Original Article

Low-dose isotretinoin therapy and blood lipid abnormality: A case series with sixty patients

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Abstract

Background: prolonged isotretinoin therapy for various skin diseases causes change in various parameters of lipid profile. Aim: to find out the effect of low dose isotretinoin on various parameters of lipid profile. **Methods:** A clinic based observational study with 60 patients of various skin diseases carried out in a skin outpatient department of a tertiary care hospital in eastern India. Patients were prescribed isotretinoin for relevant indications. Baseline lipid profile was checked and repeated after three months. The results were compared with the baseline lipid levels. **Result:** Out of 60 patients (male-32, female-28) hyperlipidemia was present in 25% (15 out of 60) patients at the end of three month's therapy. Among the hyperlipidemia, hyper triglyceridemia was the commonest (16.67%, 10 out of 60 patients) followed by elevation of VLDL (11.67%, 7 out of 60 patients), elevation of LDL (10%, 6 out of 60), hypercholesterolemia (5%, 3 out of 60). Combination of hyperlipidemia was present in 11.67% patients. Among the male patients 28.12%, while in females 21.43% had hyperlipidemia at the end of the study. Among the hyperlipidemic females, hypertriglyceridemia was present in 83.3% (5 out of 6) of patients, while in male it was 55.5% (5 out of 9 patients). **Conclusion:** Low dose Isotretinoin therapy causes variable rise in various parameters of lipid profile. It should be used cautiously in patient with risk factors of metabolic syndrome and frequent monitoring of serum lipid profile is needed.

Keywords: Hyperlipidemia, hypertriglyceridemia, isotretinoin, low dose

Introduction

Retinoids are the class of compounds that induce both natural and synthetic forms of Vitamin A. The first dermatologic use of Vitamin A dated back to 1943. Because of narrow therapeutic index of Vitamin A, synthetic retinoids with high therapeutic index and low adverse effects were initiated. Isotretinoin was first synthesized in 1955. Initially, it was studied for different disorder of keratinization, but later on, it was noted that it dramatically improves the acne patients as well as it induces prolong remission. It was approved by US Food and Drug Administration in 1982, for the treatment of severe acne.

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The bioavailability of isotretinoin enhances with food intake. Serum transport is done by serum albumin. The metabolism occurs in the liver by oxidation. The half-life is 10–20 h. The major metabolites of isotretinoin are 4-oxo-isotretinoin which is excreted in the urine and feces. Isotretinoin is completely excreted from the body within 1 month of stopping the drug.

The mode of action of the retinoids is not known completely but they have a good effect on cell differentiation, cell growth, and immune response. They also affect the pathway of inflammation and apoptosis. These actions are mediated by retinoid receptors retinoic acid receptor retinoid X receptor (RAR and RXR).[1]

The uses of isotretinoin in dermatology include acne vulgaris, psoriasis, pityriasis rubra pilaris, rosacea, hidradenitis suppurativa, Gram-negative folliculitis, epidermolytic hyperkeratosis, different

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keratodermas, discoid lupus erythematosus, Lichen planus, epidermodysplasia verruciformis, solar keratosis, and so on.

The common side effects of isotretinoin are cheilitis, dryness of the skin, photosensitivity, photophobia, paronychia, arthralgia, myalgia, headache, etc. Potentially serious side effects are teratogenicity, reduced night vision, hyperlipidemia, pancreatitis, hepatic dysfunction, depression, etc.[2] It is a category X drug in pregnancy. Proper counseling, informed consent, and frequent pregnancy test should be done in females of childbearing age while on isotretinoin.[3]

Relative lack of data regarding the relationship of different blood lipid parameters with isotretinoin therapy, particularly in the eastern part of India prompted us to undertake the study.

Materials and Methods

In this study, we have included sixty patients who were prescribed isotretinoin from the dermatology outpatient department of a tertiary care center of eastern India for various reasons between January 2015 and December 2015. The patients belonged to both ages and sexes. The ages of the patient ranged from 18 to 50 years. Careful history taking and thorough clinical examination were done. History of concomitant medications that may interact with retinoids was taken. Laboratory investigations such as complete hemogram, liver function tests, and baseline lipid profile were done. Female patients of childbearing age group were advised regarding contraception, and in suspected cases, pregnancy tests were done. Patients with medical ailments like overtly obese, diabetes mellitus, hypertension, preexisting hyperlipidemia, hypothyroidism, liver disorders, hematological disorders, and concomitant drug therapy which increase the blood lipids and interact with isotretinoin were excluded from the study. Informed consent was obtained from all the patients. Patients were given 20 mg of isotretinoin orally (following low dose regimen). Clinical evaluation in every 2 weeks for first 4 weeks then monthly for next 3 months was done. After 90 days of therapy, lipid profile test was done. The results were compared with the baseline lipid levels. After the collection of the data, it was compiled, tabulated, and analyzed by using appropriate statistical tools.

Results

Sixty patients were included in this study. The patient belonged to both sexes (male-32, female-28). Their age ranged from 18 to 50 years with a median, the study median of 27 years. In the study population, hyperlipidemia was present in 25% (15 out of 60) patients. Among the hyperlipidemia, hypertriglyceridemia was the most common (16.67%, 10 out of 60 patients) followed by elevation of very low density lipoprotein (VLDL) (11.67%, 7 out of sixty patients), elevation of low-density lipoprotein (LDL) (10%, 6 out of 60), and hypercholesterolemia (5%, 3 out of 60). The combination of hyperlipidemia was present in 11.67% (7 out of 60) patients. No changes in high-density lipoprotein (HDL) level was noted. Among the male patients, 28.12% (9 out of 32) showed hyperlipidemia following 3 months of isotretinoin therapy, while in females, the incidence of hyperlipidemia was 21.43% (6 out of 28). Among the hyperlipidemic females, hypertriglyceridemia was present in 83.3% (5 out of 6) of patients, while in male, it was 55.5% (5 out of 9 patients). There is no statistical significance between the hyperlipidemia present among the hyperlipidemic male and female group ($P = 0.6869$)

Discussion

The term retinoids include all the synthetic and naturally occurring compounds that have activity like Vitamin A. In mammals, Vitamin A exists in interconvertible forms as retinol (Vitamin A alcohol), and retinal (Vitamin A aldehyde), and retinoic acid (Vitamin A acid).[4] First dermatologic use of Vitamin A dated back to 1943, by Straumfjord for acne vulgaris. In the early 1960s, Bollag began listing various retinoid compounds (listed about 1500 retinoids).

Isotretinoin was first synthesized in 1955. In the year 1970, the efficacy of isotretinoin in the treatment of cystic acne and acne conglobata was established. In 1972, Bollag discovered two aromatic retinoids etretinate and acitretin, that possessed a good therapeutic index.[5] USFDA approved isotretinoin for the treatment of severe nodulocystic acne in the year 1982. Retinoids can be divided into three generations. At present, first generation retinoids include isotretinoin and tretinoin. The second generation retinoids include etretinate and acitretin. Third generation retinoids include bexarotene and adapalene. At present, researches for developing 3rd generation retinoids with safer therapeutic index are going on.

There are two distinct types of retinoid receptors present, like RAR family and RXR family.[6] The exact mechanism of action of isotretinoin in acne is not known. *In vitro*, isotretinoin inhibits the sebocyte proliferation. Compared to the other first generation retinoids, isotretinoin is less sebosuppressive.[4] Isotretinoin also interferes with the retention hyperkeratosis which is the initial step for microcomedone formation.

Isotretinoin should be given at a dose of 0.5–1 mg/kg/day. An initial response is seen within 8 weeks. Goulden *et al.* suggested prescribing isotretinoin until a cumulative dose of 120 mg/kg is achieved.[7] Blood lipid abnormality was more common when it is used in normal or higher dose,[8] but the present study showed it is as frequent as in low dose.

A big list of potential side effects is reported during isotretinoin therapy. Cheilitis and dryness of skin and different mucosa probably one of the most frequent side effects.[8] Other potential side effects are benign intracranial hypertension,[9] thrombocytopenia,[10] diffuse idiopathic skeletal hyperostosis,[11] depression and suicidal tendency,[12] etc. Blepharoconjunctivitis, hordeolum, and chalazion were the more common ocular

side effects. The other ocular side effects were decreased dark adaptation and corneal opacities. Pyogenic granuloma, pyogenic granuloma-like acne lesions,[13] myalgia, arthralgia, and hearing problems were also reported. Isotretinoin is potentially teratogenic, and it is a category X drug.[3]

The most frequently detected laboratory abnormalities include elevated serum lipid profile.[14] In this aspect, bexarotene is notorious. This elevation is reversible on stopping the therapy. Isotretinoin elevates the triglyceride level in 50% and cholesterol in 30% of patients.[15] In contrary, the present study showed that hypertriglyceridemia was present in near about 17% of patients, hypercholesterolemia was present in 5% patients. In addition, the study showed increase in VLDL level among 12% of patients. Ahmadvand *et al.*[16] in their study showed that the difference of both triglyceride and cholesterol level before and after isotretinoin therapy was statistically significant. Brito *et al.*[8] in their study showed significant increase in LDL cholesterol, triglyceride, and reduction of HDL level following isotretinoin therapy.[8] but the present study failed to demonstrate any abnormality in HDL level.

The exact cause of lipid elevation by isotretinoin is not known. The retinoids are usually binds to the plasma albumin. It is hypothesized that retinoid-albumin interaction in plasma displaces the triglyceride from albumin, causing its elevation. Other proposed hypothesis is isotretinoin interacts with some essential proteins or enzymes of lipid metabolism like hydroxymethylglutaryl reductase.[17]

Abnormality of serum lipid parameters may induce changes in cell membrane and cellular metabolism. Furthermore, it can aggravate oxidative stress to the cell[18] which hampers the equilibrium of different lipid parameters and these run in a vicious cycle. As a result, metabolic syndrome can be precipitated in patients who are undergoing long-term isotretinoin therapy. Oxidative stress to hepatic cells may lead to elevation of gamma glutamyl transpeptidase level.[16] Creatine phosphokinase level may be increased due to oxidative stress to different skeletal and smooth muscle cells. Oxidative stress in the cellular level can be prevented by different antioxidants. Hence, further studies are warranted to assess the benefit of using antioxidant in prevention of oxidative stress as well as alteration of lipid parameters.

Patients who develop triglyceride level over 500–600 mg/dl and cholesterol level 250–300 mg/dl should have the isotretinoin therapy withdrawn till the lipid profile come back to normal level. Monitoring of the lipid profile should be done monthly for first 3–6 months and then in every 3 months. Statins can be given to reduce the elevated lipid level following isotretinoin therapy. For hypertriglyceridemia, fibrates are better than statin which reduce the occurrence of hyperlipidemic pancreatitis.[19]

Hence, retinoids even in low dose should be prescribed judicially by the physicians being familiar with these risks, monitoring guidelines and patient education.

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Conflicts of interest

There are no conflicts of interest.

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