Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics

Part II. Strategies to reduce scar formation after dermatologic procedures

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The evidence base underpinning most traditional scar reduction approaches is limited, but some of the novel strategies are promising and accumulating. We review a number of commonly adopted strategies for scar reduction. The outlined novel agents are paradigmatic of the value of translational medical research and are likely to change the scenery in the much neglected but recently revived field of scar reduction therapeutics. (J Am Acad Dermatol 2012;66:13-24.)

Key words: antiscarring agents; cutaneous scar reduction strategies.

ANTISCARRING STRATEGIES

A cutaneous scar results from overgrowth of fibrous tissue after damage to the skin after injury or surgery and represents an exuberant healing response.[1] The type of scar depends on how exuberant the healing response is, with hypertrophic scars not extending beyond the wound borders and keloids extending. The former are clinically more favorable than the latter because they are more amenable to treatment and often even regress spontaneously.[2] Both types of cutaneous scarring are underpinned by similar pathobiologic processes, and it is not surprising that they respond to the same physical or pharmacologic interventions. They are managed similarly and we therefore refer to the two terms interchangeably in this article.

Hypertrophic and keloid scars can be associated with physical and psychological symptoms, yet no major advances have been achieved so far in scar reduction therapeutics. This is probably because of the limited commercial interest and subsequently insufficient research investment in the field. Little research investment entails little product return and little evidence basis for any conventional treatment modality.

In Part II of this review, we aim to recap and evaluate management steps that can be taken to reduce the risk of hypertrophic or keloid scarring and to treat such scars if they develop (please see Table I for an overview), and also to look to the future for therapies that may give a better result profile for skin surgery. The value of translational research will become apparent, and we recommend consulting part I of this review for a better appreciation of the molecular basis of scar therapeutics.

CAPSULE SUMMARY

- "Will there be a scar?" From minor operative procedures to trauma-related surgery, this question is often at the center of patient-related concerns.

- In order to address the aforementioned common clinical question, this review aims at critically reviewing conventional and innovative strategies that may be adopted to minimize scarring following dermatologic procedures.

- Identifying high risk is paramount to hypertrophic scar prophylaxis, as is clean surgery and good wound care.

- Nonsurgical scar reduction strategies include numerous over-the-counter products, such as onion extracts and Vitamin E -based remedies, not supported by a sufficient evidence base.

- Intralesional corticosteroids, 5-fluorouracil, bleomycin, and lasers are commonly used in clinical practice, while radiation and surgical revision are only seldom-used modalities.

- Human recombinant interleukin-10 and, to a lesser extent, mammose-6-phosphate, are innovative and promising products of translational research that are currently under development for cutaneous scar reduction.

- More extensive and better trials are essential for numerous other agents that have shown promise but have been tested only sporadically.

PRACTICAL PROPHYLACTIC CONSIDERATIONS
Key points

- **Identifying high risk is paramount to preventing hypertrophic scarring after dermatologic procedures**
- **Certain high-pressure body sites are more likely to show exaggerated scarring, and patients of Afro-Caribbean descent and those with personal or family history of scarring are at increased risk of engaging in such a response**
- **Minimizing skin tension and the inflammatory response after surgery by using the appropriate materials and ascertaining clean surgery and good wound care are simple practical prophylactic measures**

An individual at increased risk of developing a thickened scar may benefit from certain prophylactic measures to reduce this risk when skin surgery is contemplated. If surgery is urgent or if the procedure is of medical importance, such as skin cancer therapy, then a detailed approach to scar minimization measures may seem irrelevant.

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Identify high risk

Injury to the dermis and dermoepidermal junction, either related to cutting injury or intense inflammation, triggers a repair process that will usually result in a scar. In only a minority of patients does the scar become thickened and hypertrophic.

The risk of a thickened scar after surgery is higher in certain body sites; the shoulder and scapular area, anterior chest, lower abdomen, earlobe, and any other cutaneous region overlying a bony prominence is more prone to an exaggerated scarring response.[3]

There is evidence to suggest that this natural tendency is explained by the increased mechanical tension that characterizes these body sites.[4] Patients of Afro-Carribean descent and those with a personal or family history of thickened scars are more likely to produce this response. Young age (<30 years of age) is also a risk factor, especially for keloids,[5,6] and while little can be done to change the innate tendency of certain individuals or body sites, the dermatologic surgeon can take extra measures to reduce risk.

Of course, the dermatologic surgeon may well decide to adopt an approach whereby all patients are offered prophylactic treatment, especially when the latter is characterized by a safe adverse reaction profile or when cosmesis is of paramount importance to the patient.

Reduce skin tension

Based on the aforementioned increased mechanical tension hypothesis, it makes sense to minimize mechanical forces after surgery. Surgical excision scars should be positioned, whenever possible, along rather than across relaxed skin tension lines. Appropriate strength, depth, and number of sutures should ensure that the risk of dehiscence is minimized. Using materials such as paper tape would be expected to facilitate this, and there is some evidence (albeit limited) in support of this idea.[7,8] Avoiding movements after surgery that cause excessive stretching and protecting the wound from friction would therefore be expected to be helpful.

Minimize inflammation

Inflammation is also known to contribute to hypertrophic scarring,[9] and every attempt to minimize the inflammatory response should be made by ascertaining clean surgery and good wound care to prevent infection thereafter. Using inert suture materials would also be important in this context.

Skin closure considerations

With regard to skin closure after excision, a 2010 Cochrane review reported sutures to be significantly better than tissue adhesives for minimizing dehiscence.[10] The suture should be strong to avoid wound dehiscence, but it should also accommodate wound edema by allowing adequate stretching. Good eversion of the skin edges is important, as is uniform distribution of the suture tensile strength along the carefully approximated and evenly sutured skin counterparts.[11] Both vertical and horizontal mattress sutures afford excellent results—as do buried intradermal sutures[12]—and their early removal can minimize their classic "railway road" cutaneous scars.[13] Interestingly, randomized controlled trials comparing absorbable with nonabsorbable suture materials have not found any significant differences in the long-term cosmetic outcomes.[14-16] Nonabsorbable sutures have been reported to perform better in regions of high skin tension, such as the anterior chest wall.[17] A 2007 meta-analysis highlights the lack of large and methodologically sound randomized controlled trials comparing absorbable with nonabsorbable sutures.[18] In terms of suture material, monofilament sutures are preferred over braided sutures, because they have been reported to cause less inflammation[19]—but again, the conducted studies are neither large and sound nor adequate.

NONSURGICAL SCAR REDUCTION STRATEGIES

Key points

- **There are numerous antiscarring agents available over the counter, including silicone dressings, onion extract, and vitamin E−based remedies, none of which are supported by a sufficient evidence base**
- **There is some evidence base underpinning the use of intralesional corticosteroids, 5-fluorouracil, and bleomycin**

There is a multitude of commonly used over the counter scar treatment products that have little evidence-based efficacy.[20,21] Among these, silicone dressings, onion extract, and vitamin E−based remedies rank as the top selling products, despite lacking an evidence base.[20-22] Often, the advertised beneficial claims lure patients into seeking or purchasing such products, and clinicians should be aware of the disparity between advertised benefits and evidence in support of their efficacy.[22]

Silicone dressings

Silicone-based products are widely available and have long been used for hypertrophic scar prophylaxis and treatment. They have been advocated by the 2001 International Advisory Panel for Hypertrophic Scarring and Keloid Management as a

viable treatment option[23] and have also been popular among plastic surgeons.[24] Their mode of action was thought to be by temperature, oxygen tension, and hydration regulation.[6] Despite intermittent reports of positive data in clinical studies and popularity in clinical practice, a recent Cochrane analysis has concluded that most evidence is of poor quality and highly susceptible to bias and therefore weak overall.[21]

The fact that silicone-based products are relatively inexpensive, readily available, noninvasive, and even remotely possibly beneficial to an extent may explain their lasting clinical popularity. They should be better explored by additional studies and used, in the interim, as adjuncts in hypertrophic scar management.

Pressure dressings

Pressure garment therapy has been used for decades as a conservative means of preventing and managing hypertrophic scars.[25] Pressure-induced hypoxic effects leading to collagen and fibroblast degeneration[26] and matrix metalloproteinase activation[27] have been postulated as possible modes of action, to name only a few propositions. Nevertheless, a 2009 meta-analysis concluded that the overall effects of pressure garment therapy on global scar scores were of equivocal clinical significance, the associated morbidity and cost were not trivial, and no beneficial effects were proven.[28] As with other approaches, pressure dressings are still accepted as standard practice in many centers, especially for managing burn-induced scars,[25] but additional studies are clearly essential.

Onion extracts

There are in vitro studies suggesting that onion extracts may accelerate wound healing by exerting a number of effects on mast cells and fibroblasts in the inflammatory cascade, and by decreasing inflammation.[29-34] In a recent study, both crude onion extracts and querceptin, which is one of its flavonoid ingredients, were investigated for their effects on the proliferation of fibroblasts, expression of type I collagen, and matrix metalloproteinase-1. Interestingly, the proliferation rates of fibroblasts were found to be decreased in a dose-dependent manner for both the crude onion extract and querceptin and matrix metalloproteinase-1 expression was found to be upregulated.[35]

Despite the encouraging laboratory data, early clinical studies on postsurgical scars were disappointing.[36,37] More recently, a gel containing onion has been reported to exert beneficial effects, both in combination with intralesional corticosteroids[38] and alone[39] in the overall appearance of hypertrophic scars. Nevertheless, these recent studies are small-scale and not double-blind and randomized, and there is therefore no solid evidence base in support of the use of onion extract—based products.

Vitamin E—based remedies

Vitamin E is commonly used in commercially available antiscarring products. Anecdotal reports had claimed that its topical application might accelerate wound healing and enhance the cosmetic outcome of postsurgical scars via its antioxidant properties, but early clinical studies yielded disappointing results.[40] Not only did it not seem to improve the appearance of scars when applied after surgery, but there was marked incidence of localized adverse effects contributing to worse outcome.[40] Similar findings were reported when a gel containing vitamin E was used either alone or in combination with a topical corticosteroid for scars after reconstructive surgery.[41] More recently, small clinical studies reported positive data when vitamin E was used alone or in combination presurgery, postsurgery,[42,43] and in systemic sclerosis—related digital ulcers.[44]

Overall, there is very little evidence base in support of the topical use of vitamin E as a strategy to minimize cutaneous scarring. More research is essential before any recommendations for adopting vitamin E as a means for minimizing scarring are implemented in clinical practice.

Corticosteroids

Corticosteroids are thought to reduce scar formation by a number of mechanisms: by suppressing inflammation; by inhibiting fibroblast growth proliferation collagen synthesis; by causing vasoconstriction, thereby limiting wound oxygenation and nutrition; by effects on transforming growth factor-beta 1 ($TGF\beta_1$) and $TGF\beta_2$ and collagen in keratinocytes; and by promoting collagen degeneration.[45-49] Intralesional triamcinolone is most commonly used for the treatment of scars, and a number of studies have reported variable efficacy (50-100%) with recurrence varying from 9% to 50%.[50-54] The reported beneficial outcome of intralesional steroid therapy is often associated with adverse effects, such as dermal atrophy and hypopigmentation; these are fewer when steroids are used in combination with 5-fluorouracil (5-FU) and pulsed-dye laser (PDL), mainly because of the lower steroid doses that are required.[51,55-57] Despite the relative lack of well designed studies, the consensus places intralesional triamcinolone as a recommended first-line approach for hypertrophic and keloid scars.[58] Topical corticosteroids, on the other hand, have failed to reduce scar tissue formation and are not advocated as a preferred modality.[59,60]

5-fluorouracil

Case series suggest that this pyrimidine analogue antimetabolite may be of benefit in hypertrophic scars and keloids when used intralesionally.[61,62] It has been shown to inhibit human fibroblast growth, and this is a possible mechanism of action.[63] Intralesional 5-FU is generally well tolerated and is associated with a humble constellation of acceptable topical side effects comprising erythema and pigmentation.[64] Side effects are fewer, and the achieved efficacy appears to improve when 5-FU is combined with corticosteroids and PDL for treating hypertrophic scars and keloids.[65]

Bleomycin

In addition to its widespread uses as an antitumour agent, bleomycin has been reported to improve the appearance of hypertrophic and keloid scars when administered intradermally.[66-68] Direct or indirect, TGFβ-mediated, inhibitory effects on collagen[69,70] have been proposed as potential mechanisms of action. Occasionally reported complications include atrophy and hypopigmentation,[71] and intralesional bleomycin seems to be a reasonably attractive scar reduction therapeutic option. Nevertheless, additional and larger research studies are essential to assess the benefits of bleomycin.

SURGERY, LASERS, AND RADIATION
Key points
- **The surgical revision of hypertrophic scars is rarely performed because of high recurrence rates, but cryotherapy has been widely used with success**
- **Lasers are widely used in practice, and pulsed-dye laser therapy has shown efficacy, has a low-risk adverse effect profile, and is becoming increasingly popular as a pre- and postsurgery scar reduction modality**
- **Radiotherapy tends to be reserved as a late resort for resistant scars and is used sparely because of concerns over carcinogenic potential**

Surgery

Scar revision after cutaneous surgery may be essential if hypertrophic or keloid scars are a procedural aftermath. The high recurrence rates associated with simple total surgical excision of keloids are disappointing.[72] Subtotal excisions, where a rim of keloid is left behind, has been advocated to result in a better outcome because of low wound tension and decreased collagen synthesis.[73] Small hypertrophic scars may successfully be managed by the scar reorientating and tension-releasing Z- and W-plasties,

but the use of nonsurgical adjuvant therapy is recommended.[74]

It should be highlighted that the evidence base for the surgical strategies outlined above is overall inadequate and caution is advised before adopting them in clinical practice.

Cryosurgery

Cryotherapy has long been used in dermatology for hypertrophic scars and keloids. The mechanism by which the cold agent (most commonly liquid nitrogen) induces scar tissue destruction is by the direct cell freezing effects and by inferring vascular stasis after thawing.[75] A recent technological advancement has been the development of an intralesional cryoneedle, which is reported to be superior to the conventional open-spray or cryoprobe approach and is associated with fewer adverse reactions.[76] Volume reductions of 50%, 60%, and 67% of hypertrophic scars and keloids have been reported after a single intralesional cryogenic session.[76-78] Intralesional local anaesthesia and oral analgesics have been used successfully for procedure-associated pain control.[78] The safety profile of cryosurgery and the relative effectiveness in hypertrophic scars and keloids render it an attractive first-line scar reduction strategy despite a lack of level I evidence. It is often used in combination with intralesional corticosteroid therapy.

Laser therapy

Laser light can be used for preventing and revising hypertrophic or keloid scars, and several lasers and light sources have been used to improve the appearance of such scars.

The first lasers used were ablative (ie, causing tissue vaporization), nonselective lasers and comprised the carbon dioxide (CO_2) or an erbium:yttrium-aluminium-garnet (Er:YAG) laser. The former type effects wound contraction and collagen remodelling by causing thermal necrosis,[79] and it has also been reported to activate the release of basic fibroblast growth factor (bFBG) and inhibit TGFβ_1.[80] The latter laser type has also been associated with altered levels of TGFβ orchestrated by a heat shock response.[81] Neither efficiently modified the wound healing response, and both were associated with significant adverse reactions, including major burns,[82] and therefore alternative approaches were sought.

These comprised the PDL (585 and 595 nm) and laser-assisted skin healing laser (810 nm). A 2010 review reported that both of these provide excellent clinical results while being well tolerated.[82] The 585-nm pulsed laser has long been praised as
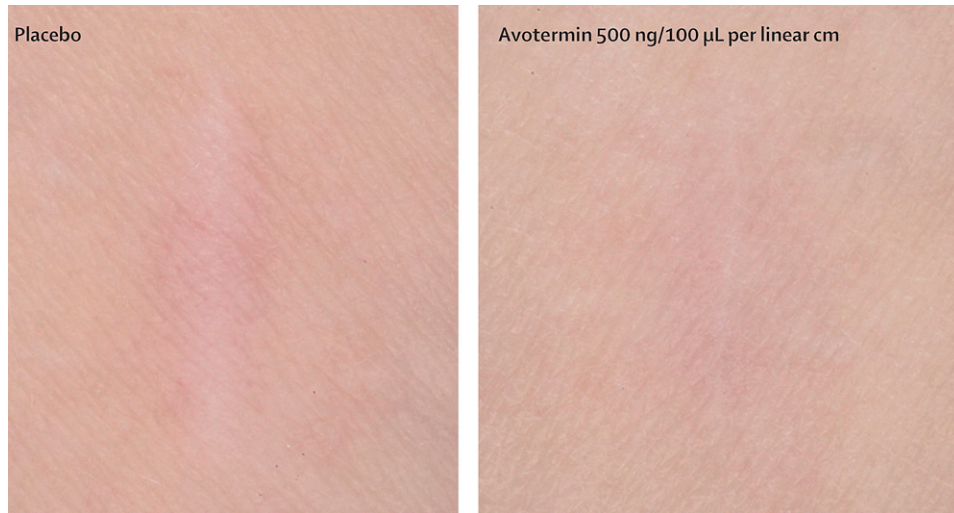
Fig 1. Therapeutic application of avotermin to incisional wounds improves scarring compared to control treatment (placebo or standard wound care). (Adapted from The Lancet (Ferguson et al[99]) with permission from Elsevier and from the author.)

an excellent and safe choice for hypertrophic and keloid scar treatment, with effects on scar erythema, scar volume, and texture.[83,84] A 2011 systematic review evaluated seven laser types and found most evidence for the PDL 585-nm followed by PDL 595-nm. It was thought that the 595-nm wavelength was more promising with a moderate efficacy (34-66% improvement) as compared to PDL 585 nm, which was found to have low efficacy (0-33% improvement).[85] On the side of caution, there are some reports suggesting rapid scar recurrence with pulsed laser treatment of keloid scars,[86] and combination treatment with intralesional corticosteroids and/or 5-FU therapy has been advocated as possibly superior to either approach alone.[56]

Fractional laser therapy and intense pulsed light therapy are relatively recent developments that are also used in clinical practice for improving the appearance of surgical scars. Nonablative fractional lasers are more favorable than ablative ones because of a reportedly better safety profile and efficacy. They are supposed to work by causing localized thermal injury and epidermal necrosis over the so-called microscopic thermal zones that are non-contiguous—that is, they are separated by zones of intact tissue. The intact tissue surrounding each thermal zone serves as reservoir of normal dermal and epidermal cells, which migrate to the damaged area to effect efficient and prompt healing.[87,88] Nonetheless, there is a limited evidence base to support the use of fractional laser therapy[89] and almost no evidence base in support of intense pulsed light therapy.[85]

Radiotherapy

Radiation therapy is a modality that is usually reserved for keloid and hypertrophic scars that are resistant to other treatments, and it is not widely used, at least in part because of concerns about carcinogenic potential.[53,90] The underlying mechanism of action involves induction of apoptosis in fibroblasts and subsequent restoration of the balance between formation and breakdown of scar collagen, while altered gene expression and connective tissue stem cell damage have also been reported.[91-94] High success rates have been reported for radiation therapy in keloid scars; recurrence is lower when radiotherapy is used as adjuvant to surgery and response varies widely according to the site of the lesion.[54,95-98] Side effects are generally minimal and include hyperpigmentation, pruritus, and erythema.[52] Interestingly, radiation relieves hypertrophic scar and keloid-associated symptoms, notably pruritus and local discomfort.[26]

INNOVATIVE MEDICAL APPROACHES
Key points
- **Avotermin, human recombinant interleukin-10, and to a lesser extent mamnose-6-phosphate are novel agents showing promising results in randomized controlled trials and are likely to change practice when they become commercially available**
- **Insulin, mitomycin C, topical tamoxifen, systemic methotrexate, topical imiquimod, retinoic acid, botulinum toxin A, calcineurin inhibitors, and calcium channel blockers**

Table I. Proposed mechanisms of action and comments on evidence base for commonly used and innovative scar-reducing modalities

Modality	Mechanism of action	Comments	Level of evidence
Silicone dressings	Temperature, oxygen tension, and hydration regulation[6]	Intermittent reports; discouraging Cochrane review[21]; still widely used (good safety profile)	III
Pressure dressings	Pressure-induced hypoxic effects leading to collagen and fibroblast degeneration[26]; MMP-9 activation[27]	Equivocal clinical significance in 2009 meta-analysis[28]; still commonly used (good safety profile)	—
Onion extracts	Affects fibroblasts and mast cells in the inflammatory cascade and by decreasing inflammation[29-34]; decreased proliferation rates of fibroblasts[35]	Small, nonrandomized, not well controlled clinical studies; still commonly used OTC product	IIB
Vitamin E—based remedies	Antioxidant properties[40]	Some negative data; little support (small clinical studies); not very commonly used	IIB/III
Corticosteroids	Inhibit fibroblast growth proliferation collagen synthesis; cause vasoconstriction, thereby limiting wound oxygenation and nutrition; have effects on $TGF\beta_1$ $TGF\beta_2$ and collagen in keratinocytes; promote collagen degeneration[45-49]	Numerous positive case studies (albeit lack of well controlled trials) for intralesional corticosteroids; topical agents not recommended; intralesional agents advocated by many as first-line; often used in combination with other modalities	III
5-Fluorouracil	Inhibit human fibroblast growth[63]	Case series; used by some in practice	III
Bleomycin	Direct or indirect $TGF\beta$-mediated, inhibitory effects on collagen[69,70]	Support for intralesional application by case studies/preliminary clinical trial; used by some in practice but associated with adverse reactions	III
Lasers	Effect wound contraction and collagen remodelling by thermal necrosis[79]; activates release of bFBG and inhibits $TGF\beta_1$[80]; altered levels of $TGF\beta$ by a heat shock response[81]	Some support for PDLs by systematic review (2011); several types are widely used in practice	IA (for PDL)
Surgery	Scar revision, reorientation, and tension release	Z- and W-plasty supported by case studies, but additional modalities recommended in combination; not used as first-line because of high recurrence rates; adjuvant treatment is recommended	III
Cryosurgery	Direct cell freezing effects and by inferring vascular stasis after thawing[75]	Support from review of numerous case studies; lack of level I evidence but widely used; often in combination with intralesional corticosteroids	III
Radiation	Induction of apoptosis in fibroblasts; restoration of balance between formation and breakdown of scar collagen; altered gene expression and connective tissue stem cell damage[87-90]	Reported success in reports and case series; not widely used because of questionable safety profile	III
Avotermin	Therapeutic application of recombinant $TGF\beta_3$ (receptor antagonist reducing scarring)	Intradermal formulation in development; shown to provide an accelerated and permanent improvement in scarring with transient and clinically insignificant adverse effects in early studies (three double-blind, placebo-controlled, phase I/II studies)[95]	IB

Table I. Cont'd

Human recombinant IL-10	Intradermal application of human recombinant IL-10, antiinflammatory cytokine that reduces scarring	A single-center, double-blind, standard care— and placebo-controlled, randomized phase II clinical trial reported a statistically significant reduction of scarring[99]	IB
Mannose-6-phosphate	Potent inhibitor of TGFβ_1 and TGFβ_2 signaling[101]	Positive phase I clinical trial results[101] but unmet primary endpoints thereafter; in development as topical formulation	IB; topical formulation not tested
Insulin	Inhibitor of myofibroblast[105]	Small pilot study with encouraging results[104]; not widely used	IB (small-scale study)

bFBG, basic fibroblast growth factor; *IL-10*, interleukin-10; *MMP-9*, matrix metalloproteinase; *OTC*, over the counter; *PDL*, pulsed-dye laser; *TGFβ*, transforming growth factor—beta.

have been tested only sporadically and in small-scale studies (some randomized)
- **More extensive well controlled trials are necessary to test agents that have shown some evidence of efficacy but have not yet passed the acid test**

The identified inadequacy in antiscarring therapeutics initiated the search for efficacious scar-reducing agents by using innovative approaches. Indeed, the wealth of data produced by molecular research on wound healing has led to the development of novel therapeutic strategies that aim to reduce human scarring efficiently.

Novel and promising

Avotermin. Avotermin is a therapeutic application of recombinant TGFβ_3 that has been shown to reduce scar size. In clinical trials assessing its efficacy at different body sites, skin colors, ages, and sexes, scar appearance after treatment with intradermal injection of avotermin has been judged by a panel of laypeople and a panel of clinical investigators over the time period of 2 weeks to 1 year. A recent paper summarizing three double blind, placebo-controlled, phase I/II studies (level IB) concludes that avotermin bears the potential to provide an accelerated and permanent improvement in scarring (Fig 1) with transient and clinically insignificant adverse effects.[99] Avotermin is aimed at both prophylaxis against and treatment of surgical scars. The ongoing European double blind placebo-controlled clinical trial is investigating the efficacy of intradermal avotermin in excisional scar revision surgery, a procedure commonly performed by cosmetic dermatologists and plastic surgeons for disfiguring, aesthetically unpleasant, or complicated scars.[101] The first data are expected to be reported in the last quarter of 2011.[100] Other injectable agents, such as antisense TGF oligonucleotides have been tested postsurgically with some success in humans.[101,102] Avotermin is the only molecule targeting TGFβ_3 to date that has been tested and progressed adequately.

Human recombinant interleukin-10. To date, a single-center, double blind, standard care— and placebo-controlled randomized phase II clinical trial has been conducted (level IB) to examine the efficacy of a therapeutic formulation of intradermal injections of human recombinant interleukin-10 on wound healing. This trial examined the appearance of healed scars after the injection of eight different doses of human recombinant interleukin-10 into the margins of surgical incisional wounds. Patients who received treatment had a statistically significant reduction of scarring.[103] An ongoing trial is aiming at primarily establishing the effects of four different intradermal doses of the same agent on incisional and excisional scars in subjects of African ancestry as compared to placebo.[104]

Mannose-6-phosphate. The recently developed formulation of mannose-6-phosphate is a potent inhibitor of TGFβ_1 and TGFβ_2 signalling and therefore a potential therapeutic agent for scar reduction. Following positive phase I clinical trial results[105] (level IB), the manufacturer investigated the application of mannose-6-phosphate in a phase II trial.[106] In this trial, the agent was applied via two different routes of administration (topically and intradermally) to the donor site of split thickness skin grafts and the resultant scar profile was examined. Although this exploratory trial did not meet its primary end points with statistical significance, a number of prespecified secondary endpoints were met, and the manufacturer believes that the agent can potentially be used for improved cosmesis following certain minor dermatologic interventions, such as dermabrasion and laser peeling.[107]

Novel but inadequately researched

Insulin. A pilot study run by National Health Service Innovation investigated the role of insulin in scar reduction. Fifteen patients undergoing bilateral breast reduction surgery received insulin injections in the wound margins of one breast and saline placebo in the contralateral breast. Although there is otherwise limited research evidence suggesting insulin has an antiscarring effect, this small but randomized controlled study reported that insulin administration improved scar profile.[108] Insulin has been recognized as an inhibitor of the fibrosis-associated fibroblast phenotype, the myofibroblast, and this has been advocated as a potential mechanism of insulin's action as an antiscarring agent.[109]

Other agents. Mitomycin C, topical tamoxifen, systemic methotrexate, topical imiquimob, retinoic acid, botulinum toxin A, calcineurin inhibitors, and calcium channel blockers have been sporadically investigated in small-scale studies.[110] The evidence base underpinning the use of such agents is inadequate. Larger, well designed, double blinded, randomized controlled clinical trials are essential before any credible suggestions for therapeutic use can be made.

CONCLUSION

It should be noted that lack of adequate evidence does not necessarily imply evidence of inadequacy. The present review is not an exhaustive account of evidence-based scar reduction strategies. The selectively discussed conventional modalities are widely available and commonly used, and there is some evidence in support of their use. Each patient is nonetheless different, and the practicing dermatologist must formulate a treatment strategy having considered guidelines on a par with personal clinical experience and individual patient needs.

The innovative promising agents that are currently being developed are a testament to the invaluable contribution of translational research in medicine—translating molecular advances into practical therapeutic modalities.

So the question "Will there be a scar?" will, perhaps one day in the not too distant future, be answered with "No, not one that you can see!"

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