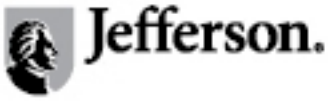

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Laboratory tests in patients treated with isotretinoin: occurrence of liver and muscle abnormalities and failure of AST and ALT to predict liver abnormality.

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Current laboratory monitoring may not be optimal.A retrospective chart review was performed on thelaboratory results of 246 patients who were treatedwith isotretinoin for acne over a 9-year period. Testsobtained were CBC, lipid panel, AST, ALT, CK, GGT,and C-reactive protein. Thirty-five patients had anelevated AST and 35 of these had an elevated CK; 32had an elevated ALT and 11 of these had an elevatedCK. Thirteen patients had an elevated GGT; in 5 thiswas the only abnormality, whereas 8 had a GGTelevation accompanied by an elevated AST or ALT.Two had an elevated GGT and an elevated CK withnormal AST and ALT. Fifty-two patients had a singleepisode of elevated CK, of which 22 were female.However, 57 had multiple CK elevations and only onewas female. Thirty-five patients had CK elevations <2 times normal; 38 had levels between 2 and 3 timesnormal, 18 had levels between 3 and 4 times normal,and 18 had levels greater than 4 times normal. Wesuggest that ALT and AST are not useful for monitoringisotretinoin therapy and that GGT and CK may be ofgreater value in managing patients.

Laboratory tests in patients treated with isotretinoin: occurrence of liver and muscle abnormalities and failure of AST and ALT to predict liver abnormality

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Abstract

Current laboratory monitoring may not be optimal. A retrospective chart review was performed on the laboratory results of 246 patients who were treated with isotretinoin for acne over a 9-year period. Tests obtained were CBC, lipid panel, AST, ALT, CK, GGT, and C-reactive protein. Thirty-five patients had an elevated AST and 35 of these had an elevated CK; 32 had an elevated ALT and 11 of these had an elevated CK. Thirteen patients had an elevated GGT; in 5 this was the only abnormality, whereas 8 had a GGT elevation accompanied by an elevated AST or ALT. Two had an elevated GGT and an elevated CK with normal AST and ALT. Fifty-two patients had a single episode of elevated CK, of which 22 were female. However, 57 had multiple CK elevations and only one was female. Thirty-five patients had CK elevations < 2 times normal; 38 had levels between 2 and 3 times normal, 18 had levels between 3 and 4 times normal, and 18 had levels greater than 4 times normal. We suggest that ALT and AST are not useful for monitoring isotretinoin therapy and that GGT and CK may be of greater value in managing patients.

Keywords: isotretinoin, laboratory monitoring, acne, muscle liver

Introduction

Laboratory monitoring of patients treated with isotretinoin is standard practice, but evaluation of the results is confounded by choice of laboratory test. In general the same tests as reported by the original investigators [1] are the ones used today in clinical practice. Numerous case reports documenting pancreatitis, liver damage, leukopenia, and thrombocytopenia [2] exist but the true incidence of clinically significant abnormalities is not known.

Results

A retrospective chart review was performed regarding patients treated with isotretinoin for acne between 2005 and 2014. Two hundred forty-six patients were identified. Patient identity was protected by assigning a code number to each individual. Laboratory tests were done at initiation of therapy and with dosage changes. Patients with abnormalities had monthly testing until they resolved. Tests obtained were CBC, lipid panel, AST, ALT, CK, GGT, and C-reactive protein. Female patients also had HCG performed. None were positive.

Thirty-five patients had an elevated AST and 32 of these had an elevated CK; 32 had an elevated ALT and 11 of these had an elevated CK. Thirteen patients had an elevated GGT (this was the only abnormality in 5); 8 had a GGT elevation accompanied by an elevated AST or ALT. Two had an elevated GGT and an elevated CK with normal AST and ALT. Five patients had elevation of GGT on more than one visit. The vast majority of elevations were less than twice the top normal value. Highest levels were AST 191, ALT 118, GGT 102.

Fifty-two patients had a single episode of elevated CK of which 22 were female. However, 57 had multiple CK elevations and only one was female. Thirty-five patients had CK elevations less than 2 times normal; 38 had levels between 2 and 3 times normal, 18 had

levels between 3 and 4 times normal, and 18 had levels greater than 4 times normal.

Thirty-nine individuals had CRP elevations. Ten were elevated at baseline and 23 had elevation at the end of therapy. Twenty-seven patients had simultaneous elevations of TG and CRP.

Ninety-five patients overall had elevation of TG; 26 were elevated at baseline, 45 had elevations at the end of therapy and 15 were elevated throughout therapy.

One hundred-eleven had elevations of cholesterol; 45 were elevated at baseline, 75 were elevated at the end of therapy, and 35 had elevations throughout therapy.

Twenty-one had high WBC at some point in therapy; 15 also had high ANC, two of which had a low ALC. Thirty patients had an episode of low WBC; 14 had low ANC, two of which had a high ALC and one had low WBC and high ANC. Modest elevations and depressions in hemoglobin were seen in many patients sporadically. Sixteen patients had elevations in platelets at some time during therapy; 6 of these were elevated on more than one occasion. No platelet elevation exceeded 480. Fifteen patients displayed a low platelet count on at least one occasion during therapy. The lowest value was 89, which returned to normal on subsequent tests. Three patients had more than one low level during therapy.

Case Discussion

Laboratory abnormalities during isotretinoin therapy are thought to be a common occurrence, but there is surprisingly little organized study regarding their severity or consequence. Zane and colleagues [2] studied the laboratory results of over 13,000 isotretinoin treated patients and found 11% had modest transaminase elevations but nearly 50% had triglyceride abnormalities at some time during therapy. A recent study by Lee and colleagues [3] reported on the mean elevation of blood tests and found it to be low and suggested that routine testing may not be cost effective.

In our practice we monitor CBC, AST, ALT, GGT, CK, and lipids and order tests at baseline and with each dosage change. Peak isotretinoin dosage is typically near 1mg/kg. Tests that are abnormal are followed until they normalize. Patients are counselled on the significance of each abnormal test and steps that should be taken.

AST and ALT are enzymes thought of as "liver tests" but they are not liver-specific, being found in liver, muscle, and other tissues including red blood cells. GGT is a liver specific enzyme. CK is a muscle specific enzyme. In the current study we found that AST elevation was usually accompanied by CK elevation, suggesting a muscle (rather than liver) source for the AST. ALT was less strongly paired with CK but there was some overlap. GGT elevation was much less common and occurred only 13 times. These findings suggest that AST and ALT are less useful for monitoring liver damage than GGT and may be redundant tests. In addition, the presence of AST and ALT in red blood cells can lead to false positive values if there is hemolysis [4].

The low incidence and severity of abnormal liver tests (indicated by GGT level) is encouraging and suggests that isotretinoin is not a major cause of liver injury. It must also be noted that other events such as alcohol ingestion or infection can cause elevations in GGT independent of isotretinoin.

Lee et al. [3] noted the low mean severity of liver abnormalities and suggested that measuring AST and ALT may not be cost–effective. This report confirms that individual liver tests (as opposed to the mean of a large group as was measured in [3]) are not usually abnormal and that when elevated they are only mildly-so. Moreover we show that much of the AST and ALT elevations appear to arise from non-liver sources.

In contrast to liver tests, muscle tests were more commonly elevated and some to quite high levels. In many cases the patients had no muscular symptoms but most gave a history of vigorous exercise. Men were at clearly greater risk of repeated elevation, which may reflect behavior. The significance of these abnormalities in CK is uncertain. CK elevations greater than five times normal accompanied by muscle pain, fatigue, and weakness can be a sign of rhabdomyolysis, which can lead to renal damage [6].

The patients in this study did not have CK elevations of that magnitude.

There are two reported cases of full-blown rhabdomyolysis in the setting of isotretinoin therapy [7, 8] and patients treated with the drug commonly report decreased exercise tolerance and achiness[1, 9]. Several studies have reported CK elevations from 5 to 41% in patients treated with isotretinoin [6]. We counsel patients to avoid strenuous exercise during therapy and await further study on the effects of isotretinoin on muscle.

Conclusion

What tests should be used to monitor patients treated with isotretinoin? Clearly HCG and lipids must be monitored, and based on this chart review, CBC appears to be of minimal value. In this population, elevations in AST and ALT were found to not usually be indicative of liver problems. If the liver is to be monitored, GGT appears to be a more useful test. Given the frequency and magnitude of CK elevations it may be helpful, especially in the physically active, to monitor this enzyme during isotretinoin therapy.

Abbreviations

ALC-absolute lymphocyte count
ALT-alanine aminotransferase
ANC-absolute neutrophil count
AST-aspartate aminotransferase
CBC-complete blood count
CK-creatine kinase
GGT-gamma glutamyltransferase
TG-triglyceride
WBC-white blood cell

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