Creatine Phosphokinase Values during Low Starting Dose Isotretinoin Therapy

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Keywords

Acne · Isotretinoin · Laboratory values · Muscle enzymes · Creatine phosphokinase · Rhabdomyolysis

Abstract

Background: The value of creatine phosphokinase (CPK) monitoring during isotretinoin therapy is still a matter of debate because of the rarity of muscular and kidney damage in this setting. The aim of the study was to investigate the incidence of CPK elevation during a low starting dose isotretinoin regimen and to discuss the clinical approach to patients with increased CPK. **Methods:** We reviewed the records of the acne patients from 2015 to 2018 at the University of Ferrara and at the University of Modena and Reggio Emilia. Routine clinical and laboratory follow-up was analyzed. **Results:** The records of 328 patients were included in the study. Abnormal CPK levels were observed in 5.5% of cases. Revised Leeds acne scores and visual assessment scale (VAS) measurements decreased significantly after isotretinoin therapy. **Discussion:** The adoption of the low starting dose isotretinoin regimen is associated with low incidence of CPK elevation. The finding of CPK over the conventional value of 5 times above the limit was rarely observed and was never as-

sociated with kidney damage. Therefore, it should be interpreted as a relatively benign phenomenon that does not require the interruption of isotretinoin therapy and that should be managed mainly through the reassurance of the patient.

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Introduction

Acne vulgaris is a disease of the pilosebaceous unit, characterized by the hyper-keratinization process, comedo formation, and inflammatory reactions [1, 2]. The choice of topical and systemic therapy is guided by the clinical symptoms and the severity of the disease [1–3]. Different therapeutic and microscopic approaches are available today for the treatment and evaluation of acne [4–8]. Oral isotretinoin (13-*cis*-retinoic acid) is strongly recommended for the treatment of severe papulopustular/moderate nodular acne based on the very good efficacy seen in clinical practice [1, 2]. Although it is remarkably effective, it was reported to be associated with numerous adverse effects (AEs), which are usually dose dependent [9–12]. Several studies discussed the indications and AEs of oral isotretinoin, but few or none of

them were based on randomized controlled trials. Some of the studies reporting isotretinoin-associated AEs, such as psychiatric outcomes, laboratory abnormalities, and inflammatory bowel disease, were prone to confounding and were affected by several methodological imprecisions [13].

The relationship between elevated creatine phosphokinase (CPK) level, isotretinoin therapy, and muscular exercise is still a matter of debate. Some *in vitro* studies showed that, in rat liver, retinoids induced apoptosis and oxidative damage. Other studies demonstrated that retinoids exert a protective effect on skeletal muscle, inducing differentiation as well as enhancing anti-apoptotic and anti-oxidative mechanisms in different cell lines and tissues [14, 15]. CPK is easily assessed in the serum and is a sensitive, but not specific, marker of muscle damage, which is considered population specific. The level of CPK needed to induce kidney damage is still a matter of debate, but some authors suggest that a dosage of >15,000 IU/L is predictive of renal impairment [16, 17]. Previous studies showed that 25.1% of athletes (51 individuals among 203) reached >10,000 IU/L CPK levels after 50 maximal eccentric contractions of the elbow flexors and none of them had myoglobinuria or required treatment for impaired renal function [18]. Other authors reported that military recruits in basic training showed mean CPK values of 734, 1,226, and 667 IU/L on days 3, 7, and 14 after exercise, with a peak of 35,056 IU/L, without any sign of rhabdomyolysis [19]. Muscle-related AEs and elevated CPK blood levels have been reported in many patients treated with isotretinoin [20–22]. Myalgia and muscle stiffness have been reported in 15–50% of patients treated with isotretinoin, while elevated serum CPK levels have been found in up to 41% [20–22]. Kaymak [22] found elevated CPK levels in approximately 5% of patients treated with isotretinoin. In our previous study conducted on 63 patients treated with isotretinoin for nodulocystic acne, 16% of them showed elevations of less than 3-fold the normal values [20]. One of the largest studies on CPK values during isotretinoin treatment was conducted by Landau and colleagues [21], and it included 442 patients treated with isotretinoin, observing elevated CPK values in 37.7% of patients and CPK values above 5,000 IU/L in 2% of them. With regard to rhabdomyolysis in the setting of isotretinoin therapy, there are 3 reported cases, one of them by Trauner and Ruben [23] who described a patient with increased serum CPK levels during isotretinoin therapy without a recent history of exercise, myalgias, musculoskeletal injury, or an intramuscular injection

At our best knowledge, all the previous studies were based on the “standard” isotretinoin regimen that consists in an initial dose of 0.6–1.0 mg/kg per day and a possible subsequent increase until a concentration of 0.8–1.0 mg/kg per day was reached. According to our previous low starting dose study, an initial daily dose of 0.2 mg/kg and a slow progressive increase until the highest dose tolerated was reached is able to reduce the occurrence of treatment side effects and increase patient compliance [24]. The aim of the current study was to investigate the incidence of CPK elevation with a low starting dose isotretinoin regimen and to discuss the best clinical approach to the patient with increased CPK during isotretinoin treatment.

Methods

We reviewed all the medical records of the acne patients receiving isotretinoin treatment from 2015 to 2018 at the acne ambulatories of the dermatology departments of the University of Ferrara and the University of Modena and Reggio Emilia. Isotretinoin prescription was administered to severe acne patients as a standard of care, in accordance to the international published guidelines on acne treatment. We retrospectively reviewed and included all the records of acne patients who completed an isotretinoin treatment with the low starting dose regimen that consists in an initial daily dose of ≤0.2 mg/kg for the first month of treatment and a subsequent increase in the dosage by 5 mg every 2 weeks, until the highest dose tolerated was reached. It was defined for each patient during the follow-up visits for isotretinoin therapy by a dermatologist expert in isotretinoin prescription. The clinical evaluation of the highest tolerated dose was based on several factors: the presence of grade I–III cheilitis despite daily lip balm usage [25], the absence of acne flare [24], and the evaluation of laboratory values according to the current guidelines [1, 2, 12]. All patients were treated until complete acne clearing was achieved, and for a further month of treatment, without exceeding a total cumulative dose of 150 mg/kg. All patients underwent baseline blood test screening and periodical monitoring of CBC, AST, ALT, GGT, Cr, CPK, and lipids and urine analysis with proteinuria. Acne severity was assessed during every visit using the Leeds revised acne grading system (Leeds RAGS) [4]. Patient global assessment was measured before and after isotretinoin treatment, through a visual assessment scale (VAS) that ranged from 0, corresponding to “no discomfort at all,” to 10, corresponding to “extreme discomfort.” The pregnancy test was repeated every month for female patients in childbearing age. Every patient enrolled in the study underwent at least 4 follow up access at our acne ambulatories, repeating blood test and clinical visit each time. The number of patients with at least one increased CPK value (normal range 0–170 IU/L) during follow-up and the recent history of muscular activity (sport or physical exercise) were recorded. Descriptive statistics, including mean (M) and standard deviation (SD) and Student’s *t* test, were calculated for the comparison of VAS and Leeds RAGS scores with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Patients showing at least one elevated CPK value during the follow-up of low-dose isotretinoin therapy

Patient	Sex	Age, years	Physical exercise (yes/no)	Isotretinoin dosage, mg/day	Months of treatment	CPK values, IU/L	Exceeding 850 IU/L
1	F	16	Y	20	2	183	N
2	F	22	Y	10	1	748	N
3	M	15	N	15	1	190	N
4	M	17	Y	20	3	322	N
5	F	24	Y	20	2	303	N
6	M	22	N	20	2	195	N
7	M	27	Y	20	3	1,015	Y
8	M	18	N	20	3	367	N
9	M	18	Y	15	2	532	N
10	M	19	Y	20	2	278	N
11	M	20	N	10	1	651	N
12	M	25	Y	20	2	872	Y
13	F	16	Y	10	2	215	N
14	M	17	Y	20	3	1,458	Y
15	M	18	Y	10	2	865	Y
16	M	18	Y	10	1	215	N
17	M	23	Y	30	4	267	N
18	M	15	Y	20	3	185	N

M, male; F, female; Y, yes; N, no.

Results

The medical records of 328 patients were analyzed and included in the study. Among them, females were 122 and males were 206. Patients' age ranged between 12 and 37 years (mean 16.2), and the duration of disease was 1–13 years (mean 2.7). Acne severity decreased significantly ($p < 0.05$) during isotretinoin treatment, from an average Leeds RAGS score of 7.3 (SD 2.3) before isotretinoin therapy to a score of 0.1 (SD 0.3) after the treatment. Patient global assessment (VAS) showed a statistically significant decrease, from an average value of 7.34 (SD 2.67) to 2.15 (SD 1.89). The number of patients with at least one episode of increased CPK value was 18 (5.5%), and in 14 of them (4.2%) the patient reported a recent history of muscular activity (sport or physical exercise). Abnormal CPK values ranged from 183 to 1,458 IU/L, with an average abnormal value of 492 IU/L. The conventional limit of CPK elevation above 5 times the normal range was observed only in 4 cases, and the patient always reported strenuous muscular exercise during the 7 days preceding the blood test (Table 1). Renal function tests and urine analysis were normal in these patients, none of them complained about myalgia, and all of them were completely asymptomatic, rejecting any muscular discomfort when specifically questioned about it.

Discussion

The adoption, 4 decades ago, of isotretinoin therapy revolutionized acne treatment because of its high effectiveness on severe grades of the disease. The classical recommended regimen for isotretinoin prescription implied the usage of high daily doses of the therapy even though associated with several adverse effects. In clinical practice, the prescription of isotretinoin was impaired by the teratogenicity of the drug and by the frequent monitoring of the patients who underwent monthly clinical and laboratory examinations. The frequent observation of elevated CPK level during isotretinoin treatment has always been a matter of concern among patients and general practitioners, even though the mechanism responsible for liver or muscular damage was never demonstrated. Although it is common to find a mild increase of CPK values in athletes, high CPK values, conventionally more than 5 times the normal upper limit, sometimes indicate serious muscular damage that is associated with the release of myoglobin from muscular cells and can result in glomerular and kidney damage, even though the level of CPK that is related to kidney damage is not demonstrated, with cases of sports athletes and military recruits reporting the frequent (51 of 203 volunteers) finding of $>10,000$ IU/L CPK

levels without myoglobinuria or impaired renal function [12]. Some reports described patients with a CPK peak of 35,056 IU/L without any sign of rhabdomyolysis during muscular strenuous exertion [13]. This huge variance in CPK elevation and muscle damage is likely to be determined by several still unknown polygenic factors that lead to different inter-individual rhabdomyolysis risk.

With the adoption of the low starting dose isotretinoin regimen, we observed a less frequent increase of CPK values, as demonstrated by the low percentage of patients who had at least one episode of CPK increase: 5.5% compared to 16% as reported in our previous study conducted with a high starting isotretinoin dosage. Many of them (4.2%) had a recent history of strainful exercise, and the elevation of CPK was not established as directly resulting from isotretinoin treatment. In our experience, none of the patients receiving isotretinoin for acne treatment developed myoglobinuria or renal impairment. The conventional limit of CPK elevation above 5 times the normal range was observed only in 4 cases and was always related to previous muscular exercise. In those few cases, we recommended the patients to increase their hydration level, drinking more than 2.5 L of water per day, avoid muscular exercise, and repeat the testing for CPK, ALT, AST, and urine analysis after 3, 7, 14, and 28 days. In those cases, isotretinoin prescription was decreased to half dose as a precaution. We observed a restoration of the normal range of CPK in 28 days for all the 4 patients, without the occurrence of other significant laboratory abnormalities or the decline of muscular or renal function.

In our experience, the routine application of the low starting dose isotretinoin therapy shows multiple benefits on the management of acne patients, reducing the occur-

rence of laboratory abnormalities and of acute acne flares but maintaining the therapeutic efficacy, as demonstrated by the significant decrease in the Leeds (RAGS) and VAS scores at the end of the therapy. To conclude, in isotretinoin-treated patients, the rare elevation of CPK more than 5 times the normal upper limit should be interpreted as a benign phenomenon that does not require the interruption of isotretinoin therapy and should be managed through the reassurance of the patient, encouraging the prosecution of the therapy, and repeating the CPK dosage until its normalization.

Statement of Ethics

This study was performed in accordance with the Helsinki Declaration.

Disclosure Statement

There are no conflicts of interest.

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Author Contributions

V.B. conceived of the presented idea. M.M. performed the statistical analysis and wrote the manuscript with support from R.F., L.P., F.F., M.C., and G.P. All authors discussed the results and contributed to the final manuscript.

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