasolabial folds and marionette lines (corners of the mouth), the depth of the atrophy was assessed, not the depth of the overhanging or redundant skin. If there was no fissure in the dermis, it was

still a class "0" fold. Only the deepest fold was assessed from each area. In the glabellar region, there may be a right and a left frown line or a medial one, which was assigned to the left side. This applied especially to the upper lip lines on the right or left side. The physician and patient also rated success by a 5-point scale at each post-treatment visit.

The investigator rated the success of the implant at each treatment area at 1, 3, and 6 months post-treatment using a 5-point rating scale, where 1 = completely successful (defined as the optimal desired outcome), 2 = very successful, 3 = moderately successful, 4 = somewhat successful, and 5 = not at all successful. Subject satisfaction with the result of each treatment area was assessed using a questionnaire at each follow-up period. Subjects rated their personal opinion of each treatment area at 1, 3, and 6 months post-treatment using a 5-point rating scale, where 1 = very satisfied, 2 = satisfied, 3 = somewhat satisfied, 4 = dissatisfied, and 5 = very dissatisfied. Comparisons were made between Artecoll and collagen using a two-sample *t*-test, and *p* values below .05 were considered statistically significant.

Table 2. Wrinkle Assessment Scale (WAS)

Class	Treatment Area*
0	No folds, no lines
1	Folds and lines just perceptible (ie, approximately 0.1 mm)
2	Shallow folds and lines (ie, approximately 0.2 mm); some well-defined edges
3	Moderately deep folds and lines (ie, approximately 0.5 mm, lines 0.3 mm); some well-defined edges
4	Deep folds and lines (approximately 1.0 mm, lines 0.4 mm); most edges well defined; some redundant folds
5	Very deep folds and lines (ie, approximately 2 mm, lines 0.5 mm)

*Glabellar folds, nasolabial folds, depressed corners of the mouth, radial upper lip lines.

Results

Forty-six patients enrolled in the study. Forty-four patients were Caucasian, one was Hispanic, and one was Native American. Forty-three patients were female, and three patients were male. The mean age was 54 years, with a range of 36 to 77 years. Ten patients were smokers, one patient was a past smoker, and the remainder of patients were nonsmokers. Eight patients smoked one pack/day, one patient smoked one to two packs/day, and two patients smoked two packs/day.

Forty-two patients were tested, and 38 patients were treated. Twenty-one patients had Artecoll. Seventeen patients were injected with collagen only. The total num-

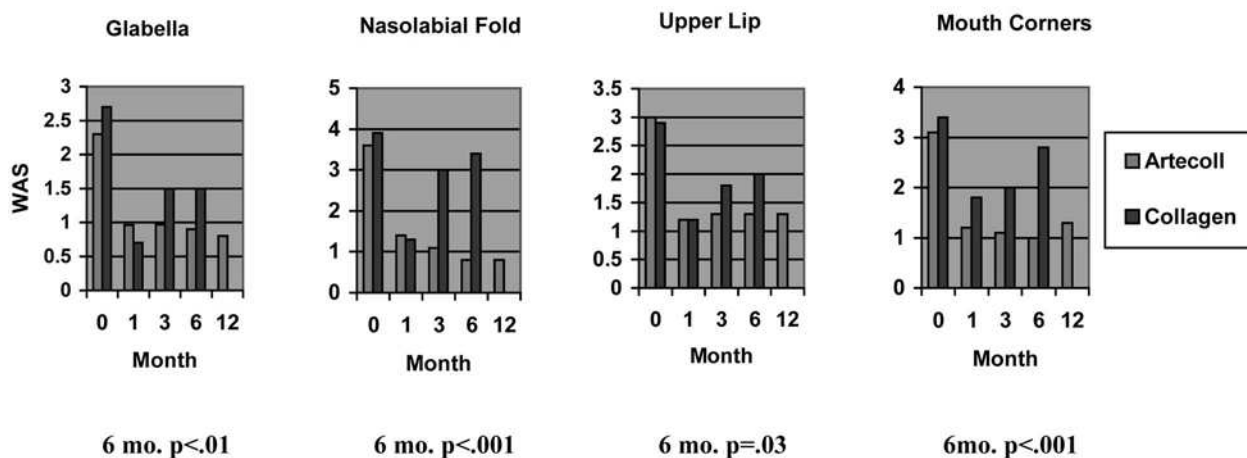


Figure 1. Investigator Wrinkle Assessment Scale (WAS) ratings for the glabella, nasolabial fold, upper lip, and mouth corners at different time intervals.

ber of sites treated was 241. The site breakdown was 47 glabellar lines, 54 nasolabial folds, 30 radial upper lip lines, and 29 mouth corners injected with Artecoll and 16 glabellar lines, 28 nasolabial folds, 16 radial upper lip lines, and 21 mouth corners injected with collagen. This disparity in the number of sites treated for collagen as opposed to Artecoll (81 vs 160) was due to a combination of the randomization process and what areas the patients desired to have treated.

Twelve patients dropped out of the study. Of these patients, one patient was allergic to beef, three patients were unassigned to treatment owing to the folds not being deep enough or the patient refusing to give consent, two collagen patients had equivocal or positive collagen skin tests, one collagen patient had an elevated IgG, and five patients were lost to follow-up. Of the latter five patients, two collagen patients and three Artecoll patients did not show for their scheduled follow-up appointments.

It was noted during the study that the quantity of product used per side of the face was almost twice as much with collagen than with Artecoll for each area of the face except for the glabella. Investigator WAS ratings of the different locations are seen in Figure 1. We found Artecoll to be superior to collagen in its longevity and degree of correction at all sites evaluated. Patients' blinded assessment also demonstrated Artecoll to be a superior product in all areas treated, with a $p < .005$ at 6 months. The masked observer agreed with these observations in the nasolabial fold and mouth corners, but the glabella and upper lip lines showed collagen equal to Artecoll until the third month, when its correction began to fall off. In the crossover data, all sites except the upper lip showed that Artecoll was statistically ($p < .05$) better than collagen in the masked observers' evaluation (Figure 2).

If one analyzes the data taken from the WAS comparing collagen at 6 months with Artecoll at 6 and 12 months, an estimated percent overall improvement for each location observed is demonstrated in Figure 3. There seemed to be a slight trend toward continual improvement with Artecoll-injected sites after 6 and 12 months, except in the upper lip. This could be due to a splinting effect of the material opposing muscular contraction. The upper lip may have been too mobile an area to exhibit change, or the severity of the wrinkles was too mild to evaluate adequately with photographs. In general, a greater than 50% improvement was noted in the glabella, 65 to 70% in the nasolabial fold, and greater than 60% in the upper lip and mouth corner at 6 to 12 months. Long-term follow-up over 5 years still demonstrates that the correction has been maintained (Figures 4 to 9).

Adverse side effects were observed almost equally in the Artecoll group of patients compared with the collagen group (18.7% vs 15.2% of all injected sites). Pain, swelling, and bruising occurred more than twice as often with Artecoll as with collagen as opposed to erythema,

which was greater with collagen (Figure 10). Most of these side effects were of minimal consequence and duration. It was found that approximately 12% of patients with these side effects lasted more than 48 hours with Artecoll as opposed to 4% for collagen. By 2 weeks, these reactions subsided. As for Artecoll and more persistent side effects, there were three patients with persistent slight tenderness or sensitivity to palpation of the implant (forehead, lip, and mouth corner) that eventually resolved in 2 to 4 months, two patients with persistent slight redness (forehead and lip) that resolved over several months, one patient with a transient perioral dermatitis-like reaction in the nasolabial fold, and one patient with temporary visibility of the implant in the mouth corner lasting a few weeks. Three patients developed persistent nodules (lower nasolabial fold adjacent to the lip, corner of the mouth, and upper lip). The latter lesions occurred within a few days after injection and were treated with intralesional triamcinolone (Kenalog) 10 to 40 mg/mL in two of the patients, which flattened them considerably. The other patient refused any further treatment because the nodules were not visible but only palpable inside her mouth. These nodules were not unsightly or visible unless the lips were stretched and usually measured 5 to 6 mm in size; persistent reactions also occurred, with five collagen patients having persistent redness lasting 2 to 4 months. No patient in the study was observed to have a true allergic reaction or elevation in anticollagen IgG antibodies to either collagen or Artecoll during the treatment phase of the study.

Discussion

In this small arm of the larger prospective, double-blinded study on Artecoll, it appears that this novel product has an acceptable safety profile and was found to be significantly more effective in reducing facial wrinkles in the nasolabial folds and mouth corners than collagen as determined by an independent panel of masked dermatology experts. Moreover, if judged by this investigator and patients alike, all sites treated with Artecoll were found to be more successfully and persistently corrected compared with collagen, even with lesser volumes used.

The different evaluations by the masked evaluators of the effects of collagen versus Artecoll in the radial upper lip lines and glabellar folds can possibly be explained by variations in lighting (even though photographic conditions were standardized), oiliness or dryness of skin, or ability to relax those facial areas. Another possibility could be that the wrinkles and folds in those areas were less severe before treatment; therefore, it was more difficult to photograph any significant change. This difficulty could have been magnified by using a ring flash, which tends to remove shadows and creates a more "two-dimensional" effect. This variability may be an inherent design flaw in this study, yet other more involved and objective methods



Figure 2. A patient who had been injected with collagen at (A) 0 months, (B) 1 month, and (C) 6 months. The same patient who crossed over to Artecoll at (D) 0 months, (E) 1 month, and (F) 6 months.

of evaluation, such as computer-generated three-dimensional topography of silicone skin replicas, could contain similar flaws (eg, using different pressure to form the molds or different facial expression or muscle movement while the mold is being formed). It may also be unique to the glabella that collagen seems to be more long lasting if enough material is used.¹⁵ The side effects of

pain, swelling, and bruising were transient, and the overall complication rate per injection site was 18.7% for Artecoll and 15.2% for collagen. Perhaps the Artecoll complication rate could be inherent to it being a thicker product, necessitating a larger-gauge needle. The rate of allergies to Artecoll's bovine collagen appears to be less than 0.1% according to a study by the Canadian distribu-

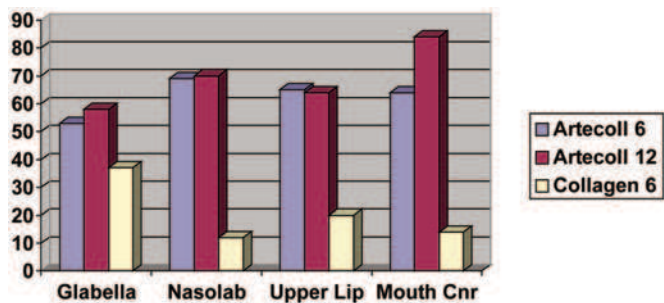


Figure 3. Estimated percent improvement in the appearance of injected sites: collagen versus Artecoll.

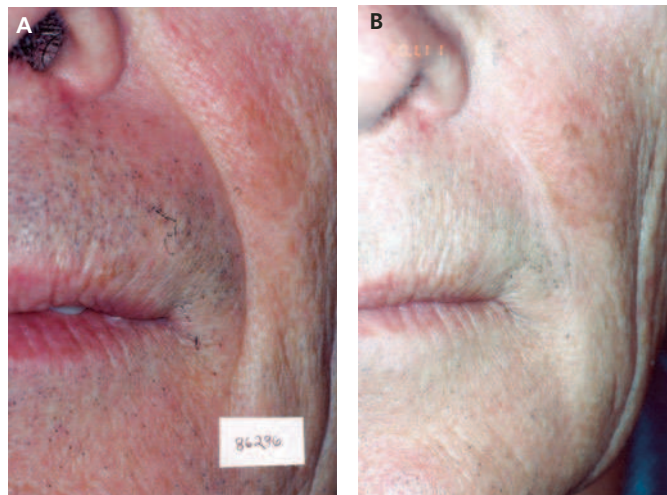


Figure 6. (A) Patient before. (B) Durability of correction in the nasolabial folds after 5 years in a man.

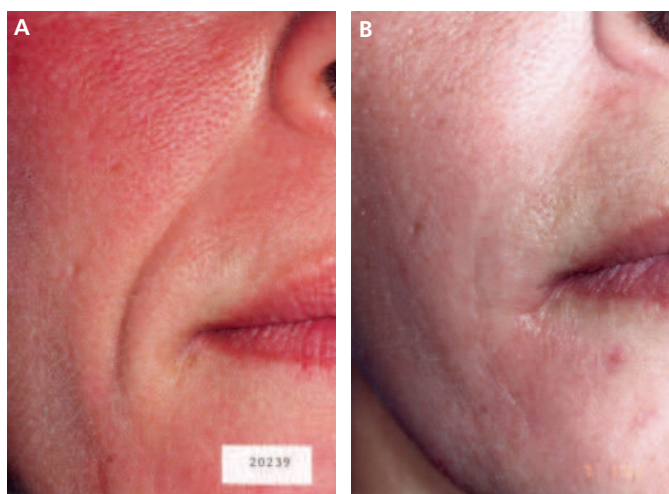


Figure 4. (A) Patient before. (B) Durability of correction in the nasolabial folds after 4½ years.

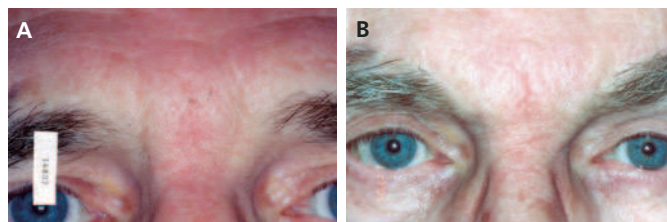


Figure 7. (A) Patient before. (B) Durability of correction in the glabellar folds after 5 years in a man.

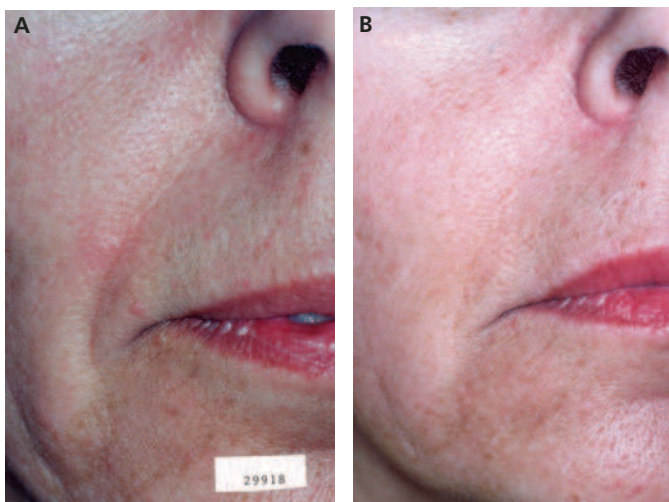


Figure 5. (A) Patient before. (B) Durability of correction in the nasolabial folds after 5 years.

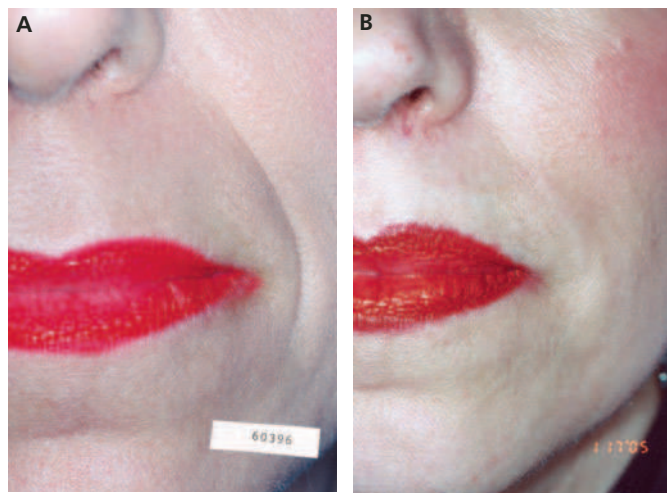


Figure 8. (A) Patient before. (B) Durability of correction in the nasolabial folds after 5 years.

tor, Canderm. This low allergy rate of Artecoll/Artefill is due to multiple extraction and purification steps, which takes Artes Medical 4 months compared with 4 weeks in the production of Zyderm and Zyplast. Equivocal or pos-

itive collagen skin tests were noted with Zyderm in 9.5% of patients (2 of 21), which is a higher percentage than reported in previous studies.¹⁴ This could be explained by our strict definition of a positive or equivocal skin test,

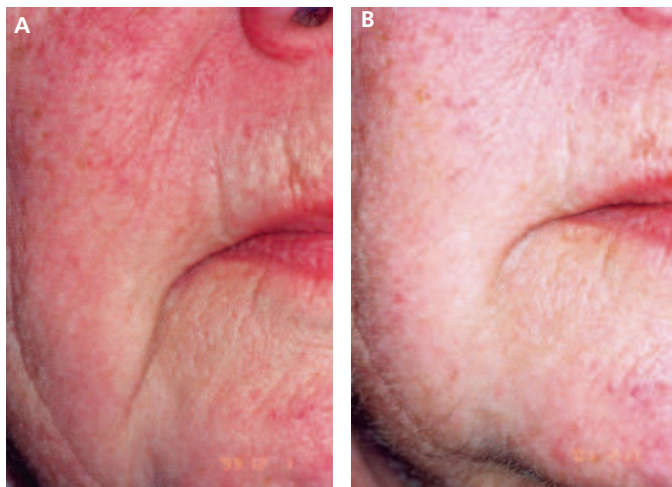


Figure 9. (A) Patient before. (B) Durability of correction in the marionette lines after 1 year.

which was the following: erythema of any degree, induration, tenderness, or swelling, with or without pruritus, which appears immediately after implantation and persists for more than 24 hours or appears more than 24 hours after implantation, or two equivocal skin tests (defined as rash, arthralgia, or myalgia but no localized skin test reaction). Persistent erythema observed in this study with collagen (29% or 5 of 17 patients) may be explained by higher than normal volumes and the frequency of injections. The erythema was nonindurated, and unlike most treatment reactions previously reported with collagen, there were no associated anti-bovine collagen antibodies.

It is comforting to note that nodule formation with Artecoll decreased with steroid injections and did not seem to recur. This suggests some unique local phenomenon occurring during treatment and that most of the volume of the lump is hypertrophied collagen. This may be due to inexperience and accidentally injecting material deeply into muscle. Muscular injections with this material may increase clumping of the microspheres and hypertrophied collagen formation. A local phenomenon seems most likely because most nodule formation has occurred around the mouth, which is a more animated part of the face. It has even been suggested by one investigator for Artecoll in Canada that the use of small amounts of botulinum toxin (6 units) in the lip lines diminishes the ability of pouting and appears to minimize the formation of these lumps.¹⁷

The following are lessons learned from this new product:

1. In contrast to collagen and hyaluronic acids, Artecoll is not a filler substance of the dermis but exerts its effect by “splinting” the wrinkle. The subdermally implanted strand splints the wrinkle or fold until the diminished thickness of the dermis in a wrinkle recovers to its former thickness. The same mechanism applies to the disappearance of wrinkles after paralysis of facial muscles by botulinum toxin or a stroke.

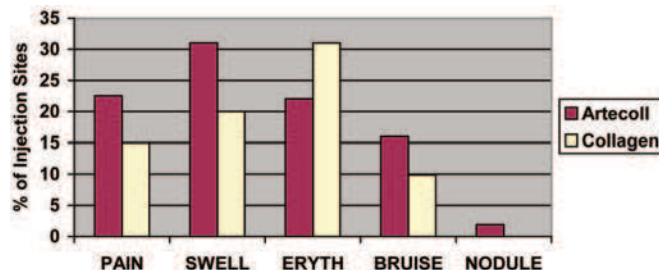


Figure 10. Adverse side effects: collagen versus Artecoll. Eryth = erythema.

Since this recovery of the dermis takes time, patients must be aware of the fact that the superficial creases of the dermis will disappear within 2 to 3 months.

2. To achieve a perfect result at the first session, additional collagen or hyaluronic acid gels can be used for filling the crease by intradermally “layering” other fillers on top of the deep or subdermally applied Artecoll strands.
3. The ongoing movement of muscles underneath folds and wrinkles during the first week after injection presses the fresh Artecoll implant, and the collagen fraction gradually dissipates or shrinks. Most patients, therefore, will need a second implantation of Artecoll at 1 to 3 months, when the newly created space between the dermis and the first implant can be easily felt with the needle tip and filled with a second strand of Artecoll. Then the splint will remain anchored in the deep dermis.
4. The implantation of Artecoll should occur absolutely parallel to the wrinkle and the surface of the skin. One should see the shape of the needle during implantation but never the gray color of the needle! The needle would then be situated intradermally, and delivering the material might result in visible Artecoll granules. To prevent this from happening, the needle has to be pulled out and inserted one needle diameter deeper into the deep dermis. The maximal thickness of the facial dermis is between 0.2 (lid) and 1 mm (glabella) compared with the outer diameter of a 26-gauge needle of 0.5 mm.
5. The glabellar dermis is about 1 mm thick, and the crease in a frown line often is 1 mm deep. Therefore, two or three thick strands of Artecoll/Artefill each about 1 mm in diameter must be delivered deep intradermally while moving the needle two to three times under pressure forth and back. Beneath deep glabellar frown lines, these “splints” must have a volume of 0.5 cc and should be felt as strands beneath the frown lines; they will soften within 2 weeks when ingrowth occurs.

6. Deep nasolabial folds may take up to 2 cc of Artecoll in three or more sessions 2 to 3 months apart. "Touch-up" injections should be done, always in the space between the crease and the first implant. Stay 1 mm medial to the crease; otherwise, one fills the overhanging skin of the cheek. Subdermal fanning of the material is indicated only in the upper triangle below the nostrils.
7. The dermis beneath radial lip lines is very thin (0.2 mm). In isolated lip lines, only one strand of Artecoll should be implanted subdermally (which is very superficial!) above the vermilion to avoid a "washboard" effect. Filling the empty space beneath the vermilion border horizontally will erase the lower 5 mm portion of the radial lip lines over time.
8. Everting the vermilion border of the lower lip with a horizontally injected strand of Artecoll can raise negative or sagging corners of the mouth. Material has to be implanted into the triangle below the commissure in a criss-cross manner, staying very superficially because there is almost no fat between the dermis and the orbicularis oris muscle. Implanting into the muscle will always result in submucosal nodules inside the lip because each muscle will compress an injected strand into a lump (just as the muscle of a clam forms a pearl over time).
9. Deep marionette lines can be raised by one single splint consisting of two to three strands of Artecoll. In shallow wide marionette lines, however, a criss-cross technique is advisable to "stabilize" the line by thickening its total width.
10. No foreign body granuloma has been reported after Artecoll injections in the United States. Reports from Europe and Canada, however, demonstrate that they will occur sporadically as the number of patients injected increases, and, rarely, granulomas may occur several years after implantation.¹⁸ It is of the utmost importance that physicians and patients are aware of this possibility and know that high doses of triamcinolone injected intralesionally can cure this sudden overreaction of macrophages within a few weeks.

In summary, compared with collagen, Artecoll was found to be effective, long lasting, and safe in the treatment of wrinkles and folds, especially in the nasolabial folds and mouth corners. There is a learning curve in injecting this thicker, more permanent product, but it is not as steep as one would presume. Overcorrection can occur, but we felt that the deeper location of injection gives an additional safety factor in preventing this unwanted occurrence. Side effects are in the same range as collagen yet still are mild, transient, and controllable. Injections

around the mouth should be conservative, especially owing to the need of a larger-bore needle when injecting this material. Moreover, it seems that this area tended to develop more problems with nodules. Overall, high patient acceptance was noted in this study and in a previous US pilot study¹⁹ and a recent overall publication of this clinical trial.¹³

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Commentary

I congratulate Drs. Thaler and Ubogy on an article that provides a clear presentation of both the painstaking mode of investigation (I wish it on all subsequent filler applicants) used in phase III of the US Artecoll (now Artefill) Food and Drug Administration trials and clinical insights gained during those trials.

I found the splintering and layering concepts an interesting way of looking at the implantation process and, even more so, the clear description guidelines for knowing the all-important parameter of the depth of deposition of this microimplant. Dermatologists on the upslope of the learning curve need such tutelage, as rudimentary as it appears. It sounds erudite and precise to recommend that one should inject Artecoll into the lower dermis at the subcutaneous junction (below this level, any synthetic filler is probably wasted); it is another to know when you are there.

In my own experience in all phases of Artecoll trials, I also observed the greatest difficulty with proper placement in the areas of the oral commissures. I should note, however, that I

found no irregularities or other untoward effects with its use in lip augmentation in phase I. In regard to irregularities, it must be understood that most nodules are probably not related to the material yielding granulomas but rather to uneven disposition resulting from the operator's technique.

Additionally, it should be noted that when less than optimal patient satisfaction is achieved (as with some patients in my phase I Rofil/Artecoll pilot study and in the phase III glabellar and perioral furrow patients noted in this report) that a more aggressive injection technique will improve the quality of the results, which then may approach those found in Professor Gottfried Lemperle's assessment, in which only one-third of patients required more than one treatment session. I have witnessed firsthand the assertiveness with which Dr. Lemperle implants Artecoll and the subsequent results. This comes from only one variable: experience.

DOUGLAS HAMILTON, MD
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Commentary

Facial contours change over time. In particular, the soft tissues shrink as the patient grows older. Permanent fillers that provided satisfactory results at first may become more visible or create a distorted appearance as aging progresses. Correction with Artecoll is no exception.

The authors of this article maintain that the incidence of adverse reactions is acceptably low and of a nonserious nature. However, it has been reported in *Cosmetic Surgery Times* that in Canada, there is almost a 50% incidence of lumps when Artecoll is injected into the lips.¹ Furthermore, the same article reports that the Swiss and German governments have warned physicians that fillers such as Artecoll should not be used. The General and Plastic Surgery Device Panel of the US Food and Drug Administration recommended approval of the use of Artecoll with specific avoidance of lip augmentation.

In a study by McClelland and colleagues, the evaluation of the results indicated that the Artecoll polymethylmethacrylate implant has the potential to elicit an immune response in humans and that polymethylmethacrylate beads are susceptible to phagocytosis and elimination.² Kim and colleagues reported on an Artecoll granuloma induced by microimplant in the treatment of neck wrinkles.³ They suggested that Artecoll not be used as implant material in thin and constantly movable skin, such as that of the neck. Alcalay and colleagues reported on a late-onset

granulomatous reaction to Artecoll in which the patient presented with hard nodules and slight erythema in the glabella and nasolabial folds 14 months after injection.⁴ This side effect was not reversible.

Even the developer of this product warns that technical mistakes in the form of uneven distribution, implantation into facial muscles, and injection into the subcutaneous fat are common at the beginning of use until the injector develops sufficient skill with the product. This has caused some physicians to stop implanting Artecoll. On the other hand, this would cause me never to start.

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Commentary

I have used permanent fillers, including silicone and fat, for many years. I have included fat because in some areas, such as the cheeks, it is usually permanent. There is no shifting or unusual look as the patient gets older. That is a myth. In fact, with silicone done correctly using the microdroplet technique, the patient will never develop deep wrinkles. I think a true story illustrates this very well. Years ago, I met the wife of one of my professors at the hairdresser. She looked great, and I asked her after we had

spoken for a while who had “done her face.” She quickly told me that she had never had her face “done,” and I, of course, did not pursue the subject. Twenty minutes later, she came over and asked if I thought that the silicone her husband had injected her with 20 years previously had made a difference. It certainly had and totally explained why she looked so young.

RHODA S. NARINS, MD
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Commentary

This well-done study is a small arm of the larger prospective study on Artecoll that was submitted for US Food and Drug Administration panel approval. It is refreshing to see a well-done objective study on what has been a controversial filler. There have been many anecdotal reports—both positive and negative—concerning clinical use of this permanent filler. The study does demonstrate efficacy against Zyplast plus safety in the short term.

I am anxious to see larger follow-up with this study population as to the incidence of delayed granulomatous formation and reemergence of nodules. The authors emphasized the importance of correct and accurate implant placement to prevent nodules

and granulomas. I emphasize the importance of avoiding muscle, especially the lip and the eyelid. This will be the first permanent filler to be approved for cosmetic use. The issue of permanent versus degradable continues to be debated, and there are proponents on each side.

Cautious discretionary use may prevent the complications reported from Europe by overzealous and poorly trained physicians. The proper role of this permanent filler is yet to be found in the general population, and as approval is given, we will only then see the results—positive or negative—in the population at large.

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