Autologous Cell Therapy
Will It Replace Dermal Fillers?

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KEYWORDS

• Autologous cell therapy • Autologous fibroblasts • Wrinkle correction • Aging face
• Facial rejuvenation

KEY POINTS

- Unlike conventional fillers, cultured autologous fibroblast cells are injected more superficially and may require months to show improvement.
- This treatment offers the promise of sustained growth of living cells, which may have greater persistence than other fillers.
- Fibroblasts are not a volume filler, and fibroblast cell injections seem to be best suited for fine lines with the current on-label indication of nasolabial wrinkle correction.
- Compared with hyaluronic acid and other inert fillers, additional costs for harvesting and culturing before injection are incurred.
- Side effects are minimal and comparable with other injected agents.

INTRODUCTION

Biologic aging of the skin, often accelerated by ultraviolet radiation, involves the loss of ground substance, hyaluronic acid (HA), subcutaneous fatty tissue, and collagen and elastic fibers. The age at which this degradation occurs depends on several factors including genetic predisposition, deleterious environmental factors, cigarette smoke exposure, and excessive alcohol consumption.

Unwanted wrinkles can be corrected using a variety of methods including lasers, both ablative and nonablative, a variety of soft tissue fillers, and botulinum toxin for dynamic rhytids. For fillers, the goal is to fill depressions but, at the same time, induce a biologic response that includes replacement of degraded components such as elastin, ground substance, and HA. A variety of fillers can be used but typically degradable or semipermanent or permanent dermal fillers are in use. Of several types of products available, the most commonly used dermal filler is HA.

HAs can be extracted from animal tissue (eg, rooster combs) or produced using gene technology or fermentative processes from equine streptococcal strains not pathologic to humans. These chemically modified, cross-linked polymers are biologically inert, water insoluble, and more or less viscoelastic. To prevent the rapid degradation of HA and prolong its persistence in the skin, cross-linked HAs are injected into the dermis or subcutaneous tissue.

Unlike fillers, the newest therapy for rhytids consists of autologous cell injection. Cell injection is not a dermal filler, not stem cells (but may contain stem cells, which is under investigation), a synthetic product or foreign material, growth factors, or a cosmeceutical. Autologous fibroblasts are the first and only autologous fibroblast cell therapy approved by the US Food and Drug Administration (FDA) for aesthetic use that is

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grown from patient-specific biopsies and injected back into facial skin. This therapy most likely injects fibroblasts lost to aging and apoptosis, as well as diminished collagen. The goal is also to stimulate a biologic response that, in turn, triggers replacement of degraded components such as elastin, ground substance, and HA. With experience still at the early stages, it is possible that this cell therapy may replace superficial synthetic fillers, but currently that is doubtful. Autologous fibroblasts have a key role as a superficial filler that may be synergistic to volume fillers already used in clinical practice. Autologous fibroblasts also have possibilities to provide a long-term solution for increase of quality and quantity of dermal collagen bundles.

PIVOTAL STUDY FOR FDA CLEARANCE OF AUTOLOGOUS FIBROBLASTS

Clinical trials for autologous fibroblast therapy have been conducted since 2001. A major trial, reported in 2007, showed initial hopeful results.[1] This was a double-blind, randomized comparison of injectable living autologous fibroblast cells and placebo for the treatment of facial contour defects (N = 215). Live fibroblasts (20 million/mL) or placebo (the transport medium without living cells) were given as 3 doses administered at 1-week to 2-week intervals. Efficacy evaluations were performed 1, 2, 4, 6, 9, and 12 months after the first injection. Results indicated that living fibroblasts produced statistically significantly greater improvements in dermal deformities and acne scars than did placebo. The difference between live fibroblast injections and placebo achieved statistical significance at 6 months ($P<.0001$). At 9-month and 12-month follow-up, patients treated with live fibroblasts continued to show benefit from treatment with response rates of 75.0% and 81.6%, respectively. No serious treatment-related adverse events were reported. This finding led to the initial conclusion that autologous fibroblast injections could safely and effectively produce improvements in rhytids, acne scars, and other dermal defects continuing for at least 12 months after injection, providing the evidence that long-term improvement with cellular therapy was possible.

The current cellular therapy product called LAVIV (Fibrocell Science, Exton, PA) is the first cell therapy cleared by the FDA for aesthetic improvement and the first to show statistically significant benefit in large blinded controlled trials. This new category of cell therapy was subject to a more comprehensive study with clear end points for success than studies of most other aesthetic therapies currently provided. For clearance to treat in the United States, autologous fibroblast therapy required a parallel design, resulting in 2 large, well-powered studies that showed clinical benefit to a high degree of statistical significance.[2] Fibroblast injection was compared with placebo injection of a saline equivalent (transport medium for biopsies). The comparison was an intersubject design rather than previous trials that were intrasubject comparisons. Previous studies to treat the nasolabial fold (NLF) area were intrasubject designs in which the new treatment was compared with an existing bovine collagen injection on contralateral NLFs.[3–6]

The results of the pivotal study included data on 372 subjects. Seventy-eight percent of subjects treated with autologous fibroblast therapy and 48% of subjects treated with placebo achieved at least a 1-point improvement on the subject assessment at 6 months ($P<.001$), and 64% of subjects treated with autologous fibroblast therapy and 36% of those treated with placebo showed at least a 1-point improvement in the evaluator's assessment ($P<.001$). Adverse events were generally mild, and the treatment was well tolerated. Adverse events are listed in **Table 1**.

PREOPERATIVE: LOGISTICS OF OBTAINING BIOPSY AND SCHEDULING INJECTION

Once a patient is identified and has been informed, Fibrocell is contacted, following which a patient-specific biopsy shipper package is cataloged.

Table 1
Adverse events with autologous fibroblast therapy

	LAVIV (508 Subjects) n (%)	Vehicle (354 Subjects) n (%)
Any injection site reaction	343 (67)	144 (40)
Erythema	81 (16)	33 (9)
Bruising	54 (11)	48 (14)
Swelling	69 (14)	15 (4)
Pain	31 (6)	6 (2)
Hemorrhage	13 (3)	16 (5)
Edema	22 (4)	0
Nodules	20 (4)	3 (<1)
Papules	8 (2)	3 (<1)
Irritation	6 (1)	1 (<1)
Dermatitis	5 (1)	2 (<1)
Pruritus	5 (1)	3 (<1)