



A SUPPLEMENT TO

Skin & Allergy News®



Skin Disease
Education
Foundation



Produced in
affiliation with the
29th Annual Hawaii
Dermatology Seminar

Contemporary Treatment Approaches to Acne and Psoriasis

Managing Acne in Adult Women

**New Developments in Therapy
for Acne Vulgaris: A Preview**

**The Role of Oral Retinoid
Treatment for Psoriasis
in the Age of Biologics**

**Advances in Combination
Topical Therapy for Psoriasis**

FACULTY

Diane S. Berson, MD

Weill Medical College of Cornell University
New York, N.Y.

Linda F. Stein Gold, MD

Henry Ford Health System
West Bloomfield, Mich.

John Y. M. Koo, MD

Psoriasis Treatment Center
University of California at San Francisco

Lee T. Zane, MD

University of California at San Francisco

President, Elsevier/IMNG
Alan J. Imhoff

Vice President,
Medical Education
& Business Development
Sylvia H. Reitman, MBA

Program Manager,
Medical Education
Margo Ullmann

Clinical Editor
Joanne M. Still

National Account Manager
Cheryl J. Gromann

Graphic Design
Lehner & Whyte, Inc.

Publication Manager
Judi Sheffer

The articles contained within this supplement are based on clinical dialogues held with the faculty. This supplement is produced in affiliation with the Skin Disease Education Foundation's 29th Annual Hawaii Dermatology Seminar, a continuing medical education program held March 18-24 2005, in Maui, Hawaii.

This educational supplement to SKIN & ALLERGY NEWS, designated by the American Academy of Dermatology (AAD) for AAD CME credit, was supported by an unrestricted educational grant from



connetics®

It was produced by the medical education department of International Medical News Group. Neither the Editor of SKIN & ALLERGY NEWS, the Editorial Advisory Board, nor the reporting staff reviewed or contributed to its contents. The opinions expressed in this supplement are those of the faculty and do not necessarily reflect the views of the supporter or the Publisher.

Copyright © 2005 Elsevier Inc. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without prior written permission of the Publisher. Elsevier Inc. will not assume responsibility for damages, loss, or claims of any kind arising from or related to the information contained in this publication, including any claims related to the products, drugs, or services mentioned herein.

Photos on pages 7 and 9 courtesy of the Derm Education Foundation, NFP (www.derm.md).



**INTERNATIONAL
MEDICAL NEWS
GROUP**

Contemporary Treatment Approaches to Acne and Psoriasis

Managing Acne in Adult Women

Diane S. Berson, MD

3

New Developments in Therapy for Acne Vulgaris: A Preview

Lee T. Zane, MD

5

The Role of Oral Retinoid Treatment for Psoriasis in the Age of Biologics

John Y. M. Koo, MD

7

Advances in Combination Topical Therapy for Psoriasis

Linda F. Stein Gold, MD

9

CME Post-Test and Evaluation

12

FACULTY

Diane S. Berson, MD

Assistant Professor of Dermatology
Weill Medical College of Cornell University
New York, N.Y.

Linda F. Stein Gold, MD

Director of Dermatology Research
Henry Ford Health System
West Bloomfield, Mich.

John Y. M. Koo, MD

Professor and Vice Chairman
Department of Dermatology
Psoriasis Treatment Center
University of California at San Francisco

Lee T. Zane, MD

Clinical Instructor
Department of Dermatology
University of California at San Francisco

CME RECOGNITION

The SKIN & ALLERGY NEWS supplement "Contemporary Treatment Approaches to Acne and Psoriasis" is recognized by the American Academy of Dermatology for 1 hour of AAD Category 1 CME credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.

Term of approval: February 2005-January 31, 2006

Estimated time to complete this educational activity: 1 hour.

TARGET AUDIENCE

This activity has been developed for dermatologists and other health care professionals involved in the treatment of acne in adult women and/or psoriasis.

EDUCATIONAL NEEDS

Acne in adult women and mild to moderate psoriasis are common conditions seen in dermatologic practices. In acne, clinicians can anticipate advances in technologies (such as new photodynamic techniques), new drugs and drug classes (including retinoic acid metabolism blocking agents, or RAMBAs), and novel drug delivery systems (such as foam vehicle for clindamycin). In psoriasis, combination therapies offer renewed hope for both patients and clinicians: oral retinoids plus other topical and/or systemic treatments for patients with moderate to severe disease, and, for those with mild to moderate disease, combinations of calcipotriene and tazarotene with corticosteroids offer enhanced efficacy in topical treatment. Improved vehicles in the topical category also offer improved efficacy, convenience, and comfort, and, therefore, are likely to improve patient compliance. Clinicians must be informed about these developments that will help them to meet the treatment challenges presented by patients with acne and psoriasis.

LEARNING OBJECTIVES

By reading and studying this activity, participants should be able to:

- Discuss the role that oral retinoids play in the treatment of patients with moderate to severe psoriasis.
- Describe how the range of systemic psoriasis treatment options (eg, cyclosporine, oral retinoids, and the biologic agents) may be used in combination or sequentially to optimize therapeutic response and long-term management in patients with moderate to severe psoriasis.
- List and describe the new and investigative topical combination treatments for psoriasis and describe their mechanism of action.
- Explain the characteristics of acne in adult women, and list the treatment options that are currently available.
- Discuss the treatments for acne vulgaris that are now in development, including the classes of retinoids, antibiotic/immunomodulatory agents, combination agents, and laser/light techniques.

FACULTY AND UNAPPROVED USE DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr Berson has served on advisory boards for Allergan, Inc., Connetics Corporation, Dermik Laboratories, Galderma International, and Medicus Pharmaceuticals Corporation. **Dr Stein Gold** is a principal investigator and consultant to Connetics. **Dr Koo** has received funding for clinical grants from Allergan, Biogen, Inc., Fujisawa Healthcare, Inc., Valeant Pharmaceuticals International, and Serono S.A. He is also a consultant to Abbott Laboratories, Amgen, Inc., Biogen, Centocor, Inc., Genentech, Inc., Novartis Pharmaceuticals Corporation, and Fujisawa. **Dr Zane** has served on advisory boards for Connetics and QLT, Inc.

Dr Koo discusses the unlabeled use of acitretin in combination with other agents. **Dr Zane** discusses the unlabeled use of new retinoic acid derivatives of isotretinoin and alitretinoin; clindamycin in a foam vehicle; dapsone in a topical formulation; zileuton in an oral formulation; clindamycin/tretinoin gel combination product; laser and light devices and photodynamic therapy using lemuteporfin.

Managing Acne in Adult Women

Diane S. Berson, MD

Acne is most commonly associated with young people of both genders between puberty and age 21, but most dermatologists also see a number of adult patients with acne. In men, acne breakouts can be severe, but men usually respond well to treatment and chronic recurrences are the exception rather than the rule. In contrast, women tend to experience chronic, low-grade acne breakouts, even after successful treatment of each episode. Patients may have had acne as adolescents and now have a persistent problem; less commonly, patients experience onset of acne in adulthood with no prior history.

Clinical Presentation

Acne in adult women tends to be characterized by lesions on a number of areas of the skin, including the forehead, chest, or back, but usually on the lower part of the face (**Figure**)—specifically, the lower cheeks, jaw line, neck, and especially the chin. These outbreaks are characterized by areas of inflamed papules and pustules. (In contrast, most teenagers with mild to moderate acne tend to present with open and closed, noninflammatory comedones—blackheads and whiteheads—in the T zone.)

Outbreaks in adult women often are mild and may be cyclic in nature, the result of hormonal fluctuations. In many women, lesions appear just before the onset of the menstrual period,¹ but acne is also associated with hormonal fluctuations resulting from other causes, including pregnancy, initiation of the use of oral contraceptives (OCs), and cessation of OC use.

Excess androgen also may be a cause of acne in adult women.² Sources of androgen include the adrenal glands and ovaries, as well as peripheral sites, the

sebaceous glands, and hair follicles. In addition, it is thought—although not yet proven—that acne flares in adult women can be associated with stress. The proposed mechanism is a stress-related release of adrenalin and cortisol from the adrenal glands, which results in a release of androgens. These increased circulating levels of androgens may stimulate production of excess sebum, causing an outbreak of inflammatory lesions.

Evaluation

A thorough history should be taken on all adult women who present with persistent acne. This should include a menstrual history as well as a pregnancy history. Women who present with acne and hirsutism, alopecia, or menstrual irregularities should be evaluated for adrenal hyperplasia or polycystic ovarian syndrome. A history of infertility is a sign of a possible hormonal abnormality. In addition, ask about OC use. Patients who stop taking the “Pill” often experience acne outbreaks for several months; usually these flares are short-lived and self-limited.

Figure. Acne on the Lower Face



In adult women, outbreaks of acne tend to appear as inflamed papules and pustules, typically on the lower part of the face, especially the chin.

Women with regular menses do not require a hormonal workup because acne associated with the menstrual cycle (“hormonal acne”) may occur without an underlying hormonal problem. In such patients, it may be that increased production of androgens occurs peripherally, at the site of the sebaceous glands, or that the receptors on the sebaceous glands may be more sensitive to the normal level of circulating hormones.

In performing the history and physical examination, it is important that clinicians take time to reassure the patient that her concerns are important. Remember that there is a psychologic aspect for many women who believe that they should have outgrown their often-embarrassing adolescent acne.

Considerations in Treatment

In addition to choosing the appropriate medication to treat acne in adult women, it is important to review proper skin care and guide them in their choices of cleansing, moisturizing, and makeup products. Whereas teenagers tend to have oily skin, many adult women have dry or sensitive skin, so the products developed and marketed as acne remedies for adolescents often are inappropriate for adults. Products for adult women must be well tolerated, nonirritating, and applied easily and compatibly with makeup.

Treatment Strategy

Initially, topical treatment with a combination of an antimicrobial medication and a retinoid should be used. This will be effective for most patients in clearing the outbreak. For treatment of facial acne, cream-, lotion-, or foam-based products may be used, but if the chest or, particularly, the scalp are in-

involved, patient compliance is more likely to be maintained with a foam-based medication. The topical retinoids currently available are tretinoin, adapalene, and tazarotene. A combination product containing tretinoin and clindamycin is now in clinical trials.

The usual maintenance treatment choice for women with chronic, low-grade, cyclic acne is a topical retinoid to help prevent new lesions plus an OC to decrease the influence of hormonal fluctuations. The estrogen component of the OC works mainly in two ways to control acne. First, it decreases production of androgens in ovaries so less androgen is available to stimulate the sebaceous glands. Second, estrogen increases sex hormone binding globulin, which binds testosterone, so less testosterone is available to stimulate the sebaceous glands.

Patients with persistent inflammation or mild acne may continue use of the topical retinoid along with the topical antimicrobial.

For patients with severe acne, in whom topical retinoid/antimicrobial therapy plus an OC fails to control lesions, oral antibiotics may be added to the regimen. When acne is severe and the potential for scarring is present, the patient should be evaluated for possible use of isotretinoin. (Of course, many women with adult acne and hormonal fluctuations are, by definition, of childbearing age, so careful attention must be paid to appropriate patient selection and compliance with birth control recommendations during treatment with isotretinoin.) Once the course of therapy with isotretinoin is complete, recurrence of acne frequently can be decreased by continuation of OCs and the use of a topical retinoid.

In some cases, a patient with acne may improve with the Pill but still ex-

perience hormonal flares. If this persists for several months, an antiandrogenic agent such as spironolactone (a diuretic agent that inhibits androgen biosynthesis and binds androgen receptors in the sebaceous glands) may be administered along with OC therapy.³

“In performing the history and physical examination, it is important that clinicians take time to reassure the patient that her concerns are important.”

Some women with acne flares do have concomitant hormonal problems. For those with polycystic ovarian syndrome, the treatment of choice is an OC. Adrenal hyperplasia is treated mainly with oral corticosteroids.

Conclusion

Many women continue to suffer from acne well into adulthood. In contrast to men, acne in adult women tends to be chronic and related to hormonal fluctuations. Although these outbreaks tend to be mild, they often are bothersome and cause patients great frustration. Fortunately, research has shown the likely contributors to acne in adult women and has resulted in the development of topical and hormonal therapies that are effective for both initial and long-term maintenance therapy.

References

1. Lucky AW. Quantitative documentation of a premenstrual flare of facial acne in adult women. *Arch Dermatol.* 2004;140:423-424.
2. Cibula D, Hill M, Vohradnikova O, Kuzel D, Fanta M, Zivny J. The role of androgens in determining acne severity in adult women. *Br J Dermatol.* 2000;143:399-404.
3. Shaw JC. Low-dose adjunctive spironolactone in the treatment of acne in women: A retrospective analysis of 85 consecutively treated patients. *J Am Acad Dermatol.* 2000; 43:498-502.

New Developments in Therapy for Acne Vulgaris: A Preview

Lee T. Zane, MD

The pathogenesis of acne vulgaris includes four important pathophysiologic factors¹: 1) altered growth and differentiation of follicular keratinocytes, 2) increased sebaceous gland size and activity, 3) follicular colonization with *Propionibacterium acnes*, and 4) an inflammatory and immune response. Acne therapies target any or all of these factors. This article will offer a preview of some new acne treatments that are either recently approved or seeking approval by the US Food and Drug Administration (FDA). These treatments may contain novel compounds or novel ways to deliver compounds and fall into four major classes: retinoids, antibiotic/immunomodulatory agents, combination products, and laser/light therapy (Table).

Retinoids

In addition to new strengths and formulations of existing retinoids, practitioners can also look forward to the in-

roduction of new derivatives of retinoids and modulators of retinoid metabolism. New topical derivatives of 13-*cis*-retinoic acid (isotretinoin), and 9-*cis*-retinoic acid (alitretinoin) are in development, along with a modified tretinoin molecule designed with the goal of being less irritating.

An exciting new entry into the retinoid group is a novel class of molecules called retinoic acid metabolism blocking agents (RAMBAs). These agents decrease retinoid metabolism, thereby maintaining higher therapeutic levels of endogenous retinoic acid. One RAMBA has received FDA orphan drug status for the treatment of congenital ichthyosis, although its application in the treatment of acne is inviting.

Antibiotic/Immunomodulatory Agents

Practitioners and scientists wage a seemingly unending war against antibiotic resistance, trying to stay one step

ahead of rapidly changing bacterial resistance patterns. New introductions within the antibiotic/immunomodulatory class push the limits of antimicrobial technology and offer different ways of thinking about antibiotic activity. In this class of new therapies, clinicians can anticipate new vehicles of delivery, novel compounds, and innovative approaches to minimizing bacterial colonization and reducing the inflammatory response.

In the antibiotic subgroup, a clindamycin product delivered in a novel foam vehicle will offer the ability to spread easily and cover large surface areas. In addition to aiding in the treatment of acne, this product could potentially be useful in the treatment of folliculitis in non-acne-prone areas as well.

A traditionally oral antibiotic, dapsone, will soon be introduced in topical form. Dapsone's antimicrobial and anti-neutrophilic activities are well known. This novel formulation introduces an innovative gel technology that can topically deliver highly water-insoluble compounds that had previously been relegated to systemic delivery only.

Expanding the way we think about antibiotic therapy is a new class of antimicrobial peptides. These short proteins often mimic endogenous defense peptides to elicit their antibacterial effects. Two highly anticipated agents in this class are a novel antimicrobial cationic peptide as well as a synthetic peptide compound derived from bactericidal-permeability-increasing protein.

In the antiinflammatory/immunomodulatory subgroup, the asthma medication zileuton is being investigated in an oral formulation for the treatment of acne. Zileuton is a 5-lipoxygenase inhibitor that blocks the formation of leukotrienes from arachidonic acid, thus modulating the inflammatory response.

Table. New Acne Treatments Anticipated

Antibiotics <ul style="list-style-type: none">◆ Clindamycin in a foam vehicle◆ Dapsone in topical form◆ Antimicrobial cationic peptide◆ Synthetic peptide compound derived from bactericidal-permeability-increasing protein	Laser and Light <ul style="list-style-type: none">◆ Short-wave-length (400 to 420 nm) light (highly absorbed by porphyrins in <i>P. acnes</i> to produce antimicrobial action)◆ Longer-wave-length (870 to 1200 nm) light (believed to penetrate deeper to affect sebaceous gland growth and secretory activity)◆ Blue light, 417 nm◆ Narrow-band (405 to 420 nm)◆ Light-emitting-diode (LED) blue-light arrays◆ Intense pulsed-light therapy
Antiinflammatory/Immunomodulatory Agents <ul style="list-style-type: none">◆ Zileuton in oral form◆ Pyridine carboxylate compound	Photodynamic Therapy <ul style="list-style-type: none">◆ Lemnateporfin + visible-light stimulation
Combination Therapy <ul style="list-style-type: none">◆ Clindamycin 1% plus tretinoin 0.025% gel◆ Other clindamycin/retinoid combinations◆ Tetracycline derivative/retinoid combinations	Retinoids <ul style="list-style-type: none">◆ Topical derivatives of 13-<i>cis</i>-retinoic acid (isotretinoin) and 9-<i>cis</i>-retinoic acid (alitretinoin)◆ Modified tretinoin molecule◆ Retinoic acid metabolism blocking agents (RAMBAs)

In addition, a novel pyridine carboxylate that binds zinc in zinc finger proteins is under development. This agent appears to have both antiviral and immunomodulatory activity in addition to being highly active against *P. acnes*.

Combination Agents

The predominant theme in the combination class is the pairing of antibiotics with retinoids. This combination strategy not only offers the convenience of a single application for two active agents, it may also improve antibiotic penetration and efficacy through the aid of retinoid action on keratinocytes. While several such combination products are anticipated, one of the first entries expected in this class is a clindamycin 1% plus tretinoin 0.025% gel. Other entries are likely to pair one of the retinoids with either clindamycin or a tetracycline derivative.

Laser, Light and Photodynamic Therapy

In the use of laser and light in the treatment of acne, the proposed mechanisms of action include the use of short wave lengths (400 to 420 nm), which are highly absorbed by porphyrins in *P. acnes*, to produce antimicrobial action, and longer wave lengths (870 to 1200 nm) which are believed to penetrate deeper to affect sebaceous gland growth and secretory activity.

In addition to the 417-nm blue light and 405- to 420- nm narrow-band light products being developed, the introduction of light-emitting-diode (LED) blue-light arrays and intense pulsed-light therapy is anticipated. There is also speculation that an intense pulsed-light unit for home use may be under development.

In photodynamic therapy (PDT) for acne, the application of a photosensitiz-

er, ideally targeting the pilosebaceous unit, is followed by stimulation with visible light, leading to selective damage to sebaceous glands. While aminolevulinic acid (ALA) PDT, the first entry into this market, has demonstrated efficacy, it unfortunately appears to lack good specificity for follicles, causing damage to interfollicular skin.²

“All of these therapies offer practitioners new options for treating the millions of patients worldwide with acne and underscore the great need for creativity and innovation in shaping the future of acne treatment.”

A new photosensitizing agent, lemuteporfin, is currently being investigated for its use in acne. Preliminary, unpublished data from experiments in mice suggest that lemuteporfin may elicit a PDT response that is more specific to sebaceous glands.

Unmet Needs

As these new therapies are introduced, clinicians will need to determine where each one fits into their individual treatment algorithms for acne. However, despite the great benefits offered by the therapies discussed here, important needs remain unmet in the field of acne treatment technology, including: 1) an inhibitor of sebaceous

glands that is specific to skin, 2) antibiotic-independent mechanisms for reducing *P. acnes* colonization, 3) targeted antiandrogen therapy for skin, 4) an agent with the efficacy of oral isotretinoin but free of its noncutaneous effects, and 5) the “single-dose, one-time magic bullet” that cures acne for life. The hope here is that the quest for these “ideal agents” will cultivate inventiveness in therapeutic mechanisms, stimulate innovation in drug design, and foster creativity in drug delivery.

Conclusion

The emerging therapies discussed here exemplify innovation in acne therapy in a number of different ways. Some employ modifications to existing agents to increase efficacy, enhance ease of use, or improve methods of delivery, while others hope to gain therapeutic synergy by combining agents together. New approaches, novel compounds, and innovative technologies will hopefully push the field of acne therapeutics in new directions. These new therapies may offer practitioners new options for treating the millions of patients worldwide with acne and serve to underscore the great need for continued creativity and ingenuity in shaping the future of acne therapy.

References

1. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: A report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49(1 suppl):S1-S37.
2. Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol*. 2000;115:183-192.

The Role of Oral Retinoid Treatment for Psoriasis in the Age of Biologics

John Y. M. Koo, MD

The educational programs aimed at clinicians who treat psoriasis are currently—quite appropriately—focused on the newest therapies, the biologic agents. The biologic agents represent hope for patients with psoriasis who have suffered for years without adequate relief. However, clinicians should not draw the conclusion that the prebiologic agents—including topical medications, phototherapy, cyclosporine, methotrexate, and oral retinoids—have become obsolete. To the contrary, the prebiologic agents are and will continue to be extremely useful, and the biologics should take their proper place among these other medications. Among the prebiologics, the oral retinoids are a safe and effective option for many patients, particularly when used in combination, sequential, and maintenance strategies with other agents.

Optimal Use of Oral Retinoid Therapy

Oral retinoid treatment should be given in low doses, either in combination, sequential, or maintenance treatment regimens. Acitretin (the only oral retinoid currently approved for use in psoriasis by the US Food and Drug Administration [FDA]*) is well tolerated by most patients at dosages of 25 mg/day or less. (Patients older than 65 years of age may better tolerate even lower dosages, such as 25 mg every other day or 10 mg/day.) Furthermore, oral retinoid therapy can be combined with practically all other psoriasis treatments—including ultraviolet B (UVB) phototherapy, psoralen–ultraviolet-light (PUVA) therapy, topical treatments, and

*Oral tazarotene has demonstrated efficacy in psoriasis, but it has not been approved by the FDA.

biologic therapies. Except for concerns regarding possible hepatotoxicity in combination with methotrexate, oral retinoids are essentially without risk for important drug interactions.

Patients who are given higher dosages of acitretin are likely to experience side effects such as dry skin, cracked lips, hair loss, gastrointestinal complaints (including bloating and diarrhea), and musculoskeletal aches and pains. Although these side effects are not serious, they are bothersome and cause additional distress to patients who are already uncomfortable from their psoriasis.

Combination Therapy

Oral retinoid monotherapy is associated with a slow and often incomplete response. It is highly effective in the resolution of scaling and thick plaques, (Figure) but is less effective for eradicating erythema. The slow onset of action, incomplete resolution of erythema, and annoying side effects at higher

dosages have led some clinicians to abandon oral retinoid use. However, this does a disservice to patients because oral retinoid treatment has great value as a therapeutic enhancer for virtually every other psoriasis therapy in use today, from the phototherapies to the biologics.

Oral retinoid treatment plus a biologic agent is a natural combination. Although the biologic agents currently approved by the FDA for the treatment of psoriasis—etanercept, efalizumab, and alefacept—have demonstrated reasonable efficacy in clinical trials, none works as well as cyclosporine or PUVA. Many patients on biologic therapy are left with residual psoriatic plaques. Vitamin A type medications—that is, the retinoids—improve skin psoriasis by enhancing cell maturation and differentiation. The result of improved maturation and differentiation is desquamation and, consequently, a flattening of plaques. Most importantly, oral retinoids are not immunosuppressive, an important benefit for combination treatment. Because the biologic agents downregulate the immune system, it is theoretically (and probably clinically) safer to avoid doubling up on immunosuppressants.

Oral retinoid treatment also is the best therapy available for enhancing phototherapy. Extensive evidence shows that UVB and PUVA work about twice as well if a patient is taking 25 mg/day of acitretin¹ simultaneously so lower doses of light can be used. Anecdotal experience in our center (as well as that of many experts) is that even topical agents seem to work better in patients taking acitretin. It makes sense that this would be so, because when acitretin eliminates scales and flattens psoriatic plaques, topical medications can better penetrate the skin.

Figure. Widespread Erythema and Scaling



The large body surface area affected makes topical therapy impractical in this patient with psoriasis. Oral retinoid therapy—alone or in combination with other agents—may be helpful.

Sequential Therapy

In patients who are in psoriatic crisis—experiencing a severe flare of their disease, involving rapid spread of inflammation and discomfort—sequential therapy should be considered. This is a strategy involving three overlapping steps: step 1, clearance; step 2, transition; and step 3, maintenance.

An example of such a treatment regimen is the administration of cyclosporine or methotrexate to bring the flare under rapid control. This is followed by the addition of acitretin, the dosage of which is optimized and maximized before cyclosporine or methotrexate is gradually and slowly tapered off. This combination would be continued for 1 to 3 months to prevent recurrence of a flare as cyclosporine or methotrexate administration is tapered and discontinued. After this transition period—and once the patient is completely off cyclosporine or methotrexate—treatment with acitretin, alone or in combination with UVB and/or PUVA, may be continued as maintenance (or another safe regimen can be used instead).

If phototherapy is not available or feasible, another safe, long-term agent, such as etanercept, can be used in combination with acitretin.

One way to conceptualize the optimum maintenance combination therapy is a model I have labeled “turtle stacking.” In this model, fast-acting but potentially toxic agents such as cyclosporine are characterized as “rabbits,” whereas the safer agents—including all of the currently approved biologics, acitretin, and UVB phototherapy—are described as “turtles.” The idea of turtle stacking is to maximize efficacy while using only the safer “turtle” agents. Thus, two or even three turtles might be stacked to maximize efficacy and still maintain a safe side effect profile.

Oral retinoid treatment is an important element in this model, particularly for long-term use. According to an extensive 10-year review of the available

“...although we embrace the importance and utility of the biologics, it is crucial to remember that the prebiologic agents maintain a useful place in that spectrum of options.”

literature,² acitretin therapy is known to be associated with a significantly longer remission time than is either cyclosporine or methotrexate. Among the currently approved biologic agents, alefacept has a long remission time, but only in the minority of patients who achieve at least a 75% improvement in the Psoriasis Area and Severity Index; etanercept has a reasonable remission time but one that probably is shorter than that of acitretin; and efalizumab has a short remission time, complicated by the risk for rebound.

Conclusion

The advent of biologic agents has provided significant treatment benefits to many patients, and they represent a welcome addition to the range of treatment options the clinician has to offer those who suffer from moderate to severe psoriasis. However, although we embrace the importance and utility of the biologics, it is crucial

to remember that the prebiologic agents maintain a useful place in that spectrum of options.

Oral retinoid monotherapy has two disadvantages: relatively slow onset of action and possibly an incomplete response (chiefly, residual erythema). In addition, excessive dosing can result in a range of annoying side effects at high doses. However, when oral retinoid therapy is combined with other psoriasis treatments—that is, as a therapeutic enhancer—its value is clear. Oral retinoid treatment appears to enhance all of the therapies—including phototherapy, topical agents, and systemic treatments such as the biologics.

In the schema described, oral retinoid therapy is an important “turtle” in the turtle-stacking model. Even the biologic agents often are not fully satisfactory to the patient as monotherapy, and because oral retinoid therapy is not immunosuppressive, it is a natural partner to enhance the action of biologic agents.

Lastly, at least theoretically, the combination use of oral retinoid therapy and a biologic agent may: (1) reduce the possible long-term neoplastic risk that may be associated with the biologics because of the chemopreventive effects of the retinoid on both cutaneous and systemic malignancies, (2) maximize the chance for synergy in efficacy because these classes of agents have very different mechanisms of action, and (3) reduce costs by making higher maintenance doses of biologics unnecessary.

References

1. Lebwohl M, Menter A, Koo J, Feldman SR. Combination therapy to treat moderate to severe psoriasis. *J Am Acad Dermatol.* 2004; 50:416-430.
2. Koo J, Lee BS, Lee CS, Lebwohl M. Psoriasis. *J Am Acad Dermatol.* 2004;50:613-622.

Advances in Combination Topical Therapy for Psoriasis

Linda F. Stein Gold, MD

Psoriasis has a chronic and often unpredictable course. The goal of therapy is always to use the least potent medication to achieve the desired efficacy while minimizing potential toxicity. Topical therapy, although the cornerstone of treatment for mild disease, also has an important place in the treatment of patients with moderate to severe psoriasis as well (Figure). Topical therapy adds significant benefit when incorporated into combination regimen with phototherapy or systemic agents for more resistant lesions.

Currently, three main topical treatments commonly are used for psoriasis: corticosteroids, calcipotriene, and tazarotene, agents that are all well known to dermatologists. In addition, pimecrolimus and tacrolimus, currently indicated by the US Food and Drug Administration (FDA) for the treatment of atopic dermatitis, are being investigated for use in psoriasis.

Modes of Action of Traditional Agents

Corticosteroids are the most commonly used topical agents for psoriasis. These range in potency from mild (class 7) to superpotent (class 1). Topical corticosteroids work by altering DNA synthesis and gene transcription, directly inhibiting inflammatory cells, and inhibiting mediators of inflammation. The potency of topical agents is related to skin thickness, hydration, and temperature, as well as to the halogenation of the parent compound and the vehicle used to deliver the active agent.

Despite good efficacy achieved with these agents, clinicians tend to avoid prolonged use of potent and superpotent corticosteroids because of the risk of adverse effects such as skin atrophy.

Calcipotriene. The skin makes vitamin D in response to ultraviolet-B

(UVB) light exposure, and active vitamin D—calcitriol—regulates the body's levels of calcium. In psoriasis, calcitriol inhibits keratinocyte proliferation and induces terminal differentiation in vitro. An individual patient's response to calcitriol varies with the state of the disease and the number of vitamin D receptors in psoriatic keratinocytes. (Vitamin D receptors are increased in patients with psoriasis.) The topical drug calcipotriene, an analog of calcitriol, acts via the same receptors as does calcitriol but is 100 times less calcitropic.

Calcipotriene is as effective as calcitriol in inducing cell differentiation and inhibiting proliferation of keratinocytes in vitro. Calcipotriene monotherapy has been shown to be as effective as a high-potency corticosteroid and to maintain efficacy in long-term use in patients with chronic plaque psoriasis.¹

Tazarotene was the first topical retinoid developed for the treatment of psoriasis. It is one of a class known as retinoic acid receptor-specific reti-

noids, which target keratinocytes, acting to modulate the major causes of psoriasis. Tazarotene is rapidly metabolized by esterase to tazarotenic acid; thus, the drug's elimination half-life is short, 1 to 2 hours. Tazarotene is classified as a pregnancy category X drug, but it demonstrates no significant tissue accumulation.

The pivotal trials leading to FDA approval of tazarotene for the treatment of psoriasis demonstrated good efficacy and safety. The side effects observed with tazarotene—chiefly, pruritus, burning, and irritation—were consistent with those expected with topical retinoids.²

In a comparative trial versus fluocinonide,³ tazarotene demonstrated comparable efficacy. The incidence of relapse was 55% for 0.05% fluocinonide versus 37% for 0.05% tazarotene and 18% for tazarotene 0.1%. (The difference between fluocinonide and the 0.1% concentration of tazarotene was significant, $P < 0.01$.)

Topical immunomodulators. Tacrolimus and pimecrolimus, approved by the FDA for the treatment of atopic dermatitis, also have been studied in psoriasis.⁴ To date, a number of clinical studies have demonstrated that these agents hold promise for facial and inverse psoriasis.

The Importance of the Vehicle

The vehicle is important in determining biologic activity, and numerous studies have shown that wide variations in drug penetration can occur depending on the vehicle used (Table on Page 10). The drug must be soluble in the vehicle to be effective, and increasing the concentration of the drug may not increase efficacy. In considering a vehicle, the importance of patient acceptance also cannot be overlooked as



Figure. Plaque Psoriasis on Elbow

This patient has a sharply demarcated, erythematous lesion. Effective topical therapy requires adequate penetration of medication through this thick plaque.

this is essential for comfort, convenience, and, therefore, compliance. Under ideal circumstances, compliance with topical therapy is, at best, probably about 50%. Over the course of an 8-week study, Carroll and colleagues⁵ found that compliance fell from 85% to 51%, as determined by electronic monitoring caps.

Tazarotene/ Corticosteroid Combination

The efficacy and safety of tazarotene plus corticosteroid therapy was evaluated in an investigator-masked, randomized 12-week study involving the retinoid plus a variety of strengths of corticosteroid creams.⁶ In this study, 300 patients applied tazarotene 0.1% once each evening. Subjects were randomly assigned to apply one of the following each morning: a low-, medium-, or high-potency corticosteroid cream, or placebo cream. The investigators concluded that all of the tazarotene/corticosteroid combinations were more effective than was tazarotene monotherapy.

Other studies have confirmed the benefits of tazarotene/corticosteroid combination therapy.⁷ A number of studies have demonstrated the efficacy of combining tazarotene with phototherapy, particularly UVB.

Calcipotriene/ Corticosteroid Combination

In a landmark study evaluating the efficacy and safety of the combined use of calcipotriene and the superpotent corticosteroid halobetasol, Lebwohl and colleagues⁸ demonstrated that the combination was superior to monotherapy with either agent. In this double-blind, placebo-controlled, parallel-group study, patients applied calcipotriene ointment each morning and

halobetasol ointment each evening for 2 weeks. Those who showed a 50% improvement were randomly assigned to one of two groups: calcipotriene twice daily on weekdays plus halobetasol twice daily on weekends or placebo twice daily on weekdays and halobetasol twice daily on weekends.

“In considering a vehicle, the importance of patient acceptance also cannot be overlooked as this is essential for comfort, convenience, and, therefore, compliance.”

Out of the original 44 subjects, 40 remained. These patients were randomized equally to two double-blind treatment groups to continue in the maintenance phase of the study for 6 months. At the end of that time, the investigators reported that 40% of patients in the placebo/halobetasol group remained in remission versus 76% of those in the calcipotriene/halobetasol group.

Innovations to enhance the penetration and, therefore, the efficacy of topical combination agents for psoriasis include the use of new vehicles, including foam. One particularly interesting combination is calcipotriene plus clobetasol; the high-potency corticosteroid is

one of the few drugs that does not interact with and inactivate calcipotriene. Foam-based clobetasol was compared with clobetasol solution in randomized clinical efficacy trials, vasoconstrictor assays, and in vitro penetration studies.⁹ The investigators found that clobetasol in the foam vehicle yielded higher penetration, more potent vasoconstriction, and greater clinical efficacy than did clobetasol solution.

To evaluate the efficacy of 0.005% calcipotriene ointment and 0.05% clobetasol foam, Blum and coworkers¹⁰ conducted a 24-week randomized, double-blind, vehicle-controlled, prospective trial in 86 patients with mild to moderate psoriasis on the trunk and extremities. The subjects were randomized in a 2:1:1 ratio to one of three groups: clobetasol foam and calcipotriene ointment combination, clobetasol foam alone, or calcipotriene ointment alone.

At the end of 2 weeks, the target lesions were evaluated for erythema, induration, and scaling, using the Psoriasis Grading Scale, and investigator and subject evaluations were performed using the Global Severity Assessment of Psoriasis. The evaluation of trunk lesions at week 2 showed a mean percent reduction in erythema, induration, and scaling of 69.3% in the subjects using combination therapy. In contrast, those who used clobetasol foam alone had a 48.1% reduction and those who used calcipotriene ointment

Table. New Developments in Combination Topical Therapy for Psoriasis

The following combinations are being studied using corticosteroids in foam vehicles:

- ◆ Calcipotriene/clobetasol
- ◆ Pimecrolimus/betamethasone*
- ◆ Tacrolimus/betamethasone*

* Pimecrolimus and tacrolimus have been studied in but are not yet approved for patients with psoriasis.

alone had a 36.6% reduction. The mean percent reduction in extremity target lesion scores at week 2 was 70.1% among subjects using combination therapy, 40.5% for subjects using clobetasol foam alone, and 31.1% for those using calcipotriene ointment alone. The second portion of the study is complete, and the results will be available soon.

Clinicians should welcome the availability of such a combination—particularly if clinical benefits prove to be enhanced by the improved delivery of calcipotriene which seems possible when paired with foam-based clobetasol.

Other Combinations

In a recent human skin study combining pimecrolimus and betamethasone 17-valerate, (BMV), Deng and colleagues¹¹ found that pimecrolimus and BMV were stable in various vehicles over a period of 24 hours at temperatures of 32°C and 37°C. They noted that application to the skin of pimecrolimus with BMV in a foam vehicle, compared to BMV cream or BMV ointment, resulted in delivery of a higher amount of both BMV and pimecrolimus. In a skin study comparing the permeation and drug distribution of BMV foam and ointment vehicle plus tacrolimus, researchers found that simultaneous application of tacrolimus and BMV foam resulted in superior permeation.¹²

Conclusion

Psoriasis is a chronic and unpredictable disease. Successful management requires the judicious use of proven treatments. Topical therapy plays an important role in the treatment of patients with a broad spectrum of disease severity. Advances in research and technology continue to provide improvements in the delivery and efficacy of topical agents, and combination therapy enhances clinical results.

References

1. Bruce S, Epinette WW, Funicella T, et al. Comparative study of calcipotriene (MC 903) ointment and fluocinonide ointment in the treatment of psoriasis. *J Am Acad Dermatol.* 1994;31(5 pt 1):755-759.
2. Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: Vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *J Am Acad Dermatol.* 1997;37:85-92.
3. Lebwohl M, Ast E, Callen JP, et al. Once-daily tazarotene versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. *J Am Acad Dermatol.* 1998;38 (5 pt 1):705-711.
4. Weinberg JM. Oral tazarotene and oral pimecrolimus: Novel oral therapies in development for psoriasis. *J Drugs Dermatol.* 2004;3:141-143.
5. Carroll CL, Feldman SR, Camacho FT, Manuel JC, Balkrishnan R. Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: Commonly used methods of measuring adherence to topical therapy overestimate actual use. *J Am Acad Dermatol.* 2004; 51:212-216.
6. Lebwohl MG, Breneman DL, Goffe BS, et al. Tazarotene 0.1% gel plus corticosteroid cream in the treatment of plaque psoriasis. *J Am Acad Dermatol.* 1998;39(4 pt 1):590-596.
7. Lebwohl M. Strategies to optimize efficacy, duration of remission, and safety in the treatment of plaque psoriasis by using tazarotene in combination with a corticosteroid. *J Am Acad Dermatol.* 2000;43(2 pt 3):S43-S46.
8. Lebwohl M, Yoles A, Lombardi K, Lou W. Calcipotriene ointment and halobetasol ointment in the long-term treatment of psoriasis: Effects on the duration of improvement. *J Am Acad Dermatol.* 1998;39: 447-450.
9. Huang X, Tanojo H, Myers JA. Directional association of preclinical, vasoconstrictor assay, and clinical results of topical clobetasol formulations. Poster presented at: 62nd American Academy of Dermatology Meeting; February 6-11, 2004; Washington, DC.
10. Blum RR, Stern D, Lebwohl M, Bandow G, Koo J, Cheplo K. A multi-center study of calcipotriene ointment, 0.005% and clobetasol propionate foam, 0.05% in the sequential treatment of localized plaque-type psoriasis. Poster presented at: American Academy of Dermatology 2004 Summer Meeting; July 28-August 1, 2004; New York, NY.
11. Deng H, Tanojo J, Lenn J, Cuesico C, Vassilieva I, Huang X. In vitro human skin study of combined application of pimecrolimus cream and betamethasone 17-valerate. Poster presented at: 62nd American Academy of Dermatology Meeting; February 6-11, 2004; Washington, DC.
12. Lenn J, Tanogo J, Huang X. Effects of co-application of betamethasone 17-valerate from different formulations, with tacrolimus ointment on in vitro skin permeation. Poster presented at: 62nd American Academy of Dermatology Meeting; February 6-11, 2004; Washington, DC.

SKIN & ALLERGY NEWS certifies that this educational activity has been recognized by the American Academy of Dermatology for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

There is no fee for this activity. If you wish to receive CME credit, please mail or fax a photocopy of this completed form to SKIN & ALLERGY NEWS before January 31, 2006 to:

Course No. 376-100 Dermatology • SKIN & ALLERGY NEWS • 60 Columbia Road, Bldg. B, Morristown, N.J. 07960-4526
(973) 290-8200 • (973) 290-8245 Fax

INSTRUCTIONS: For each question or incomplete statement, one answer or completion is correct. Circle the most appropriate response. Six correct responses are required for credit.

1. Topical calcipotriene is:
 - a. an analog of active vitamin D.
 - b. a retinoid.
 - c. likely to cause pruritus.
 - d. teratogenic.
2. Which one of the following is being studied in but is not currently indicated by the US Food and Drug Administration for the topical treatment of psoriasis?
 - a. Calcipotriene
 - b. Halobetasol
 - c. Pimecrolimus
 - d. Tazarotene
3. Mild, chronic outbreaks of inflamed papules are characteristic of acne in:
 - a. adult men.
 - b. adult women.
 - c. teenage boys.
 - d. teenage girls.
4. The initial treatment recommended for adult women with acne is:
 - a. oral contraceptives.
 - b. topical therapy, with a retinoid alone.
 - c. topical therapy, with an antimicrobial agent alone.
 - d. topical therapy, with a combination of a retinoid and an antimicrobial agent.
5. The maintenance treatment of choice for women with chronic, low-grade, cyclic acne is:
 - a. an oral contraceptive to decrease the influence of hormonal fluctuations.
 - b. a topical retinoid to prevent new lesions.
 - c. a topical retinoid plus an oral contraceptive.
 - d. testosterone.
6. One promising new area of technology in acne therapy is the development of immunomodulatory agents. An example of this is a compound that:
 - a. binds zinc in zinc finger proteins.
 - b. has antineutrophilic activities.
 - c. uses a synthetic peptide to lower bacterial counts.
 - d. uses small protein chains to decrease bacterial growth.
7. In patients with moderate to severe psoriasis, oral retinoids:
 - a. are of no value when combined with biologic agents.
 - b. cannot be combined with cyclosporine or any other immunosuppressive agent.
 - c. may be safely combined with any other agent used to treat psoriasis.
 - d. should be used cautiously in patients also using topical therapy.
8. In sequential therapy for moderate to severe psoriasis, a fast-acting agent such as _____ should be given first to bring the disease under control, and _____ may be used alone or as one element of a long-term treatment regimen to prolong remission.
 - a. Alefacept, an oral retinoid
 - b. Cyclosporine, etanercept
 - c. Cyclosporine, an oral retinoid
 - d. Etanercept, psoralen-ultraviolet-light (PUVA)

PLEASE PRINT

Name _____
 Degree _____ Specialty _____
 Address _____
 City _____
 State _____ ZIP _____
 Phone _____ Fax _____
 E-mail _____
 Signature _____

Please indicate amount of time spent on this activity:
 AAD Category 1 credit (maximum 1 hour):
 ____ hrs ____ min spent on activity

CME ACTIVITY EVALUATION

1. Were you able to meet the objectives of this CME activity?
 YES NO (circle one)
 If no, please note which objectives you were not able to meet:

2. Will the information presented in this issue be useful in your practice setting?
 YES NO (circle one)
 Comments:

3. Did you find the information presented in this publication to be objective, balanced, and free of commercial bias?
 YES NO (circle one)
 Comments:

