
This report reflects the best data available at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

Acne: 1991-2001

Diane Thiboutot, MD *Hershey, Pennsylvania*

OVERVIEW

The goal of this presentation is to update practitioners on developments in the pathogenesis and treatment of acne from 1991 to 2001.

PATHOGENESIS

The pathogenesis of acne centers on the interaction of follicular hyperkeratinization, action of *Propionibacterium acnes*, sebum production, and inflammation.

Follicular hyperkeratinization

The cause of follicular hyperkeratinization is still unknown. Follicular deficiency of linoleic acid has been implicated. Recent studies suggest that interleukin 1 and androgens may be involved in this process.

Proliferation of follicular keratinocytes

Knaggs H, Holland K, Morris C, Wood E, Cunliffe W. Quantification of cellular proliferation in acne using the monoclonal antibody Ki-67. *J Invest Dermatol* 1994;102:89-92.

Keratinocyte proliferation was assessed in normal follicles and acne follicles by using the antibody Ki-67. Cellular proliferation was greater in normal follicles from acne-affected areas compared with areas not affected by acne. Proliferation was also greater in comedones compared with normal follicles. The authors conclude that normal follicles from skin affected with acne may be "acne-prone" compared with normal follicles from areas of skin not affected by acne.

Role of cytokines: Interleukin 1

Guy R, Green M, Kealey T. Modeling of acne in vitro. *J Invest Dermatol* 1996;106:176-82.

Using a model of human infrainfundibular segments to study the process of follicular hyperkeratinization, these authors found that the addition of interleukin 1 (IL-1) to the infrainfundibular segments caused hyperkeratinization similar to that seen in comedones. This effect could be blocked by addition of IL-1 receptor antagonist. These authors suggest that changes in sebum secretion or composition could lead to the release of IL-1 by follicular keratinocytes, which in turn may stimulate comedogenesis.

Role of androgens

Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5 α -reductase exhibits regional differences in isolated sebaceous glands and whole skin. *J Invest Dermatol* 1995;105:209-14.

Activity of the type 1 5 α -reductase was shown to predominate in human sebaceous glands and epidermis. This enzyme is responsible for the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT). DHT in turn is thought to mediate androgen-dependent skin diseases such as acne, hirsutism, and androgenetic alopecia. In this study, activity of the type 1 5 α -reductase was greatest in sebaceous glands isolated from acne-prone regions of the skin compared with nonacne-prone regions. These data suggest that regional differences in the local production of DHT may contribute to androgen-mediated skin diseases and that specific inhibition of the type 1 5 α -reductase may be beneficial in the treatment of these conditions.

Thiboutot D, Knaggs H, Gilliland K, Hagari S. Activity of the type 1 5 α -reductase is greater in the follicular infrainfundibulum compared to the epidermis. *Br J Dermatol* 1997;136:166-71.

Androgen metabolism in infrainfundibular segments of follicles and in epidermal keratinocytes was studied to explore the potential role of andro-

From the Division of Dermatology, Pennsylvania State College of Medicine.

Reprint requests: Diane M. Thiboutot, MD, Pennsylvania State College of Medicine, Division of Dermatology, 500 University Dr, UPC 2, Suite 4300, Hershey, PA 17033.

J Am Acad Dermatol 2002;47:109-17.

Copyright © 2002 by the American Academy of Dermatology, Inc.

0190-9622/2002/\$35.00 + 0 16/1/123483

doi:10.1067/mjd.2002.123483

gens in follicular hyperkeratinization. Activity of the type 1 5 α -reductase was noted in infrainfundibular segments, suggesting that these keratinocytes are capable of converting testosterone to DHT. Enzyme activity was greater in the infrainfundibular keratinocytes, suggesting that these cells have a greater capacity to produce androgens compared with the epidermis. Additional studies are needed to document a role for androgens in follicular hyperkeratinization.

Propionibacterium acnes

Bacterial resistance. Before 1976, resistance of *Propionibacterium acnes* to antibiotics was not an issue. During the past several years, investigators have documented resistance to erythromycin and tetracyclines and the emergence of resistance to minocycline. How this resistance affects the use of antibiotics for acne is a matter of discussion.

Eady EA, Jones CE, Tipper JL, Cove JH, Cunliffe WJ, Layton AM. Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *Br Med J* 1993;306:555-6.

In 1992, 468 patients with acne were screened for resistant strains of *P acnes*. Among these, 178 patients carried resistant strains of *P acnes*. Resistance to erythromycin was most common (124 patients); most of these strains were cross-resistant to clindamycin. Sixty-one patients carried strains that were resistant to tetracycline and cross-resistant to doxycycline but not to minocycline. Thirty patients carried strains resistant to trimethoprim. Twenty-seven patients had 2 or more strains with different antibiotic resistance. In 1992 no strains resistant to minocycline were noted. Recommendations: (1) Do not use oral antibiotics when topical agents will suffice. (2) Treat for no longer than is necessary. (3) If further treatment is needed, reuse the same drug whenever possible. Use intervening courses of topical benzoyl peroxide to eliminate resistant strains. (4) Avoid concomitant topical and oral treatment with chemically dissimilar antibiotics to prevent the development of resistance to both.

Effective agents to decrease resistance

Coates P, Adams CA, Cunliffe WJ, et al. Does oral isotretinoin prevent *Propionibacterium acnes* resistance? *Dermatology* 1997; 195(Suppl 1):4-9; discussion 38-40.

Pilot data are presented to suggest that isotretinoin may be effective in reducing the number of antibiotic-resistant *P acnes* organisms.

Eady EA, Bojar RA, Jones CE, et al. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996;134:107-13.

In a double-blind study, 37 patients with mild to moderate acne were treated with 5% benzoyl per-

oxide/3% erythromycin for 6 weeks. This resulted in a 3 log reduction in total *P acnes* and significantly reduced the number of erythromycin-resistant strains. In contrast, erythromycin alone only produced a 1.5-log reduction in total *P acnes* counts and did not reduce the number of resistant strains after the same amount of time. In an open study of 21 patients with erythromycin-resistant strains of *P acnes*, the total counts and counts of resistant strains were reduced by 2.5 log after 6 weeks.

Sebum production

Acne in prepubescent children (role of dehydroepiandrosterone sulfate)

Lucky AW, Biro FM, Huster GA, et al. Acne vulgaris in premenarchal girls. An early sign of puberty associated with rising levels of dehydroepiandrosterone. *Arch Dermatol* 1994;130:308-14.

The relationships of pubertal maturation, sex steroid hormone levels, and the presence of acne were examined in 626 premenarchal females (mean age, 9.97 \pm 0.62 years). Girls were evaluated for acne prevalence and severity. Pubertal maturation and serum hormone levels were determined in 181 girls. Overall, 77.8% of girls had some acne: 48.3% had comedonal acne, 2.2% had only inflammatory acne, and 27.3% had both types. The level of serum dehydroepiandrosterone sulfate (DHEAS) was significantly higher in prepubertal girls with comedonal acne compared with girls without acne. The level of DHEAS was also significantly higher in the girls with inflammatory acne compared with those without inflammatory acne. Serum DHEAS is significantly and specifically associated with the development of acne in young girls.

Stewart ME, Downing DT, Cook JS, Hansen JR, Strauss JS. Sebaceous gland activity and serum dehydroepiandrosterone sulfate levels in boys and girls. *Arch Dermatol* 1992;128:1345-8.

Sebum composition, serum levels of DHEAS, and pubertal stage were examined in 111 boys and girls aged 2 to 15 years. Sebum composition was evaluated by measuring the ratio of wax esters to cholesterol + cholesterol esters, a ratio known to increase with increasing sebaceous gland activity. The sebum ratio and serum DHEAS level began to rise in children aged 7 to 10 years, before signs of puberty in many. The production of sebum, as assessed by the sebum ratio, correlated significantly with serum levels of DHEAS, indicating that adrenal androgens are a major determinant of sebaceous gland activity during the prepubertal period.

Role of 5 α -reductase type 1

Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5 α -reductase exhibits regional differences in isolated sebaceous glands and whole skin. *J Invest Dermatol* 1995;105: 209-14.

Activity of the type 1 5 α -reductase was shown to

predominate in human sebaceous glands and epidermis. This enzyme is responsible for the conversion of testosterone to the more potent androgen, DHT. DHT in turn is thought to mediate androgen-dependent skin diseases such as acne, hirsutism, and androgenetic alopecia. In this study, activity of the type 1 5α -reductase was greatest in sebaceous glands isolated from acne-prone regions of the skin compared with nonacne-prone regions. These data suggest that regional differences in the local production of DHT may contribute to androgen-mediated skin diseases and that specific inhibition of the type 1 5α -reductase may be beneficial in the treatment of these conditions.

Thiboutot D, Gilliland K, Light J, Lookingbill D. Androgen metabolism in sebaceous glands from subjects with and without acne. *Arch Dermatol* 1999;135:1041-8.

The activity of the androgen-metabolizing enzymes, 5α -reductase (converts testosterone to DHT) and 17β -hydroxysteroid dehydrogenase (interconverts androstenedione and testosterone), was measured in sebaceous glands isolated from facial skin of males and females with mild to moderate acne. Serum levels of DHEAS, testosterone, DHT, and androstenedione were determined in these patients. The mean serum levels of androgens were significantly higher in females with acne compared with those without acne, yet values were within the normal range. The mean activity of 5α -reductase type 1 was higher in sebaceous glands from women with acne compared with those without acne, although this difference did not achieve statistical significance. These data suggest that as a group, women with acne have higher serum androgen levels and possibly an increased capacity to produce potent androgens within the sebaceous glands via the type 1 5α -reductase.

Neonatal acne and *Malassezia* species

Niamba P, Weill FX, Sarlangue J, Labreze C, Couprie B, Taieb A. Is common neonatal cephalic pustulosis (neonatal acne) triggered by *Malassezia sympodialis*? *Arch Dermatol* 1998;134:995-8.

Nineteen patients with neonatal acne and 19 control subjects younger than 45 days were studied. Cultures from pustules and contralateral uninvolved skin were obtained from patients, and cultures from healthy site-matched skin were obtained from control subjects. Among 14 patients from whom adequate samples were taken, 4 had positive results for *Malassezia* species. Cultures from 6 of 16 contralateral swabs were also positive. All cultures indicated the presence of *Malassezia sympodialis*. Among the 19 control subjects, 6 had cultures positive for *Malassezia* species: 4 for *M furfur* and 2 for *M sympodialis*. The severity of the papulosis correlated

with isolation of *M sympodialis*. Common neonatal cephalic pustulosis is a well-recognized entity, which was, in the past, improperly named *neonatal acne*. The hypothesis that it represents an inflammatory reaction against *Malassezia* species is strongly suggested by this study.

THERAPY

New therapies and dosage forms

Topical retinoids. Tretinoin interacts with cytoplasmic retinoic acid-binding proteins and each subclass of retinoic acid receptor (RAR α , β , and γ). New retinoids such as tazarotene and agents with retinoid activity such as adapalene interact with RAR β and RAR γ but not with RAR α . This receptor selectivity may impart differences in efficacy and side effect profiles.

Adapalene (Differin)

Shalita AR, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol* 1996;34:482-5.

In a multicenter study of 323 patients with acne, the safety and efficacy of adapalene gel and tretinoin 0.025% gel were compared. Evaluations were performed at baseline and weeks 2, 4, 8, and 12. Adapalene gel 0.1% produced greater reductions in non-inflammatory ($P = .02$), inflammatory ($P = .06$), and total lesions ($P < .01$) at 12 weeks. There were significantly fewer incidents and less severity of erythema, scaling, dryness, and burning throughout the study in the adapalene group ($P < .05$). Of note is that tretinoin therapy is not often initiated with the 0.025% gel formulation, because it is most often prescribed once patients have become accustomed to tretinoin.

Tazarotene (Tazorac)

Shalita AR, Chalker DK, Griffith RF, Herbert AA, Hickman JG, Maloney JM, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. *Cutis* 1999;63:349-54.

The safety and efficacy of tazarotene 0.1% and 0.05% gels were compared with vehicle gel in a 12-week randomized double-blind study of 446 patients with mild to moderate facial acne. Treatment with tazarotene 0.1% gel resulted in significantly greater reductions in noninflammatory and total lesion counts at all follow-up visits and significantly greater reductions in inflammatory lesion counts at week 12 compared with vehicle gel. Tazarotene 0.05% gel resulted in significantly greater reductions in noninflammatory and total lesion counts than vehicle gel at weeks 8 and 12. At week 12, treatment success rates were 68% and 51% for tazarotene 0.1%

and tazarotene 0.05%, respectively (40% reduction for vehicle gel).

Tretinoin dosage forms. Novel delivery systems (microspheres and polyolprepolymer-2) have been developed to minimize the adverse effects associated with topical tretinoin.

Tretinoin microspheres (Retin A micro)

Webster G. Topical tretinoin in acne therapy. *J Am Acad Dermatol* 1998;39:538-544.

Data on the safety and efficacy of 0.1% tretinoin gel microspheres compared with vehicle gel are presented in this review. Tretinoin gel microspheres, applied once daily, were significantly more effective than vehicle in reducing acne lesion counts in 2 studies, each involving approximately 70 patients who were treated for 12 weeks. The mean percent reduction in noninflammatory lesions was 49% and 32% for studies 1 and 2 compared with vehicle (22% and 3%, respectively). For inflammatory lesions, counts were reduced by the active drug by 37% and 29% in studies 1 and 2 compared with reductions of 18% and 24% in the vehicle groups. Data from a double-blind, randomized, half-face study comparing 0.1% tretinoin gel microspheres with 0.1% tretinoin cream are presented and indicate improved tolerance with the microsphere preparation.

Tretinoin/polyolprepolymer polymer (Avita)

Lucky A, Cullen S, Funicella T, Jarratt M, Jones T, Reddick M. Double-blind, vehicle-controlled, multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. *J Am Acad Dermatol* 1998;38(Suppl):S24-S30.

The safety and efficacy of tretinoin cream 0.025% in a vehicle containing polyolprepolymer-2 (Avita, Penederm, Inc, Foster City, Calif) and commercially available tretinoin 0.025% cream (Retin-A, Ortho Dermatologics, Raritan, NJ) were compared in 271 patients with mild to moderate acne. Patients were treated for 12 weeks. The efficacy and safety of both formulations were comparable, and each formulation was statistically significantly better than vehicle creams.

Lucky A, Cullen S, Jarratt M, Quigley J. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter, double-blind, parallel study. *J Am Acad Dermatol* 1998;38:517-523.

The safety and efficacy of tretinoin gel 0.025% in a vehicle containing polyolprepolymer-2 (Avita, Penederm, Inc) and commercially available tretinoin 0.025% gel (Retin-A, Ortho Dermatologics) were compared in 215 patients with mild to moderate acne. Patients were treated for 12 weeks. The efficacy of both formulations was comparable, and each was statistically significantly better than vehicle gels.

Significantly less peeling and drying than the commercially available tretinoin gel was noted at day 84 of the study. Of note is that tretinoin therapy is not often initiated with the 0.025% gel formulation because it is most often prescribed once patients have become accustomed to tretinoin.

Topical antibiotics

Azelaic acid (Azelex). Azelaic acid has been widely used in Europe for several years. It was approved for use in the United States in 1996. This drug is a dicarboxylic acid with both comedolytic and antibacterial activity. It is available as a 20% cream.

Graupe K, Cunliffe W, Gollnick H, Zaumseil R. Efficacy and safety of topical azelaic acid (20% cream): an overview of results from European clinical trials and experimental reports. *Cutis* 1996;57:13-9.

The authors review pertinent clinical studies of the efficacy of azelaic acid 20% cream as monotherapy in the treatment of acne vulgaris in comparison with vehicle, tretinoin cream 0.05%, benzoyl peroxide 5% gel, 2% erythromycin gel, oral tetracycline, and oral isotretinoin. Data regarding combination therapy of azelaic acid with minocycline and azelaic acid maintenance therapy are also presented. Studies of the safety and tolerability of azelaic acid are summarized, as are studies of the safety and efficacy of azelaic acid in the treatment of rosacea.

Clindamycin/benzoyl peroxide

Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *J Am Acad Dermatol* 1997;37:590-5.

In two double-blind, randomized, parallel, vehicle-controlled trials, patients were treated once nightly with a combination clindamycin/benzoyl peroxide gel, benzoyl peroxide, clindamycin, or vehicle gel. Evaluations included acne lesion counts and assessment of global responses and irritant effects. A total of 334 patients completed the study. All 3 active preparations were significantly better than vehicle. The combination gel was significantly superior to the 2 individual agents in global improvement and reduction of inflammatory lesions. The authors conclude that topical clindamycin/benzoyl peroxide gel is well-tolerated and superior to either individual agent.

Hormonal therapies

Oral contraceptives. New progestins have been developed that have low intrinsic androgenic activity. These progestins include desogestrel, norgestimate, and gestodene (not available in the United

States). Each of these has been combined with ethinyl estradiol in an oral contraceptive. Ortho TriCyclen has been approved by the Food and Drug Administration (FDA) for treatment of acne. It contains norgestimate in combination with 35 μg of ethinyl estradiol. Newer preparations containing lower doses of estrogen (20 μg) are also being evaluated for efficacy in the treatment of acne.

Lucky A, Henderson T, Olson W, Robisch D, Lebwohl M, Swinyer L. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997;37:746-54.

Redmond GP, Olson WH, Lippman JS, Kafriksen ME, Jones TM, Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. *Obstet Gynecol* 1997;89:615-22.

Two randomized, double-blind, placebo-controlled trials of a norgestimate and ethinyl estradiol combination oral contraceptive in the treatment of moderate acne in women were performed. Each trial included approximately 250 women who were treated for 6 months and were evaluated for the presence of acne and adverse effects. In each study, the improvement in acne was significantly greater in the active group than in the placebo group, with a 50% to 60% improvement in inflammatory lesions. The drug was well tolerated. Decreases in serum free testosterone levels and an increase in sex hormone binding globulin were noted in the active group.

Thornycroft I, Stanczk F, Bradshaw K, Ballagh S, Nichols M, Weber M. Effect of low-dose oral contraceptives on androgenic markers and acne. *Contraception* 1999;60:255-62.

A multicenter, open-label, randomized trial was performed to compare androgen profiles and clinical outcomes associated with 2 oral contraceptives containing the same amounts of ethinyl estradiol (20 μg) but different progestins: levonorgestrel (LNG), 100 μg (Alesse), and norethindrone acetate (NETA), 1000 μg (Loestrin). Thirty women received 3 cycles of treatment with LNG and 28 women received NETA. These results showed that LNG reduced adrenal, ovarian, and peripheral androgen levels. NETA reduced peripheral and adrenal androgens. Despite a 2.2-fold greater relative increase in sex hormone binding globulin with NETA than with LNG, bioavailable testosterone was reduced by the same amount with NETA and LNG. Both treatments improved acne and were well-tolerated. Although these 2 progestins affected secondary markers differently, both produced an equivalent decrease in bioavailable testosterone.

Spironolactone

Shaw J. Low-dose adjunctive spironolactone in the treatment of acne in women: a retrospective analysis of 85 consecutively treated patients. *J Am Acad Dermatol* 2000;43:498-2.

Records were reviewed from 85 women treated with spironolactone, 50 to 100 mg/d, administered either as a single agent or as an adjunct to standard therapies. The maximum length of treatment was 24 months. Clearing of acne occurred in 33% of women treated with low-dose spironolactone: 33% had marked improvement, 27.4% showed partial improvement, and 7% showed no improvement. The data are further broken down according to concomitant therapies. The treatment was well-tolerated, with 57.5% of women reporting no adverse effects. Menstrual irregularities were reported in 17.5% of women; and symptoms of lethargy, fatigue, dizziness, or headache (central nervous system symptoms) were reported in 16.3%. Less common symptoms included breast tenderness, diuretic effect, postural hypotension, and nausea. Slight elevations in serum potassium levels (range, 4.8-5.3 mEq/L) were identified in 13.7% of the 73 patients examined. This was not considered to be clinically significant. The following benefits were noted in some patients: improvement in premenstrual syndrome, decreased facial oiliness, decreased metrorrhagia, reduced endometriosis pain, and increased libido. These data suggest that (1) most adverse effects of spironolactone are dose-dependent; (2) menstrual irregularities, the most common side effect, can be reduced significantly by using lower doses of spironolactone; (3) central nervous system symptoms can occur in up to 16% of patients but appear to be unrelated to dose; (4) hyperkalemia is measurable but clinically insignificant in the absence of cardiac or renal disease; and (5) reductions in blood pressure are slight but can (rarely) be associated with orthostatic symptoms. Of note is that spironolactone is not approved by the FDA for the treatment of acne.

Phototherapy for acne. The recent literature contains reports of the efficacy of visible light and photodynamic therapy in the treatment of acne.

Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. *Br J Dermatol* 2000;142:973-8.

One hundred seventeen patients with mild to moderate acne were randomly assigned to receive treatment with blue light, mixed blue and red light, cool white light, and 5% benzoyl peroxide. Daily irradiation with light was performed for 15 minutes. After 12 weeks, a mean improvement of 76% in inflammatory lesions was achieved with the blue-red phototherapy. This was significantly superior to the other treatment groups. The authors conclude that phototherapy with blue-red light, probably by

combining antibacterial and antiinflammatory action, is an effective treatment for acne.

Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol* 2000;115:183-92.

Topical aminolevulinic acid (ALA) is converted to a potent photosensitizer in hair follicles and sebaceous glands. Twenty-two subjects with acne on the back were treated in 3 sites with topical ALA plus red light, ALA alone, light alone; one site was left untreated as a control. Eleven patients were treated once and 11 patients were treated twice. Sebum excretion rate and autofluorescence from follicular bacteria were measured before treatment and at 2, 3, 10, and 20 weeks after treatment. Clinical and statistically significant clearance of inflammatory acne was associated with ALA plus red light for at least 20 weeks after multiple treatments and 10 weeks after a single treatment. Adverse effects included transient hyperpigmentation, superficial exfoliation, and crusting, which cleared without scarring. ALA plus red light caused phototoxicity to sebaceous follicles, prolonged suppression of sebaceous gland function, and an apparent decrease in follicular bacteria after photodynamic therapy.

Update on current therapies

Topical tretinoin and pregnancy

Buchan P, Eckhoff C, Caron D, Nau H, Shroot B, Schaefer H. Repeated topical administration of all-*trans*-retinoic acid and plasma levels of retinoic acids in humans. *J Am Acad Dermatol* 1994;30:428-34.

Plasma retinoid levels were measured in healthy subjects before, during, and after 14 days of topical tretinoin application (2 g) to the face, neck, and upper chest. Diurnal and nutritional factors influenced plasma levels of endogenous retinoids to a greater extent than topical administration of all-*trans*-retinoic acid in doses used for acne therapy.

Shapiro L, Pastuszak A, Curto G, Koren G. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet* 1997;350:1143-4.

A survey study of 94 first-trimester exposures to topical tretinoin compared with 133 controls showed no differences in pregnancy outcome. The incidence of major malformations did not differ. Major defects in tretinoin-exposed babies included one bicuspid aortic valve and one case of dysplastic kidneys. Neither defect is associated with retinoid embryopathy. Defects in the control group consisted of congenital hip dislocation and imperforate anus. Results failed to show an increased risk of congenital malformations for users of topical tretinoin.

Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. *Lancet* 1993;341:1181-2.

Data from 215 women exposed to topical tretinoin during the first trimester of pregnancy were compared with data from 430 matched, nonexposed control subjects. Of note is that these women were identified as having a prescription filled for tretinoin, but it is not known whether or how much tretinoin was used. The prevalence of major anomalies among babies born to exposed mothers was 1.9% compared with 2.6% among babies born to nonexposed mothers. The relative risk estimate of having a baby with a major congenital anomaly for exposed versus nonexposed women was 0.7 (95% confidence interval = 0.2-2.3), suggesting that from an epidemiologic standpoint, first-trimester exposure to tretinoin did not increase the risk of major congenital anomalies.

Isotretinoin

Mechanism of action

Tsukada M, Schroder M, Roos T, Chandraratna R, Reichert U, Merk H, et al. 13-*Cis* retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-*trans* retinoic acid and binding to retinoic acid receptors. *J Invest Dermatol* 2000;115:321-7.

Isotretinoin does not bind to retinoid receptors, and hence, it is thought to act as a prodrug in the treatment of acne. In this study, the metabolism of 13-*cis*-retinoic acid was studied in an immortalized human sebocyte cell line (SZ95 cells). Rapid isomerization of 13-*cis*-retinoic acid to all-*trans*-retinoic acid was demonstrated by using high-performance liquid chromatography. This rapid isomerization was a sebocyte-specific event because no significant isomerization of 13-*cis*-retinoic acid to all-*trans*-retinoic acid occurred in immortalized keratinocytes (HaCaT cells). These data support the hypothesis that 13-*cis*-retinoic acid exerts its action in acne by isomerization to all-*trans*-retinoic acid, which then interacts with known retinoid receptors.

Long-term safety and efficacy

Layton AM, Knaggs H, Taylor H, Cunliffe WJ. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol* 1993;129:292-6.

Eighty-eight patients were treated with isotretinoin for acne. Most patients required 4 months of therapy to produce at least 85% improvement. Patients were seen again after 10 years. Sixty-one patients were clear of their disease. Of the others, 16% required treatment with conventional antibiotics and 23% required a second course of isotretinoin. Of those who experienced relapse, 96% did so within the first 3 years. Those patients receiving 0.5 mg/kg per day or a cumulative dose of <120 mg/kg had a significantly higher relapse rate compared with

those receiving a higher dose. Long-term biochemical or systemic adverse effects were not noted.

Barth JH, MacDonald-Hull SP, Mark J, Jones RG, Cunliffe WJ. Isotretinoin therapy for acne vulgaris: a re-evaluation of the need for measurements of plasma lipids and liver function tests. *Br J Dermatol* 1993;129:704-7.

Plasma lipid profiles and liver function test results of 209 patients treated with isotretinoin were reviewed. Of these subjects, 113 were treated with 1 mg/kg per day, and 96 were treated with 0.5 mg/kg per day. There were no significant changes in liver function test results during 16 weeks of treatment. There were significant elevations in plasma cholesterol and triglyceride levels at 8 and 16 weeks for both dosage regimens. All individuals with elevated cholesterol levels during therapy had elevated cholesterol levels at baseline. There were no further elevations in plasma triglyceride levels after 8 weeks. These authors conclude that it is prudent to monitor for elevations in liver enzyme levels and plasma lipid levels at baseline and for elevations in plasma triglyceride levels at 4 weeks.

Need for repeat courses

Stainforth JM, Layton AM, Taylor JP, Cunliffe WJ. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? *Br J Dermatol* 1993;129:297-301.

Two hundred ninety-nine patients treated with isotretinoin were followed up for an average 5 years after treatment: 22.7% required repeat courses of isotretinoin; 17% had 2 courses, 5% had 3 courses, and 1% had 4 to 5 courses. Factors contributing to the need for additional courses were lower dose regimens (0.1-0.5 mg/kg per day), the presence of severe acne, being a female older than 25 years at the start of therapy, and having a prolonged history of acne.

Effects on bone in acne regimens

Margolis DJ, Attie M, Leyden J. Effects of isotretinoin on bone mineralization during routine therapy with isotretinoin for acne vulgaris. *Arch Dermatol* 1996;132:769-74.

Twenty patients were treated with isotretinoin, 0.89 mg/kg per day (range, 0.77-0.98 mg/kg per day), for 20 weeks. Markers of bone turnover and calcium homeostasis were assayed at baseline and various time intervals over the 20 weeks. Bone mineral density of the lumbar spine and hip was determined by dual-energy x-ray absorptiometry at baseline and 20 weeks. No alterations were noted in serum measurements of osteocalcin, calcium, 25-dihydroxyvitamin D, intact parathyroid hormone, or urinary hydroxyproline or calcium. A significant decrease in serum 1,25-dihydroxyvitamin D was noted after isotretinoin therapy. No changes were noted in bone mineralization of the lumbar spine or hip.

Kindmark A, Rollman O, Mallin H, Petren-Mallimin M, Ljunghall S, Melhus H. Oral isotretinoin therapy in severe acne induces transient suppression of biochemical markers of bone turnover and calcium homeostasis. *Acta Derm Venereol* 1998;78:266-9.

Eleven patients with nodulocystic acne were treated with isotretinoin (mean maintenance dose, 0.88 mg/kg per day; range, 0.66-1 mg) for 6 months. Biochemical markers of bone turnover were examined at baseline and after 1, 5, and 14 days of therapy. Bone mineral density (dual-energy x-ray absorptiometry) of the lumbar spine was determined at baseline and after 6 months of treatment. Transient fluctuations in markers of bone turnover were noted at 5 days. These values normalized by day 14. No significant radiologic changes or effects on bone mineral density were noted.

Leachman SA, Insogna KL, Katz L, Ellison A, Milstone LM. Bone densities in patients receiving isotretinoin for cystic acne. *Arch Dermatol* 1999;135:961-5.

Bone density and calcium metabolism were measured in 18 men treated with isotretinoin for cystic acne (1 mg/kg per day for 6 months) and in 14 control subjects. Bone density was measured at the lumbar spine, femoral neck, and Ward's triangle (a region of the femoral head). Bone density was variable in men with cystic acne, even at baseline. No changes in calcium metabolism as a result of treatment were noted. Changes in bone density were noted at Ward's triangle (mean decrease of 4.4%, $P = .03$) in treated patients. No significant changes in bone density were noted in the other 2 regions. The clinical significance of this change in bone density has not yet been determined.

Modified guidelines for use

Cunliffe W, van de Kerkhof P, Caputo R, Cavicchini S, Cooper A, Fyrand O, et al. Roaccutane treatment guidelines: results of an international survey. *Dermatology* 1997;194:351-7.

An international group of 12 experts on acne treatment met to formally review the survey of their last 100 patients with acne treated with oral isotretinoin to identify the types of patients treated and how their treatment was managed. Of the 1000 patients reviewed, 55% were treated on the basis of historical guidelines, and 45% were treated according to criteria that consisted of failure to respond to conventional oral antibiotic and topical therapy, scarring acne, acne causing psychologic distress, and acne that quickly relapses during or after conventional therapy. A discussion on dosing regimens and adverse effects is presented.

Intermittent isotretinoin

Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. *Br J Dermatol* 1998;137:106-8.

Eighty patients with acne unresponsive to or relapsing rapidly after 3 or more courses of antibiotics were recruited. Patients were treated with isotretinoin 0.5 mg/kg per day for 1 week every 4 weeks for a total of 6 months. Seventy-five patients completed the study. Both total acne grade and lesion counts were significantly reduced at the end of treatment. The acne resolved in 68 (88%) of patients. The response was maintained in 68 patients who responded, but 26 patients had relapses after 1 year. Higher relapse rate correlated to acne severity, truncal acne, and increased sebum excretion rate. Intermittent administration of moderate-dose isotretinoin may be a cost-effective alternative to administration of full doses in adults with facial acne, mild acne (fewer than 20 inflamed lesions), and a low sebum excretion rate.

Issues of depression/suicide

Lamberg L. Acne drug depression warnings highlight need for expert care. *JAMA* 1998;8:1057.

Lamberg presents statistics for the rates of suicide reported before 1998 in patients taking isotretinoin (12 suicides/8 million treated patients) in the context of the incidence of major depression in the acne age group of 15 to 24 years (6.1%). A brief discussion of the psychologic risks and benefits of isotretinoin therapy is included.

Jick S, Kremers H, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. *Arch Dermatol* 2000;136:1231-6.

A population-based cohort study of 7195 isotretinoin users and 13,700 oral antibiotic users from 2 health databases was performed. The prevalence rates of neurotic and psychotic disorders, suicide, and attempted suicide were compared between isotretinoin and antibiotic users and within the group of isotretinoin users (before and after treatment). Relative risk estimates comparing isotretinoin use and oral antibiotic use with nonexposure to either drug for newly diagnosed depression or psychosis were approximately 1.0. Relative risks were approximately 1.0 before and after isotretinoin use. The relative risk estimate for attempted suicide was 0.9 when current isotretinoin exposure was compared with nonexposure. The authors conclude that this study provides no evidence that use of isotretinoin is associated with an increased risk for depression, suicide, or other psychiatric disorders.

Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001;45:515-9.

An analysis was made of the reports of depression, suicidal ideation, suicide attempt, and suicide

in US isotretinoin users voluntarily submitted to the manufacturer and the FDA from 1982 to May 2000 and entered in the FDA's Adverse Event Reporting System database. There were 37 reports of suicide; 110 reports of patients hospitalized for depression, suicidal ideation or suicide attempt; and 284 reports of depression without hospitalization. With institution of the depression warning in 1998, there was an influx of reports of depression received from an increased percentage of patients and patients' families. Isotretinoin ranks in the top 10 drugs for which reports of depression and suicide attempt have been received. Case reports of patients both with and without recurrence of depressive symptoms during repeat courses of isotretinoin are presented. The authors comment that additional studies are needed to determine whether isotretinoin causes depression.

Minocycline. Adverse effects associated with the use of minocycline include systemic lupus erythematosus; serum sickness-like reactions; autoimmune hepatitis; pseudotumor cerebri; pigmentation of skin, sclera, mucous membranes, and alveolar bone; pneumonitis; and eosinophilia.

Chiu A, Chuenkongkaew W, Cornblath W, Trobe J, Digre K, Dotan S, et al. Minocycline treatment and pseudotumor cerebri syndrome. *Am J Ophthalmol* 1998;126:116-21.

A retrospective study of 12 patients from 5 neuro-ophthalmic referral centers, in whom pseudotumor cerebri developed after administration of standard doses of minocycline for acne, was performed. Seventy-five percent of cases of pseudotumor developed within 8 weeks. Two cases developed after a year. One patient was asymptomatic. No recurrences were noted after 1 year. Three patients (25%) had residual visual field loss after 1 year. Withdrawal of minocycline and treatment for increased intracranial pressure led to resolution of the pseudotumor cerebri syndrome, but visual field loss may persist.

Goulden V, Cunliffe WJ. Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996;134:693-5.

Seven hundred patients treated with minocycline for acne were studied. Two hundred patients were monitored for adverse effects and laboratory abnormalities; tests included complete blood count, determination of blood urea nitrogen and electrolyte levels, and liver function tests. Adverse effects were recorded in 13.6%. Pigmentation was the only adverse effect found to be significantly increased in patients taking higher doses of minocycline as compared with those taking lower doses. All patients with pigmentation had taken more than 70 g. No significant abnormalities were found in any of the

hematologic or biochemical profiles. Authors conclude that minocycline is safe for long-term treatment of acne in doses up to 200 mg/d. The mean duration of treatment was 10.5 months. Doses ranged from 100 to 200 mg/d.

Gough A, Chapman S, Wagstaff K, Emery P, Elias E. Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *Br Med J* 1996;312:169-72.

Eleven cases of minocycline-induced systemic lupus erythematosus and 16 cases of hepatitis were reported to the Committee on Safety of Medicines in the United Kingdom. An additional 7 cases are presented. Two patients being treated for acne died, and one needed a liver transplant. The authors stress the need for early recognition of minocycline reactions.

Sitbon O, Bidel N, Dussopont C, Azariam R, Braud ML, Lebargy F, et al. Minocycline pneumonitis and eosinophilia. *Arch Intern Med* 1994;154:1633-40.

Data are presented on 8 cases of minocycline-induced pneumonitis and eosinophilia in patients being treated for acne ($n = 4$), genital infection ($n = 3$), and Lyme disease ($n = 1$). The mean duration of treatment was 13 ± 5 days. The mean total dose was 2060 ± 540 mg. Patients presented with dyspnea, fever, dry cough, hemoptysis, chest pain, fatigue, or rash. Seven of 8 had eosinophilia.

Sturkenboom MC, Meier CR, Jick H, Stricker BH. Minocycline and lupuslike syndrome in acne patients. *Arch Intern Med* 1999;159:493-7.

A case-controlled study was conducted in a cohort of 27,688 patients with acne, aged 15 to 29 years, in general practitioners' offices in the United Kingdom. Lupus-like syndrome was defined as the occurrence of polyarthritis or polyarthralgia of unknown origin with negative rheumatoid factor or latex agglutination test results, positive or unmeasured antinuclear antibody level, elevated or unmeasured erythrocyte sedimentation rate, and absence or unmeasured antinative DNA antibody levels. Current use of minocycline was associated with an 8.5-fold greater risk of developing lupus-like syndrome.

ured erythrocyte sedimentation rate, and absence or unmeasured antinative DNA antibody levels. Current use of minocycline was associated with an 8.5-fold greater risk of developing lupus-like syndrome.

Acne scarring

Alster T, McMeekin T. Improvement of facial acne scars by the 585 nm flashlamp-pumped pulsed dye laser. *J Am Acad Dermatol* 1996;35:79-81.

Hypertrophic and erythematous facial acne scars were treated with the flashlamp-pumped pulsed dye laser in 22 patients. Scars on the opposite side of the face were used as a control. Scars were evaluated by photography, grading of erythema with reflectance spectroscopy, and skin texture analysis. Significant clinical improvement was observed in laser-irradiated acne scars compared with untreated scars after 1 or 2 laser treatments. Erythema measurements and skin texture analyses of laser-treated scars approximated those obtained in adjacent normal skin.

Walia S, Alster T. Prolonged clinical and histologic effects from CO₂ laser resurfacing of atrophic acne scars. *Dermatol Surg* 1999;25:926-30.

Sixty patients with moderate to severe atrophic facial acne scars were evaluated in the immediate postoperative period and during long-term follow-up (12-18 months) after laser resurfacing. Nineteen patients received regional cheek treatment, and 41 patients received full-face resurfacing with a high-energy pulsed carbon dioxide laser. Clinical and histologic analyses of scars were performed at baseline and at 1, 6, 12, and 18 months after resurfacing. Significant immediate and prolonged clinical improvement in skin tone, texture, and appearance of carbon dioxide laser-irradiated scars was seen in all patients. On average, scars were improved by 75% at 18 months compared with 67% improved at 6 months. Histologically continued collagenesis and dermal remodeling were observed for up to 18 months after surgery.