Most of the biologic filler materials that increase the thickness of the corium in a wrinkle line are phagocytosed within a certain time. Therefore, a lasting effect can only be achieved with nonresorbable synthetic substances. Artefill consists of 20 volume percent microspheres of polymethyl-methacrylate and 80 volume percent of bovine collagen. Beneath the crease, the microspheres with their exceptional surface smoothness stimulate fibroblasts to encapsulate each individual one of the 6-million microspheres contained in 1 mL of Artefill. Collagen is merely a carrier substance that prevents the microspheres from agglomerating during tissue ingrowth. The 20 volume percent of microspheres in Artefill provides the scaffold for the 80% volume of connective tissue deposition, a complete replacement of the injected collagen. The filler material beneath a crease acts like a splint and prevents the possibility of its further folding, thereby allowing the diminished thickness of the corium in a crease to recover. This recovery process is well known even in older patients with facial paralysis or after a stroke, whose facial wrinkles and furrows on the paralyzed side disappear over time.

SINCE 1994, Artecoll has been used in an estimated 200,000 patients worldwide (except in the United States) with a low complication rate. Because of its higher viscosity and its persistence, technique-related side effects may occur initially. A moderate learning curve on the physician’s part and the knowledge of the effect of corticosteroids, however, should prevent solvable minor side effects. Patient satisfaction after Artecoll treatment is above 90%; they usually experience the optimal result after only 3 months when the thickness of the dermis in a wrinkle or fold has recovered.

**History**

Zyderm was introduced in 1982 as the first dermal filler material and was extremely well received.1 This was the substance in which we all were waiting for. Although it is still one of the safest materials injected into the dermis, the early enthusiasm has quieted because of its short duration.

The senior author’s experience for the last 3 decades with all kinds of autologous grafts, including dermis, fat, cartilage, bone, and tendon, is that they will disappear at sites where they do not maintain their native biologic function. With most of these grafting materials, there is little left behind after a few months, except minimal scar tissue. In order to promote collagen deposition over a longer period of time, one has to stimulate the connective tissue constantly with a scaffold of nonresorbable synthetic material.2 In an attempt to find a solution to this problem, he studied all types of microparticles from different synthetic materials already used in medicine. These were suspended in Tween 80 or gelatin in order to facilitate injections into rats.3 The material with the least tissue reaction turned out to be bone cement, which consists of all sizes of polymethyl-methacrylate (PMMA) microspheres and many impurities attached to them (Figure 1).

To purify this powder further and to increase its biocompatibility, we separated a certain fraction of microspheres, 30 to 42 μm in diameter (Figure 2). This is the ideal size, as it is large enough to escape phagocytosis4 but small enough to be injected through a fine 26-gauge needle and to be able to intrude into the network of the collagen fibers of the deep dermal layer. The smaller the microspheres, the larger is the overall surface area and the promotion of collagen deposition (Figure 3). Microspheres of a diameter of 100 μm promote only approximately 56% connective tissue encapsulation; microspheres of a diameter of 40 μm promote 78% connective formation.2 The animal experiments at the University of Frankfurt (Frankfurt, Germany) in 19853 were encouraging for further experimentation in humans (Figure 4).5

**Address correspondence and reprint requests to:** Gottfried Lemperle, MD, 302 Prospect Street, La Jolla, CA 92037, or e-mail: glempere-le@aol.com.
Furthermore, in early animal experiments, we discovered a rather high amount of foreign body giant cells (1.5% of cells in the histologic samples) (Figure 5), which was probably due to PMMA nanoparticles adherent to the microspheres (Figure 1). These impurities were reduced by repeated washing of the PMMA microspheres.

The original suspension of PMMA microspheres in gelatin was called Arteplast, and the first clinical trials under the supervision of the Ethics Commission of Frankfurt University were started in 1989.5 One hundred eighty-seven volunteers received Arteplast subdermally. In this group and in additional 400 patients receiving Arteplast until 1994, a total of 15 (2.5%) patients developed granulomas6 within 6 to 18 months after treatment (Figure 6). These lumps were treated effectively with intralesional corticosteroids or in very rare instances were surgically excised.

This early rate of granuloma formation was unacceptably high. The cause of granuloma formation was still the adherence of PMMA nanoparticles to the surface of PMMA microspheres because of static electrical charges that occurred during the sieving process. In addition to a change from nylon mesh to metal mesh, a complex washing procedure and ultrasound technology were devised, which removed most of the offending nanoparticles and electrical charges and generated a perfectly smooth surface of the microspheres (Figure 2). These nanoparticles adherent to the microspheres had been a stimulus to macrophages and subsequent granuloma formation in selected patients.6–8

Figure 1. Different sizes of microspheres with impurities (the smallest ones are zirconium oxide for radio-opaity) in bone cement (×800).

Figure 2. After sieving and multiple washings, the microspheres in Artefill have a diameter of 30 to 42 μm and an absolute smooth surface (×800).

Figure 3. Histology 3 months after Artecoll implantation shows multiple fibroblasts, microencapsulation of each single microsphere, capillary ingrowth, and little foreign body reaction (×400).

Figure 4. Histology 10 years after Arteplast implantation shows substantial connective tissue ingrowth with scattered macrophages attached to intact microspheres (×100).
Furthermore, the fast absorption of the gelatin carrier within the tissue led to agglomeration of the beads, causing palpable lumps in certain patients. To address this problem, we switched to a more viscous collagen solution as the carrier material for the microspheres.

Since 1994, the suspension of clean PMMA microspheres in bovine atelo-collagen has been distributed by Rofil Medical International (Breda, Holland) under the trade name Artecoll. With this product, Rofil has received reports on only 15 additional cases of granuloma formation after Artecoll implantation in more than 200,000 patients worldwide, which represents a rate of less than 0.01% (Figure 6). As of April 2001, the bovine collagen in Artecoll has been derived from cow hides of a closed herd in the United States.

Artecoll received its certification, the “European CE mark,” as a medical device in September 1996, marketing clearance in Canada in September 1998 (Canderm Pharma, St. Laurent, QC, Canada), and in México in May 1999 (Grupo Venta Int., Guadalajara, México). Artecoll has been distributed and is well accepted worldwide except in Japan and the United States. The clinical trials in the United States (Artes Medical Inc., San Diego, CA) have been conducted at eight centers and were completed in September 2001. On February 28, 2003, the FDA advisory panel has recommended marketing approval of Artecoll. After FDA approval, the improved product will be marketed under the trade name Artefill.

**Material**

Artefill is a suspension of 20% PMMA microspheres of 30- to 42-μm diameter in 80% bovine collagen solution produced from U.S. calf hides. For the
reduction of discomfort during implantation, it contains 0.3% lidocaine. In order to meet FDA’s quality requirements, the amount of PMMA microparticles of less than 20 microns in size has been reduced to less than 1% by the number of microspheres. Artefill is supplied in 0.6-mL syringes and is designed for implantation into the deep reticular dermis (Figure 7).

The advantages of Artefill are (1) unique microsphere technology providing a complete smooth surface of the microspheres, (2) indications similar to those of collagen and hyaluronic acid, (3) ease of injection despite higher viscosity than collagen alone, (4) permanent stimulation of connective tissue and collagen deposition, (5) long-lasting aesthetic effect over many years, and (6) a low rate of granuloma formation similar to collagen and hyaluronic acid injections.

Biocompatibility

Animal experiments have revealed that the key to Artefill biocompatibility is the smooth surface of the microspheres. This is what accounts for its low incidence of granuloma formation (Figure 6). The effect of Artefill is not only that of a filler substance of itself but mostly a life-long stimulation of collagen deposition beneath the wrinkles. In comparison, all other longer lasting injectables contain particles with an irregular surface. Particulate materials such as polyurethane foam or silicone particles for instance on the surface of textured breast implants are designed to cause a chronic granulomatous tissue reaction. Microscopically, the prevalent cells are foreign body giant cells or “frustrated macrophages.” Artefill contains 6-million PMMA microspheres per milliliter. Therefore, there exist 6-million tiny capsules of connective tissue surrounding the microspheres like smooth-walled breast implants. The microspheres provide merely a scaffold to promote connective tissue deposition. The carrier volume of 80% collagen is completely replaced during the first 1 to 3 months by the body’s own fibroblasts and collagen fibers (Figure 3).

Patient Selection and Indications

Artefill is an excellent filler material to achieve minimally invasive, lasting improvement of facial wrinkles and furrows, acne scars, and other soft tissue contour deficiencies of comparable size. There is a broad spectrum of well-defined medical and aesthetic indications for the use of Artefill outlined in Tables 1 and 2; most are similar to the indications of Zyplast. The best candidates are patients with well-defined wrinkle lines and furrows and little excess skin. If a patient is unsure about the permanency of Artefill or the achieved effect, an initial implantation of a temporary filler is recommended. Patients with sebaceous skin and big pore size or extreme thin and loose skin are poor candidates for Artefill, as the implant might be palpable, may shine through, or even be visible in such patients.

Allergy testing is required by the FDA to minimize the risk of hypersensitivity reactions, especially in patients who are treated with a collagen product for the first time. We recommend an intradermal test injection 4 weeks before the planned Artefill implanta
tion. Double allergy testing can be done but does not diminish the percentage of those prospective patients who become sensitized during multiple injections.

<table>
<thead>
<tr>
<th>Table 1. Aesthetic Indications for Artefill in the Face</th>
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<tbody>
<tr>
<td>Horizontal forehead lines</td>
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<tr>
<td>Glabellar frown lines</td>
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<tr>
<td>Shadowed lower lids</td>
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<tr>
<td>Single crow’s feet</td>
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<tr>
<td>Oblique malar depressions</td>
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<tr>
<td>Malar augmentation</td>
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<tr>
<td>Irregularities of the nose</td>
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<tr>
<td>Nasolabial folds</td>
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<td>Cheek lines</td>
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<tr>
<td>Preauricular lines</td>
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<tr>
<td>Enhancement of the vermilion border</td>
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<td>Enhancement of the philtrum</td>
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<td>Unpleasant gummy smile</td>
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<td>Perioral lip lines</td>
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<td>Negative corners of the mouth</td>
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<td>Marionette lines</td>
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<td>Horizontal chin fold</td>
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<tr>
<td>Chin augmentation</td>
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<td>Horizontal neck folds</td>
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Table 2. Medical Conditions That Have Been Treated Successfully With Artecoll

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Depressed “rolling” acne scars</td>
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<tr>
<td>Bony defects in the face and hand</td>
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<tr>
<td>Small skull defects, drill holes</td>
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<tr>
<td>Enophthalmos after blowout fracture</td>
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<tr>
<td>Sunken eye prosthesis</td>
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<tr>
<td>Tripod fracture of the malar bone</td>
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<tr>
<td>Flat operated cleft lip, missing philtrum</td>
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<tr>
<td>Depressed or asymmetric alar of the nose</td>
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<tr>
<td>Uvula augmentation in snoring</td>
</tr>
<tr>
<td>Alveolar ridge augmentation in toothless patients</td>
</tr>
<tr>
<td>Scleroderma, mild Romberg’s syndrome</td>
</tr>
<tr>
<td>Facial wasting, facial lipodystrophy</td>
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<tr>
<td>Visible borders of facial implants</td>
</tr>
<tr>
<td>Vocal cord paralysis</td>
</tr>
<tr>
<td>Inverted nipples, nipple augmentation</td>
</tr>
<tr>
<td>Small funnel chest</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>Urinary incontinence</td>
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<tr>
<td>Fecal incontinence</td>
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<tr>
<td>Vesicoureteral reflux</td>
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</table>

Technique

Implanting Artefill is more technique sensitive than injecting collagen. It will take some practice and patience with a quickly mastered learning curve to develop a feel for the correct injection pressure. Therefore, it is best to start treatment on the easier creases such as the glabellar frown lines.

We recommend using the “tunneling technique,” that is, moving the needle back and forth horizontally just beneath the wrinkle. Because the viscosity of Artefill is three times higher than that of Zyplast, a higher and constant pressure must be applied throughout the injection procedure, depending on the tissue and depth of placement. This simple addition to the technique is easily and quickly mastered. Artefill will give a long-lasting correction of facial folds if implanted correctly. It is important to place it into the deep dermal plane with slight overcorrection.

Local anesthetic might be indicated, as there is slightly more discomfort during injection compared with collagen. If there is no indication for a field block as in the lips, a topical anesthetic (EMLA-cream) can be used in very sensitive patients. It is applied 30 to 60 minutes before the procedure.

Generally, 27- or 26-gauge needles of a 0.5-inch length should be used. Longer needles cause more resistance to thumb pressure, resulting in lower pressure within the tissue. Use the thickness of your needle to help determine the thickness of the dermis, similar to a depth gage. The outer diameter of a 30-gauge needle is 0.3 mm, 0.4 mm for a 27-gauge needle (Figure 7), and 0.45 mm for a 26-gauge needle. The thickness of the facial dermis varies between 0.2 (lids), 0.4 (nasolabial folds), and 0.8 mm (frown lines). The thickness of the dermis in a deep crease is diminished to approximately 0.25 of its normal thickness.

At the start of the procedure, make sure that the needle is not blocked by gently squeezing a little bit of Artefill out of its tip. Insert the needle—while maintaining constant thumb pressure to the syringe—into the skin beneath and along the line of the wrinkle and start injecting while simultaneously withdrawing the needle. The dermis is much thinner than you think! Artefill should be implanted strictly deep intradermally into the reticular dermis just above the junction between dermis and subcutaneous fat (Figure 7).

In the proper plane, resistance from the reticular dermis will be felt. If the needle is placed too deep, there will be only little resistance from the fatty tissue. If Artefill is injected within the papillary dermis, a blanching effect will be seen. Should the needle be in the papillary dermis, stop injecting immediately and restart implantation one needle diameter (0.4 mm) deeper. You should always see the outline of the needle; however, the gray of the needle must never shine through the skin. Accidentally implanted within the papillary dermis, Artefill will cause a blanch effect. To correct this easily, you should evenly distribute the injected material into the surrounding tissue with firm smoothing motions of your fingernail.

At the end of each implantation, the implant is evenly massaged with the fingertip, and slight pressure is applied to any detected lump. Be aware that vigorous massage will spread the Artefill deeper into the tissue, where its effect is lost. The goal here is not only to augment the diminished thickness of the dermis but to splint the wrinkle to protect it from further motion. In this case, the diminished thickness of the dermis recovers itself within 3 months. This fact is based on the observations of many patients, whose furrows disappeared only 3 months after implantation of Artecoll. This effect has been documented with photographs during the clinical testing of Artecoll in the United States.

Interestingly, it has been observed in older patients with facial palsy or after a stroke that in time most furrows seem to disappear on the paralyzed side of the face. This serves to demonstrate that even in older patients the dermis in a furrow is able to recover its previous thickness. This same mechanism may apply to facial creases after Artefill implantation, as the creases can no longer be wrinkled to the same extent as before.
Implant Volume

Overcorrection with Artefill is not likely, as there is usually a certain density in the deep-dermal tissue layer that will allow only a certain amount of this more viscous filler to be implanted. Therefore, a second “touch-up” implantation of Artefill layered on top of the first one at a later date gives an optimal result (Figure 8). The amount of internal scar formation differs from patient to patient, as has been learned from capsule formation around breast implants. Because granulation tissue must invade the space between the microspheres (and will eventually make up 80% of the implant), one or more treatments are recommended.

For example, a first implantation of up to 0.5 cc of Artefill will be sufficient for either the frontal furrows or both glabellar frowns, one nasolabial fold, one upper or lower lip, both corners of the mouth, both Marionette lines, or two neck folds, respectively. A second treatment may become necessary after 3 to 6 weeks. In severe acne patients, up to 30 cc of Artecoll have been used over time.

Patient Instructions

Artefill can be dislodged from the deep dermal site of implantation into deeper layers through pronounced facial mimicry within the first 3 days, diminishing the expected result. Little nodules may form, especially in the lips and corners of the mouth. To prevent this, immobility is important within the first 3 days. As a reminder to the patient and to keep Artefill evenly distributed, the implant site should be taped with Blenderm or Transpore (3M Company, St. Paul, MN) for approximately 3 days. Patients are advised that there will be some swelling for the first 24 hours and areas of slight pink discoloration along the injection sites for 2 to 5 days. These are easily covered with make-up.

Patients must be told that the treated creases will improve over time. They should be informed that a second or even third Artefill treatment may be necessary in the future—depending on the amount of the individual’s connective tissue formation.

Specific Treatment Areas

Horizontal Forehead Lines

These lend themselves nicely to treatment. The gray of the needle should not show through the skin of the line. Superficial intradermal implantation may result in the formation of small granules like a string of pearls within the line. In deeper forehead lines, a second and third session will be required.

Glabellar Frown Lines

Glabellar lines generally pose no problems because the dermis is thick and the connective tissue beneath provides good support of the implant (Figures 9–11). In case a slight overcorrection is necessary, care must be taken to not inject too far caudally—otherwise, a lump produced by gravity may appear. Deep lines and furrows will require repeated treatments. Only here can they be placed intradermally because of the thickness of the skin.

Shadowed Lower Lids

A dark ring along the nasal jugular groove or arcus marginalis, called a “tear trough deformity,” can be effectively treated with Artefill. The thin skin and the orbicularis oculi muscle must be lifted from the infraorbital rim with a strand of Artefill of 2 to 3 cm in length. The implantation has to be strictly epiperiosteal, that is, beneath the orbicularis oculi muscle and just in front of the insertion of the orbital septum. The bone must be felt with the tip of the needle. retracting the needle slightly, Artefill can be spread along the lower orbital rim. Care must be taken in withdrawing the needle without pressure, as implantation into the muscle may cause a nodule and bruising.
occurs easily in this area. In severe cases, the insertion of a small implant\textsuperscript{15} may be more effective.

**Single Crow’s Feet**

Artefill is indicated only in single crow’s feet in a patient with thick skin. However, multiple crow’s feet in a patient with thin and flaccid skin are a contraindication, as the implant may shine through and appear as fine whitish granules. Heavily wrinkled lid skin is better improved by laser resurfacing or botulinum toxin.

**Facial Wasting and Cheek Depressions**

Certain patients may develop a depression or hollowing of their cheeks in front of the canine fossa or in the submalar region. This circumscribed atrophy of the malar fat pad and adjacent subcutaneous fat is pronounced in HIV-positive patients with facial lipodystrophy, which is a well-known side effect of HIV medication.\textsuperscript{16} Artefill, implanted subdermally in mild cases or epiperiosteally in severe cases, will be of great benefit. In severe cases, the atrophied Bichat’s fat pad can be augmented by means of small silicone gel implants\textsuperscript{17} or custom-made implants, which may be less expensive than a huge volume of Artefill.

**Irregularities of the Nose**

Irregularities of the nose, especially after rhinoplasty (Figures 12 and 13) or collapsed nostrils, can be improved easily through deep epiperiosteal placement of Artefill. The patient should be instructed to mold the implant during the following 3 days, if necessary. In patients with an acute nasolabial angle, it may be helpful to implant a triangle of Artefill deep intradermally at the columellar and nasal base.

**Nasolabial Folds**

Nasolabial creases are best supported by two to three strands of Artefill implanted parallelly and precisely medial to the fold (Figures 14 and 15). During the first 3 days, Artefill is still a paste and may be moved laterally by facial muscle movement. Therefore, it should be implanted directly beneath and 1 to 2 mm medially of the crease. Care must be taken not to implant too superficially. Otherwise, patients with thin skin, the implant site may appear erythematous for several months, or the implant may be visible in form of little granules. A second implantation is often necessary, especially in the lower nasolabial crease adjacent to the corners of the mouth.

**Lip Enhancement**

Enhancement of the vermillion border is one of the most rewarding indications for Artefill. There is a
natural pocket between the vermilion border and the orbicularis oris muscle that should be filled (Figure 16). Local anesthetic is recommended for the augmentation of the upper and lower lip. In order to achieve a field block, 1 cc of 1% or 2% lidocain solution is injected beneath the mucosa of the upper and lower labiogingival fold. After 2 to 5 minutes, one can direct the needle coming from lateral into the correct plane of the vermilion border. Often, one half of the “white roll” can be implanted by withdrawing the needle while injecting. A volume of 0.5 to 1.0 cc of Artefill is sufficient for each lip. A bigger volume may result in a dense mass and pain; thus, take care to augment the lips in stages. If Artecoll is well tolerated and the lips are soft after 3 months, more Artefill can be added to the same pocket.

A flattened philtrum can be raised effectively by two vertical injections of Artefill starting from below, for example, from the two corners of the Cupid’s bow within the white roll (Figures 17 and 18). Only rarely
does the implant dislodge into the surrounding tissue during implantation. In such a case, it becomes necessary to mold the implant between two fingers into the philtrum or the white roll. Injection should be performed by linear threading. Under no circumstances should the microdroplet injection technique be used in the lips. Sensitivity to touch and kissing may last for up to 1 year.

Implantation of Artefill into the red vermilion is contraindicated as the initial strand can be transformed into lumps by movement of the lips during the first few days. Also, Artefill must never be implanted into the orbicularis oris muscle, as this may cause dislocation and nodule formation. Artefill must not be superficially injected into the red mucosa of the lip, as it will feel hard and may appear white when the lip is stretched. The patient must know that submucosally implanted Artefill may always be felt with the tongue or the teeth. The best way to prevent any lumpiness would be wearing a half-inch broad rubber or velcro band over the lip and around the neck for the first 3 days.

Avoid injecting Artefill into the red of the upper lip that has excessive vertical height, as this may further lengthen the lip and hide the front teeth even more. In this case, a prior or simultaneous lip lift through a subnasal excision is recommended. Artefill is not indicated in larger defects of the vermilion such as cleft lip whistle deformity because the implant may become hard. However, Artefill implantation has resulted in outstanding improvement of the missing white roll, Cupid's bow, and philtrum after cleft lip surgery.

**Gummy Smile**

One patient disliked her gummy smile so much that she kept a mass of chewing gum in her upper labiogingival sulcus at certain occasions. One to 2 cc of Artefill placed epiperiosteally in a horizontal direction in front of the roots of the upper incisors will remedy this problem. This works even better if you elevate the mucoperiosteum under local anesthesia, close the incisions, and then inject Artefill. In severe cases, however, the insertion of a small implant is preferable.18

**Perioral Lip Lines**

Radial upper lip lines extend from tiny notches in the vermilion border and cause the lip to appear aged and lipstick to smudge. In a younger patient with good...
projection of the white roll, these wrinkles can be treated vertically from above. In patients with more than four lines, the treatment effect can be enhanced by transversely filling the entire vermilion border (see Lip Enhancement).

In the older patient, filling of the white roll and Cupid's bow prevents future development of radial lip lines. Additional augmentation of the lost philtrum from below will give the lip a more youthful look (Figure 18).

**Negative Corners of the Mouth**

The implantation between the thin skin and the directly attached muscle appears to be difficult but is very rewarding. First, the lower vermilion border is augmented horizontally approximately 1 cm in length from the mouth corner. Then 5 to 10 vertical and horizontal strands of Artefill should be placed between skin and muscle using a crisscross technique. This supports this area and slightly lifts the corner of the mouth. It may be helpful to extend some of the implant around the upper lip in a C-shaped fashion. Be aware that the skin is relatively thin and that implanting Artefill too superficially may result in telangiectasia.

On the other hand, if the implant is placed too close to the muscle, a nodule formation may result. Preferably, Artefill should be implanted in many different tunnels and always in two sessions. If Artefill is implanted into the orbicularis oris muscle, it may be formed into a module by muscle movement and may be felt inside the cheek.

**Marionette Lines**

The vertical elongation of the dystopic corners of the mouth as they extend to the mandibular border can be greatly improved by linear threading and deep intradermal crisscross implantation of Artefill.

**Horizontal Chin Fold**

The skin in the area of the mentolabial fold is relatively tight, and this fold is relatively difficult to fill with Artefill. Therefore, most patients will need a second or third implantation. There is a danger of granule formation in the fold if Artefill is implanted too superficially in the skin. In this case, the granules can be removed easily by dermabrasion.

**Horizontal Neck Folds**

The dermis of the neck is extremely thin. Therefore, a test implantation of 2 cm in length is recommended to avoid later overcorrection. Implantation results are favorable in the young patient, but often a second treatment is needed. An aged and flaccid neck is a contraindication for Artefill. Patients with dark or Asian skin must know that underlying hyperpigmentation in the folds can be more obvious after augmentation.

**Nipple Augmentation**

Flat nipples and inverted nipples grades 1 and 2 (e.g., those that can be stimulated to protrude) and volume asymmetries can easily be augmented with 0.25 to 0.5 cc of Artefill. By applying a certain volume of local anesthetic beneath the nipple, you can estimate the amount of augmentation the patient desires. After waiting for 5 minutes until the fluid has been resorbed, the nipple is lifted up, and Artefill is implanted from the side, moving the needle back and forth in order to avoid implantation into the ducts. If some material ends up in the ducts, this can easily be removed by massage. Thus far, there is no evidence that the ducts have been blocked by external implantation of Artefill. The natural swelling during pregnancy will open these ducts anyway. If you want to treat inverted nipples grades 3 and 4, Artefill implantation without blind severance of all ducts would increase the crater. Therefore, cut the ducts first as deep as possible and implant Artefill 3 to 4 days later.

**Acne Scars**

Artefill is very effective for mature mildly depressed “rolling” acne scars19 and is currently the only permanent treatment option. These can be filled either horizontally from a distance of 5 to 10 mm or in “boxcar scars” perpendicularly downward directly into the center, continuously guiding the needle back and forth. In scars, Artefill should be implanted as superficially as possible until blanching appears. This effect can be spread and vanished with the fingernail. Fresh scars should not be treated, as they may not show any improvement and actually worsen.

Ice-pick scars require a pretreatment. They should be punched and sutured or subcised with a no. 11 blade or a double-beveled Nokor needle19 at a depth of approximately 1 mm.20,21 The fresh wound cavity can easily be filled with Artefill 3 to 8 days later, after the swelling has subsided and the incision wound has firmly closed (Figures 19 and 20).

**Combined Treatments**

**Laser Treatment**

Laser treatment is no contraindication for Artefill. It is a complimentary treatment, as both Artefill and laser.
are effective in different layers of the skin. Laser peeling of the epidermis can be performed either 3 to 6 months before or preferably immediately after Artefill implantation. Swelling (edema) of the wrinkle lines and furrows enhances the effectiveness of laser treatment.

Dermabrasion and Chemical Peelings

Dermabrasion and chemical peelings are effective as laser resurfacing in the same superficial plane such as the epidermis and papillary dermis. Therefore, none of these three interfere with the implantation of Artefill, which is implanted deeper into the reticular dermis. Artefill can be implanted before or months after the resurfacing procedure.

Botulinum Toxin

Because temporary paralysis of certain facial muscles does not permanently eliminate facial furrows or wrinkles, Artefill is an excellent adjunct to Botox treatment. Artefill can be implanted either concomitantly or at a later time. The augmentation effect of Artefill may even be enhanced by the paralyzing effect of Botox, which eliminates the motion in a particular wrinkle line and therefore increases collagen remodeling.

Potential Side Effects

Technical

Because of its long-lasting effect, Artefill is less forgiving. Uneven distribution in the form of a string of pearls can be corrected by a second implantation of Artefill into the created gaps. Artefill implanted too deeply is ineffective, and the procedure must be repeated. Implantation done too superficially (Figures 21 and 22) may cause long-lasting itching and redness, which should be treated with corticosteroid cream or intradermal corticosteroid injections.

Intradermal granules may be removed by dermabrasion. Excision and suturing is rarely necessary.

Figure 19. A 43-year-old patient with typical signs of self mutilation of her face.

Figure 20. At 2.5 years after 2.5 mL of Artecoll beneath most of the depressed scars.

Figure 21. Long-lasting redness in both nasolabial folds after too superficial implantation of Artecoll. Superficial intralesional triamcinolone injections are the treatment of choice.
Dislodged nodules caused by intramuscular implantation should be softened through intralesional corticosteroid injections or, if palpable intraorally, might require excision. Excision of a nodule should always be thorough, as any residual Artefill may potentially cause secondary hypertrophic scarring.

Allergic Reactions

The PMMA microspheres are nonallergenic; however, as with all collagen preparations, allergic reactions to Artefill are possible. Among 1,280 patients involved in a European clinical trial, there was only one patient with a systemic allergic reaction reported to the manufacturer of the same collagen used in Artecoll and Artefill. We have experienced only two acute allergic reactions among more than 3,000 patients after Artecoll implantation: Both patients had negative tests before treatment. Unfortunately, this event cannot be prevented by double testing.

One case of severe anaphylactic shock after the eighth treatment with Artecoll occurred in Italy 1997. The possibility of sensitization to collagen after multiple injections has been described and must be kept in mind for Artefill as well. Thus far, the histology of excised granulomas or secondary allergy testing has not shown an allergic cause of nodule formation. Furthermore, all late allergy reactions of type IV described for collagen must be expected after Artefill implantation as well. The treatment of choice is intralesional triamcinolone injections.

Telangiectasia

Telangiectasia may occur at the implantation site in patients with very thin skin (Figure 20). It usually disappears within 6 months; however, it may require laser treatment.

Hypertrophic Scarring

Hypertrophic scarring has been reported and seen in our patients as well (Figure 22). Artefill is supposed to evoke a tissue reaction with typical granulation tissue at the beginning and later scar formation in the form of millions of microscopic capsules around the PMMA microspheres (Figure 3). As known from smooth-walled breast implants, this capsule formation can be more or less pronounced in different individuals. After too much superficial implantation of Artefill, the treated fold may rarely result in a hypertrophic scar (Figure 23) but will react favorably to repeated intralesional triamcinolone injections.

Disappearance of the Implant

PMMA is nonphagocytosable by macrophages or giant cells and nondegradable by enzymes. Therefore,
the microspheres will remain intact beneath the crease. However, if injected too deeply, it will remain in the subcutaneous fat with reduced effect on the crease. This may happen more often at the beginning of the learning curve.

Another reason for reduced efficacy is the implantation of the collagen carrier alone. Collagen melts at 40°C or under heavy pressure. If Artefill is exposed to heat or sunlight, the gel may melt, and the collagen fluid is pushed through between the microspheres, which then remain in the syringe and block the needle.

On the other hand, facial muscle movement over several years will push the implant some 10th of a millimeter deeper, and the crease may reappear after 5 to 10 years. In this case, another Artefill implant on top of the previous “splint” (Figure 8) is advisable.

Granuloma Formation

Today, true granuloma formation is a rare event in less than 0.01% of patients and may have occurred 6 to 24 months after Artecoll treatment. The pathologist will diagnose each normal granulation tissue surrounding microspheres as a foreign body granuloma. Histologically, however, a growing granuloma shows a wide distance between the microspheres filled with macrophages, giant cells, fibroblasts, and broad bands of collagen fibers (Figure 5). The cause is not understood, as they appear to develop only after a second or third implantation of Artecoll. One half of the reported patients are tracing the onset of granuloma formation back to a severe infection (influenza) or facial injury. On the other hand, granuloma formation occurs in selected patients at a rate of 0.01% to 0.1% with all injectable tissue fillers like collagen, hyaluronic acid, and particulate injectables. Intralesional injection of corticosteroid crystals is the treatment of choice (Figures 24 and 25). The significant improvement of product quality in Artefill is expected to reduce the incidence of granuloma formation even further compared with Arteplast and Artecoll in the future.

To be absolutely safe in certain patients, one can administer a test dose of Artefill behind the ear and wait for a period of time before a more extensive Artefill treatment is performed.

Treatment of Complications

Hypertrophic scarring, nodules, accidentally dislocated, or too much Artefill, as well as real granulomas, react well to intralesional long-term crystalline corticosteroids. Local steroids inhibit fibroblast activity and collagen deposition, macrophage activity and giant cell formation, and swelling, itching, or pain. A 1:1 mixture of lidocaine and triamcinolone (Kenalog or Volon-A) up to 20 mg or betamethasone (Diprosone) up to 5 mg can be injected safely through a 1-mL syringe with Luer lock and a 30-gauge needle. It must be injected strictly into the nodule while guiding the needle back and forth as corticosteroids injected into the surrounding tissue may cause temporary skin atrophy. In the case of skin atrophy, temporary filling with collagen or hyaluronic acid will level the indentation until natural recovery occurs within 3 to 12 months.

Because every patient reacts differently to corticosteroids, one has to increase the dose eventually. Two to five settings in 3-week intervals may be necessary. If this therapy is started early and aggressively, surgical
excision will not be necessary. The danger of cortisone atrophy might be reduced by the injection of antimitotic agents. 27 5-Fluoro-uracil (mixed with one-third Diprosone and one-third Lidocain), as well as Bleomycin, has been injected intratresionally into keloids. Minocycline (2 × 100 mg daily) has been given systemically together with prednisone in a diffuse silicone granulomas. 29

Conclusion

During its 10 years of clinical use, Artecoll has proven to be a reliable and predictable soft tissue filler substance. Having almost solved its initial problems of granuloma formation, Artefill still requires a learning curve because of its higher viscosity and persistence. Technical mistakes in form of uneven distribution, implantation into facial muscles, and injection into the subcutaneous fat are common at the beginning and have caused some physicians to stop implanting Artecoll. However, if the injector’s skills improve and knowledge about the effect of crystalline corticosteroids grows to ensure self-confidence, the number of satisfied physicians and patients will increase.

There is a widening spectrum of rejuvenation procedures on the aesthetic market, 2 where every product may have its niche. Many of them are complementary to each other. Even the most sophisticated face-lifting procedure does not eliminate a deep nasolabial fold. Chemical peels and laser resurfacing of lips and cheeks are effective ways to get rid of all superficial fine wrinkles but do not level deeper radial lip lines for example. Botulinum toxin is a safe way of paralyzing frontal and orbicularis oculi muscles for a short period; however, used in the lower face by a nonexperienced injector, it may cause reversible but distressful muscle paralysis and drooling. Implants for facial bone augmentation may not be of the right size or may not fit exactly. In all these cases, Artefill can be used as a perfect adjunct initially or later.

The price of Artefill is about twice that of a collagen or hyaluronic acid treatment. However, Artefill is injected more economically, as one does not loose material during implantation because of its higher viscosity. All eight investigators of the U.S. clinical trial 30 have used nearly twice as much Zyplast than Artecoll to achieve the same results in facial wrinkles at 1 and 3 months. At all later time points, Artecoll was significantly more effective than Zyplast in the nasolabial folds, as judged by “blinded” observers from standardized photographs. Patient satisfaction and physician satisfaction were significantly higher in the Artecoll group for all treated facial areas compared with Zyplast at 6 months.

A great number of patients and physicians are unsatisfied with the necessity of repeating injections with presently available filler substances every 3 to 6 months. Other physicians voice concerns about using permanent materials in dynamic areas of the face. The patient should have a choice. If he or she is happy with an initial collagen or hyaluronic acid treatment, he or she may desire a longer lasting substance. Artefill injections require more technical skills because once implanted they are “less forgiving.” The rate of side effects and complications after Artecoll treatment in the U.S. trial was comparable to those after collagen injections. 30 However, Artecoll side effects require a wider knowledge, training, and armamentarium to salvage. On the other hand, compared with collagen patients, three times more Artecoll patients (91%) were satisfied with the treatment and would ask for it again. 9

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References

Commentary

Artecoll has been widely available in Canada since September 1998. A consensus panel of nine specialist physicians from various disciplines (Dermatology, Otolaryngology, Plastic Surgery) was convened in Toronto, Canada, on February 19, 2002, to provide the first North American long-term assessment of this product. I had the privilege of serving as facilitator for this meeting. The group, as a whole, identified and prioritized the topics to be covered before initiating a dialogue.

During this expert roundtable discussion of the clinical uses of Artecoll, consensus was reached on a number of important issues. First, and foremost, an overall satisfaction with the product’s safety and efficacy was expressed by all panelists who currently use the product. The major shortcomings of the product relate to cost, when a large amount is required for certain procedures, uneven dispersion, difficulty to inject it, and potential adverse sequelae. At this time, it is too early to determine long-term (several decades) side effects after Artecoll implantation, but based on the use of PMMA in other applications, none would be anticipated. However, short-term side effects have been reported. Granuloma formation has occurred in less than 1 in 5,000 treated patients. Some of the panelists had seen one or two instances of this, but none reported having seen greater numbers than this. Of interest is the fact that most of these reactions seem to occur in the perioral region, particularly in the lips. Whereas granulomas clinically present as large inflammatory lesions, uninflamed lumps and bumps can occur as a result of using too much material, resulting in “overfill.”

Lip enhancement was discussed specifically, and the consensus was that a two-hand approach was favored. In this method, the thumb and forefinger of the nondominant hand are used to pinch the lip and form a channel into which the material is injected. Massage will also help yield an even distribution of material into the treatment site.

The suggestions made by the consensus panel have resulted in some positive changes and additions to the use of Artecoll in Canada. The substitution of a 26-gauge needle for the previous 27-gauge needle has already been accomplished, and clinicians here are finding it easier to inject Artecoll through this slightly larger needle. In addition, the material flows more evenly through the larger gauge needle. A new educational brochure, provided by Canderm Pharma, Inc., the Canadian Artecoll distributor, is also available to Canadian clinicians for distribution to potential Artecoll patients. Other ideas that the consensus panel would like to see implemented include the encouragement of more scholarly research on safety, efficacy, and clinical applications of Artecoll and the development of formal clinical guidelines, which would help clinicians to more readily differentiate simple bumps, which tend to be more responsive to intralesional corticosteroid injection, from true granulomas.

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