Updated International Clinical Recommendations on Scar Management: Part 1—Evaluating the Evidence

Michael H. Gold, MD,* Brian Berman, MD, PhD,† Matteo Tretti Clementoni, MD,‡ Gerd G. Gauglitz, MD,§ Foad Nahai, MD,‖ and Crystal Murcia, PhD¶

BACKGROUND There is an ongoing need to standardize scar management by establishing safe and effective treatment options that can be applied in routine clinical practice.

OBJECTIVE To review available data on methods for preventing and treating cutaneous scarring.

MATERIALS AND METHODS Relevant scientific literature was identified through a comprehensive search of the MEDLINE database. Additional data and published studies were submitted for consideration by members of the International Advisory Panel on Scar Management.

RESULTS One of the most significant advances in scar management over the past 10 years has been the broader application of laser therapy, resulting in a shift in status from an emerging technology to the forefront of treatment. Accumulated clinical evidence also supports a greater role for 5-fluourouracil in the treatment of hypertrophic scars and keloids, particularly in combination with intralesional corticosteroids. Encouraging data have been reported for newer therapies, including bleomycin, onion extract–containing preparations, imiquimod, and mitomycin C, although methodologic limitations in available studies merit consideration. In general, clinical and aesthetic outcomes seem to be enhanced by a combination approach to treatment.

CONCLUSION Advances in therapeutic options and new study data necessitate a revision of algorithms for the prevention and management of cutaneous scarring.

The authors received honoraria from Enaltus, Lumenis, and Merz for their work on this panel.

Prevention and treatment of cutaneous scarring has traditionally lain outside the bounds of standardization; individual experience has been the driver of clinical practice for many years, with varying degrees of success. The 2002 consensus statement from the International Advisory Panel on Scar Management was an effort to ground treatment practices in a foundation of clinical data.[1] Members of the advisory panel reviewed the scientific literature to assess available evidence and shortcomings therein. In the interval since the consensus statement was published, a plethora of clinical trial data have been released, new agents have been tested, and technological advances have enhanced certain existing modalities. In 2012, the advisory panel reconvened to reevaluate support for various treatment methods and ensure that current practices are aligned with the evidence base. The resulting comprehensive literature review update is presented herein. In the interest of brevity, this article focuses on clinical data that have influenced the advisory panel's recommendations.

**Gold Skin Care Center and Tennessee Clinical Research Center, Nashville, Tennessee; †Center for Clinical and Cosmetic Research, Aventura, Florida; ‡Department of Laser and Surgery, Istituto Dermatologico Europeo, Milano, Italy; §Department of Dermatology and Allergy, Ludwig Maximilian University, Munich, Germany; ‖Paces Plastic Surgery, Atlanta, Georgia; ¶Inkwell Medical Communications, Novelty, Ohio*

For a complete list of the International Advisory Panel Members, see Appendix 1.

ISSN: 1076-0512 • Dermatol Surg 2014;40:817–824 • DOI: 10.1111/dsu.0000000000000049

Comprehensive Literature Review

A methodology similar to that described in the 2002 publication[1] was used to maintain consistency and allow cumulative evidence to guide this update. A MEDLINE search was conducted to identify relevant clinical trials, randomized controlled trials, comparative studies, and meta-analyses published in English from January 1, 2002, through August 3, 2012. Search terms included avotermin, bleomycin, botulinum toxin, cryotherapy, fluorouracil, hypertrophic, imiquimod, interferon, intralesional, keloid, laser therapy, mitomycin, onion extract, pressure therapy, radiotherapy, scar, silicone, steroid, and transforming growth factor beta 3. In addition, English language review articles discussing the management of hypertrophic and keloid scarring indexed by MEDLINE were assessed, and a manual search was conducted. We confirmed that pertinent literature was included and provided additional review articles, clinical studies, and recent unpublished data for consideration.

Treatment Modalities

Available therapeutic options for the management of cutaneous scarring and the supporting evidence base are outlined in the table below, in order of effectiveness.

Silicone-based products	• Well established in the management of cutaneous scarring • Continues to be widely used in clinical practice • Studies deemed susceptible to bias in Cochrane review[2] • Newer gel preparations overcome limitations inherent in gel sheeting; appropriate for face and neck[3] • Efficacious in scarring prophylaxis and management of hypertrophic scars[4–9] • Silicone gel performed as well or better than silicone gel sheeting[10,11]
Intralesional corticosteroids	• Place in therapy largely unchanged over the last decade[1] • Preferred first-line treatment for keloids[1] • Second-line choice for hypertrophic scars[12] • May be combined with other treatments to enhance efficacy Low doses may help minimize side effects, including dermal atrophy, telangiectasia,[12] and hypopigmentation[13] • Associated with low rate of keloid recurrence after surgical removal when combined with corticosteroid ointment[14]
5-Fluorouracil	• Successfully used since 1989 for the treatment of cutaneous scars[15] Response rate: 50%–70%[12,16] • Provided same clinical benefit as pulsed-dye laser therapy or intralesional triamcinolone, with fewer side effects[17] • 5-FU tattooing provided more significant improvement versus intralesional triamcinolone[18] • Addition to scar reduction therapies enhanced therapeutic efficacy versus each treatment alone[19–22] 5-FU + intralesional triamcinolone versus triamcinolone[20] 5-FU + intralesional triamcinolone versus surgical excision and triamcinolone[21] 5-FU ± pulsed-dye laser therapy + triamcinolone, versus triamcinolone[19] • 5-FU + intralesional corticosteroids reduced recurrence rate after surgical removal of ear keloids[23]
Laser therapy	• Considered an emerging technology in 2002 guidelines[1] • Pulsed-dye laser therapy first to gain widespread acceptance • 585-nm pulsed-dye laser preferred choice for both hypertrophic scars and keloids[24]

(Continued)	
	Estimated 72% efficacy rate[12]
	• Greater efficacy thought possible with 595-nm pulsed-dye laser[25]
	Significant improvement after only 2 sessions[24]
	Addition of intralesional corticosteroids has little impact on outcomes, except in highly symptomatic cases[26]
	• Ablative and nonablative fractional lasers are focus of much current research
	• Generally favorable in scientific literature for preventative and treatment applications[27–36]
	• Better outcomes with fractional versus pulsed-dye laser in postoperative treatment of surgical scars[29,32]
	• Improvements in clinical and structural features of burn scars reported with fractional CO_2 laser therapy[33–35]
	• Ablative fractional lasers require fewer sessions, thus may be preferred over nonablative lasers for burn scars[35]
	• Common side effects after fractional laser treatment: transient erythema, edema, and purpura[27,28,30]
	• Ablative fractional laser + triamcinolone acetonide may provide an efficient, safe, and effective therapy for challenging cutaneous scars[37]
Radiotherapy	• Continues to be reserved for secondary management in adults with cutaneous scarring
	• Combined with surgical excision, radiotherapy
	Decreased keloid recurrence rates[12,13]
	Produced fewer side effects and greater patient satisfaction than cryotherapy and intralesional corticosteroids[38]

(Continued)	
	Reduced recurrence rates when treatment tailored to body region[39]
	• Recurrence also prevented with high-dose-rate superficial brachytherapy after keloidectomy[40]
Cryotherapy	• Historically limited to small scars because of[1]
	Need for repeated treatments
	Prolonged healing times
	Potential for permanent pigmentation alterations
	Skin atrophy
	Pain
	• Intralesional rather than contact cryotherapy substantially reduced cutaneous scar volume during one treatment, with minimal side effects and rapid recovery[41,42]
	• Improvements in scar hardness, elevation, redness, itching, pain, and tenderness also reported; no evidence of permanent hypopigmentation[43]
	• Intralesional versus contact cryotherapy was less painful during and immediately after treatment[44]
	• Traditional cryotherapy combined with intralesional corticosteroids augments therapeutic efficacy in small keloids[45]
	• Eases corticosteroid injection through creation of an edema in the dermis, thereby increasing efficacy[41,45]
Bleomycin	• Efficacy in treatment of cutaneous scarring demonstrated in multiple small and uncontrolled studies[46]
	• Most patients experienced substantial scar flattening or regression, amelioration of pain and pruritus[47,48]

(Continued)	
	• More favorable therapeutic response versus cryotherapy + intralesional triamcinolone demonstrated in only 1 study[49]
Mitomycin C	• No keloid recurrence after 6–24 months with surgical excision and topical mitomycin C[50] • Keloid worsening and ulceration reported with intralesional mitomycin C[51] • No improvement in keloid recurrence rates reported in only 1 study[52] • Mostly small and uncontrolled studies, with high degree of methodologic variability[53] • Little available data for hypertrophic scarring; mostly clinical experience in postoperative management
Imiquimod	• 5% cream effective in prevention of earlobe keloid recurrence after excision[46,53,54] • However, high rate of recurrence reported for trunk keloids after excision and 8-week imiquimod treatment[55] • Recurrence rate also substantially different between lesions of the pinna and chest wall or neck[56]
Pressure therapy	• Longtime standard care for prevention and treatment of hypertrophic scars from burns, practice largely based on empiric evidence[1] • No change in global scar scores and only small improvement in scar height reported in meta-analysis[57] • Low pressure less effective than high-pressure treatments; patients with moderate or severe scarring experienced greater clinical benefit[58–60]
Adhesive microporous hypoallergenic paper tape	• Recommended in 2002 guidelines for prevention of hypertrophic scarring after surgical incision in low-risk patients[1] on the basis of advisory board consensus rather than controlled clinical trial data

(Continued)	
	• Significantly reduced occurrence of hypertrophic scar development versus untreated controls[61]
Onion extract (extractum cepae)	• Subject of active clinical interest • Utilization greatly expanded among the general public in recent years yet efficacy is questioned Shortcomings in the evidence base • Improvement in scar symptoms, appearance, or both observed in multiple randomized controlled trials[62–65] • Not more efficacious than a petrolatum emollient in a head-to-head comparison[66] • Showed mixed results in the context of established hypertrophic and keloid scars[11,67–70] • Not as effective as either silicone gel or silicone gel sheeting[11] • In a retrospective cohort analysis, enhanced normalization of erythema, pruritus, and consistency in hypertrophic scars versus intralesional corticosteroid with fewer adverse events[67] • Significant improvements versus placebo in cosmesis, induration, pigmentation, and tenderness of cutaneous scars reported in prospective study[70] • Greater patient satisfaction and reduction of neoangiogenic features of cutaneous scars versus placebo or comparator lotion[69] • Combination with traditional therapies believed to enhance therapeutic efficacy versus either silicone gel sheeting[68] or intralesional corticosteroid injections[71] alone • Generally well tolerated, alone or in combination

Emerging and Investigational Therapies

Reduction of muscular tensile force during scar formation and restoration of balance between fibroblast proliferation and apoptosis may represent a novel therapeutic option for the aesthetic improvement of postsurgical scars.[72] Botulinum toxin A (BTA) paralyzes local muscles and reduces skin tension caused by muscle pull, thereby decreasing scar tension and subsequent inflammation in wound edges.[53] Gassner and colleagues[73] demonstrated that BTA injections resulted in enhanced wound healing and less noticeable scars compared with placebo. Recently, intralesional injection with BTA was also proposed for the treatment of established keloids. In a prospective uncontrolled study,[74] BTA was injected into lesions at 3-month intervals for a maximum of 9 months. At 1-year follow-up, scar regression was noted from the periphery in all 12 patients, followed by flattening of lesions; no signs of recurrence were noted in any patient. However, in a recently published study, objective evaluation of BTA-treated keloids using optical profilometry did not reveal any changes after BTA therapy compared with baseline.[75] Thus, although reduction of the tensile force by prophylactic BTA injections might represent a comprehensible mechanism of action for aesthetic improvement of postsurgical scars, the suggested clinical efficacy of intralesional BTA for the treatment of existent keloids remains uncertain. More in-depth studies are needed before a comparatively expensive therapy can be suggested for this particular indication.

A novel hydrogel scaffold product was recently approved in Europe for the improvement of wound healing and resulting scars. Unpublished data from a randomized controlled trial revealed improvement in surgical scar ratings after a single application.[76] When used in the treatment of earlobe keloids, preliminary results indicated a significant reduction in 12-month recurrence rate after a single injection after surgical excision compared with historical data.[77]

Other innovative therapies that have been evaluated for the prevention and management of scarring (e.g., calcineurin inhibitors, retinoic acid, tamoxifen, verapamil) have insufficient evidence for recommendation in routine clinical practice. It is worth noting that avotermin, a human recombinant transforming growth factor beta-3 derivative, showed promising results in preclinical and early clinical development as a prophylactic treatment for scarring[78] yet failed to meet the primary or secondary end points in the Phase 3 REVISE trial.[79] Another agent with early potential, interferon α2b, has yet to clearly establish a role in the prevention and management of pathologic scarring. Accumulated evidence for interferon α2b is mixed, with some studies demonstrating a positive impact on prevention of keloid recurrence and reduction of scar size and others showing no such benefit.[46] Side effects, such as flu-like symptoms and pain at the injection site, as well as the expense of treatment limit the applicability of interferon therapy.[12]

Conclusion

Clinicians have a host of therapeutic options for the management of cutaneous scarring at their disposal. Despite a persistent gap in the scientific literature needed to support many of the procedures routinely applied, evaluation of the clinical evidence revealed appropriate scenarios wherein use of a particular therapy or combination of therapies is efficacious in improving scars. To promote application of treatment modalities consistent with the current evidence base, a revision to scar prevention and treatment algorithms is necessary.

Acknowledgments We thank Michael McGuire, MD, Thomas A. Mustoe, MD, Andrea Pusic, MD, Mukta Sachdev, MD, and Jill Waibel, MD, for their input and review of the manuscript; and Jennifer Rossi, MedThink SciCom, for providing editorial support.

References

1. Mustoe TA, Cooter RD, Gold MH, Hobbs FD, et al. International clinical recommendations on scar management. Plast Reconstr Surg 2002;110:560–71.
2. O'Brien L, Pandit A. Silicon gel sheeting for preventing and treating hypertrophic and keloid scars. Cochrane Database Syst Rev 2006: CD003826.

3. Mustoe TA. Evolution of silicone therapy and mechanism of action in scar management. Aesthetic Plast Surg 2008;32:82–92.
4. Chan KY, Lau CL, Adeeb SM, Somasundaram S, et al. A randomized, placebo-controlled, double-blind, prospective clinical trial of silicone gel in prevention of hypertrophic scar development in median sternotomy wound. Plast Reconstr Surg 2005;116:1013–20; discussion 1021–2.
5. Signorini M, Clementoni MT. Clinical evaluation of a new self-drying silicone gel in the treatment of scars: a preliminary report. Aesthetic Plast Surg 2007;31:183–7.
6. de Giorgi V, Sestini S, Mannone F, Papi F, et al. The use of silicone gel in the treatment of fresh surgical scars: a randomized study. Clin Exp Dermatol 2009;34:688–93.
7. Momeni M, Hafezi F, Rahbar H, Karimi H. Effects of silicone gel on burn scars. Burns 2009;35:70–4.
8. Stoffels I, Wolter TP, Sailer AM, Pallua N. Influence of silicone spray on scar formation: double-blind, placebo-controlled, single-center trial. Hautarzt 2010;61:332–8.
9. van der Wal MB, van Zuijlen PP, van de Ven P, Middelkoop E. Topical silicone gel versus placebo in promoting the maturation of burn scars: a randomized controlled trial. Plast Reconstr Surg 2010; 126:524–31.
10. Chernoff WG, Cramer H, Su-Huang S. The efficacy of topical silicone gel elastomers in the treatment of hypertrophic scars, keloid scars, and post-laser exfoliation erythema. Aesthetic Plast Surg 2007;31:495–500.
11. Karagoz H, Yuksel F, Ulkur E, Evinc R. Comparison of efficacy of silicone gel, silicone gel sheeting, and topical onion extract including heparin and allantoin for the treatment of postburn hypertrophic scars. Burns 2009;35:1097–103.
12. Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. Arch Facial Plast Surg 2006;8:362–8.
13. Tziotzios C, Profyris C, Sterling J. Cutaneous scarring: pathophysiology, molecular mechanisms, and scar reduction therapeutics. Part II. Strategies to reduce scar formation after dermatologic procedures. J Am Acad Dermatol 2012;66:13–24.
14. Hayashi T, Furukawa H, Oyama A, Funayama E, et al. A new uniform protocol of combined corticosteroid injections and ointment application reduces recurrence rates after surgical keloid/hypertrophic scar excision. Dermatol Surg 2012;38:893–7.
15. Fitzpatrick RE. Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg 1999;25:224–32.
16. Nanda S, Reddy BS. Intralesional 5-fluorouracil as a treatment modality of keloids. Dermatol Surg 2004;30:54–6; discussion 56–7.
17. Manuskiatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. Arch Dermatol 2002;138:1149–55.
18. Sadeghinia A, Sadeghinia S. Comparison of the efficacy of intralesional triamcinolone acetonide and 5-fluorouracil tattooing for the treatment of keloids. Dermatol Surg 2012;38:104–9.
19. Asilian A, Darougheh A, Shariati F. New combination of triamcinolone, 5-fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars. Dermatol Surg 2006;32:907–15.
20. Darougheh A, Asilian A, Shariati F. Intralesional triamcinolone alone or in combination with 5-fluorouracil for the treatment of keloid and hypertrophic scars. Clin Exp Dermatol 2009;34:219–23.
21. Davison SP, Dayan JH, Clemens MW, Sonni S, et al. Efficacy of intralesional 5-fluorouracil and triamcinolone in the treatment of keloids. Aesthet Surg J 2009;29:40–6.
22. Hatamipour E, Mehrabi S, Hatamipour M, Ghafarian Shirazi HR. Effects of combined intralesional 5-fluorouracil and topical silicone in prevention of keloids: a double blind randomized clinical trial study. Acta Med Iran 2011;49:127–30.
23. Liu W, Wu X, Gao Z, Song N. Remodelling of keloid tissue into normal-looking skin. J Plast Reconstr Aesthet Surg 2008;61: 1553–4.
24. Tanzi EL, Alster TS. Laser treatment of scars. Skin Therapy Lett 2004; 9:4–7.
25. Vrijman C, van Drooge AM, Limpens J, Bos JD, et al. Laser and intense pulsed light therapy for the treatment of hypertrophic scars: a systematic review. Br J Dermatol 2011;165:934–42.
26. Alster T. Laser scar revision: comparison study of 585-nm pulsed dye laser with and without intralesional corticosteroids. Dermatol Surg 2003;29:25–9.
27. Haedersdal M, Moreau KE, Beyer DM, Nymann P, et al. Fractional nonablative 1540 nm laser resurfacing for thermal burn scars: a randomized controlled trial. Lasers Surg Med 2009; 41:189–95.
28. Vasily DB, Cerino ME, Ziselman EM, Zeina ST. Non-ablative fractional resurfacing of surgical and post-traumatic scars. J Drugs Dermatol 2009;8:998–1005.
29. Tierney E, Mahmoud BH, Srivastava D, Ozog D, et al. Treatment of surgical scars with nonablative fractional laser versus pulsed dye laser: a randomized controlled trial. Dermatol Surg 2009;35: 1172–80.
30. Cervelli V, Gentile P, Spallone D, Nicoli S, et al. Ultrapulsed fractional CO_2 laser for the treatment of post-traumatic and pathological scars. J Drugs Dermatol 2010;9:1328–31.
31. Kim HS, Lee JH, Park YM, Lee JY. Comparison of the effectiveness of nonablative fractional laser versus ablative fractional laser in thyroidectomy scar prevention: a pilot study. J Cosmet Laser Ther 2012; 14:89–93.
32. Oh G, Ahn HH, Choi JE, Kim JY, et al. Postoperative treatment of surgical scars with ablative fractional laser versus pulsed dye laser: a randomized controlled trial. J Am Acad Dermatol 2012;66: AB12.
33. Ozog DM, Liu A, Chaffins ML, Ormsby AH, et al. Evaluation of clinical results, histological architecture, and collagen expression following treatment of mature burn scars with a fractional carbon dioxide laser. JAMA Dermatol 2013;149:50–7.
34. Qu L, Liu A, Zhou L, He C, et al. Clinical and molecular effects on mature burn scars after treatment with a fractional CO(2) laser. Lasers Surg Med 2012;44:517–24.
35. Suh D-H, Chang K-Y, Song K-Y, Shin M-K, et al. Revision of burn scars using ablative fractional CO_2 laser. J Am Acad Dermatol 2012;66: AB216.
36. Waibel J, Wulkan AJ, Lupo M, Beer K, et al. Treatment of burn scars with the 1,550 nm nonablative fractional Erbium Laser. Lasers Surg Med 2012;44:441–6.
37. Waibel JS, Wulkan AJ, Shumaker PR. Treatment of hypertrophic scars using laser and laser assisted corticosteroid delivery. Lasers Surg Med 2013;45:135–40.
38. Emad M, Omidvari S, Dastgheib L, Mortazavi A, et al. Surgical excision and immediate postoperative radiotherapy versus cryotherapy and intralesional steroids in the management of keloids: a prospective clinical trial. Med Princ Pract 2010;19:402–5.
39. Ogawa R, Miyashita T, Hyakusoku H, Akaishi S, et al. Postoperative radiation protocol for keloids and hypertrophic scars: statistical analysis of 370 sites followed for over 18 months. Ann Plast Surg 2007;59:688–91.

40. Kuribayashi S, Miyashita T, Ozawa Y, Iwano M, et al. Post-keloidectomy irradiation using high-dose-rate superficial brachytherapy. J Radiat Res 2011;52:365–8.

41. Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. Plast Reconstr Surg 2003;111:1841–52.

42. Har-Shai Y, Sabo E, Rohde E, Hyams M, et al. Intralesional cryosurgery enhances the involution of recalcitrant auricular keloids: a new clinical approach supported by experimental studies. Wound Repair Regen 2006;14:18–27.

43. Har-Shai Y, Dujovny E, Rohde E, Zouboulis CC. Effect of skin surface temperature on skin pigmentation during contact and intralesional cryosurgery of keloids. J Eur Acad Dermatol Venereol 2007;21:191–8.

44. Mirmovich O, Gil T, Goldin I, Lavi I, et al. Pain evaluation and control during and following the treatment of hypertrophic scars and keloids by contact and intralesional cryosurgery—a preliminary study. J Eur Acad Dermatol Venereol 2012;26:440–7.

45. Sharma S, Bhanot A, Kaur A, Dewan SP. Role of liquid nitrogen alone compared with combination of liquid nitrogen and intralesional triamcinolone acetonide in treatment of small keloids. J Cosmet Dermatol 2007;6:258–61.

46. Berman B, Viera MH, Amini S. Keloid and hypertrophic scar treatment and management. In: Elston DM, editor. Medscape reference: drugs, diseases and procedures. Medscape; 2012. Available at: http://emedicine.medscape.com/article/1057599-treatment.

47. Aggarwal H, Saxena A, Lubana PS, Mathur RK, et al. Treatment of keloids and hypertrophic scars using bleom. J Cosmet Dermatol 2008; 7:43–9.

48. Saray Y, Güleç AT. Treatment of keloids and hypertrophic scars with dermojet injections of bleomycin: a preliminary study. Int J Dermatol 2005;44:777–84.

49. Naeini FF, Najafian J, Ahmadpour K. Bleomycin tattooing as a promising therapeutic modality in large keloids and hypertrophic scars. Dermatol Surg 2006;32:1023–29; discussion 1029–30.

50. Gupta M, Narang T. Role of mitomycin C in reducing keloid recurrence: patient series and literature review. J Laryngol Otol 2011; 125:297–300.

51. Seo SH, Sung HW. Treatment of keloids and hypertrophic scars using topical and intralesional mitomycin C. J Eur Acad Dermatol Venereol 2012;26:634–8.

52. Sanders KW, Gage-White L, Stucker FJ. Topical mitomycin C in the prevention of keloid scar recurrence. Arch Facial Plast Surg 2005;7: 172–5.

53. Viera MH, Amini S, Valins W, Berman B. Innovative therapies in the treatment of keloids and hypertrophic scars. J Clin Aesthet Dermatol 2010;3:20–6.

54. Berman B, Harrison-Balestra C, Perez OA, Viera M, et al. Treatment of keloid scars post-shave excision with imiquimod 5% cream: a prospective, double-blind, placebo-controlled pilot study. J Drugs Dermatol 2009;8:455–8.

55. Cação FM, Tanaka V, Messina MC. Failure of imiquimod 5% cream to prevent recurrence of surgically excised trunk keloids. Dermatol Surg 2009;35:629–33.

56. Chuangsuwanich A, Gunjittisomram S. The efficacy of 5% imiquimod cream in the prevention of recurrence of excised keloids. J Med Assoc Thai 2007;90:1363–7.

57. Anzarut A, Olson J, Singh P, Rowe BH, et al. The effectiveness of pressure garment therapy for the prevention of abnormal scarring after burn injury: a meta-analysis. J Plast Reconstr Aesthet Surg 2009; 62:77–84.

58. Van den Kerckhove E, Stappaerts K, Fieuws S, Laperre J, et al. The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventive measure for hypertrophic scarring. Burns 2005;31:696–702.

59. Candy LH, Cecilia LT, Ping ZY. Effect of different pressure magnitudes on hypertrophic scar in a Chinese population. Burns 2010; 36:1234–41.

60. Engrav LH, Heimbach DM, Rivara FP, Moore ML, et al. 12-Year within-wound study of the effectiveness of custom pressure garment therapy. Burns 2010;36:975–83.

61. Atkinson JA, McKenna KT, Barnett AG, McGrath DJ, et al. A randomized, controlled trial to determine the efficacy of paper tape in preventing hypertrophic scar formation in surgical incisions that traverse Langer's skin tension lines. Plast Reconstr Surg 2005;116: 1648–56; discussion 1657–8.

62. Willital GH, Heine H. Efficacy of Contractubex gel in the treatment of fresh scars after thoracic surgery in children and adolescents. Int J Clin Pharmacol Res 1994;14:193–202.

63. Draelos ZD. The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars. J Cosmet Dermatol 2008; 7:101–4.

64. Chanprapaph K, Tanrattanakorn S, Wattanakrai P, Wongkitisophon P, et al. Effectiveness of onion extract gel on surgical scars in asians. Dermatol Res Pract 2012;2012:212945.

65. Draelos ZD, Baumann L, Fleischer AB Jr, Plaum S, et al. A new proprietary onion extract gel improves the appearance of new scars: a randomized, controlled, blinded-investigator study. J Clin Aesthet Dermatol 2012;5:18–24.

66. Chung VQ, Kelley L, Marra D, Jiang SB. Onion extract gel versus petrolatum emollient on new surgical scars: prospective double-blinded study. Dermatol Surg 2006;32:193–7.

67. Beuth J, Hunzelmann N, Van Leendert R, Basten R, et al. Safety and efficacy of local administration of Contractubex® to hypertrophic scars in comparison to corticosteroid treatment. Results of a multicenter, comparative epidemiological cohort study in Germany. In Vivo 2006; 20:277–83.

68. Hosnuter M, Payasli C, Isikdemir A, Tekerekoglu B. The effects of onion extract on hypertrophic and keloid scars. J Wound Care 2007; 16:251–4.

69. Campanati A, Savelli A, Sandroni L, Marconi B, et al. Effect of allium cepa-allantoin-pentaglycan gel on skin hypertrophic scars: clinical and video-capillaroscopic results of an open-label, controlled, nonrandomized clinical trial. Dermatol Surg 2010;36: 1439–44.

70. Perez OA, Viera MH, Patel JK, Konda S, et al. A comparative study evaluating the tolerability and efficacy of two topical therapies for the treatment of keloids and hypertrophic scars. J Drugs Dermatol 2010;9: 514–8.

71. Koc E, Arca E, Surucu B, Kurumlu Z. An open, randomized, controlled, comparative study of the combined effect of intralesional triamcinolone acetonide and onion extract gel and intralesional triamcinolone acetonide alone in the treatment of hypertrophic scars and keloids. Dermatol Surg 2008;34:1507–14.

72. Lee BJ, Jeong JH, Wang SG, Lee JC, et al. Effect of botulinum toxin type a on a rat surgical wound model. Clin Exp Otorhinolaryngol 2009; 2:20–7.

73. Gassner HG, Brissett AE, Otley CC, Boahene DK, et al. Botulinum toxin to improve facial wound healing: a prospective, blinded, placebo-controlled study. Mayo Clin Proc 2006;81:1023–8.

74. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. Plast Reconstr Surg 2009;124: 275e–7e.

75. Gauglitz GG, Bureik D, Dombrowski Y, Pavicic T, et al. Botulinum toxin A for the treatment of keloids. Skin Pharmacol Physiol 2012;25: 313–8.

76. Baranowski W, Rechberger T, Kotarski J, Green A. Evaluation of a novel hydrogel scaffold for the reduction of scars secondary to surgical incisions. Paper presented at: American Society of Plastic Surgeons Annual Meeting; 2011; Denver, Colorado.

77. Berman B, Garikaparthi S, Smith E, Newburger J. A novel hydrogel scaffold for the prevention or reduction of the recurrence of keloid scars post-surgical excision. Paper presented at: American Academy of Dermatology Annual Meeting; 2013; Miami Beach, Florida.

78. Bush J, So K, Mason T, Occleston NL, et al. Therapies with emerging evidence of efficacy: avotermin for the improvement of scarring. Dermatol Res Pract 2010;2010.

79. Renovo. Juvista EU phase 3 trial results. In: Press release; 2011.

Address correspondence and reprint requests to: Michael H. Gold, MD, Gold Skin Care Center and Tennessee Clinical Research Center, 2000 Richard Jones Road, Suite 220, Nashville, TN 37215, or e-mail: goldskin@goldskincare.com