

A CME-CERTIFIED SUPPLEMENT TO

# Seminars in Cutaneous Medicine and Surgery

SUPPLEMENT 4  
VOL. 33, NO. 4S  
JUNE 2014

EDITORS

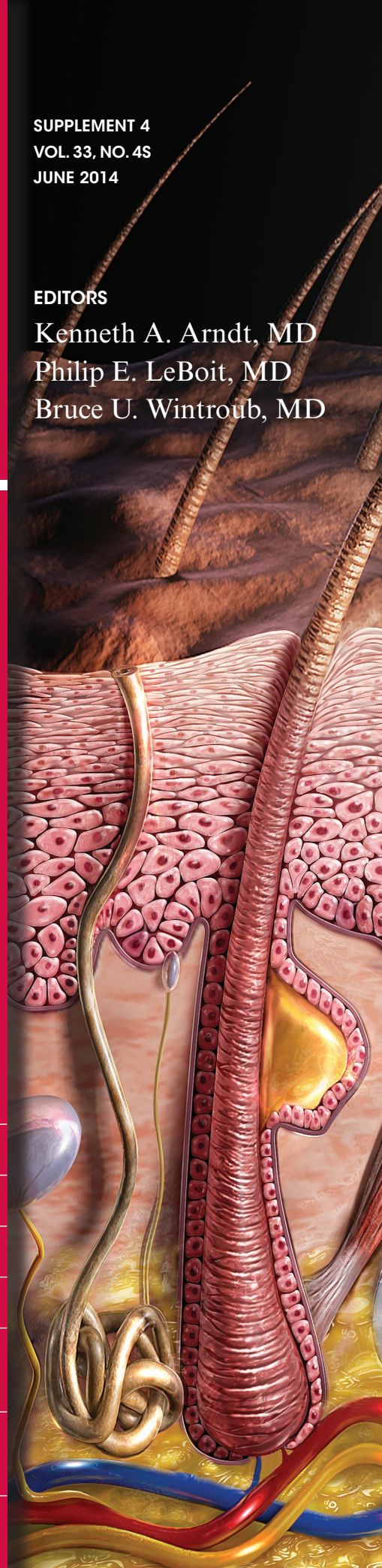
Kenneth A. Arndt, MD  
Philip E. LeBoit, MD  
Bruce U. Wintroub, MD

## Highlights of Skin Disease Education Foundation's 38th Annual Hawaii Dermatology Seminar

GUEST EDITORS

Craig L. Leonardi, MD, Chair  
Sue Ellen Cox, MD  
Michael S. Kaminer, MD  
Brian F. Mandell, MD, PhD  
Mark G. Rubin, MD  
James E. Sligh, Jr, MD, PhD  
Jeffrey M. Sobell, MD  
Nowell Solish, MD, FRCP(C)

Introduction	S63
The Role of TNF Inhibitors in Psoriatic Disease	S64
Therapeutic Development in Psoriasis	S69
Data on the Safety of Psoriasis Therapies	S73
New Therapeutic Options for Actinic Keratosis and Basal Cell Carcinoma	S76
Correcting Age-Related Changes in the Face by Use of Injectable Fillers and Neurotoxins	S81
Post-Test and Evaluation Form	S85



# Highlights of Skin Disease Education Foundation's 38th Annual Hawaii Dermatology Seminar

Original Release Date: **June 2014**

Most Recent Review Date: **June 2014**

Expiration Date: **July 31, 2016**

Estimated Time to Complete Activity: **3.0 hours**

Medium or Combination of Media Used: **Written Supplement**

Method of Physician Participation: **Journal Supplement**

Hardware/Software Requirements: **High-speed Internet connection**

To get instant CME credits online, go to <http://bit.ly/hawaiiighlights14>. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add [cmepd@louisville.edu](mailto:cmepd@louisville.edu) to your e-mail "safe" list. If you have any questions or difficulties, please contact the University of Louisville School of Medicine Continuing Medical Education (CME & PD) office at [cmepd@louisville.edu](mailto:cmepd@louisville.edu).

## Joint Providership

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Louisville School of Medicine and Global Academy for Medical Education, LLC. The University of Louisville School of Medicine is accredited by the ACCME to provide continuing education for physicians.

## Designation Statement

The University of Louisville School of Medicine designates this enduring material for a maximum of 3.0 *AMA PRA Category 1 Credit(s)*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## Target Audience

This educational activity is designed for dermatologists, primary care physicians, nurses, and other health care professionals involved in meeting the skin-care needs of patients.

## Educational Needs

Building on advances in molecular biology and clinical science, dermatology has evolved into a diverse specialty that encompasses elements of oncology, rheumatology, immunology, plastic and aesthetic surgery, and primary care. Clinical practitioners are continually challenged to remain abreast of scientific developments and emerging standards of care.

Based on the knowledge and expertise of leading clinical scientists, the following educational activity offers a concise yet thorough review of recent advances and evolving concepts in the field of dermatology. The discussions cover a variety of topics to address the informational needs of clinicians whose practices and interests reflect the diversity of their specialty.

## Learning Objectives

After reading and studying this enduring journal supplement, participants should be able to:

- Describe current approaches to treatment of psoriasis.
- Identify systemic therapies used to treat psoriasis, including biological and nonbiological agents.
- Recognize the need for ongoing evaluation of drug safety.
- Describe recent developments in the management of basal cell carcinoma.
- Utilize techniques involving the application of hyaluronic acid-based fillers and neurotoxins for facial rejuvenation.

## Acknowledgments

The authors would like to thank Global Academy for Medical Education and Charles Bankhead for assistance with the preparation of this supplement.

## Disclosure

As a sponsor accredited by the ACCME, the University of Louisville School of Medicine must ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. All faculty participating in this CME activity were asked to disclose the following:

1. Names of proprietary entities producing health care goods or services—with the exemption of nonprofit or government organizations and non-health-related companies—with which they or their spouse/partner have, or have had, a relevant financial relationship within the past 12 months. For this purpose, we consider the relevant financial relationships of a spouse/partner of which they are aware to be their financial relationships.
2. Describe what they or their spouse/partner received (eg, salary, honorarium).
3. Describe their role.
4. No relevant financial relationships.

**CME & PD Advisory Board Members** have no relevant financial relationships with any commercial interests: Soon Bahrami, MD; W. Daniel Cogan, EdD, FAODME; Douglas Coldwell, MD, PhD; Justin L. Costa, MD; James Cregg; Daniel Da Justa, MD; Adair Heyl, PhD; Christopher Jones, MD; Lucy Juett, MS; Gerald Larson, MD; Rana Latif, MD; Kimberly Moore; Karen Napoliilli; Lisa J. Pfitzer, MD; Scott Plantz, MD; Kerri Rimmel, MD, PhD; Michael D. Stillman, MD; Uldis Streips, PhD; Kathy M. Vincent, MD; Lori Wagner, MD; Angela Wetherton, MD; and Stephen Wheeler, MD.

**CME Reviewer: Cindy England Owen, MD**, Assistant Professor, Associate Program Director, Division of Dermatology, University of Louisville School of Medicine, has no relevant financial relationships with any commercial interests.

**Sue Ellen Cox, MD**, has been a consultant and/or investigator and/or speaker for Allergan Inc., Medicis, a division of Valeant Pharmaceuticals International, Inc., and Merz, Inc.

**Michael S. Kaminer, MD**, has been a consultant and/or investigator and/or speaker for Allergan, Cabochon Aesthetics Inc., Cytrellis Biosystems, Inc., Merz, Miramar Labs, Inc., Myoscience, Inc., and ZELTIQ Aesthetics, Inc.

**Craig L. Leonardi, MD**, has been a consultant and/or investigator and/or speaker and/or advisory board member for AbbVie, Inc., Amgen Inc., Anacor Pharmaceuticals, Inc., Celgene Corporation, Janssen Biotech, Inc., Eli Lilly and Company, Galderma Laboratories, L.P., GlaxoSmithKline, Incyte Corporation, LEO Pharma Inc., Maruho Co., Ltd., Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Pfizer Inc., Schering-Plough Corporation, Sirtis Pharmaceuticals, Inc., Stiefel Laboratories, Inc., TOLMAR Pharmaceuticals, Inc., Vascular Biogenics Ltd., and Warner Chilcott plc.

**Brian F. Mandell, MD, PhD**, has no relevant financial relationships with any commercial interests.

**Mark G. Rubin, MD**, has been a consultant for Allergan and Merz.

**James E. Sligh, Jr, MD, PhD**, has been a speaker and/or advisory board member for Genentech, Inc.

**Jeffrey M. Sobell, MD**, has been a consultant and/or speaker and/or investigator for AbbVie, Amgen, Celgene, Eli Lilly, Janssen Biotech, and Merck.

**Nowell Solish, MD, FRCP(C)**, has been a consultant and/or speaker and/or investigator for Allergan and Medicis, a division of Valeant Pharmaceuticals.

**Charles Bankhead** has no relevant financial relationships with any commercial interests.

**Sylvia H. Reitman, MBA**, has no relevant financial relationships with any commercial interests.

**Shirley V. Jones, MBA**, has no relevant financial relationships with any commercial interests.

## University of Louisville CME & PD Privacy Policy

All information provided by course participants is confidential and will not be shared with any other parties for any reason without permission.

Provided by



Global Academy for  
Medical Education

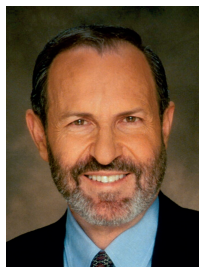


SKIN DISEASE  
EDUCATION  
FOUNDATION

Supported by educational grants from  
**AbbVie, Inc., Eli Lilly and Company, Genentech, Inc.,  
Merz, Inc., and Novartis Pharmaceuticals Corporation**

# Seminars in Cutaneous Medicine and Surgery

## EDITORS



**Kenneth A. Arndt, MD**  
Clinical Professor of Dermatology,  
Emeritus  
Harvard Medical School  
Adjunct Professor of Surgery  
Dartmouth Medical School  
Hanover, New Hampshire  
Adjunct Professor of Dermatology  
Brown Medical School  
Providence, Rhode Island



**Philip E. LeBoit, MD**  
Professor of  
Clinical Dermatology  
University of California,  
San Francisco  
San Francisco, California



**Bruce U. Wintroub, MD**  
Associate Dean  
Professor and Chair  
of Dermatology  
School of Medicine  
University of California,  
San Francisco  
San Francisco, California

## STATEMENT OF PURPOSE

*Seminars in Cutaneous Medicine and Surgery* presents well-rounded and authoritative discussions of important clinical areas, especially those undergoing rapid change in the specialty. Each issue, under the direction of the Editors and Guest Editors selected because of their expertise in the subject area, includes the most current information on the diagnosis and management of specific disorders of the skin, as well as the application of the latest scientific findings to patient care.

*Seminars in Cutaneous Medicine and Surgery* (ISSN 1085-5629) is published quarterly by Frontline Medical Communications Inc., 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Months of issue are March, June, September, and December. Periodicals postage paid at Parsippany, NJ, and additional mailing offices.

POSTMASTER: Send address changes to *Seminars in Cutaneous Medicine and Surgery*, Subscription Service, 151 Fairchild Ave, Suite 2, Plainview, NY 11803-1709.

RECIPIENT: To change your address, contact Subscription Services at 1-800-480-4851.

Editorial correspondence should be addressed to Kenneth A. Arndt, MD, Skincare Physicians of Chestnut Hill, 1244 Boylston St, Suite 302, Chestnut Hill, MA 02467. Correspondence regarding subscriptions or change of address should be directed to the Publisher, Subscription Service, 151 Fairchild Ave, Suite 2, Plainview, NY 11803-1709, 1-800-480-4851.

Yearly subscription rate: \$258.00 per year.

Prices are subject to change without notice. Current prices are in effect for back volumes and back issues. Single issues, both current and back, exist in limited quantities and are offered for sale subject to availability. Back issues sold in conjunction with a subscription are on a prorated basis.

Copyright © 2014 by Frontline Medical Communications Inc. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission from the Publisher. Printed in the United States of America.

Advertising representative: Sally Cioci, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609. Phone: 973-206-3434; Fax: 973-206-9378; e-mail: [scici@frontlinemedcom.com](mailto:scici@frontlinemedcom.com)

Publication of an advertisement in *Seminars in Cutaneous Medicine and Surgery* does not imply endorsement of its claims by the Editor(s) or Publisher of the journal.

The ideas and opinions expressed in *Seminars in Cutaneous Medicine and Surgery* do not necessarily reflect those of the Editors or Publisher. Publication of an advertisement or other product mention in *Seminars in Cutaneous Medicine and Surgery* should not be construed as an endorsement of the product or the manufacturer's claims. Readers are encouraged to contact the manufacturer with any questions about the features or limitations of the products mentioned. The Publisher does not assume any responsibility for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this periodical. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosage, the method and duration of administration, or contraindications. It is the responsibility of the treating physician or other health care professional, relying on independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient.

*Seminars in Cutaneous Medicine and Surgery* is indexed in Index Medicus/MEDLINE and EMBASE/Excerpta Medica.

## Highlights of Skin Disease Education Foundation's 38th Annual Hawaii Dermatology Seminar

**S63** Introduction

**S64** The Role of TNF Inhibitors in  
Psoriatic Disease

**Brian F. Mandell, MD, PhD, and  
Jeffrey M. Sobell, MD**

**S69** Therapeutic Development  
in Psoriasis

**Jeffrey M. Sobell, MD, and Craig L. Leonardi, MD**

**S73** Data on the Safety of  
Psoriasis Therapies

**Craig L. Leonardi, MD**

**S76** New Therapeutic Options  
for Actinic Keratosis and  
Basal Cell Carcinoma

**James E. Sligh, Jr, MD, PhD**

**S81** Correcting Age-Related Changes in  
the Face by Use of Injectable Fillers  
and Neurotoxins

**Mark G. Rubin, MD, Sue Ellen Cox, MD,  
Michael S. Kaminer, MD, and  
Nowell Solish, MD, FRCP(C)**

**S85** Post-Test and Evaluation Form

## GUEST EDITORS



**Craig L. Leonardi, MD, Chair**

Clinical Professor of Dermatology  
Saint Louis University  
Central Dermatology  
St Louis, Missouri



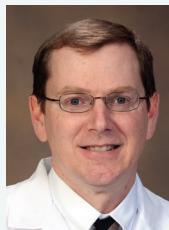
**Mark G. Rubin, MD**

Associate Professor of Dermatology  
University of California, San Diego  
Private Practice  
Beverly Hills, California



**Sue Ellen Cox, MD**

Clinical Associate Professor  
University of North Carolina at Chapel Hill  
Raleigh-Durham, North Carolina



**James E. Sligh, Jr, MD, PhD**

Division Chief, Dermatology  
The University of Arizona  
College of Medicine  
Tucson, Arizona



**Michael S. Kaminer, MD**

Assistant Clinical Professor of Dermatology  
Section of Dermatologic Surgery and Oncology,  
Yale Medical School  
Adjunct Assistant Professor of Medicine (Dermatology)  
Dartmouth Medical School  
Adjunct Assistant Professor, Dermatology  
Brown University School of Medicine  
Chestnut Hill, Massachusetts



**Jeffrey M. Sobell, MD**

Assistant Professor of Dermatology  
Tufts School of Medicine  
Director, Psoriasis Treatment Center  
Skincare Physicians  
Chestnut Hill, Massachusetts



**Brian F. Mandell, MD, PhD**

Professor and Chairman of Medicine  
Department of Rheumatic and Immunologic Diseases  
The Cleveland Clinic  
Cleveland, Ohio



**Nowell Solish, MD, FRCP(C)**

Assistant Professor  
University of Toronto  
Toronto, Ontario, Canada

## INTRODUCTION

**D**ermatology has evolved into one of the most dynamic specialties in medicine. Advances in cellular and molecular biology have translated into clinical progress in the management of multiple conditions that dermatologists treat.

The progress has increased the educational demands of dermatologists to remain up to date regarding the latest developments in the field. The Hawaii Dermatology Seminar offers dermatologists an opportunity to improve their understanding and application of the latest developments in the specialty, regardless of whether their interests lie in skin disease, oncology, or aesthetic dermatology.

This supplement provides a concise yet thorough summation of presentations at the seminar. Leading authorities in the management of psoriasis, skin cancer, and rejuvenation treatment share their expertise and insights that dermatologists will find readily applicable to clinical practice.

Dr Brian F. Mandell and Dr Jeffrey M. Sobell review the role of tumor necrosis factor (TNF) inhibitors in the treatment of psoriatic disease and its comorbidities and offer authoritative insight into new biologic therapies for the disease. Dr Craig L. Leonardi examines the process of evaluating the safety of psoriasis therapies and reviews new nonbiologic systemic therapies for psoriasis.

Dr Brian F. Mandell shares what rheumatologists have learned about the use of anti-TNF therapies, focusing on issues that apply equally to dermatologists.

Dr James E. Sligh summarizes recent developments in the management of actinic keratosis and basal cell carcinoma.

Finally, leading authorities in aesthetic dermatology discuss the use of hyaluronic acid fillers for treatment of age-related skin changes affecting the face. The contributions are by Dr Sue Ellen Cox, Dr Mark G. Rubin, Dr Michael S. Kaminer, and Dr Nowell Solish. They provide insights gained from extensive clinical experience in the treatment of the upper face, midface, lower face, and tear troughs. Additionally, Dr Rubin discusses the role of neurotoxins in facial rejuvenation. Video highlights of SDEF's 38th Hawaii Dermatology Seminar will also be available at [www.globalacademycme.com/index.php?id=8656](http://www.globalacademycme.com/index.php?id=8656).

Craig L. Leonardi, MD  
Clinical Professor of Dermatology  
Saint Louis University  
Central Dermatology  
St Louis, Missouri  
*Journal Supplement Chair*

---

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

Dr Leonardi has received an honorarium from Global Academy for Medical Education for his participation in this activity. He acknowledges the editorial assistance of Charles Bankhead, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Charles Bankhead has no relevant financial relationships with any commercial interests.

---

Craig L. Leonardi, MD, has been a consultant and/or investigator and/or speaker and/or advisory board member for AbbVie, Amgen Inc., Anacor Pharmaceuticals, Inc., Celgene Corporation, Janssen Biotech, Inc., Eli Lilly, Galderma Laboratories, L.P., GlaxoSmithKline, Incyte Corporation, LEO Pharma Inc., Maruho Co., Ltd., Novartis, Novo Nordisk, Inc., Pfizer Inc., Schering-Plough Corporation, Sirtis Pharmaceuticals, Inc., Stiefel Laboratories, Inc., TOLMAR Pharmaceuticals, Inc., Vascular Biogenics Ltd., and Warner Chilcott plc.

1085-5629/13/\$-see front matter © 2014 Frontline Medical Communications  
DOI: 10.12788/j.sder.0096

# The Role of TNF Inhibitors in Psoriatic Disease

Brian F. Mandell, MD, PhD,\* and Jeffrey M. Sobell, MD†

## ■ Abstract

In contrast to many other diseases, modern psoriasis therapy has a fairly brief history. Until about 15 years ago, clinicians and their patients had few options, with limited ability to rein in the disease process. The success of antifolate methotrexate in the treatment of rheumatoid arthritis (RA) led to clinical evaluation and adoption of the agent, a principal form of treatment for psoriasis, which, like RA, has its origin based in inflammation. The introduction of tumor necrosis factor- $\alpha$  inhibitors marked the beginning of the biologic era of psoriasis therapy. Also borrowed from the field of rheumatology, biologic therapy has evolved from improved understanding of the molecular basis of the disease process. An increased recognition of comorbid conditions that often accompany psoriasis, particularly psoriatic arthritis, can complicate clinical management. Dermatologists and other clinicians who treat psoriasis continue to benefit from insights gained in the field of rheumatology.

Semin Cutan Med Surg 33(supp4):S64-S68

© 2014 published by Frontline Medical Communications

## ■ Keywords

Cardiovascular disease; methotrexate; obesity; psoriasis; psoriatic arthritis; psoriatic diseases; rheumatologic diseases; tumor necrosis factor inhibitors

Experience in clinical investigation often does not carry over to clinical practice. Clinical trials have shown that a majority of subjects with psoriasis obtain significant benefit from treatment with a tumor necrosis factor (TNF) inhibitor. Yet, only about 40% of real-world-treated patients remain on a given self-injectable TNF inhibitor after 1 year.<sup>1</sup> Between 60% and 70% have gaps in therapy lasting 60 days or longer, and 15% to 20% of patients to whom a TNF inhibitor is prescribed switch to a different agent in the same class within a year.<sup>1</sup>

\*Professor and Chairman of Medicine, Department of Rheumatic and Immunologic Diseases, The Cleveland Clinic, Cleveland, OH.

† Assistant Professor of Dermatology, Tufts School of Medicine; Director, Psoriasis Treatment Center, Skincare Physicians, Chestnut Hill, MA.

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

The faculty have received an honorarium from Global Academy for Medical Education for their participation in this activity. They acknowledge the editorial assistance of Charles Bankhead, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Charles Bankhead has no relevant financial relationships with any commercial interests.

Brian F. Mandell, MD, PhD, has no relevant financial relationships with any commercial interests.

Jeffrey M. Sobell, MD, has been a consultant and/or speaker and/or investigator for AbbVie, Amgen Inc., Celgene Corporation, Eli Lilly, Janssen Biotech, Inc., and Merck & Co., Inc.

Address reprint requests to: Brian F. Mandell, MD, PhD, Cleveland Clinic Main Campus, Mail Code NA10, 9500 Euclid Avenue, Cleveland, OH 44195, MANDELB@ccf.org

Several factors may contribute to the low persistence and prolonged therapy gaps among patients with psoriasis treated with TNF inhibitors. For some patients, therapy may fail to meet expectations. The rate of psoriasis improvement may not be as rapid as patients had expected, and this may lead to premature discontinuation of therapy. In many instances, closer examination shows that patients did not receive the recommended loading dose, as approved by the US Food and Drug Administration (FDA) for both etanercept and adalimumab for moderate to severe psoriasis. A study by Papp and colleagues<sup>2</sup> suggests that the loading dose facilitates a more rapid onset of action and, thus, potentially may contribute to improved patient persistence with the medication.

Drug holidays are another possible explanation for low persistence rates. Patients feel better and may omit or delay injections; some may interpret their improved condition as a “cure.” Clinicians must remind patients that psoriasis is a chronic condition that requires ongoing therapy to attain or maintain disease control. Gaps in therapy may, in fact, lead to the formation of antibodies against the biologic agent that may render the therapy ineffective.

Not uncommonly, patients require interruptions in therapy, but the key is to avoid prolonged gaps leading to recurrence of disease. Clinical trials of etanercept and adalimumab showed that about 30% of patients who relapsed after discontinuation of therapy did not return to 75% improvement in Psoriasis Area Severity Index (PASI75) when they resumed treatment.<sup>3</sup>

Fear of side effects or concerns about the long-term safety of TNF inhibitors also may contribute to low rates of persistence. Patients and clinicians should be aware that multiple studies have demonstrated that long-term treatment with anti-TNF agents does not result in cumulative toxicity.

Finally, anti-TNF therapy is expensive, and patients might not persist with therapy because of high health insurance deductibles and copayments. Several organizations exist that help with the cost of therapy, and many manufacturers have patient assistance programs that should be explored.

## Loss or Diminution of Response

Some patients with psoriasis experience a loss of response to a TNF inhibitor after months of disease control. When this occurs, possible solutions include using an adjunctive concomitant medication (such as methotrexate or acitretin), increasing the dosing frequency of the TNF inhibitor, or switching to a different TNF inhibitor or a different medication.

Numerous studies have shown that loss of efficacy with one anti-TNF agent does not preclude use of a different agent in the same class. One recent study evaluated infliximab in patients who had an inadequate response to etanercept.<sup>4</sup> Within 10 weeks after starting infliximab, almost two-thirds of patients had achieved Physician Global Assessment (PGA) scores of clear or minimal body surface area (BSA) involvement.

1085-5629/13/\$-see front matter © 2014 Frontline Medical Communications  
DOI: 10.12788/j.sder.0097

In another trial, adalimumab was given to patients who had not responded to etanercept (primary nonresponse) or had responded initially but lost the response over time (secondary nonresponse).<sup>5</sup> Overall, 40 of 82 patients (48.8%) had a PGA score of clear or minimal BSA involvement after 16 weeks of treatment with adalimumab. The overall response included 15 of 26 (57.7%) patients with primary nonresponse to etanercept and 26 of 56 (46.4%) patients with secondary nonresponse.<sup>5</sup> Successful use of etanercept in adalimumab failures has also been reported.<sup>6</sup>

Some patients who lose response to a TNF inhibitor may subsequently respond to the same agent after a period of discontinuation. One case series involved 20 patients who were treated successfully with etanercept for 6 months or longer and then discontinued because of secondary loss of efficacy.<sup>7</sup> Subsequently, most of the subjects received and failed two or more different biologic agent therapies before initiating re-treatment with etanercept. After 12 weeks of re-treatment with etanercept, 8 of 18 (44.4%) had a PGA rating of 0/1 (clear/almost clear response).

In some cases, augmenting a TNF inhibitor with a drug from a different therapeutic class may be more effective than single-agent anti-TNF treatment. In one randomized trial, 478 patients with moderate to severe plaque psoriasis were randomized to receive etanercept, either alone or in combination with methotrexate, or placebo.<sup>8</sup> The primary end point was the proportion of patients who achieved at least 75% improvement in PASI75 at 24 weeks. The results showed that significantly more patients treated with etanercept plus methotrexate had achieved PASI75 ( $P<0.0001$ ) and PASI90 ( $P<0.05$ ) than those in either the etanercept monotherapy or the placebo groups. Importantly, the addition of methotrexate did not increase the incidence of adverse events, including serious adverse events, compared to etanercept monotherapy.

Extensive clinical experience with TNF inhibitor/methotrexate combinations also has shown that the combination may result in therapeutic synergy, increase the odds of durable responses, enhance protection of joint destruction in inflammatory arthritis, and decrease systemic inflammation more effectively than either agent alone.

### Impact of Comorbid Conditions

Psoriasis seldom occurs in clinical isolation. Many patients have one or more comorbid conditions that can increase the complexity of treatment decision making and influence the approach to treatment for psoriasis (Table 1).

#### Psoriatic Arthritis

As many as 39% of patients with psoriasis develop psoriatic arthritis.<sup>9</sup> Large surveys have suggested a greater prevalence of concomitant psoriatic arthritis among European patients with psoriasis than among Americans with the disease.<sup>10,11</sup> This disparity may relate to psoriasis severity. In general, European clinical trials involved patients with more severe psoriasis than seen in patients enrolled in North American clinical trials. Indeed, accumulated data suggest such a correlation between the severity of psoriasis and the presence—but not the severity—of psoriatic arthritis.<sup>11-13</sup>

Among patients with both psoriasis and psoriatic arthritis, the skin disease occurs first in about 70% of cases.<sup>9</sup> Co-occurrence of the two conditions accounts for about 15% of cases, and joint disease precedes skin disease in the remaining 15%.

As is the case with rheumatoid arthritis (RA), early recognition of psoriatic arthritis is essential to prevent joint damage. More than 50% of patients with psoriatic arthritis develop erosive arthropathy, 15% to 20% develop five or more joint deformities, and 10% to 20% of patients have functionally debilitating disease. Like patients with RA, those with psoriatic arthritis have increased mortality compared with the general population.<sup>13,14</sup>

Common signs of psoriatic arthritis include an oligoarticular asymmetric arthritis, spondylitis, enthesitis, and dactylitis. During medical history taking, clinicians should ask patients about tender or swollen joints, prolonged morning joint stiffness, and family history of psoriatic arthritis.<sup>15</sup>

Five TNF inhibitors have FDA approval for treatment of psoriatic arthritis: etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. All five agents are indicated for reducing signs and symptoms of active arthritis, inhibiting progression of structural damage, and improving physical function. Another biologic agent, the p40 antagonist ustekinumab, is approved for reducing signs and symptoms of psoriatic arthritis.

TNF inhibitors have a long track record for efficacy in psoriatic arthritis. One of the early studies evaluated etanercept versus placebo.<sup>16</sup> The primary end point was the proportion of patients who attained 20% improvement in disease status by American College of Rheumatology (ACR20) criteria. After 12 weeks, 59% of etanercept-treated patients had ACR20 responses, compared to 15% of the placebo group ( $P<0.0001$ ). After 24 weeks, the ACR20 response rates were 50% for etanercept and 13% for placebo ( $P<0.0001$ ).

Similar results have been demonstrated with all members of the TNF inhibitor class of agents. A placebo-controlled trial of adalimumab in psoriatic arthritis had a radiographic end point of improvement in modified Total Sharp Score (mTSS) after 48 weeks.<sup>17</sup> At both 24 and 48 weeks, patients treated with adalimumab had significantly greater improvement in mTSS ( $P<0.001$ ), suggesting protection from ongoing joint damage. Similar results have been seen in clinical trials of all five TNF inhibitors.

**TABLE 1 Extracutaneous Manifestations and Comorbidities of Psoriasis**

#### Musculoskeletal

- Psoriatic arthritis
- Tendonitis/enthesitis
- Gout

#### Ocular

- Uveitis

#### Cardiovascular

- Metabolic risk factors increased
- Link to systemic inflammation
- Independent risk for CAD?

**Cardiovascular Risk Factors and Disease**

Patients with psoriasis have an increased risk for cardiovascular disease and factors that contribute to cardiovascular disease.<sup>18,19</sup> The prevalence of metabolic syndrome in patients with psoriasis is almost double that of the general population. The characteristics of metabolic syndrome seen most frequently in patients with psoriasis are abdominal obesity (63%), hypertriglyceridemia (44%), and decreased levels of high-density lipoprotein cholesterol (34%).<sup>18,19</sup>

Emerging evidence has suggested that psoriasis is an independent risk factor for myocardial infarction (MI) and stroke. The magnitude of the risk increases with the severity of psoriasis and appears to be magnified in younger patients who have severe psoriasis.<sup>18</sup>

A 130,000-person cohort study of patients with psoriasis showed a 7% increase in the adjusted relative risk for stroke in association with mild psoriasis, increasing to 44% in patients with severe psoriasis.<sup>20</sup> The risk remained elevated after adjustment for age, sex, and other risk factors for stroke.

The association between psoriasis and cardiovascular risk may involve TNF, which is a key proinflammatory cytokine associated with development of atherosclerosis.<sup>21</sup> TNF modulates production or activation of other proinflammatory proteins, such as interleukin-6 and C-reactive protein. The chronic inflammation of metabolic syndrome appears to revolve around TNF, which promotes insulin resistance and adversely affects lipid metabolism.

Treatment with TNF inhibitors has been associated with favorable effects on multiple parameters associated with metabolic syndrome and cardiovascular disease (Table 2). A modest amount of data has suggested that treatment with TNF inhibitors might help reduce the risk for atherosclerosis and cardiovascular events.

In one study, patients treated with TNF inhibitors underwent carotid ultrasound to assess carotid intima-media thickness (cIMT), a surrogate for atherosclerosis.<sup>22</sup> Patients treated with TNF inhibitors had significant reductions in cIMT ( $P < 0.0001$ ).

Observational data have suggested a reduced risk for MI in

patients with psoriatic disease treated with anti-TNF agents.<sup>23</sup> The association does not prove that anti-TNF therapy reduces MI risk but, rather, is consistent with the hypothesis that anti-TNF agents favorably affect MI risk.

**Obesity**

Studies have demonstrated that patients who are overweight or obese have a less robust response to TNF inhibitors. For example, investigators in a randomized, placebo-controlled trial of etanercept evaluated PASI75 response by weight. Heavier patients had substantially lower response rates to both etanercept doses (50 mg weekly and 50 mg twice weekly) evaluated in the study.<sup>24</sup>

Similar results have been observed with other TNF inhibitors, with the exception of infliximab because this drug is dosed by weight. Data from a placebo-controlled trial were stratified by body mass index (BMI). The results showed no significant difference in response rate by BMI (<25, 25-<30, ≥30) in the placebo or infliximab treatment groups.<sup>25</sup>

**Rheumatologic Perspective on Psoriatic Disease**

Psoriasis often exhibits extracutaneous manifestations that cross different medical specialties, including several types of musculoskeletal disorders that extend into the purview of the rheumatologist. Musculoskeletal manifestations of psoriatic disease have some association with severity of the skin disease, but the association is not an extremely strong one. The musculoskeletal disorders may precede or follow appearance of the skin disease.

The musculoskeletal manifestations comprise several distinct patterns, including spondylitis, enthesitis, and dactylitis.

Spondylitis often goes unrecognized because the presentation is subtle, something as simple as a backache, which is prevalent in patients with psoriatic disease and in the general population. Nonetheless, the condition can severely restrict a person's function.

Psoriatic spondylitis is not the same as ankylosing spondylitis. About 60% of patients with psoriatic spondylitis test positive for HLA B27, whereas more than 90% of patients with ankylosing spondylitis are HLA B27 positive. For reasons that remain unclear, spondylitis appears to be especially sensitive to anti-TNF therapy and insensitive to other therapies.

■ **TABLE 2** Effects of TNF-Inhibitor Therapies on Various Comorbidities

Comorbidity	Study Outcome
Obesity with type 2 diabetes	4-week course of etanercept 25 mg BIW significantly reduced systemic inflammatory markers such as CRP and IL-6 but had no effect on vascular or metabolic insulin sensitivity (N=20) <sup>1</sup>
Metabolic syndrome	4-week course of etanercept 50 mg QW lowered CRP and fibrinogen and elevated adiponectin levels, with no effects noted on insulin sensitivity and on either BMI or waist-to-hip ratio (N=56) <sup>2</sup>
Vascular function	<ul style="list-style-type: none"> <li>• Short-term adalimumab therapy improved endothelial function in 8 patients with RA refractory to infliximab<sup>3</sup></li> <li>• 12 weeks of infliximab therapy was shown to improve endothelial function in 11 RA patients<sup>4</sup></li> </ul>
Insulin resistance	Dramatic reduction in the serum insulin levels and insulin/glucose index observed in 27 patients with RA following infliximab infusion; significant improvement of insulin resistance and insulin sensitivity <sup>5</sup>

BIW=biweekly; BMI=body mass index; CRP=C-reactive protein; IL-6=interleukin-6; QW=every week; RA=rheumatoid arthritis; TNF=tumor necrosis factor. Sources: 1. Dominguez H, et al. *J Vasc Res.* 2005;42:517-525. 2. Bernstein LE, et al. *Arch Intern Med.* 2006;166:902-908. 3. Gonzalez-Juanatey C, et al. *Clin Exp Rheumatol.* 2006;24:309-312. 4. Hürlimann D, et al. *Circulation.* 2002;106:2184-2187. 5. Gonzalez-Gay MA, et al. *Clin Exp Rheumatol.* 2006;24:83-86.



Enthesitis arises in the Achilles tendon at the junction of the tendon and bone, making it difficult to manage. Most rheumatologists are reluctant to biopsy the area or to use injection therapy because of concern about weakening the connection between the tendon and bone. When injectable therapy is administered, the frequency of injections is carefully monitored to avoid damage to the delicate connection.

Dactylitis is specific to psoriatic disease and a few other forms of arthritis and is virtually nonexistent in RA. Characterized by diffuse swelling involving a finger or toe, dactylitis involves inflammation that has spread from the joint to surrounding tissues. The condition might be more correctly characterized as a form of tenosynovitis.

### Methotrexate and Psoriatic Arthritis

Methotrexate has long been a mainstay of treatment for RA and psoriatic arthritis, although the latter condition is not an approved indication for this drug. Early experience with methotrexate in psoriatic arthritis led to some concern about hepatotoxicity. The concern likely resulted from the way the drug was used in early clinical experience. Patients received several doses a week or even daily doses, and folic acid supplements were not prescribed for concomitant use. In addition, patients were not routinely screened for underlying liver disease, including nonalcoholic fatty liver disease.

Treatment practices of 30 years ago cannot be compared to current use of methotrexate. The drug has a safety record in RA that led the ACR to eliminate its recommendation of liver biopsies for patients taking methotrexate, even in cases of prolonged use of 10 years or more. Transaminase measurement on a regular basis is still recommended.

The results of a recent randomized, placebo-controlled trial of methotrexate have given clinicians reason to reassess the use of the drug as monotherapy in psoriatic arthritis.<sup>26</sup> The trial involved 221 patients with psoriatic arthritis treated for 6 months with methotrexate or placebo. The results showed improvement in skin lesions and patient-reported outcomes, but no significant improvement in objective measures of joint disease. However, this trial has been criticized for several reasons. First, the study population was not large. Second, the target dose of methotrexate used was 15 mg a week, whereas rheumatologists routinely prescribe 20 to 25 mg weekly. Third, only 78% of patients were receiving 15 mg of methotrexate when the study ended, and they had received that dose for just 3 months. Fourth, more than 10% of patients were taking less than 15 mg of the medication. Fifth, patients in the trial did not have severe or active psoriatic arthritis, and 81% were taking nonsteroidal anti-inflammatory drugs in addition to randomized therapy, which would increase the difficulty of demonstrating a significant difference between treatment groups. Finally, a large number of patients—20%—were lost to follow-up.

Given methotrexate's long history of effectiveness in rheumatologic diseases and the methodologic problems described, the results of this single trial should not dissuade clinicians from prescribing methotrexate for patients with psoriatic arthritis. The drug is not effective for axial (spinal) disease, but more evidence is needed before determining methotrexate's efficacy over placebo in psoriatic arthritis. In addition,

methotrexate may be of value in limiting the generation of anti-drug (neutralizing) antibodies when used in conjunction with anti-TNF agents. The use of methotrexate requires monitoring of transaminase levels, and clinical guidelines have been developed to provide direction for testing.

### Anti-TNF Therapy in Psoriatic Arthritis

The TNF inhibitors have become a cornerstone of therapy for psoriatic disease, including psoriatic arthritis. These agents have proven especially effective for treating skin lesions, which might require higher doses in severe cases, as compared with effective doses for joint disease.

Activity in psoriasis-related spondylitis and spinal disease has distinguished the TNF inhibitors from other options for the systemic treatment of psoriatic arthritis. None of the other therapies can match the level of activity in spondylitis and spinal disease.

Several practical issues should be considered when using TNF inhibitors in patients with psoriatic arthritis.<sup>27,28</sup> Dosage adjustment might be required with etanercept in overweight and obese patients. A few reports in the literature have documented induction or worsening of skin disease with use of TNF inhibitors to treat arthritis. However, the phenomenon appears to be uncommon. Rarely, use of TNF inhibitors has been associated with induction of lupus and multiple sclerosis.

In addition to periodic liver enzyme (transaminase) tests, screening for hepatitis B and C virus (HBV and HCV) is recommended prior to initiating anti-TNF therapy, as drug-associated reactivation of HBV can lead to hepatic necrosis. Additionally, patients should be evaluated for exposure to tuberculosis before starting treatment with any of the anti-TNF agents. An interferon release assay should be repeated whenever a patient encounters a potential for exposures (such as travel abroad). Patients who have visited areas in which tuberculosis is endemic also should have a chest x-ray.

A patient's vaccination history should be reviewed prior to starting treatment with a TNF inhibitor. In particular, patients treated with anti-TNF agents have been advised to avoid live-virus immunization. An accumulation of retrospective data suggests that patients on TNF inhibitors may have an increased risk for perioperative infections.

### Summary

Treatment of psoriatic disease has evolved dramatically over the past several years, and new and more effective therapies have become available. In particular, TNF inhibitors have proven effective in both psoriasis and psoriatic arthritis. Comorbid conditions often complicate clinical management of psoriatic disease, as patients have an increased prevalence of metabolic syndrome and cardiovascular disease. Clinical management of psoriatic disease often encompasses several medical specialties, and patients can benefit from a multidisciplinary approach.

### References

1. Chastek B, Fox KM, Watson C, Kricorian G, Gandra SR. Psoriasis treatment patterns with etanercept and adalimumab in a United States health plan population. *J Dermatol Treat.* 2013;24:25-33.
2. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: Safety, efficacy and effect of dose reduction. *Br J Dermatol.* 2005;152:1304-1312.
3. Ramirez-Fort MK, Levin AA, Au S-C, Gottlieb AB. Continuous versus intermittent therapy for moderate-to-severe psoriasis. *Clin Exp Rheumatol.* 2013;31 (suppl. 78): S63-S70.

4. Gottlieb AB, Kalb RE, Blauvelt A, et al. The efficacy and safety of infliximab in patients with plaque psoriasis who had an inadequate response to etanercept: Results of a prospective, multicenter, open-label study. *J Am Acad Dermatol*. 2011;67:642-650.
5. Strober BE, Poulin Y, Kerdel FA, et al. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: Efficacy and safety results from an open-label study. *J Am Acad Dermatol*. 2011;64:671-681.
6. Chatzidionysiou K, Askling J, Eriksson J, Kristensen LE, van Vollenhoven R; for the ARTIS group. Effectiveness of TNF inhibitor switch in RA: Results from the national Swedish register. *Ann Rheum Dis*. 2014 Jan 15. doi:10.1136/annrheumdis-2013-204714. [Epub ahead of print]
7. Vitiello M, Abuchar A, Grant A, Kerdel F. An open-label study to evaluate the efficacy of retreatment of patients with psoriasis who have previously been treated with etanercept. *J Am Acad Dermatol*. 2011;64(suppl):AB35. P1113.
8. Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167:649-657.
9. Leonard DG, O'Duffy JD, Rogers RS. Prospective analysis of psoriatic arthritis in patients hospitalized for psoriasis. *Mayo Clin Proc*. 1978;53:511-518.
10. Van Kerkhof P, Salonen SH. EADV Spring Symposium. 2004.
11. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol*. 2005;53:573.
12. Leczinsky CG. The incidence of arthropathy in a 10 year series of psoriasis cases. *Acta Derm Venereol*. 1948;28:483-487.
13. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA)—an analysis of 220 patients. *Q J Med*. 1987;62:127-141.
14. Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM, Ballina Garcia J, Riestra Noriega JL, Lopez Larrea C. Psoriatic arthritis (PA): A clinical, immunological and radiological study of 180 patients. *Br J Rheumatol*. 1991;30:245-250.
15. Mease P, Goffe BS. Diagnosis and treatment of psoriatic arthritis. *J Am Acad Dermatol*. 2005;52:1-19.
16. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: Safety, efficacy, and effect on disease progression. *Arthritis Rheum*. 2004;50:2264-2272.
17. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52:3279-3289.
18. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1735-1741.
19. Love TJ, Qureshi AA, Wood Karlson E, Gelfand JM, Choi HK. Prevalence of metabolic syndrome in psoriasis: Results from the National Health and Nutrition Examination Survey, 2003-2006. *Arch Dermatol*. 2011;147:419-424.
20. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol*. 2009;129:2411-2418.
21. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. *Arch Intern Med*. 2006;166:902-908.
22. Del Porto F, Lagana B, Lai S, et al. Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. *Rheumatology (Oxford)*. 2007;46:1111-1115.
23. Wu J, Shen AY-J, Fisher A, Poon K-Y, Burchette R. The effect of tumor necrosis factor- $\alpha$  inhibitors on the risk of myocardial infarction in patients with psoriasis. *J Am Acad Dermatol*. 2011;64(suppl):AB7. P400.
24. Gordon K, Korman N, Frankel E, et al. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. *J Am Acad Dermatol*. 2006; 54(3 suppl 2):S101-S111.
25. Reich K, Gottlieb AB, Kimball A, Li S. Consistency of infliximab response across subgroups of patients with psoriasis: Integrated results from randomized controlled clinical trials. *J Am Acad Dermatol*. 2006;54 (3 suppl):AB215.
26. Kingsley GH, Kowalcyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)*. 2012;51:1368-1377.
27. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: A literature review and potential mechanisms of action. *Arthritis Rheum*. 2008;59:996-1001.
28. Cullen G, Kroshinsky D, Cheifetz AS, Korzenik JR. Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: A new series and review of 120 cases from the literature. *Aliment Pharmacol Ther*. 2011; 34:1318-1327.

# Therapeutic Development in Psoriasis

Jeffrey M. Sobell, MD,\* and Craig L. Leonardi, MD†

## ■ Abstract

Advances in molecular biology have provided the basis for development of new therapeutic approaches to psoriasis. New, more effective therapies target specific molecules in the inflammatory cascade involved in the pathogenesis of psoriasis. The biologic era of psoriasis therapy began with inhibitors of T-cell activation, tumor necrosis factor- $\alpha$ , and interleukin (IL)-12/23. Continued investigation has led to therapies and therapeutic candidates that target IL-17, IL-23, phosphodiesterase-4, and isomers of Janus kinase.

Semin Cutan Med Surg 33(supp4):S69-S72

© 2014 published by Frontline Medical Communications

## ■ Keywords

Apremilast; brodalumab; inflammation; interleukin-12/23; ixekizumab; JAK inhibitor-17 inhibitors; Janus kinase inhibitors; monoclonal antibody; phosphodiesterase-4; psoriasis; secukinumab; tofacitinib; tumor necrosis factors

## Pathophysiology of Psoriasis

Only relatively recently did clinicians and researchers come to recognize psoriasis as an immune-mediated inflammatory skin disease. The recognition was preceded by years of pursuing strategies to alter or correct defects in keratinocytes, the presumptive cause of uncontrolled cellular proliferation culminating in plaque psoriasis.

The concept of psoriasis as an immunologic disorder has its genesis in the observation that treatment with cyclosporine dramatically improved the condition. Even then, the proof was not definitive, because cyclosporine has a known effect on replicating keratinocytes.

\*Assistant Professor of Dermatology, Tufts School of Medicine; Director, Psoriasis Treatment Center, Skincare Physicians, Chestnut Hill, MA.

† Clinical Professor of Dermatology, Saint Louis University Central Dermatology, St Louis, MO.

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

The faculty have received an honorarium from Global Academy for Medical Education for their participation in this activity. They acknowledge the editorial assistance of Charles Bankhead, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Charles Bankhead has no relevant financial relationships with any commercial interests.

Jeffrey M. Sobell, MD, has been a consultant and/or speaker and/or investigator for AbbVie, Amgen Inc., Celgene Corporation, Eli Lilly, Janssen Biotech, Inc., and Merck & Co., Inc.

Craig L. Leonardi, MD, has been a consultant and/or investigator and/or speaker and/or advisory board member for AbbVie, Amgen, Anacor Pharmaceuticals, Inc., Celgene, Janssen Biotech, Inc., Eli Lilly, Galderma Laboratories, L.P., GlaxoSmithKline, Incyte Corporation, LEO Pharma Inc., Maruho Co., Ltd., Novartis, Novo Nordisk, Inc., Pfizer Inc., Schering-Plough Corporation, Sirtis Pharmaceuticals, Inc., Stiefel Laboratories, Inc., TOLMAR Pharmaceuticals, Inc., Vascular Biogenics Ltd., and Warner Chilcott plc.

Address reprint requests to: Jeffrey M. Sobell, MD, Tufts University School of Medicine, 145 Harrison Ave, Boston, MA 02111, jsobell@SkinCarePhysicians.net

1085-5629/13/\$-see front matter © 2014 Frontline Medical Communications  
DOI: 10.12788/j.sder.0098

The pivotal point in understanding occurred with completion of the DAB-IL-2 trial using denileukin diftitox, which specifically targets T cells. Knowledge gained from that trial confirmed the T cell as central to the pathogenesis of psoriasis and provided the impetus for evaluation of immunologic strategies to treat the disease.<sup>1</sup>

The immunologic framework of psoriasis has evolved continually with advances in understanding the molecular basis of the disease. As recently as a decade ago, psoriasis pathophysiology was thought to begin with a yet-to-be identified antigen, which was transported by an antigen-presenting cell to a skin-draining lymph node, wherein T-cell activation began. The T cells were believed to be transported back to the skin through the vasculature, and, upon re-entry, to trigger the release of inflammatory mediators, including tumor necrosis factor (TNF)- $\alpha$ . This conceptual framework of psoriasis led to development of first-generation biologic agents, alefacept and efalizumab, which targeted T-cell activation.<sup>2</sup>

As understanding of psoriasis pathogenesis has continued to evolve, so have strategies to treat the disease (**Table**). As currently understood, psoriasis pathogenesis begins with activation of myeloid dendritic cells, leading to the release of interleukin (IL)-12 and IL-23. IL-12 plays a key role in the differentiation of T cells in the T-helper (T<sub>H</sub>) 1 pathway, which has been the focus of therapeutic development for the past several years.

## New Pathway for Drug Development

Investigation of IL-23 has shown that the proinflammatory cytokine facilitates activation and survival of T<sub>H</sub>17 cells, which, in turn, stimulate release of inflammatory mediators such as IL-17 and IL-22. The inflammatory mediators interact with TNF and interferon- $\gamma$ , leading to activation of keratinocytes.

In the context of psoriasis, IL-17 has several key activities.<sup>3</sup> IL-17 recruits T<sub>H</sub>17 cells and myeloid dendritic cells into plaques, facilitates neutrophil migration and survival, and increases antimicrobial peptides to enhance innate immunity. Additionally, IL-17 stimulates angiogenesis and vascular inflammation associated with atherosclerosis, a possible clue to the increased cardiovascular risk that has been observed in patients with psoriasis.

Six isoforms of IL-17 have been identified (IL-17A, B, C, D, F, and  $\gamma$ ).<sup>4</sup> With respect to psoriasis, IL-17A is highly expressed in skin lesions and has become a target of therapeutic development.

## Secukinumab

Secukinumab is a fully human anti-IL-17A monoclonal antibody. The drug has been evaluated in four phase III trials, including two pivotal trials, known as ERASURE (Efficacy of Response and Safety of 2 Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Safety and Efficacy of Secukinumab Compared to Etanercept in Subjects With Moderate to Severe, Chronic Plaque-Type Psoriasis).

**TABLE** Biologic Agents and Small Molecules in Psoriasis

Class/Target Pathway	Generic Drug Name/Description	Current Status*
<b>Biologic agents</b>		
TNF- $\alpha$ inhibition	Adalimumab: Recombinant human IgG1 monoclonal antibody specific for human TNF	Approved for psoriasis, 2008
	Etanercept: Dimeric fusion protein consisting of the extracellular ligand-binding portion of the p75 TNF receptor, linked to the Fc portion of human IgG1	Approved for psoriasis, 2004
	Infliximab: Chimeric IgG1 $\kappa$ monoclonal antibody, composed of human constant and murine variable regions, specific for human TNF	Approved for psoriasis, 2006
IL-12 and IL-23 inhibition	Ustekinumab: Human IgG1 $\kappa$ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines	Approved for psoriasis, 2008
Direct inhibition of IL-17	Brodalumab: Fully human anti-IL-17 receptor monoclonal antibody	Phase III trials under way
	Ixekizumab: Humanized anti-IL-17A monoclonal antibody	Phase III trials under way
	Secukinumab: Fully human anti-IL-17A monoclonal antibody	Phase III trials complete
IL-23 blocker	Tildrakizumab: Humanized anti-IL-23p19 monoclonal antibody	Phase III trials under way
	Guselkumab: Fully human anti-IL-23p19 monoclonal antibody	Phase II trials complete
<b>Small molecules</b>		
PDE-4 inhibitor	Apremilast: Inhibitor of phosphodiesterase 4	Approved for psoriatic arthritis, 2014
JAK inhibitor	Tofacitinib: Inhibitor of Janus kinase	Phase III trials complete

IL=interleukin; JAK=Janus kinase; PDE-4=phosphodiesterase-4; TNF=tumor necrosis factor.  
\*The status listed for each agent is current as of June 23, 2014.

ERASURE was a randomized, placebo-controlled trial involving 738 patients with moderate or severe plaque psoriasis.<sup>5</sup> Patients received secukinumab 300 mg or 150 mg or placebo, administered once a week for 4 weeks and then every 4 weeks thereafter.

The primary end point was 75% improvement on the Psoriasis Area Severity Index (PASI75). Placebo-treated patients who did not have PASI75 responses after 12 weeks were randomized a second time to 300 or 150 mg of secukinumab. Maintenance therapy continued in all groups for an additional 40 weeks.<sup>5</sup>

The study population had a mean disease duration of about 17 years. Body surface area involvement averaged about 30%, and the patients had a baseline mean PASI score of 22. About 20% of the patients had psoriatic arthritis.<sup>5</sup>

The results showed a rapid onset of action in patients treated with secukinumab. After 12 weeks, 81.6% of patients in the 300-mg secukinumab group had met criteria for a PASI75 response, as had 71.6% of patients in the 150-mg group. By comparison, 4.5% of placebo-treated patients had a PASI75 response ( $P<0.0001$ ). The PASI75 response rate reached a peak of 87.8% in the secukinumab 300-mg group at 16 weeks.<sup>5</sup>

Increasingly, the benchmark for efficacy is focusing on PASI90 (minimal residual disease) and PASI100 (clear) responses. In the secukinumab 300-mg group, 70% of patients had PASI90 responses at 16 weeks, and 40% had PASI100 responses.<sup>5</sup>

With continued monthly maintenance doses, the responses proved to be durable out to 52 weeks, as response rates were about 80% for PASI75, 70% for PASI90, and 40% for PASI100.<sup>5</sup>

The 52-week safety data provided reassurance. The incidence of serious adverse events was low and comparable in the secukinumab groups, and less than 5% of patients discontinued because of adverse events. The most common adverse events were nasopharyngitis (20%-25%), upper respiratory tract infections (11%-12%), and headache (9%).<sup>5</sup>

FIXTURE was a four-arm randomized trial involving 1,300 patients with moderate or severe psoriasis.<sup>6</sup> Patients received one of two doses of secukinumab, placebo, or etanercept 50 mg twice weekly for 12 weeks, then weekly thereafter. Similar to the patients in the ERASURE trial, the FIXTURE study population had a mean disease duration of 16 years, baseline mean PASI score of 24, and body surface area involvement of about 34%. About 15% of the patients had psoriatic arthritis.

PASI75 response rates at week 12 were 77% and 67% in the 300-mg and 150-mg secukinumab groups, respectively, compared to 44% in the etanercept arm. The PASI90 rate reached a maximum of 72.4% at 16 weeks with the 300-mg dose of secukinumab versus 41.5% with etanercept at 32 weeks. PASI100 scores peaked at 36.8% after 16 weeks with secukinumab 300 mg and 13.0% at 32 weeks with etanercept.<sup>6</sup>

Underscoring the rapid onset of action with secukinumab, 50% of patients treated with the 300-mg dose had a 50% reduction in baseline PASI score within 3 weeks. Patients treated with etanercept did not pass the 50% improvement mark until week 8.<sup>6</sup>

The safety profile of secukinumab was similar to what was observed in the ERASURE trial. Serious adverse events occurred in a similar proportion of patients treated with secukinumab or etanercept. The most frequently reported adverse events in all groups were nasopharyngitis and headache.<sup>6</sup>

#### Ixekizumab

Ixekizumab is a humanized anti-IL-17A monoclonal antibody. Results were reported recently from a phase II trial in which 132 patients with moderate to severe psoriasis were randomized to one of four subcutaneous doses of ixekizumab (10-150 mg) or placebo.<sup>7</sup> Patients received induction doses at baseline, 2 weeks, and 4 weeks, followed by monthly treatment at weeks 8, 12, and 16. The primary end point was PASI75 at 12 weeks.

The results showed that patients treated with the three highest doses of ixekizumab (25, 75, and 150 mg) had PASI75 rates of 77% to 83% at 12 weeks as compared with 29% in the ixekizumab 10-mg arm and 8% in the placebo group. The week 12 PASI90 rates ranged between 50% and 70% for the three highest doses of ixekizumab versus 20% for the lowest dose and 0% for the placebo group. PASI100 rates reached a maximum of about 40% at week 12 with the two highest doses of ixekizumab.<sup>7</sup>

No serious adverse events occurred in any group during the study. The most frequent adverse events across all treatment groups were infection and nasopharyngitis, rates of which were low and similar to placebo. Nonserious injection-site reactions were observed with the three highest doses of ixekizumab but occurred in 10% or less of patients in the groups.<sup>7</sup>

Closer inspection of the onset of action showed that achieving a PASI50 by 4 weeks was highly predictive of PASI75 success by week 12.<sup>8</sup> Patients who responded early (PASI50 at week 4) were significantly more likely to attain PASI75 and PASI100 responses at 8, 12, and 16 weeks than were patients who did not attain PASI50 at 4 weeks ( $P < 0.05$  to  $P < 0.001$ ).

Participants in the phase II trial of ixekizumab had an opportunity to enter a 52-week open-label extension study in which all patients received 120 mg of ixekizumab every 4 weeks.<sup>7</sup>

The results showed rapid, high, and sustained rates of PASI75, PASI90, and PASI100 responses through 52 weeks in patients who initially received ixekizumab or placebo. The favorable safety profile observed during the randomized study continued through the open-label extension portion of the study.<sup>9</sup>

### **Brodalumab**

In contrast to secukinumab and ixekizumab, brodalumab is a fully human monoclonal antibody against the IL-17 receptor. The agent was evaluated in a phase II study in which patients with moderate to severe psoriasis were randomized to one of four doses of brodalumab or placebo for 12 weeks.<sup>10</sup>

Across the four dose groups, the highest response rates were 83% for PASI75, 75% for PASI90, and 63% for PASI100. The best results occurred with the two intermediate doses of brodalumab administered every 2 weeks (140 and 210 mg).<sup>10</sup>

Assessment of quality of life showed that a majority of patients had Dermatology Life Quality Index (DLQI) scores of 0 or 1, meaning that neither the disease nor the treatment had a negative effect on daily life. The findings were highest and similar in the two intermediate-dose groups.<sup>10</sup>

The drug had a favorable safety profile that included small increases in arthralgia, pharyngitis, pain in extremity, and injection-site reactions versus placebo when all brodalumab groups were combined.<sup>10</sup>

Brodalumab also was evaluated in a 96-week open-label extension study.<sup>11</sup> Patients received weight-adjusted doses at baseline and weeks 1 and 2, followed by treatment every 2 weeks. The primary outcomes were PASI response rates, adverse events, and serious adverse events.

Of 173 patients who began the study, 153 completed the 96 weeks of treatment and follow-up. By week 8, more than 90% of the patients had attained PASI75 responses, a rate that was maintained through the end of follow-up (as-observed analysis). The PASI90 rate surpassed 80% by week 12 and stabilized at that level to week 96. More than 60% of the patients had PASI100 responses by week 8, a rate that remained stable through the end of the extension study.<sup>11</sup>

### **Targeting IL-23**

Agents have been developed to target the p40 subunit common to IL-12 and IL-23, most notably, ustekinumab. However, theoretical considerations suggest that targeting IL-23 in isolation might have advantages.<sup>12</sup> In particular, IL-12 affords protection against infection and malignancy. Furthermore, recent investigations reveal elevated levels of p19 (subunit of IL-23) in the psoriatic plaque, but not p35 (subunit of IL-12).<sup>13</sup>

Tildrakizumab is a humanized monoclonal antibody against IL-23p19. Investigators in a phase IIb clinical trial randomized 340 patients to one of four doses of tildrakizumab or placebo.<sup>13</sup> The primary end point was PASI response rates at week 16. The results showed PASI75 rates of 65.5% to 76.2% for the three highest doses of the antibody. The highest dose led to a PASI90 rate of 51.2% at 16 weeks.

In the pivotal PHOENIX 1 (Psoriasis Followed by Long-Term Extension) trial of ustekinumab, PASI75 rates were 76% and 85% with two different doses of the drug. However, full efficacy was not reached until week 24. At week 16, the PASI75 rates were similar to those observed with tildrakizumab, supporting the hypothesis that blocking IL-12 has minimal therapeutic relevance in psoriasis.<sup>14</sup>

The most common adverse event in the phase IIb trial of tildrakizumab was nasopharyngitis. Overall, the frequency or type of adverse events did not differ substantially between the tildrakizumab and placebo groups.<sup>13</sup>

Patients who achieved PASI75 responses in the trial were eligible to enter an extension phase that continued to week 52. Results of the extension study showed that response to tildrakizumab remained stable out to 52 weeks.<sup>15</sup>

### **Small-Molecule Inhibitors**

Recent therapeutic development in psoriasis has focused primarily on injectable agents. However, several oral small-molecular inhibitors are in development and evaluation.

#### **Apremilast**

Apremilast is an inhibitor of phosphodiesterase-4. In contrast to specifically targeted biologic agents, the key mechanism of action is unclear, as apremilast has multifaceted anti-inflammatory properties. The agent reduces levels of TNF- $\alpha$ , IL-2, interferon- $\gamma$ , several leukotrienes, and nitric oxide synthase.

The pivotal phase III ESTEEM 1 (Study to Evaluate Safety and Effectiveness of Oral Apremilast (CC-10004) in Patients With Moderate to Severe Plaque Psoriasis) trial compared apremilast and placebo in 844 patients with moderate or severe psoriasis, including patients who had not achieved adequate responses to anti-TNF therapy.<sup>16</sup> The primary end point was PASI75 rate at 16 weeks.

A third of patients attained PASI75 responses after 16 weeks, significantly better than placebo ( $P = 0.0273$  to  $P < 0.0001$ ). The highest response rates (38.7% and 35.8%) occurred in the subgroups of patients who had no prior exposure to systemic therapy or to biologic agents.<sup>16</sup>

Placebo-treated patients could switch to apremilast after 16 weeks if they had not attained or maintained a PASI75 response. Similar to patients who started treatment with apremilast, a third of those who crossed over to apremilast attained PASI75 responses by week 32.<sup>16</sup>

Analysis of secondary end points consistently demonstrated superiority of apremilast to placebo, including pruritus, DLQI, Physician Global Assessment, and improvement in nail scores.<sup>16</sup>

Apremilast also was evaluated in a phase III trial involving patients with psoriatic arthritis.<sup>17</sup> The patients were randomized to one of two doses of apremilast or placebo, and the trial's primary end point was 20% improvement in disease status by American College of Rheumatology (ACR20) criteria at week 12.

About 30% of patients attained ACR20 responses in both apremilast groups combined versus 17% in the placebo group. After 52 weeks of treatment and follow-up, ACR20 rates were 53.4% and 58.7% with the 20-mg twice-daily and 30-mg twice-daily treatment groups.<sup>17</sup>

The ACR20 response rates at 52 weeks are comparable to rates observed in randomized clinical trials of TNF inhibitors. However, the response rates with TNF inhibitors were attained in less than half the time (24 vs 52 weeks).<sup>18,19</sup>

### Tofacitinib

A member of the Janus kinase (JAK) inhibitor class, tofacitinib has US Food and Drug Administration (FDA) approval for the treatment of rheumatoid arthritis (RA). The drug inhibits three isomers of JAK but is more specific for JAK1 and JAK3 than for JAK2. Tofacitinib has multiple downstream effects on inflammatory cytokines and chemokines and other proinflammatory cells, including T cells and natural killer cells. Trials in psoriasis have shown the agent is highly efficacious and relatively well tolerated.<sup>20</sup>

Tofacitinib was evaluated in a phase IIb randomized dose-finding study.<sup>20</sup> Patients were randomized to placebo or to one of three doses of the JAK inhibitor. The results showed a dose-dependent increase in the PASI75 response rate versus placebo, achieving separation from placebo as early as 4 weeks and continuing to 12 weeks. The 12-week PASI75 rate approached 70% in patients treated with the highest dose (15 mg twice daily).

Five serious adverse events occurred, three of which involved the same patient. Tofacitinib was associated with minor decreases in hemoglobin, transient decreases in polymorphonuclear neutrophils, and dose-related increases in both high-density and low-density lipoprotein cholesterol.<sup>21</sup>

FDA approval of the drug for RA included a required black-box warning related to a numerical increase in the rate of malignancy other than nonmelanoma skin cancer. Although not statistically significant, the observation is consistent with an association between increasing exposure to tofacitinib and increased risk of malignancy.

A recent analysis of tofacitinib-associated malignancy in patients with RA did not clearly demonstrate a numerical increase in risk over time.<sup>22</sup> However, the data also did not provide clear evidence of a decreased risk, which would be expected in the late phases of long-term treatment where there is an enrichment of study subjects who tolerate the drug and are responding well.

The FDA also has taken note of opportunistic infections, including tuberculosis, in tofacitinib-treated patients with RA. In the RA development program, almost three dozen opportunistic infections were documented, all occurring in tofacitinib-treated patients. Additionally, 14 of 15 patients who died of infection were treated with tofacitinib. The observed pattern of infectious events is consistent with significant immunosuppression, according to the FDA.<sup>23</sup>

### Summary

After years with few effective options for treatment of psoriasis, a steady pattern of market expansion has given clinicians and patients reason for optimism that the difficult, frequently treatment-resistant disease can be controlled. Therapeutic development continues at a rapid pace as compared with historical experience. New biologic agents have driven response rates to new heights. Advances in understanding the molecular biology of psoriasis has led to new therapeutic strategies that have shown promise for continued improvement of outcomes.

### References

- Martin A, Gutierrez E, Muglia J, et al. A multicenter dose-escalation trial with denileukin diftitox (ONTAK, DAB(389)IL-2) in patients with severe psoriasis. *J Am Acad Dermatol.* 2001;45:871-881.
- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med.* 2009;361:496-509.
- Girolomoni G, Mrowietz U, Paul C. Psoriasis: Rationale for targeting interleukin-17. *Br J Dermatol.* 2012;167:717-724.
- Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol.* 2009;160:319-324.
- Elewski B et al. ERASURE study of secukinumab phase 3 study. Presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey.
- Langley R et al. Secukinumab compared with placebo and etanercept: The first 52-week head-to-head comparison of two biologics in a randomized, double-blind, phase 3 study in subjects with moderate-to-severe psoriasis. Presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey.
- Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012;366:1190-1199.
- Zhu B, Edson-Heredia E, Cameron GS, et al. Early clinical response as a predictor of subsequent response to ixekizumab treatment: Results from a phase II study of patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2013;169:1337-1341.
- Gordon K, Leonardi C, Braun D, et al. Results after at least 52 weeks of open label treatment with ixekizumab, an anti-IL-17A monoclonal antibody, in a phase 2 study in chronic plaque psoriasis. *J Am Acad Dermatol.* 2014;70(5 suppl 1):AB183.
- Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med.* 2012;366:1181-1189.
- Papp K, Leonardi C, Menter A, et al. Improvement of psoriasis in patients with and without prior brodalumab (AMG 827) treatment in an open-label extension study. Presented at: Canadian Dermatology Association's 88th Annual Conference; June 27-30, 2013; Quebec City, QC, Canada.
- Yuzhalin AE, Kutikhin AG. Interleukin-12: Clinical usage and molecular markers of cancer susceptibility. *Growth Factors.* 2012;30:176-191.
- Thaci D et al. Poster presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey. P1537.
- Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet.* 2008;371:1665-1674.
- Reich K et al. Poster presented at: 22nd Annual Congress of the European Academy of Dermatology and Venereology; October 2-6, 2013; Istanbul, Turkey. Poster 1540.
- Reich K et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe psoriasis: 16-week results of a phase 3, randomized, controlled trial (ESTEEM 1). Presented at: 71st Annual Meeting of the American Academy of Dermatology; March 1-5, 2013; Miami Beach, FL.
- Schett G, Wollenhaupt J, Papp K, et al. Oral apremilast in the treatment of active psoriatic arthritis: Results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2012;64:3156-3167.
- Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: Results of the IMPACT 2 trial. *Ann Rheum Dis.* 2005;64:1150-1157.
- Bachmann F, Nast A, Sterry W, Philipp S. Safety and efficacy of the tumor necrosis factor antagonists. *Semin Cutan Med Surg.* 2010;29:35-47.
- Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: A phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol.* 2012;167:668-677.
- Mamolo C, Harness J, Tan H, Menter A. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, improves patient-reported outcomes in a phase 2b, randomized, double-blind, placebo-controlled study in patients with moderate-to-severe psoriasis. *J Eur Acad Dermatol Venereol.* 2013 Jan 7. doi: 10.1111/jdv.12081. [Epub ahead of print]
- Curtis JR, Mariette X, Lee EB, et al. Tofacitinib, an oral Janus kinase inhibitor: Analysis of malignancies across the rheumatoid arthritis clinical program. Presented at: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; October 26-30, 2013; San Diego, CA. Abstract 802.
- Arthritis Advisory Committee Meeting, May 9, 2012. NDA 203214: Tofacitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had inadequate response to one or more disease-modifying anti-rheumatic drugs. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM302958.pdf>. Accessed June 13, 2014.

# Data on the Safety of Psoriasis Therapies

Craig L. Leonardi, MD\*

## ■ Abstract

Safety remains paramount to the clinical utility of a therapy. Evaluation of safety is an ongoing process that does not end when a therapy becomes commercially available. This article reviews recent data pertaining to the safety profile of two therapeutic classes widely used in the treatment of psoriasis: inhibitors of tumor necrosis factor- $\alpha$  and agents that target interleukin-12/23.

Semin Cutan Med Surg 33(supp4):S73-S75

© 2014 published by Frontline Medical Communications

## ■ Keywords

Tumor necrosis factor; interleukin-12; interleukin-23; rheumatoid arthritis; psoriasis; Janus kinase inhibitor

Ensuring the safety of a therapy involves accumulation and analysis of data from all phases of an agent's clinical history, including registration trials (phase I, II, and III), registry data, Food and Drug Administration Adverse Event Reporting System (AERS), and postmarketing surveillance.

Registration trials have several limitations that complicate assessment of a drug's safety. The trials involve relatively few patients, and the duration of exposure to placebo control tends to be brief, usually 12 and 16 weeks, as is the follow-up period.

Concepts about long-term follow-up have evolved as experience with biologic therapies has increased. Initially, 24 weeks was considered a long-term extension trial. Today, extension studies often continue for 4 years after completion of a 1-year clinical trial.

One notable example illustrates the need to gather safety information from multiple sources and to make monitoring of safety a continuous process. The T-cell inhibitor efalizumab

was withdrawn from the US market because of a higher-than-expected incidence of progressive multifocal leukoencephalopathy (PML) that became apparent only after long-term use of the drug.<sup>1</sup> (The drug remains available in some other countries, and no other cases of PML have been reported since withdrawal of efalizumab in the United States.)

## TNF Inhibitors

A well-respected group of clinical researchers evaluated the risk of infection and malignancy in five tumor necrosis factor (TNF)- $\alpha$  inhibitors in a meta-analysis of 20 published clinical trials involving 6,810 patients with psoriatic disease.<sup>2</sup> The analysis showed a slightly higher risk of infection in patients treated with TNF inhibitors but no increase in the risk of serious infections or malignancies. The principal limitation of the data was short-term follow-up for detection of cancer and determining infection rates.

The same group of researchers examined the risk of myocardial infarction (MI) in British patients with psoriasis.<sup>3</sup> The analysis showed that patients with severe psoriasis had a significantly increased risk of MI in comparison with patients who had mild disease. Younger patients with severe disease had the highest risk of MI. The study played a major role in raising awareness among dermatologists of the association between psoriasis and cardiovascular disease.

Rheumatologists have accumulated far more clinical experience with TNF inhibitors in rheumatoid arthritis (RA) than have clinicians who manage psoriasis. Many nations other than the United States have large registry databases related to use of TNF inhibitors, and researchers have provided valuable insights regarding the association between TNF inhibitors and disease outcomes. For example, a Scandinavian study showed that patients with RA had a 35% lower mortality risk when treated with TNF inhibitors than did control groups.<sup>4</sup>

Another study from Scandinavia examined the association between treatment with TNF inhibitors and cardiovascular clinical events in patients with RA.<sup>5</sup> The results showed a 54% reduction in the risk of cardiovascular events in patients treated with TNF inhibitors versus patients who received control therapies. More recently, a meta-analysis showed a 48% reduction in the risk of MI in patients with psoriasis treated with TNF inhibitors.<sup>6</sup>

## Anti-IL-12/23 Therapy

Analysis of safety in agents that target interleukin (IL)-12/23 has yielded somewhat different results from those associated with TNF inhibitors. An overall safety analysis produced no evidence related to the risk of major adverse cardiac events (MACE) in placebo-controlled trials of ustekinumab. However, an analysis that separated the control period from follow-up suggested an increased risk of MACE during early use of ustekinumab.<sup>7</sup>

\*Clinical Professor of Dermatology, Saint Louis University Central Dermatology, St Louis, MO.

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

Dr Leonardi has received an honorarium from Global Academy for Medical Education for his participation in this activity. He acknowledges the editorial assistance of Charles Bankhead, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Charles Bankhead has no relevant financial relationships with any commercial interests.

Craig L. Leonardi, MD, has been a consultant and/or investigator and/or speaker and/or advisory board member for AbbVie, Amgen Inc., Anacor Pharmaceuticals, Inc., Celgene Corporation, Janssen Biotech, Inc., Eli Lilly, Galderma Laboratories, L.P., GlaxoSmithKline, Incyte Corporation, LEO Pharma Inc., Maruho Co., Ltd., Novartis, Novo Nordisk, Inc., Pfizer Inc., Schering-Plough Corporation, Sirtis Pharmaceuticals, Inc., Stiefel Laboratories, Inc., TOLMAR Pharmaceuticals, Inc., Vascular Biogenics Ltd., and Warner Chilcott plc.

Address reprint requests to: Craig L. Leonardi, MD, Central Dermatology, 1034 S. Brentwood Boulevard, St Louis, MO 63117; craig.leonardi@centralderm.com.

1085-5629/13/\$-see front matter © 2014 Frontline Medical Communications  
DOI: 10.12788/j.sder.0099

## ■ ■ ■ Data on the Safety of Psoriasis Therapies

In a subsequent meta-analysis, MACE rates were compared from psoriasis trials involving various types of biologic agents (Table).<sup>8</sup> The results showed 10 cases of MACE in patients treated with IL-12/23 inhibitors versus one in patients treated with TNF inhibitors, and none in patients randomized to placebo. The difference did not achieve statistical significance ( $P=0.11$ ), but the results suggested a possible safety issue.

Another meta-analysis employed a statistical technique that takes into account rare events.<sup>9</sup> The results did show a significantly higher risk of MACE in groups treated with IL-12/23 inhibitors than in control groups.

Trials of psoriasis therapies have lacked statistical power to evaluate MACE and instead are powered to determine the efficacy of a therapy. Nonetheless, the consistency of the signal raises questions about this class of agent.

### Biologic Therapy and Cancer Risk

A drug's malignancy potential always attracts interest and scrutiny. The rheumatology community has accumulated substantially more data on this issue than have their counterparts

in dermatology. Because many agents are used in both RA and psoriatic disease, the rheumatology data have relevance to the dermatology community.

One of the most comprehensive studies of biologic therapy and cancer risk involved a national database comprising 13,869 patients with RA, 6,597 of whom were treated with biologic agents.<sup>10</sup> The patients had a total follow-up of 49,000 patient-years, and all patients had been treated for at least 1 year.

An analysis of the database showed no significantly increased risk of any nonskin cancer malignancies. Treatment with biologic therapies was associated with an odds ratio of 1.5 for nonmelanoma skin cancer compared with other types of therapies.<sup>10</sup>

In some cases, a statistically significant increase in cancer risk is not necessary to attract attention. A case in point is tofacitinib, another targeted agent used to treat RA. Follow-up from initiation of treatment to 24 months showed a small but consistent increase in the malignancy rate among patients treated with tofacitinib.<sup>11</sup>

■ **TABLE** Summary of MACE in Randomized Controlled Psoriasis Trials (Meta-Analysis)

	Study author	Biologic agent	Mean baseline PASI	Mean baseline BSA (%)	No. of patients who received $\geq 1$ dose		MACE during PCP		Duration of PCP (weeks)
					Biologic	Placebo	Biologic	Placebo	
1	Krueger	Ustekinumab	19.1	27.2	254	64	3	0	20
2	Leonardi	Ustekinumab	20.2	26.7	510	255	1	0	12
3	Papp	Ustekinumab	19.6	26.4	820	410	1	0	12
4	Kimball	ABT-874	19	26	150	30	0	0	12
5	M06-890	ABT-874	19.2	25.1	981	484	5	0	12
6	M10-114	ABT-874 Etanercept	18.8	23.8	138 141	68	0 0	0 0	12
7	M10-315	ABT-874 Etanercept	18.8	24.2	139 139	72	0 0	0 0	12
8	Chaudhari	Infliximab	23	NA	22	11	0	0	10
9	Gottlieb	Infliximab	19	27	197	51	0	0	10
10	Reich	Infliximab	22.9	34	301	77	0	0	24
11	Menter	Infliximab	20.1	28.4	627	208	0	0	14
12	Leonardi	Etanercept	18.7	28.7	486	166	0	0	12
13	Gottlieb	Etanercept	18.6	32	57	55	0	1	24
14	Papp	Etanercept	16.4	23	390	193	0	0	12
15	Tyring	Etanercept	18.2	27.2	311	307	0	0	12
16	Van de Kerkhof	Etanercept	21.2	28.4	96	46	0	0	12
17	Gordon	Adalimumab	15.7	27.3	95	52	1	0	12
18	Menter	Adalimumab	18.9	25.7	814	398	0	0	16
19	Asahina	Adalimumab	28.4	46.2	123	46	0	0	24

MACE=major adverse cardiac events; PASI=Psoriasis Area Severity Index; PCP=placebo-controlled phase.

Source: Adapted from Ryan et al.<sup>8</sup> Used with permission.



Follow-up of tofacitinib-treated patients beyond 42 months did not show any obvious increase in the malignancy rate, but the rate did not decline. The absence of a clear decline is noteworthy because adverse events tend to decrease over time, as clinicians learn which patients respond to therapy and have few adverse events.

### The PSOLAR Experience

An ongoing multicenter observational study will provide data on the long-term safety and clinical outcomes with therapies given to patients with moderate to severe psoriasis. The Psoriasis Longitudinal Assessment and Registry (PSOLAR) has a target enrollment of 12,000 patients, who will be followed for 8 years or longer. Investigators at 266 sites in 15 countries are enrolling patients.<sup>12</sup>

Patients enrolled in PSOLAR receive treatment that is based on usual clinical practice and standard of care. A key objective is to accumulate data that reflect “real-world” experience in the treatment of psoriasis.

Preliminary unadjusted data based on few clinical events have shown no major differences in malignancy rates among patients treated with an IL-12/23 inhibitor, TNF inhibitors, other biologics, or nonbiologic therapy.<sup>13</sup>

Analysis of serious infections showed the highest rate among patients treated with infliximab and the lowest in patients who received the IL-12/23 inhibitor ustekinumab.<sup>14</sup> MACE rates were fairly evenly distributed among ustekinumab, TNF inhibitors, and other biologics. Patients who received no biologic therapy (mostly older patients treated with phototherapy) had the highest rate.<sup>15</sup>

PSOLAR is the largest registry of its kind and will provide the data needed to address longitudinal questions such as the natural course of the disease, development of comorbid diseases, and treatment-specific issues (infection, cancer, MACE, and unanticipated events).

### Summary

The safety of a therapy cannot be determined on the basis of a single source of data. Safety assessment is an ongoing process that involves input from multiple sources. The long-term safety of psoriasis therapies has lagged behind that of other diseases and specialties, but data from the rheumatology community have been informative. PSOLAR eventually will provide the data necessary to determine the effectiveness and safety of therapies used to treat psoriasis.

### References

- Leonardi C, Menter A, Hamilton T, Caro I, Xing B, Gottlieb AB. Efalizumab: Results of a 3-year continuous dosing study for the long-term control of psoriasis. *Br J Dermatol*. 2008;158:1107-1116.
- Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized trials. *J Am Acad Dermatol*. 2011;64:1035-1050.
- Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296:1736-1741.
- Jacobsson LT, Turesson C, Nilsson JA, et al. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:670-675.
- Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol*. 2005;32:1213-1218.
- Wu JJ, Poon KY, Channal JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol*. 2012;148:1244-1250.
- Reich K, Leonardi C, Griffiths CEM, et al. Update on the cumulative safety experience of ustekinumab: Result from the ustekinumab psoriasis clinical development program with up to 4 years of follow-up. Presented at: 22nd World Congress of Dermatology; May 24-29, 2011; Seoul, Korea. Abstract FC07-03.
- Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: A meta-analysis of randomized controlled trials. *JAMA*. 2011;306:864-871.
- Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk of major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: A meta-analysis of randomized controlled trials. *J Eur Acad Dermatol Venereol*. 2013;27:622-627.
- Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. *Arthritis Rheum*. 2007;56:2886-2895.
- Curtis JR, Mariette X, Lee EB, et al. Tofacitinib, an oral Janus kinase inhibitor: An analysis of malignancies across the rheumatoid arthritis clinical program. EULAR 2013. Abstract 802.
- Papp KA, Strober B, Augustin M, et al. PSOLAR: Design, utility, and preliminary clinical results of a prospective, international, disease-based registry of patients with psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. *J Drugs Dermatol*. 2012;11:1210-1217.
- Langley R, Strober B, Chevrier M, Lebwohl M. Malignancy events in the psoriasis longitudinal assessment and registry (PSOLAR) study: Current status of observations. *J Am Acad Dermatol*. 2013;68(suppl):AB206. P6448.
- Leonardi C, Fiorentino D, Chevrier M, Kalb R. Serious infection events in the psoriasis longitudinal assessment and registry (PSOLAR) study: Current status of observations. *J Am Acad Dermatol*. 2013;68(suppl):AB213. P6343.
- Gottlieb A, Naldi L, Chevrier M, Bissonnette R. Major adverse cardiovascular events in the psoriasis longitudinal assessment and registry (PSOLAR) study: Current status of observations. *J Am Acad Dermatol*. 2013;68(suppl):AB205. P6658.

# New Therapeutic Options for Actinic Keratosis and Basal Cell Carcinoma

James E. Sligh, Jr, MD, PhD\*

## ■ Abstract

Actinic keratosis (AK) is a common premalignant skin lesion that is frequently treated by cryosurgery. Basal cell carcinoma is the most common malignancy of man, and early-stage lesions are usually cured via surgery. Advanced basal cell carcinoma may require more extensive surgery resulting in deformity, and many advanced lesions cannot be treated surgically. Several recent developments have improved therapeutic options for both conditions. Cryosurgery is still a mainstay of treatment for AK, but the introduction of effective topical agents, imiquimod cream and ingenol mebutate, has provided alternatives to cryosurgery. For advanced basal cell carcinoma, the small-molecule inhibitor vismodegib has proven to be an effective therapy for lesions that are not amenable to surgery and has demonstrated ability to achieve dramatic improvement in advanced, potentially disfiguring cancers.

Semin Cutan Med Surg 33(supp4):S76-S79

© 2014 published by Frontline Medical Communications

## ■ Keywords

Actinic keratosis; basal cell carcinoma; imiquimod; ingenol mebutate; hedgehog pathway; vismodegib

## Actinic Keratosis

Historically, cryosurgery has been the treatment of choice for AK and remains the most common approach to treatment. Nonsurgical options for AK include imiquimod and ingenol mebutate. Imiquimod received approval from the US Food and Drug Administration (FDA) in 1997 but has been formulated into more than one concentration or strength. Ingenol mebutate is a first-in-class therapy that could be joined by one or more ingenol products in clinical development. A 1927-nm fractional resurfacing laser has shown promise for AK in early clinical experience

\*Division Chief, Dermatology, The University of Arizona College of Medicine, Tucson, AZ.

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

Dr Sligh has received an honorarium from Global Academy for Medical Education for his participation in this activity. He acknowledges the editorial assistance of Charles Bankhead, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Charles Bankhead has no relevant financial relationships with any commercial interests.

James E. Sligh, Jr, MD, PhD, has been a speaker and/or advisory board member for Genentech.

Address reprint requests to: James E. Sligh, Jr, MD, PhD, University of Arizona, Dermatology Division, PO Box 245024, 1515 N. Campbell Ave. Tucson, AZ 85724, jsligh@email.arizona.edu

## Imiquimod

Standard treatment with imiquimod has been 5% cream administered for 16 weeks for AK lesions involving 25 cm<sup>2</sup> of skin area. Recently, two additional concentrations received approval from the FDA: 2.5% and 3.75%. The less concentrated formulations offer advantages for patients who have difficulty tolerating the standard-strength formulation of the topical therapy.

The lower-concentration products were evaluated in two placebo-controlled trials involving adults with five to 20 AK lesions.<sup>1,2</sup> In both trials, patients were randomized to placebo, 2.5% imiquimod, or 3.75% imiquimod. Participants applied assigned treatment once a day to affected areas of the face and balding scalp.

In one trial,<sup>2</sup> patients completed two 2-week treatment cycles, separated by a 2-week interval of no treatment. The second trial's protocol included two 3-week treatment cycles with a 3-week nontreatment period in between.<sup>1</sup> The primary end point of each trial was the proportion of patients who attained complete or partial response (>75% clearance) 8 weeks after completing treatment.

Investigators in the 2-week trial randomized 479 patients to the three treatment arms. At the 8-week posttreatment evaluation, respective complete and partial clearance rates were 6.3% and 22.6% for the placebo group, 30.6% and 48.1% for imiquimod 2.5%, and 35.6% and 59.4% for imiquimod 3.75% (Figure 1). Both imiquimod groups had significantly higher response rates than did the placebo group ( $P<0.001$ ). The 3.75% concentration led to a higher rate of partial clearance than did the 2.5% concentration ( $P=0.047$ ).<sup>2</sup>

The median reduction in lesion count from baseline was 25% in the placebo group, 71.8% for imiquimod 2.5%, and 81.8% for imiquimod 3.75%. Both imiquimod groups had significantly greater reductions in lesion count than did the placebo group ( $P<0.001$ ), and the 3.75% imiquimod concentration outperformed the 2.5% cream ( $P=0.048$ ).<sup>2</sup>

In the 3-week trial, the 8-week posttreatment assessment showed respective complete and partial response rates of 5.5% and 12.8% for the placebo group, 25.0% and 42.7% for imiquimod 2.5%, and 34.0% and 53.7% for imiquimod 3.75% (Figure 2). Both imiquimod concentrations demonstrated superiority over placebo ( $P<0.001$ ), and the 3.75% cream led to a significantly higher rate of partial response than did the 2.5% cream ( $P=0.034$ ).<sup>1</sup>

The median reduction in lesion count was 23.6% with placebo, 66.7% with imiquimod 2.5% cream, and 80.0% with imiquimod 3.75% ( $P<0.001$  for both imiquimod groups versus placebo).<sup>1</sup>

In both clinical trials, adverse events were considered manageable. Treatment discontinuation related to adverse events was uncommon. In the 2-week trial, temporary treatment interruption rates were 6.9% with imiquimod 2.5% and 10.6% for 1085-5629/13/\$-see front matter © 2014 Frontline Medical Communications

DOI: 10.12788/j.sder.0100

imiquimod 3.75%.<sup>2</sup> Rates in the 3-week trial were 17.1% and 27.2% for the 2.5% and 3.75% imiquimod concentrations, respectively.<sup>1</sup> Placebo-treated patients had no treatment interruptions in either trial.<sup>1,2</sup>

Follow-up in both trials demonstrated durability of responses to imiquimod. In the 2-week trial, 33% of the imiquimod 2.5% group and 41% of the imiquimod 3.75% group had complete clearance of AK lesions.<sup>2</sup> In the 3-week trial, complete clearance rates at 12 months were 43% with imiquimod 2.5% and 48% with imiquimod 3.75%.<sup>1</sup>

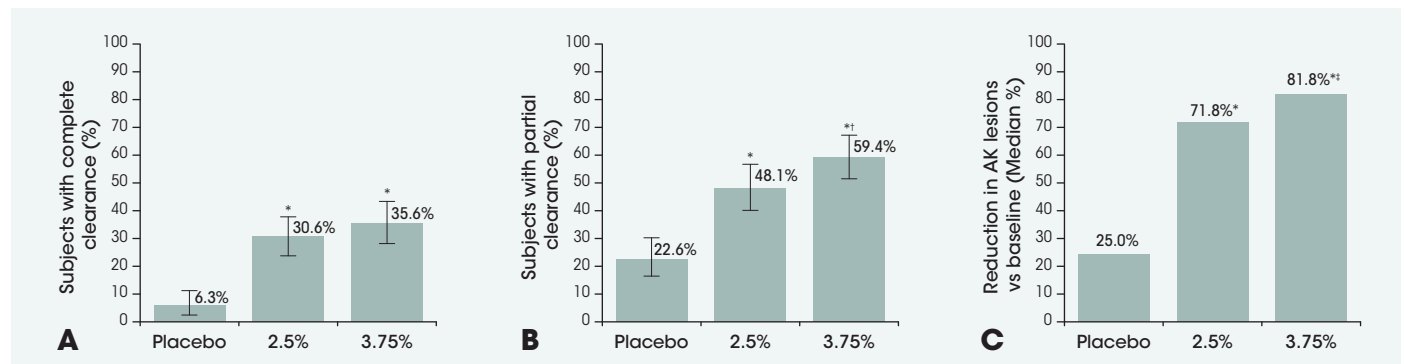
### Ingénol Mebutate

The precise mechanism of action for this agent remains unclear. The best available evidence suggests dual activity: mitochondrial depolarization within cells that make up AK lesions, followed by an internal inflammatory response that destroys the cells from the inside out.<sup>3</sup> Ingénol mebutate has a rapid onset of action that allows for brief treatment intervals of 2 to 3 days depending on lesion location.

The FDA approved ingénol mebutate for AK in 2012. Other agents in the class are in various stages of clinical development. The treatment schema for ingénol mebutate varies by the skin area treated. For lesions on the face and scalp, standard treatment is 0.0015% ingénol mebutate gel, applied daily for 3 days. Patients who have lesions on the trunk and extremities are instructed to apply 0.05% ingénol mebutate gel for 2 days.

Patients treated with ingénol mebutate often have dramatic improvement in lesion status in a relatively brief period of time. In most cases, the agent reaches peak activity within the first week after the start of treatment. The activity manifests as an inflammatory reaction on the treated area, which intensifies for several days and then begins to resolve, usually within about a week.

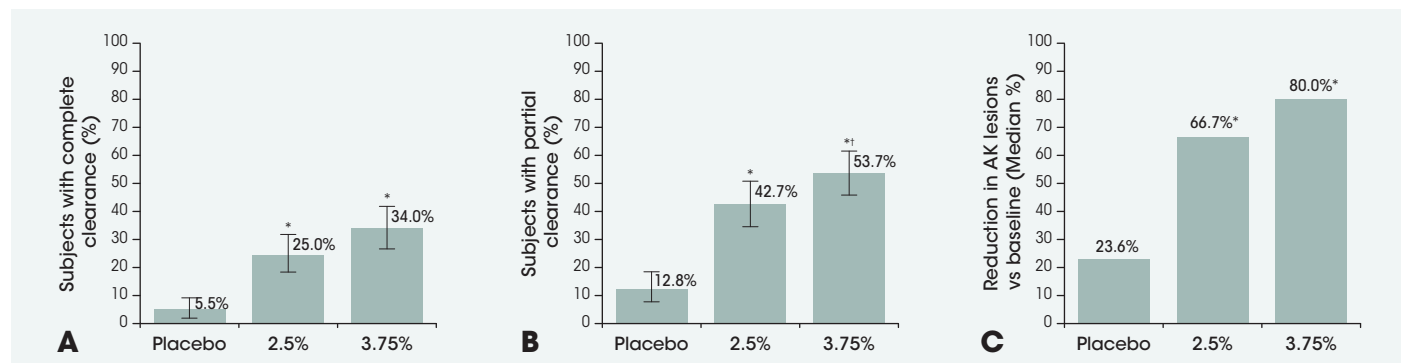
Recently, the initial report of 12-month follow-up of patients treated with ingénol mebutate demonstrated the durability of responses.<sup>4</sup> Among patients who had complete clearance of AK lesions following treatment, 87% maintained complete clearance 1 year later. The median time to recurrence of AK lesions on the face or scalp was 365 days.



**FIGURE 1** Imiquimod 2.5% and 3.75% Versus Placebo: Clearance Rates After Two 2-Week Cycles.

**A.** Complete clearance rates, with 95% confidence intervals (CI), by treatment groups for combined studies. \* $P < 0.001$  for pairwise comparison vs placebo. **B.** Partial ( $\geq 75\%$  reduction in actinic keratosis [AK] lesions compared with baseline) rates, with 95% CI, by treatment groups for combined studies. \* $P < 0.001$  for pairwise comparison vs placebo. † $P = 0.047$  for pairwise comparison 3.75% vs 2.5%. **C.** Median percent reduction in AK lesions in treatment area compared with baseline by treatment group for combined studies. \* $P < 0.001$  for pairwise comparison vs placebo. † $P = 0.048$  for pairwise comparison 3.75% vs 2.5%.

Source: Swanson et al.<sup>2</sup> Reproduced with permission.



**FIGURE 2** Imiquimod 2.5% and 3.75% Versus Placebo: Clearance Rates After Two 3-Week Cycles.

**A.** Complete clearance rates, with 95% confidence intervals (CI), by treatment groups for combined studies. \* $P < 0.001$  for pairwise comparison vs placebo. **B.** Partial ( $\geq 75\%$  reduction in actinic keratosis [AK] lesions compared with baseline) rates, with 95% CI, by treatment groups for combined studies. \* $P < 0.001$  for pairwise comparison vs placebo. † $P = 0.034$  for pairwise comparison 3.75% vs 2.5%. **C.** Median percent reduction in AK lesions in treatment area compared with baseline by treatment group for combined studies. \* $P < 0.001$  for pairwise comparison vs placebo.

Source: Hanke et al.<sup>1</sup> Reproduced with permission.

Cryosurgery remains the most frequently used treatment for AK. However, results can vary, and the technique's effectiveness is limited to visible lesions, leaving subclinical lesions untreated. Investigators in a phase III randomized, multicenter clinical trial evaluated sequential treatment of AK with cryosurgery followed by ingenol mebutate.<sup>5</sup>

The trial included 329 patients, who were randomized to 0.0015% ingenol mebutate or vehicle, applied 3 weeks after cryosurgery. The primary objectives were the rates of complete clearance at 11 weeks and 12 months.<sup>5</sup>

Recently reported 11-week results showed a significantly higher rate of complete clearance in patients treated with ingenol mebutate following cryosurgery (60.5% vs 49.4%,  $P=0.04$ ). The combination therapy also was associated with a numerically greater reduction in the number of AK lesions than with cryosurgery alone (82.7% vs 75.6%).<sup>5</sup>

The 11-week results are encouraging, but more important is the durability of results 1 or 2 years later. Combining multiple therapies with proven efficacy may offer the best strategy for attaining good long-term results.

#### Laser

Treatment with a 1927-nm fractional resurfacing laser has shown promise for AK in early clinical evaluations. A recently reported small clinical trial yielded encouraging results.<sup>6</sup>

The study involved 24 adults with facial photodamage and AK. They underwent as many as four treatments with a fractionated 1927-nm nonablative thulium laser. One month after the final treatment, the total number of AK lesions had decreased by 91.3%. At 6 months, independent clinician assessment showed an 86.6% reduction from baseline in the number of lesions. Patients reported marked or noticeable overall improvement in photodamaged skin.<sup>6</sup>

Investigators have yet to report long-term safety, tolerance, or efficacy data. Moreover, the mechanisms involved in AK clearance have not been determined. However, short-term clinical and histologic findings, combined with high patient-reported satisfaction and safety, suggest that the nonablative laser therapy has potential for treatment of AK.

#### Basal Cell Carcinoma

In 2012, the FDA approved vismodegib for locally advanced and metastatic basal cell carcinoma (BCC). Locally advanced BCC is a new diagnostic category, whose precise definition remains undetermined.

Diagnostic criteria for locally advanced BCC are not purely objective. Objective parameters include lesion size, extent of local invasiveness, location, expected morbidity and mortality from surgery or radiation therapy, low likelihood of curative resection, and contraindications to surgery (**Figure 3**).

Dermatologic specialists may apply subjective criteria to define locally advanced BCC, depending on their approach to treatment. A dermatologist who is inclined to treat a lesion surgically might define locally advanced by the extent of invasiveness, presence of perineural involvement, likelihood of curative resection, and the anticipated morbidity and mortality associated with the surgery. A dermatologist oriented toward medical treatment might apply criteria that are more relevant to a medical approach, such as requirement for therapy that goes beyond standard care to achieve definitive results (such as surgery).



■ **FIGURE 3** Patient With Locally Advanced Basal Cell Carcinoma on the Shoulder. The term "locally advanced BCC" currently is defined by clinicians' subjective assessment and several objective parameters. The objective parameters include lesion size, extent of local invasiveness, location, expected morbidity and mortality from surgery or radiation therapy, low likelihood of curative resection, and contraindications to surgery. Source: Photo courtesy of James E. Sligh, Jr, MD, PhD

Development of the science behind vismodegib began with the observation that BCC has a specific association with a loss-of-heterozygosity (LOH) polymorphism at chromosome 9q.<sup>7</sup> Additionally, Gorlin syndrome, which is characterized by development of multiple BCC lesions, tracks to LOH at 9q.

Patients with Gorlin syndrome have a predisposition to other neoplasms, including medulloblastoma, meningioma, jaw cysts, skin lesions, and mesentery fibromas of the heart and ovaries. Affected patients also have developmental abnormalities involving ribs, craniofacial structures, and mental function, as well as polydactyly, syndactyly, and spina bifida.

Subsequent genetic investigations revealed mutations in *PTCH1* (usually loss-of-function mutations) associated with both Gorlin syndrome and sporadic BCC.<sup>8-10</sup> Other studies identified mutations in the Smoothed (*SMO*) gene in sporadic BCC. Mutations in *PTCH1* and *SMO* lead to aberrant signaling in the Hedgehog pathway.

In the normal state, Hedgehog signaling is involved in regulating embryonic development, including appropriate growth, location, and cellular content tissues and organs. Hedgehog signaling has limited activity in adult tissues. However, reactivation of Hedgehog signaling has been associated with tumorigenesis.<sup>11</sup>

Abnormal Hedgehog signaling in BCC is often the result of loss-of-function mutations in *PTCH1*. Mutated *PTCH1* releases its normal inhibition of *SMO*, leading to aberrant activation of the transcriptional factor *Gli* in the cytoplasm. Once activated, *Gli* enters the cell nucleus to activate multiple genes involved in proliferation and cell-cycle regulation, including *Wnt*, *TGF-B*, *PTCH1*, and *Myc*. Oncogenic activation blocks normal programmed cell death (apoptosis), resulting in unregulated cell growth and proliferation.

The Hedgehog inhibitor vismodegib restores normal signaling by binding *SMO* protein and inhibiting *Gli* activation. A series of published reports have documented vismodegib's activity in patients' BCC lesions, often resulting in dramatic improvement in disfiguring lesions (**Figure 4**).

Although not currently approved for Gorlin syndrome, vismodegib has continued the clinical success seen in locally advanced and metastatic BCC. In many instances, single-agent vismodegib has led to complete or near-complete clearance of severe and numerous lesions in patients with Gorlin syndrome.<sup>12,13</sup>

In general, vismodegib has been tolerated with few grade 3/4 adverse events reported.<sup>14</sup> The most frequently reported adverse events have been muscle spasms, dysgeusia, alopecia, diarrhea, nausea, fatigue, and weight loss.

Most recently, the antifungal agent itraconazole has been evaluated as potential therapy for BCC. A phase II open-label study involving 19 patients with BCC showed that treatment with itraconazole had a modest impact on tumor area (a reduction of 24% from baseline).<sup>15</sup> The modest lesion improvement was associated with a 45% reduction in BCC proliferative activity (as determined by assessment of the proliferation marker Ki-67) and a 65% reduction in *Gli* activation.

Clinical experience with vismodegib in BCC has raised almost as many questions as it has answered. The minimum duration of therapy has yet to be determined, which, in turn, affects the choice and definition of the therapeutic end point. Although systemic therapy with vismodegib has proven effective, a topical formulation would be welcomed. As is true of

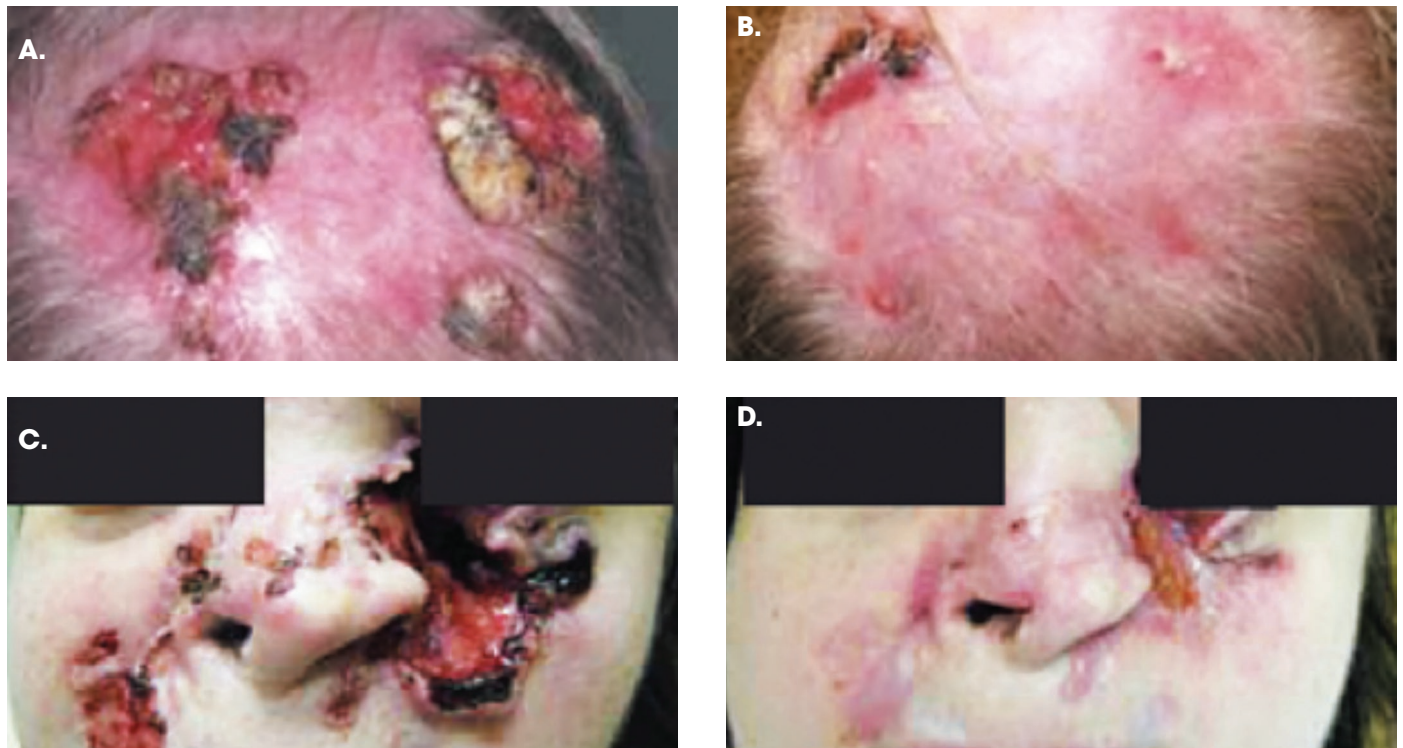
most novel agents, the drug is expensive, which could help increase the appeal of generic itraconazole (or another older drug) if its efficacy were comparable.

Reported resistance to vismodegib has been limited, unlike with the use of targeted therapies for melanoma, but clinical experience with the Hedgehog inhibitor is more limited. Data on long-term outcomes have not become available, although studies are under way. Biomarkers that correlate with response to vismodegib have not been identified.

The answers to these and other questions about vismodegib's safety and efficacy will likely influence the agent's future in the treatment of BCC.

### Summary

Advances in the treatment of AK have occurred that empower the clinician with greater treatment options. Newer lower-strength formulations of imiquimod cream have promise for improving tolerability without risking efficacy. Accumulating experience with ingenol mebutate suggests that the therapeutic effects are durable. Evaluation of ingenol mebutate as an adjunct to cryotherapy has shown promise for improving on results that can be obtained with cryotherapy alone. The development of vismodegib has been a major advance in the treatment of advanced BCC. Optimizing use of the therapy awaits resolution of issues related to duration of therapy, identification of biomarkers that correlate with treatment success (or failure), the potential for developing a topical formulation of the drug, and assessment of long-term data on safety and efficacy.



■ **FIGURE 4** Activity of Oral Vismodegib in Locally Invasive Basal Cell Carcinoma. Vismodegib, a central mediator of Hedgehog pathway signaling, was used in a trial of patients with locally invasive BCC. The photos show a 60-year-old man with basal cell nevus syndrome on the posterior scalp at baseline (A) and after 5 months of therapy (B); and a 41-year-old woman with facial lesions at baseline (C) and after 2 months of treatment (D).

Source: Von Hoff DD, LoRusso PM, Rubin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med*. 2009;361:1164-1172. Used with permission.

## References

1. Hanke WE, Beer KR, Stockfleth E, Wu J, Rosen T, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. *J Am Acad Dermatol.* 2010;62:573-581.
2. Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol.* 2010;62:582-590.
3. Rosen RH, Gupta AK, Tyring SK. Dual mechanism of action of ingenol mebutate gel for topical treatment of actinic keratoses: Rapid lesion necrosis followed by lesion-specific immune response. *J Am Acad Dermatol.* 2012;66:486-493.
4. Lebowitz M, Shumack S, Stein Gold L, Melgaard A, Larsson T, Tyring SK. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. *JAMA Dermatol.* 2013;149:666-670.
5. Berman B, Goldenberg G, Hanke CW, et al. Efficacy and safety of ingenol mebutate 0.015% gel 3 weeks after cryosurgery of actinic keratosis: 11-week results. *J Drugs Dermatol.* 2014;13:154-160.
6. Weiss ET, Brauer JA, Anolik R, et al. 1927-nm fractional resurfacing of facial actinic keratoses: A promising new therapeutic option. *J Am Acad Dermatol.* 2013; 68:98-102.
7. Quinn AG, Sikkink S, Rees JL. Basal cell carcinomas and squamous cell carcinomas of human skin show distinct patterns of chromosome loss. *Cancer Res.* 1994;54:4756-4759.
8. Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science.* 1996;272:1668-1671.
9. Hahn H, Wicking C, Zaphiropoulos PG, et al. Mutations of the human homolog of *Drosophila* patched in the nevoid basal cell carcinoma syndrome. *Cell.* 1996;85:841-851.
10. Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. *J Invest Dermatol.* 1998;110:885-888.
11. Scales SJ, de Sauvage FJ. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. *Trends Pharmacol Sci.* 2009;30:303-312.
12. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med.* 2012;366:2171-2179.
13. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med.* 2012;366:2180-2188.
14. Weiss GJ, Oro A, Chang ALS, et al. Expanded access study of advanced BCC patients treated with the Hedgehog-pathway inhibitor vismodegib. *Ann Oncol.* 2012;23(suppl 9):1111PD.
15. Kim DJ, Kim J, Spaunhurst K, et al. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. *J Clin Oncol.* 2014;32:745-751.

# Correcting Age-Related Changes in the Face by Use of Injectable Fillers and Neurotoxins

Mark G. Rubin, MD\*, Sue Ellen Cox, MD†, Michael S. Kaminer, MD‡, and Nowell Solish, MD, FRCP(C)§

## ■ Abstract

Many patients seeking rejuvenation treatment have readily apparent age-related changes in facial features. Others exhibit more subtle changes that nonetheless can be corrected to achieve a more youthful appearance. In the following article, four specialists in aesthetic dermatology discuss how injectable hyaluronic acid-based fillers and neurotoxins can achieve rejuvenation without surgery. *Semin Cutan Med Surg* 33(supp4):S81-S84  
© 2014 published by Frontline Medical Communications

## ■ Keywords

AbobotulinumtoxinA; aesthetic dermatology; botulinum toxin A injectables; hyaluronic acid; incobotulinumtoxinA; fillers; neurotoxins; onabotulinumtoxinA;

## Effects of Aging on Midfacial and Lower Facial Appearance

The aging process changes the skin and the underlying structural support provided by the musculoskeletal system. The pace of change varies considerably from one individual to another. Moreover, tissue changes are interdependent in that age-related changes in one tissue can influence subsequent alterations in other tissues.<sup>1</sup> Decreased cranial support leads to soft-tissue descent in the midface. Loss of tone in supporting musculature, increased laxity in retaining ligaments, and descent

of suborbital fat pads exacerbate the downward anatomic shift. Reabsorption occurs along the mandible and maxilla, accompanied by loss of dentition. Essentially, the midface and lower face appear to collapse.

## Facial Assessment

Patient satisfaction is integral to the achievement of successful cosmesis. During the facial assessment, patients should be encouraged to identify what concerns them most about the appearance of their face. That concern should become the focal point of treatment. The assessment should include the entire face, during which the clinician can identify for the patient other facial features that can be improved. However, the treatment plan should begin with the age-related change or changes that patients find most bothersome.

## Use of Injectable Agents

Most patients will have several age-related facial features that can be improved with the use of injectable fillers. The areas include the temples, brow, tear trough, and midface.

## Temples

Aging leads to deflation of the temple area in most patients. Diluted or reconstituted monophasic hyaluronic acid is often used to reinflate the area. Periosteal placement provides a smooth cosmetic result, which is the desired outcome.

## Brow

Age-related changes in the brow often can be improved by use of injectable hyaluronic acid gel. Placement of 0.5 mL of biphasic small-particle gel on both sides of the supraorbital rim elevates eyelid skin and increases brow projection.<sup>2</sup>

## Tear Trough

The tear trough is the depression over the medial inferior orbital rim. With aging, the fat pad descends, deepening the fold or trough in the process. One treatment option that has produced good cosmetic results in the tear trough is a newer bacteria-derived monophasic hyaluronic acid that has a uniform particle size, reduced viscosity, and greater elasticity. When injected onto the periosteum, the product fills and lifts the eyelid tissue to achieve the desired cosmetic effect. The distinct chemical structure of the product permits superficial injection without the risk of a blue discoloration known as the Tyndall effect. The biphasic small-particle hyaluronic acid product also is used frequently for this indication.

Several precautions are required when treating the periorbital area. Many older patients are treated with anticoagulants, which should be discontinued 2 weeks before injecting a filler into the periorbital area. Distinguishing between edema and fat pad is another consideration. If the patient gazes upward, the fat becomes more prominent, whereas edema does not. When evaluating the lower eyelid, it is important to do a lid snap test.

\*Associate Professor of Dermatology, University of California, San Diego; Private Practice, Beverly Hills, CA.

†Clinical Associate Professor, University of North Carolina at Chapel Hill, Raleigh-Durham, NC.

‡Assistant Clinical Professor of Dermatology, Section of Dermatologic Surgery and Oncology, Yale Medical School; Adjunct Assistant Professor of Medicine (Dermatology), Dartmouth Medical School; Adjunct Assistant Professor, Dermatology, Brown University School of Medicine, Chestnut Hill, MA.

§Assistant Professor, University of Toronto, Toronto, Ontario, Canada.

Publication of this CME article was jointly sponsored by the University of Louisville School of Medicine Continuing Medical Education and Global Academy for Medical Education, LLC, and is supported by educational grants from AbbVie, Inc., Eli Lilly and Company, Genentech, Inc., Merz, Inc., and Novartis Pharmaceuticals Corporation.

The faculty have received an honorarium from Global Academy for Medical Education for their participation in this activity. They acknowledge the editorial assistance of Charles Bankhead, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article. Charles Bankhead has no relevant financial relationships with any commercial interests.

Sue Ellen Cox, MD, has been a consultant and/or investigator and/or speaker for Allergan Inc., Medics, a division of Valeant Pharmaceuticals International, Inc., and Merz.

Michael S. Kaminer, MD, has been a consultant and/or investigator and/or speaker for Allergan, Cabochon Aesthetics Inc., Cytrelis Biosystems, Inc., Merz, Miramar Labs, Inc., Myoscience, Inc., and ZELTIQ Aesthetics, Inc.

Mark G. Rubin, MD, has been a consultant for Allergan and Merz.

Nowell Solish, MD, FRCP(C), has been a consultant and/or speaker and/or investigator for Allergan and Medics.

Address reprint requests to: Mark G Rubin, MD, 153 S. Lasky Drive #1, Beverly Hills, CA 90212, Markgrubinmd@gmail.com

1085-5629/13/\$-see front matter © 2014 Frontline Medical Communications  
DOI: 10.12788/j.sder.0101

A poor lid snap can portend possible ectropion. Additionally, excessive tissue laxity increases the likelihood that the filler will be visible following injection. It is best to counsel patients with poor tissue elasticity to consider fractionated CO<sub>2</sub> to attain tissue tightening. Migration of filler over time can give a “doughy” appearance. Injections in this area require extreme caution, even for expert injectors.

### Midface

Age-related changes involving the midface can be particularly challenging. Multiple areas often require treatment, which can involve more than one product. Midfacial filling can involve the anterior cheek, lateral malar and submalar areas, and reduction of the nasolabial area. Carefully combining the available hyaluronic acid fillers can achieve improvements that lead to subtle overall enhancement of the face.

### Randomized Trial

The issue of age-related midface volume deficit was addressed recently in a randomized, no-treatment control group, trial.<sup>3</sup> Investigators at 15 sites in North America enrolled patients who had mid-volume deficit scores  $\geq 3$  on a 6-point scale. The score was determined by evaluation of three subregions of the midface: zymatic malar, submalar, and anteriormedial cheek.

Subsequently, 235 patients were treated with the volumizing hyaluronic acid filler VYC-20L, and 47 patients were allocated to no treatment. Patients in the VYC-20L group received a single treatment and an optional touch-up treatment 1 month later. Response was defined as  $\geq 1$ -point improvement in midface volume deficit at 6 months. For the trial to be declared successful, 70% of patients in the treatment group had to meet response criteria, and the proportion of responders had to demonstrate statistical superiority over the control group.<sup>3</sup>

When the trial ended, the results showed that 85.6% of patients in the treatment group were responders compared with 38.9% of the control group ( $P < 0.001$ ). Analysis of different categories of response showed consistent superiority for the treatment group for the proportion of patients who improved by  $\geq 1.5$  (71% vs 17%,  $P < 0.001$ ),  $\geq 2.0$  (51% vs 11%,  $P < 0.001$ ), and  $\geq 2.5$  (26% vs 0%,  $P < 0.001$ ). After 2 years of follow-up, 67.1% of patients in the treatment group met response criteria. Patient satisfaction with improvement was 89.8% at 6 months and 75.8% at 24 months.<sup>3</sup>

### Aging and the Lower Face

Many of aging's effects on the lower face involve loss of structural support, leading to loss of volume and an overall descent of facial features. Surgery can restore a more youthful appearance by lifting and correcting the tissue descent. Nonetheless, judicious use of fillers can aid in restoring a more youthful appearance to the lower third of the face. Areas that can benefit from fillers include oral commissures, perioral lines, marionette lines, prejowl and postjowl sulcus, and chin enhancement.

### Focus on Fine Lines

Development of fine lines in the perioral area is a common consequence of aging in the skin. Injectable collagen once formed the basis of treatment for fine lines. When collagen was withdrawn from the market, dermatologists evaluated various dilution strategies with hyaluronic acid, which led to inconsistent results.

A newer polydensified hyaluronic acid gel filler has proven useful as an alternative to diluted hyaluronic acid products, providing more consistent results. A recent review of safety and efficacy trials showed that the gel filler achieved durable results that were noninferior and superior to bovine collagen.<sup>4</sup> A comparison with two other hyaluronic acid compounds demonstrated similar and generally favorable safety profiles, and a 5-year retrospective study of the gel filler revealed no severe adverse events, including no persistent nodules or granulomas.

Unlike other hyaluronic acid fillers, the gel compound has no anesthetic, making injections more painful. The product can be diluted with lidocaine before administration to reduce the pain. Dilutions of the gel with the addition of variable amounts of 1% lidocaine can be used to treat age-related lines, adjusting the dilution to achieve the desired amount of lift or inflation in a line. In most cases, treatment of fine lines with 1 cc of the hyaluronic acid gel diluted with 5 cc of 1% lidocaine provides durable results, lasting 4 to 5 months or longer before requiring additional correction.

### Neurotoxins and Neuromodulators

Clinicians and patients can choose from three neurotoxins or neuromodulators that have approval from the US Food and Drug Administration: onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA. All three products can achieve favorable aesthetic results when applied to age-related changes in the lower face. However, clinicians and patients may favor one product over the others because of clinical experience or subjective factors.

### Challenges of Treating the Lower Face

The lower face offers multiple potential targets for aesthetic application of neurotoxins. Facial musculature is layered, and treating one muscle without affecting an overlying or underlying muscle requires precise, careful injection of a neurotoxin. Unlike muscles of the glabellar complex, muscles of the lower face have functional roles that can be adversely affected by imprecise placement of a neurotoxin.

Clinicians often have a small margin of safety for achieving desired aesthetic results without weakening functionally important muscles by unintentional exposure to a neurotoxin. The products should be used in these areas only by experienced clinicians.

### Principles of Aesthetic Application of Neurotoxins

Regardless of the target for injection, careful examination of the muscle tone, strength, and symmetry, as well as the potential efficacy, is essential. In all cases, treatment should begin with the lowest possible dose of a neurotoxin. If a dose does not achieve the desired aesthetic result, additional product can be administered. This conservative approach is the safest way to proceed in these areas because the effects of overtreatment are irreversible until the neurotoxin wears off over the course of several months.

### Common Lower-Face Applications

#### *Nefertiti Lift*

Named for the distinct jawline of the ancient Egyptian queen, Nefertiti injections of a neurotoxin are designed to decrease the downward pull of the platysma on the lower cheek.<sup>5</sup> The aesthetic goal is to raise the jawline and reduce the jowl.



Nefertiti injections are among the simplest procedures involving neurotoxins, and complications are uncommon. A similar effect can sometimes be achieved with a volumizing filler in the midface, but a neurotoxin may offer a more efficient, less costly means to reduce jowls and improve the jawline on the lower face. Injecting a neurotoxin into the platysmal band can correct some age-related neck bands but will have little effect on skin laxity and redundancy in the neck.

#### **Marionette Lines**

Another common dermatologic manifestation of aging is the appearance of downward-turning oral commissures and curved wrinkles in the marionette area. Targeting the depressor anguli oris (DAO) muscle for neurotoxin injection can help reduce these changes. Precise injection of the neurotoxin into the DAO is essential. The DAO can be distinguished from the depressor labii by palpation of the former. The muscle also can be identified by asking patients to clench their teeth and injecting just medial to the anterior edge of the clenched masseter muscle.

In most patients, both sides of the mouth should be treated. Some patients have asymmetrical DAO musculature, in which case different doses may be needed for each side. In some cases, only one side needs to be treated.

#### **Cobblestone Chin**

Many patients have never noticed this effect until it has been brought to their attention. Tissue atrophy can result in a rippled or nodular appearance in the chin. The effect tends to be subtle or unnoticeable when the chin is relaxed. Facial animation, such as during a conversation, can reveal changes, which are most noticeable to observers, not the patient. The effect can be most easily observed by the patient with contraction of the mentalis muscle. The nodular or dimpling appearance can be corrected by injecting a neurotoxin into the mentalis muscle.

#### **Perioral Wrinkles**

Correcting perioral wrinkles requires treatment of the orbicularis oris. The challenge is to administer a neurotoxin dose that relaxes the muscle sufficiently to reduce wrinkling without creating problems in the lips, including when pursing, whistling, speaking, and perhaps even eating. Combining a small dose of neurotoxin with a filler often provides the best aesthetic results with less risk of causing the previously mentioned problems in the lips from too much neurotoxin.

Treating numerous small wrinkles above the upper lip with a neurotoxin is more difficult than correcting a few large muscle-related wrinkles. Patients with numerous small wrinkles may require a degree of correction greater than what can be expected with a neurotoxin and filler. These patients may need laser resurfacing to achieve an optimal result.

Wrinkles below the lower lip require more precise treatment and carry a substantial risk of complications related to incorrect placement of injections or an excessive dose of neurotoxin. Because the doses need to be very low in this area, neurotoxins are less effective in correcting lines radiating downward from the lower lip, and the risks might outweigh the potential benefits in many cases.

#### **Masseter Injections**

Injecting a neurotoxin into the masseter can reduce facial width, and treatment is sought more often by Asian patients than by Caucasian patients. To achieve the thinning effect, a clinician

will usually inject 15 to 20 units of neurotoxin product on each side of the face, and an injection depth of  $\frac{1}{4}$  to  $\frac{1}{2}$  inch is required. Caucasian patients who seek masseter injections often clench their teeth on a regular basis, resulting in muscular hypertrophy that can be improved by treatment with a neurotoxin.

#### **Excessive Gum Exposure**

Excessive exposure of the gums when smiling is indicative of hyperfunctional levator labii superioris alaeque nasi. Quite often, a single small-dose injection below and to the side of each nare can achieve the desired lowering of the upper lip with a concomitant reduction in gum exposure.

#### **Tear Trough Fillers**

Multiple hyaluronic acid–based fillers, used in a variety of dilution concentrations, can achieve the desired aesthetic improvement in tear troughs, the areas immediately below the lower eyelids. Although all of the available products can produce good results, the products have subtle differences in structure, consistency, and other parameters that may make one product superior to another for specific indications. To achieve the best results on a consistent basis, clinicians should determine which product is optimal for a specific technique or application and then use that product consistently for the indication.

#### **Product Choice and Dilution**

During the process of accumulating experience with specific filler products, clinicians can determine the strengths and limitations of different fillers. They might find that certain gel fillers are less likely to produce the Tyndall effect.<sup>6</sup> The consistency of a product might be too dense or too thin for a specific aesthetic application. Recognition of these subtle differences comes primarily from experience in using them.

Dilution can improve the flow characteristics of fillers when used in the tear trough, and injection-site discomfort will differ depending on anesthetic content of the dilution. No single dilution formula can be applied to all fillers or to all of the applications for which fillers are used.

#### **Injection Site**

The choice of injection site is a key decision in the use of injectable fillers to treat hollow tear troughs. One option is to inject along the perisosteum of the orbital rim, where care has to be taken to avoid injecting the orbital septum. Most anatomic drawings show the orbital septum attached to the apex of the orbital rim. However, anatomic variance can result in the insertion of the septum several millimeters inferior to the orbital rim. Inadvertent injection of the orbital septum can lead to injection of filler into the orbital fat, as well as small tears in the septum itself.

An alternative approach to injecting the tear troughs is the “potential space” technique, which requires precise injection of filler into a narrow plane deep to the orbicularis oculi muscle and superficial to the periosteum. The technique involves needle penetration deep to the orbicularis oculi muscle, usually in the mid-papillary line to start. Most injections begin a few millimeters inferior to the orbital rim. Approximately 0.2 to 0.4 cc of filler material is placed in the potential space deep to the orbicularis oculi muscle and then gently pushed or massaged medially to fill the medial tear trough adjacent to the medial canthus. Additional injection points can be added medial to the

initial site, taking care to avoid touching the periosteum with the needle. A similar technique can be used to fill the lateral tear trough, using this potential space approach.

The primary advantages of the potential space technique are avoidance of the orbital septum; fewer needle puncture sites, which can reduce trauma and bruising; and ability to mold filler in the potential space to achieve smooth contours.

### Combining Techniques for Maximal Aesthetic Efficacy

Although no two patients are alike, they share the common goal of achieving a specific aesthetic effect. In some cases, the goal can be met with a single procedure. In other cases, a combination of procedures and techniques might be required to attain the patient's aesthetic goal.

### Focus on the Patient

Focusing on the patient begins with an overall assessment of the patient's face: extent and location of volume loss, types of aesthetic improvements that can be achieved, and techniques and materials that will be required to achieve the optimal aesthetic effect for the individual patient.

The facial assessment should include examining the changes that have occurred with aging: specifically, volume loss and redistribution associated with facial fat<sup>7</sup> and muscle and bony changes that occur with aging. Replacing volume where needed will help reverse the appearance of the patient's specific aging pattern. Additionally, reallocating volume and using toxin to help shape the patient will achieve an even better overall result. Some treatments can help give the patient better proportions and balance. This may not make the patient look more youthful, but it will make the patient's overall appearance more cosmetically pleasing.

A comprehensive treatment plan should include consideration of which fat pads can be treated to achieve the optimal effect, which techniques will be required, and which materials will be needed.

The overall assessment should comprise the upper face, midface, and lower face.

### Upper Face Forehead

The assessment should begin with identification of changes involving bone, fat, and skin. Mapping the patient's face by drawing on the skin can aid in achieving the desired aesthetic effect and, at the same time, avoid structures and tissues that lead to complications if injured. One must assess the projection of the forehead. If the patient has poor projection of the forehead, it can contribute to the downward displacement of the brow and more horizontal lines on the forehead. When placing volume in this area of the forehead, it is prudent to know the position of the supratrochlear and supraorbital arteries. In addition to properly placed toxin, this volume replacement will result in elevation of the brow, diminution of the forehead lines, and a much more youthful appearance.

Injection of a volume-enhancing filler in this area can achieve excellent results that also are very long lasting.

### Midface

Assessment of the midfacial area begins with the cheek, lower lid, and submalar area. The severity of age-related laxity in these areas can determine whether a patient can be treated with fillers or will require surgery. For many patients, nonsurgical treatment can achieve the desired youth-restoring effects.

From the cheek, the assessment progresses to the junction between the lower eyelid and the cheek, the lid-cheek junction. I first add volume to the cheek to diminish the lid-cheek junction, and usually less volume is required to correct any remaining tear trough deformity. Limited treatment of this area and the midcheek often has a substantial rejuvenatory effect.

The submalar area is another common site for filler injection. This area is harder to treat as there is no bony support underneath on which to place the product. Depot or fan-technique injections can add volume that complements the midcheek treatment. Loss of volume in the submalar area is common among younger, athletic women who are well toned and have low levels of body fat. The same changes can be observed in athletic men but are more commonly seen in women.

### Lower Face

The lower face often has multiple age-related changes that can be improved by use of injectable fillers. Marionette lines, loss of chin projection, and loss of volume in the mandibular area are common age-related changes that can be corrected. Some patients find sagging jowls particularly bothersome. Judicious use of a neurotoxin and filler can achieve a lifting effect that reduces or eliminates the facial descent in the jowl area, resulting in a better-toned, more youthful appearance.

### References

1. Vleggaar D, Fitzgerald R. Dermatological implications of skeletal aging: A focus on suprapariosteal volumization for perioral rejuvenation. *J Drugs Dermatol.* 2008;7:209-220.
2. Goldberg RA. Nonsurgical filling of the periorbital hollows. *Aesthet Surg J.* 2006;26:69-71.
3. Cox SE, Murphy DK, Paradkar D, Few JW. Subject-reported outcomes over 2 years with a volumizing hyaluronic acid filler for mid-face volume deficit. In Press.
4. Lorenc ZP, Fagien S, Flynn TC, Waldorf HA. Review of key Belotero Balance safety and efficacy trials. *Plast Reconstr Surg.* 2013;132(4 suppl 2):33S-40S.
5. Levy PM. The 'Nefertiti lift': A new technique for specific re-contouring of the jawline. *J Cosmet Laser Ther.* 2007;9:249-252.
6. Douse-Dean T, Jacob CI. Fast and easy treatment for reduction of the Tyndall effect secondary to cosmetic use of hyaluronic acid. *J Drugs Dermatol.* 2008; 7:281-283.
7. Rohrich RJ, Pessa JE. The retaining system of the face: Histologic evaluation of the septal boundaries of the subcutaneous fat compartments. *Plast Reconstr Surg.* 2008;121:1804-1809.

# Highlights of Skin Disease Education Foundation's 38th Annual Hawaii Dermatology Seminar Post-Test

Original Release Date: June 2014 • Most Recent Review Date: June 2014

Expiration Date: July 31, 2016 • Estimated Time to Complete Activity: 3.0 hours

To get instant CME credits online, go to <http://bit.ly/hawaiihighlights14>. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add [cmepd@louisville.edu](mailto:cmepd@louisville.edu) to your e-mail "safe" list. If you have any questions or difficulties, please contact the University of Louisville School of Medicine Continuing Medical Education (CME & PD) office at [cmepd@louisville.edu](mailto:cmepd@louisville.edu).

**CME Questions:** For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

- 1. Treatment with tumor necrosis factor inhibitors has been associated with:**
  - A. Increased risk for cardiovascular events
  - B. Increased risk for insulin resistance leading to type 2 diabetes mellitus
  - C. Reduced risk for cardiovascular events
  - D. Reduced risk for insulin resistance leading to type 2 diabetes mellitus
- 2. Which one of the following statements most accurately describes what is currently known about the role of inflammatory cytokines in psoriasis?**
  - A. Interleukin-12 and interleukin-23 have been shown to be equally important in psoriasis pathogenesis.
  - B. Interleukin-12 is the principal proinflammatory cytokine.
  - C. Interleukin-23 appears to be the most important contributor to psoriasis pathogenesis among the proinflammatory cytokines identified to date.
  - D. Interleukin-23 is activated by tumor necrosis factor.
- 3. In patients with psoriasis, musculoskeletal signs and symptoms \_\_\_\_\_.**
  - A. May occur either before or after the onset of cutaneous disease
  - B. Occur in up to 80% of patients whose psoriasis is not adequately controlled
  - C. Rarely occur when patients have both cutaneous and joint involvement
  - D. Typically occur after the onset of joint disease
- 4. With aging, facial features appear to \_\_\_\_\_.**
  - A. Change according to a patient's history of sun exposure throughout life
  - B. Descend
  - C. Develop telangiectasias
  - D. Recede
- 5. A clinical evaluation for facial rejuvenation should begin with \_\_\_\_\_.**
  - A. Areas that can be improved but are often overlooked
  - B. Changes that are of greatest concern to a patient
  - C. Determining whether surgical or nonsurgical options would best serve a patient's individual needs
  - D. The treatment that will achieve the most obvious and cosmetically pleasing result
- 6. Even when a clinician's technique is excellent, some areas treated with some fillers can develop a blue tinge referred to as \_\_\_\_\_.**
  - A. Benign cutaneous cyanosis
  - B. Indigo phenomenon
  - C. Pseudobruise
  - D. Tyndall effect
- 7. The best available evidence for the mechanism of action of \_\_\_\_\_ suggests dual activity: mitochondrial depolarization within cells that make up actinic keratosis lesions, followed by an internal inflammatory response that destroys the cells from the inside out.**
  - A. Imiquimod
  - B. Ingenol mebutate
  - C. Interleukin-23
  - D. Photodynamic therapy with aminolevulinic acid
- 8. A systematic review and meta-analysis of 20 published randomized trials of tumor necrosis factor inhibitors by Dommasch and colleagues in patients with psoriatic disease showed that these biologic agents are associated with a slight increase in the risk for \_\_\_\_\_.**
  - A. Nonserious infections
  - B. Serious infections
  - C. Malignancies
  - D. Tuberculosis
- 9. The newer biologic agents ustekinumab, secukinumab, brodalumab, and ixekizumab have which one of the following in common?**
  - A. All have been approved by the US Food and Drug Administration for the treatment of psoriasis.
  - B. All inhibit Janus kinase pathways.
  - C. All promote phosphodiesterase-4.
  - D. All target the interleukin cytokine pathway.
- 10. The accumulated evidence from placebo-controlled trials of biologic agents that target interleukin-12/23 shows that the risk for major adverse cardiac events:**
  - A. Is a possible safety issue, based on the consistency of the signal in clinical trials
  - B. Is a statistical anomaly
  - C. Is decreased in patients who have no preexisting cardiovascular disease risk factors
  - D. Is increased during the first 6 months of use

# Highlights of Skin Disease Education Foundation's 38th Annual Hawaii Dermatology Seminar Evaluation Form

**Original Release Date:** June 2014 • **Most Recent Review Date:** June 2014  
**Expiration Date:** July 31, 2016 • **Estimated Time to Complete Activity:** 3.0 hours

To get instant CME credits online, go to <http://bit.ly/hawaiihighlights14>. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add [cmepd@louisville.edu](mailto:cmepd@louisville.edu) to your e-mail "safe" list. If you have any questions or difficulties, please contact the **University of Louisville School of Medicine Continuing Medical Education (CME & PD)** office at [cmepd@louisville.edu](mailto:cmepd@louisville.edu).

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. *Please print.*

Name: \_\_\_\_\_

Specialty: \_\_\_\_\_

Degree:  MD  DO  PharmD  RPh  NP  RN  
 BS  PA  Other \_\_\_\_\_

Affiliation: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP: \_\_\_\_\_

Telephone: \_\_\_\_\_ Fax: \_\_\_\_\_

E-mail: \_\_\_\_\_

Signature: \_\_\_\_\_

### CME CREDIT VERIFICATION

I verify that I have spent \_\_\_\_\_ hour(s)/\_\_\_\_\_ minutes of actual time working on this CME activity. No more than 3.0 CME credits will be issued for this activity.

### COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

- Utilizing the latest treatments and approaches to common dermatologic diseases.
- Identifying and prescribing newer biologics for complex dermatologic disorders.
- Aggressively diagnosing and treating patients with psoriasis and its multiple comorbidities.
- Recognizing and treating the alarming prevalence of basal cell and other NMSC.
- Defining the benefits and limitations of surgical and nonsurgical techniques as well as topical treatment options for aesthetic dermatology.

**Did participating in this educational activity improve your KNOWLEDGE in the professional practice gaps that are listed above?**

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer. \_\_\_\_\_

\_\_\_\_\_

**Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed on the left?**

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer. \_\_\_\_\_

\_\_\_\_\_

**Did participating in this educational activity improve your PERFORMANCE in the professional practice gaps that are listed on the left?**

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer. \_\_\_\_\_

\_\_\_\_\_

**Please identify a change that you will implement into practice as a result of participating in this educational activity (new protocols, different medications, etc).**

\_\_\_\_\_

\_\_\_\_\_

**How certain are you that you will implement this change?**

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

What topics do you want to hear more about, and what issue(s) in your practice will they address? \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Were the patient recommendations based on acceptable practices in medicine?**  Yes  No

If no, please explain which recommendation(s) were not based on acceptable practices in medicine. \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Do you think the articles were without commercial bias?**  Yes  No

If no, please list the article(s) that was/were biased. \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_