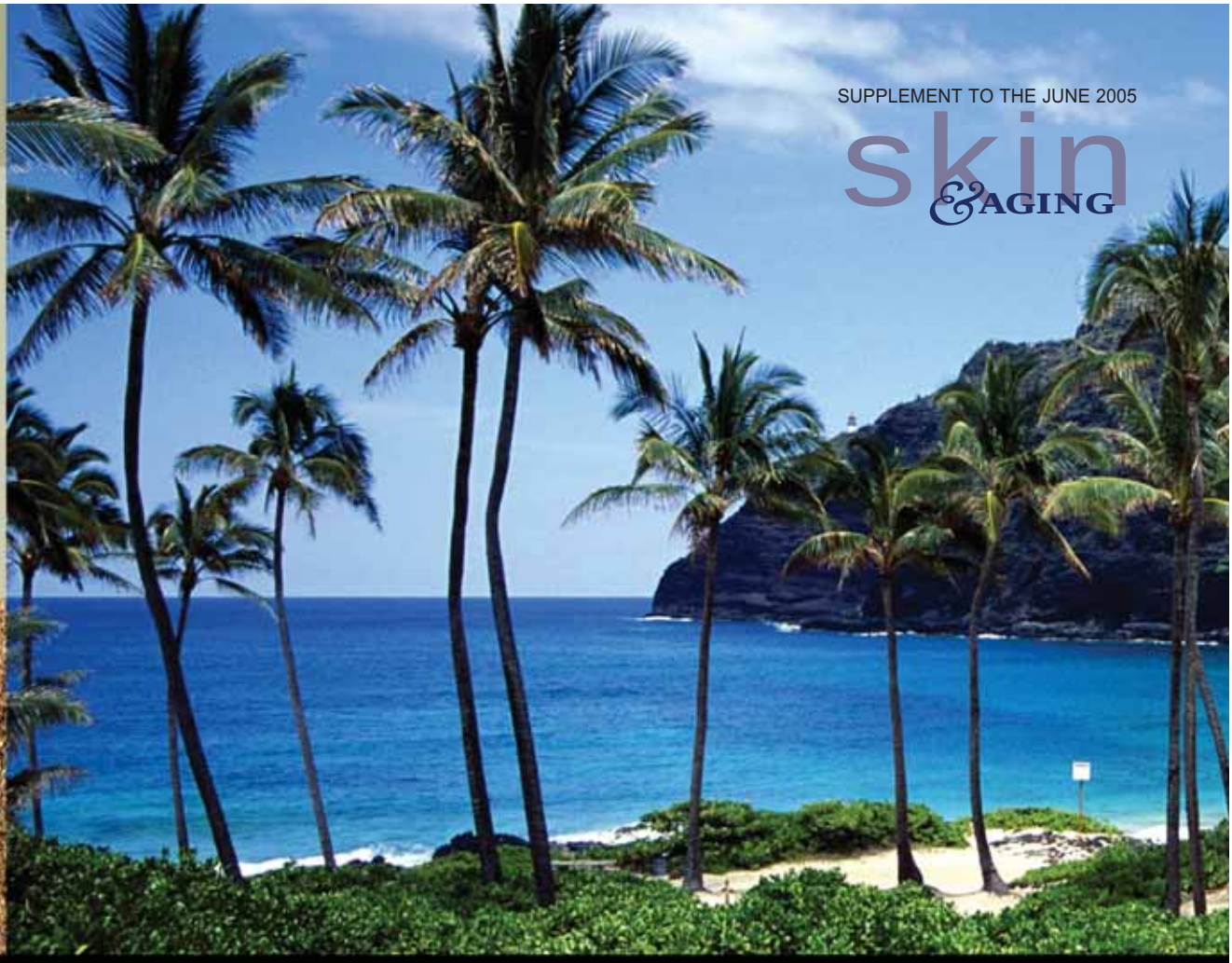
SUPPLEMENT TO THE JUNE 2005
skin & AGING



SUPPLEMENT PROCEEDINGS FROM THE 24TH ANNIVERSARY

Winter CLINICAL DERMATOLOGY CONFERENCE HAWAII™

BASED ON SELECTED PRESENTATIONS FROM
THE WINTER CLINICAL DERMATOLOGY CONFERENCE™
HELD IN KOHALA COAST, HAWAII, JANUARY 15 - 19, 2005.

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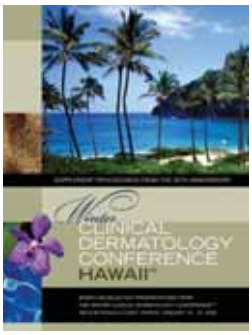


Articles in this supplement are based on selected presentations from the 2005 Winter Clinical Dermatology Conference™ held on January 15 – 19, 2005 in Kohala Coast, Hawaii.

ANOTHER LOOK AT WHAT'S NEW IN THE MEDICINE CABINET

BY JAMES Q. DEL ROSSO, D.O., F.A.O.C.D.

James Q. Del Rosso, D.O., F.A.O.C.D.

Therapeutic advances and innovations in dermatology depend on the development of new chemical compounds and novel delivery systems. In other cases, looking more closely at existing compounds provides new insights leading to options that are therapeutically useful in clinical practice. This article will review:

- the beneficial role of ciclopirox 1% shampoo (Loprox) as both initial and maintenance therapy for seborrheic dermatitis of the scalp
- effective treatment of chronic hyperkeratotic hand eczema using low-dose oral acitretin (Soriatane)
- advances in formulation science highlighting topical salicylic acid (Salex) incorporated in both a multivesicular emulsion cream and lotion used effectively to treat hyperkeratotic skin disorders.
- long-term efficacy of imiquimod cream (Aldara) used for treatment of actinic keratosis (AK).

TREATING SEBORRHEIC DERMATITIS

Ciclopirox 1% shampoo is approved by the FDA for the treatment of seborrheic dermatitis. Based on vehicle-controlled, blinded studies completed in patients with seborrheic dermatitis of the scalp, efficacy, safety and cosmetic acceptability of ciclopirox 1% shampoo has been confirmed.[1-6] Dosage finding trials inclusive of three concentrations of ciclopirox shampoo (0.1%, 0.3% and 1%) versus vehicle demonstrated superior efficacy with the 1% concentration.[3] Double-blind, vehicle-controlled, 4-week trials confirmed the efficacy of twice weekly use of ciclopirox 1% shampoo for scalp seborrheic dermatitis; 58.5% of patients treated with ciclopirox 1% shampoo twice weekly were "effectively treated" (completely clear or with very minimal disease) as compared to 45.5% treated once weekly and 31.6% treated with vehicle.[6] Ciclopirox 1% shampoo proved safe and well tolerated at all application frequencies, including up to three times weekly in some study subjects.

In a 12-week maintenance extension trial, patients who were cleared of scalp seborrheic dermatitis initially were randomized to use ciclopirox 1% shampoo once weekly or once every other week, or shampoo vehicle (Table 1). Relapse was defined as at least a two-grade deterioration in disease state parameters (e.g., erythema, scaling). In the group using ciclopirox 1% shampoo once weekly, 14.7% experienced relapse. Relapse was observed in 22.1% of patients using ciclopirox 1% shampoo once every other week and in 35% of patients in the vehicle study arm. Ciclopirox 1% shampoo used once weekly effectively maintained control of seborrheic dermatitis in 85% of patients over a 12-week study period.

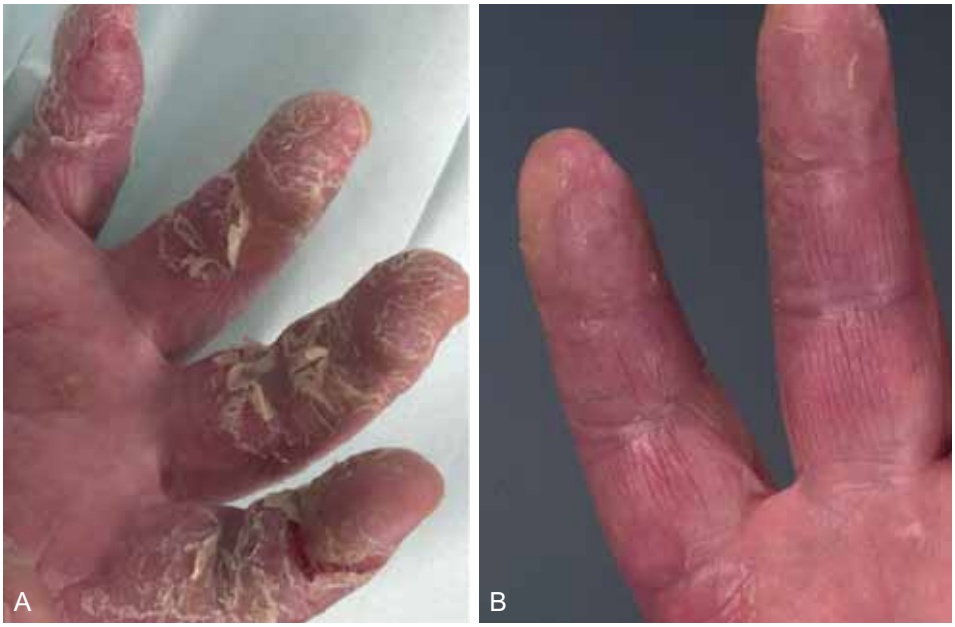
TABLE 1. CICLOPIROX 1% (LOPROX) SHAMPOO
Maintenance Therapy for Scalp Seborrheic Dermatitis

	Comparison of Ciclopirox 1% (LOPROX®) versus vehicle	Ciclopirox 1% once weekly	Ciclopirox 1% once every two weeks	Ciclopirox vehicle
ALL RANDOMIZED	Proportion of relapses	15.9% 22/138	24.2% 36/149	35.5% 50/141
	p-value	0.0001	0.0326	
INTENT-TO-TREAT GROUP	Proportion of relapses	14.7% 20/136	22.1% 32/145	35.0% 49/140
	p-value	0.0001	0.0149	

12-week study period/Relapse defined as ≥2 point worsened status

Shuster S. A Phase III, Multinational, Double-Blind, Vehicle-Controlled Study to Assess the Efficacy of Ciclopirox Shampoo for the Treatments of Seborrheic Dermatitis/Dandruff of the Scalp. Poster presentation AAD Meeting, San Francisco, Calif., March 2003.

MANAGING CHRONIC HYPERKERATOTIC SKIN DISEASE



FIGURES 1A and 1B. Chronic hyperkeratotic hand eczema. Acitretin (Soriatane) 25mg daily added to topical regimen. 1A = baseline; 1B = after 2 weeks. *Photos courtesy of David Cohen, M.D.*

Chronic hyperkeratotic hand eczema presents as dry, thickened, gray, hyperkeratotic plaques that often involve the palmar surfaces and fingers.[7-9] Scaling is common, pruritus may be present and fissuring is often a disturbing feature, especially on the fingers. Believed to be multifactorial, exogenous (allergens, irritants) and endogenous (genetic predisposition, history of atopy) factors appear to play a role in individual cases. Clinically, it may be difficult to distinguish chronic hand eczema from chronic hand psoriasis. Topical corticosteroids, topical calcineurin inhibitors, "keratolytic" agents, emollients and hand protectants are often used with varying degrees of success. The use of systemic retinoid therapy has also been suggested for chronic hyperkeratotic hand eczema.[8,9]

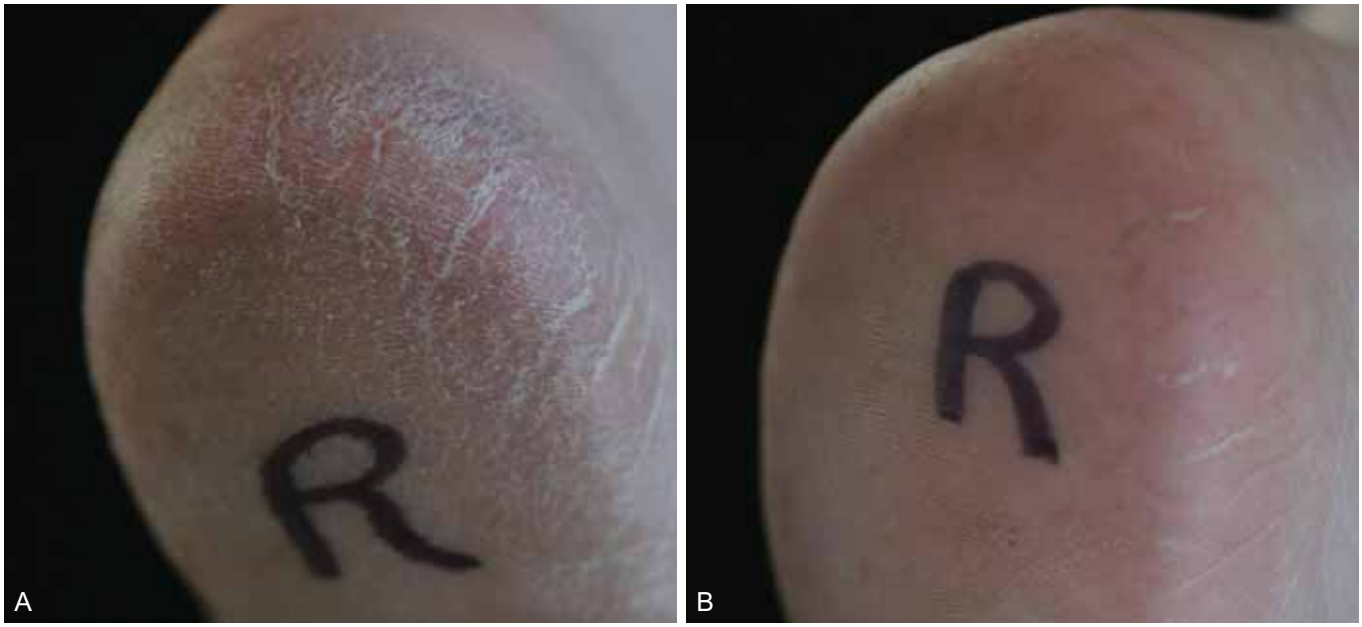
A single-blind, matched-sample trial compared oral acitretin 25 mg to 50 mg daily versus topical betamethasone 0.05%/salicylic acid 3% applied twice daily in adult patients with chronic hyperkeratotic hand eczema.[8] Each therapy was sequentially utilized for 1 month by all patients (topical regimen first) with each form of treatment evaluated over a 5-month follow-up period. Acitretin proved to be significantly superior to the topical regimen after 1 month of therapy, with greater persistence of improvement also observed over the 5-month follow-up period with acitretin use. A more rapid onset of clinical improvement was noted with acitretin, as was absence of rebound after discontinuation of use. Acitretin was preferred by patients over topical therapy. No significant adverse reactions or laboratory changes were reported; mild cheilitis and skin dryness were observed during acitretin use.

Figures 1A and 1B demonstrate response to therapy with acitretin 25 mg daily after 2 weeks of therapy. Acitretin was added to combination topical therapy with clobetasol propionate 0.05% foam (Olux) daily and tacrolimus 0.1% ointment (Protopic) daily for chronic hyperkeratotic hand eczema that was refractory to topical therapy and systemic corticosteroid use. The response to acitretin may be slower in some patients, with most demonstrating evidence of a favorable response within the first month.[8,9]

Salicylic acid is commonly categorized as a "keratolytic" agent,[10,11] but the designation is not scientifically accurate (application of salicylic acid does not lead to alteration of keratin filaments[12]). Salicylic acid disrupts corneodesmosome, resulting in reduced corneocyte adhesion with subsequent detachment of corneocytes.[12-15] This reduces corneocyte "clumping," allowing for single cell detachment, which more closely simulates physiologic corneocyte shedding. The term "desmolytic" more accurately describes the mechanism of action of topical salicylic acid.[12]

> "CHRONIC HYPERKERATOTIC HAND ECZEMA PRESENTS AS DRY, THICKENED, GRAY, HYPERKERATOTIC PLAQUES THAT OFTEN INVOLVE THE PALMAR SURFACES AND FINGERS.

The multivesicular emulsion (MVE) employs specialized formula-



FIGURES 2A and 2B. Salicylic acid 6% in a multivesicular emulsion cream formulation (Salex Cream) once daily for localized hyperkeratosis. At baseline (2A) and after 4 weeks (2B). *Photos courtesy of James Q. Del Rosso, D.O., F.A.O.C.D.*

tion technology. Concentric layers of emulsified lipids form components of an aqueous medium.[16] Active ingredients may be water-soluble or oil-soluble and may be stacked with different time-release characteristics. MVE formulation technology has been applied to brand formulations of salicylic acid 6% cream (Salex Cream) and lotion (Salex Lotion). Figures 2A and 2B demonstrate effective results for hyperkeratosis of the heels after application of salicylic acid 6% cream applied once daily with marked improvement reported within the first few weeks of use.[16]

CLEARING UP AK

Clearance of AK has been reported with application of topical imiquimod (Aldara) 2 to 3 times per week in 45% to 84% of cases.[17-19] In many patients not exhibiting complete clearance, ≥75% lesion reduction was observed. A study evaluating "cycle therapy" for AK involving scalp, cheeks, forehead and temples reported results with use of topical imiquimod applied 3 times per week for 4 weeks followed by a 4-week rest period (single cycle).[20] If residual AK were present, another cycle was used. A single cycle produced complete clearance in 46% of the treated cosmetic units. An additional 36% of cosmetic units cleared completely after a second cycle.

Table 2 outlines the results of long-term clearance of AK after treatment with topical imiquimod applied 3 times weekly for 12 weeks.[21] At follow up after 2 years, 80% of patients remained clear of AK in the treatment field as compared to 90% of patients treated with vehicle only. A larger analysis evaluating long-term response rates after use of topical imiquimod either two or three times per week has been completed with publication of results anticipated in the near future. Figures 3A – 3D demonstrate 2-year follow up with clearance of multiple AKs diffusely involving the scalp in an adult male patient treated initially by the author with two cycles of topical imiquimod, followed by no further treatment for 12 months, then followed by once weekly application over the second 12 months used empirically as a maintenance regimen ("Lebwohl regimen").

BENEFITING FROM NEWER OPTIONS

This article has provided a summary of information that assists

TABLE 2. ACTINIC KERATOSIS THERAPY
Long-Term Follow Up – Imiquimod 5% Cream

3x per week x 12 weeks (n = 25 active / n = 11 vehicle)

Study Arm	Complete Clearance	50% – 75%
Imiquimod	84%	92%
Vehicle	0%	0%

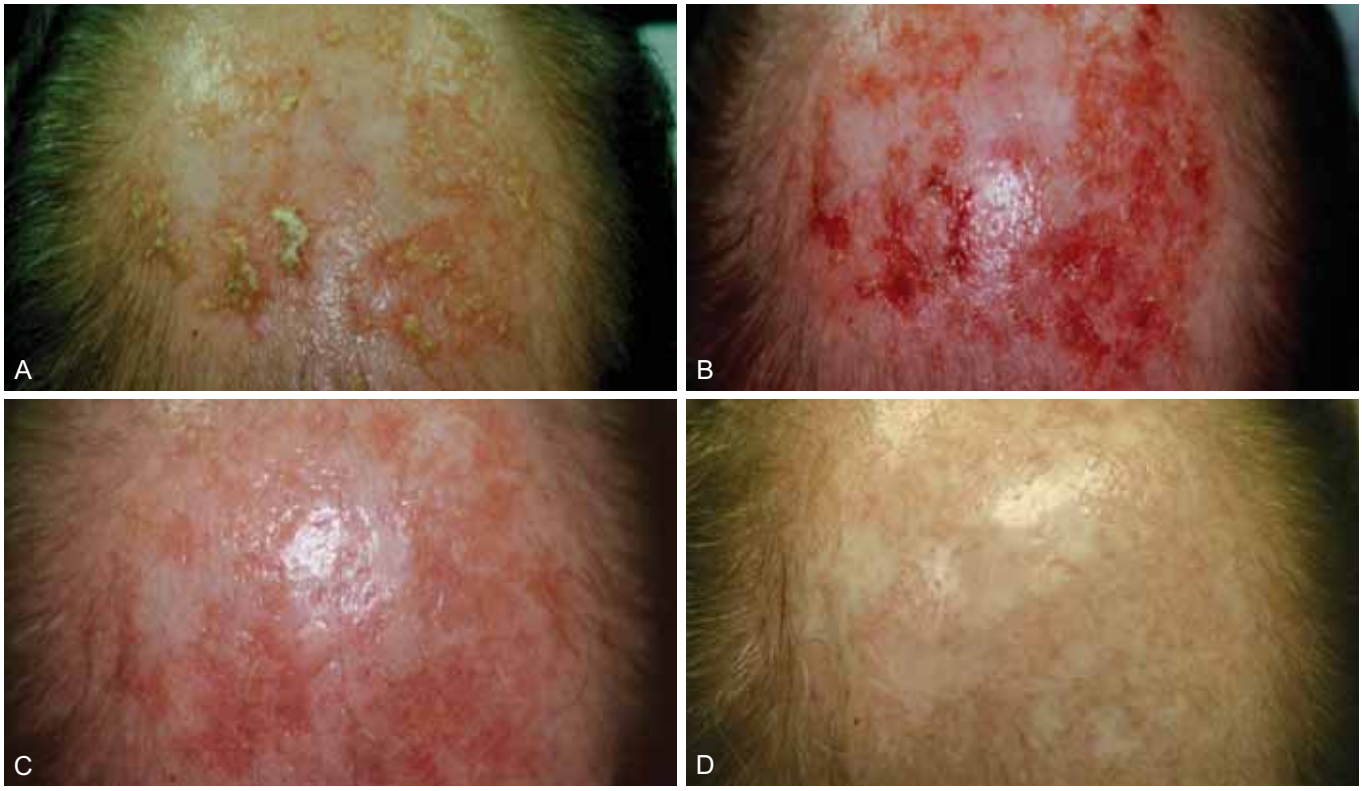
Follow-up Analysis – Imiquimod-treated patients

1 Year	8%	(2/25)
18 Months	16%	(4/25)
2 Years	20%	(5/25)

No patients with development of SCC in group treated with topical imiquimod

New actinic keratoses in 90% of vehicle arm (9/10)
1 case of SCC development in vehicle arm

Stocfleth E, et al. Arch Dermatol. 2004;140:1542-1544



FIGURES 3A - 3D. Longevity of clearance of actinic keratosis after treatment with topical imiquimod (Aldara) 3x per week x 4 weeks "cycle" therapy. Baseline before second cycle (3A), week 4 (3B), week 8 after 4 weeks off of therapy with clearance noted (3C) and follow up after 2 years with clearance maintained (3D). *Photos courtesy of James Q. Del Rosso, D.O., F.A.O.C.D.*

clinicians in patient management. The continued development of newer therapeutic options and continued research evaluating the efficacy and safety of both new and established treatments will expand our ability to optimize therapy for our patients. ■

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AVOIDING PITFALLS IN THE TREATMENT OF PSORIASIS

BY MARK LEBWOHL, M.D.

Mark Lebwohl, M.D.

The main limitations of conventional treatments for moderate to severe psoriasis are cumulative toxicity and incomplete efficacy in some patients. Elevated cytokine levels are believed to play a role in psoriasis, and psoriasis plaques show higher-than-normal levels of cytokines, in particular tumor necrosis factor-alpha (TNF-alpha). Consequently, it is often useful and necessary to transition patients from conventional psoriasis treatments (such as methotrexate or cyclosporine) to newer biologics (such as alefacept [Amevive]). These transitions must be made carefully, however, because of the association of abrupt discontinuation of certain psoriatic drugs with flares. Conversely, the overlapping of different psoriasis therapies must be done cautiously to avoid additive toxicity. This article will review these and other common pitfalls that arise when treating psoriasis as well as ways to avoid them.

> THE MAIN LIMITATIONS OF CONVENTIONAL TREATMENTS FOR MODERATE TO SEVERE PSORIASIS ARE CUMULATIVE TOXICITY AND INCOMPLETE EFFICACY IN SOME PATIENTS.

DEALING WITH SEVERE CASES

Case studies from my practice show some common scenarios in treating severe psoriasis. The first involves a 33-year-old female patient with psoriasis on 40% of her body surface area. Methotrexate cleared the psoriasis, but a liver biopsy revealed that she had developed periportal fibrosis. As a result, it was decided to discontinue the methotrexate and instead use alefacept 15 mg. However, abrupt cessation of methotrexate caused the psoriasis to flare. A Phase 3 study of alefacept has shown what many dermatologists have observed in practice: It takes about eight weekly doses of alefacept to begin to see a benefit in those patients who respond. Major improvement can take 12 to 18 weeks.

A similar case study occurred with a 54-year-old male patient who had severe psoriasis on 20% of his body surface area. Treated with cyclosporine 5 mg/kg, the psoriasis cleared. His creatinine level increased from 0.8 to 1.2 and while a 1.2 creatinine level is, in and of itself, not a cause for undue concern, the degree of change (50% increase) was alarming. The cyclosporine was discontinued and the psoriasis flared. He was treated subcutaneously with etanercept (Enbrel) 50 mg bi-weekly. Depending on dosage, improvement with etanercept is adequate to begin tapering other treatments at 4 weeks. Major improvement occurs at around week 4 to 8. Etanercept improvement is dosage-dependent. (Patients who received 50 mg bi-weekly showed 71% improvement in Psoriasis Area and Severity Index [PASI] at 24 weeks versus 62% improvement with 25 mg.)

Similar results occur with other biologic agents such as infliximab (Remicade), adalimumab (Humira) and efalizumab (Raptiva). These agents require a generous “phase-in” period before they significantly reduce psoriasis. While there is almost always some degree of improvement in the first month, it can take several months for the biologics to reach full effect. The nearly immediate flare produced by abrupt discontinuation of some psoriasis drugs (methotrexate, cyclosporine) creates a “gap” in which

patients experience the full and unpleasant effects of psoriasis for weeks and even months before the biologics take full effect. This raises an important question: "Is it safe to overlap biologics with other psoriasis therapies?"

OVERLAPPING THERAPIES

There is evidence in the literature of combination therapies being effective and well-tolerated by patients outside the dermatology clinic. In an observational study of seven juvenile idiopathic arthritis patients, investigators evaluated the efficacy of combination therapy of etanercept and methotrexate. While this study involved arthritis and not psoriasis patients, it was found that etanercept in combination with methotrexate was well-tolerated and feasible in terms of toxicity.[1]

Another paper reported the successful combination treatment of severe, recalcitrant psoriasis with infliximab and methotrexate. The combination therapy improved psoriasis outcomes and was well-tolerated by patients.[2] In another study, 18 patients with refractory rheumatoid arthritis were receiving low-dose cyclosporine (2 mg/kg/day) and prednisone and were given infliximab (3 mg/kg weight) at zero, 2, 6 and every 8 weeks after for 1 year. Multiple infusions of infliximab and low-dose cyclosporine improved refractory rheumatoid arthritis and were well-tolerated by patients.[3] For rheumatoid arthritis patients who were still active despite intensive combination therapy (methotrexate plus cyclosporine), an Italian study (n=16) treated 10 patients with the combination therapy plus infliximab and six patients with infliximab and methotrexate. While there was some evidence from the 30-week study that infliximab plus combination therapy was more efficacious in treating the rheumatoid arthritis, it was found that patients tolerated incremental infliximab along with methotrexate or methotrexate plus cyclosporine.[4]

TRANSITIONING TACTICS

Combination therapy (biologic plus methotrexate or cyclosporine) results in combined immunosuppression. Nevertheless, there is a growing body of evidence that suggests that combination therapy may be well-tolerated by most patients, at least in the short term. From my own practice and from the literature, several guidelines have emerged in terms of making a successful transition for the psoriasis patient.

When transitioning to the major biologic drugs, it is important to note the point at which the biologic reaches major effect and to plan a tapering-off period of the methotrexate or cyclosporine together with a ramping-up period of the biologic. Obviously, shorter overlaps are better for the patient. Should psoriasis flare, it may be necessary to increase the conventional drug backup slightly or to plateau it temporarily until the psoriasis is back under control (See Table 1).

Some psoriasis patients are treated with ultraviolet B (UVB) phototherapy, and in such cases, combination therapy represents less risk to the patient. To transition a UVB phototherapy psoriasis patient to a biologic, begin to taper the UVB treatments at around 4 weeks (8 to 12 weeks for alefacept). A good frequency schedule for tapering phototherapy is twice weekly for 2 weeks, then once a week for 2 weeks. Keep in mind that these are broad guidelines and must be adjusted based on the clinical response of the individual patient.

TABLE 1. SOME COMMON BIOLOGICS USED TO TREAT PSORIASIS

Drug	Onset	Major Effect
alefacept (Amevive)	8 weeks	12 weeks
adalimumab (Humira)	2 weeks	4 weeks
efalizumab (Raptiva)	2 weeks	10 weeks
etanercept (Enbrel)	2 weeks	4 to 8 weeks
infliximab (Remicade)	2 weeks	2 to 4 weeks

All time periods are approximate and may vary by patient.

For psoriasis patients treated with psoralen and long-wave UV radiation (PUVA) transitioning to biologics, the risk of combination therapy is low. Start to taper off PUVA at around 4 weeks (8 to 12 weeks for alefacept). As with UVB therapy, a good rule of thumb is 2 weeks of bi-weekly phototherapy followed by once-a-week therapy for 2 weeks.

To transition a patient on a topical retinoid, such as acitretin (Soriatane), to a biologic, begin to taper off the acitretin at around 4 weeks of biologic treatment (again, 8 to 12 weeks for alefacept). The risk of combination therapy is relatively low. Because acitretin is not immunosuppressive, it can be used long term in combination with biologics without worrying about additive immunosuppression.

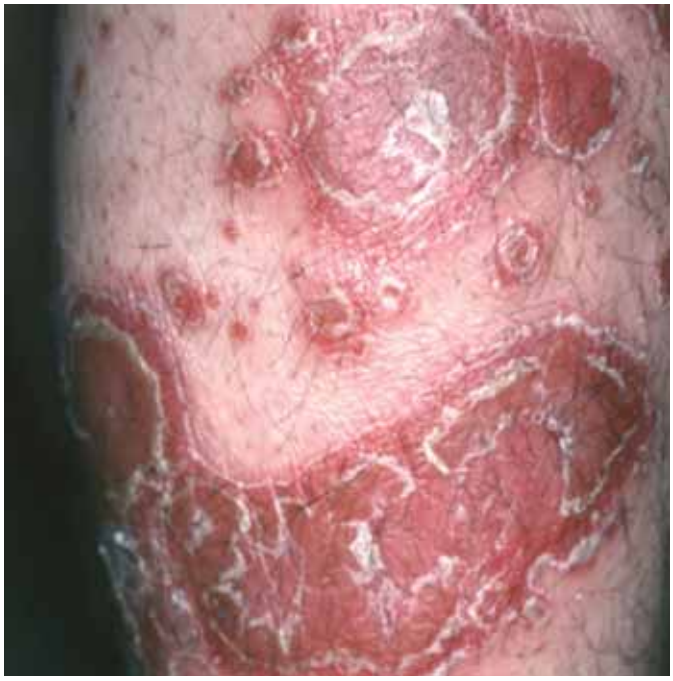
A retrospective analysis of how patients who have psoriasis on the palms and soles were treated illustrates the course of treatment of recalcitrant severe psoriasis. In this study of 26 patients, topical corticosteroids were used first in combination with calcipotriene ointment (Dovonex Ointment) or tazarotene 0.1% gel (Tazorac) or both. If this was ineffective, systemic retinoids were added (usually acitretin). After about 2 months, an excimer laser might be tried, followed by soak PUVA along with the other agents. In the past, methotrexate and cyclosporine were frequently tried at this point if previous therapies were not well-tolerated or were ineffective or both. However, the hepatotoxicity of methotrexate and the nephrotoxicity of cyclosporine have caused these drugs to be rightly regarded with some caution.[5] Biologics are increasingly assuming the role formerly played by methotrexate and cyclosporine. But can they be combined with biologics?

THE CANCER CONNECTION

Of serious concern for patients who have suppressed immune systems is their increased susceptibility to skin cancer. In a study of a small cohort of rheumatoid arthritis patients taking etanercept, it was thought that soluble TNF-alpha receptor therapy may decrease the mechanisms for controlling tumors through inhibition of a Th1 cytokine pattern and inhibition of cytotoxic effects of TNF-alpha. Several patients who developed squamous cell carcinomas (SCCs) after starting etanercept therapy were reported.[6] Infliximab may also be associated with immunosuppressive sequelae because of its action in blocking TNF-alpha. In fact, one paper reports the development of multiple SCCs and keratoacanthomas in one patient receiving infliximab for rheumatoid arthritis.[7] Despite such reports, a study with a large patient cohort (n=1,442) found no evidence for increased risk of cutaneous SCC in rheumatoid arthritis patients receiving etanercept.[8]

Renal transplant patients given acitretin were evaluated in terms of the development of keratotic skin lesions as well as squamous cell and basal cell carcinomas (BCCs). A total of 44 patients with 10 keratotic skin lesions on the hands and forearms were evaluated in a randomized, double-blind, placebo-controlled study to test whether 30 mg/d of acitretin would prevent the development of skin cancer. It was found that patients treated with acitretin had significantly fewer SCCs and fewer keratotic skin lesions than the placebo group. The effect was most pronounced in patients who had a history of SCCs and BCCs.[9]

Multiple SCCs have been associated with long-term PUVA treatment. A case study published in the *British Journal of Dermatology* reports a psoriatic patient who received 14 years of PUVA photochemotherapy as well as topical coricosteroids. The patient developed a total of 34 SCCs, three of which developed during PUVA treatment and 21 developed during a 16-month period in which the patient received cyclosporine. The patient began treatment with acitretin and in 4 years of continuous therapy (60 mg/day), no new tumors appeared. This report suggests that cyclosporine increases the occurrence of PUVA-induced carcinomas, while acitretin may prevent tumors in patients receiving long-term PUVA.[10]

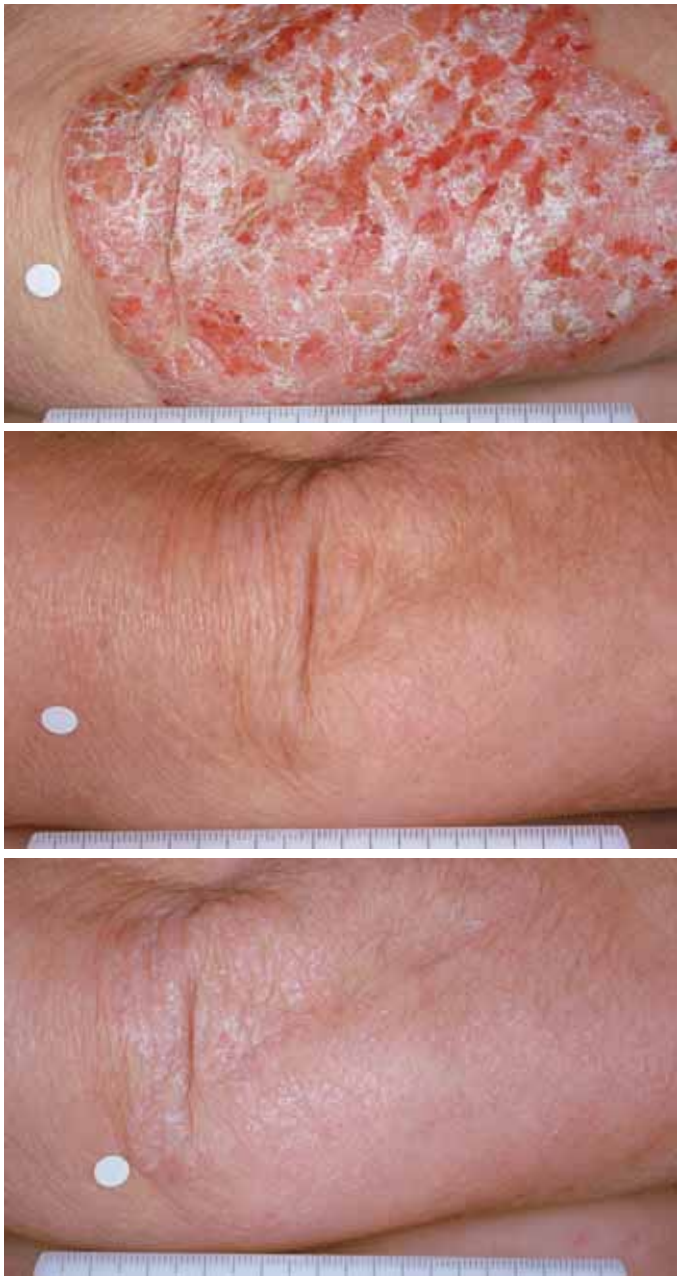


The most common form of psoriasis, occurring in more than 80% of cases, is plaque psoriasis, seen here.

KEEPING AN EYE ON THE IMMUNE SYSTEM

Since both methotrexate or cyclosporine and biologics suppress the immune systems, there is justified concern about the additive immunosuppression in patients, even those in relatively good health. While my experience and that of my colleagues indicates that combined therapy is well tolerated and not particularly dangerous in the short term, it appears prudent to truncate the period of combination therapy as much as possible. Methotrexate, for example, has been used in combination with adalimumab, alefacept, efalizumab, etanercept and inflixmab with no increase in bone marrow or liver toxicity observed. The literature reports successful combination of infliximab and methotrexate in rheumatoid arthritis patients.[11] The guidelines for transitioning from methotrexate to biologics involve starting to taper at around 4 weeks (8 or 12 weeks for alefacept) and tapering the weekly dose of methotrexate by 2.5 mg a week. Based

> “OF SERIOUS CONCERN FOR PATIENTS WHO HAVE SUPPRESSED IMMUNE SYSTEMS IS THEIR INCREASED SUSCEPTIBILITY TO SKIN CANCER.



Representative patient response to a biologic therapy (efalizumab). Researchers concluded that the therapy was well tolerated during the 24 weeks of treatment, with a decline in overall adverse events and lack of acute adverse events during the second course of a 2-week treatment. Top photo: baseline, Middle: week 12, Bottom: week 24. *Photos courtesy of Alan Menter, M.D.*

on the patient's response, that tapering schedule may have to plateau or even ramp back up slightly.

For cyclosporine, the tapering should begin at 4 weeks (8 to 12 weeks for alefacept) by reducing the dosage 50 mg a week. These are general guidelines that must be adjusted according to the patient's clinical response. Cyclosporine has been used in combination with alefacept, efalizumab, etanercept and infliximab with no observed increase in nephrotoxicity or hypertension.

PROCEED WITH CAUTION AND SUCCESS IS YOURS

On the one hand, the advent of biologic agents has given dermatologists new tools in the fight against psoriasis, particularly the recalcitrant psoriasis that had long confounded clinicians. On the other hand, while these drugs may be welcome replacements for more toxic agents, they require finesse in terms of transitioning. For patients, the flares after abrupt discontinuation of methotrexate or cyclosporine can be both uncomfortable and discouraging. Managing a successful transition from methotrexate or cyclosporine to biologics can be successfully accomplished with careful attention on the part of the dermatologist and patients educated to take a longer-range view of therapeutic effect. ■

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MANAGING DIFFICULT PATIENTS

BY EVA RITVO, M.D.

Eva Ritvo, M.D.

About 15% of the general population in the United States meets standard diagnostic criteria for at least one personality disorder as defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV),[1] so it is not surprising that psychological factors are important in up to 30% of patients seeking treatment for dermatologic conditions.[2] In addition, the prevalence of obsessive-compulsive disorder is high among dermatology patients.[3]

Although not all of these patients are "disturbed," those who have underlying psychiatric issues can present a particular challenge to the dermatologists who treat them. Understanding the psychological and psychiatric makeup of our patients, dermatologists can optimize care, avoid disappointments caused by unrealistic expectations, diminish or avoid disruptions to their practice, improve the quality of the working environment for themselves and their staffs and prevent potential litigation.

RECOGNIZING RED FLAGS

"Perfect" patients communicate well. They are educated, grateful, cooperative, pay cash and refer all of their friends. "Difficult" patients, on the other hand, are demanding, never satisfied, harbor unrealistic expectations and may be psychiatrically ill. These patients may be needy, abusive, attention-seeking, demanding, seductive or angry. Following are some red flags that indicate that "difficult" patients may have a more serious psychiatric disorder:

- Their medical history indicates they have had a high number of previous procedures — far more than what seems necessary
- They complain excessively about previous procedures, providers or both
- They have visited numerous other physicians
- They are noncompliant despite their own reports that they need treatment
- They call or visit physicians too frequently
- They request procedures they cannot afford.

MAINTAINING PROFESSIONALISM

When confronted with a potentially difficult patient, you, the dermatologist, should first take a detailed history and listen carefully for complaints about previous procedures and providers. Develop a treatment plan with realistic expectations spelled out clearly to the patient in the form of a written contract. Show patients actual before-and-after photos of other patients who have undergone the same or similar procedures. Finally, include

> WHEN CONFRONTED WITH A POTENTIALLY DIFFICULT PATIENT, DERMATOLOGISTS SHOULD FIRST TAKE A DETAILED HISTORY AND THEN LISTEN CAREFULLY TO WHAT THE PATIENT SAYS FOR COMPLAINTS ABOUT PREVIOUS PROCEDURES AND PROVIDERS.

photos of the patient as part of a thorough documentation program for the suspected difficult patient.

As the patient-physician relationship progresses, be prepared to reckon with your own anger, anxiety, guilt, confusion, depression, sexual arousal or fear. Many psychiatrically disturbed individuals are adept at manipulating others, particularly such "authority figures" as physicians. Be aware of your own coping styles (whether you fight or flee or respond in ways that are competitive, accommodating, compromising, collaborative or humorous) with difficult patients. While you should make efforts to be aware of your emotional responses to difficult patients, it is imperative *not to act on those emotions*.

THINK LIKE A SHRINK

Evaluate difficult patients for psychiatric conditions known to occur in cosmetic patients. Such conditions include body dysmorphic disorder (BDD), self-destructive denial (substance abuse), narcissism and histrionic personality disorder. It is important to remember that these are diseases, not annoying mannerisms that the patient consciously chooses.

■ BDD. Although under-recognized, BDD has been found to occur in about 10% of patients seeking cosmetic surgery and more than 14% who seek dermatologic treatment.[4] Such patients are preoccupied with an imagined defect in their appearance or are excessively concerned over slight physical anomalies. The result is significant clinical distress or even functional impairment.

Although it often begins in adolescence, BDD is usually not diagnosed until the patient is an adult. Its course waxes and wanes; men are as likely to have this condition as women. Patients who have BDD seek reassurance from other people, including physicians.[5] Interestingly, BDD patients consult dermatologists more frequently than any other physician specialists.[6]

Patients who have BDD pick their skin, gaze in mirrors and camouflage themselves with makeup, glasses and hats. They have a higher rate of dissatisfaction with their medical procedures than similar patients who do not have BDD.[7] Consider the following:

Ms. BDD is a 35-year-old single woman whose preoccupation with her looks has impaired her ability to function at her job and in personal relationships. She may be overspending — particularly for cosmetic procedures. (It is not unusual to see such patients who have had as many as 50 previous cosmetic procedures!) Despite her numerous previous procedures, she is unhappy with their results and is eager to try the newest surgery.

For Ms. BDD, the best approach is to make the diagnosis, carefully explain the procedures, establish realistic expectations (in the form of a contract), keep a detailed record (in the form of photos) and refer her to a mental health professional. This referral must be made tactfully so that Ms. BDD does not feel abandoned or stigmatized. Instead, the dermatologist should explain that this step is being undertaken to help her form realistic expectations about the procedure, which, in turn, will increase the probability that she will be satisfied with the results.

Above all, dermatologists should not yield to the sometimes considerable pressure from BDD patients to perform inappropriate procedures.

■ SELF-DESTRUCTIVE DENIAL. Although this is not a formal psychiatric diagnostic category, self-destructive deniers are familiar to most medical professionals as people who abuse drugs and alcohol. They are notoriously noncompliant, behave in outrageous ways, lack insight into their abnormal behavior and are at high risk for complications in cosmetic procedures. Compulsive smokers, sun worshippers and skin pickers are also self-destructive deniers.[8]

As an example, Mr. Martini, a 56-year-old divorced boat captain, presents with Ms. Smith, his 35-year-old exotic dancer companion. Mr. Martini wants a laser procedure to improve his photodamaged skin and droopy eyelids, but he will not comply with postoperative instructions. Ms. Smith wants a botulinum toxin type A (Botox) injection and offers the dermatologist "anything he wants" if she can get some alprazolam (Xanax) and oxycodone (Percocet) for the procedure.

> "MANY PSYCHIATRICALLY DISTURBED INDIVIDUALS ARE ADEPT AT MANIPULATING OTHERS, PARTICULARLY SUCH "AUTHORITY FIGURES" AS PHYSICIANS. DERMATOLOGISTS SHOULD BE AWARE OF THEIR OWN COPING STYLES WITH DIFFICULT PATIENTS.

With patients such as these two, remember the disease model of addiction. The best approach with such patients is setting clear and realistic goals, keeping detailed records and avoiding becoming seduced or manipulated. Above all, avoid performing

Faculty and attendees discuss presentations.

any unnecessary or inappropriate procedures. Even before appropriate procedures are undertaken, it may be advisable to refer such patients to a mental health professional to ensure that they have realistic expectations about the procedure and understand their responsibilities in compliance.

■ NARCISSISTIC PERSONALITY DISORDER. Narcissistic patients can challenge dermatologists by displaying pervasive patterns of grandiosity, a constant need for admiration and a profound lack of empathy. Narcissists are often preoccupied with fantasies of personal beauty while paradoxically having fragile self esteem. They are often dissatisfied, even to the point of rage, with the results of their cosmetic procedures, yet they may return again and again for more treatments.

The most successful approach to narcissistic patients is to help them restore control over their situation by overt reassurance and by letting them know that you are "on their side" and are working hard to achieve the same mutual objectives. With narcissistic patients, it may be useful to enlist the help of family members to keep the patient reassured that everyone is working toward the same goals. As with other personality types, be prepared to address the unreasonable expectations of these patients and to set limits on their behavior.

Ms. VIP, for example, is a 45-year-old divorced attorney who wants an appointment right away because her botulinum toxin type A "is wearing off." She approaches you by telling you that "you're the best" and that all other doctors are terrible. In the office, she acts rudely and yells at the staff. She is quick to point out a bruise another dermatologist allegedly caused and a spot he missed.

Help patients such as Ms. VIP restore their sense of control and acknowledge that they have a right to good health care. It is counterproductive to attack these patients or to disparage their feelings. If family members or staff become involved, set realistic expectations and limits on behavior. If the patient still cannot be convinced that all of the parties are on the same team and have her best interests as their mutual objective, then the patient should be referred to a mental health professional with documentation of every detail that led to that decision.

■ HISTRIONIC PERSONALITY DISORDER. Patients who have histrionic personalities are similar to narcissistic patients, but are less challenging to dermatologists. They display excessive emotionality, attention-seeking behavior, sexually seductive tendencies and rapidly shifting emotions. They are preoccupied with their physical appearance because they use it to draw attention to themselves. Histrionic patients may also address physicians by their first names and act overly familiar, even on first meeting.

As in patients who have other personality disorders, explain procedural expectations explicitly to these types of patients, carefully document treatment and take photographs.

Consider Mr. TV, a charming, attractive, 42-year-old TV anchor concerned about the age-related changes around his eyes. Believing that his coworkers are talking about him behind his back,

he may never be satisfied with any cosmetic procedure results. The best approach with Mr. TV is to make the diagnosis, communicate clearly with him, help him to set realistic expectations, keep detailed records and be prepared for his many mood shifts.

STRATEGIES TO HELP YOU COPE

Although collaborative physician-patient relationships are important, it is crucial for you, the dermatologist, to maintain authority over demanding, manipulative and sometimes emotionally charged patients. Never compromise patient care just to keep the peace. Evaluating patients for behavioral disorder clears the way for developing viable, effective and ethical techniques for patient management.

Use the following general guidelines to help you cope with all types of difficult patients:

- *The 24-hour rule.* When a patient appears upset or angry, do not react immediately. If medically possible, postpone any action for at least 24 hours so all parties have a chance to calm down and gain perspective.
- *Staff support.* Office staff members may be skillful in working with patients who are angry or upset. Use your staff to help diffuse tension.
- *Self care.* Dermatologists have personal lives too. Diet, exercise and a reasonable workload are good tools for managing stress. Just as patients must have realistic expectations about what dermatologists can do for them, you must set realistic limits for what you can do for your patients. Psychotherapy can prove useful for dermatologists who are in difficult situations or are dealing with particularly troublesome patients.
- *The patient is always right.* It is counterproductive to berate, belittle or minimize the feelings of patients, even if the patients could be called difficult or unreasonable. Many difficult patients can be managed appropriately with the right techniques. Those who cannot be managed despite the right techniques should be referred with dignity and respect to a mental health professional or other suitable physician.
- *Communication.* Take a detailed patient history for suspected difficult patients and learn more about the mental disorders that are common in cosmetic patients. You should seek to collaborate with local mental health colleagues to form a proper referral network and to help such patients form realistic expectations about dermatological procedures. Although time-consuming and sometimes tedious, you should be diligent about taking photographs and documenting all interactions with your most difficult patients.

HELP THEM BY HELPING YOURSELF

Patients who have personality disorders or other known mental health conditions frequently seek out dermatologic treatment (and sometimes for the wrong reasons). They present special challenges to dermatologists who may at first dismiss them as "difficult patients." Failing to see the special needs of these patients exposes you to potential risks, such as succumbing to pressure from the patient to perform inappropriate procedures, allowing the difficult patient to poison his or her working environment or being vulnerable to lawsuits. Personality disorders are a disease, not annoying habits, and such patients deserve respect and care.

> "EVALUATING PATIENTS FOR BEHAVIORAL DISORDER CLEARS THE WAY FOR DEVELOPING VIABLE, EFFECTIVE AND ETHICAL TECHNIQUES FOR PATIENT MANAGEMENT.

You can help such patients by setting realistic expectations for the dermatological procedure and by thoroughly documenting all interactions. In some cases, you may have to set firm and specific limitations on a patient's behavior (e.g., not shouting at the staff). With basic strategies that allow you to "think like a shrink," many so-called difficult patients can get the care they need without becoming a drain or a danger to your practice. ■

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A REVIEW OF CURRENT THERAPIES FOR PIGMENTARY DISORDERS

BY PEARL GRIMES, M.D.

Pearl Grimes, M.D.

Throughout history, pigmentary disorders (although not exactly debilitating) have had devastating effects on patients. Vitiligo, for instance, is associated with a high rate of psychiatric morbidity.[1] Unfortunately, the mechanisms of hypopigmentation and hyperpigmentation are not clearly understood and challenge dermatologists. This article will discuss some current therapies available for treating such disorders.

TREATING HYPOPIGMENTARY DISORDERS

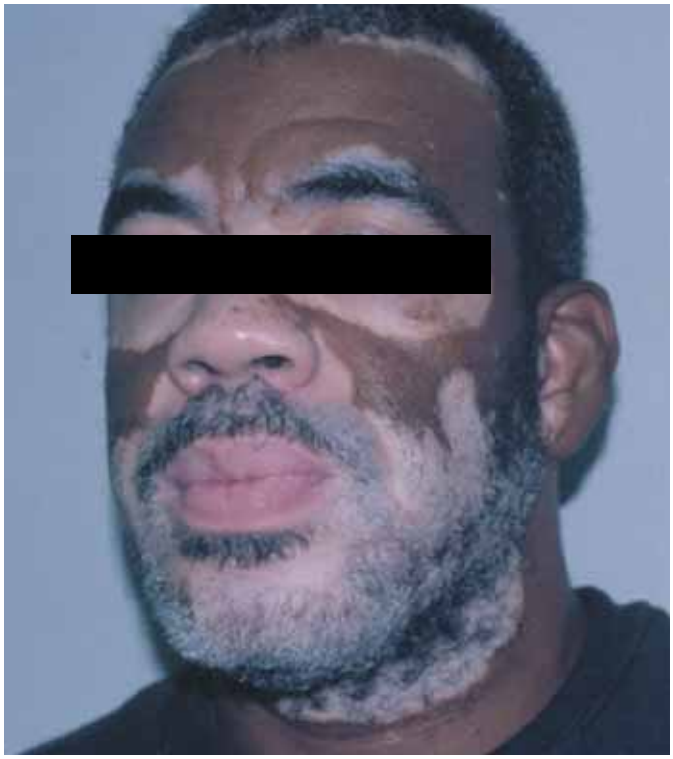
In the hierarchy of treatment options for hypopigmentary disorders such as vitiligo are topical immunomodulators such as tacrolimus (Protopic). A number of studies have also suggested that ultraviolet B (UVB) phototherapy treatments may be effective in treating this condition and targeted UVB phototherapy using xenon-chloride lasers or monochromatic excimer light is also recommended.[2] In attempting to evaluate the growing body of literature on therapies for vitiligo, we find a lack of standardization of protocol methodologies to quantify severity of disease or to assess repigmentation responses to various treatments.

> “THE EXISTENCE OF THE VITILIGO AREA SCORING INDEX (VASI) SCORE IS AN IMPORTANT CLINICAL TOOL FOR FUTURE STUDIES ASSESSING REPIGMENTATION BEYOND NARROW-BAND ULTRAVIOLET B PHOTOTHERAPY.

■ PHOTOTHERAPY. A recent paper reported a controlled study of vitiligo patients treated with narrow-band UVB phototherapy. One of the most important aspects of this paper was the creation of the Vitiligo Area Scoring Index (VASI), which obtains a standardized score for grading pigmentation. A variety of different methods have been used to assess repigmentation, but this new VASI system may allow us to standardize the grading of repigmentation. For the purposes of the paper, the VASI score was a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within the patches over time. In this particular study, patients treated with phototherapy reported a 42% mean repigmentation ($p<0.001$).[3] The existence of the VASI score is an important clinical tool for future studies assessing repigmentation beyond narrow-band (NB)-UVB phototherapy.

Since Westerhof first published his study on the use of NB-UVB phototherapy in the treatment of patients with vitiligo over more than 15% of their body surface area, subsequent studies have only reinforced his conclusions that NB-UVB phototherapy is an important therapy in a subset of vitiligo patients.[4]

In Asia, 60 vitiligo patients were treated with NB-UVB phototherapy twice a week, and 42% of the population achieved greater than 50% repigmentation during the study. In my own practice, 95 patients from diverse racial backgrounds were treated with NB-UVB. Patients were stratified into two groups. The first group had more than 15 treatments, while the second group had more than 50 treatments. A total of 36% of the patients in the first group (fewer treatments) achieved 50% or more repig-



Vitiligo in African-American patient with significant mask-like depigmentation. *Photo courtesy of Amy McMichael, M.D.*

study, biopsies were performed of lesional, perilesional and normal skin, and investigators assessed cytokine levels. Vitiligo is associated with an increased production of several cytokines including tumor necrosis factor-alpha (TNF-alpha), interferon-gamma and IL-10. Because tacrolimus and other similar immunomodulators work by suppressing the production of pro-inflammatory cytokines, the rationale exists that tacrolimus or similar immunomodulators might benefit vitiligo patients.

■ THE ROLE OF IMMUNOMODULATORS. The use of tacrolimus ointment in an uncontrolled study involving a small cohort of vitiligo patients reported excellent repigmentation results.[5] Other studies are also reporting the safety and efficacy of both the 0.03% and 0.1% tacrolimus ointments as a repigmenting agent in treating vitiligo. Since that first uncontrolled study, an expanded study was conducted, the results of which align with other recently published studies supporting the efficacy of tacrolimus in vitiligo patients. A subsequent 24-week study by Grimes et al. in 19 patients reported that 68% of the patients had 75% to 100% repigmentation for the face and neck areas. There was some repigmentation of the trunk and upper and lower extremities, but the best results were obtained in the face and neck region.[6] In terms of cytokine production, TNF-alpha decreased significantly after 6 months of tacrolimus therapy, suggesting that aberrant cytokines do play a role in repigmentation.

mentation, while 51% of the second group had such results. This suggests the cumulative benefit of NB-UVB treatment, which has been suggested anecdotally as well as in other studies.

NB-UVB is of great interest today, and comparisons of it versus psoralen and long-wave UV radiation (PUVA) phototherapeutic treatments show that they yield similar results. Many dermatologists consider NB-UVB an easier treatment option for patients. With no systemic side effects, no post-treatment requirements, and its excellent safety profile in both adults and pediatric patients, NB-UVB phototherapy is gaining in popularity. However, maximal efficacy is not usually achieved unless the patient submits to three treatments each week (and data on long-term effects of NB-UVB are not available). This is definitely an area that warrants further study.

> BECAUSE TACROLIMUS AND OTHER SIMILAR IMMUNOMODULATORS WORK BY SUPPRESSING THE PRODUCTION OF PRO-INFLAMMATORY CYTOKINES, THE RATIONALE EXITS THAT TACROLIMUS OR SIMILAR IMMUNOMODULATORS MIGHT BENEFIT VITILIGO PATIENTS.

New data provide evidence that there are many cell-mediated immunological abnormalities in vitiligo patients, which suggests that an immunomodulator might be an effective agent. In one

If the ambient increase in cytokine production can be suppressed, it creates a favorable milieu for repigmentation.

An 8-week pediatric study by Lepe et al. treated two symmetrical lesions, comparing the efficacy of tacrolimus to clobetasol (Temovate) in 20 children. Mean repigmentation for tacrolimus was 41%, but clobetasol performed better at 49%. This raises the obvious question: Is tacrolimus really superior to topical steroids? In 1998, Njoo et al. published a meta-analysis of multiple treatments of vitiligo including topical steroids. They found that roughly 60% of topical steroid patients achieved greater than

75% repigmentation.[7] In more recent tacrolimus studies, repigmentation rates were not as high, which again raises the question as to whether it is truly the superior agent for vitiligo patients. On the other hand, there are some strong points favoring tacrolimus over other topical agents. Melanocytes are slow-growing cells, so vitiligo patients require a therapy that is safe and effective over the long term. Topical steroids are not as well-tolerated in this situation because of the likelihood of telangiectasias, skin atrophy and other steroid-related side effects. However, given the recent black box label for the topical immunomodulators tacrolimus and pimecrolimus (Elidel), these agents are used in a rotational algorithm with topical steroids.

■ TARGETED LIGHT THERAPY. Targeted light therapy applies high-intensity light to localized affected areas, which helps decrease cumulative UV exposure. A combination therapy of excimer laser and tacrolimus 0.1% ointment was shown to be highly effective in a randomized, prospective, intra-individual, right-left comparison study of 43 lesions in a total of 14 vitiligo patients. Group A received combination therapy, while Group B received excimer laser monotherapy. For each treated lesion, the untreated lesion on the opposite side acted as the control. Repigmentation was observed in 69% of all Group A (combination) lesions and in 20% of Group B (laser monotherapy). These investigators concluded that combination therapy was superior to excimer laser monotherapy and was well-tolerated by patients.[8]

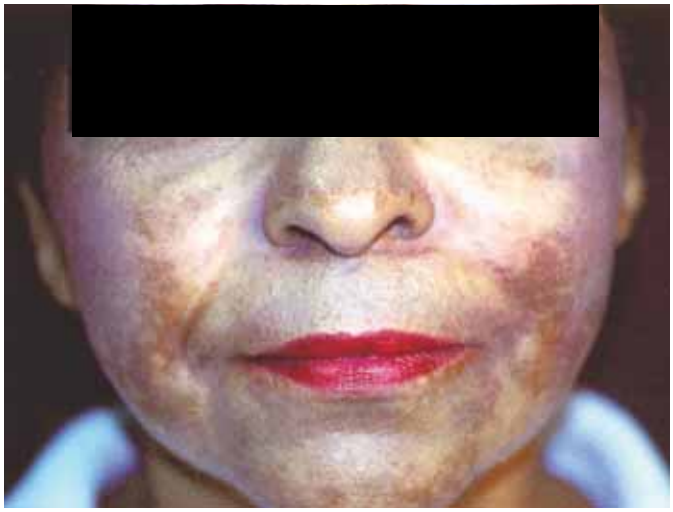
TREATING HYPERPIGMENTARY DISORDERS

Melasma is a common form of hyperpigmentation and numerous effective agents are available on the market to treat it, although most dermatologists agree that this condition can prove difficult to treat. One of the largest studies of melasma involved a patient population of 1,290 individuals from a wide variety of racial backgrounds. This open-label, multi-center study looked at a treatment of fluocinolone acetonide 0.01%, hydroquinone 4.0% and tretinoin 0.05% in a hydrophilic cream formulation (Tri-Luma) with safety and efficacy evaluated at 4 and 6 weeks. This agent significantly improved melasma at 4 weeks with further improvement at 8 weeks in all races, ethnicities and Fitzpatrick skin types. Moreover, the incidence of atrophy in that group of patients was zero and the incidence of telangiectasias was 4%.[9]

Recent studies have demonstrated the value of some of the other agents available for treating melasma and clearly, there are several viable combination agents that are safe, effective and well-tolerated. In my practice, significant efficacy can be achieved in melasma patients using combination agents such as the triple combination bleaching formula, hydroquinone combination formulations containing retinol, and those containing glycolic acid.

Many exciting new therapeutic options lie on the horizon for hyperpigmentation and it behooves us to stay educated on what's new. Resurfacing procedures, such as microdermabrasion, chemical peels and intense pulsed light can further enhance the effects of topical bleaching agents. Resurfacing procedures can enhance epidermal turnover, decrease epidermal melanin and cause disruption of melanin granules. Ablative approaches can worsen hyperpigmentation and should be used with caution.

The best and newest approaches to these ancient pigment disorders have been and continue to be combination therapies. Topical agents come first, and resurfacing procedures can indeed enhance their effectiveness. ■



This patient has diffuse melasma.
Photo courtesy of Leslie Baumann, M.D.

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NEW APPROACHES AND ISSUES IN ACNE TREATMENT

BY GUY WEBSTER, M.D., PH.D.

Guy Webster, M.D., Ph.D.

Although acne is one of the most common conditions treated by dermatologists today, there is not one common treatment that works well in all patients. Response varies widely among patients, and many patients are more effectively treated with combination therapy. New drugs and drug-delivery systems that can assist in treating previously drug-recalcitrant patients have recently been introduced. Physical modalities, such as blue light and pulsed dye laser, are gaining interest as alternative treatments. We understand acne today better than ever, and with that knowledge comes some new questions.

HOW CAN WE MINIMIZE IRRITATION WITH RETINOID USE?

Drugs have always been a mainstay in the clinical management of acne, and new drugs in the pipeline include higher-strength topical retinoids. Retinoids are chemical analogs of vitamin A and have been used in the treatment of acne for decades. In 1987, the discovery of nuclear retinoid receptors led to a new class of retinoids that include molecules to bind to and activate these receptors. Among these receptor-selective topical retinoids are such new drugs as adapalene (Differin), tazarotene (Tazorac) and tretinoin (Retin-A). When using topical retinoids, one issue has been to minimize cutaneous irritation without sacrificing efficacy. New vehicle systems, such as tazarotene gel and tretinoin (in both gel and cream formulations) have been developed to address this point.

Dapsone (DDS), a sulphone antibiotic agent, is actually an old drug used to treat Hansen's disease, inflammatory dermatoses and acne. It has resurfaced as a potential new therapeutic agent in topical form and excellent results have been reported in one study using topical dapsone in the treatment of acne inversa.[1]

Combination approaches (clindamycin gel [Cleocin T] with a topical retinoid such as tretinoin) have shown promise. Clindamycin foam (Evoclin) has met with favorable response in the clinical community, partly because this delivery system may improve patient compliance. One, as yet unpublished, study has found that clindamycin foam decreased acne lesions to a greater extent than clindamycin gel and both performed better than a vehicle foam or gel.

When using topical retinoids to treat acne, it is important to counsel patients to be patient, because treatment is best measured over months. Topical retinoids work by inhibiting the formation of microcomedo, which is the precursor of all pimples. Topical retinoids can be a good, long-term maintenance prescription.

To optimize acne therapy, it is important to consider complementary regimens that address more than one mechanism of the acne. Some of the most effective combinations are: retinoid + benzoyl peroxide/clindamycin, retinoid + anti-androgen and retinoid + doxycycline or minocycline.

WHAT ARE THE RISKS OF ANTIBIOTIC USE?

Antibiotics have been and will doubtlessly continue to be used in treating acne. It is known that *Propionibacterium acnes* is the target of the inflammatory response in acne. Antibiotics work both by dampening the inflammatory response and by suppressing *P. acnes*. It is known that *P. acnes* stimulates cytokine production in the host, and these cytokines, including interleukin, may stimulate comedogenesis. A current theory holds that reducing *P.acnes* would reduce comedones, in that it would eliminate or at least reduce the production of interleukin. Using sub-antimicrobial doses of antibiotics, in this case doxycycline hyclate 20 mg (Periostat) compared to placebo, doxycycline was shown to significantly reduce comedo counts at 2-, 4- and 6-month follow-up visits ($p<0.01$).[2]

No drug is without its risks, and antibiotics for acne, though generally recognized as safe, can cause certain side effects including dose-dependent phototoxicity, gastrointestinal disturbances and dizziness. In rare cases, antibiotic use has been associated with skin pigmentation, hypersensitivity and pseudotumor.

The most alarming association in the news lately with antibiotics is the possible link between antibiotic use and breast cancer.

A recent study on the possible association of long-term antibiotic use and breast cancer found that antibiotic agents were associated with increased risk of incident and fatal breast cancer, but it was not clear whether this was a causal relationship or whether other factors (such as a compromised immune system or indication for use) came into play. The risk was proportional to the duration of antibiotic use. Further, the study found that tetracycline (Achromycin V, Panmycin) and a macrolide increased the risk if they were used for respiratory infections or skin disease.[3] While far from conclusive, these findings prompted concern from the clinical community and raised fears in patients who learned about this association. This particular study did not provide a control for chronic infection or predisposition to infection as risk factors. At most, this paper points to the need for further investigation. Of greater concern to most practicing dermatologists is the issue of antibiotic resistance.

DEALING WITH RESISTANCE

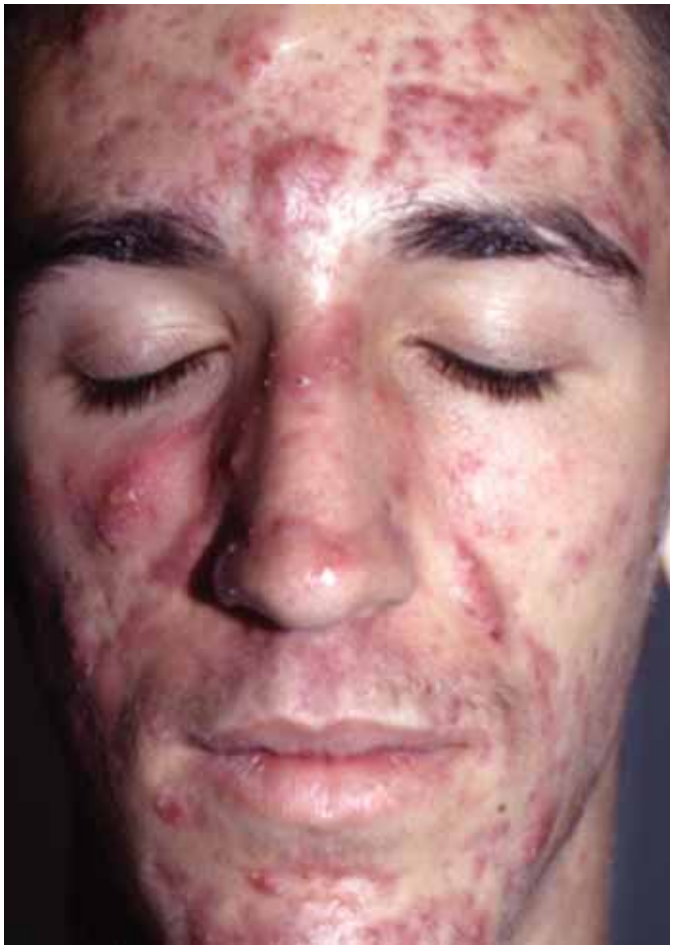
First reported in the early 1980s with the introduction of topical erythromycin, it appears that acne responds to antibiotic treatment in proportion to the degree of antibiotic resistance in the patient.[4] Antibiotic-resistant propionibacteria are being frequently isolated in patients receiving antibiotics for acne. Macrolide resistance is the greatest, but tetracycline resistance also occurs. Among the tetracycline family, minocycline is the least likely to induce resistance.[5]

It has been shown that antibiotic therapy for acne patients is associated with colonization of *Streptococcus pyogenes.* Another recent study evaluated 105 patients, of which about half (n=42) were using oral or topical antibiotics to treat acne. Of the control group not taking antibiotics, about 10% had a positive *S. pyogenes* culture in their oropharynx. In the antibiotic group, 33% had a positive *S. pyogenes* culture (p=.003). This same association was not found to exist with *Staphylococcus aureus.*[6]

Some general guidelines exist that help to minimize the induction of antibiotic resistance in acne patients. Full-dose therapy should be used only for a limited time. Benzoyl peroxide should be included with topical antibiotic regiment. Topical retinoids should be started early in therapy because they will allow antibiotic withdrawal in many patients. In general, the goal should be to maximize the benefits of antibiotic therapy while limiting the time span of the actual course of treatment.

KNOW THE BASICS

Patient compliance enhances therapeutic efficacy, so promoting compliance can improve results. Elegant delivery vehicles, convenient application schedules and patient education are all valuable in this respect. In some severe cases, it may be useful to add additional drugs, such as sulfacetamides, metronidazole, benzoyl peroxide washes, hormonal therapy (such as oral contraceptives) or spironolactone (Aldactone). In the not uncommon cases where rosacea or seborrheic dermatosis is also involved with the acne, it is important to recognize their contribution and treat them appropriately. ■



SEVERE ACNE. Acne cysts and nodules (large, tender and sometimes fluid-filled bumps). Scarring can occur.
Photo courtesy of Diane Thiboutot, M.D.

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STRATEGIES FOR MANAGING ROSACEA

BY GUY WEBSTER, M.D., PH.D.

Guy Webster, M.D., Ph.D.

Rosacea is a complex and multiphasic disease that requires a broad-based management strategy and specific treatments, which can vary by phase and manifestation.[1] A rational treatment program must be based on the causes of the disease, and even today, the mechanisms of rosacea are not well understood.[2] Just a few years ago, it was believed that the *Helicobacter pylori* bacterium was involved in rosacea[3] and the gastrointestinal disturbances common to this type of infection were frequently observed in rosacea patients. Other findings note that while there may indeed be an association between *H. pylori* and rosacea[4], it is not a causal relationship,[5] which is something many dermatologists suspected based on anecdotal evidence. It may be that the drugs that treat *H. pylori* are efficient therapy for treating rosacea, while the conditions are not otherwise connected.

A similar relationship exists between rosacea and *Demodex folliculorum,* a nonpathogenic parasite that has been implicated as a causative agent in some dermatological eruptions, including rosacea.[6] One Chinese study found that more than 74% of a total cohort of 260 rosacea patients were infected with *Demodex,*[7] but this parasite is common even in people who do not have rosacea. Treating *Demodex* with benzene hexachloride, or lindane, produces only modest results. At most, *Demodex* appears to be a cofactor in papulopustular stage rosacea.[8]

TACKLING THE DIFFICULT DISEASE

The differing phenotypes of rosacea and their subtypes suggest that rosacea may have differing etiologies in different patients. The familiar blushing and flushing of rosacea involves the vascular component of the condition. Wilkin et al. showed that rosacea patients blush longer and faster when drinking warm liquids than people who do not have rosacea,[9] so there is obviously a physiologic basis to the blushing that is not fully understood. There is some evidence that sebaceous hyperplasia and rhinophyma are caused by a neural stimulus. It could be argued that all of the signs of rosacea trace back to an inflammatory process,[10] but the causative agents of the various kinds of specifically inflammatory rosacea (papulopustular, periocular, ocular, and perioral) remain unclear.

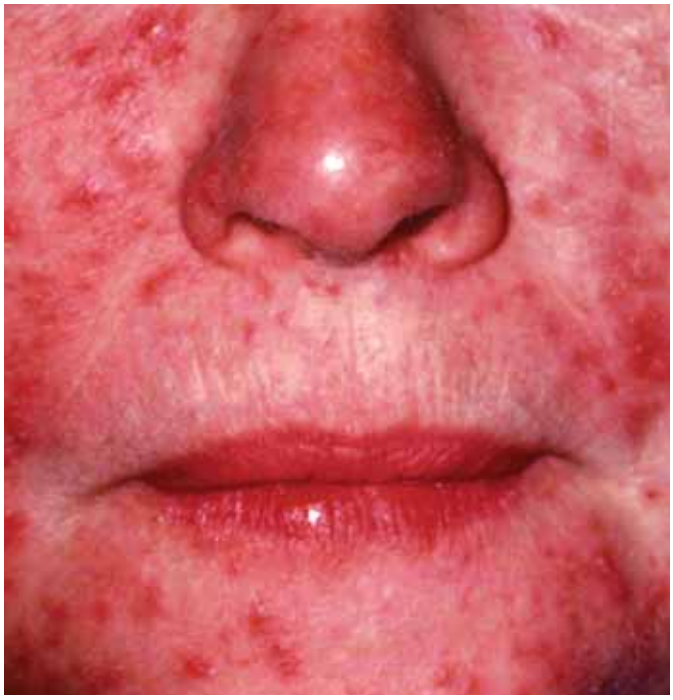
The treatment of rosacea can be complicated, simply because the condition is complex and involves some unknown factors. Etiology may vary by patient; it is certainly clear to dermatologists that patients respond differently to treatments. Most dermatologists develop a pragmatic prescribing approach to rosacea, working less with the limited (and sometimes even contradictory) empiric evidence and more with intuition and experience. It is no wonder that rosacea is one of the conditions that

> “MOST DERMATOLOGISTS DEVELOP A PRAGMATIC PRESCRIBING APPROACH TO ROSACEA, WORKING LESS WITH THE LIMITED (AND SOMETIMES EVEN CONTRADICTORY) EMPIRIC EVIDENCE AND MORE WITH INTUITION AND EXPERIENCE.

we most frequently manage with off-label prescriptions.[11] The most common agents prescribed in the treatment of rosacea appear to be metronidazole (Flagyl, Protostat), azelaic acid (Azelex, Finacea), topical immunomodulators, brand name drugs such as BenzaClin (benzoyl peroxide, clindamycin) and Duac (clindamycin, 1%-benzoyl peroxide, 5%), Retin-A (tretinoin) and topical antibiotics as well as oral antibiotics, such as tetracycline, even in sub-antimicrobial dosage.[12] To a lesser extent, macrolydes may be somewhat effective in certain patients.

DEALING WITH TWO CONDITIONS AT ONCE

The pathogenesis of acne and rosacea suggest that some treatment modalities may address both conditions.[13] Studies of the effects of tetracyclines on neutrophil function found that neutrophils were less active and inflammatory response inhibited, even at low doses. In fact, sub-antimicrobial doses of doxycycline hyclate (Periostat) have been shown effective in the treatment of acne and rosacea,[14] in that there remains an anti-inflammatory effect even if there is not an antibacterial effect. Ciprofloxacin (Cipro) and sulfamethoxazole-trimethoprim (Bactrim) are brand name agents that can work in certain patients. While isotretinoin (Accutane) can be highly effective in some patients with forms of nodular rosacea, its use should be restricted for acne treatment (rather than for rosacea treatment).[15]



ROSACEA. An example of subtype 2 rosacea or papulopustular rosacea. Persistent facial redness with bumps or pimples. *Photo courtesy of the National Rosacea Society.*

Acne rosacea with classic-looking red bumps not involving comedones in the center of the face responds well to metronidazole and azelaic acid. A subset of patients who experienced acne in their teens will present as young adults with complaints of acne, but in actuality, they will have old acne scars and new rosacea. Reducing *Propionibacterium acnes* using benzoyl peroxide and clindamycin is effective in this particular population, although results are less pronounced in other patients. Sulfacetamide-sulfur (Avor, Clenia, Plexion, Rosac, Rosanil, Rosula, Sulfacet-R, Klaron and Ovace), an old standby in the armamentarium against rosacea, is somewhat effective in a broad population of patients.

> “IT HAS BEEN OBSERVED THAT ROSACEA SOMETIMES OCCURS TOGETHER WITH ANOTHER SKIN CONDITION, WHICH CONFOUNDS ROSACEA TREATMENT STRATEGIES.

It has been observed that rosacea sometimes occurs together with another skin condition, which confounds rosacea treatment strategies. In many such cases, even if the rosacea is the dominant and more visible condition, treating the rosacea in isolation is ineffective. For instance, if a patient presents with mild atopic dermatitis and more severe rosacea, metronidzole and azelaic acid for the rosacea do not work as well as pimecrolimus (Elidel) and tacrolimus (Protopic). Yet pimecrolimus and tacrolimus would not be as effective in those patients who have acne-like rosacea. Thus, even in patients who appear more bothered by rosacea than by a sub-dermatologic or atopic condition, it appears that the co-condition worsens the rosacea and must be treated first, even when that co-condition appears relatively minor.

WHEN A STEROID IS THE CULPRIT

Steroid rosacea is increasing in prevalence, simply because exposure to steroids is rising, often in ways we don't anticipate. Many prescription-only steroid creams and ointments are more readily available over-the-counter than you would think, whether you shop in ethnic stores in the United States or overseas. One indicator of steroid-induced rosacea is the presence of rosacea under the nose or an atrophic lip. In my experience, the best treatment for steroid rosacea is to discontinue all steroids rather than to taper off them. Pimecrolimus, tacrolimus, doxycycline or minocycline should replace the steroids after advising patients that a difficult few months' transition period may lie ahead before the new drugs work. One study found that tacrolimus 0.075% ointment was effective in treating steroid rosacea.[16] (This applies to steroid-induced periocular rosacea as well.[17])

"AS DERMATOLOGISTS, IT IS IMPORTANT FOR US TO CONTINUE TO EXPLORE AND REPORT THE VARIOUS TREATMENT OPTIONS WE FIND IN HELPING THE MILLIONS OF ROSACEA PATIENTS.

DEALING WITH EYE INVOLVEMENT

Ocular rosacea is a common but underdiagnosed condition that is probably more often seen by ophthalmologists than by dermatologists. One study found ocular signs relating to patients who had diagnosed acne rosacea included lid, conjunctival, corneal, episcleral and scleral manifestations.[18] Lid disease-related manifestations of rosacea are the most common, but patients tend to present at eye clinics rather than at dermatology offices. Some rosacea patients are so used to their eye problems that they no longer notice them. Thus, it is recommended to examine the conjunctiva and meibomian glands of all rosacea patients to ascertain the presence of scars or an active sty. Such patients often respond favorably to doxycycline and report they had no idea they even had an eye problem until their facial problem was successfully treated.

THE FUTURE OF ROSACEA TREATMENT

Although our knowledge of rosacea and our treatment options have never been greater, there is still much we need to learn to treat rosacea effectively. It is a complicated condition, probably involving multiple etiologies, and occasionally confounded by the presence of seemingly minor co-conditions. It is already clear that a generic treatment paradigm for a disease as complex as rosacea does not now and may never exist. But as dermatologists, it is important for us to continue to explore and report the various treatment options we find in helping the millions of rosacea patients. ■

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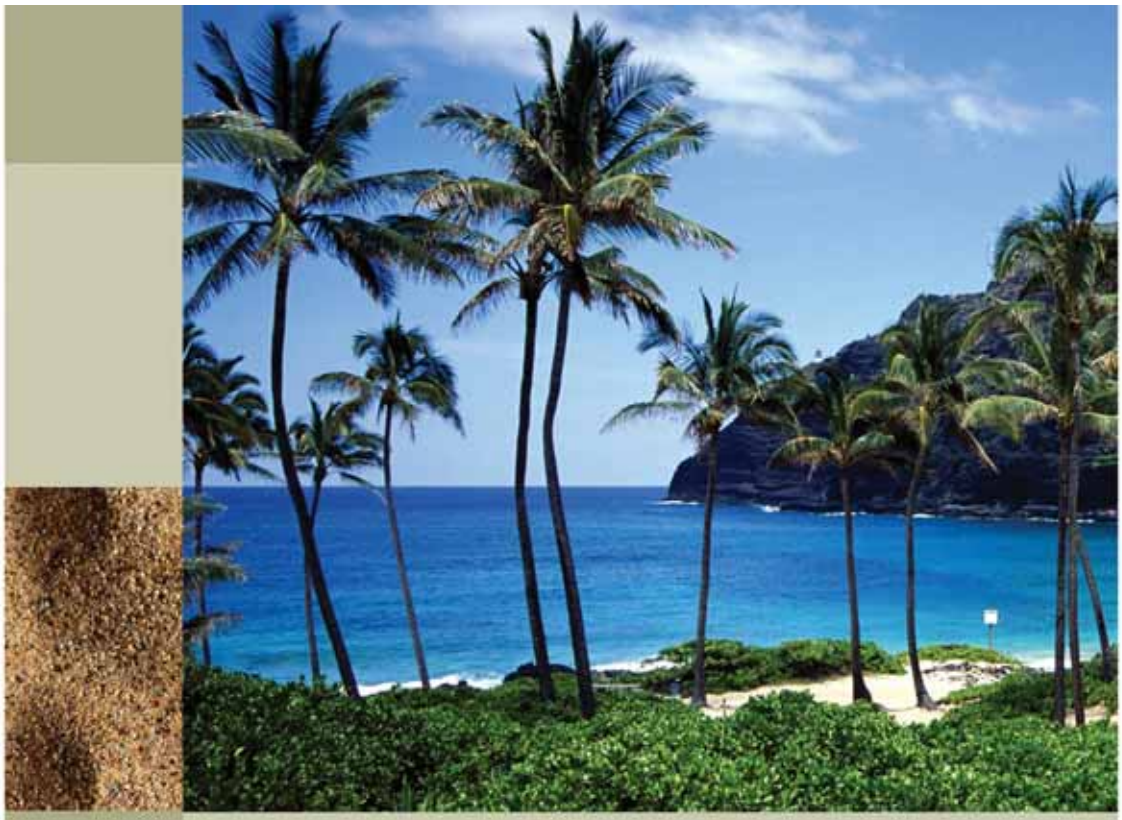

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