A supplement to
Skin & Allergy News

Use of a Topical Emulsion for Wound Healing

© Russell Kightley

Topic Highlights

Faculty

Joel L. Cohen, MD
Assistant Clinical Professor
Department of Dermatology
University of Colorado
Englewood, Colo.

Joseph L. Jorizzo, MD
Professor, Founding and Former Chair
Department of Dermatology
Wake Forest University
School of Medicine
Winston-Salem, N.C.

Leon H. Kircik, MD
Clinical Professor of Dermatology
Indiana School of Medicine
Medical Director
DermResearch, PLLC
Louisville, Ky.

Roundtable Participants

Linda Carlin, RN, MS, OCn
CJW Medical Center
Richmond, Va.

Sharon R. Hymes, MD
University of Texas
Anderson Cancer Center
Houston, Tex.

Tania J. Phillips, MD
Boston University
School of Medicine
Boston, Mass.

Skin & Allergy News®

President, Elsevier/IMNG
Alan J. Imhoff

National Account Manager
Sally Cioci

Cover Design
Louise Koenig

Production Specialist
Tracy Law

This supplement was produced by the customized publication department of Elsevier/International Medical News Group. Neither the editor of *Skin & Allergy News*, the Editorial Advisory Board, nor the reporting staff contributed to its content. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or of the Publisher.

The supplement was also published as a supplement to *The Journal of Supportive Oncology*.

The content of this supplement was developed from a roundtable program. It was supported by:

OrthoNeutrogena

Use of a Topical Emulsion for Wound Healing

Faculty:

Joel L. Cohen, MD, Joseph L. Jorizzo, MD, and Leon H. Kircik, MD

Roundtable Participants:

Linda Carlin, RN, Sharon R. Hymes, MD, and Tania J. Phillips, MD

CONTENTS

Faculty disclosures:

Dr. Cohen has disclosed that he is a consultant to Johnson & Johnson.

Dr. Jorizzo has nothing to disclose.

Dr. Kircik has disclosed that he has received research support from, is consultant to, and is on the speaker's bureau for 3M Pharmaceuticals, Abbott Laboratories, Acambis, Allergan Inc., Amgen Inc., Astellas, Bayer HealthCare Pharmaceuticals, Biogen-Idec, Biolife, LLC, Breckenridge Pharmaceutical, Inc., Centocor, Inc., CollaGenex Pharmaceuticals Inc., CombiMatrix, Coria Laboratories, Ltd., Dermik Laboratories, The Dow Chemical Company, Ferndale Laboratories, Inc., Galderma Laboratories, L.P., Genentech, Inc., GlaxoSmithKline, Healthpoint, Ltd., Intendis, Medicis Pharmaceutical Corporation, Merck Serono, NanoBio Corporation, Novartis Pharmaceuticals Corporation, NUCRYST Pharmaceuticals Corp., OrthoNeutrogena, QLT Inc., Quatrix, SkinMedica, Inc., Stiefel Laboratories, Inc., ToleRx, Inc., Valeant Pharmaceuticals International, and Warner-Chilcott.

Use of a Topical Emulsion for Wound Healing

Joel L. Cohen, MD, Joseph L. Jorizzo, MD, and Leon H. Kircik, MD

Abstract Treatment of skin trauma following removal of actinic keratoses and skin cancer lesions and following radiation therapy for breast cancer is an often under-treated problem compared to the primary condition. However, skin trauma can cause patients significant discomfort, pain, and loss of quality of life. Palliative treatments such as lotions and ointments may help soothe the skin trauma, but helping the healing process is the best way to treat the wound and relieve patients of their discomfort. In clinical trials, the use of Biafine, a topical emulsion, promoted wound healing following these clinical situations by increasing the number of macrophages recruited to a wound and thus enhancing healing. This topical emulsion has also been proven to be soothing for the patient. This review will discuss the molecular mechanisms of wound healing and the uses of Biafine in the treatment of skin damage caused by procedures for various conditions such as actinic keratosis, skin cancer lesions, and radiation dermatitis.

Skin wounds from medical conditions and medical procedures are an important quality-of-life issue for many people, and wound healing represents a significant proportion of medical care costs and physician visits.[1] For example, although medical and surgical techniques for actinic keratosis (AK) and nonmelanoma skin cancer (NMSC) treat the condition at hand, they often also traumatize the surrounding skin and can also leave significant wounds. Radiation dermatitis is another unfortunate side effect of therapy for cancer that can also be very traumatic to the skin. Because much of today's rapidly aging population experienced significant exposure to the sun in their youth, this sector of medical care will continue to grow.[1]

This journal supplement is based on the proceedings of a consensus expert panel convened in June 2007: members discussed the molecular mechanisms of wound healing; the treatment of skin trauma following AK, NMSC lesions, and radiation dermatitis; and the use of a topical emulsion, Biafine, for the promotion of healing following these clinical situations. Studies have shown that this topical emulsion can increase the number of macrophages recruited to a wound and thus may enhance the healing process. Biafine is used in the United States as a topical therapy for a variety of skin traumas, including full-thickness wounds, pressure sores, dermal ulcers including lower-leg ulcers, superficial wounds, first- and second-degree burns, sunburns, dermal donor- and graft-site management, radiation dermatitis, and minor abrasions.[2] The current discussion will focus on uses of Biafine in the treatment of skin damage caused by procedures for conditions such as AK, NMSC, and radiation dermatitis.

The Mechanisms of Wound Healing

Trauma to surrounding skin from the treatment of AK, NMSC lesions, or the use of radiation therapy sets off a wound-healing process whose goal is to repair the damaged skin. The three-phase repair process involves a complex network of interactions among cells and cellular mediators,[3] including the following steps:

- Clotting and inflammation[4]
- Cell migration and proliferation[4]
- Skin remodeling[4]

CLOTTING AND INFLAMMATION

Once a wound has occurred, platelets become activated and help form a fibrin plug. During the formation of a blood clot, growth factors and cytokines are released and recruit cells into the area (see Figure 1 on page 2).[3,4]

Dr. Cohen is Assistant Clinical Professor, Department of Dermatology, University of Colorado, and Director, About Skin Dermatology and DermSurgery, PC, Englewood, Colorado.

Dr. Jorizzo is Professor and Founding and Former Chair, Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Dr. Kircik is Clinical Professor of Dermatology, Indiana School of Medicine, and Medical Director, DermResearch, PLLC, Louisville, Kentucky.

Participating faculty in the expert panel included Linda Carlin, RN (Richmond, VA); Sharon R. Hymes, MD (Houston, TX); and Tania J. Phillips, MD (Boston, MA).

Correspondence to: Joel L. Cohen, MD, About Skin Dermatology, 499 E. Hampden Ave., Suite 450, Englewood, CO 80113; telephone: (303) 756-7546; fax: (303) 756-7547; e-mail: denverskindoc@yahoo.com

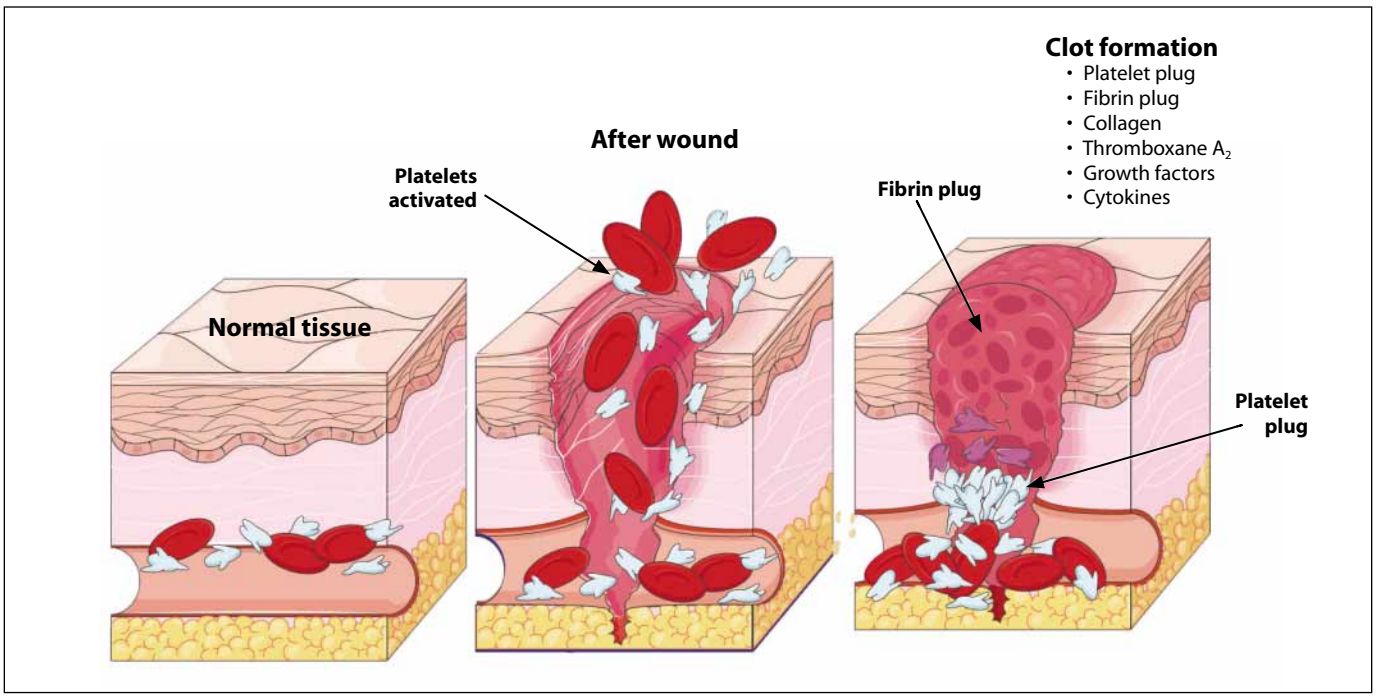

Figure 1 Clotting and Hemostasis Stage of Wound Healing

Adapted from Tsirogianni et al[3] and Broughton et al.[4] Reprinted with permission from Servier International.

During the inflammatory stage of wound healing, neutrophils are the first cells to arrive at the wound,[4] usually within 24 hours. Although neutrophils have the important roles of phagocytosis and debridement of the wound, they are not critical to the process. Monocytes, which are transformed into macrophages, do have a central role and generally arrive at the wound within 48 to 96 hours. Monocytes/macrophages are present throughout the inflammatory process, and progression of wound healing cannot occur without them.

CELL MIGRATION AND PROLIFERATION

Skin injury leads to the activation of the nuclear transcription factor κB pathway through cytokine receptors interleukin (IL)-1 and tumor necrosis factor (TNF)-α and the production of chemokines, adhesion molecules, and cytokines by resident tissue cells and migrating leukocytes. Migration of these cells to the wound space makes possible proliferation of specific cells that ultimately lead to re-epithelialization of damaged tissue.[3] Throughout the inflammatory response, macrophages not only consume available bacteria via phagocytosis but also help debride the wound and secrete collagenases and other enzymes and a large number of growth factors. Growth factors are important for the initiation of angiogenesis,[5] a critical part of the migration and proliferation stage that must take place before new tissue formation can occur. In addition, macrophages help recruit fibroblasts and keratinocytes, both of which are important for tissue formation.[3]

When tissue formation and healing begin, fibroblasts become activated and begin to synthesize collagen. Fibroblasts have been demonstrated to play a key role in extracellular matrix production, growth factor production, angiogenesis, and protease release.[4] Keratinocytes are essential for resurfacing the wound and maintaining barrier function and healing. Keratinocytes also have roles in migration and proliferation, extracellular matrix production, secretion of growth factors, and angiogenesis for wound healing.[3]

SKIN REMODELING

The final stage of wound healing is the skin-remodeling phase. During this phase, collagen is deposited by fibroblasts and formed into an organized network.[4] Initially, the collagen strands laid down in the wound are thin and run parallel to the wound surface. During remodeling, however, collagen production increases. At the same time, some destruction of the original collagen occurs, making room for the formation of new collagen, which is thicker and tends to be oriented along the lines of stress within the wound. Collagen synthesis can continue for several weeks in superficial wounds and for several years in deep wounds, but will never become as organized as collagen found in uninjured skin.[4]

The Role of Macrophages in Wound Healing

As indicated above, the macrophage is critical in directing the wound-healing process. By stimulating production of nitric oxide and reactive oxygen species, macrophages have significant antimicrobial activity. Their specific role in wound debridement includes phagocytosis and the release

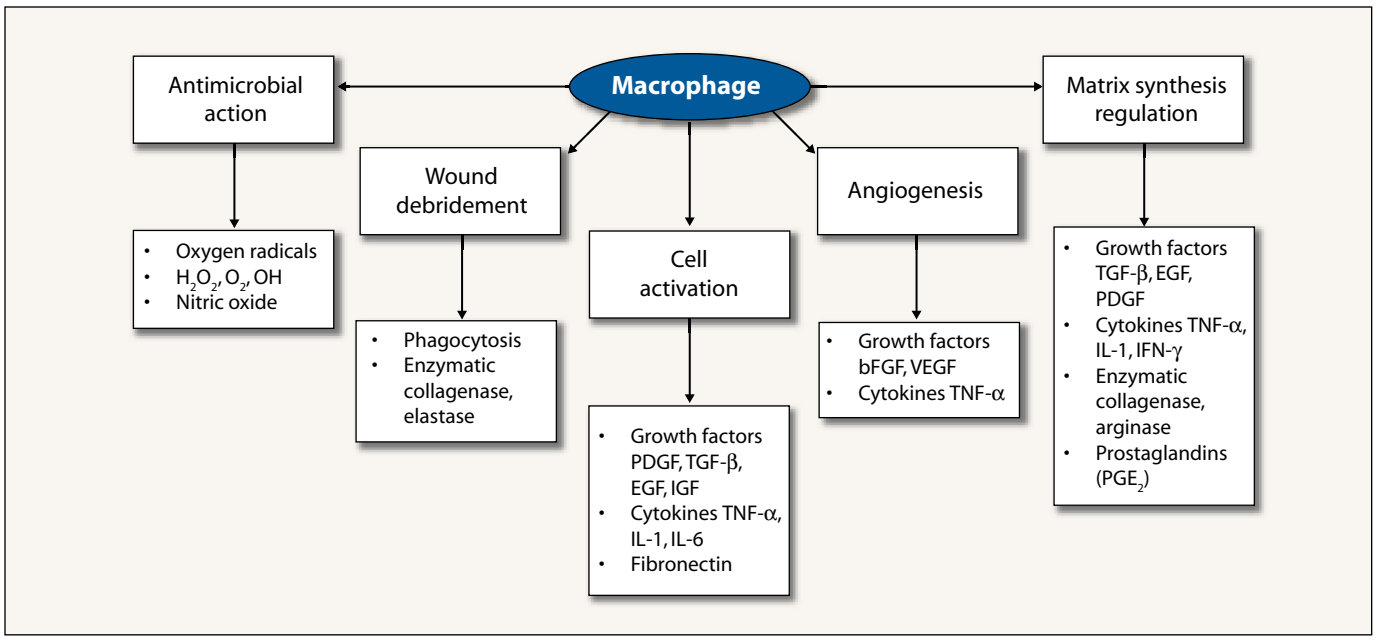

Figure 2 Role of Macrophages in Wound Healing

Reprinted from Witte and Barbul,[5] with permission from Elsevier.

Abbreviations: PDGF = platelet-derived growth factor; TGF-β = transforming growth factor beta; EGF = epidermal growth factor; IGF = insulin-like growth factors; IL = interleukin; bFGF = basic fibroblast growth factor; VEGF = vascular endothelial growth factor; TNF = tumor necrosis factor; IFN = interferon; PGE_2 = prostaglandin E-2

of enzymes such as collagenase and elastase, which help debride the wound surface.[4] These large scavenger cells secrete a great many growth factors that act on the endothelial cells and stimulate formation of new blood vessels and tissue, participating in the process of angiogenesis by releasing growth factors, such as basic fibroblast growth factor, vascular endothelial growth factor, and TNF-α, and in regulation of synthesis of the matrix through release of growth factors, cytokines, enzymes, and prostaglandins.[4] All of these functions make macrophages crucial to the wound-healing process. See Figure 2 for a summary of the many roles played by macrophages in healing.

Studying animal models of macrophage depletion has provided some clues concerning the aging process and wound healing. When people and animals age, their wound-healing capacity decreases. This process appears to be related to impairment of macrophage function. One study published in 1987 reported on mice that had been injected with antimacrophage serum to destroy macrophages. The affected mice had significantly impaired capacity for wound healing compared with that of normal, untreated mice.[6] However, when macrophage-depleted mice were subsequently injected with healthy macrophages, angiogenesis was induced, collagen synthesis was increased, and their wounds healed better.[6]

Wound healing is a very complex process, and an important area of current research examines the potential for influencing the healing process on a molecular level. One hypothesis is based on the observation that since the macrophage is one of the key cells involved in the healing process and healing can be restored by injecting deficient animals with macrophages, recruitment of macrophages to a wound site may be a possible way to augment the natural wound-healing process. Understanding this process is key to evaluating therapies that may help improve healing, but the ultimate test will be how well any such therapies work in clinical practice.

Treatment of AK and NMSC Lesions

Treatment of skin lesions caused by sun exposure has become an important part of healthcare. In all, approximately 5.2 million physician visits can be attributed to precancerous AK lesions per year in the United States, with more than $900 million spent annually on treatment of the condition.[7] In addition to sun exposure, a number of environmental and biologic factors may be implicated in the development of AK, including age, gender, and skin color.[1] If left untreated, AK, in some cases, can progress to squamous cell carcinoma.

NMSC can include basal cell carcinoma and squamous cell carcinoma.[1] Treatment of NMSC accounted for 1.8 million physician visits in 2004 and is considered one of the most economically burdensome medical conditions for the health-care system.[1]

The goal of treatment of both AK and NMSC is to treat or remove the lesion while preserving functional and cosmetic integrity. Treatment options include a variety of surgical and chemical methods that are effective but can be quite trau-

Table 1

Treatment Options for Nonmelanoma Skin Cancer and Actinic Keratosis

NONMELANOMA SKIN CANCER	ACTINIC KERATOSIS
Mohs micrographic surgery	Topical (5-FU, imiquimod, diclofenac)
ED&C	Cryosurgery
Cryosurgery	ED&C
Radiation	Dermabrasion
CO_2 laser	Shave excision
Interferon alpha	CO_2 laser
Excisions	Photodynamic therapy

Adapted from the European Dermatology Forum[8]

Abbreviations: 5-FU = 5-fluorouracil; ED&C = electrodesiccation and curettage

matic to the skin, potentially leading to significant wounds and subsequent scarring (see Table 1).[8] Electrodesiccation and curettage, for example, can lead to destruction of superficial tissue by dehydrating and scraping the skin at the treatment site,[9] and excisional surgeries penetrate deeper into the layers of the skin.[10] Topical therapies can also be effective but may be time-consuming and can be quite destructive to the skin. One example is 5-fluorouracil (5-FU), a topical treatment that destroys the cancerous foci by interfering with DNA and RNA, but may also interfere with the healing process.[8] Another example is imiquimod, a topical immune response modifier that stimulates cytokine release that may have tumoricidal activity, but can cause local skin reactions, including erythema, itching, and burning, that can lead to further skin damage.[8] Diclofenac in a hyaluronic acid gel is a topical agent with anti-inflammatory properties that works by inhibiting prostaglandin E_2 synthesis; however, application of diclofenac gel can cause pruritus and erythema.[8] Other treatment options include cryotherapy, radiation, and dermabrasion, all of which may cause trauma to the skin.[8]

Although clinical evidence supports the efficacy of all of these treatment options, there is minimal information concerning the satisfaction of either dermatologists or patients with the standard procedures for follow-up care. One group examined attitudes toward standard treatment for AK by surveying 104 patients and 68 dermatologists.[11] Of the 68 dermatologists surveyed, 50% believed that their patients were not fully satisfied with cryotherapy, 89% believed that their patients were not fully satisfied with 5-FU treatment, and 53% rated quick healing as somewhat important. Of the patients surveyed, 83% had received cryotherapy, whereas 14% had received 5-FU treatment; the patients had an average of 11 to 15 lesions on their faces, heads, and necks. Seventy-five percent of patients responded that they would be interested in new treatment options, which suggests that there is a significant unmet need within this patient population. Both groups reported that they were unsatisfied with current outcomes related to AK treatment, suggesting that standard care for AK would benefit from an increase in aftercare therapy to promote healing of traumatic skin wounds.[11]

The Use of a Topical Emulsion for Wound Healing

One strategy for enhancing post-destructive treatment healing and wound healing is to influence the cellular healing process by which it takes place. During the healing process, the inflammatory response prepares the environment for the next phase of healing by removing debris and recruiting macrophages within 48 to 96 hours.[12] One question that has interested researchers is whether earlier macrophage recruitment or early modulation of cytokines involved in angiogenesis could enhance the healing process.

This important question has been addressed by several clinical studies designed to measure the effect of Biafine on macrophage recruitment during wound healing. Biafine is a topical emulsion that has occlusive and hydrating properties, and has been used in France for more than 25 years.

COULOMB STUDY

In a study to determine whether Biafine has an effect on inflammatory cell migration, vascular permeability, and cytokine release, Coulomb and colleagues applied Biafine directly to experimentally derived human epidermal wounds that were produced by controlled vacuum suction so that the wounds were uniform in size and depth.[13] The investigators measured the subsequent migration and secretion of the cytokines IL-1 and IL-6 following the wounding process. According to this study, Biafine significantly increased the proportion of macrophages recruited to the wound site, compared to petrolatum used as a control ($P < 0.01$). The percentage of macrophages at the wound site at both 4 and 24 hours post-application of Biafine was approximately five times that of the petrolatum control, a marked improvement compared to untreated wound healing in which normal macrophage recruitment does not occur until 48 to 96 hours postinjury.[5,12] When the researchers measured levels of IL-1 and IL-6 at the wound site, they saw a nonsignificant increase in IL-1 at 24 hours and a significant decrease in IL-6 at both 4 hours and 24 hours compared to petrolatum control.[13] The increase in IL-1 may increase fibroblast proliferation, collagen formation, and wound remodeling. The primary conclusion of this study is that Biafine recruits more macrophages within 4 to 24 hours than does vehicle, which may improve wound healing in shallow, epidermal wounds.

KIRCIK STUDY

A recent clinical study examined the effect of Biafine on patients who had undergone Mohs micrographic surgery for removal of NMSC on the face, focusing on second-intention healing following the surgery.[14] Standard practice for wound healing consists of occluding the wound with an antibiotic ointment or petrolatum to keep the environment moist. This helps to accelerate healing and prevent infection. Biafine is commonly prescribed in such a clinical situation. In this 12-week, parallel-group study, 24 patients who were scheduled for Mohs micrographic surgery were randomized either to Biafine or to the antibacterial combination of bacitracin zinc/

Table 2

Mean Percent Changes in Wound Area from Baseline

TIME POINT	BIAFINE (n = 13)	ANTIBACTERIAL OINTMENT (n = 12)
Baseline	112.8 ± 77.3	101.8 ± 58.8
Week 3	22.2 ± 39.6	28.9 ± 29.9
Week 6	0.0 ± 0.0	3.8 ± 13.0
Week 12	0.0 ± 0.0	0.0 ± 0.0

Adapted from Kircik[14]

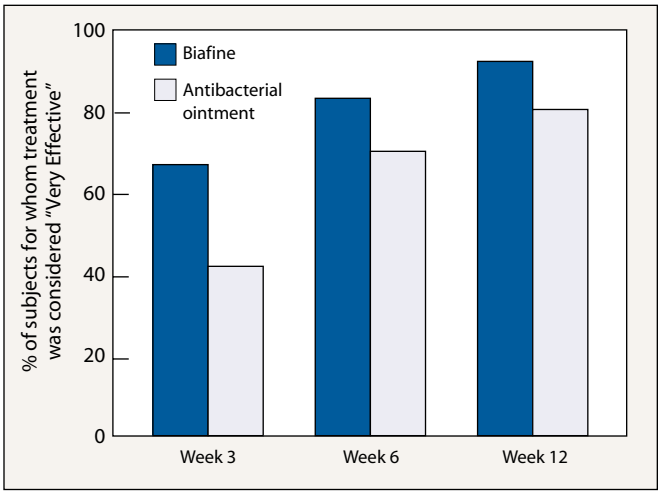

Figure 3 Study Results: Investigator Global Assessment of Efficacy

At week 3, 16.7% of subjects rated antibacterial ointment treatment ineffective versus 0% of subjects using Biafine.

Reprinted with permission from L. Kircik, MD[14]

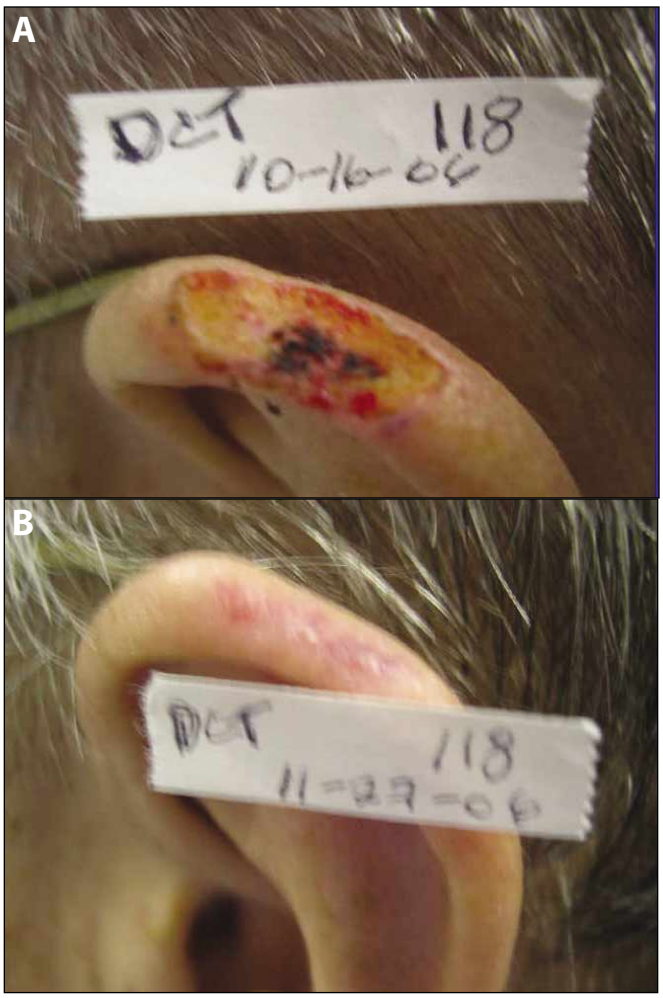

Figure 4 Use of Biafine for Patient Who Underwent Mohs Surgery on His Ear

(**A**) After surgery. (**B**) After 6 weeks of treatment with Biafine. Images courtesy of L. Kircik, MD.

polymyxin B sulfate ointment. The treatments were applied for 6 weeks or until wound re-epithelialization, whichever came first. Efficacy and safety assessments included investigator reporting of wound size and application-site appearance at weeks 3, 6, and 12. Patients self-reported any irritation, itching, burning, or other application-site adverse events at weeks 3, 6, and 12.[14]

The results from this clinical trial showed that the healing process was enhanced in the wounds treated with Biafine versus the wounds treated with antibacterial ointment.[14] By week 6, there was complete wound closure for the topical emulsion group but not for the antibacterial ointment group, and, by week 12, both groups had complete wound closure. See Table 2 for a comparison of changes in wound area from baseline in patients receiving Biafine versus those receiving antibacterial ointment. These results suggest a trend toward better healing for the patients receiving Biafine for full thickness cutaneous wounds.

In this study, 8.3% of the antibacterial ointment group experienced contact dermatitis, but there was none reported in the Biafine group.[14] Investigators used the Investigator Global Assessment of Efficacy to determine efficacy in this study and found that the differences between Biafine and the antibacterial ointment were not statistically significant at any of the time points. It is worth noting that 16.7% of patients rated the antibacterial ointment as ineffective, whereas 0% of patients rated Biafine as ineffective. See Figure 3 for a summary of the efficacy findings in the Kircik study.[14]

Investigators also examined crusting, inflammation, swelling, hyperpigmentation and hypopigmentation, and scarring of the wound site. One patient using Biafine had scarring that led to hypopigmentation, but except for that patient, safety results were similar in both groups.[14] Patients in both groups determined by self-assessment that both treatments were well tolerated. Figure 4 shows the healing process with Biafine for a patient who had Mohs surgery on his ear.

The conclusions from this study were that both Biafine and the antibiotic ointment were efficacious in post-Mohs second-intention healing in patients with NMSC but that wound

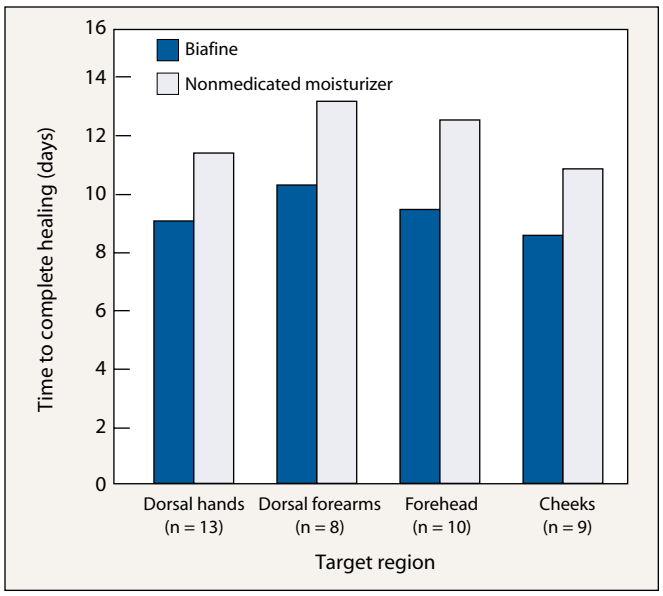

Figure 5 Mean Time to Complete Healing Following Cryotherapy

Reprinted with permission from J. Del Rosso, MD[15]

healing was enhanced in the group using Biafine, with complete healing by week 6.[14]

DEL ROSSO STUDY

Another recent study of Biafine was presented at the annual meeting of the American Academy of Dermatology in 2007, where Del Rosso and colleagues reported their findings on the ability of this topical emulsion to heal cutaneous injury following treatment of AK lesions with liquid nitrogen. This investigator-blinded, randomized, split-body (target region) 4-week trial enrolled 40 adults with AK on the dorsal hands, dorsal forearms, forehead, and/or cheeks.[15] AK lesions were treated with liquid nitrogen cryotherapy, and patients were instructed to apply Biafine twice daily to all treated regions on one side of the body and a nonmedicated petrolatum-based ointment to the treated regions on the other side of the body. Patients maintained diaries to record healing, and investigators assessed healing at week 4.[15]

The results of this study determined that the mean healing time on average when taken for all sites was enhanced by 2.53 days for the topical emulsion than for the moisturizer (9.27 days for Biafine vs 11.80 days for the moisturizer). Both Biafine and the moisturizer were well tolerated by patients. See Figure 5 for a summary of the relevant findings.[15]

The results from the three studies summarized here demonstrate that by increasing the number of macrophages that are recruited to a wound site, the application of Biafine appears to enhance the wound-healing process. Comparative clinical studies by the Kircik and Del Rosso groups demonstrated that in a clinical setting, Biafine was able to enhance the wound-healing process for full-thickness cutaneous wounds after Mohs micrographic surgery and tissue trauma following cryosurgery after treatment of AK. In addition, subjects in both studies reported satisfaction in the use of Biafine as a soothing agent for their wounds.

Clinical data also demonstrate that Biafine is effective for improved wound healing following electrodesiccation and curettage (see Figure 6). This use has not been studied in a formal clinical study yet.

Radiation Dermatitis

Radiation therapy is a critical component of the treatment of breast and head and neck cancers. The current treatment protocol for breast cancer, for example, includes megavoltage doses of x-rays that deliver tumoricidal quantities of radiation below the skin. However, radiation therapy is often associated with burdensome skin toxicities that often limit doses of therapy or disrupt treatment.[16,17] About 90% of patients treated with radiation therapy for breast cancer, for example, develop radiation-induced dermatitis, which can cause significant patient discomfort, disruption to daily life, and treatment interruption.[16]

The goal of radiotherapy is to target the tumor while limiting exposure of normal tissue. The ionizing effects and free radicals produced by radiation can result in damage to cellular DNA, which can lead to cell death.[18] Although this effect is desirable for eradication of the tumor, which requires that total cell death be achieved, it can be damaging to other tissues, such as skin, which then need to be repaired.[16] Normal tissue has a greater capacity to repair itself than do tumor cells, so

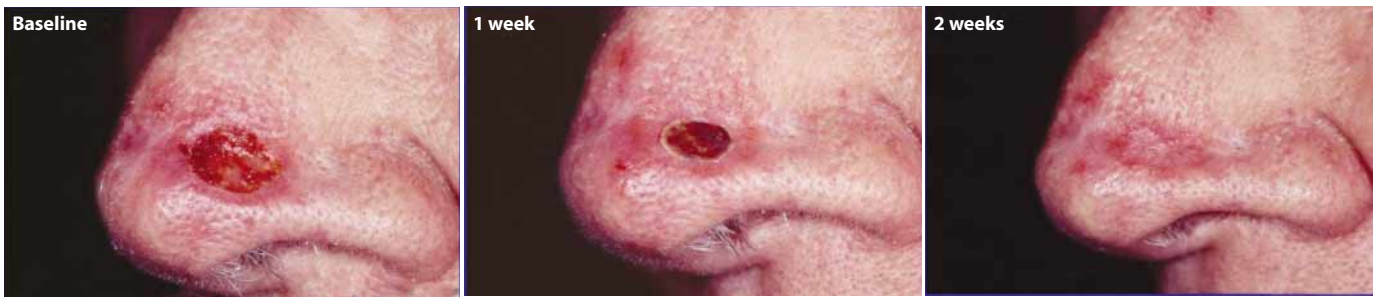

Figure 6 Wound Healing Following Electrodesiccation and Curettage With 2 Weeks of Twice-Daily Biafine Treatment

Images courtesy of J. Bikowski, MD

it is possible for an effective treatment course to find a way to destroy the tumor while causing only sublethal damage to other tissues.[16] Even with the best therapeutic regimen, however, rapidly proliferating normal tissue, such as the basal layer of epidermis, gastrointestinal mucosa, and hematopoietic cells, is at great risk for radiation damage.[16,17,19]

The physiologic damage that occurs to the skin during radiation treatment is gradual, but complex. Following the first fractionation, there is a dose-dependent loss of basal cells, and structural tissue damage occurs immediately.[17] The surviving basal cells can then repopulate the basal monolayer.[20] However, any additional fractionation destroys the remaining basal cells, which prevents repopulation of the basal cell layer and impairs functional stem cells, causing endothelial cell changes, inflammation, and epidermal cell apoptosis and necrosis.[17] The basal cell loss occurs at a cumulative dose of 20 to 25 Gy, which corresponds approximately to days 10 to 14 of therapy.[20] Maximal depletion of the basal cell layer occurs at a dose of 50 Gy.

Because of the length of time between cycles depleting the basal cell layer, radiation dermatitis may not be immediately evident. In breast cancer treatment, for example, the severity of dermatitis depends on a number of treatment-related and patient-related factors.[17] Treatment-related factors include the total dose delivered and dose per fractionation, the volume of tissue irradiated, the surface area exposed, the type and quality of the beam used, and the addition of chemotherapy.[16] Patient-related factors affecting the incidence of radiation dermatitis include such physical characteristics as being large-breasted, obese, or having problems with skin integrity or overlapping skin folds. Patients who are smokers or have poor nutritional status are also at increased risk for radiation dermatitis. One genetic factor that must be considered is whether the patient has a mutation of a DNA repair gene. Comorbidities, such as connective tissue disease and infectious diseases, can also affect outcomes. In addition, the use of radiosensitizer drugs given immediately before, during, or less than 7 days after radiation can cause increased cellular damage and impaired repair.[16,17]

Acute dermatitis usually occurs within 90 days of treatment, although undetectable erythema may be present hours after exposure.[17] Within about 2 weeks following dosing, more-sustained erythema may appear, accompanied by inflammation, dry desquamation, epilation, and dyspigmentation.[16] Dryness and epilation are a result of radiation damage to sebaceous glands and hair follicles.[17] Moist desquamation usually occurs in skin folds and creases within 4 to 5 weeks after high-dose radiation and is characterized by necrosis of the epidermis, considerable pain, fibrinous exudates, and bullae, which may become infected.[17,21] All of these effects are cumulative with the dosing schedule, peak about 1 to 2 weeks posttreatment, and gradually heal once treatment is finished.[17]

See Table 3 for a summary of the National Cancer Institute system for classification of radiation dermatitis.[17]

Radiation dermatitis can also occur 90 days or more after exposure, and it may not develop for even months or years.[16,18] This is the result of long-term effects of injury to the dermis, including inflammatory damage and alterations in fibroblasts. The late clinical changes that may be apparent include atrophy, scaling, pigmentation, and necrosis.[20]

Table 3

Classification of Radiation Dermatitis

GRADE	DESCRIPTION
0	None
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
3	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Skin necrosis of ulceration of full-thickness dermis; spontaneous bleeding from involved site

Adapted from Hymes et al[17]

In summary, radiation dermatitis is a frequent problem for patients who have undergone radiation therapy for breast and head and neck cancers. The irradiated skin is altered on a cellular level, and the resulting damage is considered a complex wound. Radiation dermatitis can be marked by instantaneous tissue damage, or it may not develop for months or years after treatment.

The Use of a Topical Emulsion for Treatment of Radiation Dermatitis

The care of radiation dermatitis is modeled after wound-care experience and includes the use of topical medications to soothe and promote healing. The goal of treatment is to minimize patient discomfort and to prevent progression of dermatitis to moist desquamation.[17] Petroleum-based emollients are commonly used. Biafine is a topical emulsion that has been used extensively in wound care, and a number of clinical trials have examined its use in the treatment of radiation dermatitis.

BOISNIC STUDY

A study examined the histochemical and biochemical modifications induced by experimental irradiation of human skin and the effect of Biafine on wounds caused thereby, using data from four experimental groups: patients who received irradiation and this topical emulsion, patients who received irradiation and petrolatum, patients who received irradiation alone, and untreated controls.[22] Investigators used a human skin model to study the effects of Biafine and Vaseline on a variety of cellular processes, such as edema, endothelial cell proliferation, collagen synthesis, and secretion of interleukins. This study showed that Biafine significantly reduced edema, increased endothelial cell proliferation, increased the number of mitotic cells in the basal layer of the epidermis, and decreased IL-1α secretion, compared with irradiated, untreated skin. Petrolatum, by contrast, was only able to decrease collagen synthesis and IL-1α secretion, compared to irradiated, untreated skin or control skin (see Table 4).[22]

Table 4

Modulation of Cellular Changes by Biafine or Petrolatum

CELLULAR EFFECT	*P* VALUE BIAFINE	*P* VALUE VASELINE
Decrease in edema	0.028*	No change
Increase in endothelial cell proliferation	0.007*	No change
Decrease in collagen synthesis by dermal fibroblasts	0.002*	0.001*
Decrease in interleukin-1α secretion	0.023*	0.026†

*Statistically significant compared with irradiated skin
†Statistically significant compared with control skin
Adapted from Boisnic et al[22]

Table 5

Skin Toxicity During Post-Radiation Therapy in Patients With Large Breast Sizes

RTOG CRITERIA	BEST SUPPORTIVE CARE (n = 21)	BIAFINE (n = 23)
0	2 (10%)	12 (52%)*
1	17 (80%)	11 (48%)
2	2 (10%)	0 (0%)

*$P = 0.0023$
Abbreviation: RTOG = Radiation Therapy Oncology Group
Reprinted from Fisher et al,[23] with permission from Elsevier.

The results from the Boisnic study complement those reported in the Coulomb study. Both studies demonstrate that Biafine appears to act at the level of tissue formation and may help recruit 3 to 10 times the normal number of macrophages to the wound site more quickly than petrolatum alone.[13,22] It also appears to enhance three phases of wound healing: inflammation, proliferation, and maturation.

FISHER STUDY

The 2000 Fisher study was a randomized phase III clinical trial comparing Biafine and "best supportive care" (BSC), defined as the use of Aquaphor Healing Ointment or aloe vera gel as prophylaxis for radiation-induced skin toxicity in women undergoing breast irradiation.[23] Patients were randomized to Biafine (n = 83) or Aquaphor or aloe vera gel (n = 89) and were instructed to apply the product three times a day for 2 weeks post-radiation treatment. Skin dermatitis was scored weekly according to the Radiation Therapy Oncology Group and Oncology Nursing Society skin toxicity scoring system. Patient satisfaction and quality-of-life questionnaires were also used.

Although no difference was found between BSC and Biafine in the prevention, time to, or duration of radiation-induced dermatitis, the group did find an interesting correlation between breast size and increased toxicity. Large-breasted women experienced more toxicity, but large-breasted women who received Biafine were more likely to have no toxicity 6 weeks post-radiation therapy than were large-breasted women who received Aquaphor or aloe vera gel. See Table 5 for a summary of these findings in large-breasted women.[23] This study also showed a slight statistical advantage for nonsmokers who used Biafine, compared to smokers.[23]

SZUMACHER STUDY

The Szumacher study was a phase II clinical trial assessing Biafine as prophylaxis for skin toxicity in women undergoing radiotherapy and chemotherapy.[23] Sixty women who received 5 weeks of radiation therapy and concomitant chemotherapy for breast cancer were given this topical emulsion to be applied daily, starting on the first day of radiation therapy and ending 2 weeks post-radiation therapy. Subjects' skin was assessed at weekly intervals during therapy and at 2 and 4 weeks posttherapy. Most patients (83%) developed grade 2 skin reactions during this study, which took place 3 weeks after radiotherapy. No treatment delays or interruptions due to skin toxicity were reported, and Biafine was well tolerated. Most of the patients described it as soothing.[24]

Conclusion

Biafine has been used in the treatment of radiation dermatitis for a number of years. Clinical studies demonstrate that it is well tolerated by patients, and patients consider Biafine to be soothing, which may improve patients' quality of life while they are receiving radiation. More studies are necessary to determine whether it enhances the healing process for a wound from radiation dermatitis. Wound healing is a complex process of highly orchestrated cellular and molecular changes. Macrophages play an important role in facilitating the wound-healing process by releasing cytokines and growth factors that recruit other cells to the site of the wound.

Enhancing the healing of tissue trauma or wounds following the treatment of AK lesions or removal of NMSC lesions can positively affect patients' quality of life. The use of Biafine may improve healing by increasing the number of macrophages recruited to the site of injury, thereby enhancing the healing process. It is used in the United States as a water-based emulsion for a variety of cutaneous traumas, such as full-thickness wounds, pressure sores, dermal ulcers, superficial wounds, burns, dermal grafts, radiation dermatitis, and minor abrasions.[2] During the consensus expert panel discussion, the authors noted that Biafine may have utility in the treatment of skin damage following excision biopsy and other procedures that have not been formally studied. Additional clinical studies with Biafine are necessary to determine the full extent of its usefulness following a variety of medical and surgical conditions.

References

PubMed ID in brackets

1. Lewin Group, Inc, for the Society for Investigative Dermatology and American Academy of Dermatology Association. The Burden of Skin Diseases 2004. Available at: http://www.sidnet.org/pdfs/Burden%20of%20Skin%20Diseases%202004.pdf. Accessed August 16, 2007.

2. Biafine prescribing information. OrthoNeutrogena, Division of Ortho-McNeil Pharmaceutical, Inc. Available at http://www.biafine.orthoneutrogena.com/prescribinginfo.asp. Accessed July 30, 2007.

3. Tsirogianni AK, Moutsopoulos NM, Moutsopoulos HM. Wound healing: immunological aspects. Injury 2006;37(suppl 1):S5–S12. [16616753]

4. Broughton G II, Janis JE, Attinger CE. The basic science of wound healing. Plast Reconstr Surg 2006;117(7 suppl):12S–34S. [16799372]

5. Witte MB, Barbul A. General principles of wound healing. Sur Clin North Am 1997;77:509–528. [9194878]

6. Cohen BJ, Danon D, Roth GS. Wound repair in mice as influenced by age and antimacrophage serum. J Gerontol 1987;42:295–301. [3571865]

7. Warino L, Tusa M, Camacho F, Teuschler H, Fleischer AB Jr, Feldman SR. Frequency and cost of actinic keratosis treatment. Dermatol Surg 2006;32:1045–1049. [16918567]

8. European Dermatology Forum, Guideline Subcommittee. Guidelines for the management of actinic keratoses. Available at: http://www.euroderm.org/content/guidelines_keratoses.htm. Accessed October 5, 2007.

9. Pollack SV. Electrosurgery. In: Bolognia JL, ed. Dermatology. St. Louis: Mosby; 2003:2197–2204.

10. Callahan E, Otley C, Roenigk R. Mohs surgery. In: Bolognia JL, ed. Dermatology. St. Louis: Mosby; 2003:2331–2340.

11. Del Rosso JQ. Actinic keratoses: evaluating management strategies. Skin Aging 2002. Available at: http://www.skinandaging.com/article/370. Accessed October 5, 2007.

12. Park JE, Barbul A. Understanding the role of immune regulation in wound healing. Am J Surg 2004;187:11S–16S. [15147986]

13. 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. [9449167]

14. 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. Abstract P3206.

15. 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.

16. Harper JL, Franklin LE, Jenrette JM, Aguero EG. Skin toxicity during breast irradiation: pathophysiology and management. South Med J 2004;97:989–993. [15558927]

17. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol 2006;54:28–46. [16384753]

18. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol 2003;4:529–536. [12965273]

19. Collen EB, Mayer MN. Acute effects of radiation treatment: skin reactions. Can Vet J 2006;47:931–932, 934–935. [17017663]

20. Archambeau JO, Pezner R, Wasserman T. Pathophysiology of irradiated skin and breast. Int J Radiat Oncol Biol Phys 1995;31:1171–1185. [7713781]

21. BC Cancer Agency. Care of Radiation Skin Reactions. Available at: http://www.bccancer.bc.ca/NR/rdonlyres/79E81484-6809-41CF-8CC2-0646DA6003F8/18669/RadiationSkinReactions2006Oct23.pdf. Accessed July 12, 2007.

22. Boisnic S, Branchet-Gumila MC, Nizri D, Ben Slama L. 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;1:9–18. [12854882]

23. 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. [11121627]

24. 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. [11516855]

ELSEVIER ONCOLOGY