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Stefanie Tuleya, Executive Editor

In an effort to help patients cope with a new diagnosis or a chronic, long-term condition, referral to organizations or resources the patient can consult between office visits can be extremely valuable. These organizations and resources can offer educational materials, support through contact with other patients and answers to frequently asked questions. Here is a look at some of the available resources to share with your patients.

Acne

The American Academy of Dermatology (AAD) offers AcneNet — www.skincarephysicians.com/acnenet — which includes an overview of the causes of acne and articles about treatment and skin care tips. The acne treatment section describes over-the-counter treatments and prescription medications, such as isotretinoin, oral antibiotics, oral contraceptives and topicals, and also includes a discussion of physical procedures from chemical peels to phototherapy. There is also a section of the site dedicated to acne scars, including frequently asked questions and available treatments.

Another site, www.acnemonth.com, which is supported by Galderma, contains information about National Acne Month, which is held in June. On this site, patients can learn about the causes of acne and treatments; it includes a section on how to talk to doctors about acne, with suggested questions they should ask and what questions from their doctors they should be prepared to answer. The Acne: Facts or Fiction page dispels several common acne myths. There are tips for patients on how to care for their skin and take control of their acne. In addition, there are videos from leading dermatologists that offer tips for parents on how to help their teens with acne.

Atopic Dermatitis

Eczema, particularly moderate to severe atopic dermatitis, can be very difficult for patients and their families to deal with on a daily basis. The burden can be attributed to painful flares, difficulty sleeping and sometimes embarrassment from the highly visible physical signs and symptoms.

Helping patients understand the condition and the best treatments and offering tips that help them comply with their treatments will go a long way in helping them control flares and cope, both physically and psychologically.

The National Eczema Association (NEA) organization supports patients with eczema and associated conditions. Its mission, as described on its website (www.nationaleczema.org), is to improve “the health and quality of life for individuals with eczema through research, support and education.”

The NEA is a national, patient-oriented organization governed by a Board of Directors and guided by a Scientific Advisory Committee of physicians and scientists who donate their time and expertise.

Through the site, visitors can sign up to receive the association’s newsletter, The Advocate. Patients can search the site for tips from others who also have eczema, watch treatment videos, find ways to get involved in advocacy, download educational pamphlets for parents as well as educators and find information about current research.

The NEA also offers programs like The Eczema & Sensitive-Skin Education (EASE) Program and the Seal of Acceptance program, which are designed to help identify products that are best for patients with eczema.

Through the organization’s website, patients can access educational references about skin care and treatment tips and a 3D eczema photo library.

The AAD also offers EczemaNet (www.skincarephysicians.com/eczemanet), which includes background information on eczema, definitions of types of eczema, how the condition is diagnosed, treatment overviews, tips for preventing flare-ups,
Psoriasis

The National Psoriasis Foundation (NPF), whose mission is “to find a cure for psoriasis and psoriatic arthritis and to eliminate their devastating effects through research, advocacy and education,” was established in October 1968. However, the organization, according to press material from the NPF, actually started on August 29, 1966, when Beverly Foster’s husband placed a classified ad in a Portland, OR, newspaper asking people with psoriasis to call her so she would have others to talk with about her severe psoriasis. After receiving more than 100 calls in a week, Beverly Foster began organizing meetings and initially formed the Psoriasis Society of Oregon, which eventually became the National Psoriasis Foundation, with a group of volunteers who are raising money to increase awareness about psoriasis and help raise money and interest for more research about the condition.

This organization, which patients can learn more about by visiting www.psoriasis.org, offers several programs and services for patients with psoriasis, lobbies on Capitol Hill and provides support to those living with psoriatic diseases.

On the website, patients can learn about psoriasis — from types of psoriasis, treatment options and answers to frequently asked questions to more information about their rights to healthcare. There is information on how to get involved with volunteer work, how to find a doctor and tips for navigating the healthcare system.

The NPF works with insurance companies to reform restrictive policies that prevent psoriasis and psoriatic arthritis patients from getting the care they need. One such initiative, its Access Action Guide, is a step-by-step guide for patients to access health care through insurance programs.

As a member of the NPF, patients can connect with others living with these conditions through message boards, networks, webcasts, mentoring programs and more. Patients can also connect to the NPF through the organization’s social networking sites on Facebook (www.facebook.com/NPF) and Facebook (www.facebook.com/NationalPsoriasis.Foundation).

The NPF also has a site, www.psome.org, for children who have psoriasis or psoriatic arthritis. On this site, patients and their parents can connect with others who are in the same situation and they can also have access to downloadable resources like handouts for schoolmates, teammates and others in the community to help explain what the conditions are.

Rosacea

The National Rosacea Society (NRS), which was started in 1992 and celebrates its 20th anniversary this year, provides support to the estimated 16 million Americans who live with rosacea. According to the organization, which patients can learn more about at www.rosacea.org, the NRS uses education and advocacy to meet its mission, which is:

• To raise awareness of rosacea.
• To provide public health information on the disorder.
• To encourage and support medical research that may lead to improvements in its management, prevention and potential cure.

The NRS also offers a grants program to encourage and support medical research to improve rosacea treatment, management and potential prevention. The program is supported entirely by donations.

The group’s website offers patients everything from an overview of treatment options to makeup tips and rosacea triggers to avoid. The NRS offers brochures, such as a “Rosacea Diary: An Easy Way to Find and Avoid Your Personal Rosacea Triggers,” and its Rosacea Review newsletter, both of which patients can order online. There are several photos depicting the types of rosacea, as well and before and after treatment photos.

Skin Cancer

Since its founding in 1979, the Skin Cancer Foundation (www.skincancer.org) has worked to educate the public and the medical profession about skin cancer, prevention by means of sun protection, the need for early detection, and prompt, effective treatment, according to its website.

Through the site, patients can access accurate information about diagnosis and treatment options — whether it’s actinic keratosis, basal cell carcinoma, squamous cell carcinoma or melanoma. It offers skin cancer facts, video descriptions, news and more. And, since prevention is one of the Foundation’s main goals, there is a significant amount of information about self examinations, signs to look for and information about sun protective clothes and sunscreens. Patients can also find the Skin Cancer Foundation on Facebook (www.facebook.com/skincancerfoundation) and Twitter (twitter.com/skincancerorg).

The Mayo Clinic also offers a skin cancer resource on its website (www.mayoclinic.com/health/skin-cancer/DS00190). This site organizes information by:

• Basic, which includes information about definitions, symptoms, how patients can prepare for appointments, treatment options, prevention tips and more.
• In-Depth, which offers more detailed information about tests and diagnosis, how treatments like Mohs surgery work, and answers about sunscreens.
• Multimedia, which includes images, videos and slideshows.
• Expert Answers, which offers a Q&A about tanning bed use.
• Resources, which includes information about Mayo Clinic services and links to other sites.

The AAD offers SkinCancerNet, which patients can access at www.skincarephysicians.com/skincancernet. The site includes recent news about advances in treatments, information about what skin cancer is, how it’s caused, prevention tips and information about diagnosis and treatment. It has a link for patients to sign up for a free, monthly e-newsletter from the AAD.
Current Treatment Options for Acne Vulgaris and Acne Rosacea

A review of the proposed pathogenesis of these conditions as well as the many different treatment options available.

Lindsay C. Strowd, MD

Acne vulgaris and acne rosacea are two distinct but related entities that affect more than 60 million Americans combined and cost upward of $3 billion yearly. These diseases have a significant, negative impact on quality of life. The terms acne vulgaris and acne rosacea represent a group of diseases and disease subtypes with different clinical features and treatments. This article will briefly review the proposed pathogenesis of these conditions and cover the many different treatment options currently available.

Figure 1. Inflamatory papules on the cheeks and periorbital skin. These papules are characteristic of both acne vulgaris and the papulopustular variant of acne rosacea. Photograph courtesy of Graham Library, Wake Forest Baptist Health Department of Dermatology.
Pathogenesis and Classification

The acne lesion originates from the pilosebaceous unit of the skin, which explains its predilection for more sebaceous skin like the face, chest and upper back. Shed keratinocytes form a plug at the level of the hair infundibulum, which prevents sebum from being extruded to the skin surface. The affected pilosebaceous unit expands until the comedo ruptures, creating inflammation. Because sebaceous glands are heavily influenced by hormonal stimulation, increases in hormone levels (such as with adrenarche) often precipitate the development of acne. Propionibacterium acnes (P. acnes) are Gram-positive rods found within the pilosebaceous unit and contribute to acne formation by inducing comedo rupture and generating pro-inflammatory cytokines.2 Despite popular belief, there is no evidence within the pilosebaceous unit to suggest that exogenous factors such as make-up or skincare products contribute to acne development.3

Acne vulgaris can be organized into two main categories based on lesion morphology: inflammatory and non-inflammatory, or comedonal. While a minority of patients will have, exclusively, one type of acne, the majority present with both types of lesions. There is a wide spectrum of disease severity among patients, ranging from mild comedonal acne to severe nodulocystic scarring acne. Several acne variants exist and include acne conglobata, acne fulminans, drug-induced acne and acne in the setting of syndromes like SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) and PAPA (pyogenic arthritis, pyoderma gangrenosum, acne). Acne conglobata, defined as severe nodulocystic acne without systemic manifestations, is often associated with dissecting cellulitis of the scalp, hidradenitis suppurativa and pilar cysts, collectively known as the follicular occlusion tetrad. Acne fulminans is the most severe form, with large, draining, ulcerated nodules accompanied by systemic signs and symptoms such as fever, malaise, leukocytosis and elevated inflammatory markers. Drug-induced acne has been reported with numerous medications but is relatively common with the use of steroids and steroid-derivatives, as well as lithium, iodides and bromides.4

Rosacea is another adnexal inflammatory disorder that often mimics acne vulgaris clinically but differs in epidemiology, pathogenesis and subtypes. While acne typically affects younger patients with any Fitzpatrick skin type, the vast majority of patients with rosacea tend to be fair-skinned individuals in the third decade of life and older. Key elements of pathogenesis include the presence of inflammation in vascular and skin tissue and vascular hyperreactivity. New studies are focusing on the presence of antimicrobial and proinflammatory canthelicidins and their impact on the altered immune response seen in rosacea patients. Infectious agents such as Demodex folliculorum mites and Propionibacterium acnes have also been implicated.5

Compared to acne, rosacea has more variable presentations, and, in contrast to acne vulgaris, rosacea can have ocular involvement. Erythematotelangiectatic rosacea is the most common variant and is characterized by episodic flushing and the presence of facial telangiectasias, giving the skin an overall ruddy appearance. Patients often complain of stinging and burning sensations. Papulopustular rosacea is the second most common subtype and more closely mimics acne vulgaris, with multiple inflammatory papules and pustules on the face. Phymatous rosacea is less common but can be extremely disfiguring, with nodular enlargement of the nose along with increased sebaceous gland production. Ocular rosacea can accompany other forms of rosacea or be the only clinical manifestation of disease. Patients complain of itching, burning and redness of the conjunctiva and lid margin. Several rare variants of rosacea exist, analogous to acne variants discussed above. Granulomatous rosacea is a rare variant in which patients develop indurated firm papules and nodules on the face that can lead to scarring. Rosacea fulminans is another rare rosacea variant that, like acne fulminans, can have systemic complications and lead to severe scarring and disfigurement.6

Topical Treatments

Numerous topical medications have been studied and used extensively in the treatment of acne and rosacea. Topical treatments are the cornerstone of therapy for these conditions and are beneficial in that they deliver the drug directly to the skin while minimizing the side effects of systemic medications. There is a significant body of literature available on different topical medications for these entities, but there are relatively few head-to-head, double blind, randomized, controlled trials comparing different topical acne and rosacea medications. Many studies compare an active drug to placebo, thereby making it difficult to say whether one topical medication is truly more efficacious than another.

The first group of medications used for acne and rosacea are topical antibiotics. This class of medications includes topical clindamycin, erythromycin, metronidazole and dapsone. Topical antibiotics exert anti-microbial effects on P. acnes as well as anti-inflammatory effects.2 These medications are more commonly prescribed for inflammatory lesions of acne and rosacea as opposed to comedonal lesions.

Topical clindamycin 1% is available in foam, gel, solution and lotion formulations as well as in combination topical medications with benzoyl peroxide and with tretinoin. Topical clindamycin tends to be well tolerated by patients with
minimal irritation and dryness. Systemic absorption is minimized with topical application, which greatly decreases the risk of serious side effects such as pseudomembranous colitis.

Topical erythromycin is an older acne and rosacea medication that also works by inhibiting the growth of *P. acnes*. Erythromycin is available in a 2% concentration as an ointment, gel, solution and in pads as well as in a 3% concentration combined with benzoyl peroxide.

Both topical clindamycin and erythromycin products have been widely used for acne and, to a lesser degree, rosacea; however, there is growing evidence and concern about the development of *P. acnes* strains, which were resistant to these antibiotics. The body of evidence is somewhat conflicting regarding increasing rates of resistant bacteria, but most providers use these topical antibiotics as short-term treatment and usually avoid them as monotherapy.

Topical metronidazole is an FDA-approved first-line treatment for rosacea, especially the papulopustular variant. Several studies have shown metronidazole to be significantly more effective than placebo in treating rosacea. Both 0.75% and 1% concentrations are available in cream, gel and lotion formulations. Studies have shown that once-daily application of either concentration is equally efficacious to twice-daily application with no difference in efficacy between the two strengths.

Topical dapsone is the newest topical antibiotic to be FDA-approved for the treatment of acne. Dapsone downregulates tumor necrosis factor, prostaglandins and leukotrienes and inhibits neutrophil function and migration. It is used in both oral and topical preparations for dermatologic conditions, although oral dapsone has serious potential risks, including methemoglobinemia and hemolytic anemia. Topical dapsone minimizes these side effects while still targeting inflammatory acne lesions. In one study, twice-daily application of topical dapsone 5% gel resulted in a 50% decrease in inflammatory lesions.

Topical retinoids have been used for decades for both acne vulgaris and acne rosacea. Retinoids treat acneiform lesions by reducing follicular keratinization, which prevents microcomedone and comedone formation. Many studies have shown that combining topical retinoids with other topical medications such as topical antibiotics and topical benzoyl peroxide or salicylic acid have a synergistic effect on acne lesions.

Three topical retinoids are currently approved by the FDA for acne: adapalene, tretinoin and tazarotene.

Adapalene is a third-generation retinoid that comes in 0.1% and 0.3% concentrations and in several vehicles, including gel and lotion. Adapalene is also available in a combination product with benzoyl peroxide and has shown synergistic effects on acne lesions. Studies show adapalene has similar efficacy to other topical retinoids but causes significantly less skin irritation, which is critically important when considering patient adherence to a topical treatment regimen.

Tretinoin is a first-generation retinoid that is available in multiple concentrations, including 0.025%, 0.04%, 0.5% and 0.1% as well as liquid, cream and gel vehicles. It is also available...
as a combination product with topical clindamycin 1%. Combining tretinoin and clindamycin results in greater reduction of acne lesions than either medicine used alone. Micronized tretinoin is a newer topical formulation designed for better skin penetration and reduced UV degradation along with less severe skin irritation.

Tazarotene is the third topical retinoid approved for acne treatment and is a third-generation retinoid. Tazarotene comes in 0.05% and 0.1% concentrations and is available as a cream or gel. Though older studies initially showed topical tazarotene to be superior to the other topical retinoids in acne lesion reduction, newer studies suggest it has similar efficacy to topical tretinoin and adapalene but is associated with significantly more skin irritation.

Topical retinoids are used much less frequently in acne rosacea and there is little evidence to provide direct support for their use for this condition. Recently, one article showed that topical tretinoin and clindamycin used in combination may improve the erythematotelangiectatic subtype but not the papulopustular subtype.

Benzoyl peroxide and salicylic acid are two topical medications often used in combination with topical antibiotics, topical retinoids or both for treatment of acne. The synergistic effect of these medications is evident in the literature and reflected in the increasing number of combination acne medications. Benzoyl peroxide is thought to improve acne via its antibacterial actions against *P. acnes*, while salicylic acid acts as both a keratolytic and an anti-inflammatory molecule. The keratolytic properties of benzoyl peroxide may enhance the penetration of topical agents like antibiotics when applied in combination. Combination therapy with benzoyl peroxide and an antibiotic has also been shown to decrease the emergence of resistant strains. One study that compared a 5% benzoyl peroxide/clindamycin gel and clindamycin monotherapy showed a >1600% increase of clindamycin-resistant *P. acnes* from baseline in the monotherapy group over a 16-week period. Benzoyl peroxide combined with topical erythromycin reduced papular lesions and Demodex populations and was comparable to topical metronidazole in rosacea patients.

Both benzoyl peroxide and salicylic acid can result in skin irritation and dryness. Benzoyl peroxide is now an over-the-counter product and comes in a wide range of concentrations from 1% to 10%. Benzoyl peroxide is available as a topical gel, cream, lotion and solution as well as a wash. Physicians...
should warn patients that benzoyl peroxide bleaches dyed fabrics. Studies have also shown benzoyl peroxide can produce an orange discoloration when combined with sulfur-containing products and with topical dapsone\textsuperscript{24} and can oxidize clindamycin over time.\textsuperscript{2} Salicylic acid is also available over-the-counter in a range of concentrations. Concentrations typically used on the face for acne are on the weaker end of this spectrum (0.5% to 3%). One study showed combining benzoyl peroxide and salicylic acid resulted in the greatest reduction of acne lesions, more than topical clindamycin or combination topical clindamycin and benzoyl peroxide.\textsuperscript{20}

Several other topical medications are used for acne and rosacea. Azaleic acid is a topical medication available in a 15% gel and a 20% cream for inflammatory acne and rosacea lesions. Currently, only the 15% concentration is FDA approved for rosacea. Azelaic acid has anti-proliferative effects on keratinocytes, antimicrobial properties against \textit{P. acnes} and decreases sebum production. Studies have also shown azelaic acid to scavenge reactive oxygen species and inhibit UVB-produced pro-inflammatory cytokines.\textsuperscript{25} Several studies have shown azelaic acid to be significantly more effective than placebo in the treatment of rosacea.\textsuperscript{7,8} Azelaic acid has the added benefit of being pregnancy class B, allowing for use in pregnant patients.

Sulfur-sodium sulfacetamide (SSS) is an older medication that has been approved by the FDA for acne and rosacea since the 1950s. Sulfur and sodium sulfacetamide possess both anti-inflammatory and anti-bacterial properties against \textit{P. acnes} with moisturizing effects.\textsuperscript{26} Along with topical metronidazole and azelaic acid, topical SSS has been extensively tested in rosacea patients. SSS is available in a lotion, cream, cleanser and foam. Newer formulations like the foam reduce lesion counts in both acne and rosacea patients while minimizing the unpleasant sulfur odor associated with older formulations.\textsuperscript{26,27,28} Azelaic acid and SSS are alternative products for patients who cannot tolerate more irritating medications. They can also be used in combination with other topical agents.

Finally, topical calcineurin inhibitors are sometimes prescribed for patients with steroid-induced rosacea for their anti-inflammatory properties. Topical pimecrolimus 1% cream and topical tacrolimus 1% ointment both significantly decrease lesion counts in rosacea and are well-tolerated.\textsuperscript{29} Other studies have reported topical calcineurin inhibitors can induce rosacea-like dermatitis.\textsuperscript{30} Topical zinc is a lesser known adjunct treatment for acne, but there are few studies examining its effectiveness.\textsuperscript{31} Botanical products have not been extensively studied in acne and rosacea patients; most of the studies available are small case series or are underpowered. Topical tea tree oil 5% gel has been shown to be comparable to 5% topical benzoyl peroxide, but, again, no large studies have been completed.\textsuperscript{7}

**Oral Treatment Options**

Oral medications are another major treatment option for acne and rosacea.\textsuperscript{32} Oral antibiotics are commonly prescribed for both conditions and are considered first-line therapy for moderate to severe disease. Due to their popularity, there is a concern about whether prolonged antibiotic therapy leads to development of antibiotic-resistant \textit{P. acnes}. Most prescribers try to minimize the risk of resistance by combining oral antibiotics with topical retinoids and benzoyl peroxide and giving these medications for a limited time.\textsuperscript{33,34}

Several different classes of oral antibiotics have been studied, including tetracyclines. Tetracyclines are a class of antibiotics, which, when given at anti-microbial doses, bind to the 50S ribosome subunit of bacteria such as \textit{P. acnes} and are bactericidal. Tetracyclines also have important anti-inflammatory effects; they downregulate inflammatory cytokines, impede neutrophil chemotaxis and inhibit certain matrix metalloproteinases.\textsuperscript{2}

Doxycycline is a second-generation tetracycline that comes in 50-mg, 75-mg and 100-mg tablets and is available in an enteric-coated form. Doxycycline has been shown to be more effective than placebo in the treatment of both acne and rosacea. Originally, doxycycline was prescribed in 100-mg to 200-mg daily doses, but studies have shown that lower doses of doxycycline, such as 40 mg daily, are just as effective at treating rosacea but with less toxicity.\textsuperscript{8} A sub-antimicrobial dose of doxycycline is available specifically for acne and rosacea use (40-mg tablet) and is FDA approved

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**FIGURE 4.** Multiple inflammatory papules and nodules coalescing into plaques on the cheeks and chin of this patient with severe nodulocystic acne. Photograph courtesy of Graham Library, Wake Forest Baptist Health Department of Dermatology.
for use for up to 12 months. Doxycycline can cause gastrointestinal symptoms in up to a third of patients but can be taken with food. Other side effects include photosensitivity, candidiasis, esophagitis and benign intracranial hypertension. Tetracyclines are contraindicated in children under 8 years of age due to risk of teeth discoloration.2,35

Minocycline is another second-generation tetracycline used in both acne and rosacea. Minocycline comes in 50-mg and 100-mg tablets or capsules and is typically dosed at 100 mg to 200 mg daily. There is now an extended-release version that is meant to be dosed at 1 mg/kg/day and, therefore, comes in a variety of strengths (45-, 55-, 65-, 80-, 90-, 105, 115-, 135-mg tablets). Minocycline can cause vertigo, photosensitivity, benign intracranial hypertension, drug-induced lupus and skin pigmentation.2

Macrolide antibiotics used to be commonly prescribed for acne patients, but increasing P. acnes resistance has limited their use.3 Azithromycin is a second-generation macrolide with a long half-life (68 hours) and comparable efficacy to doxycycline. It is considered safe to use in pregnant and breastfeeding women and is Pregnancy Class B. Clindamycin and clindamycin are also occasionally used for acne treatment, but risk of pseudomembranous colitis prevents them from being first-line agents.

Oral hormonal agents have gained popularity in off-label use for acne, particularly in older patients. Adult acne tends to affect the lower face and neck and most women with adult acne actually have normal levels of circulating androgens.3 Anti-androgens are the most common class of hormonal agents and include androgen receptor blockers, inhibitors of peripheral androgen metabolism and inhibitors of androgens via effects on the ovaries or pituitary gland.31 One meta-analysis of anti-androgen medications used for acne suggested ethinyl estradiol plus cyproterone acetate was the most effective agent; however, all agents studied were significantly better than placebo.33 Oral spironolactone is an aldosterone antagonist that was originally used as a potassium-sparing diuretic but is also an anti-androgen that inhibits sebaceous gland activity. Spironolactone decreases 5-alpha reductase activity, which is increased in acne-prone skin. Spironolactone also increases steroid hormone binding globulin, which decreases levels of free testosterone.3 These effects make spironolactone a good choice for women with hormonal acne. Spironolactone is dosed between 25 mg and 200 mg daily, though most women will respond to 75-mg/day to 100-mg/day dosing. Side effects include hypotension, diuresis, hyperkalemia, gynecomastia and decreased libido. There is a black box warning on spironolactone regarding the risk of breast carcinoma, though long-term studies have not shown an increased risk.3

Oral isotretinoin is a first generation retinoid with a half-life of 20 hours that has been used for decades to treat severe acne that is resistant to topical and other oral medications. This medication is usually dosed between 40 mg to 80 mg per day for 4 to 6 months, with the goal cumulative dose being 150 mg/kg. Oral isotretinoin works on acne by decreasing the activity of sebaceous glands as well as providing anti-proliferative effects on keratinocytes. The benefit of this medication is that it has a very high response rate in patients who have failed other first and second-line treatments.

However, isotretinoin use comes with many potential side effects and is Category X, strictly contraindicated in pregnancy due to high rate of birth defects. Due to its potential teratogenicity, all patients in the United States on this medication must enroll in the government drug-monitoring program iPLEDGE, and females must be on two forms of contraception while on isotretinoin. The most common side effects are dry skin, dry lips and mucosal surfaces, arthralgia and hypertriglyceridemia; these tend to be dose-dependent. Numerous other side effects have been reported with isotretinoin, including pseudotumor cerebri, inflammatory bowel disease and increased suicidality.

The increased risk of suicide is hotly debated in the literature. In a large cohort study from Sweden, the risk of suicide peaked 6 months after starting treatment with isotretinoin and fell to expected levels 3 years after treatment. Patients in this study with a history of suicide attempts before starting
isotretinoin made fewer attempts during treatment than those whose behavior started during treatment. In reviewing the literature, there is no direct evidence showing a clear link between isotretinoin and increased suicidality.

See Table 1 above for list of medications commonly used to treat acne.

### Procedural Treatment Options

Epidemiologic data shows the vast majority of acne and rosacea patients are treated with topical and oral medications. There is a growing body of literature to support procedural treatments as adjunctive therapy in these conditions. Photodynamic therapy (PDT) uses a combination of a photosensitizer and UV light to produce reactive oxygen species, which target specific cells. *P. acnes* produce protoporphyrin IX and coproporphyrin III within sebaceous glands, acting as an endogenous photosensitizer.

Exposure to certain light wavelengths causes destruction of *P. acnes* with resolution of inflammatory acne lesions. Peak absorption of porphyrins occurs in the blue light spectrum (415 nm) and red light spectrum (630 nm). Both blue and red light have been studied in treatment of acne and both have demonstrated significant improvement. Multiple studies have examined the use of exogenous 5-aminolevulinic acid (ALA) as a photosensitizer followed by laser treatment for acne. One study showed using ALA prior to intense pulsed light (IPL) laser was more effective than IPL alone for acne lesions.

Other studies show that relatively short incubation with ALA (15 to 60 minutes) followed by blue light is also an effective acne treatment. Other procedures use lasers, which directly destroy sebaceous glands for acne and rosacea. These lasers are near-infrared lasers with spectra between 1300 and 1600 nm. One study using an infrared laser showed 98% reduction of inflammatory acne lesions after four treatments. Diode lasers (810-900 nm) have also shown to effectively destroy sebaceous glands. IPL effectively treats telangiectasias and flushing seen in erythematotelangiectatic rosacea. Phymatous rosacea can be difficult to treat using topical and oral medications. Many patients can benefit from ablative laser resurfacing with Erb:YAG or carbon dioxide laser. Salicylic acid peels, glycolic acid peels and microdermabrasion have all been published as treatments for acne, although there are few randomized studies or studies comparing these treatments to topical acne medications.

### Conclusion

Acne and rosacea are common dermatologic conditions that have a major psychosocial impact on patients. Over the past several decades, new research has helped elucidate pathogenic factors important in these conditions, although the exact pathogenesis remains unknown. First-line treatment for both conditions involves the use of topical and oral medications. Often, topical and oral medications used in combination achieve better, more rapid lesion clearance. Topical retinoids, antibiotics and many other compounds like benzoyl peroxide, salicylic acid, azelaic acid and sulfur sulfacetamide have proven efficacious. Oral antibiotics, particularly tetracyclines, can be used at antimicrobial doses for acne and at sub-antimicrobial doses for rosacea. Careful thought needs to be given to the treatment duration with oral antibiot-
ics to prevent \( P. \text{acnes} \) resistance. For severe acne, oral isotretinoin remains an excellent treatment option but requires careful discussion of toxicity and meticulous follow-up. Procedural treatments are a growing trend in the management of acne and rosacea, with photodynamic therapy and lasers targeting vessels and sebaceous glands showing significant efficacy. Knowledge of all the different treatment options for acne and rosacea allows the provider to tailor each individual’s treatment regimen and to provide significant improvement in these disease entities.

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References

The Therapeutic Approach to Psoriasis

Recent research has shown the role that the immune system plays in the pathogenesis of this disease, which may lead to the development of immune-specific therapies. This article highlights current approaches in treating and managing patients with psoriasis.

Alyssa S. Daniel, MD

Psoriasis is a chronic, immune mediated, inflammatory skin condition with a genetic susceptibility pattern and several environmental triggers. It is characterized by the hyperproliferation of keratinocytes, dilation of blood vessels and an inflammatory infiltrate, all of which are potential targets for treatment. Psoriasis is associated with key comorbidities including cardiovascular disease, metabolic dysfunction, depression and psoriatic arthritis.\(^1\) There has been a great deal of research recently to elucidate the role that the immune system plays in the pathogenesis of this disease and to develop immune-specific therapies. This article will highlight current approaches in treating and managing patients with psoriasis.

Epidemiology

The prevalence of psoriasis was most recently approximated to affect around 3% of the US population.\(^2\) This figure varies considerably worldwide. In certain Asian, African, African-American and Norwegian Lapp populations, the prevalence may be much lower.\(^3\) Psoriasis has a bimodal age distribution.

FIGURE 1. Clinical view of plaque-type psoriasis with well-demarcated plaques and overlying adherent scale.
with a peak in the 2nd and 6th decades of life. Three-quarters of new cases occur before the age of 40. The prevalence of the disease appears to be equal among women and men. Early childhood psoriasis is relatively rare but there are reported cases of even infantile psoriasis.

Psoriasis is a polygenetic disorder. Approximately 70% of children with psoriasis have a positive family history. Many gene linkage studies and more recent genome-wide association studies have identified at least nine gene loci that are associated with a higher risk for developing psoriasis. These are designated PSORS1-PSORS9. The natural history of psoriasis is variable, usually chronic with intermittent flares.

Pathogenesis

The underlying etiology of psoriasis is still at the center of heated debates. Prior to the 1980s, psoriasis was regarded as a disease of epidermal dysfunction with several epidermal mediators being at the center of the pathogenesis, including cyclic AMP, eicosanoids, protein kinase C, phospholipase C, polyamines and transforming growth factor (TGF)-α. More recently, the pathogenesis has been clearly related, in some part, to T-cell immune dysfunction. Studies looking at the association between psoriasis and major histocompatibility complex (MHC) alleles and disease improvement with therapies that affect T-cell function make it apparent that T cells likely play a direct role. Additional support for this correlation include animal models showing that xenograft transplantation of uninvolved human psoriatic skin can induce psoriatic lesions on immunodeficient mice when given the donors’ activated T cells. Barrier maintenance may be a contributing factor in the pathogenesis as well.

Clinical Implications

Psoriasis is a papulosquamous skin condition with hallmark erythematous, well-demarcated, silver-scaling papules and plaques. These plaques can localize to sites of trauma, a clinical finding referred to as the Koebner phenomenon. There are several clinical variants, including chronic plaque, guttate, erythrodermic, pustular and inverse psoriasis. Locations such as the scalp, nails and tongue, also known as annulus migrans, can also be affected by psoriasis.

Comorbidities are frequently seen at increased rates in psoriatic patients compared to the general population. These patients have higher rates of hypertension, left ventricular hypertrophy, obesity and diabetes. They also are more likely to engage in risky behaviors such as smoking and alcohol use. Psoriatic arthritis is also a complication. Approximately one-third of patients with psoriasis will also develop psoriasis.
Biologics for Psoriasis: A Review of Recent Research and News

A recent observational study, published online ahead of print in the Journal of Dermatologic Treatment, compared clinical improvement and treatment satisfaction with biologic versus other therapies in patients with plaque psoriasis. A group of European dermatologists reported disease severity before and after starting current therapy; dermatologists and patients reported treatment satisfaction. Of 2,151 patients, 453 were undergoing treatment with topicals, 666 with phototherapy, 683 with conventional systemic therapies and 349 with biologics. A significantly greater improvement in disease severity was observed in the biologics group (70% before to 15% after treatment) compared to topicals (22% to 10%), phototherapy (20% to 11%) and conventional systemic therapy (49% to 15%) (all \( P \leq 0.03 \)). A greater number of patients and dermatologists also reported greater satisfaction with biologic therapy over other therapies. Significantly more patients (59%) receiving biologics were satisfied with treatment versus topicals (45%), phototherapy (34%), or conventional systemic treatment (50%) (all \( P < 0.001 \)). Significantly more dermatologists were satisfied with biologics (60%) versus topicals (35%), phototherapy (26%) or conventional systemics (42%) (all \( P < 0.001 \)).

Long-term Safety and Efficacy of Biologics

Results of a study published in the August 2012 issue of the Journal of the American Academy of Dermatology found that etanercept is well tolerated with no sign of risk of dose-related or cumulative toxicity over time. David M. Pariser, MD, of Virginia Clinical Research Inc. in Norfolk, VA and colleagues evaluated integrated adverse event (AE) data from etanercept trials to assess short- (up to 12 weeks from controlled trials) and long-term (up to 144 weeks from uncontrolled extension studies) safety of etanercept dosing of 25 mg once weekly to 50 mg twice weekly.

According to the abstract, long-term data were stratified by treatment regimens, and rates of noninfectious and infectious AEs and standardized incidence ratios for malignancies were determined.

The evaluation showed that rates of noninfectious and infectious AEs and serious noninfectious AEs were comparable for both placebo and etanercept groups for the short-term analyses. Both the short- and long-term analyses found no dose-related increases in any of these events. Dr. Pariser and colleagues found no significant differences in cumulative event rates for serious infections across dose groups or over time. There was no significant difference in the standardized incidence ratios for malignancies (excluding non-melanoma skin cancer). No increase in overall malignancies was seen with etanercept treatment compared to the psoriasis population. Lymphoma, demyelination, congestive heart failure and opportunistic infection were rare.

Data presented at the 9th Annual European Academy of Dermatology and Venereology Spring Symposium in Verona, Italy, in June showed that maintenance treatment with ustekinumab for up to five years resulted in consistent, significant clinical response in adults with moderate to severe plaque psoriasis.

This new efficacy and safety data come from the Phase III PHOENIX 1 study, one of two pivotal registration trials for ustekinumab. Patients were randomized to receive placebo or ustekinumab 45 mg or 90 mg at weeks 0 and 4. Following assessment of Psoriasis Area and Severity Index (PASI) 75 at week 12, the primary endpoint, ustekinumab-treated patients continued to receive treatment every 12 weeks. At week 40, PASI 75 responders were re-randomized to receive maintenance therapy with ustekinumab or to withdraw from treatment and only receive retreatment with loss of response. More than two-thirds (n=517) of all ustekinumab-treated patients (n=753) in PHOENIX 1 continued to receive ustekinumab through the last scheduled 5-year dose. Among the responders who continued treatment from week 40 through the end of the study, 48% and 59% had PASI 90 in the ustekinumab 45-mg and 90-mg groups, respectively, with up to 5 years of treatment. Efficacy was similarly maintained in an overall analysis of the study population, with 63% and 72% of all PHOENIX 1 participants achieving PASI 75, and 40% and 49% achieving PASI 90, among those individuals receiving ustekinumab 45 mg or 90 mg, respectively. Investigators also reported a consistent benefit-to-risk profile for ustekinumab through 5 years and observed treatment with the biologic therapy to be generally well-tolerated with rates of adverse events (AEs), including infections, malignancies and cardiovascular events, remaining stable over time.

— Stefanie Tuleya, Executive Editor
Topical Therapies

Vitamin D Analogues

Topical vitamin D3 analogues were first introduced in the 1990s. The mechanism of action is not entirely understood, but they seem to affect the proliferation and differentiation of keratinocytes and have immunomodulating effects as well. They may also induce apoptosis of psoriatic keratinocytes.31

Most studies of topical D3 have examined patients with chronic plaque psoriasis, but there should be caution in using this in patients who have extensive body surface area involvement, as there is an increased risk of hypercalcemia and hypercalciuria. Otherwise, the medication is safe and well tolerated (although there may be some irritation) and should be considered first line in most patients with mild to moderate plaque psoriasis.32 A systematic review that aimed to provide evidence-based recommendations about the use of vitamin D analogues found them to be a cost-effective, safe treatment, but efficacy is increased nearly twice as much of vitamin D analogues found them to be a cost-effective, safe treatment, but efficacy is increased nearly twice as much when topical corticosteroids were added as concomitant therapies.33 Calcipotriol/calcipotriene is available in the United States in cream, ointment, foam and solution forms. Calcitriol ointment is available in the United States, while tacalcitol and calcitriol are available in Europe and may be more potent than calcipotriol/calcipotriene. Calcipotriol/calcipotriene is typically used twice daily at the concentration of 50 μg/g. Most studies with calcipotriol have limited the use to no more than 100 grams/week to protect against side effects. It is pregnancy category C.

Topical Steroids

Topical corticosteroids are among the oldest treatments available for psoriasis. Corticosteroids bind to the cytoplasmic corticosteroid receptor and translocate into the nucleus; this downstream effect inhibits transcription of key genes needed to promote the inflammatory response. Corticosteroids also act to inhibit proliferation and promote vasoconstriction.34

A systematic review examined 51 randomized controlled trials of mild to severe chronic plaque psoriasis where topical corticosteroids were used as the initial treatment. Most treatment time for studies was 4 weeks. The results were highly variable, with 30% to 90% of patients showing at least 50% improvement for mild to severe psoriasis, 7% to 85% achieving at least 75% improvement and 55% to 85% experiencing at least 90% improvement. Occlusive measures were associated with better response, and intermittent maintenance therapy appeared to provide longer remission times.35

More potent topical steroids are being used than in the past,36 although it’s not clear if higher potency steroids are actually more effective. One study estimated that the effective concentrations in the skin of hydrocortisone 2.5% ointment, triamcinolone 0.1% ointment, clobetasol 0.05% foam and beclomethasone 0.1% cream to oral prednisone. Hydrocortisone 2.5% ointment, triamcinolone 0.1% ointment and clobetasol 0.05% foam were predicted to provide greater levels of potency in the skin in comparison to oral prednisone.37

There are a wide variety of formulations of topical corticosteroids, including ointments, creams, solutions, foams, gels and sprays. It was once common practice to choose the ointment formulation, as it was thought to be more potent and, thus, more efficacious. A review of the literature on the efficacy of clobetasol propionate ointment compared to other clobetasol preparations found no difference in efficacy rates among the different formulations. The authors concluded that patient preference should be foremost in decision making because, ultimately, patient compliance with the formulation that is chosen will largely dictate how effective treatment is.38

The side effects of topical steroid therapy include skin atrophy, telangiectasias, easy bruising, acneiform eruptions, increased risk for skin infections and allergic contact dermatitis. There has been much debate about the risks of suppression of the hypothalamic-pituitary-adrenal axis.38,39 In a recent review on the risk for adrenal suppression and skin atrophy by Castela et al, higher-potency steroids were associated with measurable decreased levels of morning cortisol levels, thus suggesting adrenal suppression; however, none of these measurable cases had any clinical manifestations of adrenal suppression. With once-daily application of topical steroids, the incidence of skin atrophy was 1.9%.40 Topical steroids are pregnancy category C.

Topical Retinoids

Retinoids are vitamin A derivative hormones. Retinoids decrease epidermal proliferation and reduce inflammation. The only topical retinoid approved for psoriasis is tazarotene;
INDICATIONS AND USAGE: STELARA® is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. 

CONTRAINDICATIONS: Clinically significant hypersensitivity to ustekinumab or to any of the excipients (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS: Infections STELARA® may exacerbate the risk of infection and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA® (see Adverse Reactions). STELARA® should not be given to patients with any clinically important active infection. STELARA® should not be administered unless the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Consider administering STELARA® in patients with a chronic infection or a history of recurrent infection. STELARA® may require hospitalization occurred during the psoriasis development program. These serious infections included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections. Theoretical Risk for Vulnerability to Particular Infections Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including hontypshi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients. It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA® will be susceptible to these types of infections. 

Posterior Leukoencephalopathy Syndrome One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed during the clinical development program. RPLS can occur in patients with a history of malignancy or who have a known malignancy. 

Hypersensitivity Reactions Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported post-marketing. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, discontinue STELARA® and institute appropriate therapy (see Adverse Reactions). 

Immunogenicity: The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results due to assay interference. In the controlled and non-controlled portions of psoriasis clinical trials (median follow-up of 2.6 years, representing 6791 subject-years of exposure, 70% of STELARA®-treated subjects reported infections). In the controlled and non-controlled portions of psoriasis clinical trials (median follow-up of 2.6 years, representing 6791 subject-years of exposure, 70% of STELARA®-treated subjects reported infections). 

In studies 1 and 2, 6 months, 1852 exposed for at least one year,1650 exposed for at least two years, 1129 exposed for at least three years, and 619 exposed for at least four years. Adverse reactions listed below are those that occurred at a rate of less than 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of STUDY 1 and STUDY 2 (see Clinical Studies). 

The numbers (percentages) of adverse reactions reported for placebo-treated patients (n=665), patients treated with 45 mg STELARA® (n=664), and patients treated with 90 mg STELARA® (n=666), respectively, were: 

- 51 (8%), 56 (8%), 49 (7%); 
- Upper respiratory tract infection: 30 (5%), 36 (5%), 28 (4%); 
- Headache: 23 (3%), 35 (5%), 32 (5%); 
- Fatigue: 14 (2%), 18 (3%), 17 (2%); 
- Dizziness: 12 (2%), 13 (2%), 11 (1%); 
- Pruritus: 9 (1%), 10 (2%), 9 (1%); 
- Injection site erythema: 3 (<1%), 6 (<1%), 12 (<1%); 
- Myalgia: 4 (1%), 7 (1%), 8 (1%); Depression: 3 (<1%), 8 (1%), 4 (1%); 

Adverse reactions that occurred at rates less than 1% in the controlled period of STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis and cecal perforation, anaphylaxis, pregnancy outcomes, and transmission of HIV through breastfeeding. 

The safety of STELARA® has not been evaluated in patients who have a history of malignancy or who have a known malignancy.
Inform patients that STELARA® may lower the ability of their immune system to reread the Medication Guide each time the prescription is renewed.

**Pregnancy**

There are no studies of STELARA® in pregnant women. STELARA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects were observed in the developmental and reproductive toxicology studies performed in cynomolgus monkeys at doses up to 45 mg/kg ustekinumab, which is 45 times (based on mg/kg) the highest intended clinical dose in psoriasis patients (approximately 1 mg/kg based on administration of a 90 mg dose to a 90 kg psoriasis patient). Ustekinumab was tested in two embryo-fetal development toxicity studies. Pregnant cynomolgus monkeys were administered ustekinumab at doses up to 45 mg/kg during the period of organogenesis either twice weekly via subcutaneous injections or weekly by intravenous injections. No significant adverse developmental effects were noted in either study. In an embryo-fetal development and pre- and post-natal development toxicity study, three groups of 20 pregnant cynomolgus monkeys were treated twice weekly via subcutaneous injections of 0, 22.5, or 45 mg/kg ustekinumab twice weekly from the beginning of organogenesis in cynomolgus monkeys to Day 33 after delivery. There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, hematology, or serum biochemistry in dams. Fetial losses occurred in six control monkeys, six 22.5 mg/kg-treated monkeys, and five 45 mg/kg-treated monkeys. Neonatal deaths occurred in one 22.5 mg/kg-treated monkey and in one 45 mg/kg-treated monkey. No ustekinumab-related abnormalities were observed in the neonates from birth through six months of age in clinical signs, body weight, hematology, or serum biochemistry. There were no treatment-related effects on functional development until weaning, functional development after weaning, morphological development, immunological development, and gross and histopathological examinations of offsprings by the age of 6 months. Nursing Mothers Caution should be exercised when STELARA® is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or systemic exposure to ustekinumab should be weighed against the known benefits of breast-feeding. Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. IgG is excreted in human milk, so gastrointestinal or systemic exposure to ustekinumab should be weighed against the known benefits of breast-feeding. Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. IgG is excreted in human milk, so it is expected that STELARA® will be present in human milk. It is not known if ustekinumab is absorbed systemically after ingestion; however, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulation in substantial amounts. Pediatric Use Safety and effectiveness of STELARA® in pediatric patients have not been evaluated. Geriatric Use Of the 3117 psoriasis subjects exposed to STELARA®, a total of 183 were 65 years or older. Thus the use of anthralin in the elderly is not well documented. Anthralin is one of the oldest psoriatic medications. It inhibits epidermal and T-lymphocyte proliferation. The use of this medication is limited because of the complexity of application and the propensity of anthralin to stain whatever it touches. Short-contact 0.3% anthralin ointment for 10 minutes daily combined with a topical steroid, retinoid or UV light regimen seems to have beneficial results. Anthralin comes in a cream formulation. The limitations include patient compliance, local skin irritation and mess of application. This drug is pregnancy category C.

**Topical Calcineurin Inhibitors**

Calcineurin inhibitors hinder the activity of calcineurin, a phosphorylase enzyme that is needed for successful T-cell differentiation. Calcineurin inhibitors inhibit T-cell function and inflammation. Calcineurin inhibitors are effective for facial and flexural psoriasis. It is a safe treatment but should be avoided in patients with skin barrier dysfunction, as they are at risk for increased systemic absorption. It is pregnancy category C.

**Anthralin**

Anthralin is one of the oldest psoriatic medications. It inhibits epidermal and T-lymphocyte proliferation. The use of this medication is limited because of the complexity of application and the propensity of anthralin to stain whatever it touches. Short-contact 0.3% anthralin ointment for 10 minutes daily combined with a topical steroid, retinoid or UV light regimen seems to have beneficial results. Anthralin comes in a cream formulation. The limitations include patient compliance, local skin irritation and mess of application. This drug is pregnancy category C.

**Phototherapy**

Phototherapy has long been a very useful treatment option for psoriasis. Treatment options range from broad-band ultraviolet B therapy (BB-UVB), narrowband ultraviolet B therapy (NB-UVB), photochemotherapy with UVA and ei-
ther an oral or topical dose of psoralen UVA1. More recently, excimer laser has gained FDA approval.

NB-UVB is more effective at sub-erythmogenic doses than BB-UVB.44 The efficacy of psoralen UVA (PUVA) therapy and NB-UVB has also been compared; PUVA is better at clearing psoriasis, fewer sessions are needed and longer-lasting clearance is achieved.45 However, there is an increased risk of carcinogenicity following PUVA treatment.46 The safety data for NB-UVB has not been fully determined due to a lack of prospective studies. Excimer (308 nm) laser is a safe and effective treatment for psoriasis; a number of different protocols evaluated by Mudigonda et al showed no significant differences in the protocol used to initiate treatment.47

Systemic Medications

Systemic medications for severe psoriasis include methotrexate, cyclosporine and oral retinoids. Methotrexate inhibits dihydrofolate reductase, inhibiting keratinocyte proliferation and immune function. Methotrexate is indicated for severe plaque psoriasis and psoriatic arthritis and is administered by once-weekly dosing. Side effects include gastrointestinal upset, leucopenia, thrombocytopenia, renal failure, photosensitivity, fatigue and alopecia.48 Pulmonary toxicity may occur. Side effects can be lessened by folic acid supplementation, 49 although more recent conflicting reports note the efficacy of methotrexate may be decreased secondary to folic acid supplementation.50 Hepatotoxicity is a risk associated with cumulative dose. It used to be common practice to obtain liver biopsies once a cumulative dose of 1.5 grams was reached, but more recent evidence shows this is excessive in patients with no risk factors for liver disease.51 Monitoring blood cell counts, serum creatinine levels and liver enzymes is recommended.52 Methotrexate is pregnancy category X.

Cyclosporine is a calcineurin inhibitor administered systemically and is indicated for severe plaque psoriasis. Low-dose cyclosporine, 2 mg/kg/day is useful; with the addition of topical corticosteroids, patients do significantly better still.53 It is a medication that works well as an initial therapy until a safer maintenance therapy can be implemented. Cyclosporine has nephrotoxic effects; blood pressure and renal function should be closely monitored while on this medication. The dermatologist should also monitor liver function tests, serum lipids and serum electrolytes, especially magnesium levels.52 Cyclosporine is pregnancy category C.

Systemic retinoids have the same mechanism of action and effects as topical retinoids. Acitretin is available in the United States and is indicated for severe psoriasis. In a study looking at the use of high-dose therapy, defined as approximately 50mg/day versus low-dose therapy, patients in the low-dose treatment group had better results, likely secondary to better tolerability and adherence.54 Serum triglyceride levels, liver enzymes, serum creatinine and screening for the development of hyperostosis is important.52 Retinoids have teratogenic effects, so screening for pregnancy is crucial and counseling is very important. With so many other non-teratogenic treatments available, the use of acitretin in women of childbearing potential is discouraged.

The contraindication of using methotrexate in combination with oral retinoids has been reevaluated. The combination may provide benefit for patients with recalcitrant disease.

The contraindication of using methotrexate in combination with oral retinoids has been reevaluated. The combination may provide benefit for patients with recalcitrant disease. There may be no added toxicity of using the combination, as long as care in monitoring patients is taken.55

Biologic Therapies

An important group of biologic therapies, tumor necrosis factor alpha (TNF-α) inhibitors, have made an enormous impact in the treatment of patients with severe psoriasis. Etanercept was approved for psoriatic arthritis in 2002 and for moderate to severe psoriasis in 2004. It is a fusion protein TNF-α receptor to the Fc portion of IgG1.56 The recommended dosing regimen starts with twice-weekly 50-mg subcutaneous injections and decreases to once a week after 12 weeks.57 Adalimumab was approved by the FDA for psoriatic arthritis in 2005 and for moderate to severe psoriasis in 2008. It is a fully human anti-TNF monoclonal antibody.56 The recommended dose is an 80-mg subcutaneous loading dose followed by subcutaneous doses every other week of 40 mg.55 Infliximab, a mouse-human IgG1 chimeric anti-TNF monoclonal antibody, was approved for psoriatic arthritis in 2005 and for moderate to severe plaque psoriasis in 2006. The recommended dosing starts at a dose of 5 mg/kg via intravenous infusion at weeks 0, 2 and 6 and then continued every 8 weeks.57 Golimumab is, at the time this article was written, FDA-approved for psoriatic arthritis only. It is a human IgGk antibody. The recommended dosing is 50 mg injected subcutaneously at monthly intervals.58

Ustekinumab gained FDA approval for the treatment of moderate to severe plaque psoriasis in 2009. It is a human IgG1 monoclonal antibody that binds the p40 subunit of IL-12 and IL-23.59 IL-23 promotes the differentiation and proliferation of Th17 cells. The effectiveness of ustekinumab highlighted the importance of Th17 cells in the pathogenesis of psoriasis. The recommended dosing is 45 mg injected subcutaneously for patients weighing less than 100 kg and 90 mg
The Therapeutic Approach to Psoriasis

for patients weighing greater than 100 kg. This dose is repeated at week 4 and then maintenance doses are given every 12 weeks thereafter. 61

In terms of efficacy, adalimumab and infliximab appear to be more effective than etanercept and methotrexate. 62,63 Although the approved biologics are considered safe, effective and well tolerated, serious complications may occur, including demyelination, infection, tuberculosis, malignancy, lymphoma, cardiovascular outcomes and hepatitis. 64 The approved biologics for psoriasis are all pregnancy category B. Alefacept was voluntarily discontinued and efalizumab were previously approved biologic therapies. Alefacept and efalizumab were previously approved biologics for psoriasis. 65

Special Considerations

Scalp Psoriasis

A review of 18 randomized control trials about the success of topical corticosteroid therapy for scalp psoriasis shows that 40% to 70% of patients experienced more than 75% improvement and 43% to 90% experienced more than 90% initial improvement. Topical steroids still seem to be a successful treatment option in these patients. There may also be a role for adding excimer 308 nm lasers. 65

Nail Psoriasis

Nail psoriasis is often very concerning for the patient and one of the most difficult forms of psoriasis to treat. Methotrexate is frequently used to treat nail psoriasis. With the emergence of biologics, recent data suggests that they also are effective in treating nail psoriasis. 66,67

Conclusion

The therapeutic approach to psoriasis needs to be individualized to each patient, as there are many different, effective treatment options available. Generally, combination therapies allow for the synergistic effects of multiple therapies and fewer side effects with lower doses. This will, hopefully, increase patients’ compliance with any regimen. The risk vs. benefit from any medication must be discussed and unique patient characteristics must be incorporated when choosing a medication to decrease adverse effects.

Dr. Daniel is with the department of dermatology at Wake Forest University School of Medicine in Winston-Salem, NC.

Disclosure: Dr. Daniel has no conflicts of interest to report.

References

A review of novel therapeutic approaches and combination treatments to effectively manage skin cancer.

Jenna L. O’Neill, MD

Skin cancer is the most common type of cancer worldwide. The incidence rates of both melanoma and non-melanoma skin cancers (NMSC) are increasing, which is a significant public health problem. The biological behavior of skin cancer ranges from slow-growing, locally invasive cutaneous malignancy to locally aggressive tumors that may metastasize. Melanoma is associated with significant mortality when not treated early, and death from melanoma tends to occur at a younger age than for many other cancers.

If detected early, skin cancer is curable by surgical excision or destructive modalities. The ideal treatment for NMSC should provide complete tumor eradication with the lowest risk of recurrence and use the most cost effective method with acceptable cosmetic outcome. Mohs micrographic surgery is used for intraoperative margin assessment and for tissue preservation in cosmetically sensitive areas such as the face. Despite the success of surgical intervention for skin cancers, there are drawbacks, such as the need for local anesthesia, potential risk of infection and scarring. Patient and/or tumor characteristics may necessitate other treatment methods if surgical intervention is not a viable option. Treatment options for melanoma and NMSC targeting molecular defects in tumor cells may allow for treatment without the need for surgery; however, these treatment modalities are not without potential side effects. Novel therapeutic approaches and combination therapies are often utilized in the treatment of skin cancer, which may be challenging but rewarding.

Non-Melanoma Skin Cancer

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common malignancy worldwide, with an incidence of 146 per 100,000 individuals in the United States. BCC typically affects middle age and older adults, most commonly on the head and neck, followed by the trunk. Ultraviolet (UV) radiation is thought to play a role in the development of both BCC and squamous cell carcinoma (SCC). A higher incidence of NMSC is reported in fair-skinned individuals, in those with greater outdoor exposure and in latitudes closer to the equator. The incidence of BCC is increased in patients with basal cell nevus syndrome, also known as Gorlin syndrome, in which mutations in the PTCH gene result in upregulation of the sonic hedgehog signaling pathway and subsequent development of multiple BCCs beginning in childhood or early adulthood.

Treatment of BCC may vary by clinical subtype. Superficial BCC, which presents as an erythematous, scaling telangiectatic plaque often on the trunk or extremities, may be treated with topical therapy or via electrodesiccation and curettage, while nodular BCC is typically excised surgically. More aggressive or poorly defined tumors are best treated with Mohs micrographic surgery. While BCC has an exceedingly low potential for metastasis, local tissue destruction may be extensive in advanced or aggressive malignancies and may result in considerable morbidity.

Squamous Cell Carcinoma

SCC presents as a scaling, pink to red papule, plaque or nodule that may be crusted or ulcerated, most frequently on the head and neck or other chronically sun-exposed sites. The development of SCC is more strongly linked to UV exposure in comparison to BCC, in particular to chronic sun exposure. It is generally accepted that SCC occurs on a continuum with premalignant lesions confined to the epidermis, such as actinic keratoses (AKs). Patients with AKs are 10 to 15 times more likely to develop SCC compared to those without AKs. Bowen’s disease, a form of SCC in situ, typically...
Current Treatment Strategies In Dermatology: Skin Cancer

Current treatment strategies in dermatology focus on the management of skin cancer, a significant health concern. Skin cancer, primarily squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), requires timely and effective treatment to prevent metastasis and improve patient outcomes. "The Dermatologist" provides an update on the latest treatment strategies, particularly in the case of skin cancer.

Skin Cancer Types

Skin cancer presents as a well-demarcated, brightly erythematous scaling plaque. Keratoacanthoma (KA) is a well-differentiated form of SCC that rapidly enlarges over several weeks and may spontaneously involute. Due to the risk of tissue destruction and reports of metastasis, KAs are often treated surgically. Human papillomavirus is another important pathogenic factor implicated in some cases of SCC. In addition, SCC is more common than BCC in immunosuppressed patients, including transplant recipients and individuals with HIV. In contrast to BCC, SCC is associated with a small but significant risk of metastasis, typically to regional lymph nodes. Prompt treatment with negative surgical margins is essential to minimize morbidity of both the malignancy and its treatment.

Surgical Treatment

Wide local excision is the primary treatment for NMSC, with a cure rate approaching 90% or greater at 5 years. Optimal margins for excision of SCC are 4 mm for lesions less than 2 cm in diameter and 6 mm for lesions larger than 2 cm. National Comprehensive Cancer Network (NCCN) guidelines recommend 4-mm margins for excision of primary low-risk BCC. A meta-analysis recommended 3-mm surgical margins for BCC, with a cure rate of 95% for lesions less than 2 cm in diameter. Curettage and electrodesiccation is another treatment modality that involves tumor destruction and has a comparable cure rate to excision for treatment of low-risk NMSC. NCCN guidelines recommend curettage and electrodesiccation for low-risk primary BCC or SCC on non-hair-bearing sites. If curettage is performed to the level of subcutaneous fat, complete surgical excision should be undertaken.

Mohs micrographic surgery is a specialized surgical and pathologic technique that offers intraoperative histologic examination of 100% of the tissue margins. This is a distinct advantage over conventional excision with frozen or paraffin embedded sections, in which only a small proportion of the total peripheral margin is examined via thin, cross-sectional slices of tissue in a “bread loaf” technique. Mohs micrographic surgery offers the lowest recurrence rate and smallest defect size in the treatment of BCC and SCC and is the treatment of choice for recurrent tumors. Generally accepted indications for Mohs micrographic surgery also include: size > 2 cm in diameter, high-risk anatomic location, perineural invasion and poorly defined clinical borders. Mohs surgery is time-consuming and very expensive and may require coordination with another physician to perform the reconstruction after negative margins are attained.

Table 1. Indications for Mohs Micrographic Surgery

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<td>Recurrent tumor</td>
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<td>High-risk anatomic location (periorificial)</td>
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<tr>
<td>Anatomic sites where tissue preservation is imperative (eg, digits, genitalia)</td>
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<tr>
<td>Aggressive histologic subtype</td>
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<tr>
<td>Size &gt; 2 cm in diameter</td>
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<tr>
<td>Poorly defined clinical borders</td>
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<tr>
<td>Perineural invasion</td>
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Figure 2. Keratoacanthoma type squamous cell carcinoma.
Photo courtesy of Daniel Pearce, MD and Philip Williford, MD

Figure 3. Melanoma on the right lower eyelid.
Photo courtesy of Graham Dermatopathology Library
Mohs surgery should be reserved for high-risk tumors or when excision with standard margins would result in excessive tissue loss at sensitive anatomic sites.

Non-Surgical Treatment

Radiation therapy (RT) is a valuable adjunctive therapy in patients with residual positive tumor margins after extensive Mohs surgery or wide excision or in patients with high-risk tumors or extensive perineural tumor infiltration. Narrow radiation field margins of 1 cm to 2 cm are utilized; examples of dose and treatment schedules are provided in the NCCN guidelines for treatment of NMSC. RT is also utilized in patients in whom surgical intervention is not a viable option, either due to patient or tumor characteristics or both. A recent retrospective study demonstrated a 10-year relapse-free survival of 80.4% in patients with inoperable SCC treated with superficial radiotherapy. Irradiation of nodal basins in patients with metastatic spread of SCC to lymph nodes may also be utilized in cases of inoperable lymph node disease.

Vismodegib, a novel oral small-molecule inhibitor of smooth-muscle G protein-coupled receptor kinase 1 (SMO), was recently approved by the FDA for metastatic or locally advanced BCC. SMO is normally inhibited by patched homologue 1 (PTCH), which is mutated in the majority of BCC and in patients with Gorlin syndrome. This mutation results in constitutive activation of the Hedgehog signaling pathway and unchecked tumor growth. Vismodegib is administered orally at a dose of 150 mg daily. Early studies in patients with metastatic and locally advanced BCC demonstrated promising results, with response rates of 30% and 43%, respectively, in 96 patients in an open-label, Phase II trial. A randomized, double-blind, placebo-controlled trial of vismodegib in 41 patients with Gorlin syndrome demonstrated a decrease in new BCCs as well as a decrease in size of existing BCCs. Treatment with vismodegib is associated with a high rate of adverse events, most commonly dysgeusia and hair and weight loss, which necessitated discontinuation of therapy in 54% of patients enrolled in the latter study. The potential benefits of treatment must be weighed with these potentially serious adverse events. Careful patient selection will be imperative when utilizing this agent.

Oral retinoids, specifically acitretin, have been used as chemoprevention in patients at risk for developing multiple or aggressive SCCs, especially solid organ transplant recipients. Acitretin is typically administered at the lowest effective dose in order to minimize side effects, which include cheilitis, headache, photosensitivity, palmar-plantar desquamation, episcleritis, musculoskeletal symptoms and elevated triglycerides. Abnormalities in liver enzymes were not observed in a systematic review of controlled trials of acitretin for chemoprevention in transplant recipients. Importantly, after discontinuation of acitretin, SCC development recurs. In organ transplant recipients at high risk for NMSC, changing the immunosuppressive regimen from a calcineurin inhibitor to sirolimus, a mammalian target of rapamycin (mTOR) inhibitor with anti-tumor effects, may reduce the number of new cutaneous malignancies.

Prevention and early detection of NMSC are key. Frequent monitoring of patients with NMSC, including full skin examination and counseling about the importance of daily sun protection, is imperative.

survival compared to surgery alone in one study of 122 patients with metastatic spread of SCC to lymph nodes. Adjuvant RT may also be utilized in cases of inoperable lymph node disease.

Photodynamic therapy (PDT) is a novel therapeutic method that uses a photosensitizing agent such as 5-aminolevulinic acid (5-ALA), which preferentially localizes to diseased cells. Topical application is followed by exposure to a light source with resultant selective cytotoxicity of tumor cells. PDT is FDA-approved for the treatment of actinic keratoses and has also demonstrated efficacy in the treatment of SCC in situ and superficial BCC. Methyl-aminolevulinic acid (MAL), the methyl ester of ALA, has been used after curettage for nodular BCC, with equivalent recurrence rates to standard excision. PDT has been used more recently as adjunctive therapy in the treatment of large non-melanoma skin cancers prior to surgical removal. Intraoperative PDT has been proposed as a means to decrease recurrence rates of NMSC after Mohs surgery in patients with extensive field cancerization.

Cryosurgery may also be utilized for superficially invasive NMSC, either as monotherapy or in combination with topical chemotherapeutic agents. Cryosurgery and curettage has an excellent cure rate and cosmetic outcome for select tumors. A combination of cryosurgery and topical imiquimod, termed “immunocryosurgery,” has been employed with acceptable response rates. Topical imiquimod 5% cream is an immune response modifier that activates the innate and adaptive arms of the immune response via toll-like receptor 7 (TLR7). Imiquimod has been used alone in the treatment of nodular BCC, with complete clearance rates of 78% even with intensive daily dosing regimens. Response rates for nodular BCC are greatly improved with pre-treatment curettage followed by imiquimod 5 times a week for 6 weeks. Immunocryosurgery or imiquimod alone may also be used for SCC in situ with excellent results.

Prevention and early detection of NMSC are key. Frequent monitoring of patients with NMSC, including full skin examination and counseling about the importance of daily sun protection, is imperative.
skin examination and counseling about the importance of daily sun protection, is imperative. Daily use of broad-spectrum sunscreen with SPF 30 or greater is recommended by the American Academy of Dermatology; sun-protective clothing and avoidance during peak sun hours also play an important role.

Melanoma

It is estimated that 76,250 men and women will be diagnosed with, and 9,180 will die from, melanoma in 2012. The incidence and mortality rate from melanoma have increased in recent decades. Melanocytes are neural crest-derived cells that normally reside in the basal layer of the epidermis and produce melanin. The pathogenesis of melanoma is complex and is thought to involve evasion of the host immune response by cancer cells. When detected early, melanoma is curable by wide excision. Delays in diagnosis and treatment may result in local invasion of melanoma and distant metastases, typically to regional lymph nodes and visceral organs including the lungs, liver, bones and brain. In contrast to most other solid organ tumors, melanoma recurrence may present many years after initial diagnosis and complete surgical resection. Metastatic melanoma is exceptionally resistant to treatment with conventional chemotherapy and the prognosis remains very poor, despite advances in our knowledge of melanoma pathogenesis. Recent molecular genetic studies have revealed mutations in melanoma cells that may be specifically targeted in the treatment of advanced melanoma. The mitogen-activated protein kinase (MAPK) pathway plays a crucial role in regulating cell proliferation, survival and differentiation. The BRAF gene, which encodes a protein kinase upstream regulator of MAPK, harbors an activating mutation in 40% to 60% of melanomas.

Like other malignancies, the development of invasive melanoma is thought to progress through a step-wise process with accumulation of mutations within melanoma cells, which are influenced by both genetic and environmental factors. Melanoma in situ (MIS) is a proliferation of atypical melanocytes confined to the epidermis and may precede the development of melanoma. Melanoma may arise within a pre-existing nevus, but more than half of melanomas arise de novo. Four major subtypes have been described: superficial spreading, nodular, acral lentiginous and lentigo maligna melanoma. Regardless of subtype, prognosis is primarily determined by the Breslow thickness, or depth of invasion, of the tumor. Breslow depth is important for determining excisional margins and tumor staging and is the strongest predictor of melanoma mortality. Additional predictors of poor prognosis in melanoma are male gender, presence of ulceration and distant metastases (see Table II).

### Table II. Major Prognostic Factors for Melanoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow depth: &gt;1 mm high risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td>Advanced age</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Anatomic site: head/neck and trunk high risk vs. extremities</td>
<td>High risk</td>
</tr>
<tr>
<td>Number of involved lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Site of distant metastases: visceral metastases high risk vs. skin, subcutaneous, lymph nodes</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### Table III. Surgical Margins for Primary Melanoma

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Margins (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5</td>
</tr>
<tr>
<td>&lt; 1 mm</td>
<td>1</td>
</tr>
<tr>
<td>1– 4 mm</td>
<td>1 to 2*</td>
</tr>
<tr>
<td>&gt; 4 mm</td>
<td>≥ 2 cm</td>
</tr>
</tbody>
</table>

* AAD Task Force suggests a 1 cm margin for tumors < 2 mm in depth.
Psychosocial Issues In Familial Melanoma

The Skin Cancer page from the National Cancer Institute (NCI) offers patients with both non-melanoma skin cancer (NMSC) and melanoma a variety of resources, including information about treatment, clinical trials, statistics and more. The page on the genetics of skin cancer includes information about the structure and function of the skin, clinical presentations of NMSC and melanoma, rare skin cancer syndromes and psychosocial issues in familial melanoma. The information on the psychosocial issues was updated very recently, at the end of July 2012, and discusses interest in and motivation for genetic testing to determine risk of melanoma and the behavior of individuals found to be at a high risk for the most serious type of skin cancer. The update comes on the heels of a number of new studies about genetic and lifestyle factors that may contribute to melanoma risk, as well as a new app that may aid in personal skin cancer screenings.

Limited Data, Conflicting Results

The review of the psychosocial issues in individuals with a family history of melanoma is written for healthcare professionals and is intended to help elucidate the factors involved in an individual’s perception of his or her risk, desire to undergo genetic testing, and prevention practices, all in an effort to decrease the rates of melanoma among family members of patients.

According to the authors of this review, the motivations for and interest in genetic testing for melanoma have not been extensively studied, but the general findings note there is a high — but not universal — interest in genetic testing, and individuals at a high risk for melanoma are able to articulate the benefits of testing. They also note ‘a relative lack’ of examination of the potential limitations of testing and reasons to forgo testing. The most important factor that influences an individual’s desire to be tested for melanoma susceptibility is being a parent; many studies reveal that individuals with children are more likely to be tested, primarily to determine the relative risk to their offspring. The research that focuses on individuals who have undergone genetic testing for melanoma reveals conflicting evidence. Most studies have shown no increase in psychological distress, like anxiety and depression.

Protective behaviors before and after screening for genetic susceptibility have been examined slightly more extensively. Generally, individuals who are identified as having an increased risk for melanoma from genetic testing are more likely to increase the frequency of several protective behaviors: sunscreen use, self-exams for skin changes and skin checks by a physician.

Several demographic factors may increase these proactive behaviors in an individual who has been identified by genetic testing for a higher risk of melanoma. Adoption of protective behaviors is more likely in individuals with a familial risk of melanoma who are older, female and more confident in their ability to practice such behaviors. In addition, regular sunscreen use has been correlated to higher levels of education, higher self-efficacy for sun protection and higher perceived melanoma risk.

The Psychosocial Issues in Familial Melanoma page briefly discusses the efficacy of interventions about sun protection and screening in family members of melanoma patients. The results of existing studies are also inconsistent. One study with siblings utilized telephone messages and tailored print materials about risk reduction and screening recommendations; the control group received standard-of-care physician recommendations that patients tell family members about their diagnosis. That study showed an increase in knowledge about melanoma, confidence in seeing a dermatologist for a skin check and greater self-exam practices in the intervention group. Another study that utilized a similar intervention in family members of melanoma patients showed a near two-fold increase in skin examinations by a healthcare provider in the intervention group but failed to show a change in sunscreen behaviors in either group.

To learn more about this data from the NCI, and for additional resources, please visit www.cancer.gov/cancertopics/types/skin. For more information about the recent developments in the understanding of the genetic and lifestyle risk factors for NMSC and melanoma, please visit www.the-dermatologist.com.

— Julia Ernst, MS, Assistant Editor
Surgical Treatment

Biopsy technique is essential in evaluating a suspicious lesion for accurate diagnosis and measurement of Breslow depth in the event of a melanoma diagnosis. Excisional biopsy technique with narrow margins of surrounding skin is preferred, unless lesion size or location prevents it. Following histologic diagnosis, wide local excision is the preferred treatment method, with margins based on Breslow depth (see Table III). The use of Mohs micrographic surgery in the treatment of melanoma remains controversial, due, in part, to concern about the difficulty in detecting abnormal melanocytes in frozen sections. Various modifications have been proposed to address this issue, including the use of intraoperative immunostaining for melanoma markers such as MelanA/MART1 and the use of modified or “slow” Mohs with permanent paraffin-embedded tissue sections for tumors with ill-defined margins or for tissue sparing in sensitive anatomic sites. Local tumor recurrence, sometimes after many months or years, continues after these techniques.

Skin cancers may be curable when detected early and adequately treated, but the prognosis for advanced cutaneous malignancies is poor.

Patients with melanomas greater than 1 mm in thickness may be considered for sentinel lymph node biopsy (SLNB), which provides prognostic information by detecting melanoma spread to regional lymph nodes. This practice remains controversial among dermatologists, as subsequent complete lymph node dissection for metastatic disease is not without tissue sparing in sensitive anatomic sites. Local tumor recurrence, sometimes after many months or years, continues after these techniques.

Adjuvant Therapies

Non-invasive methods for treating lentigo maligna (a type of MIS) with ill-defined tumor margins or extensive involvement of sensitive anatomic sites have been proposed as a tissue-sparing technique. A review of treatment options for lentigo maligna recommends the use of imiquimod cream with great caution due to short follow-up times and the possibility of an invasive component not detected on biopsy. Radiation therapy (RT) has also been proposed for large lentigo maligna or lentigo maligna melanoma lesions on the face or in elderly patients who may not be able to tolerate surgery, with reported cure rates greater than 90%. Palliative RT may be used in patients with symptomatic metastatic disease, particularly inoperable brain metastases. Curative resection of stable metastatic lesions, such as distant nodes or isolated visceral tumors, should be considered for appropriate patients.

Several approaches to systemic adjuvant therapy have been tried in patients with high risk or metastatic melanoma, including traditional chemotherapy, immunotherapy and vaccination. Unfortunately, these treatments have generally failed to show any significant survival benefit.

In 2011, the FDA approved two targeted therapies for metastatic melanoma, representing a significant advance in melanoma treatment. Ipilimumab is a monoclonal antibody directed against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which downregulates T-cell activation. By blocking CTLA-4, ipilimumab promotes T-cell mediated anti-tumor immunity. Ipilimumab is administered by intravenous infusion once every 3 weeks for a total of four doses. A randomized phase III trial demonstrated prolonged survival in 676 patients with advanced melanoma treated with ipilimumab compared to patients receiving a peptide vaccine (10 months vs 6.4 months, respectively, P<0.001), but the proportion of patients with an objective response (10.9%) was disappointing. Another study of 502 patients with metastatic melanoma demonstrated that ipilimumab plus dacarbazine improved survival compared to dacarbazine alone. More than 60% of patients experienced toxicity in the form of autoimmune phenomena such as vitiligo, elevated liver enzymes and colitis, which can be life-threatening.

Vemurafenib, an oral inhibitor of mutated BRAF kinase, has also demonstrated survival benefit over conventional chemotherapy in controlled trials. Vemurafenib has high specificity for BRAF harboring a V600E mutation, resulting in substitution of glutamic acid for valine at codon 600; this error is present in 90% of melanomas with BRAF mutations. In 675 patients with metastatic melanoma, overall survival was 84% in patients receiving vemurafenib versus 64% in dacarbazine-treated patients at 6 months, with an overall response rate of 48%. Treatment with vemurafenib is associated with a number of potentially serious side effects that may require modification or discontinuation of therapy; fatigue, alopecia, arthralgia and muscle spasms, rash, squamous cell carcinoma and gastrointestinal toxicity were noted most frequently. In another study of 132 patients with previously treated metastatic melanoma, representing a significant advance in melanoma treatment. By blocking CTLA-4, ipilimumab promotes T-cell activation. The mechanism of development of resistance is currently under investigation.

These novel targeted therapies are an exciting advance in the field of melanoma treatment. Further research is needed...
to develop therapies that provide sustained responses and high response rates with favorable side effects profiles. A final note is the importance of close follow-up to detect recurrent or metastatic melanoma; patients diagnosed with melanoma are at an increased risk of developing a second primary melanoma. Counseling melanoma patients and their first-degree relatives about this risk and the importance of daily sun protection is essential.

Conclusion

Skin cancer is the most common cancer worldwide, causing significant morbidity and consuming substantial healthcare resources. Skin cancers may be curable when detected early and adequately treated, but the prognosis for advanced cutaneous malignancies is poor. Various surgical and non-surgical therapeutic options exist for both melanoma and NMSC, with novel targeted therapies emerging for patients with advanced disease. The choice of therapy and determination of therapeutic goals and expectations should be discussed with the patient and his or her family to optimize treatment outcomes. A multidisciplinary approach is often critical for patients with advanced cutaneous malignancy, with input from oncology, radiology, surgery and otolaryngology colleagues. Finally, prevention of skin cancer is paramount; every patient encounter may be viewed as an opportunity to educate patients about the importance of daily sun protection.

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References


Current Trends in Atopic Dermatitis Treatment: More Than Just Steroids

As the cause of the condition is considered multifactorial, the treatment plan should include combination therapies and avoidance of triggers.

Megan A. Kinney, MD, MHAM

Atopic dermatitis is a common chronic or chronically relapsing inflammatory skin disease that affects approximately 18% to 25% of the pediatric population and causes psychosocial morbidity, impaired quality of life and a heavy economic burden. The disease presents with pruritus plus an eruption consisting of scaly to lichenified plaques most commonly manifesting in the skin creases (although in infants it is more common on the face), and, generally dry skin and possible associated allergic symptoms (see Figures 1 and 2). In fact, the progression from atopic dermatitis to asthma to allergic rhinitis is called the “atopic march,” though patients can present with these conditions in any order or all at once. While AD much more characteristically develops in childhood, a small portion of patients may develop the disease in adulthood. AD can be associated with elevated IgE levels and multiple gene mutations that can cause changes in the skin barrier itself. The condition is likely a product of gene-environment interaction.

Traditional treatment of AD is multifactorial and based on severity. Patients should avoid triggers such as allergens, rough clothing, stressors and bacteria on the skin through the use of bleach baths and antibacterial soaps, and practice good skin care habits with frequent application of emollients and use of mild soaps. For the aforementioned plaques, topical corticosteroids are first-line treatment with potency based on severity and thickness of plaques. Most agree that supplementation of topical calcineurin inhibitors like pimecrolimus and tacrolimus, can aid in long-term management of moderate AD. Light therapy may also be of benefit. For severe recalcitrant AD, oral systemic medications may be necessary, with cyclosporin, azathioprine, mycophenolate mofetil and methotrexate used most commonly. Smaller numbers of patients have also been treated with biologics. Prednisone is generally not recommended for AD unless done in a shorter taper to another steroid-sparing systemic agent, given its side effect profile and propensity to cause AD to flare more severely with its discontinuation. Multiple integrative treatments are also employed in the treatment of AD.¹

A review of current literature shows that current studies trend away from topical steroids and toward novel modalities, some of which may be unexpected. Since the cause of the disease is considered multifactorial, a treatment plan should be implemented in lieu of a single miracle cream. This article will explore these current trends in categories.

FIGURE 1. Lichenified, excoriated eczematous plaques in a child with atopic dermatitis.

FIGURE 2. The antecubital region is a common place for atopic dermatitis.
Skin Barrier

Protecting and rebuilding the skin barrier has become part of the bread-and-butter treatment regimen for atopic dermatitis. Many patients with AD have been shown to have a mutation in FLG, which codes for filaggrin, which aggregates keratin, a large component of the stratum corneum (see Figure 3). In between the cells of the epidermis, the keratinocytes, there are lipid molecules — including ceramides — that fill in the gaps and help to maintain the barrier. With less filaggrin, the barrier becomes broken allowing for water loss and the entry of antigens and infectious organisms. Recent studies have demonstrated that applying ceramide-containing emollients can help restore the skin barrier. These studies evaluated the ceramide topical in all age groups, but a recent study evaluated this topical solely in the pediatric population and further supported incorporation of ceramide-dominant topicals as an integral component in AD therapy either as monotherapy or combination therapy.2

These topicals not only replace what is lost; they actually improve keratinocyte lipid biosynthesis, which may further improve the epidermal barrier.3 This molecule has so far only been available in lotion or cream form, but recently a ceramide hyaluronic acid foam has been developed that may have the benefits of ceramides with increased compliance given the foam vehicle.4 Alternatively, patients may be able to obtain the benefits of ceramides even without applying a topical therapy. Consuming dietary sphingolipids has suggested an upregulation in the synthesis of ceramides in skin.5 Also, an oral collagen tripeptide has undergone initial animal studies and shown improvement in skin dryness.6

While ceramides have been the primary focus, other possible molecules to enhance the skin barrier are also being studied. Topical urea may enhance barrier function because it has anti-microbial properties; it also upregulates filaggrin and production of other components of the skin barrier.7 Recent studies suggest that upregulating filaggrin levels in the skin by 5% to 10% may improve clinical management of patients with AD; this may, therefore, become a more focused therapeutic target for treatment. Several compounds already shown to increase FLG gene expression include oleoanic acid and ursolic acid.8

While FLG is most prominent in the literature, known upregulated genes in AD include involucrin, a small protein-rich region (SPRR) 2C gene and alternative pathway keratin 16. All were shown to be decreased in lesional skin after treatment with pimecrolimus. Treatments targeting genes lends to a new avenue to improve the skin barrier.9

Lastly, recent studies in standard treatments of care have determined that while topical corticosteroids may be a more effective anti-inflammatory, they reduce the rate limiting enzymes for lipid synthesis and the expression of involucrin and SPRRs in the skin (which covalently binds ceramides), thus inhibiting the restoration of the skin barrier. This confirms that calcineurin inhibitors (such as pimecrolimus, which was the comparison treatment in this study) are a better option for long-term maintenance therapy.10

Fighting Infectious Organisms

Breakdown of the skin barrier allows easier access for infectious organisms. Practitioners offer many recommendations...
for decreasing bacteria generally on the skin, including anti-
bacterial soaps, oral and topical antibiotics and bleach baths.

Children with atopic dermatitis have been found to be
more prone to infectious diseases in general; they are more
frequently hospitalized than children without AD, and the
most common reason for hospitalization is pneumonia. Chil-
dren with AD also commonly suffer from chronic diarrhea,
and studies have confirmed that *Staphylococcus aureus* is more
commonly found in their stool. Some believe that *S. aureus* in
the GI tract can stimulate atopic skin changes.11

Probiotic supplementation has been suggested as a way to
deliver additional microorganisms to the GI tract and, in sev-
eral studies, have been shown to prevent AD.12,13 Addition of
other microorganisms may aid in eliminating the intestinal
overgrowth of *S. aureus*. Following a similar belief, Jang et al
argue that the addition of lactic acid bacteria (LAB) may also
aid in prevention and treatment of allergic diseases. Previous
studies have shown the LAB, *Lactobacillus plantarum*, isolated
from the traditional Korean food kimchi, reduce allergen-in-
duced airway hypersensitivity and histamine release. By isolat-
ing *Lactobacillus plantarum* K–1, they found that proinflamma-
tory cytokines and scratching behavior in mice was reduced,
indicating this may be a future treatment for allergic condi-
tions such as AD.14

While the changes in the gut mentioned above are new
discoveries, it is well known that high levels of *S. aureus* are
found on the skin of patients with atopic dermatitis. A recent
study analyzed the susceptibilities of the *S. aureus* isolated
on patients with superinfected AD versus controls and found that
there is increased resistance to clindamycin (the most com-
monly prescribed antibiotic for these patients) on the skin of
patients with AD in comparison to controls. This may lead to
changes in clinical practice to prescribe something else like
trimethoprim/sulfmethoxazole as a first line empiric antimi-

crobial choice, although culture-driven antibiotic choices for
superinfected AD should be encouraged.15

However, others do not necessarily recommend the use of
oral antibiotics for secondarily impetiginized AD, even with
culture–proven MRSA. In an argument supporting decreased
antimicrobial peptides associated with AD, one group treated
patients with impetiginized AD with a combination therapy
of topical corticosteroids, antihistamines and oral cephalexin.
They saw improvement even in patients harboring cephalexin-resistant MRSA. This
supports the belief that *S. aureus* is a trigger for AD and that
calming inflammation restores natural anti-microbial peptides
(AMPs) that can then adequately fight off the secondary im-
petiginization. This was supported by a quantified increase in
defensins after treatment.16

A new alternative that may be on the horizon is the addi-
tion of an antimicrobial component to clothing. In one study,
chitosan was incorporated into cotton clothing. The chitosan-
impregnated clothing significantly reduced *S. aureus* bacterial
content specifically and not all bacteria.17

In addition to secondary infection by bacteria, viral ex-
anthems may also be associated with eczema; molluscum
contagiosum is commonly seen in conjunction with atopic
dermatitis. In some patients, this eczematous eruption may
be a secondary id reaction to the primary infection. Given
the vicious cycle of topical steroids causing progression of
the molluscum when trying to treat the associated eczema-
tous reaction, it is recommended to treat the id reaction with
topical emollients. If patients are severely symptomatic, short
courses of topical steroids may be used, but limiting their
duration is important, as steroid use can delay the resolution
of molluscum contagiosum.18

Environment

While environment provides the source for all infectious
agents, it can also affect patients with AD in other ways. Epi-
demiologic studies have shown that higher-income countries
have a decreased frequency of infections and an increased rate
of allergic diseases.11 Some argue that better hygiene has led
to less exposure to antigens early in life.

In addition to frequency, a recently published question-
naire study revealed several environmental factors associated
with severity of AD. Though a causal relationship could not
be demonstrated, these environmental factors could perhaps
trigger an individual’s genetic predisposition for the disease.
Factors associated with AD severity included indoor remodel-
ing, those living in an apartment, higher household income
and higher educational status of the mother.19 Another study
found that, in children with AD, cat and daycare exposure ac-
tually reduced the risk of developing asthma in early child-
hood.20 Another study showed allergic AD may be more of
a result of house mites entering through the defective skin
barrier, stimulating an immune response. There is much con-
troversy over whether food allergies contribute to AD; this
will be discussed in a later section.21

The use of humidifiers is often recommended, as they can
moisten the dry air, especially associated with heating, in the
home. Studies from Korea discuss an instance where biocides
mixed in the water of humidifiers caused a fatal pulmonary
syndrome in both children and pregnant women. While it is
not suggested that patients are at risk for inhaled biocides, it
is important for the clinician to remember that patients with
AD may have more of a chance of exposure to humidified aerosols when compared with the general population.22

Psychological Issues

Sleep Deprivation

AD is not just a skin disease. The pruritus associated with
AD and the appearance of skin lesions can have a significant
impact psychologically. Recent studies in itch with AD con-
firm that intensity of pruritus correlated with declining qual-
ity of life and depressive symptoms. In addition, patients expe-
riencing sleep deprivation with AD attributed it to nighttime
itch. Sleep deprivation can even occur at the onset of the
disease.23 Use of sleeping pills has been shown to improve
quality of life and depressive symptoms greatly.24
ADHD
A study in Taiwan recently found an increased risk of attention-deficit/hyperactivity disorder (ADHD) in patients with pediatric allergy disorders. Of note, the main contributing disorder was allergic rhinitis, but bronchial asthma was also determined to be a risk factor for ADHD. Atopic dermatitis was only determined to be a risk factor in association with allergic rhinitis but was not an independent risk factor. Because of the atopic triad, clinicians should be aware of this psychiatric co-association.

Stress
While there are no randomized controlled studies, stress has been suspected to worsen AD. Multiple techniques of relaxation are present in the literature including massage, hypnosis, biofeedback and progressive muscle relaxation. Small studies have indicated improvement in AD with massage.

One study looked at Dead Sea climatotherapy. In this study, patients were treated at a spa hotel near the Dead Sea. Treatment consisted of bathing in the Dead Sea and then exposing the skin to UV radiation. The treatment environment was also kept stress-free. Using the SCORAD index for disease severity and the Skindex–29 score for quality of life, the treatment regimen did show significant improvement in both modalities, but confounding variables such as feeling as though one is on vacation may skew these results.

In addition to causing the patient psychological distress, AD also causes family stress.

In addition to causing the patient psychological distress, AD also causes the family stress. Patient education programs have shown to be successful in improving patient disease and psychological well being. Schut et al recently demonstrated that parents with little social support or parents with high active problem solving behavior would likely benefit more from such programs and that such patients and their parents should be offered this additional education for greater success in treating AD.

Positive Reinforcement
Because AD is more commonly a pediatric disease, psychological approaches to treatment should also take the child’s mindset into account. Most children strongly dislike the sticky ointments and gooey creams prescribed. Poor adherence to topical treatments leads to worse outcomes and possibly progression to a systemic medication with greater side effects. Using positive reinforcement techniques may increase motivation to use topical medications. For example, sticker charts have been shown to improve outcomes in other chronic diseases that require long-term compliance with treatment regimens.

Integrative Medicine
There are scores of recommendations when one considers integrative treatments. We will focus on some of the most recent research on oatmeal, silk, clothing and traditional Chinese medicine (TCM).

Oatmeal
Oatmeal has been shown to inherently possess antioxidant and anti-inflammatory properties, and studies have shown that using a topical formulation of colloidal oatmeal, avenanthamide, restores the cutaneous barrier, alleviating symptoms. Some studies offer this as adjunctive treatment to limit topical steroids, but others suggest that applying oatmeal to a damaged epidermal barrier may lead to oat allergy.

Silk and Other Textiles
Silk and similar materials have been a mainstay in integrative medicine. Recently, oral administration of silk peptides to mice was shown to decrease IgE levels in an atopic dermatitis mouse model. This may be an indication that silk has the ability to modulate the immunological T-helper cell (Th1/Th2) balance.

Studies have also looked at more traditional use of silk as textiles. Certain fabrics can be irritating to the skin. Some have proposed silk as a softer alternative; in atopic dermatitis, however, this textile is not always practical, as it can reduce transpiration and may still cause irritation. Knitted silk alternatives, however, some impregnated with an antimicrobial component, have been shown to, at times, demonstrate a reduction in pruritus and severity of AD by SCORAD index. This initial success spawned the development of a synthetic silk-like fabric, which has been cleared by the FDA as a Class I medical device for use by patients with AD. The fabric is even being used in bedding and has been marketed to prevent bacterial infections (as they have an antimicrobial coating), absorb perspiration and serous exudates and reduce skin irritation, leading to reduced disease severity and pruritus and improved quality of life.

A silver-loaded cellulose fabric with incorporated seaweed was also shown to decrease the modified SCORAD atopic dermatitis index, trans-epidermal water loss and the patient’s subjective severity of their AD compared to cotton clothing.

Traditional Chinese Medicine
There has been an increasing trend in medicine to use herbal medications. And trends in the treatment of atopic dermatitis are no different. TCM is based in more than 2,000 years of experience in herbal medicines, acupuncture, massage and...
Nutrition and its relationship with AD is a controversial topic with dermatologists and primary care physicians.

Nutrition

Nutrition and its relationship with AD is a controversial topic with dermatologists and primary care physicians. In the literature, discrepancies remain about when to introduce new foods and which foods to expose to the newborn. Roduit et al found that introduction of diverse complementary foods and yogurt within the first year of life actually might have a protective effect against the development of AD. A reduction in the risk of AD onset after the first year of life was found. Early introduction of cow’s milk and different infant formulas and their association with the development of AD is also controversial. For breast-feeding mothers, maternal diet supplementation has also been investigated. Upon review of current literature, the American Academy of Pediatrics suggests that lactating mothers avoid peanuts and tree nuts in infants with a high risk for developing AD. They should also consider elimination of eggs, cow’s milk and fish. The World Health Organization (WHO) recommends breastfeeding children up to age 2. Limited research in the area has not determined whether or not breastfeeding has a protective role against development of AD.

A recent review of studies using dietary supplements in children with atopic dermatitis unfortunately showed no benefit in improving AD with oral supplementation of olive oil, corn oil, oral zinc sulphate, selenium, selenium plus vitamin E, vitamin D, sea buckthorn seed oil, sea buckthorn pulp oil, hempseed oil, sunflower oil and DHA. Two small studies with fish oil did indicate some slight improvement in pruritus and quality of life with AD, but larger trials would have to be completed to make any recommendations to the general public.

Another study showed that a combination supplement containing five polyunsaturated fatty acids, vitamin C, vitamin E and zinc demonstrated significant improvement in patient symptoms. The idea behind supplementing polyunsaturated fatty acids is that they have been employed in restoring the stratum corneum and skin barrier. Other supplements such as vitamin B6, vitamin D, folic acid, vitamin B12 and zinc have been studied in solitary. Vitamin B6 or pyridoxine is an essential cofactor for many biochemical reactions in the body and it was suspected that a diet deficient in this vitamin might lead to AD. While deficiencies themselves were not studied, there was no improvement in AD with supplementation of vitamin B6. Vitamin D has been thought to be promising in the treatment of AD, as it can induce keratinocytes, increase synthesis of platelet-derived growth factor, facilitate wound healing, decrease synthesis of inflammatory cytokines, and promote cathelicidin expression. Studies have confirmed that patients with milder AD do have higher levels of vitamin D and that supplementing vitamin D stimulates production of cathelicidin. However, there have been inconsistencies with both supplementation of vitamin D for treatment of AD and vitamin D deficiency associated with AD.

Another study looked at folic acid versus IgE levels in patients with atop dermatitis. IgE levels were correlated with AD severity and were most increased in patients with allergic rhinitis. Previous studies have suggested that low serum folate levels may contribute to the risk of high IgE levels. This study, however, did not find similar results, although patients with AD did have lower levels of folic acid than controls. More studies would need to be done in order to recommend folic acid supplementation in patients with AD.

Kieft-de Jong looked at plasma levels of both folic acid and vitamin B-12 during pregnancy and found that elevations during the first trimester were associated with the development of atop dermatitis in offspring, but not wheezing or shortness of breath.
Though similar studies have shown conflicting results, they bring to light that this should be taken into consideration before institution of government-mandated folic acid fortification. Vitamin B12 or cobalamin has also been theorized to treat AD through its known function of suppressing inflammatory cytokines. A study with topical vitamin B12 demonstrated improvement in AD. It has also been suggested that patients with AD may have decreased zinc levels.

New Tricks

Pruritus, which is commonly associated with AD, can be difficult to control. Oral antihistamines are not usually effective, as the itch associated with AD is not generally mediated by histamine release. Topical corticosteroids are also not always effective and there is the added effect of thinning the normal skin with chronic use. Chronic itching can cause atopic dermatitis to worsen, re-starting the itch-scratch cycle after induction therapy is complete. Takeuci et al compared the use of tacrolimus versus emollients as maintenance therapy in patients who had already undergone induction therapy with topical steroids. They found that 100% of the emollient group had recurrence of pruritus, while only 24% of the tacrolimus group did. This argues that tacrolimus may be a better option for maintenance therapy in patients with AD.

Tacrolimus is already a mainstay treatment in AD as a non-steroid ointment that does not have the same side effect profile as topical steroids. Despite this, patients have difficulty applying the sticky ointment and some complain of local side effects like burning, warmth and redness with the medication. To alleviate some of these local side effects, a study compared tacrolimus-loaded lipid-nanoparticles head-to-head with standard tacrolimus. The tacrolimus-loaded lipid-nanoparticles better targeted the deeper layers of the skin, which is desirable. The worry with deeper penetration is more systemic side effects, but this didn’t seem to be the case in animal models. These nanoparticles, which were delivered in a gel vehicle, may be a better alternative to a greasy ointment.

Ustekinumab, a relatively new biologic FDA-approved for psoriasis, is a monoclonal antibody with affinity for the p40 subunit of interleukin 12 (IL-12) and IL-23. These interleukins promote proliferation of IL-17 through stimulation of T-helper 17 (TH17) cells. AD is also associated with TH17 cells, possibly suggesting a common pathway for both inflammatory conditions. Puja et al speculated this to be the case and had success in treating one patient with resistant AD through its known function of suppressing inflammatory cytokines. A study with topical vitamin B12 demonstrated improvement in AD. It has also been suggested that patients with AD may have decreased zinc levels.

Monitoring Severity of AD

Many have noted the presence of an infra-auricular fissure in patients with AD. Kwatra et al took this clinical finding a step further and found depth of the fissure to be associated with the severity of AD. This bedside clinical assessment has been found to be helpful assessing AD severity across all age groups.

Severe Cases

A pilot study was recently completed with apremilast, an oral phosphodiesterase (PDE) inhibitor, for the treatment of AD in adults. Results were promising, with reductions in pruritus, Eczema Area Severity Index (EASI) and the Dermatology Life Quality Index (DLQI) scores depending on dosing at 3 and 6 months. The leukocytes in patients with AD have elevated levels of PDE type 4 when compared to controls and this elevation leads to hyperactivity of leukocytes and inflammation. Oral PDE4 inhibitors have been studied for other conditions such as asthma, psoriasis, psoriatic arthritis and chronic obstructive pulmonary disease (COPD), but this is the first use of this medication for AD.

Extracorporeal photochemotherapy is a procedure where the patient’s blood goes through a process called leukopheresis, which removes the patient’s white blood cells while the red blood cells and plasma are returned to the patient. The white blood cells are treated with UVA radiation for several cycles and then returned to the patient. The process has been a treatment for cutaneous T-cell lymphoma, but has more recently been studied as a potentially successful long-term treatment to stabilize AD in patients with severe disease that has been resistant to other systemic therapies without the immunosuppression that makes other systemic medications risky.

Cyclosporin is a systemic agent used for the treatment of severe resistant atopic dermatitis. Subcutaneous allergen immunotherapy (SCIT) is a process of subcutaneously administering gradually increasing doses of allergens to patients with allergic conditions to reduce clinical symptoms from exposure to the allergen over time. Allergic responses to common environmental allergens can be responsible for the chronicity of AD. Using house dust mite extract in patients with known hypersensitivity for SCIT combined with cyclosporine, Nahm and Kim saw clinical improvements in all patients treated offering this initial study for this combined treatment option.
On the Horizon

Recent studies have suggested that sprouting of epidermal nerves is seen with the pruritus associated with AD. Nerve growth factor (NGF), released by keratinocytes, is a major growth factor regulating these new nerve connections, and increased levels of this molecule have been seen in AD patients. A nerve repulsion factor, epidermal semaphorin 3A (Sema3A), acts in opposition to NGF and the two are said to work together as axonal guidance molecules. Sema3A is found in decreased concentrations in AD patients and could be a new target for calming pruritus associated with anti-histamine resistant itch. Initial animal studies with an ointment containing Sema3A have so far shown positive results.50

In a separate study, Samukawa et al looked at another possible new treatment modality, red ginseng extract (RGE), and its effect on NGF. In a study where 2,4-dinitrofluorobenzene was applied to mouse ears to induce pruritus, the 1% RGE was shown to be just as effective as tacrolimus in attenuating NGF, while dexamethasone was less effective. RGE also inhibited histamine-induced vascular permeability and the same result was observed clinically, with a decrease in scratching behavior by mice.51

Fucoidan, a sulphated polysaccharide extracted from brown seaweed known to have anti-allergic and immunologic activities, was recently tested for the treatment of AD in a mouse model. It was compared topically head-to-head with dexamethasone and was shown to be just as effective both symptomatically and histologically, showing a decreased number of mast cells and decreased thickness of epidermis.52

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that have long been known to be associated with adipocytes and involved in insulin sensitization and adipogenesis, but have more recently been seen to be involved in anti-inflammatory activity. In an AD mouse model, topical application of a PPARα activator showed clinical improvement in dermatitis, reduced inflammatory infiltrate in the dermis and decline of serum IgE elevation. Therefore, a topical PPARα activator could be a topical steroid alternative in the future.53

Lastly, a new non-steroidal topical medication currently referred to as WBI-1001 has been shown to be efficacious in treating mild to severe atopic dermatitis after completion of a multi-center Phase IIB randomized, parallel-group, double-blind, placebo-controlled trial. Only a single-center, 4-week trial had been completed previously, so, after further testing, this may be a new non-steroidal topical treatment on the horizon.54

Conclusions

For patients with AD, the future looks promising. While this update only skims the surface of the current literature exploring new and different treatment modalities in AD, considering a treatment plan — versus a single ‘miracle’ cream — and focusing on rebuilding the skin barrier seem to be the current treatment trends. Finding medications that patients will use with a lesser side effect profile than topical and oral corticosteroids and going back to our roots in medicine with TCM and integrative medicine may cause less co-morbidities to our patients. Considering the environment outside patients’ bodies and also what they are putting into their bodies through nutrition may help in preventing flares or the disease itself. It is also important to consider the psychological effects of AD on both patients and those around them when trying to implement successful treatment. Finding new ways of using the tried and true medications and treatment modalities can help recalciitrant cases. Lastly, better understanding of AD on the molecular and genetic level gives us a positive outlook of what’s on the horizon.■

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References

www.the-dermatologist.com

The Dermatologist® Current Treatment Strategies in Dermatology 2012

August 2012
Current Trends in Atopic Dermatitis Treatment: More Than Just Steroids


Topix Pharmaceuticals Introduces Replenix Clarifying Brightening Polish

The new Replenix Clarifying Brightening Polish from Topix Pharmaceuticals is a mild cleanser with exfoliating microbeads that is designed to refine skin “gently and effectively.”

The Brightening Polish has smoothing, softening, exfoliating, brightening and purifying qualities and includes ingredients such as glycolic and salicylic acids, arbutin, bisabolol, CoQ10, green tea polyphenols and vitamin C. The Brightening Polish helps slough away surface skin cells in order to enhance texture, suppleness and moisture levels while diminishing fine lines and wrinkles, all without irritation.

The new Brightening Polish from Topix Pharmaceuticals is both paraben-free and non-comedogenic. It is suitable for all skin types.

Replenix Clarifying Brightening Polish sells for $32.40 and can be purchased through a variety of websites.

For more information, please visit www.topixpharm.com.

Liftactiv Serum 10 from Vichy Laboratories

LiftActiv Serum 10 is a new anti-aging serum from Vichy Laboratories that firms, tightens and softens the skin.

LiftActiv Serum 10 combines Rhamnose in a 10% concentration with hyaluronic acid, ceramides and antioxidant-rich Vichy Thermal Water. Rhamnose is a naturally derived plant sugar that is proven to stimulate rejuvenation of all skin surface layers simultaneously, according to the company.

LiftActiv Serum 10 results in a clinically proven reduction of the appearance of the four main types of facial wrinkles (eye contours, crow’s feet, forehead wrinkles and laugh lines) after one month, according to the company. In addition, the new LiftActiv Serum 10 from Vichy Laboratories reduces the appearance of pores. The Serum is gentle enough for all skin types.

The new LiftActiv Serum 10 will be available in September 2012 for $52. It can be purchased at select CVS, Duane Reade and Walgreens locations.

For more information, please visit www.vichyusa.com.

Polish and Plump Peel is a Two-Step Anti-Wrinkle System

The new Polish and Plump Peel from HydroPeptide is a microdermabrasion peel system that includes two anti-wrinkle systems.

The first peel, Anti-Wrinkle Polishing Crystals, contains vitamin C for collagen support and works to destroy reactive oxidizing agents and promote skin tone consistency by inhibiting melanin production. The second peel, the Anti-Wrinkle Plumping Activator, contains lactic acid, which sloughs away dead skin cells, diminishes dryness, promotes a more uniform complexion and primes the skin for hydration, and has an additional wrinkle-smoothing boost because of the trylagen and SNAP 8 peptides, according to the company.

The new Polish and Plump Peel from HydroPeptide is available for $68. It can be purchased at spas nationwide and online at www.hydropeptide.com.

For more information, please visit www.hydropeptide.com.

Glytone Anti-Aging Night Cream Improves Deep Lines, Wrinkles

Glytone has released its new Anti-Aging Night Cream, a new night cream indicated for daily use.

The Anti-Aging Night Cream, the latest addition to Glytone’s antioxidant anti-aging range of products, is formulated with natural peptides, antioxidants and glycolic acid. The Anti-Aging Night Cream is designed to improve the appearance of deep lines and wrinkles and increase the production of the proteins that preserve and strengthen the epidermal layers of the skin.

The new Anti-Aging Night Cream from Glytone is available exclusively through physicians. It has a suggested retail price of $89 for 1.0 fl. oz./30 mL.

For more information, and to locate a physician, please visit www.glytone-usa.com.
## Calendar of Events

### September 27 to 30, 2012

Prague, Czech Republic — The 21st European Academy of Dermatology and Venereology Congress - Skin is Vital - to be held at the Prague Congress Centre in Prague, Czech Republic. The 21st EADV Congress offers a platform for disseminating scientific and practical knowledge among dermato-venereology professionals.

For more information, please visit www.eadv.org.

### October 4 to 7, 2012

Las Vegas, NV — The Fall Clinical Dermatology Conference to be held at the Encore at the Wynn in Las Vegas, NV. This 4-day conference is designed to provide increased knowledge for the practicing dermatologist by presenting a comprehensive update on the diagnosis and treatment of a variety of conditions related to medical, surgical and cosmetic dermatology. The program offers daily lectures, panels, live patient workshops and Q&A sessions.

For more information, please visit www.clinicaldermconf.org.

### October 11 to 14, 2012

Atlanta, GA — The 2012 Annual Meeting of the American Society for Dermatologic Surgery to be held at the Hyatt Regency in Atlanta, GA. This is an educational forum for dermatologists committed to excellence in cosmetic, medical, reconstructive and Mohs procedures.

For more information, please visit www.asds.net.

### October 19 to 21, 2012

San Francisco, CA — The Women’s & Pediatric Dermatology Seminar 2012 to be held at the Grand Hyatt San Francisco in San Francisco, CA. This conference will explore the chief clinical topics relevant to skin diseases in women and children. Dermatologists, pediatricians, OB/GYNs and other healthcare providers who manage these conditions are invited to attend.

For more information, please visit http://bit.ly/xB89a3.

### October 24 to 27, 2012

Durban, South Africa — The International Society of Dermatology’s 3rd Annual Continental Congress of Dermatology and the 65th National Congress of the DSSA to be held in Durban, South Africa. This conference allows dermatologists from all over the world to interact and attend sessions encompassing all fields of dermatology, with information presented by leading dermatologists.

For more information, please visit www.pedsderm.net.

### Calendar of Events Submissions

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