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Non-surgical Approaches to the Treatment of Non-melanoma Skin Cancer

by MARC D. BROWN, MD, and NANA SMITH, MD

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Non-melanoma skin cancer (NMSC) is not only common but imparts a substantial morbidity to the patient and cost to society. It is frequently quoted that more than one million cases of basal cell carcinoma (BCC) occur each year in the United States, but more recent estimates indicate that 3 to 4 million cases or higher occur each year. The incidence of NMSC has been increasing worldwide at a rate of 3 to 8 percent per year over the last four decades. There is also an increasing incidence among younger adults.

The goals of any treatment for NMSC are the same. A high cure rate is desired considering the local destruction of tissue that can be caused. Because many NMSCs present on the head and neck, an acceptable cosmetic result is desired and, ideally, at a reasonable cost. Finally, for many patients, the simplicity of treatment is of great importance.

Nonsurgical treatments are desirable for many reasons. Topical approaches are less invasive and may be especially important for medically frail and elderly patients. Topical approaches also cause less initial pain. Improved cosmetic outcomes are often achieved, especially in potentially complex surgical cases or cosmetically sensitive locations. In patients with multiple lesions, nonsurgical modalities may offer a more simplistic treatment option. Lastly, treatment of subclinical disease can be achieved with topical approaches, in contrast to surgery.

Disadvantages to topical or medical treatment of NMSC exist. Surgery (including Mohs micrographic surgery) is no doubt the “gold standard” of care and offers higher cure rates. The main reason for this is the lack of margin control with nonexcisional therapy. For this reason, high-risk BCCs and invasive squamous cell carcinomas (SCCs) are best treated by excisional procedures.

This review will focus on the nonsurgical treatment of “low-risk” NMSC. These entities are defined by the following: primary tumors lacking any prior treatment, smaller size, superficial or nodular BCCs, SCC in situ, and location outside of the H-zone on the face. Unless otherwise stated, the efficacy results quoted are the as-treated data from the particular study and not intention-to-treat.

Although traditional procedural approaches like cryotherapy, curettage, and radiotherapy are appropriate treatments for NMSC, we did not include these to limit the scope of the review. Discussion about actinic keratoses is also excluded. Readers are encouraged to read a recent paper by Tull et al for a more comprehensive review.1
This paper will focus on the clinical evidence for topical treatment of NMSC.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a modality that combines topical application of a photosensitizer with some method of light energy. Most commonly, blue (417nm) or red (570–670nm) light is used. The topical agent available in the United States is 5-aminolevulinic acid (ALA), which is preferentially taken up by tumors and dysplastic cells and then enzymatically converted to protoporphyrin IX (PpIX). This is done by leaving the ALA on the skin, with or without occlusion, for several hours. The initial studies recommended between 14 and 18 hours; however, more recently, success has been seen with shorter contact (i.e., 1–3 hours). The ALA is then washed off. Upon exposure to red or blue light or lasers (pulsed dye, intense pulsed light, light-emitting diode, etc.) the intracellular PpIX induces an oxygen-dependent cytotoxic reaction. PDT is Food and Drug Administration (FDA) approved for the treatment of actinic keratoses (i.e., Levulan, Dusa Pharmaceuticals, Wilmington, Massachusetts). Studies have also been done on PDT in the treatment of Bowen’s disease and superficial and nodular BCCs.

PDT is not without disadvantages. Photosensitivity is a side effect of treatment and can lead to discomfort and pain. The light energy itself can also be painful. Multiple treatments are sometimes required. Also, issues arise when reimbursement from insurance companies is sought. A promising alternative to ALA, methyl aminolevulinate (MAL), is not available in the United States yet, but is widely used in Europe. Advantages of MAL over ALA include less pain and potentially better efficacy, as MAL is more lipophilic and better absorbed into the skin.

PDT for nodular BCCs. Rhodes et al conducted a randomized, non-blinded, controlled trial comparing PDT with MAL versus surgical excision for biopsy-proven nodular BCCs. Most tumors were less than 2cm. Subjects were randomized to PDT (MAL cream 160mg/g, Metvix, Galderma and PhotoCure ASA) or surgical excision with 5-mm margins. Metvix was occluded for three hours and illuminated with red light (570–670nm, fluence 75J/cm², fluence rate 50–200mW/cm²). Subjects in the PDT group were treated with one or two cycles (each one week apart), depending on clinical response.

For this follow-up study, the authors took all patients who achieved a complete clinical response at three months post-treatment and followed them yearly for five years for recurrence. The primary endpoint was clinical recurrence, but suspected recurrences were confirmed by biopsy. Initially 101 subjects were treated.

Sixty-six subjects had five-year follow-up data. There were similar numbers of men and women in each group. Most baseline characteristics of the groups were similar; however, subjects in the surgery group had significantly more lesions on the face and scalp. Using a time-to-event analysis, the lesion recurrence was found to be 14 percent for PDT (7/49 lesions) versus four percent for surgery (2/52 lesions). After five years, “good” or “excellent” cosmetic outcomes were found in 87 percent (CI 70–96%) in the PDT group and in 54 percent (CI 37–71%) in the surgery group (p=0.007). Therefore, a trend toward a higher cure rate with surgery was seen; however, PDT showed significantly better cosmetic outcomes.

International guidelines for PDT in NMSC. Perhaps the most comprehensive review of treatment for NMSC by PDT comes from an international consensus put forth by the International Society for Photodynamic Therapy in Dermatology. The consensus (based on an extensive Medline literature review) is based on data that tended to be heterogeneous. The included studies used different light sources, different number of treatments, and various times of application. The consensus also discusses both ALA and MAL. Because of this, the recommendations may or may not be generalizable to a particular patient population.

Regarding PDT for SCC in situ or Bowen’s disease, 16 open-label and four randomized, controlled trials were found. Recurrence rates were between 12 and 15 percent. The conclusion was that PDT for Bowen’s had similar efficacy to cryotherapy or 5-fluorouracil (5-FU), but with less side effects. PDT should not be used for invasive SCC, as the evidence does not support it. Finally, the studies warn that patients not responsive to PDT should be considered for surgery.

For the treatment of superficial BCCs with PDT, 12 studies were found. Two retrospective studies; eight open-label, nonrandomized studies; and two randomized, controlled, open-label studies were included. Initial clearance rates were between 80 and 97 percent with a four-year follow-up recurrence rate of 22 percent. Cosmetic outcomes were good to excellent. The conclusion was that PDT should be considered for large or multiple lesions.

Treatment of nodular BCCs with PDT was also summarized. Twelve studies were found of which two were randomized, placebo-controlled, and double blind. Of the remaining studies, one was retrospective; seven were open-
label, nonrandomized; and the rest were randomized but open label. Initial response rates were 73 to 94 percent with a five-year recurrence rate of 14 percent. Because MAL is more lipophilic, it had better efficacy than ALA. Although PDT achieved better cosmetic outcomes, the authors believe that surgery remains the “gold standard” for treatment of nodular BCCs.

5-FLUOROURACIL

5-FU is an antimitabolite that exerts its cytotoxic effects by inhibiting DNA synthesis and provoking cell death. Although mostly used for actinic keratoses, 5-FU has been studied in both BCC and SCC. Disadvantages to 5-FU include local side effects, which can be quite uncomfortable. Therefore, patient compliance is unpredictable. Common local side effects include erythema, erosions, and dermatitis.

5-FU for BCC. Although 5-FU is FDA approved for the treatment of superficial BCCs, there are few published studies to cite. In a study conducted by Valeant Pharmaceuticals (Aliso Viejo, California), the success rate of 5-FU (cream and solution combined) for superficial BCCs was 93 percent based on 113 lesions in 54 subjects. The company states that 5-FU should be used after a confirmatory biopsy as efficacy has not been established for other types of BCCs. Valeant also states that with “isolated, easily accessible BCCs,” surgery is the recommended method of treatment. In other words, 5-FU should be reserved for patients with multiple BCCs or lesions in “difficult treatment sites.” The recommended dosage is twice daily for 3 to 6 weeks or as long as 12 weeks, if necessary.³

Gross et al conducted an open-label, single-arm study in two centers.³ Twenty-nine subjects with 31 biopsy-proven, superficial BCCs on the trunk or limbs received 5-FU twice daily for a maximum of 12 weeks. Treatment was curtailed if response was noted earlier. At three weeks post-treatment, the initial lesion was excised. Beginning tumor size was 0.5cm to 2cm in diameter. The histologic cure rate was 90 percent (28/31); mean time to clinical cure was 10.5 weeks. Most subjects had only mild or moderate erythema and/or erosions. Sixteen percent of subjects had mild scarring at 15 weeks, but most had good cosmetic outcomes.

5-FU for Bowen’s disease. Salim et al conducted a randomized trial comparing PDT versus 5-FU for the treatment of Bowen’s disease.³ Forty-two subjects from two centers were initially enrolled who had previously untreated, biopsy-proven Bowen’s disease, measuring 0.5 to 4.0cm in largest diameter. The PDT group was treated with 20 percent ALA applied four hours before illumination with 100J/cm² narrowband red light (630nm). 5-FU was applied to lesions once daily for one week and then twice daily for up to four weeks. Two subjects withdrew. After 12 months, complete clinical clearance rates were 82 percent and 48 percent in the PDT and 5-FU groups, respectively. More adverse reactions were found in the 5-FU group. No histologic confirmation of recurrence was performed.

IMIQUIMOD

Imiquimod is FDA approved for the treatment of actinic keratoses and superficial BCC. It is used in an off-label fashion for a number of other dermatologic conditions. It works through toll-like receptor 7 to induce local cytokine and chemokine release, activate dendritic cells, and then enhance innate and cell-mediated immunity.

Imiquimod for BCC. Geisse et al studied treatment of superficial BCCs in two randomized, controlled, double-blind Phase 3 trials.³ These studies were the basis for FDA approval of imiquimod for this indication. Subjects were treated with imiquimod or vehicle once daily for five or seven days per week for six weeks. The lesions were examined at 12 weeks post-treatment and were then excised with 3 to 4-mm margins. Data from both studies were pooled to finally represent 55 centers in the United States. Lesions were 0.5 to 2.0cm² in diameter. Of the 724 subjects randomized, 663 applied at least 80 percent of the required doses and were included in the final analysis. More subjects in the seven-day-per-week group had to take rest periods than in the other groups. In the intention-to-treat analysis, histologic cure rates were 82 percent (CI 76–87%) for the five-days-per-week group and 79 percent (CI 73–85%) for the seven-day-per-week group. The differences between each active group and the corresponding vehicle were significant (p<0.001). There was no significant difference between active groups in histologic cure. More local skin reactions (erythema, crusting, edema, itching, etc.) were found in the seven-day-per-week group than in the five-day-per-week group (p=0.002) and the severity of reaction corresponded significantly with both clinical and histologic clearance. The negative predictive value for clinical assessments (if the clinical assessment was negative, what is the likelihood that the histologic finding was negative) was greater than 90 percent.

Golnich et al present results from an interim two-year results from a five-year study using imiquimod to treat superficial BCCs.⁴ This is an ongoing, Phase 3, open-label study using imiquimod five times per week for six weeks. Twenty-five European centers enrolled 182 subjects. BCCs had to be 1cm from the hairline, eyes, ears, nose, and mouth. Diameter was between 0.5cm and
2.0 cm². Tumors with aggressive histology were excluded as were tumors deeper than 1 mm. Subjects were seen at Weeks 2, 4, and 6 of treatment. Follow-up was at 12 weeks post-treatment and at Months 3, 6, and 12 post-treatment. Subjects were then followed annually. Initial clinical clearance rate (intention-to-treat) was 89.6 percent at 12 weeks post-treatment. The clinical response rates increased as local site reaction severity increased. Nineteen percent of subjects had to take rest periods because of local site reactions.

Preliminary five-year data for sustained clearance rates are promising. The two-year clinical clearance rate is 91 percent, which is higher than the 79.4 percent the initial study predicted. Five-year sustained clearance rates are approaching 87 percent. Most subjects who had clinical recurrences did so within the first two years.

Shumack et al used imiquimod to treat biopsy-proven nodular BCCs in two different studies. The first was a six-week, open-label trial at 10 sites in Australia and New Zealand. Ninety-nine subjects were treated with imiquimod once daily, three or seven days per week or twice daily three days per week. In a 12-week randomized, controlled, double-blind trial in the United States, 92 subjects at 12 sites were treated with imiquimod or a corresponding vehicle for three, five, or seven days per week. Both groups initially had a twice-daily, seven-days-per-week arm, but this was eliminated because of the frequency of local skin reactions. Tumors were between 0.5 cm and 1.5 cm², and were >1 cm from the eyes, nose, mouth, ear, or hairline. The entire tumor area was excised six weeks after treatment with 3 to 4-mm margins. Both studies reported data from an intention-to-treat analysis.

In the 12-week study, 88 of 92 subjects had complete follow-up. Complete histologic cure was found in 13 percent (3/24), 60 percent (12/20), 70 percent (16/23), and 76 percent (16/21) of subjects in the vehicle, three-days-per-week, five-days-per-week, and seven-days-per-week groups, respectively. Compared to vehicle, all active treatment groups showed statistically significantly better response rates. Significant correlations were found between the intensity of local side effects and response rate in the five-day-per-week group ($p=0.003$) only. The negative predictive value for complete response was 91 percent and the positive predictive value for recurrence was 54 percent. Local skin reactions were mostly mild or moderate.

In the six-week study, 95 subjects (mostly men) had complete follow-up. A significant correlation between intense erosion and response rate was found in the once daily, seven-days-per-week group ($p=0.046$), but not in other groups. Similar side effects were seen as in the 12-week study. Complete histologic response rates were seen in 59 percent (19/32), 42 percent (13/31), and 71 percent (25/35) of subjects in the once daily, three-days-per-week; twice daily, three-days-per-week; and once daily, seven-days-per-week groups, respectively.

Eigentler et al conducted a Phase 3, randomized, open-label study using imiquimod for biopsy-proven nodular BCCs three times weekly for eight or 12 weeks. Tumors had a maximum diameter of 1.5 cm. At eight-weeks post-treatment, excision was performed with 3-mm margins. Ninety subjects completed the study. The clinical response rate was 78 percent and the histologic cure rate was 64 percent. Not surprisingly, smaller (>1 cm at randomization) tumors had higher cure rates (both clinically and histologically). Local site reactions were seen in 92 percent of subjects and included erythema, edema, vesicles, erosions, ulcers, desquamation, and drainage and pigmented problems. Most side effects were moderate, as per the physician’s judgment. Almost one third of the lesions were found to have residual tumor by histology.

**Imiquimod for Bowen’s disease.** Mackenzie-Wood et al treated 16 subjects with Bowen’s disease in a Phase 2, open-label study. Imiquimod was applied daily for 16 weeks. Six weeks post-treatment, a biopsy was performed. Tumors ranged from 1 to 5.4 cm (median diameter >3 cm²) in diameter and most were on legs. Previously treated lesions, lesions on the face, and subjects on immunosuppressive or immunomodulating drugs were excluded. At the six-week post-treatment visit, 93 percent of specimens were clear. Local site reactions were seen in 15 of 16 subjects. In five subjects, satellite reactions occurred, which manifested as skin irritation involving an area up to double the size of the initial tumor. Six subjects had to discontinue treatment at four weeks secondary to local site reactions, and four subjects eventually needed oral antibiotics.

In a retrospective study, Rosen et al treated subjects with imiquimod for Bowen’s disease. Subjects used imiquimod daily for six weeks. Almost all subjects were male and lesions were mostly on the extremities. Lesions on the genitalia were treated every other day. Forty-nine subjects had a clinical response rate of 86 percent. The remaining subjects required additional treatment.

There are several disadvantages to the use of imiquimod. Local skin reactions are common. Erythema is the most common side effect. Edema, ulceration, burning, erosion, pruritus, scabbing, and...
Dyspigmentation are also common. Although uncommon, flu-like symptoms can occur. The extent of reaction by a particular patient is difficult to predict. The cream is also expensive and packaged inconveniently. The regimen of six weeks of treatment may also be cumbersome to some patients. Finally, the histologic cure rate is about 80 percent, which is arguably impressive for a topical cream. Imiquimod is indicated for superficial BCCs, which are <2cm and not on the face. The advantages of imiquimod in the treatment of superficial BCCs include the following: it is patient administered, leads to excellent cosmesis, is usually well tolerated, can treat subclinical disease, and has good cure rates.

**Imiquimod as adjuvant treatment.** Another use for imiquimod is as adjuvant treatment following curettage. Imiquimod can be useful when superficial margins are positive after excision. It can also be used to clean-up background actinic damage prior to Mohs surgery. Additionally, several studies have investigated the adjuvant use of imiquimod after curettage (with or without electrodessication).

Spencer conducted a double-blind, vehicle-controlled, pilot study using imiquimod after electrodessication and curettage (ED&C) in patients with nodular BCC, compared to ED&C alone. Tumors were 4 to 17mm in diameter. Twenty-two subjects received three cycles of ED&C, followed by either imiquimod or vehicle daily for one month. Twenty subjects completed the trial. At eight weeks (four weeks post-treatment), residual tumor was identified histologically in 10 percent and 40 percent in imiquimod and vehicle groups, respectively. All sites were well healed by eight weeks, although the vehicle group healed more quickly. More subjects in the vehicle group had atrophic and/or hypopigmented areas by gross inspection. Imiquimod was well tolerated in most subjects. In conclusion, imiquimod plus ED&C had a much higher histologic cure rate but the treated areas took longer to heal.

In an open-label, pilot study, Neville et al treated 15 subjects with 17 nodular BCCs with 5% imiquimod after initial treatment with curettage. Curettage was performed on the lesion as well as 3mm of surrounding normal skin. One week later, imiquimod was applied once daily, five times per week for six weeks. Six weeks after this, patients returned to have the area excised with 3-mm margins. There was a 100-percent histologic clearance rate. Local site reactions occurred in 67 percent (10) of subjects, and nine subjects required rest periods.

Rigel et al conducted an open-label, pilot study in 57 subjects with both nodular and superficial BCCs using 5% imiquimod following curettage. One week post-curettage, imiquimod cream was applied once daily, five times per week for six weeks. At one-year post-treatment, zero percent of subjects had clinical recurrences. Cosmetic results were good to excellent. No hypertrophic scars were noted, which is important because one of the most common adverse cosmetic outcomes with curettage is hypertrophic scarring.

Tillman and Carroll enrolled 90 subjects in an open-label study using imiquimod 5% cream after curettage for biopsy-confirmed BCCs (61% nodular, 13% infiltrative, 13% mixed, 7% superficial, and 7% recurrent). Sixty-six percent were in high-risk anatomical areas. Of 101-treated tumors, a 96-percent clinical clearance rate was found at an average of 36 months follow-up. Although no histologic cure rate was reported, the clinical cure rate is very high for such a large percentage of high-risk tumors.

Advantages to adjuvant therapy of BCCs with imiquimod following curettage include lower cure rates (than ED&C alone) and improved cosmesis. Disadvantages include a higher cost, slower healing, and increased work by the patient.

**CONCLUSION**

Imiquimod, topical 5-FU, and PDT all show effectiveness in the treatment of superficial, low-risk tumors. Imiquimod has especially good efficacy for superficial BCCs with clinical cure rates approaching 90 percent. The results are not as good for nodular BCCs. In general, imiquimod is well tolerated and results in a good cosmetic outcome. 5-FU is not well studied for BCCs and Bowen's disease although it is FDA approved for the treatment of superficial BCCs. The major use for 5-FU is still for actinic keratoses. PDT is widely used in Europe for Bowen's disease and BCCs. It is likely to be more widely accepted in the United States when MAL is available and with shorter contact time employed.

Cosmesis is consistently good to excellent with all topical therapies discussed. The combination of curettage with imiquimod, topical 5-FU, or PDT may improve the cure rate.

Surgery, particularly Mohs surgery, continues to show the highest cure rates and remains the treatment of choice for high-risk BCC and invasive SCC.

**REFERENCES**


What’s New in Acne

by GUY WEBSTER, MD, PHD

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Limiting antibiotic usage in treating acne is becoming a topic of great interest as the problem of antibiotic resistance increases in both importance and in public awareness. The antibiotics that we use most, the tetracyclines, have recently assumed a greater role in treating infections since they are one of the few inexpensive drugs to which methicillin-resistant Staphylococcus aureus strains respond. Situations that promote resistance such as long-term treatment occur routinely in dermatology. For example, many acne patients require antibiotics for an extended period, but for many others there are methods to limit antibiotic use and still obtain an excellent clinical response.1,2

LIMITING THE DURATION OF ANTIBIOTIC TREATMENT

One technique to limit the duration of antibiotic treatment is to optimize topical retinoid use. Used as monotherapy, topical retinoids are a slow way to treat acne. Patients need to use topical retinoids for about 12 weeks for optimal response. However, few acne patients persevere long enough for retinoids to be effective. Typically, dermatologists add retinoids later in therapy, but this is not optimal. Several studies document that if a patient with inflammatory acne begins topical retinoid therapy at the same time as an oral antibiotic, the oral antibiotic can be discontinued after three months and the patient can be maintained on topical retinoid alone from that point forward.2,3 The patients in whom this works are those who had a good response at three months (i.e., about a 75% improvement). It must also be emphasized that the topical retinoid must be faithfully used from the start. If it is started late or used sporadically, results will be less rewarding. About 70 percent of acne patients in my practice are treated in this manner.

Another technique to limit antibiotic use is to use subantimicrobial dosages of doxycycline. At very low doses, beneath the minimal inhibitory dosage, the drug still has significant anti-inflammatory activity. Although approved for rosacea usage, anti-inflammatory-dose doxycycline also has some benefits in acne, especially in those patients with an overlap of acne and rosacea. A logical question arises as to whether antimicrobial dosages of doxycycline are as anti-inflammatory as higher doses, and it seems this is true. An analysis of the effects of weight, dosage, and clinical response in rosacea show that a nearly four-fold difference in weight has no effect on outcome, suggesting that 40mg of doxycycline is as effective as 160mg in the treatment of rosacea.4 A second recent study compared lesion counts in rosacea patients treated with topical metronidazole and either 40 or 100-mg doxycycline and found the regimens to be equivalent (data not yet published).

The possibility of subantimicrobial minocycline arises frequently. However, minocycline is concentrated in certain tissues (e.g., the sebaceous glands), and although blood levels might be subinhibitory, tissue levels may not be so.

THE EMERGENCE OF TOPICAL DAPSONE

Topical dapsone is soon to be an addition to the acne arsenal. Although approved two years ago, its release was delayed until it could be shown that the drug was safe for patients with G6PD deficiency. Those studies have been performed and the drug was shown to have no effect on
hemoglobin levels. No blood test is needed to prescribe topical dapsone and it may be safely given to patients with G6PD deficiency. In Phase 3 studies, topical dapsone showed good activity against both inflammatory and noninflammatory acne lesions (Figure 1). As yet, there are no comparisons available with other topical or oral acne medications, but these will certainly be forthcoming after the drug becomes available later this year.

THE iPLEDGE PROGRAM

The results of the first year of the iPledge program show no decrease in reported pregnancies compared to the preceding year, but it can be safely assumed that the iPledge number is an accurate one and is probably lower than the number of pregnancies in earlier years. Nothing is known regarding the illicit use of isotretinoin outside of the iPledge program. There are legitimate concerns that some patients may be acquiring the drug in other countries or via internet pharmacies.

ANTIMICROBIAL PEPTIDES

Antimicrobial peptides, part of the innate immune system, have received a lot of attention as potential acne medications, but, to date, have failed in clinical trials, perhaps because of inactivity in the lipid environment of the follicle. Early trials suggest that these medications may have some activity in rosacea. Research is ongoing in this area.

LIGHT AND LASER THERAPY

Light and laser therapy of acne continues to be a promising area of investigation. There are many targets for phototherapy in acne; the follicle wall, P. acnes, the sebaceous gland, and the inflammatory response itself. Numerous case reports and collections of cases suggest that various light-based treatments have some activity in acne, but because of numerous variations between patients’ regimens and co-treatment with other agents, it is impossible to say how effective light-based treatments truly are and what role they should play in treating the disease.

One proof-of-concept study has shown what might be possible with phototherapy in acne. Anderson et al sensitized patients with aminolevulinic acid and then delivered a large amount of light. After healing they found a dramatic suppression in sebaceous activity. Although this regimen is too unpleasant for routine use, it does demonstrate that a topical agent can reach the sebaceous gland and cause its destruction when photo-activated. An isotretinoin-like effect would seem possible.

A photo-active drug currently under development may make such a promise real. Lemuteporfin is a molecule that is photoactive and will target sebaceous glands only, sparring the rest of the skin. In animal studies the drug was shown to selectively destroy sebaceous glands when activated by light. Human trials are set to begin soon.

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Update on the Medical Management of Rosacea

by JAMES Q. DEL ROSSO, DO, FAOCD

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The pathogenesis of rosacea remains poorly understood and as a result, there is a conspicuous absence in the development of new active agents to treat rosacea. Importantly, rosacea is best viewed as a spectrum of clinical presentations with multiple features, which may or may not be present in a given patient.1 This perspective led to the definition of distinctive rosacea subtypes, the most common of which include erythematotelangiectatic (subtype 1) and inflammatory (subtype 2). The latter is also referred to as papulopustular rosacea.2 Multiple pathophysiologic mechanisms have been reported to be associated with rosacea, such as degradation of dermal matrix by some matrix metalloproteinase enzymes (MMPs), increased cutaneous oxidative stress due to exhaustion of the inherent protective effect of superoxide dismutase, and innate epidermal barrier dysfunction of the central face leading to increased transepidermal water loss (TEWL) and “sensitive skin”3,4. However, how these specific mechanisms may or may not be involved with individual subtypes of rosacea has not been clearly defined. Additional research is needed to further define the pathogenesis of rosacea and its subtypes as such information assists in the development of therapies that target defined pathophysiologic mechanisms.

While we await new research on the pathogenesis of rosacea, clinical trials have been performed more recently evaluating therapeutic results for patients with the inflammatory (papulopustular) subtype. In addition, multiple studies evaluating subantimicrobial dosing of doxycycline have defined its efficacy more completely and have established lack of antibiotic selection pressure. These trials are summarized next.

Role of Skin Care in the Management of Rosacea

With additional research, it becomes increasingly apparent that symptoms of “sensitive skin” observed in patients with both erythematotelangiectatic and inflammatory rosacea relate to inherent epidermal barrier dysfunction.5,6 The importance of proper skin care as a component of the management program for rosacea is well recognized, as use of a gentle cleanser and moisturizer serves to decrease signs and symptoms of sensitive skin that are common in rosacea patients and can improve the tolerability of topical medication.6,7 Recently published Rosacea Management Guidelines from the American Acne and Rosacea Society (AARS) support the importance of appropriate skin care and rational product selection as important components of optimal rosacea management.9

A question often asked by clinicians and their support staff who are involved with educating patients about rosacea is, “What gets applied first, the moisturizer or the medication?” This question has been addressed in a recently performed percutaneous absorption kinetics study using human skin.10 In this study, the percutaneous absorption kinetics of azelaic acid formulated as the commercially available 15% gel (Finacea, Intendis, Berlin, Germany) were documented utilizing an established in-vitro human skin model. These results were compared to the percutaneous absorption profiles of azelaic acid when the 15% gel was applied.
before or after application of one of three brand moisturizer lotions (CeraVe Lotion, Coria Laboratories, Fort Worth, Texas; Cetaphil Lotion, Galderma Laboratories, Fort Worth, Texas; Dove Lotion, Englewood Cliffs, New Jersey). The results demonstrated that the application of any of the three brand moisturizer lotions did not impair the percutaneous penetration of azelaic acid if applied first.

METRONIDAZOLE

Multiple studies have confirmed the efficacy of topical metronidazole in the treatment of rosacea, including 0.75% gel, lotion, and cream formulations applied twice daily and 1% gel and cream formulations applied once daily.\(^6^{11}\) Metronidazole gel 1% (MetroGel 1%, Galderma Laboratories, Fort Worth, Texas) is incorporated into a new water-based gel technology called HSA-3, which utilizes betadex (cyclodextrin) to solubilize metronidazole, a very low concentration of propylene glycol which serves as a humectant, and a low concentration of niacinamide which is proposed to assist in maintaining epidermal barrier integrity.\(^6\) The HSA-3 vehicle technology is not associated with increased TEWL and may produce some hydrating effect based on corneometry. Metronidazole gel 1% has been shown to be therapeutically equivalent to metronidazole cream 1%, and to azelaic acid gel 15% in controlled noninferiority studies.\(^6^{11}\)

AZELAIC ACID

Azelaic acid 15% gel applied twice daily has been shown in multiple studies to be effective for the treatment of inflammatory rosacea.\(^1^{11}{13}\) A recent, controlled, 12-week study has demonstrated that azelaic acid 15% once daily is therapeutically equivalent to twice daily application based on quantitative assessment (inflammatory lesion reduction) and both static and qualitative investigator assessments.\(^4\) The importance of these findings are clinically relevant as once daily application is anticipated to correlate with improved compliance and lower cost of therapy per unit time.

ANTI-INFLAMMATORY-DOSE DOXYCYCLINE

Anti-inflammatory-dose doxycycline refers specifically to doxycycline 40-mg delayed release, formulated as a 30-mg immediate-release and 10-mg delayed-release capsule (Oracea, CollaGenex Pharmaceuticals, Inc., Newtown, Pennsylvania) administered once daily. Therefore, the term anti-inflammatory-dose doxycycline is used interchangeably with doxycycline 40-mg delayed-release capsule once daily. Anti-inflammatory-dose doxycycline is approved by the US Food and Drug Administration (FDA) for treatment of inflammatory rosacea.\(^15\) Importantly, anti-inflammatory-dose doxycycline is devoid of antibiotic activity, even with prolonged administration, based on pharmacokinetic and long-term microbiologic studies.\(^15^{16}\) The approved labeling for anti-inflammatory-dose doxycycline includes nine-month microbiologic and safety data, supporting both the lack of antibiotic activity and a favorable safety profile with prolonged administration.\(^16^{17}\)

A recent, double-blind, 16-week trial compared the efficacy and safety in patients randomized to receive metronidazole gel 1% once daily and either doxycycline 100mg daily or doxycycline 40-mg delayed-release capsule once daily. Efficacy as measured by inflammatory lesion reduction, investigator global assessment, and erythema reduction was confirmed and was essentially equivalent in both study arms. In addition, the speed of onset and time course of clinical efficacy were the same in both groups, based on assessment of all three efficacy parameters. In this same trial, adverse reactions (especially gastrointestinal side effects such as nausea and abdominal pain) were markedly higher in the group of subjects receiving doxycycline 100mg once daily.

What is the clinical significance of the findings from the study comparing anti-inflammatory-dose doxycycline versus doxycycline 100mg once daily in subjects also treated with metronidazole gel 1% once daily? Several observations can be made from the study results.

First, it is important to recognize that clinical studies evaluating conventional antibiotic dosing of tetracyclines and other antibiotics used to treat rosacea are limited, and that no dose-response studies have been performed.\(^1^{11}{13}\) As such, the finding that doxycycline 40-mg delayed-release capsules once daily is therapeutically equivalent to doxycycline 100mg once daily suggests that “more” is not necessarily synonymous with “better” for rosacea, as sufficient and potentially optimal anti-inflammatory activity is achieved using anti-inflammatory-dose doxycycline.

The observation that anti-inflammatory-dose doxycycline and doxycycline 100mg once daily exhibited the same onset and time course of clinical efficacy suggests that anti-inflammatory effects, and not antibiotic activity, are responsible for therapeutic benefit when a tetracycline derivative is used to treat inflammatory rosacea. Third, the greater incidence of adverse reactions, especially gastrointestinal side effects, supports a more favorable safety profile with anti-inflammatory-dose doxycycline as compared to doxycycline 100mg once daily.

ROSacea MEDical MANAGEMENT GUIDELINES

The AARS has independently developed and published Rosacea Management Guidelines, which
discuss available medical therapy options, including topical therapies, systemic therapies, and skin care.530 These guidelines were developed solely by the AARS and approved by its leadership, not to create a structured treatment algorithm, but rather to provide an overview of the various options and types of evidence which support their use. The AARS Rosacea Management Guidelines are easily accessible, succinct, referenced, and reflective of a consensus among several dermatologists who are very interested and knowledgeable regarding rosacea. It is also hopeful that these guidelines may prove to be a helpful reference to those evaluating formulary access and third-party coverage in order to assure that an adequate menu of therapeutic choices is available for clinicians treating rosacea patients.

SUMMARY

Although much more fundamental research needs to be performed to further elucidate the pathophysiologic pathways involved in rosacea, clinical trials serve to further the development of treatment advances despite the conspicuous absence of new active compounds. In addition, such research defines potentially better ways to apply therapeutic options that are already present in our armamentarium. Examples of more recent advances and/or observations in rosacea include vehicle technology employed with metronidazole gel 1%, therapeutic equivalence of azelaic acid gel 15% applied once daily as compared to twice daily, information on moisturizer use and order of application, and confirmation that anti-inflammatory-dose doxycycline is therapeutically equivalent to doxycycline 100mg daily.

REFERENCES

BRIEF SUMMARY OF PREscribing INFORMAtION

Duac®
Topical Gel
(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.
Not for Ophthalmic Use.
No Oral Use

INDICATIONS AND USAGE
Duac® Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.
Duac® Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS
Duac® Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional entinitis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

WARNINGS
ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIMICROBIAL FROM THE SKIN SURFACE.
DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXICITY PRODUCED BY CLOSTRIDIUM DIFFICILE IS THE PRIMARY CAUSE OF ANTIMICROBIAL-ASSOCIATED COLITIS. THE COLITIS IS USUALLY CHARACTERIZED BY SEVERE PERISTALTIC DIARRHEA AND SEVERE ABDOMINAL CRAMPS AND MAY BE ASSOCIATED WITH THE PASSAGE OF BLOOD AND MUCUS. ENDOGENOUS EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR CLOSTRIDIUM DIFFICILE AND STOOL ASYMIPTOMATIC TOXIN MAY BE HELPFUL DIAGONSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIBIOTIC-ASSOCIATED DIARRHEA SUCH AS OPIATES AND DIFENOXIATE WITH ATROPINE MAY PROLONG AND/OR WORSE THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEG IN UP TO SEVERAL WEEKS FOLLOWING CESSION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against Clostridium difficile.

PRECAUTIONS
General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or ablative agents.
The use of antibiotic agents may be associated with the growth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.
Avoid contact with eyes and mucous membranes.
Clindamycin and erythromycin-containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vivo antagonism is not known.

Information for Patients: Patients using Duac® Topical Gel should receive the following information and instructions:
1. Duac® Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.
4. Patients should report any signs of local adverse reactions to their physician. Patients who develop allergic reactions such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.
5. Duac® Topical Gel may bleach hair or colored fabric.
6. Duac® Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.
7. Before applying Duac® Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.
8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with Duac® Topical Gel. Clindamycin phosphate was not genotoxic in Salmonella typhimurium or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with Duac® Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 360 mg/kg/day of clindamycin (approximately 150 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Duac® Topical Gel, based on mg/m2) revealed no effects on fertility or mating ability.

Pregnancy, Teratogenesis Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Duac® Topical Gel or benzoyl peroxide. It is also not known whether Duac® Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Duac® Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (200 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m2, respectively) or subtoxic doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m2, respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether Duac® Topical Gel is secreted into human milk after topical application. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS
During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment was as follows:

<table>
<thead>
<tr>
<th>Local Reactions with use of Duac® Topical Gel</th>
<th>% of patients using Duac® Topical Gel with symptom present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined results from 5 studies (n = 397)</td>
<td></td>
</tr>
<tr>
<td>Before Treatment (Baseline)</td>
<td>During Treatment</td>
</tr>
<tr>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Erythema</td>
<td>28%</td>
</tr>
<tr>
<td>Peeling</td>
<td>6%</td>
</tr>
<tr>
<td>Burning</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Percentages derived by # subjects with symptom score/total Duac® Topical Gel subjects, n = 397)

Aphtholytic, as well as allergic reactions leading to hospitalization, has been reported in post-marketing use with Duac® Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate a causal relationship to drug exposure.

HOW SUPPLIED
Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in:
- 45 gram tube
- Core System (CS) Convenience Kit
  - Includes Duac® Topical Gel
  - clindamycin, 1% - benzoyl peroxide, 5%
  - 45 grams
  - SFC® Lotion 106.6 ml (3.8 Fl Oz)

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.
Dispensing Instructions for the Pharmacist: Dispense Duac® Topical Gel with a 60 day expiration date and specify “Store at room temperature up to 25°C (77°F). Do not freeze.”
Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent No. 5,466,446
Patent Pending
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301135 Rev. July 2008
OTG-84-2008-USA

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One less battle in the fight against acne

Answer irritation with hydration — Duac® Care System (CS)

Irritating acne treatments can discourage compliance

- Increasing irritation correlates with increasing transepidermal water loss (TEWL)
- Poor compliance has been reported to be the most common cause of nonresponse to acne medication

DUAC Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Important Safety Information

DUAC Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops.

Side effects may include erythema, peeling, burning, and dryness.

Please see brief summary of prescribing information on the following page.

References:

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US Patent No. 5,466,446. Patents Pending.

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