Highlights of Skin Disease Education Foundation’s 39th Annual Hawaii Dermatology Seminar

Guest Editors

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Christopher B. Zachary, MBBS, FRCP
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Kristina Callis Duffin, MD, MS
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Linda F. Stein Gold, MD
Jerry K. L. Tan, MD, FRCPC

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

- Differentiate the characteristics of the tumor necrosis factor (TNF) inhibitors approved for use in treating psoriasis and apply that information to clinical practice.
- Demonstrate familiarity with the impact of comorbid conditions on patients with psoriasis and incorporate the effect of psoriasis therapy on these comorbidities into patient management.
- Integrate new therapies for rosacea into practice and describe current theories about rosacea pathophysiology.
- Explain the use of new treatments for tinea pedis and toennail onychomycosis.
- Apply current knowledge about anti-acne antibiotic dosing, maintenance therapy, topical therapy, and diet to clinical practice.
- Identify current and updated techniques to improve tattoo removal.

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Field Testers: This activity was pilot-tested for time required by Physicians: Zac Handler, MD, Brian Lee, MD, and Vijay Vanchinath, MD; Nursing: Kathleen Brown, LPN, Claudia Carron, MSN, RN, NE-BC, and Carol Ruland, RN; The field testers have no relevant financial relationships to disclose.

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INTRODUCTION

The breadth and diversity of dermatology, the speed at which our understanding of skin pathophysiology has improved, and the introduction of new therapies combine to make this field interesting and challenging. The expanding scope of our specialty also creates a broad range of educational needs for practicing clinicians.

Skin Disease Education Foundation's 39th Hawaii Dermatology Seminar offers updates from experts addressing a broad range of skin diseases, and covers advances in both medical and aesthetic dermatology. The articles in this educational supplement summarize the highlights of clinical sessions presented during the CME/CE conference by leading experts in the field of dermatology.

Tumor necrosis factor (TNF) inhibitors are the cornerstone of treatment for psoriasis, but choice of agent can be confusing. This supplement includes a comparison of the TNF inhibitors approved by the US Food and Drug Administration (FDA) for the treatment of psoriasis. Psoriasis has been linked to an elevated risk of several comorbidities. Can choice of psoriasis therapy alleviate any of these conditions? Our faculty evaluates how risk or presence of comorbid conditions might inform the choice of psoriasis therapy, and whether control of psoriasis can alleviate any coexisting conditions.

Accumulating evidence suggests that rosacea, like psoriasis, is a disorder of the immune system – specifically, of innate rather than adaptive immunity. This CME/CE supplement summarizes those findings. It also reviews studies of new therapies for this condition, as well as new evidence validating the use of a commonly prescribed agent.

Moving from the face to the feet and from immune disorders to fungal infection, our faculty addresses the diagnosis and therapy for tinea pedis and toenail onychomycosis. The FDA last year approved two topical therapies developed specifically for toenail onychomycosis, and in 2013 approved a treatment for interdigital tinea pedis. These highlights summarize the evidence for these therapies, and also cover other publications about diagnosis and management of these infections.

Acne is a common problem in dermatological practice. Our faculty reviews recent studies addressing topics such as antibiotic dosing, maintenance therapy, diet, and treatment of acne on the trunk of the body.

In the realm of aesthetic medicine, this educational supplement addresses techniques for reducing the number of sessions required for tattoo removal and newer lasers that may improve removal of certain types of tattoos.

The broad range of dermatology care and new therapies for skin conditions challenge the busy clinician to remain abreast of the latest information. We hope that you can apply these updates from our seminar to your clinical practice.

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Dr Fowler and Dr Zachary have received an honorarium for their participation in this activity. They acknowledge the editorial assistance of Eileen McCaffrey, MA, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

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Onychomycosis is a common fungal infection affecting the nails. It occurs in roughly 10% of the general population, with higher prevalence in men, older individuals, and in people with psoriasis, diabetes, or immunosuppressive conditions (eg, HIV). Dermatophytes are the most frequent cause of onychomycosis. Of these pathogens, Trichophyton rubrum is the most common, accounting for 70% of onychomycosis cases. Dermatophyte infection of the toenails is usually not a primary condition but is secondary to tinea pedis, a dermatophyte infection of the soles of the feet and interdigital spaces. T. rubrum is also a common cause of tinea pedis. Prevalence of subclinical dermatophyte infection of the toenail is higher among patients with tinea pedis but clinically normal toenails (n=35) compared with individuals without tinea pedis (n=66) (17% vs 1.5%; P=0.0066). Patients with either tinea pedis or toenail onychomycosis should be evaluated for the other infection.

If topical therapy is chosen for toenail onychomycosis, then separate agents must be prescribed to treat tinea pedis.

Tinea Pedis Therapy
Two topical antifungal agents are commonly used to treat tinea pedis. Luliconazole 1% cream received approval from the US Food and Drug Administration (FDA) in 2013 for the treatment of interdigital tinea pedis, but has been available in Japan for many years. It appears to inhibit the synthesis of ergosterol, a constituent of fungal cell membranes. According to an animal study, it was more effectively retained in the stratum corneum than terbinafine cream. Luliconazole 1% cream is also indicated for tinea cruris and tinea corporis. Naftifine 2%, available as a gel or cream, is also FDA-approved specifically for interdigital tinea pedis. It interferes with sterol biosynthesis, decreasing the amount of ergosterol.

A publication of two phase III trials (n=1,174) of naftifine 2% gel reported efficacy rates separately for interdigital (43.3%) and moccasin-type tinea pedis (56.7%). Rates of complete clearance, effective treatment, and mycological cure were similar for patients with interdigital and moccasin-type tinea pedis at 4 weeks post-treatment (22% vs 20%, 52% vs 51%, and 62% vs 65%, respectively).

Onychomycosis
Some clinicians incorrectly view onychomycosis as a cosmetic condition not worthy of treatment. However, this infection is progressive if untreated. It can disrupt skin integrity, permanently damage the nail plate, and spread to other individuals and to other body parts on the infected individual.

The most sensitive diagnostic test for onychomycosis is periodic acid–Schiff staining (82% sensitivity in one analysis). The severity of onychomycosis can be scored based on the proportion of a nail affected multiplied by the proximity of the infection to the nail matrix (Figure 1), with 10 points added if dermatophytoma (longitudinal streak or a patch) or subungual hyperkeratosis (>2 mm) is present (Figure 2). Mild disease is classified as a score of 5 or less, moderate as 6 to 15, and severe as 16 to 35. Severe involvement requires systemic treatment and carries a poorer prognosis. Host-related poor prognostic factors include immunosuppression, poor peripheral circulation, and poorly controlled diabetes.

Oral Therapies
Systemic agents used to treat onychomycosis include terbinafine, itraconazole, and fluconazole. A meta-analysis reported a mycological cure rate of 76% ± 3% with terbinafine (n=18 studies, 993 patients), 63% ± 7% with itraconazole pulse therapy (n=6 studies, 318 patients), and 48% ± 5% with fluconazole (n=3 studies, 131 patients).

A trial of terbinafine (12 or 16 weeks of therapy, 5-year follow-up) in toenail onychomycosis reported complete cure (ie, mycological plus clinical cure) in 35% of patients and mycological cure in 46% of patients. The recommended dose for toenail onychomycosis is 250 mg once daily for 12 weeks.

A pulse regimen is FDA-approved for fingernail infection but not toenail infection. Among patients receiving itraconazole for toenail onychomycosis in three double-blind, controlled trials (n=110), complete cure was reported in 14% of patients and mycological cure in 54% of patients. Therapy was deemed effective (mycological cure plus clear or minimal nail involvement) in 35% of those receiving itraconazole. Mean time to effective therapy was about 10 months. The recommended dose of itraconazole for toenail onychomycosis is 200 mg once daily for 12 consecutive weeks.

Fluconazole is sometimes used off-label to treat onychomycosis. When given once weekly for up to 1 year (n=362), it has produced clinical cure rates of 37% (150 mg/wk), 46% (300 mg/wk), and 56% (400 mg/wk).
48% (450 mg/wk) at 6-month post-therapy follow-up. Clinical cure was defined as a clinically normal target nail with complete regrowth of healthy tissue. Mean time to clinical success was 6.6, 6.2, and 6.7 months with 150-, 300-, and 450-mg weekly doses, respectively.20 The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with a statin. 21 Consider advising patients on statin therapy to withhold that agent on the day they take fluconazole. The once-weekly regimen may improve adherence.

Notably, ketoconazole oral tablets are no longer indicated for cutaneous fungal infections. The FDA withdrew the indication as of July 2013 due to the risk of severe liver injury and adrenal gland problems. 22 Topical formulations of ketoconazole are unaffected by this change.

Consider obtaining a complete blood count and hepatic panel prior to initiating oral antifungal therapy. 4 Fluconazole and terbinafine have rarely been associated with serious hepatic toxicity. 18, 21 Itraconazole is metabolized primarily in the liver. 19 Patients at elevated risk for hepatic or other adverse events, or receiving medications that may interact with antifungal therapy, should be monitored closely.

Systemic therapy does not cure all patients. Reasons for treatment failure include treatment nonadherence, incorrect diagnosis, a nondermatophyte pathogen, and patient factors (eg, immunocompromised, poorly controlled diabetes, peripheral vascular disease). 4 A certain level of recurrence is associated with systemic antifungal therapy. A 7-year prospective study (n = 73) reported a 16.4% recurrence at a mean of 3 years following successful therapy. The recurrence rate was higher following treatment with itraconazole than with terbinafine (35.7% vs 11.9%, respectively; \( P = 0.046 \)). 23
that fungal cultures were negative at week 52 in 87.0% and 85.4% of patients treated with tavaborole. Negative fungal culture is distinct from mycological cure in that the latter was defined as negative KOH wet mount and negative fungal culture.29

Summary

The current classification system for onychomycosis divides cases into mild, moderate, and severe disease.15 Severe disease requires oral therapy. Two recently FDA-approved topical antifungal agents—efinaconazole 10% solution and tavaborole 5% solution—have demonstrated effectiveness in mild to moderate onychomycosis. Topical luliconazole 1% cream and naftifine 2% cream and gel offer effective options for tinea pedis. Patients with either toenail onychomycosis or tinea pedis should be evaluated for the other fungal infection.

References

Using the Anti-TNF Agents in Psoriasis
Kristina Callis Duffin, MD, MS*

Abstract
The introduction of tumor necrosis factor (TNF) inhibitors greatly improved the level of care available for patients with psoriasis. The three anti-TNF medications that have received approval by the US Food and Drug Administration (FDA) for use in plaque psoriasis have many similarities and differences in terms of efficacy, safety, dosage route and frequency, and effectiveness in comorbid conditions. Familiarity with their characteristics can inform the choice of therapy for each patient. This article reviews the major clinical trials of each agent as well as real-world evidence.

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Keywords
Psoriasis, tumor necrosis factor inhibitors, efficacy, safety, psoriatic arthritis

Tumor necrosis factor (TNF) is among the cytokines that play key roles at multiple points in the pathophysiology of psoriasis.1 It induces the release of interleukin (IL)-23 from dendritic cells and contributes to the differentiation of T cells into the production of IL-17, another important substance in the psoriasis inflammatory cascade. TNF regulates tissue remodeling and expression of genes for inflammatory responses. It appears to act synergistically with IL-17 to induce changes in psoriasis-related gene expression.

Five TNF-α inhibitors are available in the United States. Three of these agents are FDA-approved for both psoriasis and psoriatic arthritis (PsA)—etanercept, adalimumab, and infliximab—and two agents are FDA-approved for PsA but not psoriasis—golimumab and certolizumab.2-4 Certolizumab is now in phase III trials for use in psoriasis (http://dermira.com/dermira-and-ueb-announce-start-of-phase-3-program-for-cimzia-certolizumab-pegol-in-psoriasis/). The Table on page S66 summarizes some of the characteristics of and differences among the agents that are currently approved for psoriasis.

Etanercept
Unlike the other two anti-TNF-α agents FDA-approved for psoriatic etanercept is a fusion protein of the TNF receptor rather than a monoclonal antibody.2,5,6 The recommended dosage is 50 mg twice weekly for 3 months, followed by 50 mg once weekly thereafter.2

Advantages of etanercept include extensive experience (FDA-approved 10 years ago for plaque psoriasis), consistent efficacy across clinical studies (~50% of patients achieving Psoriasis Area and Severity Index [PASI] 75),7-9 and long-term safety.9 Nearly half (49%) of participants in a randomized, placebo-controlled, double-blind, parallel-group, phase III clinical trial achieved PASI 75 (ie, ≥75% improvement) with etanercept 50 mg twice weekly at week 12. This proportion rose to 59% after 24 weeks on this high dose.7 Response is dose dependent, with higher efficacy at higher doses. Proportions achieving PASI 90 (≥90% improvement) with high-dose etanercept were 22% and 30% at weeks 12 and 24, respectively.7

Another phase III study of etanercept in plaque psoriasis produced similar results: At week 12, 49% of patients randomized to high-dose therapy (50 mg twice weekly) achieved PASI 75 and 21% achieved PASI 90.9 This study reduced the highest dose to 25 mg twice weekly after 12 weeks, yet 54% of those whose dose was reduced from 50 to 25 mg twice weekly at week 12 achieved PASI 75 at week 24. As in the other phase III trial, response rates rose with dose: 34% of those initiated at the lower dose (25 mg twice weekly) achieved PASI 75 at week 12. A long-term extension of a phase III randomized study (n=591) reported that at 96 weeks, 51.6% of patients demonstrated PASI 75 and 23.2% attained PASI 90 with etanercept 50 mg twice weekly.7

Etanercept has the lowest efficacy (measured as PASI 75 at 10 to 16 weeks) of all the anti-TNF agents approved by the FDA for the treatment of psoriasis, with the caveat that this comparison does not come from head-to-head studies.7,8,10-13 Anecdotally, patients and clinicians often observe a reduction in efficacy when patients decrease the dose from 50 mg twice weekly to weekly at 12 weeks, as recommended in the prescribing information.2 It is FDA-approved for PsA and has demonstrated long-term safety, with rates of exposure-adjusted adverse events (other than injection site reactions) and infections over 96 weeks similar to those of placebo.9 It requires the most frequent injection schedule of the three anti-TNF inhibitors that are FDA-approved for plaque psoriasis.11 Only non-neutralizing antibodies have been observed, which did not affect efficacy or safety.9 Etanercept syringes and autoinjectors can be stored at room temperature for up to 14 days prior to use, which offers convenience for patients who travel.7

Combining etanercept with other agents can increase its efficacy. Adding no more than two courses of clobetasol propionate foam to etanercept for up to 2 weeks (at weeks 11 and 12, and weeks 23 and 24) increases the proportion of patients achieving PASI 75 at week 12 (65.2% with combination [n=295] vs 48.3% with etanercept alone [n=297]; P<0.001), though not at week 24.14

Adding narrow-band ultraviolet light B therapy to etanercept (single-arm study; 86 patients) led to 85% of patients achieving PASI 75 and 58% reaching PASI 90 at 12 weeks.12 Combining methotrexate (7.5-15 mg/wk; n=239) or placebo (n=239) with...
etanercept (50 mg twice weekly for 12 weeks followed by 50 mg once weekly for 12 weeks) was associated with significantly higher rates of achieving PASI 75 at week 24 (77.3% vs 60.3%; \( P<0.0001 \)). Methotrexate was associated with a higher incidence of elevated hepatic transaminases classified as adverse events (2.9% with methotrexate, 1.7% with placebo).18

**Adalimumab**

Two major clinical trials documented the efficacy of adalimumab in plaque psoriasis. Nearly three-quarters (71%) of the 814 patients randomized to adalimumab (40 mg every other week) in the Randomized controlled EValuation of adalimumab Every other week dosing in moderate to severe psoriasis TriAL (REVEAL) attained PASI 75 at week 16,10 substantially more than the roughly 50% reaching this threshold at week 12 with etanercept in pivotal studies.9 Nearly half (45%) of patients receiving adalimumab achieved PASI 90 at 16 weeks, and 20% of patients reached PASI 100.10

In the Comparative Study of Humira vs Methotrexate vs Placebo in Psoriasis Patients (CHAMPION; \( n=271 \)), 79.6% of adalimumab-treated patients achieved PASI 75 at week 16, compared with 35.5% receiving methotrexate and 18.9% randomized to placebo (\( P<0.001 \), adalimumab vs either comparator). Response with adalimumab was rapid (57% improvement in mean PASI at week 4), possibly due to the loading dose (80 mg initial dose).11 The study discontinuation rate was higher with methotrexate than with adalimumab, primarily because of hepatic-related adverse events. Methotrexate reduces adalimumab clearance, though no dose adjustment of either agent is required.3

One of the primary disadvantages of using adalimumab is its association with the formation of anti-drug antibodies and a resultant loss of drug efficacy. In REVEAL, 8.8% of patients had detectable anti-adalimumab antibodies (AAA) at least once over a 1-year period. Nearly half (43%) of AAA-positive patients and 28% of AAA-negative patients lost an adequate response to the drug.10 The prescribing information reports an immunogenicity rate of 20.8% in the subset of patients with psoriasis in which AAA could be measured. The rate of AAA formation in patients with rheumatoid arthritis (RA) is lower when methotrexate is added to adalimumab.3 Clinicians may wish to consider adding methotrexate to adalimumab, especially in patients with severe psoriasis and PsA who have failed other therapies.

**Infliximab**

This monoclonal antibody, delivered by intravenous infusion, displays a rapid onset of action and the highest efficacy rates of all three anti-TNF agents approved for the treatment of plaque psoriasis. Again, this comparison is not based on head-to-head trials but on proportions of patients achieving PASI 75 at 10 to 16 weeks in landmark trials.7,8,10-13 In two phase III studies, 80% and 75.5% of patients randomized to infliximab at the recommended dose of 5 mg/kg reached PASI 75 at week 10; 57% and 45.2% reached PASI 90 at week 10.10,12,13 Infliximab requires an induction period with infusions at 0, 2, and 6 weeks, followed by infusions every 8 weeks.6

Efficacy in these studies for patients receiving 5 mg/kg every 8 weeks was sustained at week 24 or 26 (PASI 75 in 82% and 78%, PASI 90 in 58% and 56%) but declined at week 50 (PASI 75 in 61% and 54.5%, PASI 90 in 45% and 34.3%).12,13 Giving infliximab as needed (ie, when PASI response drops below 75) led to a greater reduction in efficacy.13 It is important for clinicians to explain to patients the need to obtain the infusion on schedule even if their skin is clear, as delaying a dose until symptoms recur can lead to loss of efficacy. Increasing the dose to 7.5 or 10 mg/kg, or reducing the dose interval (eg, to every 6 weeks) at the first sign of a diminution in efficacy, can forestall further reduction in effectiveness.17 Adding another immunosuppressive agent such as methotrexate can also increase efficacy (documented in RA), decrease the risk of anti-drug antibodies, and reduce the risk of infusion reactions, though it may also increase the risk of serious infections.6

Along with the loss of efficacy, the high risk of infusion reactions is one of the major drawbacks to treatment with infliximab. Infusion reactions have been reported in 20% of clinical trial participants, compared with 10% of those randomized to placebo. Manifestations can range from flu-like symptoms to dyspnea or anaphylaxis.6 Infusion reactions were two to three times more common in patients who developed anti-drug antibodies, and occurred more frequently in those who were re-treated following a break in therapy.4 A serum sickness-like reaction that can occur following therapy is also more common among patients who develop anti-drug antibodies, and in those who stop and then restart infliximab therapy.4 Anti-drug antibodies were detected in 19% of patients receiving infliximab for psoriasis through week 46 in one study.12,13 The prescribing information reports rates of 36% and 51% in patients with psoriasis treated for 1 year.6

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**TABLE Characteristics of TNF Inhibitors Approved for Use in Plaque Psoriasis**

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<td><strong>Structure</strong></td>
<td>Fusion protein of the TNF receptor</td>
<td>Human monoclonal antibody</td>
<td>Chimeric monoclonal antibody</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5-6 days</td>
<td>10-20 days</td>
<td>8-10 days</td>
</tr>
<tr>
<td><strong>Dose/frequency</strong></td>
<td>Self-administered, 50 mg subcutaneous injection, 2x/wk for 3 mo, then weekly</td>
<td>Self-administered, 40 mg: 80 mg on day 1, then 40 mg on day 8, then every other week</td>
<td>IV infusion, 5 mg/kg; weeks 0, 2, 6, then every 8 weeks</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>49% at week 12* and 51.6% at week 96† with 50 mg 2x/wk</td>
<td>71% and 79.6% at week 16* and 10††</td>
<td>80% and 75.5% at week 10, 61% and 54.5% at week 50 (5 mg/kg)* and ††</td>
</tr>
<tr>
<td><strong>PsA</strong></td>
<td>FDA-approved</td>
<td>FDA-approved</td>
<td>FDA-approved</td>
</tr>
</tbody>
</table>

*% reaching PASI 75 at specified time points in phase III clinical trials referenced.
TNF Inhibitors in Children With Psoriasis

No anti-TNF inhibitors are FDA-approved for children with psoriasis. However, the efficacy of etanercept in children and adolescents (n=211, ages 4-17 years old) has been documented in a rigorously conducted randomized controlled trial. A total of 57% of patients receiving etanercept achieved PASI 75 at week 12.20 Long-term follow-up demonstrated continued efficacy (PASI 75 in 61% at week 96) and safety (five serious adverse events, none of which were treatment-related).21 Most children and adolescents regained efficacy after withdrawal and re-treatment; 80% of the 65 patients maintained or regained PASI 75 under such circumstances.22

Use in Patients With Comorbid Conditions

Roughly 30% of patients with psoriasis also have PsA.23 All three anti-TNF agents approved by the FDA for psoriasis are also marketed for use in PsA. Efficacy (measured as a 20% improvement, or ACR20) is similar for all three agents: 59%, 58%, and 58% for etanercept, adalimumab, and infliximab at weeks 12, 12, and 14, respectively.24-26

Obesity affects an estimated 13% to 34% of individuals with chronic plaque psoriasis.27 Of the three TNF inhibitors approved for psoriasis, only infliximab offers weight-based dosing.8 This may be an advantage when treating patients who are obese. Adalimumab and infliximab are FDA-approved for use in Crohn’s disease and ulcerative colitis3;6; psoriasis has been associated with both of these conditions.28

Real-World Evidence

A study including 713 patients from 10 outpatient clinics at a single point in time reported somewhat lower efficacy with TNF inhibitors than the rates observed in clinical trials (Figure).29 Eligible patients were those receiving phototherapy or commonly used systemic therapies. The primary outcome was achieving a score of clear or almost clear (0-1) on the Physician’s Global Assessment (PGA) scale. Among the most commonly used treatments, rates of reaching this threshold were 47.7% for adalimumab, 36.1% for the non-TNF biologic agent ustekinumab, 34.2% for etanercept, 27.6% for narrow-band UV-B, and 23.8% for methotrexate.29

Other noteworthy findings from this study were that less than 5% of patients were treated with infliximab, and many patients were treated with higher than recommended doses. Specifically, 30% of patients receiving etanercept were treated with 50 mg twice weekly despite having passed the 12-week mark. Roughly 11.5% of patients treated with adalimumab received the agent weekly despite having passed the 12-week mark. Roughly 11.5% of patients receiving etanercept were treated with 50 mg twice weekly instead of every other week as recommended, or injected double the recommended dose every other week.29

Safety

Considerations with all three TNF inhibitors approved by the FDA for plaque psoriasis include risk of serious infections (eg, tuberculosis, bacterial sepsis, invasive fungal infections), onset or exacerbation of demyelinating diseases (eg, multiple sclerosis, optic neuritis) or heart failure, risk of lymphoma or leukemia, or a lupus-like syndrome.2,3,6 An ongoing observational study (N=12,095) of patients receiving or eligible to receive biologic or other systemic therapy for psoriasis has reported that exposure to infliximab (hazard ratio [HR], 3.101, P<0.001) or other biologics (HR, 1.954, P=0.005) predicted the risk of serious infections. Use of biologics did not predict the risk of death, malignancy, or major adverse cardiac events compared with nonbiologic therapy.30

Summary

TNF inhibitors have revolutionized the field of psoriasis management. These agents are now the cornerstone of therapy for psoriasis and PsA. Their efficacy rates are high, they have been thoroughly evaluated in controlled clinical studies, and they can be used in combination with other medications to improve safety and efficacy.

Distinguishing factors among the three anti-TNF agents approved by the FDA for use in psoriasis and PsA therapy include the following:

- When comparing the proportion of patients who achieve PASI 75 at 10 to 16 weeks in clinical trials, etanercept offers the lowest rate of efficacy (~50% at 12 weeks, compared with 71% and 80% at week 16 with adalimumab10,11 and 75.5% and 80% at week 10 with infliximab2,21).
- Infliximab is associated with the loss of efficacy over time.12,13
- Etanercept is not associated with neutralizing anti-drug antibodies, unlike adalimumab and infliximab.3,6,9
- Etanercept’s efficacy in the pediatric population has been evaluated in a randomized controlled trial.
- Etanercept requires the most frequent dosing.2,3,6
- Risk of infusion reaction is high with infliximab.6
- Infliximab offers weight-based dosing, which may be helpful in patients who are obese.9

References

Psoriasis has been associated with an increased risk of a variety of concomitant conditions (Table 1). The link between psoriasis and at least some associated comorbidities is thought to be T-cell and cytokine (eg, tumor necrosis factor [TNF]) activation. Recent studies have evaluated if psoriasis treatment—especially treatment directed at the underlying inflammation—affects these comorbidities and if any improvement in comorbidities associated with psoriasis treatment is linked to psoriasis treatment response (Table 2 on page S71).

### Chronic Kidney Disease

A recently published claims data analysis (n=143,883 with psoriasis and n=689,702 without psoriasis) reported an association between severe psoriasis and an increased risk of incident chronic kidney disease (CKD), independent of risk factors (eg, age, sex, hypertension, diabetes, cardiovascular disease [CVD], body mass index, and use of nonsteroidal anti-inflammatory drugs [NSAIDs]). Specifically, individuals with severe psoriasis had nearly twice the risk of incident CKD compared with controls, after risk factor adjustment. Severe psoriasis was also associated with a four-fold increased incident risk of end-stage renal disease (Table 1). Among those with severe psoriasis, younger age was associated with a higher relative risk of CKD. Further study is needed to evaluate if psoriasis therapy can alleviate concomitant CKD.

### Impact of Psoriasis Therapy and Patient Monitoring

Of all the conditions associated with psoriasis, CKD probably has the greatest impact on the choice of psoriasis therapy. Patients with psoriatic arthritis (PsA) are often prescribed NSAIDs, which are associated with deterioration of kidney function as well as acute renal failure. The dosage of apremilast must be reduced to 30 mg once daily (from twice daily) in patients with severe renal impairment (creatinine clearance <30 mL/min).

Methotrexate is eliminated primarily through the kidneys so that excretion is reduced in patients with impaired renal function. As reduced kidney function is common in older individuals, consider using only low doses of methotrexate in these individuals, with close monitoring for toxicity. Consider monitoring renal function in older adults using creatinine clearance rather than serum creatinine as the latter may overestimate renal function in this population. Cyclosporin A is associated with nephrotoxicity and should not be prescribed for patients with impaired renal function.

### Crohn’s Disease

Psoriasis has been linked to a roughly four-fold increased risk for developing Crohn’s disease (CD) in the Nurses’ Health Study (Table 1). Risk of CD was even higher among women with psoriasis (relative risk [RR], 6.43, 95% confidence interval [CI] 2.04-20.32). Psoriasis and CD share autoinflammatory pathophysiology as well as genetic associations, which may explain the comorbidity. Clinicians should ask patients with psoriasis about gastrointestinal symptoms. Patients who report persistent diarrhea should be evaluated for possible CD.

### Impact on Choice of Psoriasis Therapy

Patients with both CD and psoriasis may benefit from therapy with the anti-TNF agents adalimumab or infliximab; these two agents are approved by the US Food and Drug Administration (FDA) for both conditions. Ustekinumab, an interleukin (IL)-23 and 12 antagonist that has received FDA approval for use in plaque psoriasis, is under study as a therapy for CD.

### Table 1 Psoriasis and Risk of Comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk associated with psoriasis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>Adjusted HR 1.93; 95% CI 1.79–2.08</td>
</tr>
<tr>
<td>ESRD</td>
<td>Adjusted HR 4.15; 95% CI 1.70–10.11</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Adjusted RR 4.00; 95% CI 1.72–9.27 (NHS) 3.76; 95% CI 1.82–7.74 (NHS II)</td>
</tr>
<tr>
<td>Depression</td>
<td>Adjusted HR 1.39; 95% CI 1.37–1.41</td>
</tr>
<tr>
<td>MACE</td>
<td>Adjusted HR 1.53; 95% CI 1.26–1.85</td>
</tr>
<tr>
<td>CV death</td>
<td>Adjusted HR 1.57; 95% CI 1.26–1.96</td>
</tr>
<tr>
<td>Unemployment</td>
<td>Adjusted OR 1.78; 95% CI 1.40–2.26</td>
</tr>
</tbody>
</table>

*Compared with controls without psoriasis unless otherwise noted. Severe psoriasis: CI=confidence interval; CKD=chronic kidney disease; ESRD=end-stage renal disease; HR=hazard ratio; MACE=major adverse cardiovascular events; NHS=Nurses’ Health Study (1990–2008); NHS II=Nurses’ Health Study II (1991–2007); OR=odds ratio; RR=relative risk.
Secukinumab, an IL-17A antagonist approved by the FDA for use in plaque psoriasis and PsA, has exacerbated CD in studies evaluating active CD. A proof-of-concept study evaluating seuciknumab as a treatment for CD (n=59) reported superior results with placebo, along with an increased rate of serious adverse events (14 events in 10 patients [7 receiving seuciknumab, 3 randomized to placebo]). Consider avoiding use of this seuciknumab in patients with active CD.

Depression
Risk of depression, anxiety, and suicidality is 39%, 31%, and 44% higher, respectively, in people with psoriasis (n=146,042 with mild psoriasis, n=3,956 with severe psoriasis) compared with controls (n=766,950), according to an analysis of electronic medical records from the UK-based General Practice Research Database (GPRD). Severe psoriasis was associated with a higher risk of depression than mild psoriasis (72% and 38%, respectively; hazard ratio [HR] 1.72, 95% CI 1.57-1.88; and HR 1.38, 95% CI 1.35-1.40, respectively). Risk of depression was higher in younger patients than in older patients with mild psoriasis.

A case-control study using information from an outpatient database in Germany reported similar findings (3,147 with psoriasis matched to 3,147 without psoriasis). The adjusted risk of depression associated with psoriasis was 49% higher with psoriasis (odds ratio [OR] 1.49, 95% CI 1.20-1.86). Effect of Psoriasis Therapy on Depression
Evidence suggests that treating psoriasis does alleviate symptoms of depression. Patients randomized to receive etanercept for moderate to severe psoriasis (n=311) were more likely than those receiving placebo (n=306) to show at least a 50% improvement in depression symptoms (Hamilton Rating Scale for Depression [HAM-D] or the Beck Depression Inventory [BDI]) in one study. Roughly one-third of the participants had mild or moderate to severe depression at baseline, based on BDI scores.

Ustekinumab (45 or 90 mg) therapy has also been associated with improvements in depression and anxiety symptoms compared with placebo (n=1,230 with moderate to severe psoriasis). Specifically, depression and anxiety scores improved by 29.3% and 13.9% (Hospital Anxiety and Depression Scale–Depression [HADS-D] and Hospital Anxiety and Depression Scale–Anxiety [HADS-A], respectively) at 12 weeks in patients randomized to treatment with ustekinumab compared with those receiving placebo (P<0.001). Improvement in Psoriasis Area and Severity Index (PASI) scores at week 12 was significantly though modestly correlated with easing of depression and anxiety symptoms (r=-0.32 and r=0.24, respectively; P<0.0001 for each correlation).
The proportion of patients with mild to severe anxiety or depression symptoms fell from baseline to week 12 by 34% and 55%, respectively, in the ustekinumab groups, but increased by 1.4% and 10.2%, respectively, in those randomized to placebo (P<0.001 vs placebo for each value).

These changes occurred in a population in which about one-fourth (26.7%) of participants displayed depression and two-fifths (40.3%) showed anxiety symptoms at baseline (HADS-D or HADS-A scores ≥8), with roughly one-tenth (11%) and one-fifth (20%) meeting the criteria for moderate to severe depression or anxiety (HADS-D or HADS-A scores ≥11). Impact of disease on quality of life was high at baseline, with 54.6% of study participants reporting Dermatology Life Quality Index (DLQI) scores >10. Those assigned to ustekinumab saw DLQI scores improve by 76.2% at week 12 compared with placebo (P<0.001).

Another investigation found that improvement in depression symptoms (measured by the Zung Self-rating Depression Scale [ZDS]) among patients with moderate to severe psoriasis (n=96) randomized to receive adalimumab was significantly correlated with improvement in PASI (r=0.5; P<0.0001) and in the DLQI (r=0.5; P<0.0001). Depression symptoms were significantly more likely to improve in adalimumab responders (≥PASI 75 at week 12 or termination of therapy) than in nonresponders (Table 2). Baseline levels of depression were similar for both adalimumab and placebo groups as measured by mean ZDS scores, proportions with ZDS score ≥50, and proportion reporting a history of depression.

Nonbiological therapy also has been associated with improvement in depression and anxiety. The proportions of patients with definite depression or anxiety (measured on the HADS-D and HADS-A, respectively) decreased significantly from pre- to post-treatment with 1 month of the modified Goekerman regimen (diluted topical tar treatment followed by phototherapy; n=48). Specifically, rates of definite depression fell from 20% to 3%, and rates of definite anxiety decreased from 24% to 5%.

Cardiovascular Disease
Similar to psoriasis, atherosclerosis, CVD, and myocardial infarction (MI) have been linked to immunological abnormalities and markers of system inflammation. Psoriasis has been associated with an increased risk of MI, major adverse cardiovascular events (MACE), and CV mortality in analyses of data from the UK GPRD.

The risk of MI in patients with psoriasis was higher among younger patients and those with severe psoriasis compared with older patients and those with less severe psoriasis. Adjusted RR of MI was 1.08 (95% CI 1.03-1.13) for a 60-year-old with mild psoriasis, 1.29 (95% CI 1.14-1.46) for a 30-year-old with mild psoriasis, 1.36 (95% CI 1.13-1.64) for a 60-year-old with severe psoriasis, and 3.10 (95% CI 1.98-4.86) for a 30-year-old with severe psoriasis.

After adjustment for CV risk factors, severe psoriasis was associated with a 53% increased risk for MACE (Table 1) as well as a 6.2% attributable risk of MACE over 10 years. It has also been linked to an increased risk of CV death (Table 1): the risk was higher among younger patients, with a nearly 2.7-fold increased risk for a 40-year-old with severe psoriasis and a 1.9-fold increased risk for a 60-year-old with severe psoriasis (RR 2.69; 95% CI 1.45-4.99, and RR 1.92; 95% CI 1.41-2.62, respectively).

A meta-analysis confirmed these findings, reporting a 39% increased risk of CV death and a 70% increased risk of MI with severe psoriasis, and a 29% increased risk of MI with mild psoriasis (RR 1.39; 95% CI 1.11-1.74; RR 1.70; 95% CI 1.32-2.18; RR 1.29; 95% CI 1.02-1.63). These investigators attributed 1,269 excess CV deaths and 6,479 excess MIs per year in the United States to psoriasis.

Effect of Psoriasis Therapy on Risk of Cardiovascular Disease
Data indicate that methotrexate reduces CV risk, and that anti-TNF therapy leads to a greater degree of risk reduction than methotrexate. A meta-analysis reported that methotrexate was associated with a 21% lower risk of CV death (n=10 studies, 95% CI 0.73-0.87, P<0.001), and an 18% lower risk of MI (n=5, 95% CI 0.71-0.96, P=0.01). Most studies (9 of 10) included evaluated patients treated for rheumatoid arthritis, with one study focused on psoriasis and one study focused on polyarthritis.

Analysis of a US claims database (2000-2011) focused on individuals with psoriasis and compared CV risk in those prescribed either methotrexate (n=8,581) or a TNF inhibitor (n=9,148). At 12 months, use of an anti-TNF agent rather than methotrexate was associated with significantly lower incidence of a major CV event (1.87% vs 5.52%; P<0.01). Each incremental 6 months of cumulative TNF inhibitor exposure was associated with a 12% reduction in risk of a major CV event over a median of 23 months.

Still unanswered is the question of whether the difference in CV risk reduction results from anti-TNF agents reducing inflammation more effectively or of some other effect of the medications.
**Economic Health**

Multiple studies of data from National Psoriasis Foundation surveys indicate that psoriasis, especially severe disease, negatively affects income and ability to work. Among individuals working full time, the probability of low income (<$30,000) was significantly higher among individuals with severe psoriasis compared with mild psoriasis (21% vs 13%, \( P=0.0002 \)) based on 2003-2005 survey data (n=601). Compared to individuals with mild disease, those with severe psoriasis were less likely to work full time (56.1% vs 62.0%; \( P=NS \)) and more likely to cite their disease as the reason for not working (17% vs 6%; \( P=0.01 \)).

A subsequent analysis (2003-2011; n=5,604) reported that 12% of patients with psoriasis were unemployed, and 92% of those cited psoriasis alone or along with PsA as the sole reason.

Over half (54%) worked part time, and 22% were retired. As in the earlier study, psoriasis severity was linked to unemployment. Individuals with severe psoriasis were nearly twice as likely to be unemployed as those with mild disease, after adjustment for age and sex (Table 2).

**Impact of Psoriasis Therapy on Work Productivity**

Does psoriasis therapy improve income, ability to work, or work productivity? A study of 246 patients receiving etanercept for moderate to severe psoriasis reported significant reductions in degree of work impairment as measured by the Work Productivity and Activity Impairment questionnaire. Over the first 3 months of treatment, mean degree of impairment while working decreased from 22.7% to 6.6% (\( P<0.0001 \)). Mean activity impairment outside of work also decreased from 31.4% to 12.9% (\( P=0.01 \)).

A subsequent analysis (2003-2011; n=5,604) reported that 12% of psoriasis responders (ie, \( \geq \)PASI 75 at week 16) demonstrated significant improvement in work productivity? A study of 246 patients receiving etanercept for moderate to severe psoriasis, 12.9% to 12.9% (\( P=NS \)) and more likely to cite their disease as the reason for not working (17% vs 6%; \( P=0.01 \)).

Summary

Patients with psoriasis, especially severe disease, face a higher risk of developing renal, gastrointestinal, CV, and psychiatric comorbidities as well as a higher likelihood of unemployment and low income.2,8,16,24,26,30 Therapy for psoriasis has been linked to improvements in depression, CV risk, and work productivity.22,31 Clinicians managing patients with psoriasis should screen and monitor patients for these concomitant conditions and consider them in their choice of therapy.

**TABLE 2 Unemployment and Psoriasis Severity**

<table>
<thead>
<tr>
<th>Psoriasis Severity</th>
<th>Unadjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild psoriasis</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Moderate psoriasis</td>
<td>0.99</td>
<td>0.77–1.26</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>1.75</td>
<td>1.38–2.21</td>
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</tbody>
</table>

<table>
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<td>Moderate psoriasis</td>
<td>0.99</td>
<td>0.77–1.28</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>1.78</td>
<td>1.40–2.26</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.02–1.04</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>2.33</td>
<td>1.93–2.83</td>
</tr>
</tbody>
</table>

**References**

S ystemic and topical antibiotics form the cornerstone of acne therapy. Studies have examined if increasing the dose of oral antibiotics improves efficacy. Minocycline (extended release) has demonstrated similar efficacy compared with placebo at daily doses of 1, 2, and 3 mg/kg in patients with moderate to severe acne for treatment of acne for 12 weeks (n=233, a randomized, double-blind study). Each dose reduced the number of inflammatory acne lesions by roughly 50% from baseline. However, higher doses were associated with increased incidence of side effects (acute vestibular and central nervous system adverse events).1

In contrast, higher doses of doxycycline calcium do lead to improved efficacy. A randomized, double-blind phase II study evaluating 3 doses (0.6, 1.2, and 2.4 mg/kg daily, or placebo for 12 weeks in patients with moderate to severe inflammatory acne) found that only the highest dose yielded results superior to those of placebo. Efficacy was measured as change in inflammatory lesion count and Investigator’s Global Assessment (IGA) score. Incidence of gastrointestinal adverse events also rose with dose.2

What’s New in Acne
Linda F. Stein Gold, MD*

Abstract
Recent studies about the treatment of acne address antibiotic dosing, maintenance therapy, topical antibiotics and benzoyl peroxide in facial and truncal acne, the link between antibiotics and risk of inflammatory bowel disease, and the role of diet in acne. Semin Cutan Med Surg 34(supp4):S72-S74 © 2015 published by Frontline Medical Communications

Keywords
Acne, antibiotic dosing, minocycline, doxycycline, benzoyl peroxide, isotretinoin, diet, lauric acid, probiotics

Maintenance Therapy
Once acne is under control, can treatment be stopped or stepped down? Two studies found that topical therapy was sufficient to maintain efficacy achieved with systemic antibiotic plus topical treatment. Patients with severe acne were randomized to an induction regimen of doxycycline plus either vehicle or adapalene 0.1% – benzoyl peroxide 2.5% for 12 weeks. Those who achieved at least 50% global improvement then received maintenance therapy with either the topical regimen or vehicle for 24 weeks. Starting with systemic plus topical therapy and continuing with topical maintenance therapy yielded the best results: 50.0% of participants assigned to these regimens were rated “clear” or “almost clear” and total lesion count fell by 76% at week 36. Comparable figures for those started with combination therapy but maintained on vehicle were 26.2% and 51%, respectively. Initiating therapy with both topical and systemic treatment led to faster onset of action compared with systemic therapy alone (P<0.05 at week 2).1

- A similar study with oral minocycline (100 mg twice daily) and topical tazarotene (0.1%) as induction therapy found that maintenance results were similar with systemic therapy only, topical therapy only, or both treatments.4 Patients with moderately severe to severe acne who achieved at least 75% global improvement after a 12-week initiation phase were randomized (n=90) to continue both therapies or to continue one of the treatments plus a placebo for another 12 weeks. More than 80% of patients in each group maintained at least a 50% global improvement from baseline, and more than half retained at least a 75% global improvement at the end of the maintenance phase. Topical tazarotene was sufficient to maintain the benefit induced with systemic plus topical treatment.4

Topical Antibiotic Therapy
Benzoyl Peroxide
Benzoyl peroxide cleanser (6%) applied to the face once daily for 3 weeks reduced counts of antibiotic-resistant facial Propionibacterium acnes. Participants (n=30) were acne free but had high counts of organisms resistant to erythromycin (30/30), clindamycin (25/25), tetracycline (29/30), doxycycline (25/30), and/or minocycline (19/30). Total P. acnes counts and counts of each resistant strain decreased by at least 2 log after 3 weeks of treatment.3

Benzoyl peroxide efficacy for acne on the back varied with formulation. Two weeks of once-daily therapy with a topical emollient “leave-on” foam benzoyl peroxide (5.3%) significantly reduced counts of P. acnes on the back (n=20 adults). P. acnes colonies were reduced by 1.9 log at week 1 and by 2.1 log at week 2. In contrast, 2 weeks of therapy with a benzoyl peroxide wash (8%) had little or no effect on P. acnes counts.6

Another study evaluated a higher-concentration (9.8%) benzoyl peroxide emollient foam to be left on the back for 2 minutes. It was compared with a 5.3% emollient foam (used once daily for 2 weeks). Efficacy as measured by reduction of P. acnes organisms on the back was similar with the two products.7 Patients with acne on the trunk of the body therefore appear to benefit from a “leave-on” or short-contact product rather than a wash. Patients should be informed that benzoyl peroxide typically bleaches towels and other fabrics, so that white towels may be a good choice while using these treatments.

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Acne Medication and Inflammatory Bowel Disease: Antibiotics?

A retrospective cohort study using a UK database (n=94,487 with acne) found that tetracycline antibiotics, especially doxycycline, may be associated with an increased risk of inflammatory bowel disease (IBD) and especially of Crohn’s disease (CD) (Table). Individuals exposed to a tetracycline class antibiotic had a 39% increased risk of developing IBD (hazard ratio [HR] 1.39; 95% CI 1.02-1.90).8

Analysis of data from the University of Manitoba IBD Epidemiologic Database (2001-2008; n=2,234 with IBD and 22,346 controls) and the Manitoba Drug Program Information Network also reported an association of IBD with a history of receiving at least three courses of oral antibiotics. A total of 12% of those with IBD received at least three antibiotic prescriptions 2 years before their first IBD diagnosis date, compared with 7% of controls.9

Diet and Acne

Acne is ubiquitous in Western societies but absent in at least two non-Westernized populations (Kitavan people on the Trobriand Islands near Papua New Guinea and the Ache hunter-gatherers of Paraguay). Genetic influences may contribute to this finding. However, diet may also be a factor. The Kitavan people, in particular, consume a diet with a low glycemic index, consisting of tubers, fruit, fish, and coconut.10 Foods with a high glycemic index, such as those commonly consumed in a Western diet, lead to increased levels of insulin in the blood. Insulin and androgen growth factor 1 (IGF-1) stimulate androgen synthesis. Androgens, in turn, stimulate the production of sebum, required for acne development.10

Compared with a high-glycemic-load diet, eating low-glycemic-load foods for 12 weeks reduced lesion count and free androgen index in 43 males with acne. Patients eating the low-glycemic-load diet also lost weight, a confounding factor.11

Milk consumption has been associated with acne. A prospective cohort study of boys (mean age, 11.75 years at baseline; n=4,273) found that higher consumption of skim milk (>2 servings/day) was associated with higher prevalence of acne (multivariate prevalence ratio, 1.19; 95% CI 1.01-1.40; P=0.02 for trend).12 Milk may affect acne formation, as it contains androgens. Additionally, milk consumption has been associated with higher levels of IGF-1, which stimulates androgen synthesis.10,12 Whey protein supplementation (eg, used to gain weight and/or build muscle) has also been temporally associated with acne development in case reports. Acne did not respond to oral antibiotics, topical retinoids, and benzoyl peroxide but resolved in four of five patients upon discontinuation of whey protein supplementation.13

Coconut Oil, Probiotics

Lauric acid, a main ingredient in coconut oil, has demonstrated greater antimicrobial effectiveness against P. acnes than benzoyl peroxide. The minimal inhibitory concentration for lauric acid against P. acnes in vitro was 15 times lower than that of benzoyl peroxide. Lauric acid also reduced inflammation without cytotoxicity to sebocytes in an animal model, and retained its killing effectiveness in this model when delivered intradermally and epicutaneously.14 Lauric acid is poorly soluble in water but retained its anti-P. acnes effectiveness when incorporated into a liposome formulation in an experimental study.15

Bowe and Logan have reviewed small studies in non-English language journals of oral probiotic supplements in acne. Adding 250 mg of freeze-dried Lactobacillus acidophilus and Bifidobacterium bifidum to standard care improved clinical outcomes compared with standard care only. Probiotics were also associated with better tolerance and adherence to antibiotic therapy. Another study reported shortened time to clinical improvement after adding probiotics. A third publication indicated that consuming a Lactobacillus-fermented dairy beverage was associated with significantly reduced total lesion counts and reduced sebum production.16

New Topical Antibiotic

A topical clindamycin phosphate 1.2% and benzoyl peroxide 3.75% (clindamycin-BP 3.75%) aqueous gel received approval by the US Food and Drug Administration (FDA) for acne in patients ages 12 years and older as of November 2014.17 Compared with vehicle, clindamycin-BP 3.75% reduced inflammatory and noninflammatory lesions as well as acne severity at 12 weeks in a double-blind controlled study (n=498). The agent was well tolerated, with no withdrawals due to adverse events.18

Summary

Antibiotics, both topical and systemic, remain the key to acne therapy. Oral doxycycline is characterized by a dose-response curve, while oral minocycline effectiveness does not increase with dose.1,2 Once systemic plus topical therapy has led to at least a 50% global improvement in acne, topical therapy is sufficient to maintain efficacy.3,4 Benzoyl peroxide topical wash is effective on the face but not on the back; a leave-on, short-contact preparation is superior for truncal acne.5,7 Systemic antibiotic therapy should be used for the shortest possible time, as antibiotic use has been associated with an increased risk for IBD.8 Consumption of skim milk and whey protein supplements has been associated with acne in an observational study and case reports, respectively.12,13 A small study has reported a link between a low-glycemic-load diet and improvement in acne lesion count, though weight loss may confound results.11 Clindamycin-BP 3.75% gel, which received FDA approval for use in acne as of November 2014, offers another option for treatment.17

Table: Risk of IBD Associated With Tetracycline Class Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>IBD Hazard Ratio (95% CI)</th>
<th>UC Hazard Ratio (95% CI)</th>
<th>CD Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>1.63 (1.05-2.52)</td>
<td>1.06 (0.53-2.13)</td>
<td>2.25 (1.27-4.00)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>1.19 (0.79-1.79)</td>
<td>1.10 (0.76-1.82)</td>
<td>1.28 (0.72-2.30)</td>
</tr>
<tr>
<td>Tetracycline/oxytetracycline</td>
<td>1.43 (1.02-2.02)</td>
<td>1.27 (0.78-2.07)</td>
<td>1.61 (0.995-2.63)</td>
</tr>
</tbody>
</table>

CD=Crohn’s disease; IBD=inflammatory bowel disease; UC=ulcerative colitis.
References


Rosacea: Pathogenesis and Therapy

Jerry K. L. Tan, MD, FRCPC*

Abstract
Recent studies have illuminated the pathophysiology of rosacea. Evidence supports the hypothesis that rosacea is caused by dysregulation of the innate immune system, resulting in vasoactive and neuroinflammatory consequences. New treatments have been approved by the US Food and Drug Administration (FDA) in recent years, and studies have further documented the benefit of other therapies. Semin Cutan Med Surg 34(supp4):S75-S77 © 2015 published by Frontline Medical Communications

Keywords
Rosacea, inflammation, innate immunity, cathelicidins, brimonidine, ivermectin

Rosacea is diagnosed based on the presence of one or more primary features: transient erythema (flushing), nontransient erythema (most common sign of rosacea), papules and pustules, and/or telangiectasia (small blood vessel lines). Patients may also display one or more secondary features: burning or stinging, plaque, dry appearance, edema, ocular manifestations, phymatous changes, and peripheral (ie, nonfacial) location of manifestations.1 Rosacea is divided into three cutaneous and one ocular subtype, plus one variant (granulomatous: characterized by hard, brown, yellow, or red cutaneous papules or nodules of uniform size, generally less inflammatory than papules and pustules). Some evidence suggests that rosacea may evolve from one subtype to another; patients may also progress from mild to severe disease.1

Reported figures for incidence and prevalence vary, with the highest prevalence rates in people of northern European or Celtic ancestry (2.7%-10%).2 Rosacea is more common among women than men, and in individuals with fair skin. Incidence peaks between menopause, and microbes (310x438).

Pathogenesis
A growing body of evidence has accumulated in recent years supporting the hypothesis that rosacea develops because of a disordered innate immune system.2 Individuals with rosacea express abnormally high levels of cathelicidin in facial skin, compared with matched control.3 A form of cathelicidin found in rosacea (LL-37) is typically present in neutrophils that are recruited to infected or injured skin. In patients with rosacea, this cathelicidin appears to result from abnormal activity of serine protease kallikrein 5 (KLK5; also known as stratum corneum tryptic enzyme). Injecting cathelicidin-producing peptides into murine skin produced skin inflammation resembling rosacea-like changes.4 Cathelicidins can cause both vasoactive and inflammatory changes, consistent with those observed in rosacea.5

Mast cells, found in increased numbers in the dermis of individuals with rosacea, are among the primary sources of the cathelicidin peptide (LL-37) demonstrated to induce rosacea in murine skin. Mast cells have also been shown to mediate skin inflammation induced by cathelicidin.6

The skin of people with rosacea also expresses toll-like receptor 2 (TLR2) highly compared with healthy individuals. Increased TLR2 leads to increased production of cathelicidin. Recent experimental findings suggest that high levels of TLR2 in skin increases susceptibility to microbial and environmental stimuli, increasing cathelicidin and KLK5 expression.5

Reverse transcriptase polymerase chain reaction and gene array analysis support the concept of rosacea as an inflammatory disease. Proinflammatory genes involved in vasoregulation and neurogenic inflammation are upregulated in early rosacea, before clinical signs such as papules, nodules, or pustules have emerged. Different genes are upregulated in each subtype.3

A wide range of stimuli can trigger symptom exacerbations, including emotional stress, spicy food, hot beverages, alcohol consumption, high environmental temperatures, sun exposure, menopause, and microbes (Figure).5 Many of these same triggers activate the transient receptor potential vanilloid receptor 1 (TRPV1), a cell surface receptor nerve fiber. The density of TRPV1+ nerve fibers is increased in erythematotelangiectatic rosacea compared with healthy skin. In individuals with healthy skin, TRPV1 activation produces brief periods of flushing and burning pain. It has been suggested that patients with rosacea experience hyperactive or dysregulated TRPV1, with sustained flushing and neurogenic inflammation.3

Treatment
It is important to set patients’ expectations appropriately regarding the benefits of therapy. Rosacea cannot be cured but treatment can control the disease’s signs and symptoms. Avoiding triggers, the use of gentle skin cleansers, and frequent moisturizing can help heal and minimize further skin damage. In the last few years, new treatments have been FDA-approved for some rosacea subtypes, and studies have documented the benefit of other treatments (Table).

Erythematotelangiectatic Rosacea
Intense pulsed light has been used to treat rosacea for many years and is clinically accepted despite the absence of high-quality evidence supporting its value.8 A small (n=34) study reported

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Dr Tan has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Eileen McCaffrey, MA, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

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significant improvements in erythema (46%) and telangiectasia by 55% from baseline after four treatments administered at 3-week intervals. Benefits were sustained at 6 months, with minimal and self-limiting side effects.9

Brimonidine gel 0.33%, a selective alpha 2-adrenergic receptor agonist with vasoconstrictive activity, received FDA approval for persistent facial erythema of rosacea in August 2013.10,11 When studied at a concentration of 0.5%, it significantly reduced erythema severity compared with vehicle when applied once daily for 4 weeks in phase III studies. Benefit was observed within as little as 30 minutes of application. No tachyphylaxis or rebound was reported after treatment cessation.10 Efficacy was maintained over 1 year (n=345). Some patients experience exacerbation of rosacea signs and symptoms (flushing 10%, erythema 8%, rosacea 5%, and skin burning sensation 4%).12

Papulopustular Rosacea

Isotretinoin has been used for decades to treat rosacea despite the lack of evidence-based support. A double-blind, randomized, 12-week study conducted in 35 centers in Germany (n=573 with papulopustular or phymatous rosacea) compared oral isotretinoin (0.1, 0.3, or 0.5 mg per kg body weight) to doxycycline (100 mg daily for 14 days, then 50 mg daily) and placebo. The 0.3 mg/kg dose proved to be the most effective, demonstrating significant superiority to placebo and noninferiority compared with doxycycline. Lesions were reduced by 90% with isotretinoin 0.3 mg/kg and by 83% with doxycycline. Investigators determined that isotretinoin led to complete remission in 24% of patients and marked improvement in another 57% of patients. Comparable figures for doxycycline were 14% and 55%, respectively. The safety profile of isotretinoin 0.3 mg/kg was similar to that observed when it is used in the treatment of acne.13

Ivermectin 1% cream received FDA approval for inflammatory rosacea lesions as of December 2014.14 Roughly 40% of patients with papulopustular rosacea randomized to ivermectin were rated “clear” or “almost clear” on the Investigator’s Global Assessment (IGA) in two 12-week phase III trials (38.4% and 40.1%, respectively; P<0.001 vs vehicle). Ivermectin reduced lesion count by 76% and 75% in the 2 trials. Fewer subjects reported dermatologic adverse events with ivermectin than with vehicle, and more subjects experienced no skin drying or itching as compared with vehicle.15

Once-daily ivermectin 1% also demonstrated superiority compared with an active control (twice-daily metronidazole cream 0.75%) for 16 weeks (n=962). Inflammatory lesions were reduced from baseline by 83% with ivermectin and by 73.7% with metronidazole (P<0.001). The proportion of subjects attaining “clear” or “almost clear” (IGA rating) was also superior with ivermectin (84.9% and 75.4%, respectively; P<0.001). Ivermectin demonstrated better local tolerability than the comparator.16

A low-dose formulation of oral minocycline (45 mg extended release, once daily) demonstrated efficacy in papulopustular rosacea, alone or when used with once-daily 15% azelaic acid. Participants in a double-blind study (n=60) were randomized to receive one of these regimens for 12 weeks. Both treatments significantly reduced lesion count and improved IGA and Clinical Erythema Assessment compared with baseline, with no significant difference in efficacy or safety between the two regimens. Benefits were maintained 4 weeks after therapy discontinuation.17
Ocular Rosacea
The diagnosis of ocular rosacea is often missed, as symptoms are nonspecific and there is no specific test to confirm diagnosis. Most but not all patients also have cutaneous signs and symptoms of rosacea. Manifestations include watery or bloodshot eyes, sensation of a foreign body, burning or stinging, dryness, itching, light sensitivity, and blurred vision. Ocular rosacea should be considered in patients with corneal damage, a history of blepharitis, recurrent conjunctivitis, iritis, keratitis or styes (chalazion, hordeolum), and meibomian gland dysfunction. Periocular erythema, or telangiectases at the eyelid margins or lid, may be present. Ocular rosacea can lead to vision loss; treating cutaneous rosacea without addressing the ocular component may be insufficient to prevent this consequence.

Treatment with cyclosporine ophthalmic emulsion 0.05% was associated with an increase in Schirmer test scores (a measure of tear production), compared with a decrease (worsening) with artificial tears. Patients with rosacea-associated eyelid and corneal changes (ie, lid margin telangiectasia, meibomian gland inspissation, and/or fullness of the lid margin; n=37) were randomized to receive topical cyclosporine or artificial tears for 3 months. Quality-of-life scores also improved with therapy.

Summary
An increasing body of pathophysiologic evidence supports the hypothesis that rosacea results from disordered innate immunity, which leads to neuroinflammation and vasoactive changes. The introduction of brimonidine gel 0.33% for erythematotelangiectatic rosacea and ivermectin 1% cream for papulopustular rosacea offers new options for managing this common condition. A large (n=573), double-blind randomized trial has documented efficacy of oral isotretinoin (0.3 mg/kg) in papulopustular rosacea. Low-dose (45-mg), extended-release oral minocycline has demonstrated efficacy in papulopustular rosacea, alone or when used in conjunction with once-daily 15% azelaic acid. Topical cyclosporine 0.05% has demonstrated efficacy in ocular rosacea.

References
Tattoo Treatment: Current State of the Art

Christopher B. Zachary, MBBS, FRCP*

Abstract
Lasers can remove tattoos effectively but many treatments can be required for effective fading. New techniques have been shown to improve the speed and practicality of therapy, and new lasers may improve fading of recalcitrant or multicolored tattoos. Semin Cutan Med Surg 34(supp4):S78-S79 © 2015 published by Frontline Medical Communications

Keywords
Tattoo removal, Q-switched lasers, perfluorodecalin, picosecond laser, R20, R0

Quality-switched (Q-switched) lasers are the instrument of choice for tattoo removal. As many as 15 or 20 treatments can be required to remove professional tattoos. One of the limiting factors in any one treatment session is the whitening that immediately follows Q-switched laser treatment. This reaction results from the formation of gas bubbles in the dermis. The bubbles lead to optical scattering, limiting laser penetration for the roughly 20 minutes required for the reaction to subside.

R20 Method
In an effort to shorten the number of sessions required for tattoo removal, Kossida and colleagues evaluated a method in which patients are treated in four consecutive passes separated by 20-minute intervals (the “R20 method”). Treatments were performed with a Q-switched alexandrite laser. Eighteen tattoos on 12 adults were divided in half, with half receiving the R20 treatment and half receiving a single pass from a laser. Reviewers blinded to treatment assignment evaluated tattoos 3 months later.

Compared with results from a single pass, tattoo lightening was significantly more effective with the R20 method (P<0.01 for all tattoos). The majority (61%) of the tattoo sites treated with the R20 method cleared completely, compared with no tattoo sites with the single-pass method. No scarring or textural changes occurred, and no infection or postinflammatory hyperpigmentation was observed. One patient experienced transient mild hypopigmentation, which had resolved completely at 6 months post-therapy. Investigators noted that less whitening developed immediately following each subsequent laser pass with the R20 method, potentially facilitating deeper optical penetration.

R0 Method
The R20 procedure is effective but the time required (≥1 hour) renders it impractical for the office setting. Applying topical perfluorodecalin (PFD) after a laser treatment resolves the immediate whitening reaction quickly, within a mean of 5 seconds (range 3-10 seconds). PFD works by absorbing the gas released in the dermis.

Tattoos receiving three passes with PFD to remove the frosting after each pass (the “R0 method”) demonstrated fading equal to that observed with the R20 method, and superior to that seen following a single pass. Total treatment time with the R0 method in this study averaged 5 minutes, making it feasible for clinical practice. Figure below illustrates the impact of PFD on treatment results.

Laser Type, Pulse Width, and Duration
The tattoo color should be considered when choosing the type of laser. Any of the three types of Q-switched lasers (ruby [694 nm], alexandrite [755 nm], and Nd:YAG [only the 1064 nm]) can treat black or dark blue tattoos. Both the QS ruby and alexandrite lasers may cause hypopigmentation in darker skinned individuals, though these are preferred for removal of green pigment. Red or orange ink requires the Nd:YAG 532 nm laser.

The particle size of tattoo pigments generally falls between 30 to 300 nm, with a thermal relaxation time (TRT) of approximately

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Dr Zachary has received an honorarium for his participation in this activity. He acknowledges the editorial assistance of Eileen McCaffrey, MA, medical writer, and Global Academy for Medical Education in the development of this continuing medical education journal article.

Christopher B. Zachary, MBBS, FRCP, Consultant: Cutera, Inc. and ZELTIQ Aesthetics, Inc.; Speakers Bureau: Cynosure, Inc. and Solta Medical, a division of Valeant; Advisory Board: ZELTIQ.

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FIGURE Results Following Three Passes and Topical Perfluorodecalin.
A. Blue and black tattoo
B. Significant fading 1 month post-single treatment with three passes QSRL with topical PFD. Total treatment time 4 minutes pre-treatment. PFD=perfluorodecalin; QSRL=quality-switched ruby laser.

Source: Photos courtesy of Roy Geronemus, MD.

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Lasers for treating tattoos should therefore have a pulse duration that matches these TRTs, in the nanosecond range ($10^{-9}$ sec) or shorter. While the Q-switched lasers do provide the upper range of pulse durations, newer picosecond lasers offer pulse times measured in picoseconds ($10^{-12}$ sec), which often improve tattoo removal.¹

One study evaluated tattoo removal results with a picosecond laser in 12 green and/or blue pigment tattoos on 10 patients. Two of the tattoos had clinically apparent pigment after at least 10 prior treatments with traditional Q-switched lasers (designated recalcitrant tattoos); the remainder (n=10) were multicolored.⁶ Investigators used an alexandrite laser (755 nm) with variable pulse duration of 750 to 900 picoseconds, repetition rate of 5 Hz, and spot sizes from 3.0 to 3.6 mm. At 1-month follow-up after one treatment, 11 of the 12 tattoos demonstrated at least 75% clearance of the blue and/or green pigment. The remaining tattoo required two treatments to achieve >75% clearance. Patients reported average pain scores of 1.08 on a 10-point scale (1=no pain, 10=worst pain). One individual reported blistering.

**Summary**

The traditional Q-switched lasers historically have provided variable outcomes. While some tattoos can be removed easily with these nanosecond devices, the multicolored tattoos, and others recalcitrant for various reasons, have often required numerous treatments and still had modest outcomes. The new treatments utilizing topical PFD between treatments can more efficiently fade tattoos. However, the biggest development has been the newer picosecond lasers because of their highly effective ability to remove blue and/or green tattoos more easily than the black or dark blue colors.

**References**

POST-TEST CME/CE QUESTIONS

1. Of the TNF inhibitors approved for the treatment of psoriasis, which has the highest efficacy rates (ie, proportions of patients achieving PASI 75 to 10 to 16 weeks) in landmark clinical trials for psoriasis?
   A. Etanercept
   B. Adalimumab
   C. Infliximab
   D. Golimumab

2. Nearly half of those who develop anti-drug antibodies to which of the anti-TNF agents approved for the treatment of psoriasis experience a loss of adequate drug response?
   A. Etanercept
   B. Adalimumab
   C. Infliximab
   D. Golimumab

3. Which of the following agents represents a new, boron-based class of antifungals approved to treat toenail onychomycosis?
   A. Tolnaftate
   B. Luliconazole
   C. Efinaconazole
   D. Naftifine

4. Clinical trials of which one of the following topical antifungal agents have demonstrated a mycological cure rate in toenail onychomycosis comparable to that of oral itraconazole?
   A. Tolnaftate
   B. Luliconazole
   C. Efinaconazole
   D. Naftifine

5. Which of the following agents used to treat psoriasis has been shown to exacerbate Graham’s disease in some cases?
   A. Adalimumab
   B. Infliximab
   C. Secukinumab
   D. Ustekinumab

6. Which of the following statements most accurately describes the relationship of psoriasis therapy to CVD risk?
   A. Psoriasis therapy does not affect CVD risk, regardless of specific therapy used.
   B. Compared with methotrexate, anti-TNF therapy for psoriasis was associated with significantly reduced risk of a major CV event.
   C. Compared with no therapy, methotrexate and anti-TNF therapy each significantly reduced risk of CVD, and risk reduction is similar regardless of type of psoriasis therapy.
   D. Evidence demonstrates that reduced inflammation is responsible for the decreased risk of major CV events observed with anti-TNF therapy.

7. The preponderance of evidence about rosacea pathophysiology indicates that rosacea results from:
   A. A disordered innate immune system
   B. A disordered adaptive immune system
   C. Something other than a disorder of the immune system
   D. Little is known about rosacea pathophysiology.

8. Which of the following treatments approved for rosacea has demonstrated superiority compared with metronidazole?
   A. Bimatoprost
   B. Ivermectin
   C. Isotretinoin
   D. Azelaic acid

9. Which of the following statements accurately describes the 820 and 840 methods of tattoo removal?
   A. Both involve multiple treatments in a single session
   B. Both involve the use of topical perfluorodecalin to increase the amount of tattoo ink removed at each treatment
   C. R0 involves the use of topical perfluorodecalin to speed resolution of the immediate whitening reaction and facilitate delivery of multiple treatments within a brief single session
   D. A and C

10. Once acne has been controlled with 12 weeks of induction therapy with oral plus topical antibiotic therapy, which of the following best describes clinical trial findings regarding maintenance therapy?
    A. Continued therapy is unnecessary to maintain efficacy
    B. Continued therapy with either oral or topical therapy alone is sufficient to maintain efficacy
    C. Oral therapy is required to maintain efficacy after successful induction therapy
    D. Both oral and topical therapy must be continued to maintain efficacy

ACTIVITY EVALUATION FORM

Please indicate your profession/background:
☐ MD/DO ☐ MSN/BS/VN ☐ RN ☐ APN/NP ☐ PharmD/RPh ☐ Resident/Fellow Researcher ☐ Administrator ☐ Student ☐ Other; specify ________________

LEARNING OBJECTIVES: Having completed this activity, you are better able to:

1. Differentiate the characteristics of the tumor necrosis factor (TNF) inhibitors approved for use in treating psoriasis and apply that information to clinical practice.
2. Demonstrate familiarity with the impact of comorbid conditions on patients with psoriasis and incorporate the effect of psoriasis therapy on these comorbidities into patient management.
3. Integrate new therapies for rosacea into practice and describe current theories about rosacea pathophysiology.
4. Explain the use of new treatments for linea pedis and toenail onychomycosis.
5. Apply current knowledge about anti-acne antibiotic dosing, maintenance therapy, topical therapy, and diet to clinical practice.
6. Identify current and updated techniques to improve tattoo removal.

If you do not feel confident that you can achieve the above objectives to some extent, please describe why not.

Based on the content of this activity, what will you do differently in the care of your patients/regarding your professional responsibilities? (check one)
☐ I don't plan to do anything differently.
☐ I plan to change my practice/workplace.
☐ I don't plan to change my practice/workplace.

If you plan to change your practice/workplace, may we contact you in 2 months to see how you are progressing?
☐ Yes, E-mail address: ________________
☐ No, I don't plan to make a change.

If you are not able to effectively implement what you learned in this activity, please tell us what the system barriers are (eg, institutional systems, lack of resources, etc)? ________________

OVERALL EVALUATION

The information presented increased my awareness/understanding of the subject.
1. Strongly Agree
2. Agree
3. Somewhat Agree
4. Disagree
5. Strongly Disagree

If you anticipate changing one or more aspects of your practice/professional responsibilities as a result of your participation in this activity, please briefly describe how you plan to do so.

The information presented will influence how I practice/do my job.
1. Strongly Agree
2. Agree
3. Somewhat Agree
4. Disagree
5. Strongly Disagree

The information presented will help me improve patient care/my job performance.
1. Strongly Agree
2. Agree
3. Somewhat Agree
4. Disagree
5. Strongly Disagree

The program was educationally sound and scientifically balanced.
1. Strongly Agree
2. Agree
3. Somewhat Agree
4. Disagree
5. Strongly Disagree

Overall, the program met my expectations.
1. Strongly Agree
2. Agree
3. Somewhat Agree
4. Disagree
5. Strongly Disagree

I would recommend this program to my colleagues.
1. Strongly Agree
2. Agree
3. Somewhat Agree
4. Disagree
5. Strongly Disagree

What topics do you want to hear more about, and what issue(s) regarding your practice/professional responsibilities will they address?

Please provide additional comments pertaining to this activity and any suggestions for improvement.

Rutgers, The State University of New Jersey, thanks you for your participation in this CME/CE activity. All information provided improves the scope and purpose of our programs and your patient care.

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