Soft tissue fillers for wrinkle treatment and facial reshaping offer numerous advantages for both doctors and patients. They are extremely well tolerated and efficacious and can produce long-lasting improvement with regular use. In this article a detailed, thorough review of the resorbable injectable filler implants available on the international market is offered and the most suitable for various treatment areas are identified. The chemical nature, formulation, indications, recommendations for technique, and possible side effects of each family of fillers are described. (Aesthetic Surg J 2004;24:33-46).

Comparison of Resorbable Soft Tissue Fillers

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The ideal injectable material for filling wrinkles and restoring volume to the face should not only offer aesthetic, reproducible, and long-lasting results but should also be safe, with minimal complications and risk of migration. It should also be easy to use and reasonably priced.

In recent years, a variety of injectable fillers has appeared on the international market, including both synthetic products and those derived from natural substances or extracted from animal or human cells. I have drawn up a list of the available resorbable filler products, particularly those most frequently used, and have studied their chemical natures, formulations, methods of injection or implantation, most common indications, and possible side effects.

The different families of resorbable filling materials are:

• Collagen-containing fillers, comprising substances containing collagen obtained from human or animal cells;
• Autologous fat;
• Fillers containing hyaluronic acid, either of animal origin or biosynthetic; and
• Products containing polylactic acid.

Products of mixed composition that contain both resorbable and nonresorbable components were excluded from this study.

Human Collagen

A number of firms market human collagen, either in the form of autologous collagen obtained from the donor or isogenic collagen obtained from a donor or even cadavers. These products have a very limited distribution in Europe but are used more widely in the United States.

Autogenic human collagen

The use of autogenetic human collagen eliminates any risk of virus or prion transmission. However, the preparation time for the product is relatively long and requires a prior surgical procedure for sampling of the material, which is reinjected after treatment by a competent laboratory. Autologen. Introduced at the end of the 1980s, Autologen (Collagenesis, Inc., Beverly, MA) was the first autologous injectable agent on the market. Autologen is a dispersion of intact collagen fibers and a matrix of collagen tissue obtained from the clean skin of the patient during a plastic surgery procedure (mammaplasty, abdominoplasty, face lift, blepharoplasty). A skin biopsy is inadequate. Because the injected material is autologous and no allergic reactions were reported in a sufficient number of patients, the United States Food and Drug Administration (FDA) does not consider it necessary to perform a test before Augologen injection.

The skin excision, placed in a sterile container, is sent to the manufacturer’s laboratory for treatment. As a general rule, 10 to 13 cm² of excised skin is required to produce 1 mL of Autologen 5%.

The dermis is sprayed into a sterile buffer to form a dispersion of intact collagen fibers. The dispersed collagen fibers are washed in a sterile phosphate buffer and concentrated by means of centrifugation. The substance obtained is packaged in sterile 1-mL Luer-Lok syringes.
and labeled with a unique identification code for the donor-recipient. Preparation of Autologen by the laboratory takes 3 to 4 weeks; the practitioner may then store the finished product in a refrigerator for as long as 6 months.

Autologen is injected into the middle dermis with a 30-gauge needle. Because the injection is painful and the preparation does not contain an anesthetic, anesthesia (EMLA, AstaZeneca Pharmaceuticals, Wilmington, DE; or lidocaine injection) of the treatment area is recommended. It is also recommended that the syringe be taken out of the refrigerator approximately 1 hour before the injection. At least 3 injections, a few weeks apart, are needed to obtain a satisfactory result, provided that each treatment is overcorrected by 30%.1

A comparative trial between Zyplast (Inamed, Santa Barbara, CA) and Autologen has shown no significant difference between these fillers with respect to clinical persistence 12 weeks after injection. Unfortunately, the trial was not continued beyond 12 weeks.2

A trial in 25 patients demonstrated that 1 injection produced correction of 50% to 75% for as long as 3 months or 50% at 6 months, that 2 injections produced correction of 75% after 6 months, and that 3 injections produced correction of more than 75% at 12 months.3 Fagien1 described results 6 months after treatment of deep glabellar wrinkles with Autologen (4 sessions, 1.5 mL of Autologen in total). This author also noted good results 6 months after injection of 4.0 mL of Autologen (3 sessions) in the treatment of deep nasolabial folds.

The duration of treatment depends on the region treated, the injection technique, and the volume of Autologen administered. No significant side effects have been reported. It must be noted, however, that moderately severe erythema may last for 48 hours after the injection.3,4 Preparation of the autologous collagen from a patient-tissue sample is expensive5 ($995/sample), and yield varies, depending on the individual and the anatomic areas from which collagen is harvested.

Isolagen. Since 1998, autologous fibroblast cultures have been used to correct wrinkles, scars, and other skin defects. Boss et al6 described a method of injecting autologous fibroblasts obtained from a 3-mm skin excision from the retroauricular area, an area protected from UV light. The sample is immediately placed in a culture medium provided by Isolagen Laboratories (Houston, TX) and must reach the laboratory by the day after sampling in an isothermic container. The fibroblasts and type I collagen are developed in a culture medium for 4 to 6 weeks. Six weeks after sampling, an injection test (0.1 mL) is administered to the patient in the forearm; any sign of an allergic reaction is recorded. Two weeks after the test, approximately 1 mL of the autologous material is available for implantation. Additional injections, 1 mL each, are available every 2 weeks until optimal correction is obtained.

Isolagen is a very fluid liquid that is injected into the superficial dermis with a 30-gauge needle. Overcorrection of 300% is recommended for suitable aesthetic results.5,7 When the material is implanted, the carrier is absorbed and the overcorrection rapidly disappears. As a rule, 4 to 6 injection sessions are required.

The level of correction achieved depends on the defect, the patient’s age, and the ability of the patient’s fibroblasts to create collagen. Patients older than 60 years are not good candidates for this technique because their skin is no longer able to produce vigorous fibroblasts. Boss et al6 reported a study in which 92% of 94 patients were satisfied with the results 12 months after treatment. In another study, histologic sections taken 6 months after treatment (3 1-mL injections administered at 2- to 3-week intervals) demonstrated an improvement in the thickness and density of collagen.8

This technique has several disadvantages. The Isolagen preparation must be injected within 48 hours. It offers more effective correction of periorbital wrinkles or perioral wrinkles than of deep furrows.9 The improvement obtained is poor compared with that of other techniques, such as bovine collagen implants or hyaluronic acid, and correction is not immediate. Fagien and Elson10 concluded that the results obtained with this technique were rather disappointing. In addition, Isolagen is expensive ($495/1 mL).

**Isogenic human collagen**

**Alloderm and Cymetra.** Alloderm (LifeCell, Branchburg, NJ) has been used in the treatment of burns and for transplantation in periodontal surgery. In aesthetic surgery, it is used to increase lip volume, to correct nasolabial folds, and to treat scars. Alloderm is an acellular dermal graft material obtained from cadavers or from a tissue bank that provides an acellular matrix of dermal components, including collagen, elastin, and glycosaminoglycans. The cell components of the epidermis and dermis that induce an antigenic reaction and implant rejection are removed from the donor tissue.

The dermis skin is examined in accordance with FDA requirements and regulations relating to human tissue,
which include blood tests on the donor for hepatitis B and C, human immunodeficiency viruses 1 and 2, syphilis, and human T-lymphotrophic virus type I. The donor’s medical and social history must also be closely examined to identify risk factors for viral infection. In addition, the tissue-treatment process, which comprises 2 stages, is designed to prevent transmission of viral diseases. No cases of transmissible viral disease have been reported in patients who have received this treatment since its introduction in 1992.

AlloDerm is offered in the form of sheets that are implanted through an incision in the treatment area. It must be reconstituted in a saline solution approximately 10 minutes before implantation. Implantation requires the use of a local anesthetic. AlloDerm is used to increase lip volume, to correct nasolabial folds, and to treat scars.

Infection of the incised/sutured sites has been attributed to abscess formation around the suture rather than to the graft itself. Cases of labial herpes have also been reported; prophylactic antiviral therapy must be prescribed for patients with a history of labial herpes.

AlloDerm has recently become available in a micronized injectable form, marketed under the name Cymetra (average particle size 123 μm). Cymetra is provided in the form of an aseptic powder reconstituted with lidocaine 0.5% with 1:200 000 epinephrine immediately before injection. It is injected with a 26-gauge needle.

A comparative study of treatment with Cymetra (19 patients) versus Zyplast (25 patients) for lip rejuvenation has shown that 1 week after injection, the clinical effects are more visible with Zyplast than with Cymetra. No significant difference was noted between the 2 substances at 3 and 6 months, but it appears that the results at 12 months are better (although more heterogeneous) with Cymetra than with Zyplast.

Dermalogen. Dermalogen (Collagenesis Corp., Beverly, MA) is obtained from cadaver tissues that have been carefully selected to help eliminate the risks of viral and bacterial infection. The tissues are then treated to (reportedly) guarantee safety in accordance with a procedure that includes 2 virus- and prion-inactivation stages, followed by sterilization in accordance with standard methods.

The injection technique for Dermalogen is the same one used for Autologen: injection into the middle dermis/deep dermis with a 30-gauge needle. Because the injection is painful, use of a local anesthetic is recommended.

Clinical indications for the use of Dermalogen include correction of obvious nasolabial folds, perioral wrinkles, glabellar wrinkles, and depressed scars, as well as increasing lip volume. Overcorrection of 20% to 30% is recommended at each session. An average of 3 injection sessions is required for satisfactory correction.

Prolonged erythema and acneiform rashes were noted in 10% of patients in a study of 130 patients. The manufacturer does not recommend a pretreatment allergy test, although 1 case of foreign-body reaction 4 weeks after a test injection of 1 mL of Dermalogen in the forearm has been described by Moody and Sengelmann. Klein also reported several positive skin tests with Dermalogen and 1 case of secondary reaction characterized by redness, swelling, and hyperpigmentation of the treated sites after Dermaologen implantation.

A comparative study of Dermalogen and Zyplast was conducted by Scalfani et al. Seventeen patients received 2 injections (0.5 mL of each product) into the periauricular region. No specific clinical differences between the 2 implants were found 12 weeks after implantation.

Facian. Facian (Fascia Biosystems, Beverly Hills, CA) is a biomaterial extracted from the fascia lata muscles of human cadavers and treated in accordance with FDA standards to help eliminate the any risk of viral or bacterial contamination. The product is available in particles of different sizes (<2 mm, <1 mm, <0.5 mm) and must be rehydrated with 3 mL of lidocaine 0.3% or a saline solution before injection. The implant is injected into the subdermis with a 16- to 22-gauge needle, depending on particle size. Clinical follow-up of 6 to 9 months in 81 patients who received injections of particulate fascia lata demonstrated a satisfactory duration of results for 4 months. No local or systemic hypersensitivity reactions were reported in this study. Few other studies of this product have been conducted.

Section summary

Implantable materials containing autogenous or isogenous human collagen have a limited presence on the European market because preparation of the injectable solutions is relatively difficult, only a small number of long-term clinical trials of the substances have been performed, and the cost of these products is relatively high. By contrast, substances such as bovine collagen and hyaluronic acid are offered in ready-to-use syringes and offer both considerable safety and satisfactory efficacy.
Bovine Collagen

American bovine collagen is currently the most widely used filler material. Three products, manufactured and distributed by Inamed, are available: Zyderm I, Zyderm II, and Zyplast.

Chemical nature of the molecule

Collagen is the most abundant protein in the human body and is one of the fundamental constituents of connective tissue, particularly of elastic fibers of the skin. A collagen molecule consists of a triple helix of large peptide chains (300 nm long). Each chain consists mostly of glycine (1 of 3 amino acids), lysine, and proline. It does not contain tryptophan. Zyderm and Zyplast consist of a suspension of bovine dermal collagen in physiologic saline solution containing lidocaine. After purification, this collagen is subjected to selective hydrolysis of the peptide ends of the molecule, the most antigenic fractions.

Although the immunogenicity of these products is high compared with that of other fillers, it varies in different reports. The authors of various studies have reported that 1.3% to 5% of patients demonstrate reactions to the implants during the test or, subsequently, at the injection sites. These reactions may occur days or months after the injection, so it is essential to perform 1 or even 2 tests before starting injections. Zyderm and Zyplast must be stored in a constant cold chain between 2°C and 8°C.

Indications and injection techniques

Table 1 summarizes the indications for Zyderm I, Zyderm II, and Zyplast and lists the recommended injection technique for each. After intradermal injection, Zyderm and Zyplast implants mix with the skin’s natural collagen and subsequently disappear over the following 3 to 12 months, depending on the nature of the product and individual patient factors.3

Table 1. Collagen: characteristics and indications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Zyderm I</th>
<th>Zyderm II</th>
<th>Zyplast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Fluid</td>
<td>Fluid</td>
<td>Dense</td>
</tr>
<tr>
<td>Concentration</td>
<td>35 mg/mL; noncrosslinked</td>
<td>65 mg/mL; noncrosslinked</td>
<td>35 mg/mL; crosslinked</td>
</tr>
<tr>
<td>Level of injection</td>
<td>Superficial dermis</td>
<td>Middle dermis</td>
<td>Deep dermis</td>
</tr>
<tr>
<td>Indications</td>
<td>Fine wrinkles</td>
<td>Moderate wrinkles</td>
<td>Deep wrinkles and volumes</td>
</tr>
<tr>
<td>Needle</td>
<td>30-gauge 1/2</td>
<td>30-gauge 1/2</td>
<td>27-gauge 1/2</td>
</tr>
<tr>
<td>Injection technique</td>
<td>Retrotracking, multipuncture</td>
<td>Retrotracking, multipuncture</td>
<td>Retrotracking</td>
</tr>
</tbody>
</table>

Contraindications and tests

Contraindications and precautions for use for bovine collagen include:

- history of serious allergy and allergies to lidocaine (a component of Zyderm and Zyplast implants),
- autoimmune and inflammatory disorders,
- history of anaphylactic reactions, background of allergy,
- previous skin hypersensitivity reactions to collagen implants,
- immunosuppressant therapy,
- pregnancy or breastfeeding.

Detailed questioning of the patient, including personal and family medical history, is necessary to exclude patients with these contraindications before the patient’s reaction to the material is tested. A double test is recommended because positive reactions to treatment have been reported in 0.3% to 1.5% of patients even after clinical selection and initial testing.

The first injection (0.1 mL) is given in the anterior aspect of the forearm, followed by a reading at 72 hours. A positive reaction is characterized by a change in the contour of the injected implant, erythema, edema, occasionally pruritus and, rarely, by an indurated papule or inflamed dermal nodule. All positive reactions contraindicate collagen injections. If there is any doubt, bovine (ACACB) and human (ACACH) anticollagen antibodies must be measured.

Duration of treatment

The clinical results I have obtained with Zyderm and
Zyplast implants are consistent with findings published by other authors.\cite{20, 21} Zyderm I corrects fine lines quite well, particularly fine perioral and crow’s-feet lines. One of the disadvantages of this product is the white color of the gel. If the implant is injected into very thin skin, it may be seen through the skin, resulting in a slight off-white coloration at the injection site. The results last approximately 3 months. Depending on the quality of the skin and the type of correction, superior efficacy may be obtained over time. In the case of more obvious lines, a superficial multipuncture injection may be performed. Zyderm II, which is designed to correct average lines, offers an average duration of 3 to 6 months. It may also be used in patients with extremely thin, estrogen-deficient skin. This implant may be injected into the middle or deep dermis.

Zyplast is designed to correct deep wrinkles in thick skin and to restore facial volume (lips and outline of the face). It generally lasts 6 to 12 months.

As is the case with all resorbable implants, longevity of collagen implants depends largely on the quality of the patient’s skin, the nature of the lesions being treated, and the patient’s age. As a general rule, the younger the patient, the longer the interval between injection sessions. In older patients, the interval between injection sessions must be shorter to retain the benefits of treatment.

### Table 2. Side effects produced by collagen injections despite negative test-injection results

<table>
<thead>
<tr>
<th>Reference</th>
<th>Product</th>
<th>Area treated</th>
<th>Time before side effects are triggered</th>
<th>Description of side effects</th>
<th>Treatment of side effects</th>
<th>Duration of side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz-Esparza, Bailin, and Bailin\cite{48}</td>
<td>Zyderm</td>
<td>Perioral wrinkles</td>
<td>A few weeks</td>
<td>Nodules, induration, erythema; granulomas confirmed by biopsy</td>
<td>Betamethasone 9 mg IM + Temovate cream + prednisolone 40 mg per os</td>
<td>6 months</td>
</tr>
<tr>
<td>Baumann and Kerdel\cite{49}</td>
<td>Zyderm I and Zyplast</td>
<td>Forehead, glabellar region, crow’s feet, nasolabial folds</td>
<td>3 days</td>
<td>Swelling, redness, itching at injection sites</td>
<td>Start treatment with cyclosporin 175 mg per os (5 mg/kg/day) for 18 days: complete resolution of the hypersensitivity reaction</td>
<td>47 days</td>
</tr>
<tr>
<td>Moscona, Bergman, Friedman, and Birnbaum\cite{50}</td>
<td>Zyderm I</td>
<td>Nasolabial folds, glabellar region, around the lips</td>
<td>2.5 years</td>
<td>Swelling, indurated erythematous plaques around mouth and on lips; indurated nodules or nasolabial folds and glabellar region</td>
<td>Prednisolone 60 mg/day for several weeks; Recurrence of side effects: injections of triamcinolone acetonide for 1 year</td>
<td>&gt; 1.5 yr</td>
</tr>
</tbody>
</table>
Side effects

Table 2 summarizes recent reports on the side effects of treatment. A study performed by Castrow and Krull, on behalf of 316 practitioners, covering approximately 7,000 patients who demonstrated negative test results revealed a side-effect rate at the injection site of 1.5%. The reactions were mostly limited to the injection site: erythema, induration, itching, and pain. In general, these reactions lasted 4 to 6 months; in a few cases they lasted more than 1 year. Other reactions included arthralgia (6.5%) and local granulomas (5%, confirmed in 4 of 5 cases through biopsy). Abscesses were reported at a frequency of 4 cases per 10,000 patients. These reactions develop, on average, 8 to 12 weeks after the injection, after 1 or more collagen injections. They are characterized by a nodule or papule at the injection site, severe swelling, erythema, and induration of the surrounding tissues. The abscess is different from the collagen hypersensitivity reaction, which is also characterized by induration and erythema but is not fluctuant. The punctured or evacuated pus is generally aseptic. The patients carry bovine anticollagen antibodies. These abscesses are considered the expression of a hypersensitivity reaction.

Cases of necrosis have been reported at a rate of 9 per 10,000. The local necrosis reaction after injection of collagen is not related to the implant itself but to obstruction of a blood vessel or ischemic necrosis. Bovine collagen remains the reference filling implant, although delayed hypersensitivity is common. However, some patients do not wish to receive a product of animal origin. They are increasingly choosing treatment with fillers consisting of hyaluronic acid of nonanimal origin.

Autologous Fat

Reinjection of autologous fat—the autologous biologic implant par excellence—is a useful technique that has many applications in plastic surgery. Illouz, followed by Fournier, was the first surgeon to use autologous fat extensively as a filler. More recently, Coleman developed a technique of short centrifugation that facilitated both implantation of the product (obtaining a true spaghetti of fat to be reinjected) and appeared to increase the implant’s longevity by reducing the presence of impurities and the risk of cystic steatonecrosis of the injected fat.

For perfect asepsis, the fat must be removed under locoregional or even general anesthesia in the operating theater. It is then centrifuged and purified to extract the plasma and destroy adipocytes and hemoglobin generated by the microtrauma of sampling. The purified fat can then be reinjected.

This technique is commonly used in the context of facial liposhaping and can be used to add volume to thin faces when patients have areas from which to extract fat. It may or may not be associated with other surgical rejuvenation procedures such as cervico-face lift followed by augmentation of the cheeks, the cheek-palpebral furrow, the nasolabial furrows, and, possibly, reshaping of the lips. One disadvantage of the procedure is that postoperative side effects of severe edema and bruising prevent patients from returning immediately to their social lives.

Resorption of the reinjected fat is extremely variable. If too much fat is injected, considerable edema and inflammation at the injection site can occur because the technique is relatively traumatic. This in turn results in severe destruction part of the reinjected fat by classical inflammatory mechanisms, including phagocytosis by macrophages, in the first posttreatment weeks. Excess reimplantation also tends to promote local devascularization, which may lead to the development of small clusters of cystic steatonecrosis.

Optimal technique requires the use of an appropriate volume of filler for augmentation, including moderate over-correction, followed by a reinjection session 1 year later.

With this protocol, average persistence of 50% of the reinjected product is obtained after 2 years (range 30%–70%). This level of persistence was earlier reported in Illouz’ studies. The technique is useful but requires surgical conditions of asepsis, minimal anesthesia, and a patient with an available fat mass. It is not indicated for very thin patients.

Hyaluronic Acid

Hyaluronic acid is a ubiquitous molecule present in all connective tissue, the dermis, joints, interstitial membranes, and the vitreous body of the eye. Chemically, hyaluronic acid is a long-chain polysaccharide of high molecular weight formed from repeated disaccharide units of glucuronic acid and N-acetyl glucosamine (Figure). The main biologic function of hyaluronic acid in the extracellular matrix is stabilization of extracellular structures and formation of the matrix fluid in which collagen and elastic fibers are intermixed. The polyanionic hyaluronic matrix is highly permeable and regulates transport of solutions in the extracellular space, acting as a charged molecular trap for metabolites of different sizes and charges.
Hyaluronic acid also plays an important role in regulating the movement and function of cells and in developing and remodeling tissues. The biologic functions of hyaluronic acid are related to its physical and rheologic characteristics of elasticity and viscosity. Because of its viscoelastic properties, stabilizing role, and protective action on cell membranes, hyaluronic acid represents an ideal material with which to fill skin depressions (Table 3). However, it degrades quickly (within days) in skin tissues. Three mechanisms contribute to its degradation: free radicals; hyaluronidases, specific enzymes; and temperature. For its in situ life to be extended, hyaluronic acid must be crosslinked with multifunctional agents. Crosslinking involves the binding molecules of hyaluronic acid to each other by chemical bridges at the anchorage sites of the molecule to yield a single molecule. This chemical modification changes the physical and rheological characteristics of the hyaluronic acid but does not reduce its biocompatibility. Crosslinked hyaluronic acid remains bioresorbable, although it is resorbed more slowly because the crosslinked material is rendered more resistant to heat and enzymatic degradation than unmodified hyaluronic acid and the enzymes cannot enter the network as easily. In addition, because the molecules are linked there is no possibility for migration.

### Products, uses, and associated injection techniques

Products consisting of noncrosslinked hyaluronic acid such as AcHyal (Meiji Seika Keisha Ltd., Japan), Hyaluderm (LCA, La Rochelle, France), and Ial-System...
and Hyal-System (Fidia SpA, Abano Terme, Italy) are all indicated for use in aesthetic practice. However, they are not designed to fill skin depressions or wrinkles because their longevity is generally less than 3 months; they can be used only for skin rehydration or facial revitalization. Consequently, they will not be discussed further here.

In the European Union, implants for filling wrinkles consisting of hyaluronic acid are classified as medical devices. As such, they must meet the requirements of directive 93/42/CEE relating to medical devices. These products are approved for use in Canada. In the United States, Restylane was recently approved by the FDA, and an FDA panel has recommended approval of Hylaform. The implants available on the European market — of animal origin (extracted from the coxcomb) or nonanimal origin (obtained through biotechnology) are listed in Table 4.

So that they may offer the most appropriate implants for different types of wrinkles and skin, manufacturers generally offer several products that differ with respect to viscosity and concentration or particle size (Table 5). Juvéderm (Leaderm, Paris, France) is available in hyaluronic acid concentrations of 24 mg/g (Juvéderm 18) or 24 mg/g (Juvéderm 24, 24HV, and 30). Products in the Restylane/Perlane range (Q-Med, Uppsala, Sweden) have a concentration of 20 mg/g. Perlane has approximately 10,000 particles of gel per milliliter, Restylane 100,000, and Restylane Fine Lines 200,000. The products in the Hylaform range (Hylaform, Hylaform Plus, and Hylaform Fine Lines; Genyme, distributed by Inamed) all have a hyaluronic acid concentration of 5.5 mg/g and differ only with respect to the mechanical properties of the gel. The contraindications for hyaluronic acid products are similar to those for collagen. Hylaform is contraindicated in patients who are allergic to products of bird origin. Unlike collagen, these products are stored at ambient temperature.

**Duration of results**

The authors of a double-blind, randomized multicenter trial involving 138 patients compared the efficacy and tolerability of hyaluronic acid (Restylane) and bovine collagen (Zyplast) in the treatment of nasolabial folds. These authors found that for an optimal cosmetic result, a lower implant volume was required for hyaluronic acid

### Table 5. Characteristics of fillers containing hyaluronic acid

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hylaform</th>
<th>Restylane/Perlane</th>
<th>Juvéderm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Animal</td>
<td>Nonanimal; bacterial strain <em>Streptococcus</em></td>
<td>Nonanimal; bacterial strain <em>Streptococcus equi</em></td>
</tr>
<tr>
<td>[NaHa]AQ43</td>
<td>5 mg/g for the 3 implants in the range</td>
<td>20 mg/g for the 3 implants in the range</td>
<td>18 mg/g for Juvéderm18; 24 mg/g for the other 3 implants in the range</td>
</tr>
<tr>
<td>Crosslinking Proteins</td>
<td>Not stated by manufacturer 43 μg/mL</td>
<td>Not stated by manufacturer 107 μg/mL; 155 μg/mL; 13-17 μg/mL</td>
<td>BDDE (butane-diol-diglycidylether) 39 μg/mL (manufacturer’s data established from 7 consecutive production batches defined randomly; values determined with the Lowry et al method in accordance with current European Pharmacopoeia)</td>
</tr>
<tr>
<td>Side effects</td>
<td>Hypersensitivity; inflammatory and granulomatous reactions; edema or erythema, associated pruritus; acneiform lesions</td>
<td>Immediate or delayed hypersensitivity (inflammatory nodules or nodules) Before 2000 (144,000 patients), 12 of 10,000 cases After 2000 (262,000 patients), 4 of 10,000 cases</td>
<td>Arterial embolism, bacterial infection, cystic acneiform lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edema, redness, bluish discoloration along the area treated (hemosiderin deposition; vascular injury); immediate development in all cases; Transient side effects lasting a maximum of a few weeks</td>
<td></td>
</tr>
</tbody>
</table>
than for bovine collagen. The findings also demonstrated that the frequency, severity, and duration of reactions at the injection site were similar for the two products. On the other hand, the efficacy of hyaluronic acid was superior at 6 months.

In another multicenter trial, this one involving 348 patients, the aesthetic results and tolerability of Restylane in the treatment of wrinkles (glabellar region, nasolabial folds, oral commissures, upper lip, lower lip, and vermilion border) and acne scarring was assessed. Each patient received an average of 1.68 mL per implant. In some cases, a touch-up session was performed 20 days after the initial session. This trial demonstrated that the level of correction fell by 20% between 3 and 6 months and by another 20% from 6 to 10 months. Patients therefore experienced good correction (60 to 70%) at 3 months, slight correction (40 to 50%) at 6 months, and poor correction (10 to 30%) at 10 months.

Piacquadio et al. conducted a 1-year trial in 177 patients to assess the tolerability and efficacy of Hylaform in filling wrinkles and treating scars. Depending on the practitioner, correction levels of more than 33% compared with the initial stage were obtained in 78% of patients at 3 months, 44% of patients at 6 months, and 8% of patients at 12 months. The satisfaction rate among patients was similar to that among practitioners.

Using implants from the Juvéderm range, Zbili obtained a satisfaction rate of 85% at 12 months. He offered his patients with mild to moderate wrinkles a maintenance session every 6 to 9 months after the first 2 sessions, which were performed 1 month apart. For patients with deep wrinkles, he proposed biannual follow-up sessions 30-day intervals after the initial 3 sessions. Using this protocol, Zbili obtained a satisfaction rate of 60% at 12 months.

A retrospective clinical trial of Juvéderm 30, including qualitative and quantitative evaluation by the practitioner and patients, was conducted in 49 patients over the course of 12 months. Seventy percent of patients received 2 injections, 1 to 2 months apart, of Juvéderm 30; the average amount injected at each session was 0.6 mL. The correction estimated by the practitioner to be better than 50% more than 6 months after the first injection in 45% of patients and better than 50% more than 9 months after the first injection in 20% of patients. Thirty-nine percent of patients were satisfied with the result 8 to 11 months after the first injection.

My experience with hyaluronic acid is similar. Using the most fluid implants designed to correct fine lines, such as Juvéderm 18 and Restylane Fine Lines, I see effective results between 3 and 6 months. The same effective period is obtained with the use of superficial multipuncture injections of these products.

In the case of intermediary (e.g., glabellar, cheek, or perioral) wrinkles, the efficacy of an implant such as Juvéderm 24 or Restylane ranges from 6 to 9 months. For the most noticeable wrinkles, such as nasolabial folds and oral commissures, Juvéderm 30 offers a filling effect that lasts for 12 to 15 months. Perlane appears to be a better volume expander in the immediate postoperative period, although it is thicker and more difficult to inject. It appears to have a considerably shorter duration.

To fill moderate wrinkles in patients with thin skin and to correct skin breaks, Juvéderm 24 Haute Viscosité (High Viscosity) offers efficacy lasting 12 to 15 months. It is very fluid, is particularly easy to handle, and offers high-quality filling.

**Side effects**

As is the case with all filling implants, side effects have been reported after injection of hyaluronic acid (Table 6).

The authors of a study summarizing the side effects reported after injection of Restylane and Perlane reported a side-effect rate of 1.5% in 1999 (144,000 patients) and 0.6% in 2000 (262,000 patients), including 0.7% and 0.2% hypersensitivity reactions. The authors cited 2 causes for the decline in the side-effect rate after 1999. First, dating from the middle of 1999, the composition changed with the introduction of a protein trace content 6 times lower than that of the original formulation. Second, the strain of bacteria used to produce hyaluronic acid for Restylane was changed.

In the report of their clinical experiences with Juvéderm fillers, Zbili and Bès did not describe any lasting side effects, other than transient redness and edema occurring, as a rule, immediately after injection. In addition, after 2.5 years’ use and more than 250,000 syringes of material implanted, the safety-monitoring data provided by the company show a total side-effect rate after injection of Juvéderm of less than 0.1 per 1,000 syringes. These side effects included discoloration (0.04%), edema and swelling (0.05%), 1 case of inflammatory reaction (0.004%), and 1 case of induration (0.004%). The case of induration involved a patient in whom Juvéderm 30 had been used to fill skin depressions. The skin depressions came from in situ injections...
### Table 6. Side effects reported after injection of fillers containing hyaluronic acid

<table>
<thead>
<tr>
<th>Reference</th>
<th>Product</th>
<th>No. of patients</th>
<th>Area treated</th>
<th>Time elapsed before development of side effects</th>
<th>Side effects</th>
<th>Treatment of side effects</th>
<th>Duration of side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duranti et al56</td>
<td>Restylane</td>
<td>13 (trial of 158 patients)</td>
<td>Lips</td>
<td>Week after injection</td>
<td>Intermittent swelling of implanted material</td>
<td></td>
<td>8 months</td>
<td>Reactions stimulated by exercise, sun exposure, and menstruation</td>
</tr>
<tr>
<td>Lupton et al55</td>
<td>Restylane</td>
<td>1</td>
<td>Nasolabial folds</td>
<td>2 weeks after 3rd injection</td>
<td>Multiple red, sensitive nodules</td>
<td>Minocycline, 250 mg per os twice a day for 7 days and methylprednisolone, 4 mg per os for 6 days; intralesion injections of triamcinolone acetonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shafir et al56</td>
<td>Restylane</td>
<td>1</td>
<td>Nasolabial folds</td>
<td>&lt; 2 months</td>
<td>Nodules, appearance of abscesses</td>
<td></td>
<td>6 weeks</td>
<td></td>
</tr>
<tr>
<td>Raulin et al57</td>
<td>Hylaform</td>
<td>1</td>
<td>Perioral wrinkles</td>
<td>2 days after the 2nd injection of Hylaform</td>
<td>Eczematous reaction progressing to granulomatous reaction after a few days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macedo and Recio56,59</td>
<td>Restylane</td>
<td>4</td>
<td>2-44 days after final injection</td>
<td>Itching and erythema at injection sites followed by papulocystic nodules exuding yellowish viscous material</td>
<td>Antibiotic therapy and in situ injection of methylprednisolone in 3 patients; 1 patient refused local systemic treatment: drainage of nodules</td>
<td>3-6 months</td>
<td>2 cases resolved without scarring; 1 case with slight scarring, 1 case with slight depression in injected area</td>
<td></td>
</tr>
<tr>
<td>Micheels46</td>
<td>Restylane and Hylaform</td>
<td>8 (total of 219 patients treated)</td>
<td>2 days–11 months after injection</td>
<td>Painful redness, pruritus, and edema of treated areas and, in 2 subjects, urticarial reaction in treated area</td>
<td></td>
<td>Up to 4-5 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowe et al60</td>
<td>Restylane and Hylaform</td>
<td>6 (total of 709 patients treated)</td>
<td>6-8 weeks after injections</td>
<td>Delayed inflammatory reaction characterized by induration and inflammation at injection sites, abscess in region of nasolabial furrows; on palpation, firm, sensitive, edematous, erythematous area</td>
<td>3 patients required injection of triamcinolone acetonide</td>
<td>6-24 weeks</td>
<td>All cases resolved</td>
<td></td>
</tr>
<tr>
<td>Distante et al11</td>
<td>Restylane</td>
<td>7 (trial of 348 patients)</td>
<td>1 month</td>
<td>1 case of edema and localized indurations of moderate severity; 4 cases of pain on palpation, slight but</td>
<td>Dermal corticosteroid for edema and indurations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

continued
of corticosteroids prescribed for inflammatory nodules that developed after the injection of a nonresorbable filling implant. The case of an inflammatory reaction, which occurred immediately after the injection, resolved less than 7 days after prescription of oral corticosteroids and antihistamines.

The cases of discoloration of the injected area consisted of redness (40%), hyperpigmentation (40%), and bluish discoloration of part of the nasolabial folds that were treated (20%). In all cases, these reactions occurred immediately after the injection, resolved over a few weeks, and required application of a depigmentary cream in some cases of hyperpigmentation. The bluish discoloration represents traces of hemosiderin associated with vascular injury. This type of discoloration has already been described after the injection of Restylane.42 Before reinjecting an area with this type of pigmentation, the practitioner must wait until the pigmentation has resolved; otherwise he or she runs the risk of perpetuating it. The cases of edema reported after injection of Juvederm all occurred rapidly after the injection. All resolved after a few days, either spontaneously or after oral corticosteroid treatment (64% of cases).

It is interesting to note that the protein concentrations measured in Juvederm fillers are not the lowest among the published values, obtained with the use of different analytical protocols. The side-effect rate reported after implantation of Juvederm is, however, less than 1 case per 10,000 syringes). This excellent tolerability is probably due to the choice of bacterial strain and to the purification processes used throughout the manufacture of the Juvederm implants.

### Polylactic Acid: NewFill

NewFill (Biopharmex, Luxembourg) is a synthetic implant consisting of a mixture of polylactic acid, carmellose, and mannitol (sugars) in the form of microbeads. It is a volume expander that has been used frequently for facial restructuring with a triple therapy.43

The product is presented in the form of a lyophilized powder. The practitioner must prepare the injectable solution by diluting the lyophilized powder in 2.5 mL of distilled water and 0.5 mL of 1% xylocaine. Use of xylocaine is recommended because the injection is quite painful. The manufacturer recommends that the solution be prepared at the time of use, but many practitioners say it is preferable to prepare it 12 hours before the injection through the use of mechanical shaking. Because of the microbeads, the product is injected with 26-gauge needles and requires injection of large volumes.

When used in orthopedic surgery, polylactic acid produces delayed hypersensitivity reactions, resulting in the development of foreign-body inflammatory granulomas.44,45 Similarly, in plastic surgery, many cases of granulomas have been reported after use of NewFill, particularly after implantation in the lips.42,46,47 These

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**Table 6. Side effects reported after injection of fillers containing hyaluronic acid (continued)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Product</th>
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<th>Time elapsed before development of side effects</th>
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<th>Duration of side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schanz et al41</td>
<td>Restylane</td>
<td>1</td>
<td>Glabellar</td>
<td>Minutes after injection</td>
<td>Arterial embolism</td>
<td>Low molecular weight heparin</td>
<td>5 weeks</td>
<td>Completely resolved</td>
</tr>
<tr>
<td>Honig et al42</td>
<td>Hyaluronic acid, brand not stated</td>
<td>1</td>
<td>Nasolabial folds</td>
<td>Painful erythematous nodules progressing to abscesses several months after injection; severe granulomatous allergic reaction</td>
<td>Drainage of some abscesses; recurrence of reactions necessitated excision</td>
<td></td>
<td></td>
<td>Resolved without incident after surgery</td>
</tr>
<tr>
<td>Narins et al36</td>
<td>Restylane</td>
<td>138</td>
<td>Nasolabial</td>
<td>14 days after final folds</td>
<td>Moderate to severe injection</td>
<td>None redness</td>
<td>2-3 months</td>
<td></td>
</tr>
</tbody>
</table>
granulomas may develop 6 to 12 months after injection. The granulomas are characterized by renitent nodules of fibrosis, which are painful and often inflammatory. They result from the physicochemical configuration of the microbeads and crystallization of the sugars in the beads when they dehydrate. These granulomas are very difficult to treat and require injection from the outset of a mixture of corticosteroids and 5-fluorouracil in closely spaced sessions, or even the use of hydroxychloroquine hydrochloride (Plaquenil) per os, after in situ injections have failed.

**Conclusion**

The different resorbable fillers reviewed here produce satisfactory results in terms of efficacy, tolerability, and ease of handling. Their tolerability is good, although some are better tolerated than others. The most widely used implants remain Zyderm bovine collagen, Zyplast, and 3 brands of crosslinked hyaluronic acid: Hylaform, Juvéderm, and Restylane/Perlane. The use of NewFill is on the increase, but reports of its side effects are on the increase as well.

Successful use of resorbable fillers requires scrupulous injection technique to minimize trauma produced during the injection, thorough asepsis, careful patient selection, and avoidance of blatant contraindications. It is also essential to screen patients for contraindications that are not always apparent and that may have few clinical signs, such as Hashimoto’s thyroiditis and autoimmune diseases. It is essential to adapt one’s technique to the quality of the skin and to avoid performing injections in the presence of acute disease, infection, or inflammation, even if only a viral infection is involved. Injection should be avoided during exacerbations of acne, herpes, or eczema.

It is desirable to establish injection protocols involving regular management, which maintains the patient’s level of satisfaction and increases his or her commitment to the treatment. Finally, common sense dictates that multiple filler products not be used simultaneously in the patient’s skin and that traceability labels be maintained in the patient’s records to facilitate the identification of any side effect and its possible cause. Resorbable products offer greater safety than nonresorbable products because they produce fewer side effects and because the side effects they do produce are far easier to treat. As a result, their use is particularly advisable if the practitioner has any concerns about the quality of the patient’s skin, possible estrogen deficiency, or problems associated with follow-up (e.g., patients living abroad, those who seek little medical advice, and those who are noncompliant with postinjection recommendations).

The main limitation of resorbable injectable fillers is the necessity of repeated treatments, which is both expensive and timeconsuming. Despite this drawback, the resorbable products Zyderm/Zyplast/Juvéderm and Restylane/Perlane are the most widely sold implants in Europe and seem to meet patients’ demands. They also encourage patient follow-up over time and provide good hydration for the skin, particularly the hyaluronic acids.

To use any of these products, a physician requires appropriate training to help ensure optimal patient outcomes. Although some injectable fillers now coming onto the market are described as resorbable by their manufacturers, in reality their chemical nature is incompatible with resorption.

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