Hypertrophic Scars and Keloids, Part 2: Newer and Investigational Therapies

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Hypertrophic scars (HTSs) and keloids are benign proliferative scar tissues that represent a dysregulation in the wound healing process. These lesions not only result in disfigurement but also can cause symptoms such as pain and pruritus. Although treatments for HTSs and keloids have been extensively studied, even the most successfully proven methods can be ineffective for some patients. To treat patients refractory to more conventional therapies, newer therapies constantly are being investigated for these recalcitrant lesions. Some of these modalities employ new uses for old drugs, such as angiotensin-converting enzyme inhibitors and verapamil, while others, such as gene therapy, represent cutting-edge treatments. In part 2 of this series we highlight various new and investigational therapies; although they are not yet available for use, these therapies demonstrate exciting and promising potential for successfully managing HTSs and keloids.

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There are many emerging and innovative modalities that are in different phases of investigational study and already have shown promising results as potential treatment options for hypertrophic scars (HTSs) and keloids that are refractory to more conventional therapies. Some of these therapies include angiotensin-converting enzyme inhibitors, verapamil, tamoxifen citrate, calcineurin inhibitors, mitomycin-C, imatinib mesylate, adenovirus-mediated gene therapy, transforming growth factor β (TGF-β), IL-10, basic fibroblast growth factor (bFGF), and botulinum toxin type A (BTX-A).

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ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors are best known for their use in the treatment of cardiovascular disorders. Angiotensin-converting enzyme is responsible for the conversion of angiotensin I to angiotensin II, a vasoactive hormone that mediates many of its effects through the renin-angiotensin system.[1] Angiotensin II has been found to support tissue repair in many different organ systems (ie, vasculature, heart, brain, lung, kidney, liver, skin)[2-4] by increasing collagen production, cell migration, and promotion of growth factors and cytokines.[2] The ability of angiotensin-converting enzyme inhibitors to prevent remodeling and collagen deposition in postinfarction cardiac tissue, which correlates with improvement of ventricular function, has been well studied.[5-7] More recently,

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the role of angiotensin II in cutaneous wound healing and pathologic scarring also has been revealed.[3] It has been found that angiotensin II has similar properties in dermal tissue, as it causes increased proliferation, migration, and matrix production in human fibroblasts.[8,9] Bond et al[10] studied the mechanism of fibroblast migration by angiotensin II and found that it increased migration by increasing expression of nonmuscle myosin II, the principal motor protein in fibroblasts.[11] Bond et al[10] also found that angiotensin II receptor 1 inhibitors suppressed this increase in migration.

Angiotensin-converting enzyme inhibitors have been found to be beneficial in the treatment of keloids and HTSs in animals and humans. Captopril was found to effectively prevent HTS development in New Zealand white rabbits.[12] In one study, treatment of a hypertensive patient with low doses of enalapril (10 mg once daily) and hydrochlorothiazide (3 mg once daily) coincided with nearly complete recovery of a keloid scar after 15 days as well as complete disappearance of cesarean section scars of 25 and 30 years' duration after 3 to 4 months of treatment. Another patient who followed the same treatment regimen also showed good results after 6 months.[13] Application of captopril solution 5% in cold cream twice daily for 6 weeks led to marked improvement in a postburn keloid lesion, including reduction in scar height and erythema as well as elimination of pruritus. This topical application was not associated with any noted side effects.[14]

VERAPAMIL

Verapamil is a phenylalkylamine calcium channel blocker that alters fibroblast shape (from bipolar to spherical), induces procollagenase expression, and reduces proteins that make up extracellular matrices.[15] Increased levels of cytokines IL-6 and vascular endothelial growth factor (VEGF) have been shown to be expressed in fibroblasts from keloids, contributing to matrix abnormalities and cell proliferation.[16,17] In cell cultures, verapamil has been observed to decrease IL-6 and VEGF production in central keloid fibroblasts, translating to decreased cell proliferation and increased apoptosis.[18] In addition, intralesional verapamil appears to increase the expression of decorin, an inhibitor of fibroblast proliferation and migration.[19,20] In a prospective study of 45 earlobe keloids, the application of intralesional verapamil 7 to 14 days following surgical keloid excision and again at 1 month postprocedure, if necessary, combined with the use of pressure earrings for at least 6 months resulted in resolution of 22 keloids (55%; 40 keloids were included in follow-up) at an average follow-up interval of 28 months.[21] A single-blind, parallel-group study demonstrated that intralesional verapamil was comparable to intralesional triamcinolone acetonide in the treatment of HTSs and keloids. Both were found to produce similar end results (reduction of scar vascularity, pliability, height, and width), with intralesional triamcinolone achieving these effects faster but with a greater incidence of adverse reactions than intralesional verapamil.[22] Intralesional verapamil alone and in conjunction with intralesional triamcinolone has been observed to decrease viability and proliferation of fibroblasts in HTSs despite no changes in scar weight as compared with intralesional saline.[19]

TAMOXIFEN CITRATE

Tamoxifen citrate is a nonsteroidal agent and selective estrogen receptor modulator used in the treatment of breast cancer.[23,24] It affects keloid fibroblasts through alterations in transcription, delay, or arrest in the Gap_1 (G_1) phase of the cell cycle, as well as inhibition of different growth factors.[25] Specifically, tamoxifen citrate decreases TGF-β production in a dose-dependent manner.[26] It also has been shown to inhibit proliferation in keloid fibroblasts.[27]

Mousavi et al[24] conducted a double-blind, randomized, controlled trial of 300 patients with a history of HTSs who were undergoing surgical operations to assess the efficacy of tamoxifen citrate in preventing the development of postsurgical HTSs. The patients were randomly split into the treatment or control groups 1 month following surgery. The treatment group was administered 10 mg of tamoxifen citrate twice daily for 2 months, while the control group received a placebo. The authors found that only 52% of patients in the treatment group developed HTSs compared with 92% of the control group.[24] It has been reported that topical application of tamoxifen citrate 0.1% leads to smaller and less erythematous HTSs.[28] A prospective study of 46 burn patients with HTSs who applied tamoxifen citrate 0.1% noted improvement of all scars after 6 months of treatment.[29] Adverse reactions to treatment with tamoxifen citrate have been reported, most commonly flushing and occasionally nausea and urinary retention.[30]

CALCINEURIN INHIBITORS

Tacrolimus is a macrolide lactone derived from *Streptomyces tsukubaensis* that binds to the immunophilin FKBP-12 that inhibits calcineurin and its phosphatase activity to suppress IL-2 production. Tacrolimus also inhibits the expression of tumor necrosis factor α, a profibrotic cytokine. An elevated expression of glioma-associated oncogene homologue *gli-1* has been documented in scars and keloids[31]; *gli-1* also has been observed as a target of tacrolimus, which justifies the application of this drug in the treatment of keloids.

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In clinical practice, tacrolimus ointment 0.1% has been investigated in an open-label pilot study in which it was applied to keloids twice daily for 12 weeks. Although the results were not statistically significant, tacrolimus was observed to decrease induration, tenderness, pruritus, and erythema in the treated keloids.[32] In another clinical trial, 1 patient who applied topical tacrolimus for treatment of both atopic dermatitis and a keloid noticed clearing of the scar.[31]

Sirolimus is a mammalian target of rapamycin inhibitor. By inhibiting the mammalian target of rapamycin, a serine/threonine kinase that regulates the cell cycle and expression of extracellular proteins, sirolimus decreases collagen expression and extracellular matrix deposition.[33] In addition, sirolimus also blocks the action of IL-2 and imparts dose-dependent downregulation of the expression of VEGF, which has been found to be overproduced in keloids, particularly by the epidermis.[34,35] By decreasing VEGF production, angiogenesis is suppressed in the keloid.

MITOMYCIN-C

Mitomycin-C is an antibiotic isolated from *Streptomyces caespitosus* with antimitotic and antineoplastic properties. It is used intravenously for chemotherapy to treat a variety of cancers. Mitomycin-C inhibits DNA synthesis by forming a cross-linkage of double helix strands, thereby suppressing DNA replication. In high doses, mitomycin-C inhibits RNA and protein synthesis[36] and also has been shown to prevent scar tissue formation following glaucoma surgery, subglottic surgery (in a canine model), tracheal stenosis repair, pediatric choanal atresia surgery, and maxillary antrostomy.[37]

In the skin, mycomycin-C has been shown to inhibit fibroblast proliferation and angiogenesis, thereby limiting collagen production and serving as a treatment option for keloids and HTSs. In one study, treatment of full-thickness skin wounds with mitomycin-C resulted in decreased wound area and contraction in mice.[38] An in vitro study by Simman et al[39] first showed a decrease in keloid fibroblast density when the fibroblasts were treated with mitomycin-C versus a control.

More recently, mitomycin-C has been used topically to treat keloids in combination with surgical excision to prevent recurrence. Studies of postexcision keloids that were treated with topical mitomycin-C have noted high patient satisfaction rates and reduction of symptoms; however, these studies also reported delayed healing, incomplete disappearance of lesions, and manageable local pain.[40,41] In contrast, Stewart and Kim[42] found that 9 of 10 patients with head and neck keloids that were surgically excised and subsequently treated with topical mitomycin-C demonstrated 0% recurrence 8 months after surgery. Successful results also were achieved with topical application on earlobe keloids following surgical excision.[43]

Intralesional mitomycin-C appears to cause negative effects, such as severe pain, erythema, blistering, necrosis, and ulceration. Other side effects include mild hyperpigmentation or hypopigmentation and skin atrophy, but no serious adverse events have been reported.[44]

IMATINIB MESYLATE

Imatinib mesylate is a tyrosine kinase inhibitor used for cancer treatment. Imatinib mesylate inhibits 4 kinases: bcr-abl, c-abl, c-kit, and platelet-derived growth factor[45]; c-kit, along with its ligand, stem cell factor, or mast cell growth factor, is important in wound healing. Activated c-kit triggers mast cell degranulation, leading to fibroblast proliferation and collagen synthesis and subsequent fibrosis at sites of wound healing.[46-48] Mukhopadhyay et al[49] studied this pathway and found that stem cell factor and c-kit were upregulated in keloid scar tissue. When imatinib mesylate was applied in varying concentrations (2.5 or 5 µg/mL) to keloid fibroblasts, the authors found reduced collagen, fibronectin, and α-smooth muscle actin; diminished contraction of the collagen lattice; and decreased adenosine triphosphate synthesis in keloid fibroblasts.[49]

ADENOVIRUS-MEDIATED GENE THERAPY

Gene therapy is a new treatment modality that shows promise in the successful management of keloids. A recombinant adenovirus commonly is used as the gene delivery system, as it can infect many different cell types and does not rely on cell division for infection.[50] Topical transduction of these vectors in skin and wounds only produces transient gene expression, which lasts up to 14 days.[51] The transient property of gene therapy prevents permanent alteration of dermal tissue.[50] Transfection of various genes through the adenovirus vector has been studied both in vitro and in vivo to assess their potential as therapy for keloids, including metalloproteinase and thrombospondin 1 (METH1),[52] relaxin (RLX),[51] and IL-24.[53]

Angiogenesis is an important factor in wound healing, and microvascular abnormalities are seen in pathologic scar tissue, including increased vascularity in keloids.[54,55] Metalloproteinase and thrombospondin 1 has strong antiangiogenic activity[56]; Song et al[52] studied this property by injecting the periphery of wounds in rabbits intradermally with either high-titer recombinant adenovirus-mediated METH1 or an equal amount of empty adenovirus AdEasy-1 ten days after epithelialization. Scars from the

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treatment group were flatter and softer, less erythematous, and had reduced microvessel counts and total collagen content.[52]

Relaxin is a hormone that has been found to selectively inhibit collagen synthesis and expression in fibroblasts stimulated to overexpress collagen while not affecting basal collagen production.[57] It also causes collagen degradation, likely resulting from the upregulation of matrix metalloproteinases.[58,59] In keloid spheroids treated with adenovirus-expressing RLX (dE1-RGD/lacZ/RLX), there was marked reduction in levels of types I and III collagen, fibronectin, and elastin, as well as an increased expression of matrix metalloproteinases 1 and 3.[51]

Originally classified as a tumor suppressor molecule, IL-24 now is recognized as a cytokine that is known to cause apoptosis in cancer cells.[53,60] Some preliminary experiments have found decreased levels of IL-24 messenger RNA in keloid fibroblasts when compared to normal skin.[61,62] When an adenovirus vector–expressing green fluorescent protein and IL-24 gene (Ad-GFP/IL-24) was transfected into keloid fibroblasts and normal dermal fibroblasts, suppression of growth and induction of apoptosis were selectively seen in keloid fibroblasts but not in normal fibroblasts.[53]

Although it still is in the beginning phases of investigation, gene therapy represents a novel treatment modality with seemingly limitless potential in the treatment of keloids.

TRANSFORMING GROWTH FACTOR β

Research has revealed the importance of TGF-β in the pathogenesis of keloids. Transforming growth factor β is a protein involved in regulation of cellular proliferation, differentiation, migration, and apoptosis.[63] There are 3 isoforms of TGF-β—TGF-β1, TGF-β2, and TGF-β3[64]—each with a different role in the pathogenesis of keloids. Expression of TGF-β1 and TGF-β2 is increased in keloidal fibroblasts, leading to upregulation of collagen production.[65] On the other hand, expression of TGF-β3 is decreased[66]; it is found in high levels in embryonic tissue, which displays scarless healing.[67] Administration of TGF-β3 to wounds in animals has been found to accelerate the healing process, revealing a potential pathway for the suppression of keloid development.[68-70] Three studies of topical TGF-β3 (avotermin) applied to the wound margin have shown improvement in scar appearance compared with placebo and standard care[71]; however, the results of a phase 3 trial were unable to meet their primary and secondary end points.[72] No safety or tolerability issues were encountered during these studies.[71,72] Inhibition of TGF-β1 also appears to play a role in keloidal prevention, as it has been found to suppress the growth of keloidal fibroblasts in vitro.[73] Future studies are needed to further investigate this new therapy.

IL-10

IL-10 is a cytokine that reduces inflammatory responses. It is necessary for scarless wound repair, and its anti-inflammatory effects are mediated through the reduction of IL-6 and IL-8, which are proinflammatory cytokines.[74] The absence of IL-10 leads to an amplified inflammatory response and abnormal collagen deposition.[63] An adult murine model of wound healing revealed that injection of IL-10 forty-eight hours before wounding led to decreased inflammation and decreased expression of proinflammatory mediators compared with the control. At 3 weeks, the treated wounds showed decreased inflammation, normal dermal architecture, and no abnormal collagen deposition.[75] Currently, a phase 2 dosing study is investigating which concentration of IL-10 presents the greatest scar-reducing potential compared with placebo and standard care treatments (James Bush, unpublished data, 2009).

BASIC FIBROBLAST GROWTH FACTOR

Basic fibroblast growth factor is a polypeptide that promotes differentiation and proliferation of various cell types, including fibroblasts and keratinocytes.[76,77] Its properties allow it to regulate tissue remodeling, wound healing, angiogenesis, and tumor growth.[78-81] In rabbit models, HTSs treated with bFGF were found to have an increased expression of matrix metalloproteinase 1[82] and decreased type I collagen expression.[83] In patients with short-term suture wounds, treatment with intralesional or topical rinse bFGF immediately after surgery prevented formation of HTSs compared with controls.[84] Basic fibroblast growth factor also has been demonstrated to accelerate wound healing, thereby reducing scar formation.[83] In adult patients with second-degree burns, those treated with bFGF demonstrated significantly faster wound healing ($P<.01$), greater scar elasticity ($P<.01$), and less direct scar hardness ($P<.01$) compared with nontreated patients.[85]

BOTULINUM TOXIN TYPE A

Botulinum toxin type A (BTX-A) is a potent neurotoxin derived from *Clostridium botulinum* that causes flaccid paralysis of striated muscle[86] by inhibiting acetylcholine release at the neuromuscular junction. It is an accepted standard treatment of upper face rejuvenation.[87] Although the exact molecular mechanism of action through which BTX-A improves the appearance of keloids and HTSs is not completely understood, anti-HTS properties and a decrease in the tensile force and continuous muscle contraction during the process of wound repair have been acknowledged as possibilities.

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In one in vitro study, fibroblasts from 8 keloids were divided into control and experimental groups; the experimental group was treated with BTX-A. Measurement of cell cycle distribution demonstrated a notably higher number of experimental fibroblasts (64%) in the nonproliferative phases (G_0 and G_1) compared with the control (36%).[88]

Another study supported the ability of BTX-A to reduce the expression of TGF-β1 in fibroblasts derived from HTSs. Transforming growth factor β1 is thought to be the main regulator in the pathogenesis of HTSs and keloids and is associated with an excessive deposition of scar tissue and fibrosis.[86] Botulinum toxin type A was found to repress the growth of keloid fibroblasts and the expression of TGF-β1; in HTSs it also was found to decrease levels of connective tissue growth factor, a downstream regulator of TGF-β1 and an independent mediator of scarring and fibrosis.[89]

In a study of 19 patients, each with 1 HTS, lesions were treated with BTX-A in a single dose of 2.5 U/cm^3 (not exceeding 100 U per patient).[90] At 6 months posttreatment, all patients reported acceptable clinical improvement and high satisfaction rates. Decreases in erythema, itching sensation, and pliability scores from baseline all were statistically significant ($P<.01$).[90]

Botulinum toxin type A also has analgesic properties that are not yet completely understood but may disrupt the neuropathic painful symptoms present in some keloids.[91] No known serious adverse events have been reported.

Botulinum toxin type A appears to be a safe and effective potential treatment option that can influence cellular apoptosis and proliferation, favoring a cellular state that ultimately leads to prevention and treatment of keloids and HTSs.

CONCLUSION

Hypertrophic scars and keloids remain difficult to treat. Although many conventional therapies are available and some are used as the standard of care,[92] efficacy rates fail to reveal satisfactory results in a substantial number of recalcitrant lesions. Newer therapies constantly are being investigated as potential treatments for these lesions. Although some new therapies have only been researched on the benchtop, others have already been used to treat patients and have revealed exciting clinical results. Most are limited by a lack of research in humans and/or double-blind, controlled trials, and thus further investigation is warranted to reveal the full potential of these therapies.

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