Methodological Limitations of the Study “Isotretinoin Use and Risk of Depression, Psychotic Symptoms, Suicide, and Attempted Suicide”

The studies conducted by Jick et al1 in the Canadian Saskatchewan Health database and the United Kingdom General Practice Research database did not find an increase in the relative risk of depression, psychotic symptoms, suicide, and attempted suicide in individuals prescribed isotretinoin compared with those prescribed antibiotics for acne. However, aside from noting that their sample size was too small to "generate stable estimates for suicide and attempted suicide," the investigators did not mention several methodological problems that limited their ability to draw the conclusion of no increase in risk. These include underascertainment of psychiatric disorders (apparently only diagnosis codes and not psychoactive drug prescriptions or interviews were used to define cases); underascertainment of suicides (death certificate data were not included as a source of information); and lack of data on acne severity and dose and duration of isotretinoin treatment. Also, because there was no control group without acne, a result of no difference in rates of depression between the groups might be due to an effect of acne.

Additionally, the results may have limited applicability to the United States because the recommended doses in the United States are higher than in England and Canada. The maximum recommended dose in the United States is 2 mg/kg per day compared with 1 mg/kg per day in England and 2 mg/kg per day in exceptional instances in Canada.2,3 In England, isotretinoin is restricted to hospitals only and is prescribed by dermatologists or under the supervision of consultant dermatologists.4 Consequently, patients prescribed isotretinoin would not be fully represented in the general practice research database.

Although comorbidity of psychiatric disorders is well recognized,5 the investigators reported higher frequencies of anxiety disorders than mood disorders in the patients with acne. In Saskatchewan, 61% of patients had diagnoses of anxiety disorders (anxiety and neurosis) compared with 29% with diagnoses of mood disorders (depressive disorders), 6% with diagnoses of affective disorders (bipolar disorder), and 3% with diagnoses of nonaffective disorders (schizophrenia and paranoid states). Nevertheless, the title of the article and the terminology used in the text imply that the major outcomes were depression, psychotic symptoms, suicide, and attempted suicide rather than anxiety disorders.

The US Food and Drug Administration, Rockville, Md, has received reports of depression, suicidal ideation, suicide attempt, and suicide in patients prescribed isotretinoin for treatment of cystic acne and other skin disorders.6 The industry-sponsored study conducted by Jick et al1 was intended to help resolve the question of etiology of depression in patients treated with isotretinoin. However, because of the limitations of the study, we believe that the findings are inconclusive and that further studies on the association between isotretinoin and depression should be initiated.

One additional point should be mentioned—the text states that there were 37 cases of suicide or attempted suicide, although Table 3 contains data for 38.

The views expressed herein are those of the authors and do not necessarily represent the official position of the Food and Drug Administration.


In reply

Wysowski and Beitz point out several limitations of our study on isotretinoin and the risk of depression, psychotic symptoms, and attempted suicide.1 Indeed, we have addressed some of these in our manuscript. Other concerns are perhaps not of relevance in this instance. Whereas it is likely that we missed some cases of depression, psychotic behaviors, or suicidal behaviors, it is unlikely that there would be any differential underascertainment between the patients treated with isotretinoin and those treated with antibiotics, and thus...
Cutaneous warts in HIV-positive patients undergoing highly active antiretroviral therapy

Cutaneous warts in patients with human immunodeficiency virus (HIV) are prevalent and respond poorly to conventional treatment. Recent studies suggest that highly active antiretroviral therapy (HAART) is associated with wart regression (unpublished data, November 2000).1 The purpose of this study was to determine whether immune reconstitution plays a role in the natural history of cutaneous warts in HIV-positive individuals.

Patients and Methods. This is a prospective cohort study that included 12 HIV-positive patients (primarily homosexual white men) with a clinical diagnosis of cutaneous warts. All patients underwent 3 examinations at the San Francisco General Hospital Dermatology Clinic from 1996 through 1999. This period was selected because it is when the patients began HAART, which is defined as a combination therapy with 2 nucleoside reverse transcriptase inhibitors and either 1 protease inhibitor or 1 nonnucleoside reverse transcriptase inhibitor.

The original diagnosis was based on retrospective review of the charts of patients who had documented evidence of cutaneous warts. Information including the presence of cutaneous warts, absolute CD4 cell counts, CD4 nadirs, and viral loads was obtained for each patient for each clinic visit. Statistical analysis was performed using the exact χ² test for stratified and nonstratified 2 × 3 tables (StatXact, version 3; Cytel Software Corp, Cambridge, Mass).

Results. During the 3-year follow-up period, 7 HIV-positive patients had persistent warts (duration, >2 years) (mean age, 40 years; median age, 35 years), and 5 patients had warts that regressed (mean age, 45 years; median age, 49 years). The mean CD4 nadir was lower in patients with persistent warts (0.047 × 10³/µL; range, 0.010-0.104 × 10³/µL) than in patients whose warts regressed (0.141 × 10³/µL; range, 0.114-0.383 × 10³/µL) (P = .01). The median values were 0.044 and 0.229 × 10³/µL, respectively.

The mean absolute CD4 cell count was lower in the HIV-positive patients with persistent warts (0.141 × 10³/µL) than in those with regressed warts (0.411 × 10³/µL) (P = .01). The mean values were 0.127 and 0.411 × 10³/µL, respectively. Most HIV-positive patients experienced an increase in their CD4 cell counts between the first and third visits. The increase in the number of CD4 cells over time was higher in the regressed wart group. The persistent wart group had an average increase in CD4 cells of 0.037 × 10³/µL per month vs 0.088 × 10³/µL per month in the regressed wart group (P = .45). More than half of the patients with regressed warts had viral load levels recorded as zero. Therefore, the median and mean viral load values could not be determined.

Comment. Cutaneous warts are one of the most commonly diagnosed skin diseases in HIV-infected patients, accounting for 2.9% to 27% of all skin diseases (unpublished data, November 2000).2 In immunocompromised patients, cutaneous warts can be extensive (in both size and area of involvement) and refractory to conventional therapy.

It has been suggested that an intact cell-mediated immune system is an important factor for wart regression, although the mechanism is not completely understood.3 In a cohort of 60 HIV-infected patients examined in the dermatology clinic at San Francisco General Hospital, there was an association between an increasing CD4 cell count and the absence of cutaneous warts (unpublished data, November 2000). In addition, there has been at least 1 case report of an HIV-infected patient with recalcitrant hand warts that resolved only after initiating potent antiretroviral therapy.4 In non–HIV-infected patients, the role of immune mechanisms is supported by findings that cutaneous warts regress after administration of compounds that stimulate the immune system such as interferons and di-nitrochlorobenzene.5

In a subset of HIV-positive patients, however, cutaneous warts persist despite an increase in the number of CD4 cells. Results from this study demonstrate that HIV-positive patients with low CD4 nadirs (<0.120 × 10³/µL) or low mean CD4 cell counts (<0.135 × 10³/µL) will have persistent warts despite rising CD4 cell counts. This suggests that although CD4 cell counts may increase after HAART, individuals with low CD4 nadirs or low CD4 mean cell counts may not yet have the fully functional CD4 cells necessary for eradication of human papilloma virus and regression of warts. It may also be that pa-
patients with low CD4 nadirs will require a longer period to obtain CD4 cells that are fully functional before the resolution of warts can occur.

This is supported by a slower rate of increase in the number of CD4 cells over time in the persistent wart group than in the regressed wart group (0.037 × 10^3/µL vs 0.088 × 10^3/µL per month, respectively). Clinicians who care for HIV-positive patients undergoing HAART should consider the CD4 nadir when advising patients on the natural history of their warts.

Lori K. E. Rodrigues, MD
San Francisco
Timothy Baker, MD
Davis, Calif
Toby Maurer, MD
Department of Dermatology
University of California, San Francisco
1001 Potrero Ave
Bldg 90, Room 224
San Francisco, CA 94110
(e-mail: tamaurer@orca.ucsf.edu)


Pancytopenia After Treatment of Keratoacanthoma by Single Lesional Methotrexate Infiltration

Lesional infiltration with methotrexate for the treatment of keratoacanthoma (KA) has been proposed as a safe, efficient, and cost-effective alternative therapy when size, localization, and patient-related factors contraindicate surgery.1,2 We report a case in which single intrallesional methotrexate injection led to severe pancytopenia.

Report of a Case. A 69-year-old man presented with a dome-shaped, symmetrical, sharply demarcated, erythematous tumor of 12-mm diameter that developed within 3 weeks at the left nasal orifice. Results from a biopsy were compatible with the clinical diagnosis of KA. Because this patient additionally had multiple internal diseases, including chronic renal failure requiring hemodialysis, to avoid hospitalization for surgery a total of 7.5 mg of methotrexate was injected into 4 separate sites of the KA. Three days later, stomatitis developed. Thirteen days after methotrexate infiltration, the patient complained of black and tarry stools. Diagnostic evaluation revealed bleeding from a previously unrecognized gastric ulcer and pancytopenia (thrombocyte count, 1.4 × 10^9/µL; leukocyte count, 1.2 × 10^9/L; erythrocyte count, 2.06 × 10^12/L; hemoglobin level, 7.3 g/dL; mean corpuscular volume, 105 fL; reticulocyte fraction, 0.1%; and folate level, 2.7 ng/mL). Platelet and (following treatment with granulocyte colony-stimulating factor) leukocyte counts recovered within 6 days, allowing the patient's discharge from the hospital.

Comment. One of the most severe adverse reactions associated with methotrexate therapy includes serious, and at times fatal, pancytopenia. Whereas the incidence of hematological reactions related to low-dose systemic methotrexate therapy is estimated to be 1.5% to 3%,3 such an adverse effect has, to the best of our knowledge, never been described after lesional application in dermatological settings. The case reported here is even more intriguing because usually, despite optimal techniques, 30% to 50% of the methotrexate solution injected into the KA immediately leaks,1 ie, the dose applied to tissue was approximately 8 to 9 mg at best. Findings from a meta-analysis of the literature describing 65 patients with bone marrow toxic reactions related to systemic low-dose methotrexate therapy showed a mean cumulative dose of 675 mg of methotrexate intake on diagnosis of pancytopenia4; however, in several cases a minimal cumulative dose of 10 mg was found. Of the patients in these reports, 54% had underlying renal abnormalities. Other factors increasing the risk of pancytopenia included folic acid deficiency, advanced age, infection, obesity, diabetes mellitus, and concomitant use of other drug, especially of agents with antifolate activity such as trimethoprim-sulfamethoxazole.4

The exact mechanism for the development of pancytopenia in the patient presented here remains unclear. Most likely, systemic resorption from the cutaneous application site without relevant clearance in the time intervals between hemodialysis might have favored the potentially toxic accumulation of methotrexate or its metabolites. Folic acid deficiency, exacerbated by loss during dialysis and/or poor nutrition, amplified the cytotoxic effect of methotrexate on bone marrow and oral mucosa.

The case of severe pancytopenia presented here underscores the need for greater awareness of potentially life-threatening risks, especially hematologic adverse effects of methotrexate, which may occur even in dermatological settings with single applications to the skin. It should be mandatory that physicians and staff monitor associated risk factors, particularly impaired renal function and folate deficiency, in patients undergoing lesional methotrexate treatment of KA. Folate supplementation should be taken into consideration.

Matthias Goebeler, MD
Department of Dermatology
University of Würzburg
Josef-Schneider-Str. 2
97080 Würzburg, Germany
(e-mail: goebeler-m.derma@mail.uni-wuerzburg.de)
Christa Lurz, MD
Maria-Elisabeth Kolve-Goebeler, MD
Eva-Bettina Bröcker, MD
Würzburg

Methods. We performed a survey of the 110 dermatology residency programs in North America and Puerto Rico. A 10-question questionnaire that asked about the style and function of journal club meetings and about the characteristics of the participants was sent to dermatology program directors.

Results. Of the 110 program directors we contacted, 89 responded. All of these include journal club in their residency programs and require resident attendance.

The frequency and duration of journal club meetings varies. Most programs conduct hour-long meetings, either weekly (42) or twice monthly (22). Some meet once a month for 1 (6) or 2 hours (4). Most programs hold their meetings during the workday (43 programs) or in the mornings before the beginning of the workday (33 programs). Three programs hold noontime journal club, and 10 meet in the evening hours over dinner for educational and social interaction outside of the workplace.

Faculty participation in journal club ranges from none (1 program) to the entire faculty (20 programs). Most of the programs have from 1 to 3 faculty members present for journal club. Uniquely, one journal club program that holds weekly meetings invites a community dermatologist to participate once a month.

The most common approach to journal club is resident presentation of articles. Residents at most institutions are responsible for reading and being prepared to present every article in the reviewed journal. Other methods include (1) group discussion of a single article, (2) faculty and resident presentation of articles, and (3) resident presentation of a single article.

What journals are being reviewed? The Archives of Dermatology and the Journal of the American Academy of Dermatology are reviewed by every program. A number of nondermatology journals are also reviewed. Of the 21 journals named by the responding program directors, 8 are primarily nondermatology journals. Two of the top 5 were the New England Journal of Medicine and the Journal of the American Medical Association (Table).

All residency program directors believe that journal club is an integral part of a dermatology residency. Reasons they gave ranged from patient care to “a must” for the boards. Some programs stress critical analysis of the methods and data sections of a study.

Comment. Journal club is an integral part of residency education. As is the case with journal clubs conducted in internal medicine residency programs, the format of journal club meetings in dermatology training programs varies from program to program. Dermatology shares the educational goals of journal club across medical specialties, which include improving clinical practice, critical appraisal of the literature, and keeping up-to-date on the current medical knowledge. An idealized journal club incorporates these goals and fosters reading habits that continue past residency.

Many dermatology residency programs do not limit journal review to strictly dermatology journals. That 2 of the top 5 journals reviewed are the Journal of the American Medical Association and the New England Journal of Medicine is an attempt, we speculate, to keep abreast of current medical literature. Two examples of the dermatology-related articles presented in these 2 journals include “Absence of Toxicity of Oats in Patients with Dermatitis Herpetiformis” and “Increased Cancer Mortality Following a History of Nonmelanoma Skin Cancer.” In a recent editorial, Dr Bernhard so eloquently wrote, “Read the Lancet, or Else” you may miss important dermatology articles. In that article he calls for dermatologists to read journals such as the Lancet. Are we preparing residents to continue reading these important journals when our survey shows that 34% of responding programs review the Lancet?

We hope this survey triggers a reevaluation of how journal club is conducted in residency training. Should faculty members present articles as a model for resident presentation? Are nondermatology journals being reviewed? Are residents critical in their review of an article? Should community dermatologists be invited to journal club to lend their perspective? An important question not addressed in this survey is, How do we foster an interest in our residents to continually read the journals beyond residency training?

Journal club plays and will continue to play a significant role in dermatology residency education. It is a
wonderful means to keep abreast of current literature. We are happy to see the commitment that each program has to their respective journal clubs. We make just one request to all dermatologists... Continue Reading!

Bryan E. Anderson, MD
Division of Dermatology, HU 14
UPC II, Suite 4300
500 University Dr
PO Box 850
Hershey, PA 17033-0850
(e-mail: Drbryan@hotmail.com)

James G. Marks, Jr, MD
Jeffrey J. Miller, MD
Hershey

3. Hardman, CM, Garroch JJ, Leonard JN, et al. Absence of toxicity of oats in skin, and in 50-cm3 pools of each substance in plastic containers. We tested both chlorhexidine and povidone-iodine with the following 4 lasers: a 10,600-nm continuous-wave, carbon dioxide laser at 5 and 15 W and 1-mm spot size; a 585-nm pulsed dye laser at 10 J/cm2 and 5-mm spot size; a 532-nm pulsed diode laser at 20 J/cm2 and 0.7-mm spot size; and a 755-nm pulsed alexandrite laser at 25 J/cm2 and 15-mm spot size. As quickly as the machine could recover, 10 consecutive pulses were given with the pulsed lasers, whereas the carbon dioxide laser was continuously fired for 20 seconds. The carbon dioxide, pulsed dye, and alexandrite lasers were used with their focal pieces lightly touching the media; the diode laser was held at a distance of 1 to 2 cm from the media. We tested both chlorhexidine and povidone-iodine on heavily saturated gauze pads, on heavily saturated pigskin, and in 50-cm3 pools of each substance in plastic containers. Regardless of the substrate, none of the lasers ignited any of these 3 substances. We also attempted to ignite ethyl alcohol-saturated gauze and pigskin under the same conditions. Neither ignited.

Comment. Chlorhexidine will not sustain combustion and povidone-iodine is not flammable and does not have a flashpoint. When vaporized, chlorhexidine produces primarily carbon dioxide and carbon monoxide. Povidone-iodine can produce "iodine fumes." Laser plume evacuation units can evacuate these potentially problematic products and toxic reactions from inhalation are managed simply by transference to fresh air. Both material safety data and our study support the safe use of povidone-iodine and chlorhexidine if a laser plume evacuator is concomitantly used.

Our study addresses only the flammability of surgical cleansers. However, there are 2 additional issues. Is sterile surgical preparation even necessary for laser procedures, and if it is used, will it decrease laser efficacy? We can only offer our hypotheses and justify our practices.

Whereas it is reasonable to surgically prepare the skin when the laser will be used as a cutting device, we believe that surgical preparation is not necessary unless the integumentary barrier is violated. Moreover, cleanser pigments and residua could compete with endogenous chromophores and alter laser reflectance, transmission, and absorption. We do not routinely prepare the skin for superficial laser ablation or for laser treatment of vascular lesions, pigmented lesions, or tattoos; however, prior to carbon dioxide laser resurfacing, we prepare the skin with a 3-minute chlorhexidine scrub followed by a 3-minute sterile saline rinse.

Daniel A. Davis, MD
University Of Iowa College of Medicine
Department of Dermatology
200 Hawkins Dr, 2045-1BT
Iowa City, IA 52242
(e-mail: daniel-a-davis@uiowa.edu)

Ryan S. Owlsley, MD, RPh
Duane C. Whitaker, MD
Iowa City


Photoinduced Sweet Syndrome

Sweet syndrome is a neutrophilic dermatosis that selectively affects photoexposed areas such as the face, neck, and forearms. However, the triggering or aggravating role of solar irradiation has not been mentioned in the large series reported in the literature. To the best of our knowledge, we describe the first case of exclusively photoinduced Sweet syndrome.
Report of a Case. A 71-year-old man was referred in July 1998 for a febrile (temperature, 38.5°C) cutaneous eruption that had recurred 1 or 2 days after prolonged exposure to the sun every summer for the past 8 years. Previously, he had 1 flare per year, in midsummer, after intense solar exposure outside during half a day, with an average of 1 to 5 lesions per flare. The skin lesions had resolved spontaneously within 1 month, with residual pigmentation persisting for several months. At admission, he had 4 plaques with a diameter of up to 5 cm, clearly delimited, raised, erythematous, and painful. They were located only on directly sun-exposed areas: the face (forehead and lower eyelids), the lower third of the external surface of the arm (sparing the inner aspect of the limb) (Figure 1 A), the forearms, and the backs of the hands. No other cutaneous or mucosal lesions, accompanying clinical and/or functional signs, drug intake prior to the eruption, or preceding infectious episodes were noted. The results of physical examination were otherwise unremarkable.

Laboratory findings revealed an inflammatory syndrome: erythrocyte sedimentation rate, 58 mm in the first hour; C-reactive protein, 6 times the normal level; leukocyte count, $11.1 \times 10^3$ cells/µL with $8.55 \times 10^3$ neutrophils per microliter. Results of histological examination of a skin sample indicated neutrophilic infiltration of the upper and mid dermis. Direct immunofluorescence did not reveal a lupus band. Other biological and morphological test results demonstrated no infectious, chronic inflammatory, autoimmune, or malignant etiology. Lesions resolved slowly over 1 month with daily topical application of dermocorticosteroids and rigorous protection against sun exposure.

Photobiological tests were conducted using a solar simulator (Dermolum; Müller Elektronik-Optik, Moosing, Germany) equipped with a high-pressure 1000-W xenon lamp, a dichroic mirror (stopping 95% of the wavelengths up to 600 nm), a 2-mm Schott cutoff filter WG (Schott Glaswerke, Mayence, Germany), and a grating monochromator. Output of the solar simulator was measured with a thermopile (sensitivity, 270 nm to 4 µm; Müller Elektronik-Optik). The upper back and upper third of the arm, where no lesion had ever occurred, were exposed the following fall after the lesions had cleared. The 24-hour minimal erythema dose of polychromatic rays was normal at 1500 mJ/cm² (normal value for skin phototype II, 1200-2200 mJ/cm²). Localized polychromatic phototests and a monochromatic phototest on the upper arm using a UV-B wavelength of 290±10 nm induced, within 48 hours after exposure, the same clinical lesions of bright red papules, without fever or reactivation of the distant original cutaneous plaques (Figure 1B). Histologically, the reproduced lesions were typical of Sweet syndrome (Figure 2). Localized phototest results with 310±10- and 330±10-nm UV-B and UV-A wavelengths were negative. Based on these findings, the patient was advised to use a high-activity sunscreen (sun protective factor [SPF] 60) the following summer, which efficiently prevented the eruptions from recurring.

Comment. To the best of our knowledge, this is the first observation of seasonally recurrent and exclusively photoinduced Sweet syndrome, as suggested by the following characteristics: phototriggering during the first prolonged exposure to summer sun, distribution only on exposed areas, and reproduction of clinical and histological lesions after localized phototests with short UV-B bands. Only 1 case report described the worsening of Sweet syndrome after sun exposure and the reproduction of similar lesions after short-wavelength UV-B irradiation, as happened with our patient. The pathomechanism could involve either an isomorphic Koebner reaction, classically described in neutrophilic dermatoses, or the direct action of UV-B on neutrophilic infiltration of the upper and mid dermis.

Figure 1. A, Erythematous plaques of Sweet syndrome on the external surface of the forearm. B, Clinical lesions resulting from polychromatic and monochromatic photobiological tests with 290±10-nm wavelength UV-B.
phil activation and recruitment in skin through the production of cytokines such as interleukin 8 and tumor necrosis factor α. This case emphasizes the need of a systematic search for prior sun exposure in Sweet syndrome, including photobiological testing, especially for the so-called idiopathic forms.

Didier Bessis, MD
Service de Dermatologie-Phlébologie
CHU Montpellier, Hôpital Saint-Éloi
80 ave Augustin-Fliche
34295 Montpellier CEDEX 5, France
(e-mail: d-bessis@chu-montpellier.fr)

Olivier Dereure, MD
Jean-Louis Peyron, MD
Didier Augias, MD
Jean-Jacques Guilhou, MD
Montpellier


Chronic Penile Lymphedema: A Report of 6 Cases

We report our experience with the management of 6 cases of chronic penile lymphedema (CPL). This is a distressing condition that probably occurs as the result of chronic or persistent lymphatic irritation and scarring for which there is no satisfactory treatment.

Chronic penile lymphedema is a relatively rare entity, and there is very little literature on the subject and its management. It differs from penile venereal edema and acute idiopathic penile edema in several ways: it is persistent, has no demonstrable infective cause, and there is no documented effective treatment. Although it may occur as a consequence of primary hypoplastic lymphatic channels, in our opinion it usually occurs as a result of recurrent unidentified infections and/or another concomitant penile dermatosis and infection thereof, with subsequent damage to the lymphatic vessels. We report our experience with 6 patients with CPL observed in our penile dermatosis clinic.

Report of Cases. Six patients with CPL were identified from our clinic from 1994 through 2000. The age range of the patients was 33 to 71 years (Table). The duration of penile lymphedema varied from 1 to 5 years. All patients complained of penile or preputial swelling and sexual dysfunction or phimosis. One patient had a history of treated syphilis infection some 30 years prior to the onset of CPL. Another patient complained of recurrent episodes of candidal infection following sexual intercourse. One patient had 2 episodes of nonspecific balanitis (with negative microbiological results). Another patient had long-standing hidradenitis suppurativa affecting his groin and gluteal region; he had undergone several surgical procedures to drain scrotal and perineal abscesses. One patient had not had sexual relations at all but had a history of lichen planus affecting the penile shaft a year prior to the onset of CPL. One other patient had a history of perineal and gluteal psoriasis and recurrent erysipelas. Three patients had undergone previous circumcision, but 1 of these had residual preputial tissue. No other patients had a history of venereal disease, nor was there any relationship to sexual intercourse elicited. No patient was thought to have a relevant drug history or a history of atopy or intermittent angioedema.

Examination findings from all patients revealed a "saxophone" penis with gross preputial and penile shaft edema (Figure 1 and Figure 2). In uncircumcised patients the prepuce was nonretractile, and the glans could not be examined. Inguinal lymphadenopathy was found by palpation in 1 patient.

Investigations have included antistreptolysin antibody titers (positive in 2 cases) and penile swabs; the swabs of 2 patients yielded enterococcus that was thought to be opportunistic. Results of full blood count, erythrocyte sedimentation rate measurement, and routine biochemical and liver function tests were normal in all patients.

At first presentation, all patients were empirically prescribed antibiotics: 500 mg of erythromycin stearate
4 times a day for 2 weeks initially and then a maintenance dose of 500 or 250 mg twice daily for an indefinite period, depending on clinical response. Nonresponders were given an alternative antibiotic (ciprofloxacin or minocycline) or a combination (rifampicin and trimethoprim). For acute relapses, short courses of prednisolone (30 mg daily for 2 to 3 weeks) were prescribed as well as antibiotic cover, to good effect. Antihistamines (cetirizine) were prescribed at the recommended dose for 2 patients, without benefit; higher doses were not used.

Acute on chronic lymphedema was markedly reduced in all patients, but maintenance treatment has been required in all cases. All patients have sustained a reasonable quality of life with these measures, although none has achieved remission.

Comment. Chronic penile lymphedema is a reactive disfiguring condition that causes sexual dysfunction and phimosis. It has previously been described as tumorous lymphedema or elephantiasis verrucosa nostrae.¹ A possible cause can usually be identified from the patient’s history and examination results; for instance, 2 of our patients had circumstantial clinical or laboratory evidence of streptococcal infection, while 2 other cases (patients with penile lichen planus and previous treponemal disease) were idiopathic. However, the underlying resultant pathology is presumably the same in all cases, namely “scarring” of the lymphatic channels. No definitive treatment is available, although all of our patients have partially responded to long-term antibiotics or short courses of prednisolone in the acute phase. This approach stabilizes the process and improves the appearance and function of the penis. It also allows time for consideration of surgical intervention (circumcision).

There have been reports of penoscrotal edema, and attributed causes include continuous ambulatory peritoneal dialysis,² amputation of septic limbs in the context of diabetes,³ strangulation, thrombosis, acute necrotizing pancreatitis,⁴ and streptococcal infections.⁵ Penile venereal edema has been associated with gonococcal and herpes infection and scabies infestation and resolves after treatment of the underlying disease.⁶ Similarly, childhood penile edema is self-limiting.⁷ It is probable that cases of CPL are the result of any of the aforementioned causes or indeed due to temporally unrelated but repetitive venereal disease. Perineal, scrotal, gluteal, and penile skin drains to superficial inguinal lymph nodes, and deeper structures to the internal iliac nodes.

All may be involved in a regional inflammatory process, and persistent lymphatic insult from whatever cause can lead to this recurrent entity. Hence, all cases of penoscrotal edema should be treated aggressively at first presentation.

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>CPL Duration, y</th>
<th>ASO Titer, IU/mL</th>
<th>Association</th>
<th>Circumcised</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/47</td>
<td>4</td>
<td>&lt;200</td>
<td>Lichen planus</td>
<td>Yes</td>
</tr>
<tr>
<td>2/71</td>
<td>4</td>
<td>&gt;800</td>
<td>Psoriasis/erysipelas</td>
<td>No</td>
</tr>
<tr>
<td>3/69</td>
<td>5</td>
<td>200-400</td>
<td>Previous syphilis</td>
<td>Yes</td>
</tr>
<tr>
<td>4/67</td>
<td>4</td>
<td>&lt;200</td>
<td>Balanitis</td>
<td>Yes</td>
</tr>
<tr>
<td>5/33</td>
<td>5</td>
<td>&lt;200</td>
<td>Candida</td>
<td>No</td>
</tr>
<tr>
<td>6/55</td>
<td>1</td>
<td>&lt;200</td>
<td>Hidradenitis</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*CPL indicates chronic penile lymphedema; ASO, antistreptolysin.

Figure 1. A, Chronic penile edema. B, Restoration of function following treatment with oral antibiotics and circumcision.

Figure 2. Chronic penile lymphedema.
Only 1 case of recurrent adult idiopathic penile edema has been reported. This patient had a history of surgical renal procedures and an orchidectomy as a child for an undescended testis. The patient partially responded to terfenadine but without clinical remission. His disease was attributed to “allergy,” but we think that it was more likely to have been a typical case of CPL.

The aim of treatment of CPL must be prophylaxis against further infective episodes, aggressive treatment of relapses, and in uncircumcised patients, amelioration of signs to enable institution of surgical measures if necessary (for instance, for patients with underlying penile dermatoses whose affected glans cannot be treated topically because of their CPL, which itself causes phimosis). Imaging of lymphatic channels is unlikely to shed further light on the cause of this enigmatic condition, though imaging may be used to differentiate between primary and secondary lymphedema. Further investigation is required if we are to offer a more effective treatment to these unfortunate patients.

William Porter, MRCP
Michael Dinneen, MD, FRCS
London, England
Christopher Bunker, MD, FRCP
Department of Dermatology
Chelsea & Westminster Hospital
Imperial College School of Medicine
369 Fulham Rd
London SW10 9NH
England
(e-mail: bill4mands@aol.com)


Ceramide-Dominant, Barrier-Repair Lipids Improve Childhood Atopic Dermatitis

We report here the initial promising results of a phase 1 trial of a ceramide-dominant, barrier-repair moisturizer in childhood atopic dermatitis (AD). Atopic dermatitis is a multifactorial, polygenic skin disorder that affects up to 20% of preadolescent children in Western countries and is commonly viewed as immunologic in origin.1,3 Whereas anti-inflammatory agents (eg, topical glucocorticoids and immunosuppressive agents) are mainstays of therapy in AD, reliance on these drugs carries potential risks, particularly in children, and AD typically relapses or flares after discontinuation of therapy.3

Alternatively, the xerosis and/or permeability-barrier abnormality could drive disease activity in AD and other inflammatory dermatoses. These abnormalities seem to provoke and sustain AD through activation of an epidermis-initiated cytokine cascade, which then recruits the specific immunologic phenotype.4 Both involved and clinically uninvolved skin in AD exhibit a barrier defect,5 which correlates with a reduction in the stratum corneum (SC) ceramide fraction.6 Although moisturizers are mainstays in the management of AD,7 currently available emollients neither address nor correct the underlying SC lipid abnormality.

Recent studies have shown that topical mixtures of the 3 key SC lipids, including not only ceramide, but also cholesterol and free fatty acids, when applied in optimized proportions (ie, a 3:1:1 molar ratio), accelerate barrier repair following a variety of external, acute, or sustained perturbations.8,9 Hence, we tested a new ceramide-dominant, barrier-repair complex (TriCeram; Osmotics Corp, Denver, Colo) in 21 children with moderate to severe AD, all of whom were already receiving optimal topical therapy (ie, topical glucocorticoids or tacrolimus, antihistamines, and emollients). All subjects continued to use their standard medications, substituting only our ceramide-dominant, barrier-repair complex for their prior moisturizer, which was applied twice daily to both involved and uninvolved skin. We computed pretreatment and posttreatment Severity Scoring of Atopic Dermatitis (SCORAD) scores; transepidermal water loss (TEWL) levels (Tewameter; Courage-Khazaka, Cologne, Germany); SC hydration levels by corneomembrane structures.

The combined SCORAD scores for all participants declined significantly by 3 weeks, with a further improvement at 6 weeks (Figure 1A). Almost all subjects (19/21) demonstrated a reduction in their individual SCORAD scores, with the greatest reductions apparent in the most severely affected children. The lack of improvement in 2 subjects correlated with intercurrent, infectious episodes. The TEWL levels also declined significantly at 3 and 6 weeks in involved skin vs pretreatment measurements (Figure 1B) and normalized further in adjacent, uninvolved skin by 6 weeks (mean ± SD posttreatment TEWL levels in AD-uninvolved skin, 8.82 ± 1.2 g/cm² per hour; normal, ≈8 g/cm² per hour). The integrity of uninvolved SC skin sites also improved significantly after 3 and 6 weeks of treatment (Figure 1C). Finally, electron microscopy of tape-stripped SC showed significant replenishment of the SC interstices with lamellar membrane bilayers in the skin sites treated with the ceramide-dominant, barrier-repair complex (Figure 2).
These preliminary results demonstrate the potential efficacy of a ceramide-dominant, barrier-repair formulation in children with recalcitrant AD. Since external humidities declined during this study, seasonal changes could not have produced the observed benefits. Physiologic lipids differ in their mechanism of action from standard emollients, which typically form an occlusive, semipermeable layer on the skin surface. The physiologic lipids, instead, become part of the lipid-secretory machinery of the stratum granulosum. Depending on the number of species in the mixture (ie, ceramide, cholesterol, free fatty acids), and their proportions, barrier recovery either slows, proceeds as usual, or accelerates. Mixtures of the 3 key SC species in optimal molar ratios (3:1:1 mixtures) at concentrations higher than 1% to 2% accelerate barrier recovery leading to rapid normalization of permeability barrier function. We suggest that the improvement in our patients can be attributed to a normalization of barrier function, which in turn dampened the cytokine cascade that could initiate and sustain AD. The improvement in barrier function and SC integrity that occurred in the uninvolved skin of these subjects was an unanticipated benefit, implying a decreased propensity for disease provocation. The promising results of this preliminary trial in patients with recalcitrant AD should stimulate follow-up, multicenter, double-blinded trials of ceramide-dominant, barrier-repair formulations in chil-

Figure 1. A, Changes in Severity Scoring of Atopic Dermatitis (SCORAD) scores for all subjects (asterisk indicates \( P < .001 \)); B, changes in transepidermal water loss (TEWL) levels over involved skin (asterisk indicates \( P < .01 \)); and C, changes in stratum corneum integrity (uninvolved skin) (asterisk indicates \( P < .01 \)).

Figure 2. A, Atopic dermatitis after treatment with standard moisturizer; note the paucity of lamellar bilayers. B, The same patient after 3 weeks of treatment with a ceramide-dominant, barrier-repair complex (TriCeram; Osmotics Corp, Denver, Colo). Two types of changes occur in multilamellar structure after switching to TriCeram treatment: increased numbers of normal extracellular bilayers (white solid arrow) and additional intercellular lamellar membranes with a distinctive morphology (black solid arrows). The open arrows in both A and B indicate amorphous, nonlamellar material from other substances in the moisturizers ( ruthenium tetroxide stain used postfixation, original magnification for both A and B, \( \times 65000 \)).
dren and adults, and an exploration of their efficacy for
the prevention of AD in infants.5,6

Sarah L. Chamlin, MD
Ilona J. Frieden, MD
Ashley Fowler, BS
Mary Williams, MD
Jack Kao, MD
Mary Sheu, BS
San Francisco
Peter M. Elias, MD
Department of Dermatology
University of California, San Francisco
Dermatology Service (190)
Veterans Administration Medical Center
4150 Clement St
San Francisco, CA 94121
(e-mail: eliaspm@itsa.ucsf.edu)

Dr Elias is a paid consultant to Osmotics Corp, which spon-
sored the research for this article, but he did not partici-
pate in the clinical studies.

343:1338-1341.
4. Elias PM, Wood LC, Feingold KR. Epidermal pathogenesis of inflammatory
5. Seidenari S, Giusti G. Objective assessment of the skin of children affected by
atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and
of ceramides in stratus corneum of atopic dermatitis: an etiologic factor in
physiologic vs physiologic lipids: divergent mechanisms for correction of per-
8. Man MM, Feingold KR, Thornfeld CR, Elias PM. Optimization of physiologi-

Errors in Abstract, Affiliations, and Conclusions. In the review by Yosipovitch et al titled “Suggested Rationale for Pre-
vention and Treatment of Glucocorticoid-Induced Bone Loss in Dermatologic Patients,” published in the April issue of the
ARCHIVES (2001;137:477-481), some errors occurred on pages 477 and 479-481.

On page 477, the first paragraph of the introduction of the main text beginning with “We recommend that patients who
are receiving a long-term regimen of corticosteroids be managed with a 3-pronged approach. . . .” should have been the last
paragraph of the abstract. The author listed in the byline as Goh Chee Leok, MD, should have read Chee Leok Goh, MD, and
the authors’ affiliations should have read, “From the National Skin Center, Singapore (Drs Yosipovitch, Hoon, and Goh).”

On page 479, in the last sentence of the first paragraph, “hyperkalemic” should have been spelled “hypercalcemic.”

On pages 480 and 481, the guidelines in the “Conclusions” section should have read as follows:

Risk Assessment:
• Baseline lumbar spine and femoral neck bone mineral density assessment (DXA testing) at the beginning of therapy
  and twice annually thereafter.
• In patients 60 years of age or older, a yearly radiography assessment of the spine to exclude fractures.

Prevention:
• Weight-bearing and non–weight-bearing exercises and physical therapy.
• Refraining from smoking and excessive alcohol consumption.
• Administration of 800 IU/d of vitamin D, plus 1000 mg/d of calcium, on commencing high-dose, long-term gluco-
corticoid treatment, excluding those with hypercalcemia, hypercalciuria, and/or nephrolithiasis.
• Women with early and late menopause receiving high-dose, long-term glucocorticosteroid treatment should be given
0.625-1.25 mg/d of conjugated estrogen or 50 µg/d of transdermal estradiol, alone or with progestogen preparations.
• Patients who have osteopenia defined as T scores below –1 at the beginning of systemic glucocorticoid treatment and
patients with accelerated bone loss during the first 6 to 12 months of treatment may be considered for treatment with
a bisphosphonate (eg, 5 mg/d of alendronate, 5 mg/d of risedronate, or 400 mg/d of cyclical etidronate).

Treatment:
• In patients with bone densities more than 2.5 SDs below the young normal mean (T score less than –2.5) or in those
patients with previous osteoporotic fractures or significant osteoporosis on radiography, the addition of a bisphos-
phonate should include 10 mg/d of alendronate (approved by the Food and Drug Administration for patients receiv-

ing prolonged glucocorticoid therapy), 5 mg/d of risedronate, or 400 mg/d of cyclical etidronate. Patients with severe
osteoporosis, especially those with symptoms and fractures, may add 200 IU/d of nasal calcitonin to their regimen.
• Postmenopausal women with low bone density should be given 60 mg/d of raloxifene hydrochloride.

Follow-up:
• Yearly assessment of serum blood and urine calcium excretion and alkaline phosphatase levels.
• Referral to a rheumatologist or endocrinologist specializing in the treatment of osteoporosis for assessment and long-
term management.