

Scar Treatments: Preclinical and Clinical Studies

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Despite advancements in knowledge of the mechanisms of wound healing and scar formation, both normal and hypertrophic scars remain difficult to treat and impossible to prevent. Numerous therapeutic strategies have been described for the reduction and prevention of scars, yet there is no universal consensus in the literature about optimal treatment. Therapeutic approaches fall into three broad categories: alteration of the inflammatory response, modification of collagen metabolism, and surgical and physical manipulation of the shape of the scar. Current management of normal and hypertrophic scars encompasses a wide range of techniques, from traditional invasive methods such as gross excision and radiation to intralesional and topical application of agents designed to take effect on a cellular level. In this review, we present and evaluate preclinical and clinical studies of the treatment and prevention of scars using evidence-based literature to assess therapeutic strategy. Preclinical studies of emerging treatment strategies cover the transforming growth factor (TGF)- β superfamily, NSAIDs, gene therapy, and several other novel modalities. Current clinical studies of scar reduction and prevention to be assessed in this review include topical and intralesional corticosteroids, 5-fluorouracil, bleomycin, pressure therapy, silicone gel sheeting, laser therapy, surgical treatment, radiation, and combinations of techniques.

Pathophysiology of scar formation

The stages of wound healing include inflammation, proliferation, and matrix remodeling, and scar formation.¹ After initial injury, a robust inflammatory cascade is incited, during which much of the downstream outcomes of scar development is mandated. Neutrophils are the first inflammatory cells to infiltrate the wound site. Neutrophil-specific enzymes such as matrix metalloproteinases (MMPs) and collagenases likely contribute to scar formation by causing excessive tissue loss in the wound area during the inflammatory phase, leaving a large area of tissue devoid of matrix that is subsequently replaced with scar tissue during the remodeling phase. Later, macrophages

elaborate a variety of cytokines that play a central role in wound healing and granulation tissue formation.

In the final stage of wound healing, there is migration and proliferation of fibroblasts, collagen production and deposition, and angiogenesis. Neocollagenesis is induced by cytokines that are initially produced by macrophages, such as fibroblast growth factor-2, TGF- β , and insulin-like growth factor.² The remodeling process of collagen synthesis and lysis can last up to 2 years after tissue injury. There is a complex interplay between various cells, growth factors, cytokines, and components of the extracellular matrix during the wound healing process, and excessive scars result from an aberration in this orderly pattern of healing.

The etiology and mechanism of hypertrophic scarring are not fully understood. Hypertrophic scars represent an exaggerated fibroproliferative response of the dermis, which creates an imbalance of matrix degradation and collagen synthesis, resulting in excess accumulation of dermal collagen, fibronectin, glycosaminoglycan content, and increased collagen turnover.³ Dermal fibroblasts under the influence of persistently high levels of fibrogenic cytokines have been shown to play a major role in stimulating matrix production.⁴ The collagen of hypertrophic scars is a disorganized, whorl-like arrangement rather than in the normal parallel orientation.

Central to the understanding of scar formation has been the identification of some of the molecular mechanisms involved in the process. Growth factors and cytokines, such as tumor necrosis factor (TNF)- α , platelet-derived growth factor (PDGF), TGF- β , and basic fibroblast growth factor (bFGF), play a significant role during granulation tissue formation and extracellular matrix remodeling.⁵ MMPs and their inhibitors, which are responsible for homeostasis between matrix degradation and deposition, also play an important role in the pathophysiology of hypertrophic scarring.⁶

Although the exact mechanism by which the inflammatory response promotes scarring is not known, it is clear that the early inflammatory phase of wound repair drives the production of scar tissue and may dictate the final outcomes of scar. Although an inflammatory response is believed to be a key event for proper wound healing in adult skin, studies of fetal wound healing suggest that high levels of inflammation may not be a requirement for wound healing, but rather, may promote scar formation. Debate remains about whether inflammation is necessary for wound healing in adult skin, and additional studies will

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
bFGF	=	basic fibroblast growth factor
COX-2	=	cyclooxygenase-2
MMP	=	matrix metalloproteinase
PDL	=	pulsed dye laser
PGE ₂	=	prostaglandin E ₂
TAC	=	triamcinolone
TGF	=	transforming growth factor

be needed to provide conclusive evidence. It appears that the development of the scar is programmed during and by parts of the inflammatory process.

Preclinical studies

The goals of preclinical studies in development of antiscarring agents are simple and effective delivery of drug, optimal efficacy of scar reduction without complicating wound healing, minimal other side effects, and minimal drug interaction with concomitant treatments. Investigators have used numerous animal models including a rabbit ear model,⁷ mice,^{8,9} rats,¹⁰ pigs,^{11,12} and chickens¹³ to study properties of both normal and abnormal scar formation in the setting of incisional, excisional, and burn models of injury. A previous criticism of animal models was that these animals do not form hypertrophic scars similar to those found in humans. Multiple investigators have demonstrated, by direct comparison, the similarity of hypertrophic scars in animal models to human hypertrophic scars by gross, histologic, and immunohistochemical evaluation.^{14,15} An understanding of the processes of normal and abnormal scar formation in animal models is paramount to the development of new methodologies to successfully manage and potentially prevent abnormal healing of hypertrophic scars in humans. There are several emerging agents and novel applications of older agents that are currently being investigated for their potential scar reductive properties in the preclinical forum of animal models, including the TGF- β superfamily, NSAIDs, minocycline, angiotensin-converting enzyme (ACE) inhibitors, collagen synthesis inhibitors, tamoxifen, and gene therapy.

TGF- β superfamily

There has been interest in TGF- β as a potential scar-reducing agent since the 1980s.¹⁶ As previously reviewed, the fibrogenic isoforms of TGF- β have been demonstrated to have major roles in scar production.¹⁷ Both in vitro and in vivo studies of animal models have demonstrated the importance of TGF- β 1, 2, and 3 in cutaneous scarring and scarring in other organs.¹⁸ After initial injury, high levels of

TGF- β are released from degranulating platelets at the site of injury. TGF- β is a potent stimulator of chemotaxis, signaling the migration of lymphocytes, fibroblasts, monocytes, and neutrophils.¹⁹ Sustained levels of TGF- β in wound tissue are subsequently produced by macrophages, fibroblasts, keratinocytes, and endothelial cells.

Fetal wound healing differs from adult wound healing in a number of parameters including altered and downregulated inflammatory response, rapid reepithelialization, decreased angiogenesis, altered growth factor response, different rates of extracellular matrix deposition, and restoration of the architecture of the involved tissue.²⁰ By contrast, adult wound healing is characterized by a robust inflammatory response, increased neovascularization, excessive extracellular matrix deposition, and scar formation.

TGF- β was one of the first mediators found to be differentially expressed in fetal healing and was shown to promote scar tissue deposition when introduced into fetal wounds.²¹ There are major differences in the TGF- β isoforms present in fetal and adult wounds. Fetal wounds express very high levels of TGF- β 3, a skin morphogenetic factor predominantly synthesized by keratinocytes and fibroblasts and very low levels of TGF- β 1 and 2. By contrast, adult wounds express predominantly TGF- β 1 and 2,²² suggesting that the relative proportion of each isoform is likely crucial for repair with reduced scar formation. More recent studies have shown that differential expression of TGF- β isoforms, receptors, and activity modulators, rather than the mere presence or absence of TGF- β , has a major role in the regulation of fetal wound healing.²³

In normal wound healing, TGF- β 1 and 2 are potent activators of extracellular matrix gene expression and stimulate collagen and fibronectin synthesis by dermal fibroblasts.²⁴ Enhanced activity of the TGF- β isoforms 1 and 2 can lead to excessive scarring, as demonstrated in multiple animal models.^{25,26} Studies have shown that TGF- β 1 and 2 are major factors inducing collagen gene expression leading to tissue fibrosis. TGF- β 1 expression parallels increased type I collagen gene expression in fibrotic lesions.²⁷ The skin fibrillar collagen genes, *COL1A1*, *COL1A2*, *COL3A1*, and *COL5A2*, have been identified as direct targets downstream of TGF- β .²⁸ TGF- β acts through autocrine and paracrine mechanisms to regulate the interactions between cells and between cells and matrix, enhancing the production of extracellular matrix.²⁹ This ability of TGF- β to induce its own production may be important in the development of progressive scarring in pathologic fibrosis.

The broad strategy used by investigators examining TGF- β modulation as a potential scar-reducing agent has been to simulate the fetal wound healing environment by increasing the relative ratio of TGF- β 3 to TGF- β 1 and

TGF- β 2 to minimize scarring. Investigators have used anti-TGF- β 1 and 2 antibody topical treatment to decrease collagen production in vitro and reduce scarring in vivo in several animal models.³⁰ Similar results have been demonstrated by the treatment of human proliferative scar xenografts in nude rats with exogenous TGF- β 2 resulting in a significant increase in endogenous TGF- β 2, collagen I, and collagen III production. By contrast, exogenous addition of anti-TGF- β 2 antibody significantly decreased endogenous TGF- β 2, collagen I, and collagen III production.³¹ In an in vitro model using the fibroblast-populated collagen lattice, addition of TGF- β 2 antibody inhibited the function of keloid and burn hypertrophic scar fibroblasts reversed the increased contraction of fibroblast-populated collagen lattice s by proliferative scar fibroblasts treated with TGF- β 2.³² Antisense phosphorothioate oligonucleotides (OGN) against TGF- β 1 and 2 in vivo have also been used to significantly reduce postoperative scarring in rabbit and mouse models of glaucoma surgery.³³ Exogenous TGF- β 3 has been applied at the time of initial wound, resulting in reduced scarring.³⁴

Despite numerous in vitro and in vivo animal studies over the past two decades showing reduction of scar with either application of exogenous TGF- β 3 or neutralizing techniques for TGF- β 1 and 2, there have been no published reports of a large double-blinded randomized trial in humans evaluating the efficacy of the TGF- β superfamily on scar reduction. It remains to be seen what practical role, if any, the TGF- β superfamily will play in future therapeutic protocols for reduction and prevention of scars.

Nonsteroidal antiinflammatory drugs

The use of NSAIDs, such as cyclooxygenase-2 (COX-2) inhibitors, to reduce scar tissue production has been studied by multiple investigators, initially in the 1970s and more recently, within the past decade. There has been growing interest in the role of the COX-2 pathway in wound healing because studies have demonstrated the critical importance of early events of the inflammatory cascade in the downstream regulation of the outcomes of wound repair and scar formation.³⁵

A well-established early response to injury in the inflammatory cascade is induction of COX-2, which catalyzes the conversion of arachidonic acid to prostaglandin E₂ (PGE₂) and other arachidonic acid pathway end-products.³⁶ COX-2 undergoes immediate-early upregulation in response to an inflammatory stimulus and functions by producing prostaglandins that control the induction of vascular permeability and the activation and infiltration of inflammatory cells.³⁷ Although the role of prostaglandins in scar formation is not fully understood, it has been shown that enhanced expression of both COX-2 and PGE₂ can

enhance fibroblast proliferation in vitro and collagen production in wounds in vivo in rats³⁸ and mice.³⁹ These studies suggest that prostaglandins and the inflammatory cascade induced by these mediators have a role in regulation of the amount of fibrosis that occurs during wound repair.

Topical application of celecoxib, a selective COX-2 inhibitor, immediately after wounding resulted in a statistically significant reduction in local neutrophils, PGE₂ levels, TGF- β 1, collagen deposition, and scar tissue in a mouse study.⁴⁰ Topical application of COX-2 inhibitors does not have a negative effect on wound re-epithelialization or tensile strength.⁴¹ There is conflicting evidence on whether constitutive inhibition of COX-1 and COX-2 results in delayed wound healing. One study has suggested that inhibition of COX-1 may cause delayed wound healing;⁴² another study has shown that COX-1-selective inhibitors do not delay wound healing or neangiogenesis and have no effect on tensile strength in wounds.⁴¹

To investigate the function of the COX-2 pathway, several investigators have examined the healing response in the presence of the COX-2 enzymatic product and inflammatory modulator PGE₂. A study in mice showed that an intralesional injection of an exogenous PGE₂ analog caused the production of a scar when introduced into early fetal wounds.³⁹ PGE₂ likely promotes scar formation through induction of the inflammatory cascade and subsequent recruitment and activation of inflammatory cells, or it could directly stimulate fibroblasts to proliferate, amplifying collagen production and scarring.

Additional animal studies are needed to assess the efficacy and side effects of NSAIDs and COX-2 inhibitors in scar reduction and wound healing. Given the strong role of inflammation in scar formation and the fact that NSAIDs are inexpensive and readily available, there will likely be keen interest in future investigation of their potential as scar reducing agents.

Gene therapy

Few and limited studies have been performed in animal models using a gene therapy approach to investigate scar reduction. Theoretically, delivery of an antiscarring gene into fibroblasts or even keratinocytes could potentially result in reduced scarring. To date, there has not been convincing evidence that such an antiscarring gene exists. A major obstacle to successful use of gene therapy in scar reduction is that scarring is a very complicated process involving many different factors, with activation and feedback through multiple pathways, and many of the outcomes of scar formation are likely determined by the early inflammatory response to wounding.

A recent study demonstrated that adenoviral-mediated delivery of fibromodulin into human dermal fibroblasts in vitro induced a decrease of expression of TGF- β 1 and 2

precursor proteins, and an increase in expression of TGF- β 3.⁴³ The study also evaluated the effect adenoviral-mediated overexpression of fibromodulin on human dermal fibroblasts into full-thickness incisional wounds in vivo in a rabbit model, but demonstrated only modest improvements in wound healing and inconclusive results on scar formation.⁴³ In another study, dermal fibroblasts were infected in vitro with adenovirus encoding a truncated TGF- β receptor II and studied in full-thickness incisional wounds in rats. Experimental wounds had significantly less inflammatory reaction and a 49% reduction of scar area ($p < 0.05$).⁴⁴ A recent study demonstrated a modest though statistically significant reduction in hypertrophic scar formation after administration of retrovirally delivered dominant negative mutant TGF- β receptor II in a rabbit ear model of hypertrophic scarring.⁴⁵

It remains to be seen what, if any, role gene therapy will play in scar treatment. Currently, application of gene therapy strategies in animal models of scarring remains limited to a small number of studies. With further investigation and genetic coding of genes such as TGF- β 3, fibromodulin, and others, it seems likely that investigators will continue to study the potential role of gene therapy in scar prevention in the future.

Other emerging agents

A recent study found that high dose systemically administered minocycline, an antibiotic and MMP inhibitor, significantly reduced the severity of hypertrophic scarring in a rabbit model.⁴⁶ The mechanism by which minocycline reduces scar formation in this model remains unknown. Several plausible mechanisms include MMP inhibition and subsequent inhibition of keratinocyte or fibroblast migration, alteration of the inflammatory response, inhibition of apoptosis, inhibition of angiogenesis, or simply antibacterial activity in an infected or contaminated wound environment.⁴⁷ Additional studies will be needed to elucidate the mechanism of this intriguing scar reducing agent.

Several groups have investigated the role of ACE inhibitors in wound healing and scar formation. It is well accepted in the cardiovascular literature that upregulation of angiotensin-converting enzyme participates in adverse fibrous cardiac remodeling.⁴⁸ But the relationship between ACE and cutaneous fibrous remodeling is less clear. It has been demonstrated that a locally functioning tissue renin-angiotensin system operates in human skin.⁴⁹ In recent studies ACE and the AT1 receptor were detected in human keratinocytes, endothelial cells, and myofibroblasts, and ACE activities in human pathologic scar tissue were shown to be significantly higher than those in normal skin and wounded skin.⁵⁰ ACE inhibitors have potential as novel

therapeutic agents for treating of scars, and further investigation of ACE inhibitors in scar reduction is warranted.

Various steps in collagen metabolism are also potential targets to prevent excessive scar formation. One step in collagen metabolism that has been recently investigated is the intracellular hydroxylation of proline residues catalyzed by the enzyme prolyl 4-hydroxylase (P4H). A study of a rabbit ear hypertrophic model demonstrated a 26% decrease in scar elevation index in wounds treated with 1% prolyl 4-hydroxylase inhibitor topically for 1 week post-wounding.⁵¹ Another critical step of collagen metabolism that has been targeted is the extracellular cleavage of the C-terminal propeptide from the precursor molecule to form collagen fibrils, a reaction catalyzed by procollagen C-proteinase (PCP). A recent study in a rabbit ear model demonstrated a modest reduction in scar elevation index with use of a procollagen C-proteinase inhibitor.⁵²

Several investigators recently examined tamoxifen as a potential keloid modulating agent. Tamoxifen is a synthetic nonsteroidal antiestrogen that has been shown to inhibit keloid fibroblast proliferation and decrease collagen production in vitro.⁵³ Tamoxifen has been shown to decrease TGF- β 1⁵⁴ production by keloid dermal fibroblasts in vitro. More recent studies using fibroblast-populated collagen lattices demonstrated that tamoxifen significantly decreases fibroblast activity likely through decreased production or secretion of TGF- β 2.⁵⁵ Tamoxifen shows promise as a potential novel keloid reducing agent and further investigation is warranted.

Clinical studies

The limited success of any one technique of scar prevention has given rise to numerous treatment protocols in humans, with variable results. It is difficult to assess the efficacy of the existing treatment modalities because of a paucity of large, controlled clinical trials comparing the effectiveness of various treatment methods. There remains a great need for further clinical studies of scar-reducing agents using well-designed, double-blind, placebo-controlled, multicenter randomized trials with objective and standardized evaluative measures. Current clinical strategies include use of topical and intralesional corticosteroids, 5-fluorouracil, bleomycin, pressure therapy, silicone gel sheeting, laser therapy, surgical management, radiation, and combinations of techniques.

Topical and intralesional corticosteroid injections

Topical and intralesional corticosteroid injections have been widely used to treat keloid and hypertrophic scars since the 1960s.⁵⁶ The most commonly used corticosteroid for treatment of scars is triamcinolone. Multiple studies have shown 50% to 100% efficacy of intralesional injec-

tion of triamcinolone as a monotherapeutic agent in reducing scar.^{57,58} The dosage and treatment intervals have varied from 10 mg to 100 mg administered at intervals of 3 to 6 weeks for several months.

Most of the known effects of corticosteroids are thought to be primarily from suppression of the inflammatory response, and secondarily, to diminished collagen synthesis, inhibition of fibroblast growth, and enhanced collagen degeneration.^{59,60} A recent study demonstrated that corticosteroids alter the expression of multiple genes that participate in scar formation, including inhibition of TGF- β 1, TGF- β 2, and SMAD-1 (MADH-1) and collagens (COL4A1 and COL7A1) in keratinocytes.⁶¹ Corticosteroids suppress the expression of TGF- β 1 and 2 but do not affect TGF- β 3; this may be an additional mechanism by which corticosteroids contribute to the reduction of scar formation.

It is of great importance to note that although corticosteroids have been effective in reducing scar formation, the outcome has been associated with multiple adverse effects in up to 63% of patients, including hypopigmentation around the injection site, dermal atrophy, telangiectasia, widening of the scar, and delayed wound healing.⁶²

Corticosteroids have been investigated for efficacy of combination therapy with several other modalities, and these studies have yielded fewer adverse effects of therapy because polytherapy allows the use of lower doses of corticosteroids. In a study examining the effects of triamcinolone (TAC) used in combination with 5-fluorouracil (5-FU) and pulsed dye laser (PDL) in 60 patients, the overall efficacy of TAC, TAC + 5-FU, and TAC + 5-FU+PDL were compared. In comparison with TAC group, TAC + 5-FU and TAC + 5-FU+PDL combinations were more effective, provided more rapid response, and perhaps most importantly, produced fewer side effects.⁶³ Comparable results have been reported by other investigators.⁶⁴

5-Fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine analog and antimetabolite. In 1999, Fitzpatrick⁶⁵ was the first to report using 5-FU to effectively reduce scar in his 9-year experience, administering more than 5,000 injections to more than 1,000 patients. Since then, the use of intralesional 5-FU in combination or as a sole agent for treatment of hypertrophic scars has been shown to be effective in multiple studies, with up to 75% of patients showing a reduction in scar size of at least 50%.^{66,67}

Various combinations of 5-FU with intralesional corticosteroids and PDL have been used to achieve better results than 5-FU as a monotherapy.⁶⁵ Used in combination with other agents, 5-FU showed reduction in scar size of 50% to

100% with intralesional corticosteroids, 72% to 92% with radiation, and 57% to 83% with PDL.⁶⁸ Also, the combination of 5-FU with these agents has been shown to decrease the side effects related to prolonged therapy with a single agent, particularly corticosteroids.⁶⁵

The mechanism by which 5-FU reduces scarring has not been fully elucidated, but it has been shown that 5-FU inhibits fibroblast proliferation⁶⁹ by blocking DNA synthesis and transcription through competitive inhibition of thymidylate synthesis. Rapidly proliferating cells, such as fibroblasts, which are synthesizing increased amounts of DNA, are preferentially targeted by 5-FU. 5-FU also has an inhibitory effect on TGF- β 1—induced type I collagen gene expression in human fibroblasts.⁷⁰

Adverse sequelae of 5-FU with up to 1 year followup include transient hyperpigmentation (100%), tissue sloughing (21.4% to 30%), transient burning sensation (7.1%), or pain (100%) at the injection site.⁶⁶ No studies to date have reported systemic complications in patients treated with 5-FU for scar reduction. Longterm followup studies show no adverse sequelae.⁷¹

Intralesional 5-FU may be effective in the treatment of scars as a monotherapy, but likely has greater utility in polytherapy. Intralesional 5-FU mixed with low-dose corticosteroid may be a possible alternative for the treatment of scars after traditional treatments have failed and may have fewer undesirable side effects than intralesional potent corticosteroids alone.

Bleomycin

Bleomycin is a polypeptide antibiotic with well-known antitumor, antibacterial, and antiviral activity.⁷² Multiple studies have shown that intradermal injections result in significant improvement in keloids and hypertrophic scars.^{73,74}

Bleomycin was first investigated as a scar-reducing agent in the mid 1990s in a study of 36 patients.⁷⁵ After administering three to five intralesional injections of bleomycin within a 1-month period, the authors observed complete regression in 69.4% of the lesions. Subsequent studies have shown comparable results.^{73,74}

The exact mechanism by which bleomycin reduces scarring has not been fully elucidated. Studies have shown that bleomycin inhibits collagen synthesis in dermal fibroblasts through decreased stimulation by TGF- β 1.⁷⁴ Hypertrophic scars have higher concentrations of lysyl-oxidase, the cross-linking enzyme involved in maturation of collagen, than normal skin does.⁷⁶ Bleomycin reduces lysyl-oxidase levels in cultures of human dermal fibroblasts *in vitro*.⁷⁶ The effect of bleomycin in hypertrophic scars may be from a reduction of collagen synthesis, increased destruction from inhibition of lysyl-oxidase or TGF- β 1, or both.

Adverse sequelae of bleomycin treatment include hyperpigmentation (75%) and dermal atrophy in the skin surrounding treated scars (10% to 30%).⁷³ To date, no systemic toxicity has been reported with low doses of bleomycin when used to treat hypertrophic scars. Future investigations will provide more information about the mechanism by which this drug acts.

Pressure dressings

Despite a paucity of controlled clinical studies showing its efficacy, pressure therapy has been a well-established conservative management of scars since the 1970s.⁷⁷ There are numerous clinical reports advocating the use of compression therapy, but the current literature is generally lacking in reports on effectiveness and optimal pressures. The traditional consensus is that an applied pressure of 25 to 40 mmHg may represent ideal loading, but more recent studies suggest that comparable clinical results may be achieved at lower compression levels.⁷⁸ The largest randomized controlled trial of 122 burn patients showed no significant differences in scar reduction compared with controls.⁷⁹

The mechanism of action of pressure therapy remains poorly understood. Pressure treatment is thought to accelerate scar reduction by several mechanisms, including thinning of the dermis, decrease in edema, and a reduction of oxygen tension in the wound through occlusion of small vessels. Reduced oxygen tension is hypothesized to decrease fibroblast proliferation and collagen synthesis and increase collagen lysis.⁸⁰ Mechanical stress can be communicated from stressed to unstressed cells to elicit a remodeling response and increase in production of fibronectin, collagen types III and V, and MMP-9.⁸¹ In an *in vitro* model, mechanical compression was able to strongly increase apoptosis in the hypertrophic scar, as observed during granulation tissue regression in normal wound healing, and induce expression of interleukin-1 β and tumor necrosis- α , which likely play a key role in scar hypertrophy regression.⁸²

Drawbacks of compression therapy include its limited use in anatomic depressions, flexures, or areas of frequent movement, patient discomfort, the need to be worn at all times, and skin ulceration. Patient compliance can be a major problem, with reports of noncompliance ranging from 8.5% to 59%.⁸³ Pressure therapy is influential primarily while the scar is active and loses efficacy after 6 months of treatment.⁸⁴

In conclusion, there are many clinical reports purporting evidence that compression therapy may be effective in scar reduction, but more definitive, large, controlled clinical studies are needed to clarify the role of pressure dressings in scar-reduction protocols and to evaluate optimum treat-

ment parameters. If pressure therapy is to be continued in future protocols, it will most likely be best used as an adjunctive treatment as part of a polytherapeutic strategy of scar management.

Silicone gel sheets

Topical silicone gel sheeting has been widely used since its introduction in the early 1980s, and its therapeutic effects on hypertrophic scars have been well documented in the literature.^{85,86} An early large yet uncontrolled study of silicone gel sheeting in 125 patients with hypertrophic scars reported improvement in scar parameters in 81% of patients.⁸⁷ Subsequent controlled studies have yielded similar results.⁸⁵

In addition to treating preexisting scars, silicone gel sheeting has also been investigated for its potential use in scar prophylaxis when applied in the immediate postoperative period. Controlled studies of silicone gel sheeting applied to wounds beginning 2 weeks postoperatively for 12 hours a day resulted in significantly decreased scar volume over that in controls in mirror image incisional wounds of the body after 2 months of treatment.⁸⁸ But a large controlled study of 129 breast reduction patients treated with silicone gel sheeting at the time of operation, for 24 hours a day for 3 months, demonstrated no improvement in scar prophylaxis compared with controls with 1-year followup.⁸⁹

The mechanism of action of silicone gel sheeting has not been conclusively elucidated and currently remains a subject of controversy. There has been significant controversy about the effects of silicone itself on the wound. Early investigators postulated that release of silicone fluid from the gel was most likely responsible for its efficacy.⁹⁰ Other investigators have hypothesized that hydration, rather than an inherent property of silicone itself, modulates the effect on scar reduction.⁸⁶ In support of this, a study found no histologic evidence of silicone in biopsy specimens of silicone gel sheet-treated scars.⁹¹ Likewise, another study found that scar hydration and occlusion without the addition of silicone resulted in significant improvement in scar symptoms.⁹² These findings suggest that hydration and occlusion are likely the mechanisms of the therapeutic action of silicone gel sheeting rather than an inherent antiscarring property of silicone.

Several early and recent studies have suggested that silicone gel sheeting likely acts by reducing fibroblast-induced collagen deposition.⁹⁰ An early study examined dermal cytokine mRNA levels in silicone-gel-treated hypertrophic scars and found that treatment of hypertrophic scars by either occlusive dressing or silicone gel resulted in increased mean levels of bFGF mRNA.⁹³ A more recent study has supported this by demonstrating that silicone gel causes

increased bFGF levels in vitro in cultured human dermal fibroblasts.⁹⁴ It is well known that bFGF is a key cytokine involved in the scar formation process, and an increased level of bFGF would be expected to reduce collagen proliferation, decreasing scarring.⁹⁵

Another interesting potential mechanism by which silicone gel could cause scar reduction is through downregulation of fibrogenic cytokines. Using an in vitro fibroblast-populated collagen lattice, investigators demonstrated that hypertrophic scar fibroblasts exposed to silicone sheeting have decreased contraction compared with an unexposed control, and TGF- β 2 is downregulated in the silicone exposed group. These results suggest that silicone sheeting may act by downregulating fibrogenic cytokines.⁹⁶

In summary, there is controversial evidence concerning the benefit of silicone gel sheeting for scar reduction and prophylaxis. The largest controlled trial reports no benefits in preventing hypertrophic scarring; several other studies purport a benefit. It has been 25 years since the introduction of silicone sheeting, and there is still no conclusive evidence of the mechanism for its effectiveness in scar treatment and prevention. The most widely accepted theory for its mechanism of action is that it produces hydration of the scar by occlusion and more recently, that it causes a downregulation of fibrogenic cytokines. Further investigation will likely yield greater understanding. Despite a lack of conclusive evidence of its efficacy and mechanism, silicone gel will likely continued to be used in scar treatment protocols because it is a noninvasive modality and is preferred by many patients over intralesional injections.

Laser therapy

The vessel-specific 585-nm pulsed dye laser (PDL) is currently considered the laser of choice in treating pigmented and hypertrophic scars. The use of PDL for treatment of hypertrophic scars has been well documented.⁹⁷ PDL is used primarily to reduce erythema, but also has been shown to reduce scar volume and improve the texture of the scar surface.⁹⁸

There is no universal consensus on the mechanism by which PDL achieves its effects on scars. Laser therapy for scar reduction is based on the principle that vascular proliferation plays a key role in scar formation. Most studies have shown that PDL likely mediates its effects through selective photothermolysis, in which energy emitted from the laser is absorbed by oxyhemoglobin, generating heat and leading to thermal injury to the scar microvasculature, which leads to thrombosis and ischemia, ultimately resulting in reduced collagen within the scar.⁹⁹ Destruction of the vascular supply to the scar may disrupt the stimulus from endothelial cells and fibroblasts, which release

growth factors in scars. Additionally, early intervention with PDL may control the extent of angiogenesis within the wound and assist in minimizing scarring. PDL has been shown to reduce TGF- β expression, fibroblast proliferation, and collagen Type III deposition and increase MMP-13 activity.¹⁰⁰

The most common side effect of 585-nm PDL treatment is post-treatment purpura, which usually subsides after 7 to 10 days.¹⁰¹ Hyperpigmentation has been reported with a frequency of 1% to 24%¹⁰¹ and is mostly seen in darker-skinned patients. It may be related to thermal injury of the epidermis from melanin absorption. Overall, PDL carries a relatively low risk of significant adverse effects and complications.

Most studies have supported the efficacy of PDL in scar reduction. One of the earliest controlled studies of PDL in 16 patients with sternotomy scars treated with PDL demonstrated significant improvement in color and thickness compared with baseline and controls. Subsequent studies have demonstrated comparable results.^{97,102}

There have also been studies that have shown contradictory results concerning the efficacy of PDL in scar reduction. A prospective, randomized controlled study comparing 20 patients with hypertrophic scars did not demonstrate significant improvement with silicone gel or PDL compared with controls.¹⁰³ Another controlled study of 23 scars treated with PDL also demonstrated symptomatic improvement of pruritis, but no significant reduction of erythema and scar thickness.¹⁰⁴ Likewise, another controlled study of 56 patients using PDL for three to six treatments at 8-week intervals indicated that although there was significant symptomatic improvement of pruritis, there was an insignificant degree of objective improvement in terms of scar thickness and elasticity in the PDL-treated group compared with the control group.¹⁰⁵

The contradictory results of PDL therapy can be from several factors including scar location and duration, different laser settings, skin types, followup duration, and outcomes measurement methods. Additionally, it has been suggested that PDL may not work on thick hypertrophic scars because of a lack of penetration of the laser to deeper target vessels. Hypertrophic scars can be up to several millimeters thick,¹⁰⁶ and many of the target vessels might be deeper than the 0.4-mm and 1.2-mm vessel coagulation depth of the PDL.¹⁰⁷ Another factor that may account for the lack of efficacy in some of these studies is the higher percentage of dark-skinned patients in the studies demonstrating lack of efficacy of PDL because melanin acts as a competing chromophore for the PDL.¹⁰⁸

PDL has been successful as an adjunct to other treatments. Most commonly, PDL has been used in conjunc-

tion with intralesional steroids, with the latter directed at flattening hypertrophic scars and keloids and the former used to reduce erythema and enhance pliability.¹⁰⁹

In summary, PDL has been used with variable degrees of success in the treatment of hypertrophic scars, and although earlier reports suggested a significant degree of improvement, more recent studies have raised concern about its effectiveness. Given its potential high efficacy and low adverse effect profile, PDL may be more frequently used in many treatment protocols if additional large controlled trials support its efficacy.

Surgical treatment

There are many different surgical strategies for scar revision, including excision with linear closure, excision with split- or full-thickness skin grafting, z-plasty, w-plasty, and if all other options fail or are impractical for the magnitude of the defect, excision followed by a well-designed flap coverage. Tissue expansion and serial scar excision may be used to provide more tissue for advancement or local flap coverage of revised scars.

There are several different excisional techniques, including lenticular excision and serial partial excisions. Lenticular excision requires adequate undermining to produce wound edges in an even and tension-free manner, and wound eversion is critical, especially for deep defects. Serial partial excisions have also been commonly used for large scars with insufficient surrounding tissue laxity for a single excision. If numerous procedures are required, tissue expansion may be used to reduce the number of necessary excisions.

Z-plasties are frequently used in areas where the skin is relatively redundant and where there are pronounced creases. In the face, z-plasties are particularly useful around the eye, around the mouth, and in the nasolabial creases. W-plasties are useful over the zygoma, the chin, and the forehead. It is important when designing a w-plasty to make each straight line shorter than 5 mm.¹¹⁰ Z-plasties are also useful in scar revisions in the rest of the body, particularly in the hand. When webbing is present in areas such as the anterior and posterior axillary folds, large w-plasties can be used. It is often advantageous to deepen the tips of the v-shaped incisions, turning them into multiple y- to v-plasties. The literature often depicts z-plasties and w-plasties with symmetrical and identical limbs. It is often helpful to vary the size of the limbs and make them smaller, particularly at the ends of the scars. It is also often beneficial to make them asymmetric to better blend in with the existing landmarks and creases.

Timing of surgical treatment is an important consideration in the treatment protocol of scar revision strategy. Scars mature over at least a 1-year period and can show

decrease of contractures, flattening, softening, and repigmentation. Nonsurgical therapies should at least be considered before surgical intervention, as discussed elsewhere in this review.

Radiation

Beta radiation is a particulate radiation consisting of high-speed electrons, which are rapidly attenuated by biologic tissues, making it very useful for superficial treatments where deep tissue penetration is undesirable. Radiation therapy has been used in scar reduction protocols primarily in the treatment of keloids and has frequently been used as an effective adjunct to surgical excision. Radiation is thought to mediate its effects on keloids through inhibition of neovascular buds and proliferating fibroblasts, resulting in a decreased amount of collagen production.¹¹¹

Surgical excision in combination with radiotherapy is considered the most effective treatment available in severe keloids. Surgical excision as a sole treatment of keloids has a very high recurrence rate, between 45% and 100%.¹¹² Surgical excision followed by radiation therapy for treatment of keloids provides the highest reported regression rates. A study of 75 patients with 113 keloids showed that administration of 12 Gy radiation in three fractions over 3 days resulted in a regression rate of 73% with no complications after a mean followup of 9.5 years.¹¹³

Radiation therapy for keloid reduction has been associated with adverse effects such as hypo- and hyperpigmentation, erythema, telangiectasia, and atrophy. Radiation-induced malignancies from scar treatments are rare. The total-body radiation dose from a superficial low-voltage radiotherapy technique is low, and it is difficult to definitively implicate scar reductive radiation treatment as the cause of neoplasm.

In summary, there is no agreement in the literature on optimal dosage, fractionation, indications for treatment, or timing of radiotherapy with respect to surgical procedures. For these reasons, studies of radiotherapy treatment are difficult to compare. But a single dose given within 24 hours of surgical excision appears to give the highest cure rate in recurrent keloids.¹¹⁴ Additional controlled prospective trials using standardized treatment protocols and objective outcomes measures need to be undertaken to define optimal treatment parameters.

Conclusion: the need for an approach to polytherapy

Numerous therapeutic strategies have been described for reduction and prevention of scars, yet there is no universal consensus in the literature about optimal treatment. After initial injury, a robust inflammatory cascade is incited, during which much of the downstream outcome of scar devel-

opment is mandated. Inhibition of the inflammatory process is the main factor that can decrease scar formation. Numerous methods can inhibit the inflammatory cascade at different levels of the pathway. There is a need to strategically block the inflammatory pathway and other pathways to scar formation with a polytherapeutic protocol. Such an approach includes inhibiting inflammation at upstream and downstream targets and addressing other mechanisms of scarring such as infection, cell signaling, collagen metabolism, and fibroblast migration and proliferation.

There remains a great need for additional clinical studies of scar-reducing agents using well-designed, double-blind, placebo-controlled, multicenter randomized trials with objective and standardized evaluative measures. A polytherapeutic approach to scar reduction likely holds the greatest potential for successful amelioration of both normal and pathologic scars, and future studies should focus on evaluating the efficacy of such an approach in addition to exploring the potential role of emerging and novel agents of scar reduction.

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