Isotretinoin Made S.M.A.R.T.™ and Simple

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With the introduction of oral isotretinoin 20 years ago, an incredible triumph was achieved in the treatment of acne vulgaris. Much has been learned of the pathogenesis of acne and the mechanism by which isotretinoin affects acne. The teratogenicity of isotretinoin has cast a shadow on this effective drug with recent concern about the regulation of its use. The S.M.A.R.T.™ program has been implemented to address this concern. Alleged depressive mood effects of isotretinoin have resulted in further controversy. The efficacy of and indications for isotretinoin use are discussed here, with elaboration on the reported side effects. Given its established risks, treatment with isotretinoin may become severely curtailed if caution is not exercised.

Acne vulgaris is a common skin disorder affecting almost everyone at some point in life. Acne has been in existence at least since ancient times, with paleopathologic evidence of comedones demonstrated in mummies dating as far back as ancient Egypt.[1] Thousands of years have passed since these first documented cases, and pimples still plague humanity. Twenty years ago, oral isotretinoin was introduced to fill the need for an effective therapy for this scourge of the skin and has proven to be a wonder drug. Unfortunately, auspicious isotretinoin is a teratogen. Controversy also has surrounded the psychiatric side effects allegedly attributed to this drug. The following is an update on the complexities involved in isotretinoin use for acne management.

Why Use Isotretinoin for Acne?

The causes of acne vulgaris are multiple. Acne is a consequence of the disordered function of the pilosebaceous unit.[2] Acne's pathogenesis has been ascribed to the formation of the microcomedo, an essential acne precursor, in the context of abnormal follicular epithelial differentiation. Elevated sebum production and secondary *Propionibacterium acnes* growth and inflammation also contribute to acne's pathogenesis.[2,3] In addition, exposure to moisturizers; tars; halogenated hydrocarbons; and medications such as phenytoin, isoniazid, iodides, phenobarbital, lithium, ethionamide, and steroids may exacerbate acne.[4]

Isotretinoin is the only treatment that affects all major etiologic factors implicated in acne.[5] Endogenous retinoids mediate their biologic effect through modulation of DNA transcription via nuclear retinoic acid receptors.[6] Isotretinoin does not bind directly to retinoic acid receptors but is thought to behave as a prodrug, converted by sebocytes into active species that bind retinoid receptors.[7] Isotretinoin normalizes keratinocyte maturation and adhesion, resulting in reduced comedo formation. Isotretinoin also causes a decrease in sebocyte-mediated androgen synthesis[6] and an 80% reduction in sebum synthesis within a month of initiating therapy.[8] Oral isotretinoin reduces the total number of resistant bacterial organisms on the skin[9] and directly reduces neutrophil chemotaxis.[10,11]

Unlike other treatment modalities that merely temporize,[3] isotretinoin results in long-term acne remission for 70% to 89% of treated patients, with beneficial effects persisting after its discontinuation.[12] Most relapses occur within the first 18 months after treatment ends.[13,14] Patients failing the first course frequently respond better to the second course.[2] Subsequent courses for nodulocystic acne are rarely needed.

The official indication for isotretinoin use is for patients with severe recalcitrant nodular acne that is unresponsive to conventional therapies, including topical and oral antibiotics and oral contraceptive treatments.[15] Many patients, however, have inflammatory lesions that do not qualify as severe acne but can result in physical and psychologic scarring if alternative treatments are instituted.[13] Oral isotretinoin has been shown to reduce the severity of scarring.[16] An international survey revealed that dermatologists worldwide use isotretinoin for broader indications, including moderate acne with a less than 50% response rate to other therapies and acne that scars, induces

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relapse after withdrawal of therapy, or induces psychological stress.[17] The past 20 years have seen prescribing trends shift from treatment of severe nodular acne in the 1980s to less severe but treatment-resistant moderate acne in the 1990s.[18] Thus, even in milder cases of acne, isotretinoin may be the drug of choice. Another indication that favors isotretinoin therapy is patients with high sebum excretion rates who frequently respond poorly to antibiotic therapy.[13] Resistance to antibiotics by *P acnes* also has curtailed their therapeutic efficacy in acne treatment.[19] Oral antibiotic therapy also can harbor significant side effects. Finally, oral isotretinoin has demonstrated significant cost savings compared with other acne treatment modalities.[17,20]

The current dose recommendation for oral isotretinoin is a single 20-week course in the range of 0.5 to 2 mg/kg per day.[17] Twice-daily dosing is used to increase absorption.[21] Most physicians aim for a cumulative dose of at least 1 mg/kg per day.[23] Although isotretinoin at lower doses is effective in treating acne, relapse is more frequent for nodular acne with doses below 1 mg/kg per day.[2,23] Because continued clinical improvement may be seen 4 to 5 months after treatment completion, several months may be allowed to elapse before considering re-treatment.

Food increases the bioavailability of isotretinoin.[24] A new micronized formulation of isotretinoin with enhanced bioavailability allows for about a 50% lower dose to be taken once daily without the need for concomitant food ingestion.[25] Although micronized isotretinoin could increase compliance and offer a modest improvement in mucocutaneous side effects and lipid level changes compared with standard isotretinoin therapy,[26] this formulation has not yet received US Food and Drug Administration (FDA) approval.

Certain patients respond poorly when treated with isotretinoin.[13] Inadequate dosing and noncompliance are frequent causes of relapse. Young men with extensive truncal acne tend to relapse.[27] Other causes for relapse include sinus tracts, acne of short duration, hemorrhagic crusted acne,[28] and hyperandrogenic women.[13,29] Carbamazepine, phenytoin, and valproate also can lower serum concentration and efficacy of isotretinoin.[30] *Staphylococcus aureus* colonization complicating isotretinoin therapy can result in "nonresponse."[31] Thus, for nonresponders with generalized dermatitis, skin culture and the judicial institution of oral antibiotics is indicated.[31]

Treatment failures also have been reported from the inappropriate expectation that isotretinoin will effectively treat non-acneform lesions such as scars, acne excorea, macrocomedones, microcysts, syringomas, adenoma sebaceum, acne keloidalis nuchae, pseudofolliculitis barbae, hidradenitis, and pilonidal cysts.[4,29] Alternative therapeutic approaches may be instituted as deemed appropriate, such as electrodesiccation of macrocomedones,[32] acne surgery for microcysts, and psychotherapy for excoriated acne.[33] Acne fulminans, sometimes treated effectively with isotretinoin, can be precipitated by isotretinoin in rare instances.[28] Therapy should be halted in these patients, and systemic steroids should be instituted.[34]

Side Effects and Complications of Isotretinoin

Systemic adverse effects are rarely severe (2%) with isotretinoin therapy.[17]

Teratogenicity—Teratogenicity is the most serious adverse effect of oral isotretinoin therapy. Although isotretinoin is a naturally occurring molecule in humans and vitamin A is required for normal embryonic development,[35] first trimester pregnancy exposure to isotretinoin can cause retinoic acid embryopathy.[36] Isotretinoin is the most highly used teratogenic drug in the United States.[37] Between 1982 and early 2000, the manufacturer received reports of 1995 exposed pregnancies.[37] The number of infants born with congenital malformations after intrauterine isotretinoin exposure is not known, although the manufacturer has received reports of 71 infants with congenital malformations.[37] Most of the exposed pregnancies were not because of contraceptive failure but rather failure to use contraception.[37] Studies indicate that patient education in pregnancy prevention is key and that physicians must use greater caution in prescribing isotretinoin.

To improve pregnancy avoidance, Hoffmann-La Roche Inc instituted the Pregnancy Prevention Program for Women on Accutane® in 1988. Exposed pregnancies, however, continued to occur. Most recently, the FDA agreed to the continued use of isotretinoin under the System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.) program, a registry designed to enhance the present pregnancy prevention risk management program.[15] S.M.A.R.T. introductory packets have been mailed to all US dermatologists. To prescribe isotretinoin and be in compliance with the product label, dermatologists must read the S.M.A.R.T. Guide to Best Practices and sign and return to the manufacturer the S.M.A.R.T. Letter of Understanding.[15] The manufacturer-issued yellow qualification stickers must be applied to every isotretinoin prescription written.[15] Pharmacists have been instructed to fill prescriptions within 7 days of their being written

and to dispense no more than a 30-day supply at one time.[15] Women must sign an informed consent prior to starting therapy. Two reliable forms of contraception used simultaneously are required for at least one month before, during, and one month after isotretinoin therapy in sexually active women of reproductive age.[15] Before initiating therapy, prescribers must obtain 2 negative pregnancy test results, the second of which must be taken during the first 5 days of the woman's menstrual period immediately preceding isotretinoin therapy.[15] For patients with amenorrhea, the second test must be done at least 11 days after the last act of unprotected sexual intercourse.[15] Each month of therapy, women must have a negative pregnancy test prior to receiving their prescription.[15] The manufacturer continues to offer a free gynecologic evaluation with contraceptive counseling, as well as expanded written and video contraceptive counseling information.

Saint-John's-wort (*Hypericum perforatum*) should be avoided in a patient relying on hormonal contraception while on isotretinoin therapy because of possible decreased efficacy of the contraceptive.[38] Although men have fathered healthy children while taking systemic retinoids, subtle effects on spermatogenesis have been noted; therefore, it is wise for men to avoid retinoid therapy while trying to father children.[27]

Mucocutaneous Side Effects—Mucocutaneous adverse effects are ubiquitous in patients using isotretinoin. The most bothersome side effect observed in more than 90% of patients is cheilitis.[39] Cheilitis is observed within days of instituting therapy and is dose dependent.[39] In fact, the absence of cheilitis in an apparent treatment failure should raise a suspicion of noncompliance or poor absorption.[3] Xerosis, dermatitis, localized exfoliation (peeling fingertips), skin atrophy, and fragility are experienced by more than 50% of isotretinoin users and are most bothersome one month into therapy.[39] Pruritus is more common in individuals with generalized skin xerosis and a history of atopy.[34] Asthma exacerbation has been seen from drying of pulmonary mucosa.[40] Starting isotretinoin therapy at a low dose (≤0.5 mg/kg per day) and then titrating up can prevent mucocutaneous side effects that frequently result in noncompliance.[29,41] Vitamin E (alpha-tocopherol) 800 IU/d has been reported to prevent isotretinoin-induced cheilitis and other side effects (hair loss, myalgia, arthralgia) in cancer patients but has not had the same result in acne patients, possibly because of the much higher doses used for cancer chemotherapy.[42-44]

About a third of patients experience dry nose and epistaxis.[39] Brittle nails, dry mouth, and thirst also have been reported.[39] Alopecia is less prevalent with isotretinoin than with acitretin.[39] Permanent alopecia, although rare, has been reported after long-term isotretinoin therapy.[45] There also have been reports of worsening acne that, if severe, can be controlled by prednisone.[44] Keloids can appear after recent isotretinoin therapy either spontaneously in acne scars or from dermabrasion.[46] Therefore, it is prudent to delay surgical or laser interventions until at least 18 months after isotretinoin therapy is completed.

Neuropsychiatric Complaints—The most common nonmucocutaneous side effect reported is fatigue, usually transient, that occurs during the initiation of treatment.[39] Although headaches were reported by more than 10% of treated patients, they had a prevalence and preponderance in women similar to that of the general population.[39] Because headache can be a symptom of pseudotumor cerebri, it should be evaluated carefully. Although headaches are idiosyncratic, it may be wise to avoid the concomitant use of other drugs associated with pseudotumor cerebri, such as tetracycline.[3] Interestingly, one recent report found that patients had increased cravings for cigarettes during isotretinoin administration.[47] Tinnitus is rare, dose related, and reversible.[13]

An area of controversy is the alleged association between isotretinoin and depression. The FDA has received reports of 431 cases of depression and 31 suicides in patients treated with isotretinoin.[48] Positive dechallenge and rechallenge temporal association between drug use and depression prompted investigations into the possible association.[48] Studies on this subject, however, concluded that there is no evidence to support a causal connection between isotretinoin and major depression or suicide.[49-53] Overall, the rates of depression and suicide in patients on isotretinoin in clinical studies were far below the baseline rate of the general population. This was in light of the fact that these patients may be considered at higher risk for suicide because of their age, gender, and level of self-esteem as it relates to their dermatologic condition. Nevertheless, because idiosyncratic psychological effects cannot be ruled out, caution and inquiry into a patient's emotional status while on isotretinoin is advisable. Isotretinoin is not contraindicated in patients with a history of mood disorder.[53] Indeed, some reports discuss the use of isotretinoin to alleviate psychiatric symptoms.[50,54] Some have even advocated the use of isotretinoin as a first-line therapy for severe acne in patients at risk for depression because of its known superior clinical efficacy.[55] The importance of addressing

the psychological needs of patients while managing their dermatologic condition is not unique to acne management. Indeed, some studies have found an increased risk of suicidality as high as 10% in dermatologic patients compared with primary care and general medical populations.[56,57]

Musculoskeletal Complaints—Arthralgia and myalgia are most common in isotretinoin-treated patients who undergo strenuous physical exertion or who have a history of injury.[27,34] Hyperostotic bone spurs or calcification of anterior spinal ligaments that resemble diffuse idiopathic skeletal hyperostosis are the most frequently seen changes, also observed as a normal sequel of advanced age.[27] Stiffness and back pain can result.[39] Rare cases of premature epiphyseal closure, fibrodysplasia ossificans progressiva, bone demineralization, osteoporosis, and slender long bones have been reported with long-term high dose retinoid therapy.[27] In general, bone effects are dose dependent and become clinically relevant only after long-term exposure; however, they warrant awareness because they can persist and even progress with advancing age despite discontinuation of therapy.[27,58] Following patients with radiologic surveys can be misleading because radiologic involvement does not correlate well with symptoms.[59] Currently, baseline and periodic skeletal surveys are used mainly to monitor patients on long-term retinoid therapy.[27]

Ocular Complaints—About 30% of isotretinoin-treated patients experience significant xerophthalmia secondary to decreased Meibomian gland function.[3,39] Contact lens intolerance, blurred vision, blepharitis, conjunctivitis, exposure keratitis, and, in extreme cases, corneal ulceration have been seen in patients.[3] Corneal opacities are rarely of visual significance and resolve spontaneously within 2 months of discontinuing therapy.[3] Nyctalopia (decreased dark adaptation) of slow or rapid onset is rarely irreversible.[60] Both loss of color vision and eye sicca syndrome, also rarely irreversible, have been reported.[60] Obtaining a baseline history regarding visual dark adaptation, color vision, and ocular sicca is wise. A baseline ocular examination is rarely indicated unless ocular pathology is suspected (so the drug is not unjustly implicated).[60]

Gastrointestinal Complaints—Although short-term hepatotoxicity with mild and reversible transaminase elevation occurs in 15% of treated patients, despite continued treatment, chronic hepatotoxicity and mortality have not been linked to isotretinoin therapy.[61,62] Isotretinoin has been implicated in inflammatory bowel disease flare-ups, but no cause-and-effect relationship has been established.[3] It is wise, however, to monitor these patients closely.[63]

Blood Parameter Abnormalities—The package insert for isotretinoin[64] recommends baseline and monthly measurements of liver function and lipid parameters during therapy; however, studies have led physicians to question the need for repeat laboratory tests after initial reference values are established.[17,65] Reversible hypertriglyceridemia, usually mild to moderate (300–400 mg/dL), has been seen in 25% of treated patients within the first month of therapy.[39] Patients with preexistent hyperlipidemia or obesity, especially android obesity (spindly legs and flat buttocks with large upper body), have a tendency toward hypertriglyceridemia during therapy.[34] Dietary changes, weight control, or antihyperlipemic agents are useful in management. Discontinuation is warranted for very high levels of triglycerides (>500 mg/dL) because pancreatitis may occur.[66] Changes in red and white blood cell counts are usually clinically insignificant.[3] Creatine phosphokinase elevation has been reported in patients with myalgia.[67] Isotretinoin is not associated with any renal toxicity and even can be safely used in end-stage kidney disease.[3]

Conclusion

Twenty years of experience in treating 5 million faces for acne with oral isotretinoin have demonstrated its singular efficacy. Accepted as the best treatment for patients with severe acne, isotretinoin application has broadened over the years to include more moderate acne, with the goal of preventing both physical and psychological scars. The psychological effects of acne should not be understated because diminished self-esteem, social withdrawal, depression, and unemployment all have been reported consequences.[68] Failing to offer a patient oral isotretinoin therapy may be risky for physicians as well. Alleged litigation involving physicians who failed to offer isotretinoin to appropriate candidates has been rumored at recent conferences, but no corroborative literature is available. Thus, it behooves the physician to at least mention this therapeutic option to qualified candidates.

Although tremendous efforts in patient education have been made, the dramatic rise in direct-to-consumer advertising has raised consumer demand, and, in turn, concerns over the potential for overprescribing of medications.[37,69,70] The statistics of continued pregnancy occurrence in women on isotretinoin are sobering. Just as human nature is not likely to change, it is unlikely that we will succeed in getting pregnancy rates of patients on

isotretinoin down to zero. If we don't get "SMARTer" about oral isotretinoin use, a valuable weapon in our arsenal against acne may be removed from our reach.

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