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† The most frequent adverse event reported was dryness. Erythema, stinging/burning, and scaling may also occur.

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Differin\textsuperscript{®} Lotion, 0.1\% is indicated for the topical treatment of acne vulgaris in patients 12 years and older. A thin film of Differin\textsuperscript{®} Lotion, 0.1\% should be applied once per day to the face and other areas of the skin affected by acne. In clinical trials, the most common adverse event (>1\%) reported with use of Differin\textsuperscript{®} Lotion, 0.1\% was mild to moderate skin dryness. Erythema, scaling, stinging and burning may also occur. Excessive exposure to sunlight and sunlamps should be avoided during treatment, and use of sunscreen products and protective clothing is recommended. Concomitant use of drying or irritating topical products (like products containing resorcinol, salicylic acid or sulfur) should be used with caution. Instruct patients to avoid the eyes, lips and mucous membranes when applying Differin\textsuperscript{®} Lotion, 0.1\%, and not to apply to areas that have been depilated with wax products. Differin\textsuperscript{®} Lotion, 0.1\% has not been tested in pregnant or nursing women, or with the elderly. Pregnancy Category C.

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BRIEF SUMMARY

INDICATIONS AND USAGE
DIFFERIN Lotion is a retinoid product indicated for the topical treatment of acne vulgaris in patients 12 years and older.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Ultra violet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided.

ADVERSE REACTIONS
Dry skin of mild to moderate severity was the most frequently reported (≥ 1%) treatment related adverse event. Erythema, scaling, dryness, burning/stinging were also seen during treatment.

DRUG INTERACTIONS
Concomitant use of topical products with a strong drying effect can increase skin irritation. Use with caution, especially in using preparations containing sulfur, resorcinol, or salicylic acid in combination with DIFFERIN Lotion. Wax depilation should not be performed on treated skin.

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with DIFFERIN Lotion. Therefore, DIFFERIN Lotion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with DIFFERIN Lotion. Furthermore, such studies are not always predictive of human response.

Human Data
In clinical trials involving DIFFERIN Lotion, 0.1% in the treatment of acne vulgaris, women of childbearing potential initiated treatment only after a negative pregnancy test. Two women became pregnant while using DIFFERIN Lotion, 0.1%. One patient delivered a healthy full term baby and the other patient electively terminated her pregnancy.

Animal Data
No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day, up to 25 times (mg/m²/day) the maximum recommended human dose (MRHD) of 2 grams of DIFFERIN Lotion. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 123 and 246 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele and skeletal abnormalities in rats; and umbilical hernia, exophthalmos and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day [25-59 times (mg/m²) the MRHD] exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

Systemic exposure (AUC 0-24h) to adapalene at topical doses (6.0 mg/kg/day) in rats represented 101 times the exposure to adapalene in patients with acne treated with DIFFERIN Lotion applied to the face, chest and back (2 grams applied to 1000 cm² of acne-involved skin).

Nursing Mothers
It is not known whether adapalene is excreted in human milk following use of DIFFERIN Lotion. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Lotion is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of DIFFERIN Lotion in pediatric patients under the age of 12 have not been established.

Geriatric Use
Clinical studies of DIFFERIN Lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity, mutagenicity and impairment of fertility studies were conducted with DIFFERIN Lotion.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, and 12 mg/m²/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m²/day). In terms of body surface area, the highest dose levels are 9.8 (mice) and 7.4 times (rats) the MRHD of 2 grams of DIFFERIN Lotion.

In the rat study, an increased incidence of benign and malignant pheochromocytomas in the adrenal medulla of male rats was observed.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g. retinoids) when exposed to UV irradiation in the laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) or in vivo (mouse micronucleus test).

In rat oral studies, 20 mg adapalene/kg/day (120 mg/m²/day; 98 times the MRHD based on mg/m²/day comparison) did not affect the reproductive performance and fertility of F₁ males and females, or growth, development and reproductive function of F₂ offspring.

PATIENT COUNSELING INFORMATION

• Apply a thin film of DIFFERIN Lotion to the affected areas of the skin once daily, after washing gently with a mild soapless cleanser. Dispense a nickel size amount of DIFFERIN Lotion (3-4 actuations of the pump) to cover the entire face. Avoid application to the areas of skin around eyes, lips and mucous membranes. DIFFERIN Lotion may cause irritation such as erythema, scaling, dryness, stinging or burning.

• Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply DIFFERIN Lotion to the entire face or other acne affected areas as a thin layer, avoiding the eyes, lips and mucous membranes.

• Exposure of the eye to this medication may result in reactions such as swelling, conjunctivitis and eye irritation.

• Patients should be advised not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.

• Advise patients to minimize exposure to sunlight including sunlamps. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.

• Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.

• This medication should not be applied to cuts, abrasions, eczematous, or sunburned skin.

• Wax depilation should not be performed on treated skin due to the potential for skin erosions.

• This product is for external use only.

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Marcia Ramos-e-Silva, MD, PhD  
*Rio de Janeiro, Brazil*
For the past several decades, the aim of applying medical knowledge gained by the scientific method (evidence) to clinical decision making has been called evidence-based medicine. Dermatology has been in the forefront of evidence-based medicine from its inception with the development of the Combined Clinical Trials, beginning in 1916,1 for evaluating neoarsphenamine treatment for syphilis.2

The gold standard of evidence is the randomized clinical trial (RCT), which is in large measure undertaken for the purpose of complying with regulatory requirements.3 The results of RCTs are thought to also provide the basis for selecting appropriate therapeutic modalities.

The question arises as to whether an RCT can really provide the necessary information for using a therapeutic agent for a given patient (this has also been called evidence-based individual decision making). Put simply, can the results of RCTs really be applied each day in dermatologic practice?

RCTs select a defined population of participants by way of inclusion and exclusion criteria. Usually, the population is fairly homogeneous, which, in the not too distant past, consisted entirely of adult men and women not able to bear children. Although, today, women of childbearing capacity are more often included, children are rarely studied in the initial approval studies. The RCT study population is also restricted as to what medications, supplements, and so forth may be taken, in addition to the study medication or control. A part of the concomitant medication restriction is that the study population will, as much as possible, have no medical condition other than the one for which the study drug is being evaluated. For example, a serious concomitant condition will not be allowed. Even the definition of the disease or condition for which the therapeutic agent is being evaluated is usually more stringent in an RCT than it might be in a practice setting. The level or extent of disease is often calibrated to fit with the expected therapeutic response.

Importantly, difficult or marginally compliant subjects are excluded, when possible. Because the study population is a volunteer population, their motives, time constraints, and willingness to deal with consents, patient logs, and other nonstandard requirements also make them a somewhat nonrepresentational population. Unfortunately, the study population may be considerably unlike the population that might be treated with the study agent once it is approved and widely used in a practice situation. In fact, the tightly selected study population combined with the intense monitoring, frequent return visits, and special inducements toward compliance, result in a situation in which both the safety and the efficacy of an agent is never likely to be greater than that found in the RCT.4

The problem of the RCT producing nongeneralizable information has been recognized by many. One attempt to generate study information that is relevant to practice circumstances is the large simple trial (LST)5,6 or practical/pragmatic clinical trial (PCT).7 In an attempt to generate results relevant to questions such as:

- For whom is this drug effective?
- For how long?
- Under what clinical circumstances?

LSTs are conducted in the office practices of many physicians, have study populations of thousands and very broad eligibility criteria, require simple or few procedures, collect minimal data, and use major illness or death as end points. To our knowledge, these LSTs have not yet been undertaken in dermatology. Because RCTs have a relatively small study population, are often aimed at documenting moderately sized treatment effects, and have such distinct study populations, two or more RCTs of the same treatment not uncommonly produce different results.
These circumstances have led to the use of meta-analyses that attempt to combine a number of RCTs. Unfortunately, meta-analyses suffer from selective reporting errors and the assumption that heterogeneous trial populations may be combined to obtain results that are translatable to a given patient.8,9

CONCLUSIONS

All of the above is not aimed toward the conclusion that RCTs are without value, especially concerning regulatory approval. The regulatory requirement for evidence generated in such trials has enormously improved the nature of the information available to clinicians about the therapeutics used.

There is a general recognition, however, that the answers being generated by the current approach are not sufficient to guide medical decision making. This has led to the introduction and recently the federal allocation of $1.1 billion for what is being called comparative effectiveness research.10,11 The word effectiveness is deliberately chosen over efficacy, which usually measures whether treatment works or does not. By contrast, the word effectiveness is selected to call out the intent to measure final outcomes, such as functional status, quality of life, and disability. Importantly, these are to be outcomes in a typical patient population.12

Presumably, comparative effectiveness research would utilize LST/PCTs and other data to compare the options of interest. It is to be anticipated that comparative effectiveness research and LST/PCTs will eventually find their way into dermatology.13

Disclosure: William H. Eaglstein, MD, is employed by Stiefel, a GSK company, Porter Drive, Palo Alto, CA.

REFERENCES

6 Wright JM. Why don’t we initiate more large simple randomized controlled trials? CMAJ. 2003;169:1170–1171.
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1 Draelos, Z. The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars. Cosmetic Dermatology, June 2008.
Alopecia: The Case for Medical Necessity

Kehinde O. Ogunmakin, BA;1 Rashid M. Rashid, MD, PhD2

ABSTRACT

Although alopecia is one of the most prevalent dermatologic conditions in the United States, it is typically viewed as a benign process with only cosmetic consequences. Androgenic alopecia has an especially strong perception as a cosmetic management issue. This contribution reviews literature gathered through MEDLINE from PubMed to emphasize the value of hair as a part of the system and to illustrate that androgenic alopecia, like psoriasis, can have severe consequences and serve as a risk factor for the development of life-threatening diseases. Individuals with alopecia experience psychosocial and psychiatric illness and may be at risk for cardiovascular disease, prostatic cancer, and squamous cell carcinoma of the scalp. All persons with alopecia should be evaluated and treated by a physician to minimize its psychosocial effects and reduce the risk of developing other medical conditions and be further assessed for the presence of commonly associated comorbid conditions. (SKINmed. 2011;9:79–84)
the lives of affected individuals has become a topic of academic interest. One study has revealed that both men and women view balding men as less physically and socially attractive compared with their nonbalding counterparts. Additionally, men affected with androgenic alopecia consider it a serious condition with damaging effects, such as feelings of reduced attractiveness, teasing, anxieties about others’ perceptions of them, and self-conscious preoccupation with current and future alopecia. Similarly, it was found that women with this condition also experience feelings of diminished attractiveness, helplessness, and anxious preoccupation with their hair. In comparison with nonbalding women, they not only have increased dissatisfaction with their hair, but they experience more negative overall body image feelings and report more social anxiety and poorer self-esteem.

Androgenic alopecia has also been linked to increased social isolation. In one study, 88% of the patients adopted various precautionary behaviors to conceal their hair loss. Many patients stated that they stayed home when it was raining or very windy to prevent exposing their hair loss. These women, however, also avoided sunny days because of increased burns to their scalp resulting from their hair loss. Several patients stated that they were very uncomfortable in public places and would often experience neck cramps from holding their heads upright to limit others from uncovering the hair loss. In addition, 22% of the patients admitted that they avoided specific locations with strong illuminations and would avoid sitting in the center of a room where people might be able to see the top of their head. This study went on to conclude that the psychosocial problems in women with androgenic alopecia was comparable to those in women with chronic dermatologic diseases such as acne, eczema, and psoriasis, with the social life of 50% of patients with alopecia being affected as opposed to 40% of individuals with one of the other dermatologic conditions. This is of interest because another study has revealed that patients with psoriasis have a reduction in physical and mental function comparable to those seen in patients with cancer, hypertension, heart disease, and diabetes. These findings are interesting and suggest that alopecia, like psoriasis, may also decrease the mental and physical functions of affected individuals at levels similar to those in individuals with the aforementioned disabling diseases. It would be of benefit to explore this hypothesis in future studies.

Alopecia Areata

Although it is also often viewed as a focal, local cosmetic problem, alopecia areata has the potential to be a symptom of systemic disease with several associated systemic problems, including immune dysregulation. Despite being only 2% of all alopecia cases in outpatient clinics, it has an onset before the age of 20 years and, therefore, has a big impact on children and adolescents. With increasing peer pressure and hormonal changes that occur during development, adolescents find balding to be an additional stressor. One study has shown that children with alopecia areata have increased depression and anxiety compared with unaffected peers. In fact, 78% of patients had at least one psychiatric disorder, with major depressive disorder (50%) and obsessive compulsive disorder (35.7%) as the most common conditions. Similarly, adults with alopecia areata also experience a multitude of psychiatric disorders. In one study, it was demonstrated that 74% of all patients with alopecia had one or more lifetime psychiatric diagnosis, with major depression (39%) and generalized anxiety disorder (39%) as the most prevalent. The increased prevalence of major depressive disorder in this population is remarkable, as it has been reported that patients who have terminal illnesses such as pancreatic cancer and human immunodeficiency virus infection have rates of comorbid depression of 22% to 45% and 33% to 50%, respectively. Furthermore, patients with alopecia areata experience decreased self-esteem and body image and poorer quality of life and state that their alopecia affects their personality and relationships with others. This evidence supports the concept that alopecia areata can lead to emotional and social dysfunction and that management of the alopecia itself should be the primary goal when treating these patients. Although it has not been specifically elucidated whether comorbid psychiatric conditions precede or occur as a result of alopecia, it would also be of benefit to consider psychiatric assessment when evaluating patients with this condition.

ASSOCIATED SYSTEMIC RISK FACTORS

Risk of Cardiovascular Disease

Cardiovascular disease is the leading cause of morbidity and mortality worldwide and claims 17.1 million lives every year. With such high morbidity rates, screening and modification of risk factors associated with the development of heart disease has become an important focus of preventive medicine. While hypertension, diabetes mellitus, dyslipidemia, and smoking traditionally have been used to evaluate cardiovascular risk, scientific research has led to the emergence of nontraditional risk factors such as ankle-brachial index, homocysteine level, and increased common carotid artery intima-media thickness (CCA-IMT) as additional predictors of heart disease. Likewise, several epidemiologic studies have shown a strong association between cardiovascular disease and androgenic alopecia, and have proposed its adoption as a screening factor for the occurrence of cardiovascular events. In a case-control study, it was shown that CCA-IMT was significantly increased in patients with severe vertex pattern alopecia (grade VI and VII on the Hamilton-Norwood scale) compared with patients with lower levels of hair loss. Currently, CCA-IMT is an accepted measure of subclinical atherosclerosis and is associated with high risk of myocardial infarction, stroke, and vascular death. Acceleration of common carotid artery intima-media thickening is a process not unique to androgenic alopecia and has also been associated with the already-established risk factors such as
as diabetes, hypertension, hyperlipidemia, and smoking. With CCA-IMT as an underlying predictor of cardiovascular disease, it is clear that conditions such as androgenic alopecia that mediate endothelial dysfunction and increase intimal thickening may also serve as cardiac risk factors. In fact, in a study that elucidated a strong association between androgenic alopecia and hypertension, it was suggested that alopecia be considered a clinical marker for the development of hypertension and possible cardiovascular disease.

In a population-based case-control study, the prevalence of androgenic alopecia occurring before age 35 was significantly higher among men who had undergone a coronary revascularization procedure before the age of 60 compared with their controlled counterparts (41.7% vs 16.7%). This study produced an unadjusted odds ratio (OR) of 3.57 (95% confidence interval [CI], 1.19–10.72) for coronary revascularization under the age of 60 years in men with an early onset of androgenic alopecia compared with those with normal hair or late-onset alopecia. Similarly, after adjustments for traditional coronary artery disease risk factors, the patients with early-onset alopecia still had an increased risk for early revascularization, with an OR of 3.18 (95% CI, 1.01–10.03). This study showed that while androgenic alopecia is a risk factor for cardiovascular disease, early onset of the disease further increased the severity of disease and the need for early revascularization via coronary artery bypass graft or percutaneous transluminal coronary angioplasty. Based on this evidence, it would be of good consideration to include androgenic alopecia as an additional risk factor for the development of cardiovascular disease. If affected patients are screened for cardiovascular disease, there might be an associated decrease in the occurrence of negative cardiovascular events within the population.

Additionally, as insulin is found in hair follicles, and may play a role in the regulation of androgen metabolism and the hair-growth cycle, many studies have investigated the relationship between androgenic alopecia and insulin resistance. In one study, it was revealed that there was no relationship between androgenic alopecia and serum fasting insulin level, fasting blood glucose, and insulin resistance. In another study, however, it was recommended that insulin resistance and cardiovascular-related features should be assessed in all men aged 18 to 35 years with stage III or higher androgenetic alopecia, according to the Hamilton-Norwood classification. With the current debate on the relationship between insulin resistance and androgenic alopecia, further investigation of this topic is warranted.

More recently, a study demonstrated a significant association between androgenic alopecia and metabolic syndrome after adjusting for confounding factors such as age, family history, and smoking status. Specifically, the most significant association was identified with high-density lipoprotein (HDL) (OR, 2.36; 95% CI, 1.41–3.95; \( P < 0.001 \)). It demonstrated a negative relationship between the level of HDL and the risk for moderate or severe androgenic alopecia. Furthermore, the study showed that total cholesterol/HDL cholesterol ratio was significantly higher in men with moderate or severe androgenic alopecia and suggested a greater susceptibility to cardiovascular disease. This study revealed that patients with androgenic alopecia are at increased risk for the metabolic syndrome and stressed the importance of evaluating patients with alopecia for components of the metabolic syndrome, particularly HDL levels.

While there are no existing studies that report direct cardiac risk reduction with the treatment of androgenic alopecia, there is evidence that demonstrates the use of 5-α-reductase inhibitors has a beneficial effect on the metabolic profile of treated individuals, which, in turn, may reduce cardiovascular risk factors and negative cardiovascular events. In one study, it was demonstrated that the use of 1 mg/d of finasteride in patients with androgenic alopecia had a significant decrease in glycated hemoglobin \( \alpha_1 \), and a borderline decrease in insulin resistance, suggesting that patients with androgenic alopecia treated with finasteride may undergo slight amelioration of glucose metabolism regulation. Similarly, in a study that focused on lipid profile changes in men with benign prostatic hyperplasia after 6-month treatment with finasteride, a significant increase in HDL cholesterol and lipoprotein(a) was demonstrated. Within this study, treatment was associated with an increase in HDL cholesterol of 24%, which consequently resulted in a low-density lipoprotein/HDL cholesterol decrease of 19% vs no change in either parameter in the control group. Furthermore, lipoprotein(a) concentrations were increased by 27% after a 6-month treatment of finasteride. It is of note that this study administered 5 mg of finasteride daily for treatment of patients rather than the 1 mg/d dosage currently approved for the treatment of androgenic alopecia. This does not, however, preclude the idea that finasteride has beneficial lipid profile changes when administered at 1 mg daily; rather, more investigate attention should be directed toward the changes in lipid profile in patients with androgenic alopecia treated with 1 mg of finasteride.

**Risk of Carcinogenesis**

Skin cancer is the most common form of cancer in the United States, with more than 1 million new cases diagnosed annually. The most important risk factor for the development of skin cancer is increased exposure to UV radiation. With this said, it is obvious that patients with decreased shielding from the sun, as seen with hair loss, would have an increased predisposition to develop skin cancer of the scalp. It is for this reason that the American Society for Dermatologic Surgery has stated that bald men are at increased risk for scalp-related skin cancers and should be particularly attentive to any scalp changes. Similarly, a recent study showed an increase in squamous cell carcinoma of the scalp in male organ transplant recipients with alopecia, and suggested that this population be educated about sun protection and avoidance.
While it has been reported that balding scalps undergo early benign clinical changes, such as faint mosaic melanoderma and actinic lentigines, these scalps may also undergo late changes as a result of chronic actinic damage that appear as scaly pink patches and indicate the presence of actinic keratoses, lesions with known malignant potential. Although little investigative attention has been given to the histologic changes that occur in the balding scalp, one study has observed epidermal transformations in this population that may represent early signs of actinic carcinogenesis. In this study, which examined skin surface changes in hairless photoaging scalps, nuclear atypia, cell dysplasia, and increased epidermal thickness were noted at elevated proportions in this population. This study also showed increased scaliness of the scalp that further revealed keratinocyte dysplasia under microscopic evaluation that suggested the process of actinic field carcinogenesis. As there is a predicated continuum between actinic field carcinogenesis, actinic keratoses, and squamous cell carcinomas, findings from this study may suggest an increased predisposition to epithelial carcinomas in the balding population. While there are no current data elucidating the pathologic mechanism between hair loss and the development of skin cancers, there is evidence that suggests that alopecia may increase the risk of development for skin cancer of the scalp as a result of epidermal changes. With this said, it is clear that methods which prevent photoaging of the scalp should be employed. Since hair provides shielding of the scalp, it follows that treating alopecia should have a protective effect against epidermal changes resulting from increased exposure to UV radiation.

As its name implies, androgenic alopecia is a condition that results from an excess of androgens, specifically dihydrotestosterone and testosterone. Dihydrotestosterone is a hormone that functions in prostate growth and has been implicated in both the development of benign prostatic hypertrophy and prostatic carcinoma when at excessive levels. Since both androgenic alopecia and the pathogenesis of prostate cancer are androgen-dependent, it is of no surprise that studies have suggested a correlation between the two processes. In one study, data suggested a positive correlation between vertex baldness and prostatic cancer, with an approximately 2-fold increase in risk for men with vertex baldness by age 30. In addition, other studies have demonstrated that 5-α-reductase inhibitors reduce low-grade prostate cancer risk, which further suggests a correlation between both conditions. Prostate cancer is the most prevalent cancer among men in the United States and has long latency. As such, it is an ideal target for chemoprevention. Previous studies have assessed the role of 5-α-reductase inhibitors in chemoprevention for prostate cancer. One study suggested that finasteride has the potential to provide a protective effect against tumor formation and growth with minimal toxic effects. Similarly, in a randomized controlled study, it was revealed that men with high risk factors for prostate cancer had reduced risk of incident prostate cancer detected by biopsy when treated with 0.5 mg of dutasteride daily. This study produced a relative risk reduction of 22.8% (95% CI, 15.2–29.8; P < .001) in those treated with dutasteride vs placebo during the 4-year study period. This is interesting because another study has suggested the use of 0.5 mg of dutasteride as an alternative treatment for androgenic alopecia. In the recent case report, a woman with androgenic alopecia recalcitrant to 5% minoxidil gel and with minimal improvement with 1 mg of finasteride achieved clinically undetectable alopecia after 0.5 mg of dutasteride daily for 12 months. The study observed a reduction in hair diameter variability, increase in mean hair diameter, and normalization of trichogram results after treatment with dutasteride. Although the exact relationship between androgenic alopecia and prostate cancer is yet to be elucidated, there is evidence to suggest that treatment of androgenic alopecia may provide chemoprevention for the development of prostate cancer. It would be of importance to direct investigative attention to the topic in order to determine whether androgenic alopecia is in fact a potential biomarker and risk factor for the development of prostate cancer, and to determine whether chemoprevention can be achieved with treatment of alopecia.

CONCLUSIONS

As illustrated throughout this contribution, alopecia can have both psychosocially and physically debilitating effects on affected individuals. The condition not only alters one’s physical appearance but may result in reduced physical and mental functioning at levels comparable to patients with chronic illnesses such as hypertension, diabetes, and cancer. As it is undisputable that treatment and management of conditions such as diabetes and hypertension is imperative to improving patient’s overall health and quality of life, it is likewise reasonable to consider that medical management of alopecia will also result in an improvement in quality of life and reduce the risk of developing further illness.

With the heightened correlation between the presence of androgenic alopecia and negative cardiac events, androgenic alopecia may prove to be an ideal screening risk factor for future development of cardiovascular disease. Since cardiovascular disease is a leading cause of morbidity and mortality in the United States, it is of dire importance to use all sources that may indicate its presence or development, which includes the use of screening factors such as alopecia, in addition to the already accepted risk factors such as hypertension, diabetes mellitus, and smoking. As it has
been shown that androgenic alopecia may increase scalp susceptibility to epidermal changes that may result in the development of squamous cell carcinoma, it is imperative that these individuals be evaluated by a physician to facilitate early detection of possible underlying carcinogenesis. Further, as evidence has shown that androgenic alopecia has a significant association with prostate cancer, it is also important to direct more investigative attention to the topic in order to elucidate whether androgenic alopecia is in fact a potential biomarker and risk factor for the development of prostate cancer and to determine whether chemoprevention can be achieved with treatment of alopecia.

Additionally, despite the cosmetic and classic appearance of alopecia, one must be aware of the rising role of alopecia pattern mimics. In one study, it was shown that a significant number of occult inflammatory and scarring scalp processes may mimic the classic clinical pattern of androgenic alopecia. So, while a patient might present with what appears to be the classic appearance of androgenetic alopecia, it in fact may be much worse.

While alopecia may seem like a condition that only “looks” bad, it may indicate the presence of life-threatening disease. Armed with this knowledge, it is clear that strategies should be devised to manage alopecia in order to minimize psychosocial distress, as well as possibly reduce risk factors for cardiovascular disease and cancer. Like many other chronic illnesses, it is more cost-effective to manage and treat alopecia itself than to battle disease and cancer. Like many other chronic illnesses, it is more distress, as well as possibly reduce risk factors for cardiovascular diseases/en/. Accessed March 28, 2010.

REFERENCES


Naftin® (naftifine HCl 1%) Cream and Gel are indicated for the topical treatment of tinea pedis, tinea cruris and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum* and *Trichophyton tonsurans* (Gel only).

Naftin® Cream and Gel are contraindicated in individuals who have shown hypersensitivity to any of their components and are for topical use only.

During clinical trials with Naftin® Cream and Gel, the following side effects were most commonly reported: burning/stinging, dryness, erythema, itching, local irritation, skin tenderness and rash.

Please see brief summary on the following page.
Acne vulgaris is a universal and the most common skin disease, affecting up to 95% of the adolescent population. In men and women older than 25, approximately 50% have some degree of facial acne, persisting into middle age in 12% of women and 3% of men. The disease is limited to pilosebaceous follicles of the face and the upper aspects of the trunk and is characterized by open and closed comedones (non-inflammatory lesions) and/or inflammatory lesions such as papules and pustules.

Acne vulgaris has a complex multistage etiology, because the disease arises from the interplay of several pathogenic factors. They include sebum production, follicular hyperkeratinization, hormonal dysfunction, microbial colonization of the pilosebaceous unit by Propionibacterium acnes, and immune hypersensitivity. Although P. acnes is a part of a normal flora and is harmless in normal sebaceous follicles, the proliferation and colonization of that bacteria in pilosebaceous ducts give rise to the inflammatory lesions. The organism metabolizes triglycerides, releasing free-fatty acids and, as a result of growth and metabolism, produces neutrophil chemoattractants, releases inflammatory mediators into the follicle and the surrounding dermis, and activates complement, causing inflammation.

Oral antibiotics have been a standard choice in the treatment of moderate to severe inflammatory acne for more than 40 years. In general, they should be administered for at least 2 months but not for more than 4 to 6 months. The most commonly prescribed antibiotics are tetracyclines, doxycycline, minocycline, and erythromycin, which reduce intrafollicular P. acnes colonization and inhibit the production of bacteria-induced inflammatory cytokines.

Researchers performed the first double-blind, placebo-controlled, crossover study in 1970, which evaluated the efficacy of doxycycline in acne vulgaris. The study showed superiority of doxycycline over placebo in the reduction of the total number of inflammatory lesions. There have been additional reports since, confirming noninferiority of azithromycin as compared with doxycycline. (SKINmed. 2011;9:86–94)
confirming these results with the whole group of tetracyclines, making them a gold standard in the treatment of acne.\textsuperscript{11,15} In the past 2 decades, an increased number of reports of antibiotic resistance of \textit{P. acnes} to commonly prescribed antibiotics\textsuperscript{16–19} have been published. The increased resistance and poor patient compliance to long-term treatment regimen, together with the anticipatory possibilities of adverse effects, have given rise to the need of a new antibiotic with a more favorable route of administration, shorter treatment duration, and better safety and tolerability profile.\textsuperscript{18,20,21} Besides antibacterial activity and safety, immunomodulatory activity is also required.\textsuperscript{22}

Azithromycin has been demonstrated to act against anaerobic bacteria, with an excellent in vitro activity against \textit{P. acnes} (minimum inhibitory concentration required to inhibit the growth of 90\% of organisms $[\text{MIC}_{90}]=0.03$ \textmu g mL\textsuperscript{−1}).\textsuperscript{23} Azithromycin penetrates well into the skin and exerts prolonged therapeutic effect after the last dosage. The peak azithromycin concentration in the skin is 35-fold of that achieved in serum, exceeding $\text{MIC}_{90}$ for \textit{P. acnes}.\textsuperscript{24} Due to its improved pharmacokinetic effects, high tolerability profile, activity against \textit{P. acnes}, and immunomodulatory action,\textsuperscript{22} azithromycin appears as a promising agent for the treatment of acne.\textsuperscript{21}

Several clinical trials have shown azithromycin to be an efficacious and safe agent in the treatment of acne.\textsuperscript{25–29} Also, clinical trials have been conducted comparing azithromycin treatment for acne vulgaris with minocycline\textsuperscript{10} and tetracycline\textsuperscript{31} treatment, as well as several clinical studies comparing azithromycin with doxycycline treatment for acne.\textsuperscript{32–34} Although these studies showed the same or similar effect of azithromycin and other studied antibiotics in the treatment of acne, with significantly improved patient compliance with azithromycin use,\textsuperscript{28,32} most of these studies had some limitations, such as a small number of patients.

The aim of this randomized, double-blind, double-dummy study was a comparison of efficacy and safety between azithromycin and doxycycline in the treatment of moderate acne vulgaris in a larger population. The main result was a measure of a reduction in the number of inflammatory facial lesions and an assessment of changes in acne severity based on this reduction.

**PATIENTS AND METHODS**

**Study Design**

The study was designed as a prospective, multicenter, double-blind, double-dummy, randomized noninferiority trial. Fifteen centers from Poland participated in the study. Recruitment started on December 18, 2003, and was completed on July 16, 2004. During the study, 5 clinical visits were performed: at baseline and subsequently at weeks 4, 8, 12 (end of the treatment [EOT]), and 16 (end of the study [EOS]). At baseline and at all subsequent visits, each patient's face was examined using a fluorescent lamp with a white circular tube at a distance of up to 30 cm from the patient's face in a well-illuminated room by fluorescent ceiling lighting. The number of inflammatory and noninflammatory facial lesions was recorded. Papules, pustules, and nodulocystic lesions were considered as inflammatory lesions and comedones as noninflammatory lesions.

The following grading of the disease severity was used: 0, normal: clear skin with no evidence of acne vulgaris; 1, almost clear: presence of $\leq 7$ inflammatory lesions (papules/pustules); 2, minimal to mild acne: 8 to 20 inflammatory lesions (papules/pustules) and no nodulocystic lesion; 3, moderate acne: $\geq 21$ inflammatory lesions (papules/pustules) were present and with or without 1 small nodulocystic lesion; and 4, severe acne: a high degree of inflammatory disease with papules/pustules being a predominant feature and variable number of comedones with or without a few nodulocystic lesions.

**Selection of Patients**

Patients were eligible for enrollment in the study if they were 14 years or older and had a clinical diagnosis of moderate acne vulgaris. Patients with severe acne vulgaris, other facial dermatoses, and other diseases with acne as a part of clinical presentation (adrenogenital syndrome, Cushing's disease, 21-hydroxylase deficiency, polycystic ovary syndrome), and patients with beards and moustaches, and signs of hirsutism were excluded. Women of childbearing potential were asked to use reliable methods of mechanical contraception, following negative pregnancy test before treatment.

**Treatment**

Patients were randomly assigned at a 1:1 ratio to receive either azithromycin (Sumamed) 500 mg daily for 3 days in the first week, followed by 500-mg tablets weekly to complete 10 weeks of treatment, or doxycycline (Hiramicin) 100-mg capsules twice a day on the first day of the treatment, followed by doxycycline 100-mg capsules once a day during 12 weeks of treatment. Patients also received 12 placebo tablets in the doxycycline or 85 capsules in the azithromycin groups.

Patients were advised to apply a keratolytic lotion (2\% solution of salicylic acid in 40\% ethyl alcohol) on the face twice a day until EOS for the respective patient. Use of any systemic or topical antibiotics or retinoids within the past 4 weeks of treatment with systemic retinoids within the past 6 months was not allowed.

**Evaluation of Clinical Efficacy**

Efficacy analysis was performed in the intention-to-treat (ITT) and per-protocol (PP) populations. The ITT population included...
Aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, bilirubin in serum were determined at baseline and at all subsequent visits. Adverse events were recorded at each visit. Patient compliance was assessed by the number of tablets/capsules used.

**Sample Size**

Azithromycin was to be considered noninferior to doxycycline if the upper 95% confidence limit (CL) of the difference (azithromycin-doxycycline) between the two treatments with respect to a change (negative change indicated improvement) in facial inflammatory lesion count from baseline to the EOT was <9.

Delta value was set in accordance with clinical significance, regulatory recommendations, and a study showing superiority of the active comparator (doxycycline) to placebo. It was approximately 80% of the mean difference in reduction of 11 facial inflammatory lesions between doxycycline and placebo.

A sample size of 120 patients per arm was required to give the power of 80% for the upper bound of 1-sided 95% confidence interval (CI) to be <9 inflammatory lesions (noninferiority margin), with a common standard deviation of 24 and minimum attrition rate of 30% when there was no difference between the treatments.

**Randomization and Blinding**

Participants had an equal probability of assignment to either group. The randomization code was developed using a computer random number generator to select random blocks. The block length was 8. Each randomization number with allocated treatment information was sealed in a separate envelope. Study drugs were centrally packed according to the randomization schedule and distributed to the investigators. Each patient received active drug and placebo from the physician. All study personnel and participants were blinded to treatment assignment for the duration of the study. Only the statisticians and data monitoring committee saw unblinded data, but none of them had any contact with study participants.

**Statistical Analysis**

All statistical analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC). The assay sensitivity was deduced from historical evidence of sensitivity to drug effects and appropriate trial conduct. Analysis of variance (ANOVA) was used to test differences between the two treatment groups for a change in the number of lesions. The change from baseline was a dependent variable and treatment, baseline count (if significant, P < 0.1), and center (if significant, P < 0.1) were independent variables. One-way ANOVA models, with treatment as the independent variable, were used for other comparisons based on continuous data (such as

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Figure 1. Flow chart of all patients entered into study. A total of 240 patients were randomized to study treatment: 120 to receive azithromycin and 120 to receive doxycycline. Eleven patients were withdrawn from the azithromycin group and 5 patients were withdrawn from the doxycycline group.

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Patients who took at least one dose of the study drug and had at least one on-study visit on inclusion in the study. The PP population included patients who took at least 80% of the study drug or >80% of the study drug, but therapy was terminated because of treatment failure.

The primary efficacy parameter was change in facial inflammatory lesion count from baseline to the EOT. Primary inference of noninferiority was performed in the PP population.

Secondary efficacy parameters were change in the number of inflammatory lesions from baseline to EOS, total (inflammatory and noninflammatory) facial lesions from baseline to EOT and EOS, and the investigator's assessment of the severity of acne at EOT and EOS. Additionally, reduction in the number of facial inflammatory lesions was expressed as a percentage from baseline to EOT and EOS visits. Based on this information, we defined treatment outcome as follows: cure: ≥75% reduction; improvement: 50% to 74% reduction; moderate improvement: 25% to 49% reduction; and failure: <25% reduction.  

All aforementioned evaluations were performed in the ITT population for conformation of the primary results.

**Evaluation of Safety and Patient Compliance**

Complete blood cell count and levels of urea, creatinine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and bilirubin in serum were determined at baseline and at all subsequent visits. Adverse events were recorded at each visit. Patient compliance was assessed by the number of tablets/capsules used.
as demographics, baseline characteristics, vital signs, and laboratory tests). Chi-square test and Fisher exact test were used for comparisons based on categoric data. Cochran-Mantel-Haenszel test was used to compare the two treatment groups for investigator’s assessment of efficacy. Adjustment for multiple comparisons was not performed. Missing values were replaced by the last observation carried forward. Safety analysis (clinical safety and tolerability assessments) was performed in all patients who received at least one dose of the study drug.

ETHICS
The study was approved by 3 regional ethics committees, and written informed consent was obtained from all patients before entering the study. If a patient was younger than 18 years of age, signature from a parent or guardian was required.

RESULTS
A total of 240 patients (119 women and 121 men), 120 in the azithromycin and 120 in the doxycycline group, were randomized. The flow chart shown in Figure 1 provides details of study patients’ profile in both groups. Two groups did not differ according to age (20.3±4.8 years vs 20.5±6.3 years; \( P = .791 \)) and sex (45% women vs 54% men; \( P = .156 \)). Efficacy variables were analyzed in the PP and ITT populations.

EVALUATION OF TREATMENT EFFICACY IN THE PP POPULATION
There were 224 patients in the PP population: 109 in the azithromycin group and 115 in the doxycycline group (Figure 1). The groups were comparable according to the number of facial lesions at baseline (40±14 in the azithromycin and 41±14 in the doxycycline groups; \( P = .05 \)) (Table I).

The number of inflammatory lesions at the EOT was slightly higher in the azithromycin compared with the doxycycline group (13±11 and 10±9, respectively; \( P < .05 \)). Consistently, calculated reduction in inflammatory lesions from baseline to the EOT visit (primary efficacy parameter) was lower in the azithromycin than in the doxycycline (27±12 and 30±12) group (\( P < .05 \)); therefore, the between-group difference in the number of lesions from baseline to EOT was 2.6 lesions (95% CI, 2.6 [0.5–4.7]) (Table I) (Figure 2).

Similar results were obtained with the number of inflammatory lesions at EOS visit: 12±12 in the azithromycin and 10±9 in the doxycycline group (\( P = .05 \)), and calculated change in inflammatory lesions from baseline to the EOS (secondary efficacy parameter) was 28±14 in the azithromycin and 31±12 in the doxycycline group (95% CI, 2.2 [–0.2 to 4.5]; \( P < .05 \)) (Table I) (Figure 2). A statistical criterion for noninferiority of azithromycin to doxycycline was, such as at the EOT, completely satisfied (Table II), as the upper 95% CI in both cases was approximately 5 lesions, well below the predefined noninferiority margin of 9 lesions.

Another secondary efficacy parameter, change in total (inflammatory and noninflammatory) facial lesion count from baseline to both the EOT and EOS (Table II), showed consistent results. The number of lesions was comparable in both the azithromycin and doxycycline groups at baseline (79±24 and 81±25, respectively; \( P = .05 \)), and the reduction in the number of lesions was smaller in the azithromycin group than in the doxycycline group (51±21 and 57±22, respectively; \( P = .05 \)) (95% CI, 3.9 [0.0–7.8]) at the EOT and not significantly lower (53±22 and 58±22, respectively; \( P > .05 \)) (95% CI, 3.2 [–0.7 to 7.1]) at the EOS visit (Table II). The noninferiority criterion was also met at both the EOT and EOS visits, as the upper 95% CI of approximately 8 and 7 lesions, respectively (Table II), was still below the predefined margin of 9 lesions.

The investigator’s global assessment of acne grade for each treatment group at baseline, EOT, and EOS has shown that the two

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<th>Table I. Facial Inflammatory Lesion Count at Baseline and Therapeutic Effect at EOT and at EOS Visit (PP Population)</th>
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<td><strong>NUMBER OF INFLAMMATORY LESIONS PER VISIT</strong></td>
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<td><strong>P value</strong></td>
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<tr>
<td><strong>Difference between groups (95% CI)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EOS, end of study; EOT, end of treatment; PP, per-protocol; SD, standard deviation.
treatment groups had similar profiles, reflecting substantial improvement, with a majority of patients in each treatment group improving from “moderate” to “almost clear” or at least “minimal to mild” at both the EOT or the EOS compared with baseline (Table III). There was no statistically significant difference between the two groups.

In addition, there was no significant difference between the azithromycin- and doxycycline-treated groups with respect to the proportion of patients categorized as “cured,” “improved,” “moderately improved,” and “failed,” as shown in Table IV.

**Evaluation of Treatment Efficacy in the ITT Population**

The ITT population consisted of 115 patients in the azithromycin group and 116 patients in the doxycycline group (Figure 1). The groups were comparable according to the number of facial lesions at baseline (40±14 for azithromycin and 41±14 for doxycycline; *P*>.05) (Table V).

The number of inflammatory facial lesions was slightly lower in the doxycycline than in the azithromycin group at both the EOT and EOS visits (Table V). Despite the fact that treatment duration was 2 weeks longer in the doxycycline group, the observed reduction in the number of inflammatory lesions from baseline was similar at the EOT visit: 27±12 for azithromycin and 30±12 for doxycycline (*P*<.01) (95% CI, 3.0 [0.9–5.0]) and at the EOS visit: 27±14 for azithromycin and 30±12 for doxycycline (*P*<.05) (95% CI, 2.5 [0.2–4.8]) (secondary efficacy parameters).

Statistical criterion for noninferiority of azithromycin to doxycycline was satisfied, as the upper 95% CI was approximately 5 lesions at both the EOT and EOS visits, which was substantially lower than the predefined upper margin of 9 lesions (Table V).

**Safety and Patient Compliance**

The incidence of adverse events (AEs) during the 12-week treatment trial did not differ between the two treatment groups. AEs were reported by 26 (21.7%) and 29 (24.2%) patients in the azithromycin and doxycycline groups, respectively (*P*=.759). The majority of events (29 of 51 [52.7%] for azithromycin and 26 of 46 [47.3%] for doxycycline) was categorized as unrelated to the study drug. Of AEs related to the treatment, the most common were those related to gastrointestinal problems. Generally, nausea was the most common AE related to the treatment (31.4% of all AEs and 55.0% of gastrointestinal

<p>| <strong>Table II. Total Facial (Inflammatory and Noninflammatory) Lesion Count at Baseline and Therapeutic Effect at EOT and EOS Visits (PP Population)</strong> |
| <strong>NUMBER OF INFLAMMATORY LESIONS PER VISIT</strong> |</p>
<table>
<thead>
<tr>
<th><strong>BASELINE</strong></th>
<th><strong>EOT</strong></th>
<th><strong>DIFFERENCE FROM BASELINE TO EOT</strong></th>
<th><strong>EOS</strong></th>
<th><strong>DIFFERENCE FROM BASELINE TO EOS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
<td><strong>Mean ± SD</strong></td>
<td>79±24</td>
<td>29±20</td>
<td>−51±21</td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
<td><strong>95% CI</strong></td>
<td>(74.9–83.9)</td>
<td>(24.7–32.3)</td>
<td>(−55.0 to −46.9)</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>81±25</td>
<td>24±19</td>
<td>−57±22</td>
<td>23±19</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>(76.2–85.4)</td>
<td>(20.9–27.7)</td>
<td>(−60.5 to −52.5)</td>
<td>(19.7–26.9)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>.4191</td>
<td>.0839</td>
<td>.0497</td>
<td>.2102</td>
</tr>
<tr>
<td><strong>Difference between groups (95% CI)</strong></td>
<td>3.9 (0.0–7.8)</td>
<td>3.2 (0.7 to 7.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EOS, end of study; EOT, end of treatment; PP, per-protocol; SD, standard deviation.
problems), reported by 2 and 9 patients \((P=.035)\) for azithromycin and doxycycline, respectively. One serious AE (fainting of moderate severity) was reported by a patient receiving doxycycline; however, it was not related to the study drug and was resolved by the end of the study. No serious AE was observed in the azithromycin group. In addition, there was no significant difference shown for laboratory results.

Because patients in both groups were given the same amount of both tablets and capsules (double-dummy), patient compliance was assessed by the number of returned (not used by the patient) tablets and capsules. The result has shown slightly better, although not significant, compliance in taking the tablets (azithromycin) compared with the capsules (doxycycline) (data not shown).

**DISCUSSION**

During the past decade, 3 clinical trials were conducted comparing azithromycin with doxycycline treatment. They had different designs (randomized, comparative; nonrandomized, controlled; randomized, investigator-blinded), used different treatment regimens, and included a small number of patients (51 to 70), and their results were not completely consistent.

We, therefore, conducted the first such rigorously designed (randomized, double-blind, double-dummy, multicenter, noninferiority) clinical trial comparing pulsed azithromycin therapy with standard daily doxycycline therapy in the treatment of moderate acne vulgaris in a larger population (240 patients). Clinical efficacy, safety, and patient compliance were analyzed. The primary efficacy parameter was strictly defined, decreasing physicians’ subjectivity in the evaluation of treatment efficacy: azithromycin was to be considered noninferior to doxycycline if the upper 95% CL of the difference between the two treatments with respect to a change in facial inflammatory lesion count from baseline to the EOT was <9.

The results of our study undoubtedly confirmed noninferiority of pulsed azithromycin therapy to once-per-day doxycycline treatment. Evaluations of a difference in reduction of inflammatory acne lesions with two treatments in both the PP and ITT populations at both the EOT and EOS visits unexceptionally showed a difference lower than the predefined margin for noninferiority.

To obtain a noninferiority result, a primary efficacy parameter (the reduction in inflammatory acne lesions at the EOT visit from baseline in the PP population), was first calculated. It was shown that there are fewer inflammatory acne lesions after doxycycline than after azithromycin treatment; however, the difference of 2.6 lesions in favor of doxycycline was not considered clinically significant. Reduction in the number of inflammatory lesions at the EOS in the PP population, a secondary efficacy parameter, confirmed the primary efficacy result, showing a difference of only 2.2 lesions in favor of doxycycline. Of note is that there was a tendency of decreasing difference between two treatments with time. In addition, a statistical difference that was obtained at the EOT visit \((P<.05; 95\% \text{ CI}, 2.6 [0.5–4.7])\) was lost after 4 weeks, by the time of the EOS \((P>.05; 95\% \text{ CI}, 2.2 [–0.2 to 4.5])\). This result confirms the noninferiority of azithromycin and leads to the conclusion that azithromycin is at least as good as doxycycline for the treatment of acne.

<table>
<thead>
<tr>
<th>GLOBAL ASSESSMENTS</th>
<th>AZITHROMYCIN</th>
<th>DOXYCYCLINE</th>
<th><em>P</em> VALUE</th>
</tr>
</thead>
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<tr>
<td>Baseline</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>109</td>
<td>115</td>
<td>1.0000</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Almost clear</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Minimal to mild</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>109 (100%)</td>
<td>115 (100%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>EOT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>109</td>
<td>115</td>
<td>.0671</td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0.0%)</td>
<td>4 (3.5%)</td>
<td></td>
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<tr>
<td>Almost clear</td>
<td>47 (43.1%)</td>
<td>51 (44.3%)</td>
<td></td>
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<tr>
<td>Minimal to mild</td>
<td>39 (35.8%)</td>
<td>47 (40.9%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>23 (21.1%)</td>
<td>13 (11.3%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>EOS</td>
<td></td>
<td></td>
<td>.2799</td>
</tr>
<tr>
<td>No.</td>
<td>109</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>5 (4.6%)</td>
<td>5 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Almost clear</td>
<td>42 (38.5%)</td>
<td>54 (47.0%)</td>
<td></td>
</tr>
<tr>
<td>Minimal to mild</td>
<td>42 (38.5%)</td>
<td>41 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>20 (18.3%)</td>
<td>15 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EOS, end of study; EOT, end of treatment; PP, per-protocol. *P* values using Cochran-Mantel-Haenszel test.
Although there was a statistically significant reduction in acne lesions with doxycycline than azithromycin, we can, therefore, conclude that there was consistently higher investigator's global assessment in acne grade, and the percentage of decreasing both acne lesion count and statistical significance of the difference in their pharmacokinetics and pharmacodynamics. Moreover, at the last measured time point, the EOS, there was no statistical significance in the PP population for both inflammatory and total acne lesion count, implying, again, that azithromycin is at least as efficacious as doxycycline in acne treatment. This result is similar to the result of another clinical study conducted in 2005 that concluded that there was no difference between these two treatments. It is important to mention that the last measurement in that study was performed 2 months after the treatment. In addition, our result is in line with the results of the recent clinical trial study comparing the clinical efficacy of azithromycin and doxycycline in the treatment of rosacea, another common inflammatory disorder.

Our results are not, however, in line with two other clinical studies’ results that have shown generally significantly better or significantly better efficacy after azithromycin treatment than after doxycycline treatment in an ITT population only. This discrepancy could be due to different designs of the studies, treatment regimen concerning a cumulative dosage and the ratio of two antibiotics during the study, involvement of an additional topical antibiotic treatment of the skin in the course of the study, and a much smaller population.

There was generally no significant difference between azithromycin- and doxycycline-treated groups concerning safety. A definite advantage of azithromycin compared with doxycycline treatment shown in this study, however, lies in the fact that there was a significantly higher incidence of nausea as a related AE in patients who received doxycycline therapy. That is in line with the safety result in a recent study that showed lower incidence and severity of side effects in the azithromycin group compared with the doxycycline group.

Although some topics such as microbiologic efficacy and potential development of bacterial resistance are certainly of scientific interest, they are not part of daily routine and therefore they were not evaluated. The impact of P. acnes resistance on clinical outcome is controversial. A case of clinical efficacy was reported despite in vitro resistance. Clarification of the correlation between erythromycin-resistant P. acnes and clinical response to macrolides resides in the fact that the MIC of macrolides for resistant strains is much higher than the concentration possible.
to achieve in follicles upon oral administration of the drug.38 Despite these limitations, our study was designed and conducted in accordance with the accepted guidelines for noninferiority trials and good clinical practice and followed published suggestions on research in the treatment of acne.39

CONCLUSIONS

Results of this first such rigorously designed clinical study, conducted in a large population of patients, shows that 10 weeks of azithromycin pulse therapy is safe, has good patient compliance, and is efficient in the treatment of acne vulgaris. This study also firmly demonstrated azithromycin to be noninferior to doxycycline—the standard tetracycline therapy for the management of acne vulgaris. Azithromycin, with its shorter duration of therapy and simpler dosage regimen, should, therefore, be beneficial for patients with moderate acne vulgaris.

Acknowledgements and disclosures: This study was supported by PLIVA Croatia Ltd. RM and KTU are both PLIVA investigators and received research fees from PLIVA Croatia Ltd. MO and JV are employees of the sponsor, PLIVA Croatia Ltd. BB is a paid consultant for PLIVA, Sanofi-Aventis, and Abbott and is on the Speakers Bureau of PLIVA, MSD, and Pfizer. The authors have no ownership interests (stocks, stock options, or other ownership interests). We wish to thank the following investigators who contributed to this study: Marek Brzewski, MD, private dermatology practice, Kraków, Poland; Bożena Mamecarz, MD, Foundation for the Development of Sports Medicine, Medical Clinic, Warsaw, Poland; Małgorzata Politowska, MD, Medical Center-Aesthetic Dermatology “Derm-Medik,” Kraków, Poland; Dorota Prandocka, MD, Dermatology Laser Center “LaserMed,” Warsaw, Poland; Danuta Szencel, MD, aesthetic medicine practice, Kraków, Poland; Elżbieta Zahluga, MD, dermatology practice, Szczecin, Poland; Acne Study PLIVA team members: Livija Cvitkovic, BSc; Maja Gasparic, MSc; Aleksandra Welle-feras, BSc; and Artur M. Banaszk. MD.

REFERENCES

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Self-Test Review Questions
W. Clark Lambert, MD, PhD, Section Editor

In the Self-Test Review Questions following Durdu M, Seçkin MD, Baba M. The Tzanck smear test: rediscovery of a practical diagnostic test. SKINmed. 2011;9:23–32., which appeared on page 32, the answer to question 4 should have been, “b. Erythema toxicum neonatorum.”
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Amyloidosis is a spectrum of diseases consisting of deposition of amyloid proteins in various tissues. Classification of the amyloidoses is generally based on the biochemical amyloid protein fibril derivation, although clinical classification does exist. Most dermatologists divide amyloidosis into both primary and secondary forms of systemic amyloidosis, hemodialysis-associated amyloidosis, heredofamilial amyloidosis syndromes, and primary and secondary forms of cutaneous amyloidosis. Chemical composition of amyloid varies from one condition to the other (Figure 1), leading to variabilities in disease course, progression, prognosis, and associated risks with each form of amyloidosis.1–3 Amyloid deposition can occur locally or systemically, which leads to a large variety of cutaneous and systemic manifestations.

Fibril protein is the building block for amyloid. Amyloid precursors are composed of glycoproteins and glycosaminoglycans. Initially soluble, protein precursors form an aggregate and pass through a polymerization process, followed by fibril formation. Once deposited in tissues, the fibril becomes insoluble, thus giving rise to the amyloidosis pathway.

Cutaneous biopsies are commonly examined with the hematoxylin and eosin stain, where the amyloid appears as distinct amorphous, eosinophilic, fissured masses. Confirmation of amyloid protein is achieved with a Congo red stain, as well as thioflavin, methyl violet, Periodic acid-Schiff, sirius red, pagoda red, and dylon staining. With Congo red staining, amyloid deposition appears orange-red under light microscopy, and green birefringence is identified under polarized light. This staining pattern is largely due to the cross-β-pleated sheet configuration of amyloid.1–5

**PRIMARY SYSTEMIC AMYLOIDOSIS**

In primary systemic amyloidosis (PSA), the fibrils are composed of amyloid light (AL) proteins consisting of immunoglobin light chains, usually kappa or lambda subtype. Amyloid precursor proteins are also distributed via the circulation to distant tissue sites, where they are deposited in internal organs.4 Transformation and subsequent deposition of amyloid fibrils in organs leads to pressure atrophy and abnormal functioning.2,5

PSA is commonly associated with plasma cell dyscrasias and abnormal immunoglobin light chain proteins found in diseases such as multiple myeloma and Waldenström macroglobulinemia. Other associations have been reported with Alzheimer’s disease, diabetes, and trauma.2,5 Up to 25% of patients exhibit some kind of skin involvement presenting as waxy, translucent or purpuric papules, nodules, or plaques. Infiltration typically occurs on the face, neck, scalp, and anogenital region, but it can also occur on the palms and fingertips. Scleroderma-appearing lesions on the scalp, hemorrhagic blisters, and other bullous lesions can be an initial presentation.

Systemic presentation varies depending upon the organ involvement. Signs and symptoms include edema, proteinuria/
nephrotic syndrome, congestive heart failure, hepatomegaly, neuropathies, postural hypotension, decrease in gastrointestinal motility, pleural effusions, and impotence. Infiltration of amyloid into blood vessel walls causes a classical presentation of patients who develop periorbital purpura, termed raccoon eyes, following coughing, pinching or rubbing the skin, Valsalva maneuver, or post-biopsy. Deposition of amyloid within joints and surrounding structures is thought to cause arthropathies, such as carpal tunnel syndrome. Infiltration also occurs within muscle, causing a pseudohypertrophy. Infiltration of amyloid deposits in the deltoid muscle or synovial membranes, along with visible enlargement of the anterior shoulder due to fluid in the glenohumeral joint, is known as the shoulder pad sign. A fan-shaped displacement of the teeth is noted with macroglossia. Patients presenting with bilateral carpal tunnel syndrome together with the presence of macroglossia should prompt an investigation for amyloidosis.

Diagnosis of PSA is confirmed via biopsy. Biopsies are directed at the organ of involvement. Many clinicians agree that abdominal fat aspiration and rectal biopsy are the initial methods of confirming diagnosis and are considered the standard of care. Biopsies of the liver, kidney, and lung are recommended for suspected organ involvement. Scintigraphy with radioisotope-labeled serum amyloid P component (SAP) has been used to identify the dissemination of amyloid within body tissue and provide an estimate of the total body deposits of fibril proteins. This estimation can provide the clinician with important information about expected treatment measures and where treatment should be directed. With a sensitivity of 90% and a specificity of 93% for both serum amyloid A (SAA) and AL protein, the value should be directed. With a sensitivity of 90% and a specificity of 93% for both serum amyloid A (SAA) and AL protein, the value should be directed. With a sensitivity of 90% and a specificity of 93% for both serum amyloid A (SAA) and AL protein, the value should be directed. With a sensitivity of 90% and a specificity of 93% for both serum amyloid A (SAA) and AL protein, the value should be directed.

Current recommendations for treatment are based on a patient’s eligibility for hematopoietic cell transplant (HCT). Patients who do not meet criteria for HCT are typically treated with melphalan and dexamethasone or in clinical trials. Other options include thalidomide, cyclophosphamide, or lenalidomide. Clinical evidence is weak regarding the most effective method of treatment.

SECONDARY SYSTEMIC AMYLOIDOSIS

Secondary systemic amyloidosis (SSA) is characterized by the deposition of SA proteins within tissue. SSA protein is considered an acute-phase reactant. Acute-phase reactants provide a homeostatic defense mechanism to many processes, including infection, trauma, infarction, inflammatory arthritis, and various neoplasms. SSA is generally a result of a chronic inflammatory condition or infection. Examples include rheumatoid arthritis, ankylosing spondylitis, tuberculosis, scleroderma, leprosy, dermatomyositis, systemic lupus, psoriasis, and dystrophic epidermolysis bullosa. Deposition of amyloid proteins occurs in the heart, liver, and kidneys and is rarely observed cutaneously. Therapy in these patients is directed at controlling the underlying inflammatory condition or infectious process. Improvements have been noted with tumor necrosis factor α antagonists, thus decreasing the production of acute-phase reactants and proteinuria.

OTHER FORMS OF SYSTEMIC AMYLOIDOSIS

Hemodialysis-associated amyloidosis is related to decreased excretion of β2-microglobulin in long-term dialysis patients and amyloid protein formation. By unknown mechanisms, increased blood β2-microglobulin leads to deposition of amyloid fibrils in the synovial membranes, leading to the development of bone cysts, carpal tunnel syndrome, and destructive spondyloarthropathies. Heredofamilial amyloidosis syndromes are autosomal-dominant and associated with a mutation in the transthyretin gene on chromosome 18. Paresthesias, carpal tunnel syndrome, trophic ulcers, impotence, and hypotension can be observed clinically. Effective treatment for removal of transthyretin protein is orthotopic liver transplant. Hemodialysis conditions known to have the presence of amyloid fibrils are Muckle-Wells syndrome, familial Mediterranean fever and multiple endocrine neoplasia (MEN) Type IIa, or Sipple syndrome. Although these conditions lead to forms of amyloidosis, the derivation of the amyloid fibrils differs.

PRIMARY CUTANEOUS AMYLOIDOSIS

Primary cutaneous amyloidosis (PCA) is associated with deposition of amyloid in the epidermis and dermis, which is derived from epidermal keratinocytes or plasma cells. The exact mechanism is yet to be fully understood. Several proposals have been made, including genetic predisposition, friction, trauma, Epstein-Barr virus, and environmental factors.
cutaneous amyloidosis is subdivided into 3 variants: macular, lichen, and nodular amyloidosis (Table).

**MACULAR AMYLOIDOSIS**

Amyloid deposits found in macular cutaneous amyloidosis (MCA) are limited to the papillary dermis. Amyloid fibrils are keratin-derived from local keratinocytes. Altered keratin within the tissues is used as a source by the sulfhydryl-containing amyloid deposits. The sulfhydryl group on the amyloid allows the cytokeratin to become basic in nature, thus avoiding rapid degradation. This is an important distinguishing feature, because the typically acidic cytokeratins undergo rapid degradation. Frequently termed friction amyloidosis due to its often pruritic nature, MCA often presents in early adulthood. It is believed to affect women more than men. Hyperpigmented lesions appearing in confluent or “rippled” patterns is most commonly seen on the extensor surfaces of the extremities and the upper back/scapula. When present on the upper back or scapular area, it is often associated with notalgia paresthetica. Notalgia paresthetica is a form of sensory neuropathy consisting of localized pruritus affecting the interscapular area, especially the T2-T6 dermatomes. Spinal nerve impingement from corresponding degenerative changes in the spine is thought to be a contributing cause.1,2,7

<table>
<thead>
<tr>
<th><strong>LICHEN AMYLOIDOSIS</strong></th>
</tr>
</thead>
</table>
| Lichen cutaneous amyloidosis (LCA) differs in that deposition of amyloid may extend beyond the upper dermal layer. The epidermal layer often becomes hyperkeratotic, acanthotic with a sparse perivascular lymphohistiocytic infiltrate. Amyloid fibrils in lichen amyloidosis are keratin-derived from cutaneous keratinocytes. Considered to be the most common form of PCA, LCA is typically seen on the extensor surface of the extremities, in particular the lower anterior limbs. Initially, LCA presents as discrete, firm, skin-colored papules with scaling that later coalesce into persistent pruritic plaques with a rippled pattern. The lesions are more often observed unilaterally than bilaterally.7,18

<table>
<thead>
<tr>
<th><strong>LICHEN AND MACULAR AMYLOIDOSIS OVERLAP</strong></th>
</tr>
</thead>
</table>
| Both MCA and LCA have an association with connective tissue disorders such as scleroderma, dermatomyositis, and systemic lupus erythematosus, largely in part to their origination from keratin filament degeneration.6 Due to the nature of amyloid deposition, anti-keratin antibodies such as CK1–8 (AE3) and CK5/6/18 (LP34) can be used to detect both MCA and LCA. The cytokeratins detected in amyloid deposits are usually of the basic type (type II). This may be because, in amyloidogenesis, acidic cytokeratins are degraded faster than basic types. CK5 is the classic antibody used for amyloid cytokeratin staining. Importantly, anti-keratin antibodies are absent in nodular cutaneous amyloidosis (NCA) because they are derived from cutaneous plasma cell clones, thus making another distinguishing factor in proper diagnosis.18,26

Treatment of both macular and lichen amyloidosis is directed toward eliminating the trigger of pruritus. Pruritic relief can be achieved with antihistamines and topical dimethyl sulfoxide.28 Treatment with UV-B light can also provide symptomatic relief. Improvements have been documented with pulsed dye laser therapy, resulting in a favorable decrease in local pruritus and cutaneous plaque eruptions.25,30

**NODULAR CUTANEOUS AMYLOIDOSIS**

Characterized by amyloid deposits in the dermis, subcutis, and within blood vessel walls, NCA is the rarest form of PCA. Histologically, a perivascular infiltrate of plasma cells is seen with the identification of immunoglobin light chains. Local plasma cell clones produce the immunoglobulin light chains, therefore leading to AL proteins that are later deposited in the dermis and subcutis.25,31 Immunohistochemistry specifically demonstrates the presence of immunoglobin lambda and/or kappa light chains, with lambda predominating, and is negative for cytokeratin epitopes. In contrast to PSA, where immunoglobin light chains are noted in the circulation, usually only local cutaneous production is seen with NCA; therefore, NCA may be considered a localized plasmacytoma or plasma cell dyscrasia.18 Historically, women were thought to be more predisposed than men to the lesions of NCA; however, recent studies indicate that there is no sex predilection. Age of presentation of cutaneous lesions varies from 20 to 87 years, with a mean of 55 years.32,33 Clinical presentation is a single yellow-brown nodule or plaque. The surface is often shiny with well-defined borders (Figure 2). Occasional atrophic or bullous forms have been noted. Lesions are frequently identified on acral surfaces, legs, head, trunk, arms, and genitalia.32–34 Clinical and histologic findings help distinguish NCA from PSA and myeloma-associated forms of amyloidosis.35,36 The likelihood of progression of NCA to systemic disease has yet to reach a consensus. In 1970, Brownstein and Helwig studied several cases of PCA. Of the 39 cases, 10 cases were of the nodular type. Five of the 10 patients with NCA developed a systemic disease; a
progression rate of 50%. Detailed clinical data regarding these 10 patients is limited, and newer studies are predicting a much lower progression. A long-term follow-up study was performed in 2001. The investigators presented data from patients with PCA treated between 1968 an 1999. They estimated the rate of progression to be 7%, which is far less than the traditionally quoted rate of 50.36

There remains no question that patients with NCA should continue to undergo rigorous testing for evaluation of systemic progression.34,35 Until subsequent studies prove that progression to systemic disease is a certainty, it remains important to continually screen patients for development of systemic disease at regular intervals. Follow-up with a complete blood cell count, comprehensive metabolic panel, erythrocyte sedimentation rate, serum protein electrophoresis, and urinalysis with urine protein electrophoresis should be performed at least annually. Further skin biopsies with hematoxylin-eosin staining followed by Congo red staining should be performed on any new cutaneous lesions that develop. Fine needle aspirate of the abdominal fat pad, rectal tissue biopsy, immunohistochemical analysis, and x-ray crystallography are suggestions for further analysis of progression to systemic forms of amyloidosis.31,35–37 Treatment of NCA varies by opinion and treatment method.

In part, due to the extension of amyloid masses beyond the subcutaneous fat with deposition in blood vessels, choosing a therapy with a substantial positive outcome can be difficult.19 Treatments include cryotherapy, electrodesiccation, curettage, dermabrasion, etretinate, carbon dioxide (CO2) laser therapy, and excision. A case of microdermabrasion treatment performed on a lesion of nodular amyloidosis after surgical debulking was reported. Follow-up 26 months later reported no clinical evidence of recurrence.38,39 In 1986, the first case of CO2 laser treatment was described with good cosmetic results.39 Although cosmetic results were reported to be excellent, achieving homeostasis due to highly friable tissue proved to be difficult. Excessive bleeding is thought to be largely due to amyloid deposition within blood vessel walls leading to friability during the procedure.

The results from pulsed dye laser (PDL) treatment remain speculative. Ease of application with minimal postoperative course is a positive benefit. Ease of application with minimal postoperative course is a positive benefit. Several treatments are required, however, leading to an increased expense to the patient. Investigators reported clinical improvement in size, color, and pliability of nodules after treatment with PDL. Even though a decrease in local inflammation was achieved, minimal histologic change was noted with the dermal deposition of amyloid.40 Of the numerous treatment modalities available, improvement is inconsistent. Patients should be aware of available treatment options and the speculative nature of results until further studies can be evaluated.

SECONDARY CUTANEOUS AMYLOIDOSIS

Secondary cutaneous amyloidosis (SCA) is usually associated with tumors of epidermal origin. The homogenous amyloid deposits are keratin-derived. Deposits may be identified within cutaneous tumors such as dermatofibromas, basal cell carcinomas, intradermal melanocytic nevi, seborrheic keratoses, pilomatrixcomas, sweat gland tumors, Bowen disease, porokeratosis, and trichoepitheliomas. SCA is generally considered to be an incidental finding in these skin tumors and does not affect prognosis and poses no additional threat or risk to the patient.18

CONCLUSIONS

The classification of amyloidosis has importance for understanding the disease. Systemic and cutaneous forms of amyloidosis exist, and in each of these types are both primary and secondary forms. In each classification of amyloidosis, the derivation of the amyloid fibrils differs. Recognizing the amyloid protein forms associated with each specific type of amyloidosis is significant, as certain types can progress to significant comorbidities or even mortality. The nodular form of PCA continues to be the rarest type of PCA. A recent study claiming the rate of progression from the nodular type to a systemic amyloidosis may be <7% has raised questions regarding current screening and follow-up recommendations. At present, there are minimal and inconsistent data regarding the nature of progression of nodular amyloidosis to a systemic form. Close monitoring of clinical symptoms and biopsy of new lesions remain important for early identification of disease and detection of progression. Treatment should not only target cosmetic improvements, but also the eradication of amyloid deposits within the tissue to prevent recurrence and potential vascular spread.

Figure 2. Lesions of nodular cutaneous amyloidosis.
REFERENCES

SELF-TEST REVIEW QUESTIONS

W. Clark Lambert, MD, PhD, Section Editor

Instructions: For each of the following numbered questions, choose the appropriate lettered response(s). Unless directed to choose only one lettered response, all, some, or none of the responses may be correct.

1) Secondary cutaneous amyloidosis may result from amyloid deposits derived from: (Answer as many as apply.)
   a. basal cell carcinomas.
   b. Bowen’s disease.
   c. dermatofibromas.
   d. intradermal melanocytic nevi.
   e. pilomatricomas.
   f. porokeratoses.
   g. seborrheic keratoses.
   h. sweat gland hamartomas.
   i. trichoepitheliomas.

2) Nodular primary cutaneous amyloidosis progresses to primary systemic amyloidosis in approximately: (Choose the single best response.)
   a. 99% of cases.
   b. 95% of cases.
   c. 90% of cases.
   d. 75% of cases.
   e. 50% or less of cases.

3) Notalgia paresthetica is a form of sensory neuropathy consisting of localized pruritus primarily affecting the: (Choose the single best response.)
   a. extensor surfaces of the hands and feet.
   b. extensor surfaces of the upper extremities.
   c. interscapular area.
   d. intertriginous areas.
   e. perineum.

4) In which of the following types of amyloidosis are the amyloid deposits usually derived from acidic cytokeratin derived from keratinocytes? (Answer as many as apply.)
   a. Lichenoid primary cutaneous amyloidosis
   b. Macular primary cutaneous amyloidosis
   c. Nodular primary cutaneous amyloidosis
   d. Secondary cutaneous amyloidosis
   e. Primary systemic amyloidosis
   f. Secondary systemic amyloidosis

5) In which of the following types of amyloidosis are the amyloid deposits usually derived from basic cytokeratin derived from keratinocytes? (Answer as many as apply.)
   a. Lichenoid primary cutaneous amyloidosis
   b. Macular primary cutaneous amyloidosis
   c. Nodular primary cutaneous amyloidosis
   d. Secondary cutaneous amyloidosis
   e. Primary systemic amyloidosis
   f. Secondary systemic amyloidosis

ANSWERS TO SELF-TEST REVIEW QUESTIONS:

1. a, b, c, d, e, f, i, 2. e, 3. c, 4. a, b, c, d, e, f, i, 5. a, b, d

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A New Tretinoin Therapy
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In a contribution entitled “Childhood Nail Diseases,” it was shown that, in the first few years of life, nails tend to be fragile. In addition, transverse lamellar changes in the free edge of the nail are also common findings in the first few years of childhood. These changes are most frequently seen on the big toe and thumb, with thumb-sucking being an exacerbating factor.

It was shown that 92% of healthy infants between 8 and 9 weeks of age had a single transverse depression (Beau’s line) of the fingernails. The depression typically occupies the proximal portion of the nail at 4 weeks of age, and gradually extends to cover the distal edge by 14 weeks. Accordingly, a small degree of onycholysis, deviation from the midline, and distal thickening of onycholysis are transient features, usually lasting no more than 24 months. The peri-ungual skin may peel without obvious dermatitis/inflammation; however, involvement of the toenail is rare. A school survey of 160 healthy school children aged between 5 and 14 years found nail changes such as “herringbone nails,” nail biting, lamellar dystrophy, koilonychia, malalignment, and nail thickening.

Herringbone nails are also referred to as Chevron nails. A debate has been raised regarding the condition’s pathogenesis. It is unclear whether it is a pattern of the midline or one with a series of different central axes. Its clinical significance is also uncertain. In another interesting study from the United Kingdom, it was found that 36% of children aged 5 years, 57% of children aged 12 years, and 31% of children aged 16 years bit their nails. The study also recorded complications such as paronychia, growth of spurs into lateral nail folds, and distal ingrown nails with inflammation.

Koilonychia and lamellar dystrophy were observed in the halux, while lamellar dystrophy alone was seen in the fingers. Koilonychia is defined as “a concave dorsal surface to the nail, sufficient to hold a drop or more of water”; however, this test is not often feasible in children, and the condition usually resolves by 10 years of age.

To a great extent, onychomycosis in childhood resembles that in adults, although superficial white onychomycosis was found to be more common in children, and involvement of multiple digits was rare. When present in children, a positive family history could be regarded as a factor in transmission as well as susceptibility to onychomycosis. Severe onychomycosis in children should raise concerns with respect to human immunodeficiency virus (HIV), mucocutaneous candidiosis, and other forms of immunosuppression.

There are reports of multiple patterns of leukonychia in children. Leukonychia is classified into complete or total, patchy or partial, and punctate leukonychia.

The histologic changes represent waves of nail production, during which the nail plate contains a greater number of nucleated cells that, in turn, might be associated with lack of cohesion between the corneocytes. This production alters the reflective properties of the nail so that light is reflected off the imperfections within the nail plate rather than transmitted to and from the nail bed. Such leukonychia is attributed to mild or acute trauma, autoimmunity, and alopecia areata. At times, there is no specific underlying cause, and leukonychia becomes less frequent with age. Some major structural genodermatoses might...
present with nail manifestations, where the diagnosis usually evolves from a specific constellation of features, of which nail involvement is only a part. Occasionally, nail problems could either be the only clue for the diagnosis or regarded as the only manifestation. The pattern of odd nails in infancy may range from thickened toenails, distortion of the shape, or subungual hyperkeratosis. Pachyonychia congenita (PC) may be suspected when such a pattern is seen in multiple nails. Eliciting a detailed family history and attention to other possible manifestations of the disease may be required to make a precise diagnosis, which could take years to evolve. Analysis of putative mutations on genes for keratins 6a and 16 for PC-1 and keratins 6b and 17 for PC-2 will confirm the diagnosis.11

The variety of epidermolysis bullosa could present with anything between normal nails to complete loss and interdigital fusion. In occult epidermolysis bullosa, often the only clue is in the family history of acquired childhood nail dystrophy, mainly of the big toe. While, in dystrophic epidermolysis bullosa, abnormalities of collagen-VII make nail attachments vulnerable to mild trauma, and the nail dystrophy of the big toe could be regarded as the only sign. Recurrent nail loss leading to scarring and nail dystrophy might point to epidermolysis bullosa, but a history of occasional blistering of the palms and soles in humid weather might be indicative. Since blistering is not always present, the final diagnosis may rest on mutational analysis.12

A longitudinal dark streak, melanonychia (Figure 1), has always been regarded as the reflection of a dysplastic melanocytic lesion in the nail matrix, and such pigmented streaks are likely to resolve spontaneously.13 Dysplastic changes, however, could not be identified by other studies.14,15 Although dysplastic histology may not be revealed in younger patients (younger than 12), the situation might change in early adulthood. A significant number of children diagnosed with subungual melanoma could have had a long-standing melanonychia.14

Viral warts are the most common form of periungual tumors in children and are relatively easy to diagnose. They have no association with any other underlying dermatologic disorders and may spread easily to other fingers, because children often bite their nails (Figure 2). A review of congenital hypertrophy of the lateral nail folds of the hallux16 with clinical pictures and follow-up in 7 cases revealed that ingrown toenails, in the first 2 years of life, could be associated with distal abnormalities. This problem could be a pattern in the first months of life, when the nail never grew over digit pulp.

The nail in infancy is soft and flexed upward. As it grows over the soft tissues, there is a mild koilonychia, which is accentuated when the child starts crawling and walking, due to a downward force working on the tips of the toes.

Ingrown nails may occur in adolescents, where the classic patterns of lateral growth are seen. A combination of factors such as poorly fitting footwear, participation in kicking or running sports, sweaty feet, and a big bulbous great toe may contribute to it. The big and bulbous great toe, with prominent soft tissue, may trigger it and the nail may have pronounced downward curvature at the lateral margin. The risk may increase with cutting the nail short and allowing the free edge of the nail to become lost in the nail fold. Various studies found no associated dermatologic causes for ingrown nails and malalignment, irrespective of their occurrence either in children, adolescents, or adults. Malalignment may start early and, in its common mild forms, could resolve on its own.17,18 It presents as a slight shift in the long axis of the big toenail in comparison with the underlying distal phalanx, with no obvious alterations of the nail plate.

At advanced stages, the nail plate becomes thick and yellow, with marked transverse ridging, increased transverse curvature, and viable loss of attachment to the nail bed. The nail might become triangular, with the apex lying medial to the midline distally. Once the nail looses its attachment, the prognosis is worse, the
nail being prone to catching, with upward lifting and further loss of attachment. Once loss of attachment becomes chronic, it becomes irreversible.17,18

**NAIL ABNORMALITIES INDUCED BY COSMETICS**

In one study, investigators19 addressed the advent of cosmetics on nail health. They focused on the nail plate and the dead part of the nail unit. Detailed accounts of different procedures such as acrylic painting, application of preformed plastic tips, metal nail sculptures, filing, and polishing were described.20 Nail artists as well as patients consider eponychium unsightly and encourage various means of removal, focusing on the advantage of “even application of nail lacquer, acrylic monomer, and gel films.” Roughening the nail plate with mechanical or electric files, using dehydrators, applying cyanoacrylate glue, positioning metal or plastic sculptures, excessive pressure with glue to allow fixation, and finally shaping and polishing are procedures that, if repeated, could cause permanent damage by mechanical trauma, irritants, and allergic reactions.20

Acute bacterial (Figure 3) and chronic fungal paronychia, candidosis of nails, onycholysis, onychoschizia (lamellar splitting/dystrophy), and brittle nails are all such cosmetic-induced complications that may be diagnosed by carefully eliciting the history and observing the nails minutely.19

**NAIL ABNORMALITIES PROVOKED BY DRUGS**

Most nail changes caused by drugs are the outcome of acute toxicity to the nail epithelia, but other mechanisms could also be involved. Drug-induced nail changes usually involve several or all 20 nails and appear in temporal correlation with drug intake. Some nail changes could be asymptomatic and may cause only cosmetic problems, whereas others may cause pain and discomfort to the extent of impairment of manual activities or even amputation. These changes are usually transient, and may disappear with drug withdrawal. The diagnosis is likely to be complicated by the slow rate of growth of the nail plate, in which nail changes may be delayed, and because symptoms often improve or resolve without drug withdrawal or rechallenge may be negative.

Paronychia and pseudopyogenic granulomas of the fingernails and toenails may be observed in patients treated with lamivudine, azidothymidine (AZT), and indinavir.21,22 Indinavir may produce cutaneous side effects such as tissue granulation, with the formation of painful bleeding nodules located either in the proximal or lateral nail folds or even in the nail bed. The exact pathogenesis remains unclear; however, it is suggested that indinavir might activate angiogenic factors. The same side effects are also seen with retinoids, probably because the HIV-1 protease catalytic site and the retinoid cellular receptor CRABP have structural analogies.23

A decreased rate of nail growth has been observed in patients treated with AZT, which may be explained by a decreased mitotic activity of the nail matrix keratinocytes. AZT could also be responsible for different patterns of nail pigmentation; blue-brown nail discoloration, and transverse/longitudinal bands. Apart from this, ganciclovir is incriminated in causing splinter hemorrhages.24

Beau’s lines and onychomadesis are frequent in the course of chemotherapy, and they are typical signs of acute and/or severe toxicity to the nail matrix keratinization, with transient decrease or arrest in the nail plate production. The depth of depression indicates the degree of damage, and the width indicates the duration of the insult. A drug should always be suspected when these changes affect all nails at the same level. Superficial nail fragility, elkonyxis, results from a toxic effect on the proximal nail matrix, whereas diffuse damage to the nail matrix gives rise to a thin, brittle nail plate. Onychomadesis results from acute toxicity to the nail bed epithelium, with loss of nail plate and nail bed adhesion. True transverse leukonychia is a sign of transient impairment of the distal nail matrix keratinocytes, resulting in the persistence of cell nuclei in the nail plate. One or several parallel transverse bands affect all nails at the same level and they move along with the nail distally. Apparent leukonychia appears as transverse, parallel, pale white bands (Muehrcke’s lines), resulting from nail bed damage. It could be distinguished from true leukonychia because it fades with digital compression and does not migrate with nail growth.25
Paronychia and pyogenic granuloma are also associated with cetuximab/C225 (anti-epidermal growth factor antibody) and gefitinib (epidermal growth factor receptor tyrosine kinase inhibitor).26–28

Cancer chemotherapeutic agents, especially the taxanes, may cause subungual hemorrhages and hematoma as a consequence of thrombocytopenia or extravasation of blood. They are dose-related and cease after drug withdrawal.25

Chemotherapeutic agents might also activate clusters of nail matrix melanocytes to produce melanin, giving rise to melanonychia. A diffuse activation of nail matrix melanocytes may produce pigmentation of the entire nail plate. Clofazimine might produce a dark brown pigmentation of the nail plate, where the drug is stored.29

Subungual hyperkeratosis, onycholysis, and melanonychia are other well-known untoward effects of drugs. Patients undergoing therapy with psoralens plus UV-A (PUVA) radiation might develop photo-onycholysis, in which the detachment of the nail plate or nail bed might be caused by a photo-mediated toxic or allergic effect of the drug, where the thumbs are usually spared.30

Beau’s lines, onychomadesis, and true transverse leukonychia are consequences of nail matrix damage caused by the drug. Nail fragility, especially lamellar onychoschizia, may occur during etretinate therapy. Retinoids are also associated with decreased nail growth.31

Tetracycline, doxycycline, and minocycline are also known to produce nail changes, with tetracycline producing yellow lunulae fluorescent under Wood’s lamp, minocycline causing blue-gray pigmentation of the proximal nail bed, and doxycycline causing photo-onycholysis.32,33

**NAIL BIOPSY**

Appraisal of morphologic changes in the nail is paramount, for it may provide a glimpse into the provisional clinical diagnosis of cutaneous disorders. It may require confirmation with microscopic pathology. Biopsy of a representative nail lesion is therefore a useful adjunct. Current procedures, namely longitudinal nail, punch, and scalpel wedge biopsy may achieve effective results. The biopsy specimen is fixed by keeping it overnight in 10% buffered formalin solution, followed by placing the specimen in 3% phenol for 5 days to soften the nail plates to facilitate cutting serial sections. The sections are subjected to hematoxylin and eosin and periodic acid–Schiff stain.34–39

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**Table. Nail Structure Components for Prospective Case/Original Study**

<table>
<thead>
<tr>
<th>Development</th>
<th>Shape</th>
<th>Attachment</th>
<th>Surface</th>
<th>Color</th>
<th>Infections of the Nail Unit</th>
<th>Iatrogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonychia</td>
<td>Clubbing</td>
<td>Onycholy-sis/salmon patches/”oil drop” sign</td>
<td>Pitting (gross and fine)</td>
<td>Leukonychia (true/apparent/punctate)</td>
<td>Acute paronychia/chronic paronychia</td>
<td>Drug-induced</td>
</tr>
<tr>
<td>Nail patella syndrome</td>
<td>Koilonychia</td>
<td>Pterygium</td>
<td>Transverse grooves/Beau’s lines</td>
<td>Terry’s nail/half-and-half nails/Neapolitan nails Muehrcke’s lines</td>
<td>Onychomycoses</td>
<td>“Fashion statement” – induced</td>
</tr>
<tr>
<td>Pachyonychia congenita</td>
<td>Pincer/trumpet nail</td>
<td>Ventr al pterygium/pterygium inversum unguis</td>
<td>Longitudinal grooves/onychon- rhexis/median canaliform dystrophy of Heller</td>
<td>Yellow nail syndrome</td>
<td>Subungual wart</td>
<td></td>
</tr>
<tr>
<td>Macronychia</td>
<td>Subungual hyperkeratosis</td>
<td>Trachyonychia/rough nails/sand-blasted nails</td>
<td>Red lunulae</td>
<td>Herpetic whitlow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronychia</td>
<td>Thickened nails</td>
<td>Beading and ridging</td>
<td>Erythronychia/splinter hemorrhage</td>
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</tr>
<tr>
<td>Anonychia</td>
<td>Onychomadesis</td>
<td>Brittle nails</td>
<td>Onychoschizia/la- mellar splitting Brittle nails</td>
<td></td>
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</tr>
</tbody>
</table>

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SKINmed. 2011;9:103–107
CONCLUSIONS

It is important to observe the abnormalities of the nail, including its development, shape, attachment, surface, and color (Table). The clinical assessment of abrasions of the nail should be gathered to form a handy reference point, and a prospective case/original study should take note of these changes to facilitate the diagnosis and to establish a uniform pattern of nail disease.

REFERENCES

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Nanoparticles are defined as single particles with a diameter <100 nm; agglomerates that tend to form in cosmetic formulations often have a larger particle size.1,2 Nanoparticles in the form of a nanoemulsion and microscopic vesicles are formulated in sunscreen products as titanium dioxide (TiO2) or zinc oxide (ZnO) nanoparticles. ZnO and TiO2 have been used in sunscreens for many years. They are known to filter UV-A and UV-B radiation, providing broader protection compared with other sunscreen agents. Nanosized versions of TiO2 and ZnO minimize the undesirable white color and sticky feel of the materials. Nanosized TiO2 and ZnO have been used in sun care products since the early 1990s.3 Initially, nanoparticle safety focused on inhalation of the particles. More recent concern is the ability of nanoparticles to be absorbed into skin cells. If nanoparticles enter the skin, a possibility exists for the material to circulate to other tissues and, ultimately, an immunologic reaction might result. Another concern is the possible interaction with sunlight to increase the risk of damage to the cells.3 Since products incorporating nanomaterials are currently not regulated and the particle size may not be indicated in the ingredient listing, consumers may be unaware that they are using a product with nanotechnology.

ARE NANOPARTICLES ABSORBED INTO SKIN?

Sunscreens contain insoluble, mineral-based materials whose performance depends on particle size. Particles such as TiO2 reflect and scatter UV light most efficiently at a size of 60 nm to 120 nm.4 Sunscreen-grade nanosized TiO2 particles range from an ultrafine particle to form with a primary diameter of 15 nm, which will often form stable larger aggregates. ZnO is generally used in the form of particles at a size of 30 nm to 200 nm.4 The results of various published studies regarding penetration of TiO2 in human skin were summarized in a report issued by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP). These studies suggest that micro- and nanosized TiO2 particles remain on the skin surface or outer layers of the stratum corneum. Primary particle size of materials tested was in the range of 10 nm to 100 nm.4 Other studies have also shown that ZnO does not penetrate skin.4

CYTOTOXICITY AND FORMATION OF REACTIVE OXYGEN SPECIES

Nanoparticles of TiO2 were reported to induce cytotoxicity and formation of reactive oxygen species (ROS) following UV illumination to animal cell lines, including human lines. Coating TiO2 was found to minimize the reactivity and maintain the ability to absorb UV radiation.5 In 2006, the Australian Therapeutic Goods Administration conducted a review of scientific literature addressing ROS formation of nanosized ZnO and TiO2 in skin. It was concluded from evidence from isolated cell experiments that both materials can induce free radical formation in the presence of light and that this may damage cells.3 This would be of concern only if the nanosized ZnO and TiO2 penetrated skin cells. The weight of evidence is that they remain on the surface of the skin and the outer layer of the stratum corneum.3 A study conducted using Chinese hamster ovary cells exposed to UV irradiation found that various forms of TiO2 coated and uncoated, did not result in an increase of chromosomal aberration frequency.6

CURRENT STATUS OF NANOTECHNOLOGY IN COSMETIC PRODUCTS

As recently as July 6, 2010, the Office of Science and Technology Policy announced in the US Federal Register a notice for...
input from nanotechnology stakeholders to provide research priorities, investment, coordination, partnerships, evaluation, and policy to enhance the value of the National Nanotechnology Initiative. Literally hundreds of documents are now available online discussing nanotechnology.7 Other studies conducted by different investigators using nuclear microscopy techniques have confirmed that nanosized TiO₂ and ZnO do not penetrate skin.³ Australian sources estimate that 70% of titanium sunscreens and 30% of zinc sunscreens are formulated with nanoparticles.³ In the United States there is no labeling requirement, and commercialization of products containing nanoparticles are at the discretion of the manufacturer. A 2006 publication estimates that 1000 tons of nanoparticulate materials are used in sunscreen products globally.⁵

CONCLUSIONS
General consensus is that nanoparticles of TiO₂ and ZnO as used in cosmetic products are safe. Safety-related investigations continue to be conducted on a global basis to address speculation regarding the ability of nanoparticles in cosmetics to penetrate skin. There is no universal definition of a nanoparticle, confounding issues that nanoparticles often aggregate in cosmetic emulsions to a larger-than-nanoparticle size; further, there is no single agreed method to measure nanoparticles and the results are technique dependant.

REFERENCES
The biopsy and diagnosis of dermatoses can be plagued with many obstacles. These may occur during the removal, orientation, labeling, analysis, or diagnosis stages. The procedures involved in biopsy fixation and tissue processing can result in alterations of the size, shape, and structure of specimens, which can mislead the pathologist and ultimately lead to misdiagnosis. As the microscopic form of a processed specimen is essentially a snapshot of what is going on in the body, it is critical that the removal of the specimen does not bring about more distortion than necessary.

Often, poor biopsy techniques result in misrepresentation of the specimen and poor histologic examination. For example, poor injection and misguided placement of the injection of local anesthetic can result in missing the diagnosis of mastocytosis. Because epinephrine and local disruption of tissue may result in mast cell degranulation, their presence may go undetected under standard staining techniques. This error can be avoided by simply modifying biopsy techniques, such as injecting local anesthetic without epinephrine adjacent to, rather than directly into, the lesion. A metachromatic stain, such as toluidine blue, and a CD117 (c-kit) immunohistochemical assay may be required to confirm accurately the presence of increased mast cells and their excess activity.

**BACKGROUND**

Mast cells are bone marrow–derived CD34+ granulocytes found in peripheral tissues. They have central roles in inflammatory and immediate allergic reactions and wound healing and the immune system’s defense against foreign pathogens. Typically, mast cells surround small blood vessels and nerves in the dermis. They are approximately 9 μm to 16 μm in diameter and have a central, round to ovoid dark-staining nucleus. Characteristically, mast cells contain small, cytoplasmic granules that carry preformed mediators, such as heparin, histamine, and various cytokines. These contents are released on degranulation of the cells, which may cause symptoms such as flushing, urticaria, diarrhea, abdominal pain, headache, dyspnea, syncope, and palpitations.

It is also important to note that mast cells express a cell-surface tyrosine kinase receptor, c-kit. Its ligand, stem cell factor, appears to be important for mast cell proliferation and differentiation.

Mast cells can be identified using an immunohistochemical assay, targeting c-kit. In addition, mast cells may be identified using toluidine blue, which targets heparin in the granules. β-tryptase, a neural serine protease, serves as a marker of mast cell activation. It is the most abundant mediator within its granules and its release is a characteristic feature of mast cell degranulation. As serum β-tryptase concentration is increased in mast cell activation, a patient’s total serum tryptase level may be measured and results above 20 ng/mL serve as a minor criterion for the diagnosis of systemic mastocytosis.

Mastocytosis is a group of rare disorders involving the uncontrolled proliferation of mast cells and its precursors. It is divided into 2 categories: cutaneous and systemic. Generalized eruption, in both the pediatric and adult populations, represents the most common form of mastocytosis. Urticaria pigmentosa is the most common childhood manifestation of cutaneous mastocytosis, present in 80% of affected individuals. It presents with yellowish brown to yellowish red, urticarial and pruritic papules or nodules. These lesions are usually oval to round and range between 5 mm and 15 mm in diameter. When an urticaria pigmentosa lesion is rubbed or irritated, an erythematous flare is induced; this is known as Darier’s sign. The generalized eruption that classifies the most common adult type of mastocytosis presents as reddish purple or brown macules, papules, or nodules, which typically resemble common nevi. These lesions may also urticate upon rubbing. Confirmation of the diagnosis is obtained on biopsy of the lesion with the demonstration of dermal mast cell aggregates.
Systemic mastocytosis is more severe and is diagnosed by finding dense infiltrates of mast cells in bone marrow or other extracutaneous tissues. A mutation in the c-kit receptor gene has been noted to lead to uncontrolled stimulation of the receptor in cases of adult-onset systemic mastocytosis.

Histopathologically, a typical skin lesion shows a dense dermal aggregate of mast cells with a rich basophilic cytoplasm. The specimen is often stained with toluidine blue, which identifies heparin found within the cytoplasmic granules (Figure 1). The hematoxylin and eosin (H&E) stain, however, does not readily reveal these granules; therefore, H&E staining is not a reliable or specific method for identifying the presence or degranulation of mast cells. Other histochemical and immunohistochemical stains, in addition to toluidine blue (such as mast cell tryptase) and c-kit, are more specific for mast cells (Figure 2). If these stains are not carried out, although the physician may correctly suspect mastocytosis, the pathology report could be returned as a false-negative, leading the physician down a vague pathway, chasing a number of differential diagnoses.

In addition to errors that occur with the use of H&E staining in the reliable identification of mast cells, errors in biopsy techniques can cause the mast cells to degranulate and essentially render them “invisible” to the pathologist. For example, injection of local anesthetic directly into the lesion and the use of anesthetic with epinephrine can result in mast cell degranulation. Both H&E and toluidine blue would then be problematic in identifying degranulated mast cells. With c-kit staining, however, which targets receptors on mast cells’ membranes, the presence of mast cells may be identified accurately.

**CONCLUSIONS**

As cutaneous mastocytosis is a common presenting condition to the dermatologist, it is of the utmost importance to ensure the accuracy of the diagnosis. The symptoms of cutaneous mastocytosis can be relieved and treated readily. Injection of local anesthetic without epinephrine adjacent to, rather than directly into, the lesion or injection of the anesthetic proximal to the nerve innervating the area can avoid mast cell degranulation, which complicates histologic examination. If these precautions are taken and the physician still suspects mastocytosis despite a negative pathology report, then a metachromatic stain, such as toluidine blue, and an immunohistochemical assay for c-kit may be requested for confirmation. It is important that both these stains be requested simultaneously, as toluidine blue stains the contents of the granules and the assay for CD117 targets the mast cell membranes. There are limitations to antibody staining that make it valuable to apply both stains to confirm the diagnosis of mastocytosis. A patient’s total serum tryptase level may also be obtained to determine the presence of excess mast cells and increased mast cell activity. Thus, on assessment of these two parameters, both the presence and degranulation of mast cells can be verified.


REFERENCES


HISTORICAL DIAGNOSIS & TREATMENT

Diagnosis and treatments have advanced over the past century. This feature depicts conditions from a collection of steroptic cards published in 1910 by The Stereoscopic Skin Clinic, by Dr. S. I. Rainforth.

(continued on page 126)
A 78-year-old man was admitted to the hospital for pneumonia with multiple comorbidities including congestive heart failure, chronic obstructive pulmonary disease, and type II diabetes mellitus. On physical examination, he was found to have multiple decubitus ulcers (DUs), as well as multiple sacral and leg ulcers for which the wound care team empirically prescribed Dakin’s solution (sodium hypochlorite) for some ulcers, wet-to-dry dressings for others, and elaborate bandaging for most.

Despite the DUs’ long history, guidelines for appropriate treatment have remained somewhat arbitrary. Treatment options are often limited to those measures that are in vogue, rather than those proven effective by evidence-based studies. Witness, the once-popular remedy of Maalox and Merthiolate, with the antacid being used, because it was good enough for gastrointestinal ulcerations and the antiseptic added for its color.

Much like this case, patients suffering from ulcers are often critically ill and are facing multiple, severe medical problems, including end-organ failure, one example being skin failure. Treatment goals for patients might range from supportive therapy to complete cure.

INFECTION

Infection can lead to cellular injury and should be addressed, if present. Contrary to popular belief, not all DUs are infected. Care should be taken in determining whether an ulcer is actually infected. The use of anti-infectives in uninfected ulcers is not only unnecessary, but it may even be detrimental, given that they have been shown to retard wound healing. When there are signs of infection (purulent discharge, surrounding redness, induration, warmth, or foul odor), systemic antimicrobial agents are appropriate. For superficial infection, topical agents such as metronidazole have been found to be useful. Once infection is evident, such therapy should be employed.

Empiric use of Dakin’s solution, even diluted, or povidone-iodine, moreover, may be detrimental. It is especially important not to destroy healthy tissue. Dakin’s solution (sodium hypochlorite) was originally used to treat gas gangrene during World War I.

While a trench wound is not the same as a DU, sodium hypochlorite may offer initial antisepsis. Use for more than a few days can lead to impaired wound healing, and continued use may actually be harmful to the already injured tissue. Sodium hypochlorite can complicate the problem by preventing wound healing due to its cytotoxic effect on fibroblasts, prevention of cell migration, and potential for collagen degradation.

Similarly, compresses with povidone-iodine can be useful but should only be used when infection is evident. Povidone-iodine also impedes healing with chronic use. Povidone-iodine at a concentration of 0.001% has been shown to be bactericidal and noncytotoxic, but, much like sodium hypochlorite, its use should be limited to no more than a few days. Long-term use offers limited benefit with the potential of adverse outcomes, such as contact dermatitis and delayed wound healing.

DEBRIDEMENT

After any infection is treated, necrotic tissue should be debrided on the basis that necrotic tissue promotes bacterial growth and impairs wound healing. The devitalized and contaminated tissue mechanically obstructs wound contraction and re-epithelialization. Removing the necrotic tissue by surgical, mechanical, or chemical means is an effective means for promoting wound healing. Debridement can take the form of surgical elimination with a scalpel, chemical removal with enzymatic preparations or 5-fluorouracil application, or mechanical destruction with wet-to-dry dressings. A wet-to-dry dressing is a damp sponge applied to the wound, allowed to dry, and removed, hopefully, with debris. It is not a wet sponge, covered by a dry sponge.

Covering the wound with a sponge will do nothing to aid in the healing of current ulcers or the prevention of additional ulcers. It may be aesthetic, but that is it. Using an occlusive dressing is another story and can be highly useful.
SKIN FAILURE
Contrary to some well-wishers, not all ulcers can heal, and not all DUs can be prevented. Just as the heart fails and the kidneys stop functioning, so the skin can fail. The skin, like other body organs, can simply wear out.\textsuperscript{11}

CONCLUSIONS
The old adage of doing no harm is important in treating all wounds, whether they be DUs, arterial ulcers, or venous ulcers. No treatment, instead of inappropriate treatment, has merit. Not all patients have the capabilities of healing. No matter how good the nursing care is or attentive the physicians are, not all DUs can be prevented.\textsuperscript{12}

*Sodium hypochlorite was also the stop bath used in developing film in the pre-digital age.

REFERENCES
1 Parish LC, Witkowski JA. The infected decubitus ulcer. \textit{Int J Derma-}
2 Anthony D. The treatment of decubitus ulcers: a century of mis-
3 Alvarez OM. Pressure ulcers: critical considerations in preven-
10 Witkowski J, Parish LC. Debridement of cutaneous ulcers: medi-
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**References:**

*In vitro activity does not necessarily correlate to in vivo activity.*

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The concept of heritable traits and disease is by no means a new one. Long before Gregor Mendel, evidence suggests that selective breeding was used as far back as prehistoric times to improve crops and animal livestock traits. Genetics, from the Ancient Greek, γένεσις genesis or origin, is a discipline of biology and medicine, examining the heritable factors at play within and around us.

Basal cell nevus syndrome (BCNS), also known as Gorlin-Goltz syndrome, is a rare autosomal-dominant condition with complete penetrance and variable expressivity. It is the result in a defect in the expression of the gene PTCH. The disease was first reported in the literature by Jarisch and White in 1894. The spectrum of disease associated with this syndrome was described in detail by Gorlin in 1960; however, an archeologic finding documents this disease in the paleorecord more than 3000 years ago.

EGYPTIAN SKELETONS

Two Egyptian skeletons of the Dynastic period were excavated with findings consistent with BCNS. Supporting evidence includes odontogenic cysts, bifid ribs, incompletely fused sacral laminae, brachymetacarpalia, and occipital asymmetry (Figure 1, Figure 2, Figure 3).

DIAGNOSIS

Diagnosis of BCNS is made in the presence of 2 major criteria or 1 major and 2 minor criteria. The major criteria consist of the following: (1) >2 basal cell carcinomas or 1 basal cell carcinoma in patients younger than 20 years; (2) odontogenic keratocysts of the jaw (proven by histologic analysis); (3) ≥3 palmar or plantar pits; (4) bilamellar calcification of the falx cerebri; (5) bifid, fused, or markedly splayed ribs; and (6) first-degree relative with BCNS. The minor criteria include the following: (1) macrocephaly; (2) congenital malformations, such as cleft lip...
or palate, frontal bossing, coarse facies, and moderate or severe hypertelorism; (3) other skeletal abnormalities, such as Sprengel deformity, marked pectus deformity, and marked syndactyly of the digits; (4) radiologic abnormalities, such as bridging of the sella turcica, vertebral anomalies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands and the feet; and (5) ovarian fibroma or medulloblastoma. Typically, the condition is diagnosed with the presentation of multiple basal cell carcinomas or odontogenic keratocysts, both presenting in the second or third decade of life.4,5

CONCLUSIONS

The cases presented support the diagnosis of BCNS with several major criteria met (nonhistologic evidence of odontogenic cyst, bifid rib, and affected family member) and are arguably the earliest documented cases of this genodermatosis, occurring 3000 years before Gorlin’s famous paper.

REFERENCES


Pseudoxanthoma Elasticum: Clinical, Histologic, and Genetic Studies—A Report of Two Sisters

Dieudonne Kaimbo Wa Kaimbo, MD, PhD;1 Anne Mutosh, MD;2 Anita Leys, MD, PhD;3 Rita Parys-Van Ginderdeuren, MD, PhD;4 AAB Bergen, MD, PhD4

Case 1: A 24-year-old black woman was referred to our clinic in September 1999 by the Department of Dermatology. She was referred to confirm the diagnosis of pseudoxanthoma elasticum (PXE). Her medical history was normal. Dermatologic examination revealed confluent papules that gave the skin a “plucked chicken” appearance on the flexural surfaces in the neck, axillae, clavicle, thigh, and periumbilical area (Figure 1). The patient stated that the changes in her skin had begun in the periumbilical region at about 5 years of age and had since been slowly progressive. Physical examination showed brownish black pigmentation on the left side of the face, left eyelid, and left sclera, which was diagnosed as Nevus of Ota (Figure 2). Her visual acuity was 20/10 in both eyes, with no afferent pupillary defect. Intraocular pressure in both eyes was normal. Slit lamp examination showed no abnormalities. Findings from fundus examination revealed angioid streaks that formed an incomplete ring around the optic disc and anteriorly radiated toward the equator of the globe, multiple calcified drusen-like structures, and “peau d’orange” changes. Skin biopsy (skin tissue from the neck) was taken and the diagnosis of PXE was confirmed. Histopathologic findings revealed calcification of the elastic fibers and abnormalities of the collagen (Figure 3). The patient was not known to have sickle cell anemia or sickle cell trait, and her blood pressure levels had never elevated. Other systemic causes of angioid streaks were excluded by findings from extensive laboratory examination. Her relatives were asked to come in for examination but lived far away. One of the patient’s sisters lived in Kinshasa, Africa, however, and is presented in case 2. Case 2: The 27-year-old sister of the previous patient was examined on April 19, 2000. At examination, she was found to have PXE. Her medical history was significant for systemic hypertension since 1998 and genital hemorrhage. She underwent an ablation of a cyst of her left ovary in 1988. Her ocular history was unremarkable. On physical examination, raised (yellow) papillary lesions, typical of pseudoxanthoma, were found on the neck, axillae, clavicle, thigh, and periumbilical regions. External and anterior segment examinations (of her eyes) were unremarkable. She was found to have a best-corrected visual acuity of 20/10 in both eyes. Intraocular pressure was normal. Funduscopy revealed bilateral angioid streaks, crystalline bodies, and “peau d’orange,” but to a lesser extent than in her sister. In both cases, after informed consent, peripheral blood cells were taken and sent for extraction of DNA. Analysis was performed but could not demonstrate the known gene defects of PXE.
Multiple organs are affected, including the skin, eyes, and cardiovascular system, and the pathogenic changes include lax and inelastic skin, angioid streaks in the retina, and mineralization of the internal elastic lamina of midsized arteries, including the cerebral, coronary, gastrointestinal, and peripheral vasculature.12

The characteristic eye signs of PXE are angioid streaks, which are irregular, reddish brown or gray lines that radiate from the optic disc. Angioid streaks appear to be present in at least 85% of patients with PXE, and the typical age of onset is between 15 and 25 years.9,13 They result from degeneration and calcifications of the elastic fibers of the retina leading to breaks in the Bruch’s membrane. Angioid streaks are not pathognomonic and have been described in a variety of other systemic disorders including Ehlers-Danlos syndrome, Paget disease of the bone, Marfan syndrome, sickle cell anemia, thalassanemia, and lead poisoning.7,14–19

Other common findings in the eye include “peau d’orange appearance” (a yellowish mottled hyperpigmentation of the retina) that may precede angioid streaks by up to 10 years,9 colloid bodies, macular degeneration, optic nerve head drusen (whitish yellow irregularities of the optic disc), and “owl eyes” (paired hyperpigmented spots).20,21

The histology of PXE is characteristic. In skin lesions, swollen, clumped, and fragmented elastic fibers and calcium deposits are found in the middle and deep reticular dermis with normal morphology in the papillary dermal layers.1,2,22 Similar changes occur in elastic fibers of the blood vessels, Bruch’s membrane of the eye, endocardium, and other organs.

Currently, diagnosis of PXE relies on clinical examination for characteristic skin lesions and angioid streaks or von Kossa staining of a biopsy of skin lesions looking for calcification of dystrophic dermal elastic fibers.20

Our cases, the first in Central Africa, confirmed these findings. The two patients described in this study were both women and presented with ocular and skin lesions of PXE. Characteristic skin lesions exhibiting typical histopathologic manifestation and characteristic ocular change were present. In one patient, the changes in the skin had begun in the periumbilical region at about 5 years of age. One patient had systemic hypertension and genital complications, which could be related to PXE. General examination and laboratory tests excluded sickle cell disease in the two sisters. The first case presented coexisting PXE and Nevus of Ota (blue sclera), probably a fortuitous association or a link between the two conditions. The patients’ DNA was available for analysis, but typical known mutations in the ABCC gene were not found.

These cases demonstrated that PXE affects all races and can also occur in the geographic region of Central Africa.

REFERENCES

17 Schultz PN, Sobol WM. Angioid streaks and pseudoxanthoma elasticum. JAMA. 1991;265:45.

**Figure 3.** Histologic findings: calcification of the elastic fibers and abnormalities of the collagen fibrils (hematoxylin-eosin stain, original magnification ×100).
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Lymphangiomas are benign hamartomatous malformations that consist of dilated lymph channels lined with normal, single-cell lymphatic endothelia. They are thought to arise from progressive dilatation of maldeveloped sequestered primitive lymphatic sacs. Lymphangioma circumscriptum (LC) is divided into two main groups: classic and localized. Classic LC is usually present at birth or appears soon afterward, and lesions are >1 cm² in area. There is usually a diffuse subcutaneous swelling or thickening beneath or adjacent to the vesicular region. The lesions are particularly common over proximal parts of the limbs and to adjacent limb girdles. They are associated with leakage of clear fluids, minor bleeding, and secondary infection. The other group, localized LC, may become apparent at any age, and typically involves a lesion area of ≤1 cm², has no definite area of predilection, and is usually asymptomatic. Recurrence is frequent and rapid in classic LC, while localized LC has a better cure opportunity. Lymphangiomas are also classified according to the depth and size of the lesion. Superficial lesions are classified as LC, while deep-seated ones are classified as cavernous lymphangioma.

In a classic study, it was proposed that the lesions are composed of an ectopic system of lymphatics, separated from the normal network of lymph vessels, yet communicating with superficial lymphatics that become dilated from the continued rise and fall of pressure transmitted from the muscle walls of deep cisterns. This anatomic structure is reminiscent of an “iceberg,” in which more lymphatic involvement below the surface is appreciated (Whimster’s hypothesis).

Histologically, LC is characterized by solitary and grouped dilated cystic spaces that often contain red blood cells or lymphatic fluid in the papillary dermis. Dilated lymphatics are also seen in the dermis and subcutaneous fat.

Other modalities that are useful in evaluating LC are lymphangiography, duplex ultrasonography, and MRI. These techniques can be used before surgery to limit the risk of recurrence, but may not be reliable for detecting smaller lymphatic cisterns.

Treatment of LC is a major challenge because of the persistent nature of the disease and the large variation in lesion size, depth, and anatomic location. Certainty in healing requires not only removal of the superficial component, but, more importantly, removal of the deeper lymphatic cisterns. The most widely accepted therapy has been surgery; however, surgery can be complicated by a high incidence of recurrence and local nerve damage. Nonsurgical therapies such as carbon dioxide laser ablation, cryotherapy, and sclerotherapy have been attempted to avoid the risk of recurrence and disfigurement.

An 11-year-old boy was referred to our department for vesicular lesions of the buttocks of 7 years’ duration (Figure 1). He also complained of intermittent oozing of serosanguineous fluid, which caused social impairment. On clinical examination, clusters of flesh-colored to translucent papules were present over the buttocks, perianal area, and left calf. The lesions were excised 4 years ago, after confirming the diagnosis of lymphangioma circumscriptum on histopathology. They started recurring on and around the surgical site within 6 months of surgery. Magnetic resonance imaging (MRI) was performed to evaluate the deeper extension of the lesion. The lymphangioma previously identified by cutaneous examination manifested as an altered T2 signal, spreading to subcutaneous tissues and major and minor muscles and infiltrating the sacral vertebrae and presacral area (Figure 2). Although the muscles were infiltrated, the boy was asymptomatic. He did not have pain, tenderness, or difficulty in the movement of the back and hip muscles. Renal function was also normal. Options of surgical resection and sclerotherapy were rejected by the parents because of the extensive spread of lymphangioma and fear of disfigurement. Carbon dioxide laser ablation was performed, and the parents were asked to follow up regularly for control of any symptoms, if they appear in the future.
surgery-related complications, but the results have not been satisfactory and all are palliative measures.

The idea of treating lymphangiomas with sclerosing agents is an old one. Intralesional injection of various sclerosants, such as bleomycin, hypertonic saline, and OK-432 (lyophilized mixture containing the cells of group A Streptococcus pyogenes Su strain of human origin combined with benzyl penicillin) have been used.5–7 These agents may seep outside the thin-walled lesions, however, and cause damage to the surrounding structures, including extensive scarring. Local inflammatory reactions, such as post-treatment fever, swelling, or tenderness, may develop.8 Other complications of sclerotherapy include purple-brown hyperpigmentation, telangiectatic matting, cutaneous ulcerations and necrosis, superficial thrombophlebitis, pulmonary embolism, and arterial injection.9

Therapies such as CO₂ laser vaporization and more recently high-energy, short-pulse CO₂ laser have been found to yield functionally and cosmetically acceptable results.10 Given the nature of the lesion, the potential for recurrence exists no matter what modality is chosen.

In our patient, radical surgery was not feasible because the lymphangioma had spread to the sacrum and the presacral vertebrae. Sclerotherapy was considered in consultation with radiologists and pediatricians but was also discarded. After discussing with the patient’s parents, we decided to perform CO₂ ablation, with annual follow-up to control any symptoms (pain or tenderness) should they appear.

CONCLUSIONS

The aim of this report is to apprise clinicians of this rare condition and to highlight its high recurrence rate postoperatively, which remains a clinical challenge to patients and physicians alike.

REFERENCES

 Lupus vulgaris (LV) is a chronic granulomatous form of cutaneous tuberculosis that occurs in persons with a moderate to high degree of immunity. It is one of the commonest forms of cutaneous tuberculosis and is seen in 55% of Indian cases of cutaneous tuberculosis with variable presentations. In developing countries, the most common sites are the buttocks, extremities, and trunk; rarely is the face involved, whereas in Western countries, it usually appears on the face and neck. The clinical variants include plaques, papules, nodules, ulcerative, vegetative or tumorous lesions, and sometimes post-exanthematous or miliary lupus. In very rare instances, LV may present with multiple lesions that affect the face, trunk, and extremities. LV may result from hematogenous, lymphatic, or contiguous spread from a tuberculous lesion. Investigators have reported 2 elderly patients with disseminated LV in whom no overt immunosuppression was present.

In addition, dissemination of disease in the whole spectrum of cutaneous tuberculosis in 22.1% of cases has been observed, but it has been seen more often in the presence of gumma and scrofuloderma. Other investigators have reported disseminated lupus vulgaris with multiple lesions of varying morphology at different sites with pulmonary tuberculosis and healed lymph node involvement.
cutaneous tuberculosis in immunocompromised states such as in acquired autoimmune deficiency syndrome and varicella infection, respectively. Our patient, however, was immunocompetent, with disease for the past 4 years that was not diagnosed and has probably led to dissemination through the lymphatic route and dissemination to involve lung parenchyma for the past 2 months. There were two recent reports of disseminated LV; one initially misdiagnosed as a port wine stain and the other with multiple atypical lesions.8,9 The diagnosis in our patient was further confirmed by the dramatic response to antitubercular treatment after 4 weeks, revealing a flattening of the skin lesions and diminution of the constitutional symptoms.

CONCLUSIONS

Disseminated LV, accompanied by pulmonary and lymphadenopathy tuberculosis, is a rare finding.

REFERENCES


HISTORICAL DIAGNOSIS & TREATMENT: PSORIASIS (continued from page 113)

Psoriasis is a chronic frequently relapsing disease of the skin, characterized by more or less numerous, small or large masses of white or yellowish dry imbricated scales loosely adherent to circumscribed red patches of epidermis. The redness nearly always extends a little distance beyond the scales. The primary lesions are pinhead sized slightly elevated papules. By peripheral growth they develop into pea sized, glis-tening white scaly lesions that look like drops of mortar on the skin. When the scales are completely removed a smooth red surface is exposed upon which several minute bleeding points may be seen but often only with the aid of a lens. Further growth and coalescence of the lesions give rise to coin-sized plaques and larger irregular patches. Occasionally lesions may undergo involution at the center; in this way ring formed, segmental and serpiginous figures are formed. The efflorescences vary greatly in number and are rarely of uniform size. The scales are more abundant on some patches than others. Now and then there may be large red plaques covered with only a single translucent, wrinkled film. Only in old lesions is there any infiltration of the skin, but in extreme cases the thickening may be sufficient to cause fissuring about the joints. The evolution of a lesion may occupy a few weeks or many months. The distribution is roughly symmetrical. Marked preference is shown for the extensor surfaces of the extremities, particularly in the neighborhood of the elbows and knees, and for the scalp. Any part of the trunk may be affected. The palms and soles are very rarely involved. The nails may be brittle and stippled with minute depressions. On the scalp the thick masses of scales often mat the hair, but alopecia is uncommon. Not infrequently the patches extend a half inch or more onto the forehead. The face is otherwise rarely affected. Itching may be present in some cases but is not often intense. Psoriasis begins most often after puberty, sometimes in childhood, rarely in infancy or old age.

DIAGNOSIS: The scales of lichen planus are less abundant, more adherent, and their removal does not cause punctate hemorrhages; disappearing patches leave pigmented areas; the gray striations and polygonal papules are pathognomonic. Dermatitis exfoliativa begins in the flexures, attacks the hands and feet, becomes universal and causes constitutional symptoms. Dermatitis exfoliativa may develop from a generalized psoriasis. Eczema seborrhoicum on the scalp does not leave areas of normal skin between the patches as does psoriasis, and its scales are greasy.

TREATMENT: Internally arsenic is most often administered in increasing doses to the limit of tolerance. It is said to be used only in very chronic cases. Saline diuretics and large doses of potassium iodid may be given at any stage and are often quite as helpful. For external use chrysarobin is the drug of choice. Tar and salicylic acid are also valuable and an excellent preparation is a combination of these: Acid, salicyl. 10, Chrysarobin., Ol. Rusci, aa 20, Sapo. Moll., Petrolati, aa 25. This should be applied to the lesions only after the scales have been removed with water and soft soap. When chrysarobin causes too intense a dermatitis its use should be suspended. It is not to be employed on the face for it may produce a severe conjunctivitis. Its staining of the skin is temporary, but of the clothing permanent. Ung. Hydrargyri amoniate is a clean and efficient application for mild cases and for use on the face and scalp.
The term paraffinoma describes a characteristic histopathologic pattern showing the replacement of normal subcutaneous tissue by cystic spaces; there are also dense fibrous tissue and foreign body giant cells encircling these lakes of oil.1 Paraffinomas have been encountered with the injection of numerous oily foreign substances, such as mineral and vegetable oils, paraffin, vaseline,2 silicone, and automobile transmission fluid,3 which incite a granulomatous foreign body reaction. Interestingly, these oils have been used since the late 19th century for cosmetic purposes, including cleft palate, wrinkles and other facial deformities, baldness, and muscle, breast, and penile augmentation. As a result, many adverse effects from the use of these substances have been reported.1 Despite not being used by medical professionals at the present time, these injections are still occasionally performed by nonmedical personnel as well as patients themselves, who may be reluctant to admit this practice.1 Previous reports of self-inflicted facial paraffinomas are rare, and this is the third case reported in the English literature to our knowledge (Table).

Although complete surgical excision of all involved tissue is the treatment of choice to prevent the chronic granulomatous processes that lead to necrosis and severe deformity.3,4,6,7 In our case, we decided upon a conservative treatment due to the size and location of the lesions. In addition, psychiatric treatment may be appropriate in cases of self-injection.3

In dermatitis artefacta, the patient creates skin lesions to satisfy an internal psychological need, usually a need to be taken care of.8 This is a rare condition with difficult management and treatment, especially due to the patients’ denials of having inflicted the lesions on themselves.8 The clinical presentations of

**Figure 1.** Symmetric erythematous plaques in the periocular region.
self-inflicted lesions vary widely in their morphology and distribution, do not conform to those of known dermatoses and are located on easily reached parts of the skin. While our patient was in her seventh decade of life, the highest incidence of onset is in late adolescence to early adult life. Most patients are young women who have a personality disorder, including borderline features. About 2% of the general population have BPD, which is associated with many possible symptoms, such as alterations in the impulsive, affective, cognitive sphere; in the attachment systems; and with feelings of emptiness and identity disorders. In the present case, we suggest that development of the self-injuries was due to impulsive symptoms and affective instability.

Although BPD was basically treated by psychotherapy until a few years ago, the use of psychodrugs to treat symptoms is currently the common practice. Fluoxetine is a selective serotonin reuptake inhibitor that has demonstrated efficacy in the management of impulsiveness, affective liability, and the depressive symptoms in patients with this disorder.9

### CONCLUSIONS

The face is a rare location of self-induced paraffinomas and lesions may be confusing, especially if the diagnosis is dermatitis artefacta. In these patients, the diagnosis is reached by excluding other conditions. Cooperation between the dermatologist and the psychiatrist becomes necessary.

### REFERENCES

Pruritus as an Unusual Symptom in Multiple Piloleiomyoma
Giti Sadeghian, MD; Hengameh Ziaei

A 30-year-old woman presented with multiple pruritic raised skin lesions at the proximal part of her left arm for the past 15 years. At the age of 15, the patient noticed red nodules accompanied with severe pruritus over the arm, which started to spread and involved the dorsal aspect of her scapula (Figure 1). They had been increasing in number during the past 15 years. There was no history of pain either spontaneously or in response to cold, tactile, or emotional stress, with no bleeding or oozing. There was no family history of similar skin lesions; however, she had a history of gynecologic problems for 10 years, and examination of her uterus showed uterine leiomyomas. The patient complained about severe pruritus. This symptom was exaggerated with sun exposure, cold, emotional stress, and rough cloths. It was so severe that it caused sleep disturbances. Clinical examination showed multiple pink and red nodules ranging from 5 mm to 20 mm over the above-described sites. The lesions were firm, smooth, not mobile, and nontender, with no pain on touch. Routine hematologic and biochemical investigations were normal. Kidney and pelvic ultrasonography showed myomatous uterus and normal kidneys. Microscopic examination of one of the nodules in hematoxylin and eosin–stained sections showed proliferation of smooth muscle cells with fascicular aspect in dermis. These cells had thin, elongated eel-like nuclei with blunt edges (Figure 2 and Figure 3). The diagnosis of leiomyoma was made and the patient was referred for surgical excision. Due to the extension and site of the lesions, the plastic surgeon did not recommend surgical procedure and the patient was treated with an antihistamine (loratadine 10 mg/d).

Leiomyoma is a benign tumor of smooth muscle derived from the arrectore pilli muscle, media of blood vessels and smooth muscle of scrotum, labia majora and nipples.1 Piloleiomyoma is the commonest type which may be solitary or multiple. Onset of disease is usually early in life in 2nd or 3rd decade.1 The lesions occur over the face, anterior trunk, and extensor surfaces of extremities.2 Leiomyomas are usually painful, either spontaneously or paroxysmal in nature, with stabbing, burning, or pinching qualities.3 The pathogenesis of pain associated with these lesions is unknown. Some authors suggest that it is due to local pressure caused by the tumor on the nerve fibers or it is related to smooth muscle contraction or constriction of the vessels, causing local ischemia.3

Treatment of cutaneous leiomyomas is based on symptomatic concern and is usually limited to excision of single lesions. Asymptomatic lesions are left untreated, especially when multiple lesions are present, because of the likelihood of recurrence. Symptomatic lesions that are not amenable to resection are more difficult to treat.4 Calcium channel blockers, particularly nifedipine, relieve pain associated with piloleiomyoma.5 They act by...
inhibiting the movement of extracellular calcium ions across the cell membrane into the smooth muscle cell, thereby inhibiting muscular contraction. Phenaxybenzamine and oral nitroglycerin, which is aimed at relaxing smooth muscle and gabapentin, a novel anticonvulsant with an uncertain mechanism of action, have also been tried for piloleiomyoma-associated pain. Surgical excision is effective in solitary cases. Carbon dioxide laser ablation has been tried in multiple leiomyoma.

Cutaneous leiomyomatosis appears to be associated with uterine leiomyomas, and women with multiple piloleiomyoma should undergo further investigation for uterine leiomyoma. If the latter is present, the patient is likely to have a familial condition called familial myomatosis cutis et uteri, or Reed syndrome, which is inherited as an autosomal-dominant trait. This patient had uterine leiomyomas, but she did not have a familial history of skin or uterine leiomyomatosis.

**CONCLUSIONS**

Pruritus is not a symptom of leiomyoma, but, in the past, a rare example of nipple leiomyoma was reported, with itching of the nipple and no associated pain. This is a rare case of multiple piloleiomyoma that presented with pruritus. There is no clear explanation for this symptom. Due to extension and location of the lesions, the patient did not undergo surgical intervention and she was prescribed an antihistamine for pruritus.

**Acknowledgments:** Professor Klas Nordlind made many helpful suggestions.

**REFERENCES**

Coexistence of Generalized Morphea and Lichen Sclerosus et Atrophicus Mimicking Systemic Disease

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A 70-year-old white housewife presented with a rare presentation of coexistent generalized morphea and lichen sclerosus et atrophicus with unusual clinical aspects. The patient had disseminated erythematous lesions that evolved into indurated large plaques. Hypopigmentation and hyperpigmentation developed later, in addition to ivory, white, and shiny plaques on the trunk (Figure 1). The skin of the arms and legs showed a wavy contour (Figure 2). Various areas were markedly sclerotic and some had edematous papules (Figure 3). Multiple indurated, ivory, white, shiny, large, and hypochromic plaques were seen on the trunk. Laboratory examinations showed increased immunoglobulin A and antinuclear antibodies 1:200 speckled. Scl-70, anti-centromere, anti-ribonucleoprotein, and anti-DNA tests were negative. Esophageal manometry and abdominal and pelvic ultrasound findings were all normal. Complete blood cell count, blood profile, and urinalysis were also within normal limits. Skin biopsy of an arm lesion showed an atrophic epidermis with orthokeratotic hyperkeratosis and follicular plugging. A broad area of homogenization and edema was seen in the papillary dermis with dilated capillaries and a perivascular lymphocytic infiltration. There was also collagen sclerosis throughout the reticular dermis, and thickened, homogenized collagen bundles replaced the subcutaneous fat. Vessel walls showed proliferated intima with mucin deposition and sclerosis, as well as multiplied elastic layers. There was edema of the papillary dermis in some areas and incipient deposition of calcium (Figures 4–7).

Cutaneous lesions with clinical or histopathologic characteristics of both LSA and morphea simultaneously occurring in the same patient can be seen in patients with combined features, presenting or causing
diagnostic difficulties. Recently, there was a report of a 7-year-old boy with guttate morphea on the trunk and upper limbs and plaque morphea on his right foot who, 12 years later, developed lesions of LSA, diagnosed clinically and histopathologically. In 2009, two cases were published: one of coexistence of localized morphea and LSA associated with submucosal fibrosis and another of LSA and morphea with bilateral symmetry.

Concomitant or sequential occurrence of LSA and morphea is well-known. For the relationship between the two diseases, several possibilities have been discussed. Some view LSA as a subset of morphea, others believe them to be two manifestations of the same disease. Still others believe there are enough clinical and histologic differences between LSA and morphea to accept that they are distinct diseases.

Histopathology of the LSA lesion shows hyperkeratosis with follicular plugging; atrophy of the Malpighian layer with vacuolar degeneration of the basal layer; and edema and homogenization of the collagen in the upper dermis; however, these findings are not always present.

It was opined that LSA and morphea can coexist and that both histological findings could be seen in the same lesion. It was also suggested, after examining biopsies of 24 patients, that LSA is not related to morphea; however, in 2001, LSA was described as a superficial variant of morphea.

CONCLUSIONS

This is a rare case showing clinical lesions of both scleroderma and LSA. Although the patient did not have systemic complaints, there was calcinosi of the reticular dermis and severe vessel alterations.

REFERENCES


Patterson JA, Ackerman AB. Lichen sclerosus et atrophicus is not related to morphea. A clinical and histologic study of 24 patients in whom both conditions were reputed to be present simultaneously. Am J Dermatopathol. 1984;6:323–335.

LETTER TO THE EDITOR

Topical Griseofulvin in Dermatophytoses

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TO THE EDITOR

Although early studies suggest that topical griseofulvin may be effective in the treatment of dermatophytoses, this antibiotic has been mostly administered orally since its introduction in 1958. This report describes results of an open study of 30 patients with dermatophytoses employing a highly penetrating topical solution. Local application twice daily was carried out during 4 weeks. Rapid response with clinical and mycologic cure occurred in 83.3% of the patients. Although this investigation, together with the available clinical and experimental data, indicates that topical griseofulvin is effective, final confirmation will require the performance of double-blind studies and prolonged follow-up.

Although griseofulvin in dermatophytoses has been mainly administered orally, early studies using topical forms have also shown effectiveness.1 Topical griseofulvin has been commercially available in some countries for a number of years, but it is not widely used as a standard treatment for dermatophytoses. Experimental data indicate that topically applied griseofulvin may result in cutaneous penetration, followed by significant concentration of the antibiotic in the stratum corneum.2 The development of a highly penetrating griseofulvin solution3 provided an opportunity for evaluation of the topical effect of this agent in dermatophytoses.

Thirty adult patients with tinea pedis, tinea corporis, and tinea cruris were included in this study (Table). All patients showed chronic involvement, namely dry scaly lesions that were not vesicular or exudative. The alcoholic nature of the vehicle was not considered appropriate for treatment of these acute lesions. The diagnosis was confirmed mycologically (positive direct examination and cultures) in all patients. They were treated with 1% griseofulvin dissolved in an anhydrous vehicle containing benzyl alcohol (10%), acetone (40%), and isopropanol (50%). The solution was provided in a specially designed sprayer bottle that was metered to deliver 0.05 mL of the solution per depression of the pump. It was applied through direct spraying of the affected areas twice daily for 4 weeks. Rapid clinical response (Figure 1 and Figure 2) with mycologic cure (negative direct examination and cultures) was observed in 25 patients (83.3%). The remaining 5 patients (16.7%) showed only partial clinical response, with direct examination and cultures remaining positive after 4 weeks. Tolerance was excellent in all patients.

This investigation supports the results found in previous clinical and experimental studies with topical griseofulvin. Investigators4 compared the effect of a topical griseofulvin solution (1.0%) vs
an oral solution (30 mg/kg) in experimental Trichophyton mentagrophytes infection of guinea pigs and found that the solution was more effective than the oral form. The mean clinical improvement in lesion severity was 83% with the topical solution and 60% with the oral solution.

In another study, gel preparations of griseofulvin to treat tinea corporis during 3 weeks were employed. Excellent results were found. In addition, investigators treated 100 patients with tinea pedis caused by various dermatophytes. After 4 weeks of topical application once daily, 80.9% of the patients experienced clinical and mycologic cure. Researchers have also described marked effectiveness of a 2% griseofulvin ointment in tinea corporis, tinea cruris, and tinea versicolor, and others demonstrated that concentrations of griseofulvin in the stratum corneum after a single topical application may be greater than those reported after oral administration. Finally, in a double-blind study, clearing of tinea versicolor employing the same griseofulvin solution used in the present study was found.

We (LFM) had an opportunity to observe the surprisingly dramatic response to oral griseofulvin of the first patient with a severe Trichophyton rubrum granuloma treated in Miami. Afterwards, we employed mainly this form of administration. Following the initial era of griseofulvin usage, it has been assumed that its topical action was ineffective; however, the results of this study, as well as previous data, indicate that the early observation of the effectiveness of topical griseofulvin was indeed accurate.

Although this experience, together with the available clinical and experimental data, indicates that topical griseofulvin is effective, final confirmation with double-blind studies, as well as prolonged follow-up are needed.

REFERENCES
Membership in the International Academy of Cosmetic Dermatology is open to physicians with an interest in cosmetic dermatology and to members of the pharmaceutical and cosmetic industry who share similar goals.

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INDICATIONS AND USAGE

Locoid Lipocream is a topical corticosteroid indicated for: relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults and the treatment of mild to moderate atopic dermatitis in patients 3 months to 18 years of age.

WARNINGS AND PRECAUTIONS

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if Locoid Lipocream is applied to large surface areas or used under occlusion. If HPA axis suppression is noted, reduce the application frequency, discontinue use, or switch to a lower potency corticosteroid. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria.

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infections develop. Discontinue use if irritation develops.

ADVERSE REACTIONS

The most common adverse reactions (>1%) are HPA axis suppression and application site reactions. The following additional local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions included: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria and telangiectasia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Systemic corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women. Therefore, Locoid Lipocream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Please refer to full prescribing information for detailed information regarding systemic embryofetal development studies.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Locoid Lipocream is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below 3 months of age have not been established. Because higher skin surface-to-body-mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at a greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing’s syndrome while on treatment.

Eighty-six (86) pediatric subjects (5 months to less than 18 years of age) with moderate to severe atopic dermatitis affecting at least 25% of body surface area (BSA) treated with Locoid Lipocream three times daily for up to 4 weeks were assessed for HPA axis suppression. The disease severity (moderate to severe atopic dermatitis) and the dosing regimen (three times daily) for which Locoid Lipocream is indicated. Five of the 82 evaluable subjects (6.1%) demonstrated laboratory evidence of suppression, where the sole criterion for defining HPA axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter after cosyntropin stimulation. Suppressed subjects ranged in age from 5 months to 16 years and, at the time of enrollment, had 25% to 95% BSA involvement. These subjects did not develop any other signs or symptoms of HPA axis suppression. Safety of Locoid Lipocream in pediatric patients has not been established beyond 4 weeks of use.

Geriatric Use

Clinical studies of Locoid Lipocream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies were conducted to determine the photocarcinogenic or dermal carcinogenic potential of Locoid Lipocream.

Hydrocortisone butyrate revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames test and L5178Y/TK+ mouse lymphoma assay) and one in vivo genotoxicity test (mouse micronucleus assay). No evidence of impairment of fertility or effect on mating performance was observed in a fertility and general reproductive performance study conducted in male and female rats at subcutaneous doses up to and including 1.8 mg/kg/day (0.7X maximum human dose [MHD]). Mild effects on maternal animals, such as reduced food consumption and a subsequent reduction in body weight gain, were seen at doses ≥0.6 mg/kg/day (0.2X MHD).

PATIENT COUNSELING INFORMATION

Patients using Locoid Lipocream should receive the following information and instructions:

- Apply a thin layer to the affected skin two or three times daily for corticosteroid-responsive dermatoses in adults. Consult with your physician to determine if treatment is needed beyond 2 weeks. Apply a thin film to the affected skin area, as diapers or plastic pants may constitute occlusive dressings.
- Do not use Locoid Lipocream in the diaper area, as diapers or plastic pants may constitute occlusive dressings.
- Do not use Locoid Lipocream on the face, underarms, or groin areas unless directed by your physician.
- Avoid contact with the eyes.
- Rub in gently.
- Do not bandage, otherwise cover, or wrap the affected skin area so as to be occlusive unless directed by your physician.
- Protect from freezing. Keep out of the reach of children.
- Do not use other corticosteroid-containing products while using Locoid Lipocream without first consulting your physician.
- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from freezing. Keep out of the reach of children.

BRIEF SUMMARY

Locoid Lipocream® Cream, 0.1% Rx Only
(hydrocortisone butyrate 0.1% cream)
For Topical Use Only

Manufactured for: Triax Pharmaceuticals, LLC
Crandon WI 07016
Marketed and Distributed By: Triax Pharmaceuticals, LLC
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(hydrocortisone butyrate 0.1%) Cream

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Locoid Lipocream is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, including the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.

Safety and effectiveness in pediatric patients below 3 months of age have not been established.

Reversible HPA axis suppression may occur, with the potential for corticosteroid insufficiency. Consider periodic evaluations for HPA axis suppression if applied to large surface areas or used under occlusion. Systemic effects of topical corticosteroids may also include manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria. Pediatric patients may be more susceptible to systemic toxicity due to their large skin surface-to-body-mass ratios. Initiate appropriate therapy if concomitant skin infection develops. Discontinue use if irritation develops. Please see full Prescribing Information on adjacent page.

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