Editorial

Retinoids in Dermatology

Retinoids are compounds derived from vitamin A (retinol). They are new and important therapeutic additions for a wide variety of dermatologic conditions. Their actions on the skin are similar to those of vitamin A and include inhibition of inflammation, keratinization, and cell growth.[1] The side effects of retinoids are also similar to the findings in hypervitaminosis A.[2]

Vitamin A has been used with some success for acne, psoriasis, and disorders of keratinization.[1] Although the recommended daily allowance of vitamin A for adults is 5,000 IU, the dosages used for therapy are at least 100,000 IU daily and sometimes as high as 1,000,000 IU daily. The toxicity associated with these high doses limits the duration of treatment.

A naturally occurring vitamin A acid, tretinoin, became available for dermatologic conditions,[1] but its systemic use offered no therapeutic or safety benefit over vitamin A. Topically applied tretinoin (Retin-A), however, has proved to be extremely effective in the treatment of acne vulgaris. In the United States, it is commercially available as a gel, cream, or liquid. Typical side effects of topical retinoid use are dryness, irritation, and possibly photosensitivity at the site of treatment. Topically administered tretinoin can also be used for a wide variety of skin conditions, including flat warts, disorders of keratinization, oral lichen planus, and sun-damaged skin and wrinkles.[1,3]

Synthetically Created Retinoids.—More than 1,000 retinoids have been synthesized during the past 20 years. The goal has been to produce retinoids with a high therapeutic effect yet a low incidence of induced symptoms of hypervitaminosis A. Currently, two orally administered retinoids are in common use in the United States—isotretinoin for cystic acne and etretinate for the treatment of psoriasis. With use of both of these drugs in therapeutic doses, the side effects of hypervitaminosis A can occur, but they provide more benefit with less toxicity than does high-dose vitamin A therapy.

The first synthetic orally administered retinoid to become approved for general use in the United States was an isomer of tretinoin, isotretinoin (13-*cis*-retinoic acid, Accutane). Isotretinoin is the greatest single advance thus far in the treatment of acne. After a 4-month course of therapy with isotretinoin at 1.0 to 1.5 mg/kg daily, acne clears dramatically in many patients, and the skin remains clear in most of them for extended periods after therapy has been discontinued. Because patients experience some side effects of hypervitaminosis A with use of isotretinoin at the therapeutic dose, it is recommended only for severe and recalcitrant cases of acne. Also, isotretinoin is a potent teratogen, a common finding with retinoids. Fortunately, however, it has a half-life of only 1 day and is rapidly eliminated from the body. Therefore, after only 1 month off therapy and the completion of one full menstrual cycle, women may safely become pregnant.

Isotretinoin is also effective for a wide variety of other cutaneous diseases. It is the therapy of choice (and essentially a cure) for gram-negative folliculitis. Isotretinoin therapy leads to substantial improvement in all types of ichthyosis; moreover, acne rosacea, hidradenitis suppurativa, cutaneous neoplasms, and pustular psoriasis may respond favorably to this agent. The latter conditions are chronic problems, and isotretinoin is merely a treatment, not a cure. Therefore, the long-term side effects, especially hyperostotic skeletal changes, may outweigh the benefits in some patients.

The most recent addition to retinoid therapy is an aromatic retinoid, etretinate (Tigason). It became available in the United States in December 1986 for the treatment of psoriasis. It is also effective for various disorders of keratinization but is not particularly useful in the treatment of acne. Etretinate can be used as monotherapy for psoriasis[4] but is even more effective in combination with traditional therapies including topical corticosteroids and anthralin, ultraviolet B wave-

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length therapy (alone or as part of the Goeckerman regimen), and psoralen and ultraviolet A wavelength treatment (PUVA).[5]

Etretinate therapy also causes the symptoms of hypervitaminosis A at therapeutic doses.[5] Unlike treatment with isotretinoin for acne, however, patients are treated for indefinite periods, and the long-term problems of retinoid therapy become important. Also, etretinate is lipophilic and has a half-life of 120 days.[5] It can be detected in low levels in the serum for more than 2 years after a course of therapy has been discontinued. Etretinate is a potent teratogen, and women of childbearing potential who receive this drug must avoid pregnancy for an as yet undetermined period after treatment.

In this issue of the *Proceedings* (pages 1084 to 1089), Madhok, Muller, and Dicken discuss the use of an experimental retinoid, acitretin (etretin, Ro 10-1670). Acitretin is the free acid and principal metabolite of etretinate. Initial studies in which acitretin was used for psoriasis—as monotherapy in the United States[6,7] and in combination with conventional therapies in Europe[8,9]—indicated that it may be similar to etretinate in efficacy and toxicity. The advantage of this new retinoid over etretinate is that it has a half-life of 50 hours; therefore, acitretin cannot be detected in serum 3 weeks after discontinuation of treatment.[10] Acitretin is also a potent teratogen,[11] but because of its shorter half-life, women may safely conceive far sooner after discontinuing therapy than is currently possible with etretinate.

A new class of retinoid currently being tested only in Europe is the arotinoids.[1,5] Arotinoids are 1,000 times more potent on a weight basis than the currently available retinoids. They seem to be more efficacious for the treatment of psoriasis than etretinate and associated with fewer systemic side effects. One problem with arotinoids is that the therapeutic dose is too small to allow detection of the drug in the serum. Therefore, if they are teratogens in humans, difficulty will be encountered in determining how long they persist in the body.

Retinoid Treatment of Psoriasis.—The most severe forms of psoriasis can be extremely resistant to therapy. The development of the synthetic retinoids now provides another option for treatment of this condition. It is not surprising that psoriasis, a disease of inflammation and increased cell proliferation, responds to retinoids with their anti-inflammatory and antiproliferative effects.

Although etretinate has only recently been approved for general use, extensive information is available from experimental trials performed during the past 10 years in the United States. Even when used as monotherapy, etretinate is successful in the treatment of psoriasis.[4,5] Approximately 80% of patients have good to excellent results with use of a daily dose of 0.6 to 1.0 mg/kg.

Because of side effects associated with use of etretinate, this therapy should generally be reserved for recalcitrant cases of psoriasis. Pustular psoriasis (both the localized and the von Zumbusch type) responds quickly and dramatically to a daily dose of 0.75 to 1.0 mg/kg of etretinate.[5] Erythrodermic psoriasis also responds extremely well to this drug, and lower dose therapy (0.3 to 0.5 mg/kg daily) is usually effective.[5] Common plaque psoriasis does not respond as effectively to etretinate as the two aforementioned types, but the drug is still efficacious in most patients with this dermatologic disorder.

We currently use etretinate as a first-line drug in erythrodermic and pustular psoriasis because these conditions respond so well and are usually resistant to other therapies. Patients with psoriasis vulgaris should be resistant to conventional therapy before they are treated with etretinate. In general, we have found that the more severe the psoriasis, the better is the response to etretinate therapy.

The new retinoid acitretin is now being tested in the United States to evaluate its efficacy for psoriasis. Many investigative groups, including our own, have used this drug as monotherapy in double-blind and open studies. In their preliminary report of acitretin as a treatment for psoriasis in this issue of the *Proceedings*, Madhok, Muller, and Dicken describe good to excellent results in six of eight patients treated for 6 months. This outcome is similar to that reported by Kingston and associates[6] and our own experience with 38 patients who had psoriasis.[7]

Some confusion remains about whether etretinate or acitretin is actually effective for psoriasis when used as monotherapy. Contributing to this uncertainty is the fact that many practitioners begin treatment with a daily dose as low as 0.3 mg/kg. This dose is not efficacious yet can cause many of the minor side effects of hypervitaminosis A. Therefore, the dose often is not increased

and the patient experiences no improvement. If the beginning dose is 0.6 mg/kg daily, the patient's psoriasis usually will be alleviated; although the side effects of hypervitaminosis A are present, they are not substantially worse than those occurring at lower doses. Once the patient's condition improves, the dose can be tapered.

Etretinate has been used even more successfully when combined with conventional therapies for psoriasis.[5] Combination therapy with PUVA and etretinate (sometimes called RePUVA) has produced excellent clearing of psoriasis. Using the two therapies together increases the response rate, allows for a lower dose of etretinate, and decreases the number of PUVA treatments and the ultraviolet energy needed. These circumstances prevail for etretinate and ultraviolet B wavelength therapy as well. Even the topical use of corticosteroids or anthralin can enhance the efficacy of etretinate.

Therefore, we now frequently use etretinate in combination with conventional therapy for psoriasis. Our results are better than those we achieved using etretinate as monotherapy during strict experimental protocols. In Europe, use of acitretin in combination with other psoriatic therapies yielded improved results.[8,9]

Both etretinate and acitretin cause the side effects of hypervitaminosis A.[2,4-9] Although they have a far better therapeutic index than vitamin A, even at routine doses these side effects become evident. The most common side effects, however, are mucocutaneous and thus relatively minor. Although they are bothersome, rarely are they severe enough to necessitate discontinuation of therapy. Most patients will experience chapped lips (cheilitis), peeling palms and soles, and dry skin at a daily dose of 0.3 mg/kg or greater of etretinate[5] or acitretin.[7] In some patients, hair loss can become a severe cosmetic problem. Such side effects should be discussed extensively with patients before administration of a systemic retinoid, as patients are far more compliant when they know what side effects are expected. The mucocutaneous side effects begin after only a few weeks of therapy and rapidly resolve after discontinuation of treatment.

Another common problem is a retinoid dermatitis that can occur in up to half the patients.[5] It may mimic a flare of the psoriasis and prompt the physician to increase the dose of retinoid; however, raising the dose will exacerbate the dermatitis. Such patients will show improvement with a lower retinoid dose or a temporary discontinuation of therapy.

Both acitretin and etretinate can cause various other side effects. Myalgias, arthralgias, headaches, edema, fatigue, and chills have been encountered. Although these adverse effects occur less frequently than the mucocutaneous side effects,[5,7] they may be more troublesome for the patient.

Hyperlipidemia has been a frequent problem associated with etretinate therapy[5,12] and seems to be a problem with acitretin also. Two of the eight patients in the current report by Madhok, Muller, and Dicken had elevation of triglyceride levels, but no change in cholesterol levels was noted. We have found substantial elevations in triglyceride levels and, to a lesser degree, elevations of cholesterol levels in many of our patients who received acitretin.[7] This finding correlates well with data on etretinate that indicate that 45% of treated patients will have elevation of triglycerides and 16% of patients will have elevation of cholesterol levels. Because patients frequently are treated with systemic retinoids for long periods, even modest elevations of cholesterol can lead to an increased risk of atherosclerotic disease. When lipid levels increase in such patients, every effort should be made to lower them by instituting an appropriate diet, decreasing the intake of alcohol, or reducing the retinoid dose.[5]

Another difficulty of systemic retinoid therapy is the possibility of hepatotoxicity. Approximately 20% of patients will have slight elevations of their transaminases during etretinate treatment.[5] Madhok, Muller, and Dicken noted a mild and transient elevation of results of liver function tests during acitretin therapy. Rarely, during etretinate treatment acute hepatitis has developed—apparently as an idiosyncratic reaction. Therefore, monitoring of liver function tests during etretinate or acitretin therapy is indicated.

A controversial issue is whether serial liver biopsies are necessary during etretinate and acitretin therapy. Several studies of liver biopsies performed during a 6-year period of etretinate therapy demonstrated no severe liver damage.[5] In a recent report,[13] 4 of 18 patients who underwent long-term etretinate therapy had liver damage found on biopsy specimens but undetected by any change in liver function tests; however, only

4 patients had pretreatment biopsies, and 9 patients had previously been treated with methotrexate. We believe that the current evidence does not support a need for routine liver biopsies, and we do not obtain liver biopsy specimens in our patients on long-term etretinate therapy.

A further consideration with long-term etretinate use is hyperostosis. After 5 years of etretinate therapy, more than 80% of patients have radiographic evidence of hyperostosis in predominantly extraspinal sites.[14] The tendons and ligaments of the feet and ankles are most commonly involved. We now obtain lateral roentgenograms of the feet annually to monitor our patients during etretinate therapy. Our patients taking acitretin in our experimental protocols are monitored by yearly roentgenograms of the lateral spine and feet to determine whether this agent also will cause hyperostoses with long-term use.

Although etretinate has only recently been introduced in the United States as an approved therapy for severe psoriasis, acitretin is already being tested as a possible replacement for it. The only advantages or differences that we have noted with acitretin to date are its short half-life and rapid elimination from the body. Women of childbearing potential could be treated with acitretin and could possibly conceive safely as early as 1 month after therapy was discontinued. On the basis of preliminary reports and our own experience, the therapeutic benefit and toxicity of acitretin are otherwise identical to these properties of etretinate. The search continues for new retinoids that have even better therapeutic benefit and less toxicity.

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