Retinoid Therapy for Severe Dermatological Disorders

Committee on Drugs

Isotretinoin is approved for the treatment of severe recalcitrant cystic acne, and etretinate is approved for the treatment of severe recalcitrant psoriasis. Women of childbearing age place their infants at risk should these compounds be used during pregnancy and, in the case of etretinate, even before pregnancy. The purpose of this statement is to describe the indications for the use of these drugs and to advise physicians of their common side effects and their teratogenic potential.

Isotretinoin, 13-cis-retinoic acid (Accutane, Hoffmann-La Roche), is a vitamin A derivative that is effective in the treatment of severe cystic acne. This type of acne, affecting adolescents and young adults, is severe, nodular, cystic, and conglobate—a scarring disease that resists treatment with topical or systemic antibiotics, benzoyl peroxide, all-trans-retinoic acid, and intralesional corticosteroids. Adolescents with less severe forms of acne who learn about the therapeutic triumphs of isotretinoin in severe recalcitrant nodular and cystic acne may assume that the drug also would be beneficial for them. Physicians should explain to these adolescents why isotretinoin is not indicated in the treatment of typical acne.

Another retinoid, etretinate (Tegison, Hoffmann-La Roche), is now available for the treatment of severe psoriasis that is unresponsive to standard therapies (topical tar with UVB light, anthralin, UVA light and psoralens, systemic corticosteroids and methotrexate). Etretinate is used for severe psoriasis of both the erythrodermic and generalized pustular types. Individualization of etretinate dosage is important. Most patients are started at a dosage of 0.75 to 1.0 mg/kg of body weight per day in divided doses. Maximum dose is 1.5 mg/kg per day. Some patients may respond to lower doses. The initial treatment period (to clinical response) is from 8 to 16 weeks; maintenance dose is usually lower than the initial dose. The decision to terminate therapy is made by the treating physician based on clinical response.

Patients with multiple, active, deep dermal, or subcutaneous cystic and nodular acne lesions are usually given 0.5 to 2 mg of isotretinoin per kilogram of body weight per day (although dosage as low as 0.05 mg/kg per day has been reported as beneficial), orally, in two divided doses. Therapy is continued for 15 to 20 weeks or until the total cyst count decreases by 70% if this happens sooner than 15 to 20 weeks. Use of this drug is associated with a reduction in sebaceous gland size and activity (a decrease in sebum excretion by as much as 75% to 90%), with inhibition of sebaceous cell differentiation, and with a reversion to prepubertal skin surface lipid composition. Although isotretinoin is expensive, a course of treatment usually results in significant clearing of lesions and a prolonged remission often follows.

Both isotretinoin and etretinate have also been used for other severe dermatological disorders.

Side effects do occur with both compounds and are similar; these appear to be lessened by reduction in dosage and to be reversible when the drug is discontinued. Vitamin A supplements may increase toxic effects and should not be taken with isotretinoin or etretinate. Cheilitis is found almost universally. Conjunctivitis (frequently staphylococcal blepharokeratoconjunctivitis), dryness of the skin and nasal mucosa, epistaxis, and pruritus are common. Arthralgia, myalgia, and hair loss occur less frequently. Hyperostosis occurs in greater than 80% of patients treated with etretinate for more than 5 years. Hyperostosis also occurs with isotretinoin therapy, but to a less extent.

Decreased night vision, corneal opacities, and blurred vision have occurred with retinoid therapy.

Alterations in patients' laboratory test results also may occur with the administration of both isotretinoin and etretinate. Studies have indicated that plasma triglyceride levels increase in 25% to 45% of patients; therefore, these levels should be measured before treatment and monitored at 1- or 2-week intervals thereafter by the physician treating the patient. If there are high triglyceride levels, dietary manipulation or reduction of dosage should be considered. Decreased serum high-density lipoprotein levels were found in 15% to 37% of patients, and 7% to 16% had increased serum cholesterol levels. Mild to moderate elevations in liver enzymes occur in 15% to 25% of patients. These elevations are usually transient and disappear with continued therapy or dose reduction. Elevated erythrocyte sedimentation rates occur in 40% of patients, 13% have high platelet counts, and some have changes in other standard hematological test results. The type and frequency of laboratory testing should follow labeling instructions.

Isotretinoin is a human teratogen. The risk of teratogenesis appears to be 20%. This represents the most serious potential complication from retinoid use. Isotretinoin produces defects in the central nervous system (hydrocephalus, microcephaly, microphthal-
mia), ears (microtia, anotia), and cardiovascular system. Other abnormalities have been reported less frequently. More than 50% of infants with and without external abnormalities show subnormal intelligence and other neuropsychological impairments. There is an increased incidence of spontaneous abortion among recipients.

Etretinate is a known animal teratogen. Its use during pregnancy has also been associated with human fetal malformations, such as myelomeningocele, encephalocele, dysmorphic facies, syndactyly, abnormal ears, and multiple synostoses. There is a report of an abnormal infant born 51 weeks after cessation of etretinate therapy who had the same constellation of malformations seen with isotretinoin. Etretinate has a long half-life and detectable plasma levels have been measured 2 to 3 years after cessation of the drug. For this reason, women of childbearing potential should not be given this drug.

RECOMMENDATIONS

1. Isotretinoin should be prescribed only for patients with severe cystic acne who are unresponsive to standard therapies.

2. Isotretinoin should not be given to women of childbearing potential unless the following conditions are met: (a) the patient visits a health professional for contraceptive counseling, with which the patient must be able to comply, before beginning the drug; (b) results of serum pregnancy test are negative within 2 weeks of beginning the drug and every month during treatment; (c) the drug is started on the third day of a normal menstrual period; and (d) the patient has received oral and written warning of the reproductive hazards of isotretinoin and etretinate during pregnancy and has acknowledged in writing her understanding of those warnings. It must be emphasized that one third of the affected infants reported by Lammer et al were born to mothers using contraception. The manufacturer recommends that two contraceptive measures be used simultaneously.

3. Etretinate should not be prescribed for women of childbearing potential.

4. Isotretinoin and etretinate should be prescribed only by those physicians with experience in the therapy (total and stepwise) of severe dermatological disorders.

REFERENCES

5. Lammer EJ. Embryopathy in infant conceived one year after termination of maternal etretinate. Lancet. 1988;2:1080–1081
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