Trolamine-Containing Topical Emulsion: Clinical Applications in Dermatology

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Trolamine-containing topical emulsion is used to promote and expedite wound healing. This agent has been shown to recruit macrophages, which serve important functions in the wound healing process, and increase the IL-1:IL-6 ratio, which enhances formation of granulation tissue and collagen synthesis. Therapeutic applications have included acute radiation dermatitis and postoperative wounds, and application after cryotherapy for actinic keratosis (AK). This article reviews the mechanism of action and information on clinical applications of trolamine-containing topical emulsion.

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Management of cutaneous wounds continues to be a challenge in dermatology. One challenge is finding topical agents that expedite the healing process, depending on the type of wound and its cause. The management of postoperative wounds is another challenge, especially because habitual use of some topical antibiotics post–dermatologic procedures is associated with a high risk of allergic contact dermatitis without proven benefit in the prevention of infection.[1] Trolamine-containing topical emulsion has been used for more than 3 decades in both Europe and the United States for the management of multiple conditions affecting skin integrity, such as radiation dermatitis and cutaneous wounds. In addition, trolamine-containing topical emulsion has been used for many indications and dermatologic applications, ranging from superficial wounds and skin ulcers to postoperative wounds (Table).[2,3]

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What is the mechanism of action of trolamine-containing topical emulsion?

The trolamine-containing oil-in-water topical emulsion provides both occlusive and hydrating properties, increases recruitment of macrophages to wound sites to enhance healing at the dermal level, and stimulates formation of granulation tissue. In a study of identical epidermal wounds in healthy volunteers, researchers demonstrated that trolamine-containing topical emulsion is chemotactic for macrophages, the cells that serve to enhance formation of granulation tissue.[4]

Macrophages are capable of secreting the cytokine IL-6, which is known to accelerate epidermal growth and to inhibit the proliferation of fibroblasts. By down-regulating secretion of IL-6 and inducing IL-1 release, trolamine-containing topical emulsion increases the IL-1:IL-6 ratio.[4] The end result of these changes in cytokine profile is granulation tissue formation and modulation of extracellular matrix reorganization by influencing collagen and collagenase synthesis. These findings were confirmed in an ex vivo study of the ability of trolamine-containing topical emulsion to heal irradiated skin, which verified radiotherapy-induced modifications, including a 50% reduction in basal cell proliferation.[5] In the first 24 hours, irradiated skin typically shows extensive vasodilation and altered capillary permeability accompanied by decreased CD34 transmembrane protein expression, which are factors that together

can result in cell necrosis. After application of trolamine-containing topical emulsion to skin in this study, collagen synthesis and IL-1α secretion were enhanced, capillary alterations were decreased, and CD34 expression and epithelial cell proliferation were restored. It was concluded that application of trolamine-containing topical emulsion made it possible to modulate fibroblast metabolism and subsequent collagen synthesis in a way that may be advantageous in limiting postradiation fibrosis.[5]

How may trolamine-containing topical emulsion modulate the wound-healing process?

Trolamine-containing topical emulsion has been shown to promote the wound-healing process. Wound healing is a complex biologic process involving a complex interaction between many cell types, a variety of mediating secretions, and immunologic phenomena.[4,5] The process can be divided into the following 3 phases: (1) hemostasis and inflammation; (2) cell migration and proliferation; and (3) skin remodeling.[6,7] Transition from one phase to another is not abrupt because there is overlap of the biologic processes that occur during wound healing.

The hemostasis and inflammation phase includes the time of skin injury through days 4 to 6.[3-7] Immediately after a cutaneous wound occurs, platelets help to form a fibrin plug while growth factors and cytokines are being released and recruited into the area of the injury. Within 24 hours, the inflammatory stage of healing coincides with the arrival of neutrophils, which are involved with phagocytosis and wound debridement. Monocytes, transformed into macrophages, arrive within 48 to 96 hours and play an important role in wound healing.

Cell migration and proliferation, the second phase of wound healing, occurs from day 4 through day 14.[6,7] After an injury to the skin, the nuclear factor-κB pathway is activated through cytokine receptors IL-1 and tumor necrosis factor-α, among other chemokines, adhesion molecules, and cytokines produced by local tissue cells and migrating leukocytes. Continued migration of inflammatory cells and macrophages into the wound space ultimately leads to granulation tissue formation and reepithelialization as the infiltrating cells perform the following: (1) consumption of bacteria via phagocytosis; (2) secretion of collagenases, which modulates wound debridement; (3) release of growth factors, which promotes angiogenesis and further healing; (4) stimulation of the deposition of new collagen formation by fibroblasts; and (5) recruitment of fibroblasts and keratinocytes by macrophages.[6,7]

The final stage of wound healing is skin remodeling, which occurs from day 14 through 1 year.[6,7] In this final stage of wound healing, collagen deposited by fibroblasts is formed into an organized network. Within the wound, there is interaction between collagen degradation and new collagen production, as overall collagen formation increases to accommodate the new thicker collagen that is oriented along the stress lines within the wound.[6,7] The duration of skin remodeling correlates with the depth of the wound, with the process continuing over weeks in superficial wounds and for up to one year or more in deep wounds, though replacement tissue is not created with the degree of organization equivalent to that found in uninjured skin.

Trolamine-containing topical emulsion appears to promote and expedite healing by increasing the number of macrophages recruited to the injury site, thereby decreasing the time needed for healing.[2,4,5] Macrophages have been referred to as the "orchestra leaders" of wound healing because their role is to direct the course of the wound-healing process.[7] They serve to complete the debridement initiated by neutrophils and participate directly in the inflammatory cascade with the release of cytokines and growth factors, which produces a cytokine profile conducive to wound healing.[4,5,7]

Is trolamine-containing topical emulsion helpful in the treatment of radiation dermatitis?

Trolamine-containing topical emulsion has a history of use for radiation dermatitis, with information on its mechanistic role already reviewed.[2,3,8,9] The use

Trolamine-Containing Topical Emulsion[2,3]

Indications and Dermatologic Uses

- Full-thickness wounds[a]
- Superficial wounds[a]
- First- and second-degree burns, including sunburn[a]
- Dermal ulcers[a]
- Graft site management[a]
- Radiation dermatitis[a]
- Minor abrasions[a]
- Postoperative wounds

[a]Indication approved by US Food and Drug Administration.

of ionizing radiation to treat primary tumors and palliate metastatic disease sometimes may lead to acute or chronic skin injury. These insults are considered adverse effects and are not fully ameliorated by the development of more modern equipment or of more sophisticated therapeutic regimens intended to minimize skin toxicity. Even with modernized equipment and techniques, radiation-induced cutaneous injury continues to be a challenging side effect, sometimes associated with discomfort and pain, and it may limit the duration of treatment or dose delivered.[9]

In addition to interfering with the normal maturation, reproduction, and repopulation of epidermal and hair matrix cells, radiotherapy targets both fibroblasts and cutaneous vasculature.[9] A radiation-induced injury is considered a complex wound in which adverse structural tissue changes occur immediately and are characterized by DNA damage and alteration of cellular proteins and lipids. Repeated exposure to radiation contributes both to direct tissue injury and impairment of healing via inhibition of granulation tissue formation, fibrogenesis, and angiogenesis.[9]

For acute radiation dermatitis, trolamine-containing topical emulsion appears to reduce discomfort and provide moisturization; however, as with other topical formulations, it has not been proven to be radioprotective.[8-11] In one study, trolamine-containing topical emulsion was shown to prevent treatment delays or interruptions due to radiation-induced skin toxicity. The study demonstrated that the overall treatment time of chemotherapy and radiotherapy was reduced because the modalities could be administered simultaneously rather than sequentially.[8]

What other uses of trolamine-containing topical emulsion have been reported to be effective?

Treatment of actinic keratosis (AK), especially with physical modalities such as cryotherapy, causes disruption of epithelium. The impact of trolamine-containing topical emulsion on the healing time of treatment sites after cryotherapy for AK was evaluated in an investigator-blinded pilot study (N=40).[2,12] Study participants with symmetric involvement of AKs on the dorsal hands, dorsal forearms, forehead, and cheeks were treated with liquid nitrogen cryotherapy followed by twice-daily application of trolamine-containing topical emulsion to all treated target regions on one side of the body and a designated petrolatum-based ointment (nonmedicated white

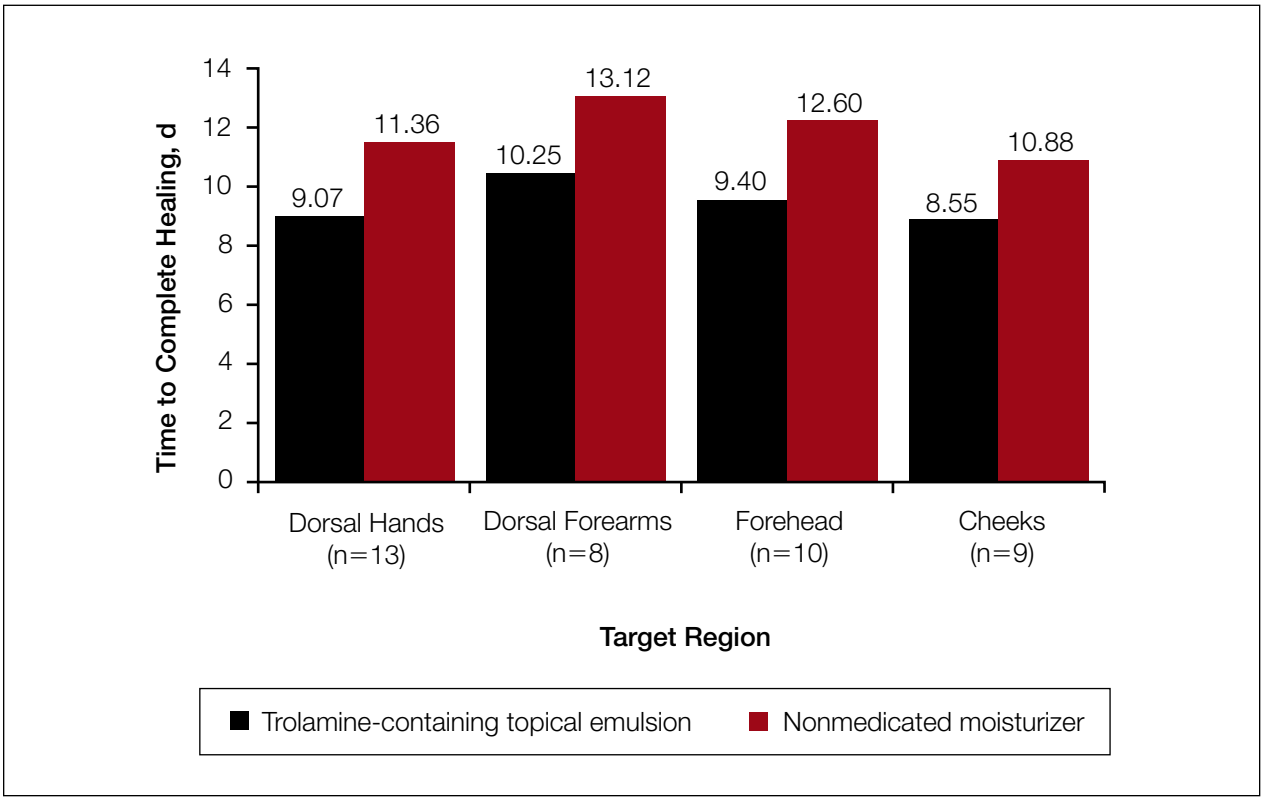

Figure 1. Mean time to complete healing of actinic keratosis site following cryotherapy and application of trolamine-containing topical emulsion or petrolatum-based ointment (nonmedicated moisturizer) to the dorsal hands, dorsal forearms, forehead, and cheeks. Reprinted from Del Rosso,[12] with permission from HMP Communications.

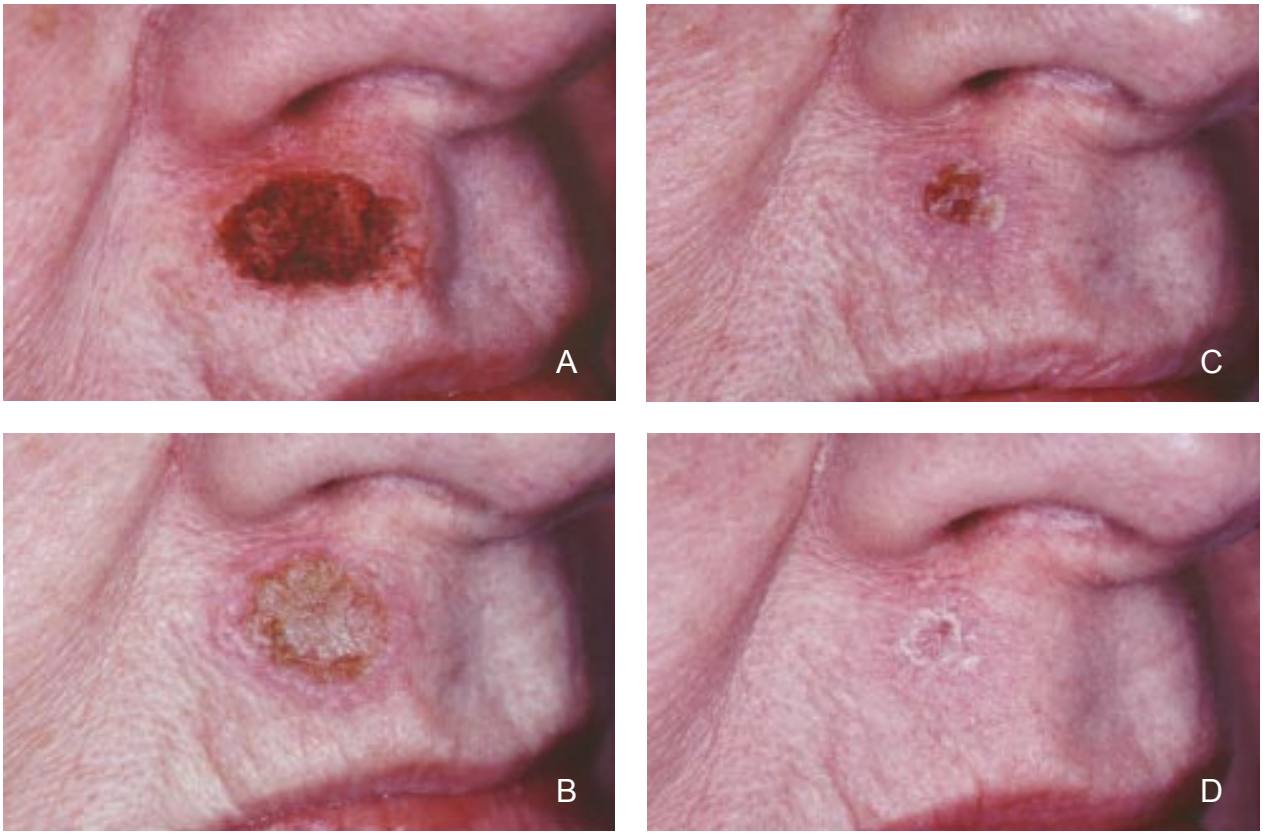

Figure 2. Patient with surgical excision of a basal cell carcinoma on the right side of the upper cutaneous lip followed by second-intention healing before (A) and after application of trolamine-containing topical emulsion (B, 7 days; C, 14 days; D, 21 days).

petrolatum) twice daily on the other side of the body. The number of treated AKs in each target region on both sides of the body was 5 on the dorsal hands, 8 on the dorsal forearms, 5 on the forehead, and 5 on the cheeks. The total number of target regions treated with liquid nitrogen cryotherapy was 13, 8, 10, and 9, respectively. None of the treated lesions were hypertrophic AKs. The mean time to complete healing was reduced by at least 2.29 days in the treatment group that used the trolamine-containing topical emulsion, with results varying slightly based on the site treated (Figure 1). Complete healing at all cryotherapy-treated sites was faster by 2.29 days, 2.87 days, 3.20 days, and 2.33 days on the dorsal hand, dorsal forearm, forehead, and cheek, sides that were treated with trolamine-containing topical emulsion as compared with the sides treated with petrolatum-based ointment, respectively.[2,12]

Trolamine-containing topical emulsion also has been reported to enhance wound healing after Mohs micrographic surgery, excisional surgery, and other dermatologic surgical procedures that are followed by second-intention healing, such as curettage and shave or saucerization techniques.[2,12,13] Figure 2 demonstrates healing over 21 days from application of trolamine-containing topical emulsion after surgical excision of a basal cell carcinoma on the right side of the upper cutaneous lip followed by second-intention healing. Figure 3 demonstrates healing over 14 days from application of trolamine-containing topical emulsion after curettage and electrodesiccation of a basal cell carcinoma on the left postauricular surface followed by second-intention healing.

What is the safety profile of trolamine-containing topical emulsion?

No major adverse effects have been reported with trolamine-containing topical emulsion. Local tolerability has been excellent, with a low potential risk for signs and/or symptoms of cutaneous irritation and little to no risk of contact sensitization.[2,8,10-13]

How does the use of trolamine-containing topical emulsion differ from other topical agents commonly used in dermatology for wounds that are frequently encountered in clinical practice?

In dermatology, commonly used topical agents for treatment of cutaneous wounds, including those

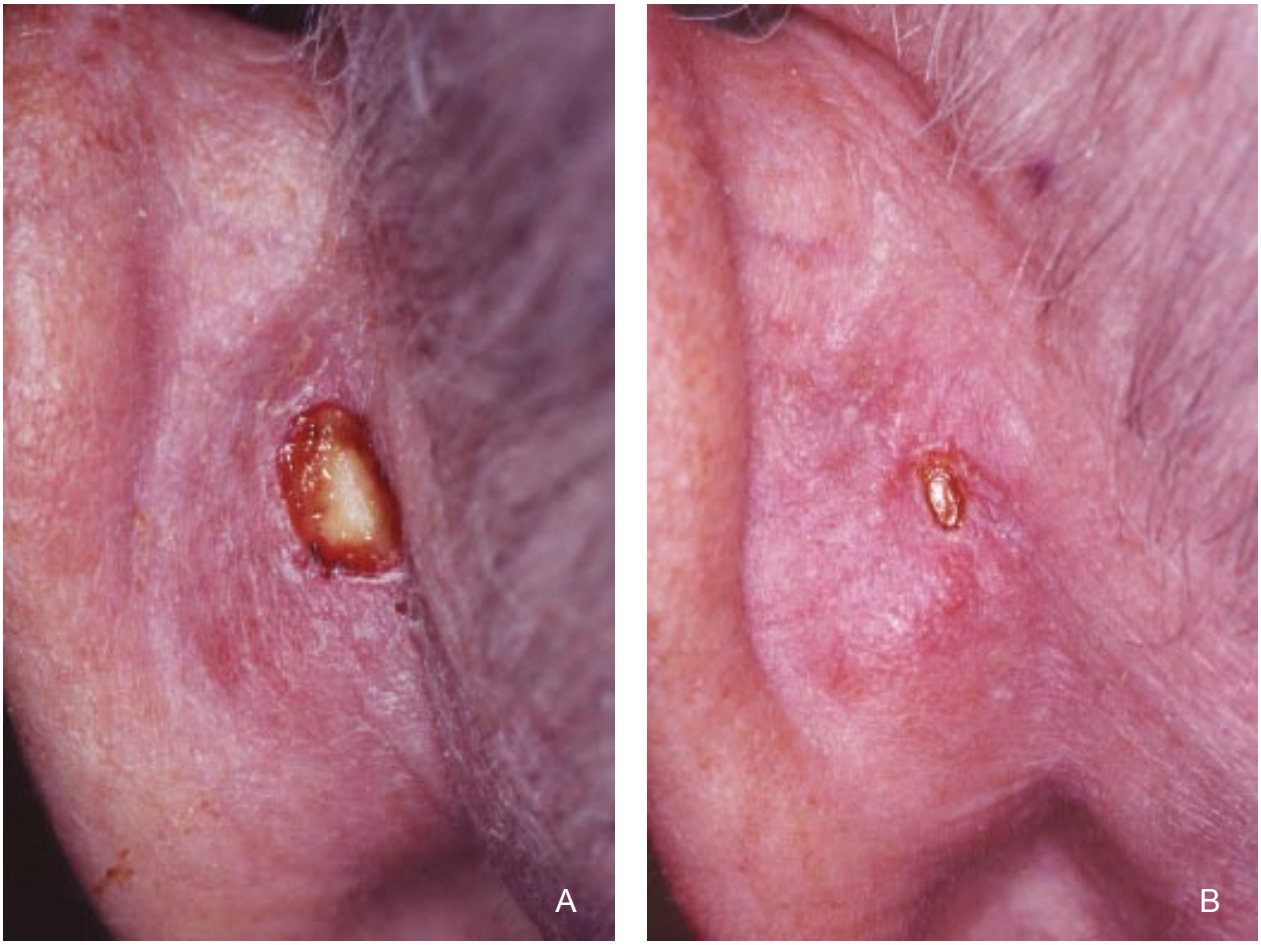

Figure 3. Patient with curettage and electrodesiccation of a basal cell carcinoma on the left postauricular surface followed by second-intention healing before (A) and 14 days after application of trolamine-containing topical emulsion (B).

wounds that occur after surgical procedures, are topical antibiotics, which frequently contain neomycin and/or bacitracin, and petrolatum-based ointments. Topical antibiotics are prophylactically used with the hope of preventing wound infection. Ointment formulations produce a moist environment that is believed to be conducive to wound healing.

Trolamine-containing topical emulsion differs from petrolatum-based occlusive agents in that the former provides a moist environment to the wound site and also promotes wound healing through stimulation of macrophage recruitment and modulation of the cytokine profile in the wound region. By increasing the IL-1:IL-6 ratio, trolamine-containing topical emulsion enhances formation of granulation tissue and collagen synthesis.[4,5]

Although there is no definitive data to support the benefit of prophylactic use of topical antibiotics after common dermatologic procedures performed in the ambulatory setting, topical neomycin- and/or bacitracin-containing formulations are often recommended postoperatively as well as for the treatment of dermal wounds, such as leg ulcers.[1,2,14] Trolamine-containing topical emulsion differs from topical neomycin and bacitracin because the latter 2 agents are well-recognized as common causes of contact allergy.[15] Additionally, topical antibiotics used after dermatologic surgical procedures have been shown to exhibit little to no benefit in preventing infection and appear to select for emergence of gram-negative organisms when infection does occur.[1,14]

Comment

Trolamine-containing topical emulsion is an oil-in-water formulation that has been used in both Europe and the United States for more than 3 decades in the treatment of a variety of cutaneous traumas, such as full-thickness wounds; superficial wounds, including those that are postoperative; dermal ulcers; radiation dermatitis; minor abrasions; and AK treatment sites after cryotherapy. Wound healing is promoted, at least in part, by macrophage recruitment to wound sites, which exhibits a variety of functions including stimulation of granulation tissue

formation and production of a cytokine milieu conducive to wound healing. Studies and clinical observations have supported the therapeutic benefit of trolamine-containing topical emulsion for cutaneous ulcers and radiation dermatitis, AK treatment sites after liquid nitrogen cryotherapy, and wounds that require second-intention healing after dermatologic surgery. The use of trolamine-containing topical emulsion for the treatment of radiation dermatitis has made it possible to reduce overall treatment time of chemotherapy and radiotherapy because the modalities could be administered simultaneously rather than sequentially. Importantly, trolamine-containing topical emulsion differs from topical neomycin and bacitracin because the latter 2 agents are well-recognized as common causes of contact allergy.

REFERENCES

1. Smack DP, Harrington AC, Dunn C, et al. Infection and allergy incidence in ambulatory surgery patients using white petrolatum vs bacitracin ointment. a randomized controlled trial. *JAMA*. 1996;276:972-977.
2. Del Rosso JQ, Hawkes S, Sanglay L. Use of a trolamine-containing topical emulsion to evaluate healing after treatment of actinic keratoses. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC.
3. Biafine [package insert]. Los Angeles, CA: OrthoNeutrogena.
4. Coulomb B, Friteau L, Dubertret L. Biafine applied on human epidermal wounds is chemotactic for macrophages and increases the IL-1/IL-6 ratio. *Skin Pharmacol*. 1997;10:281-287.
5. Boisnic S, Branchet-Gumila MC, Nizri D, et al. Histochemical and biochemical modifications induced by experimental irradiation of human skin maintained in survival conditions and modulation by application of an emulsion containing trolamine. *Int J Tissue React*. 2003;25:9-18.
6. Tsirogianni AK, Moutsopoulos NM, Moutsopoulos HM. Wound healing: immunological aspects. *Injury*. 2006;37(suppl 1):S5-S12. Epub April 17, 2006.
7. Broughton G 2nd, Janis JE, Attinger CE. The basic science of wound healing. *Plast Reconstr Surg*. 2006;117 (suppl 7):12S-34S.
8. Szumacher E, Wighton A, Franssen E, et al. Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *Int J Radiat Oncol Biol Phys*. 2001;51:81-86.
9. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol*. 2006;54:28-46.
10. Fisher J, Scott C, Stevens R, et al. Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys*. 2000;48:1307-1310.
11. Harper JL, Franklin LE, Jenrette JM, et al. Skin toxicity during breast irradiation: pathophysiology and management. *South Med J*. 2004;97:989-993.
12. Del Rosso JQ. Pharmacotherapy update: healing wounds after cryotherapy. *Skin & Aging*. 2007;15(4):76-78.
13. Kircik L. A study of the use of a topical emulsion of trolamine/sodium alginate in second intention healing after Mohs micrographic surgery. Poster presented at: 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC. P3206.
14. Hirschmann J. Use of antibiotics in leg ulcers. Presented at: Scientific Panel on Antibiotic Use in Dermatology (SPAUD) 2nd Annual Meeting; November 10, 2007; Las Vegas, NV.
15. Pratt MD, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 2001-2002 study period. *Dermatitis*. 2005;16:176-183.