Oral Isotretinoin and its Association with Liver Functions and Cholesterol Level among Acne Patients

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Abstract

Background & Objective(s): Isotretinoin has a dramatic effect in treating acne vulgaris but it has numerous widespread adverse effects. The study aimed to investigate the association between isotretinoin and liver functions and cholesterol level among acne patients.

Methods: A cross-sectional study was conducted in outpatient clinic of Dermatology Department of Alexandria Main University Hospital among 285 acne patients on isotretinoin for more than one month and less than 6 months with normal baseline serum liver enzymes and cholesterol laboratory investigations. An interview questionnaire was used to collect sociodemographic data, pattern of drug use, and laboratory investigations data following treatment with isotretinoin.

Results: The mean age of patients was 20.84±3.4 years and 68.4% of them were females. Regarding pattern of using the drug, 36.8% of cases took 80 mg/day for 4-6 months. Almost 30% of cases had elevation in alanine aminotransferase (ALT) level, 23.2% had elevation in aspartate aminotransferase (AST) level and 21.1% of the cases had elevation in cholesterol level. There was a weak positive correlation between dose, duration of taking the drug and elevation in the liver enzymes and cholesterol level.

Conclusion: There was a significant difference in level of liver enzymes and serum cholesterol level before and after using the drug. The dose and duration of taking the drug are factors affecting the elevation of serum liver enzymes and cholesterol level.

Keywords: Acne patients, Isotretinoin, Cholesterol, Liver functions.

INTRODUCTION

Acne vulgaris is one of the most common skin disorders which mainly affect adolescents. It is a multifactorial chronic inflammatory disease of pilosebaceous units.\textsuperscript{(1)} Globally, acne vulgaris is the tenth leading cause of disability-adjusted life years in the late adolescent period (15-19 years old).\textsuperscript{(2)}

One of the most common complications is physical scarring. The legacy of acne often remains visible long after active disease has ended.\textsuperscript{(3)} Acne has severe psychological complications making patients more prone to depression, anxiety, embarrassment, social withdrawal and anger.\textsuperscript{(4)} There are four pathogenic mechanisms involved in development of acne namely follicular hyperkeratinization, increased sebum production, propionibacterium acnes colonization and inflammatory response.\textsuperscript{(5)} Many different treatment options are available for the treatment of acne vulgaris. The commonly used acne topical treatments include benzoyl peroxide, antibiotics and topical retinoids. Systemic treatment is frequently used as a combination therapy with the topical treatments and includes the use of systemic antibiotics or oral retinoids (e.g. isotretinoin) which are the last choice for severe acne.\textsuperscript{(6)} Isotretinoin is considered superior to the other systemic treatment options as it affects the four pathogenic mechanisms, involved in the development of acne at the same time. It produces complete or near complete clearing of acne in about 95% of people who complete the treatment period that ranges from 16-20 weeks.\textsuperscript{(7)}

Despite its dramatic effect in treating acne vulgaris, isotretinoin affects the entire body systematically and was found to have numerous widespread side effects affecting more than 80% of the patients.\textsuperscript{(8)} Elevation in serum cholesterol level and liver enzymes [(aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] is one of the most important adverse effects associated with the use of isotretinoin.\textsuperscript{(9)}
Oral isotretinoin is considered by dermatologists to be the gold-standard monotherapy for treatment of severe acne. That is why it is very important to investigate isotretinoin and its association with liver functions and cholesterol level among acne patients treated with isotretinoin.

METHODS

The study was conducted in the outpatient clinic of the Dermatology Department of Alexandria Main University Hospital using a cross-sectional approach. Severe acne patients on oral isotretinoin for more than 1 month till less than 6 months with normal baseline serum liver enzymes and cholesterol laboratory investigations and attending the previously mentioned study setting were included in the study. The researchers excluded cases without documented normal baseline laboratory investigation results. Those having hypercholesterolemia or history of any disease affecting liver function such as hepatitis whether viral or autoimmune or toxic, and liver cirrhosis, those who started the drug without doing baseline laboratory investigations and those who discontinued the drug were also excluded from the study.

The sample size was calculated using Epi Info 7.2.0.1, 2016. Based on the prevalence of elevation in liver transaminases among acne patients receiving oral isotretinoin of 20%, (8) and with 5% confidence limit, the minimum required sample size at 95% confidence level was calculated to be 246 and was rounded to 285. Acne patients fulfilling the inclusion criteria were enrolled consecutively in the study till reaching the required sample size.

A predesigned structured interviewing questionnaire with acne patients treated with isotretinoin was used to collect socio-demographic data, pattern of using the drug (dose, frequency, duration), and baseline laboratory investigations before treatment with isotretinoin. At time of interview, patients were referred to a private laboratory to assess serum level of liver enzymes and cholesterol following treatment.

A pilot study was carried out on ten patients to pretest the study tools, estimate the average time needed to obtain the required information and to be acquainted with various problems and obstacles that could be faced during the implementation of the study. The pilot study revealed that the time needed to obtain the required information was 15 minutes. The researchers found difficulty in finding patients with baseline investigations and hence the researchers took more time than expected to reach the required severe acne patients with the predetermined inclusion criteria.

Based on the results of the laboratory investigations following treatment, patients were classified according to the classification of the United States National Cancer Institute (9) into normal (≤40 IU/L ALT or AST) and (≤200 mg/dl cholesterol), grade I (41–100 IU/L ALT or AST and 201–300 mg/dl cholesterol), grade II (101–200 IU/L of ALT or AST and 301–400 mg/dl cholesterol), grade III (201–800 IU/L ALT or AST and 401–500 mg/dl cholesterol), grade IV (>800 IU/L ALT or AST and >500 mg/dl cholesterol).

Statistical analysis

Data were revised, coded and analyzed using SPSS version 20 software for tabulation and analysis. (11) Descriptive statistics like mean ± SD, count and percentage were calculated. Analytical statistics like chi-square test, Monte Carlo correction, paired t-test, and Spearman coefficient were used. Multiple linear regression analysis was used to detect factors associated with the elevation of serum cholesterol and liver enzymes. The regression model included all variables which were significantly related to the elevation in serum ALT, AST, and cholesterol in the bivariate analysis. The difference between baseline and post treatment levels of ALT, AST and cholesterol are considered significant when p <0.05.

Ethical considerations

The study was approved by the Ethics Committee of the High Institute of Public Health. The researchers complied with the International Guidelines for Research Ethics. An informed written consent was obtained from each study participant after explanation of the purpose and benefits of the study. Anonymity and confidentiality of participants were assured and maintained. Patients with elevated liver enzymes and cholesterol were informed to check the course of treatment with their treating physician.

RESULTS

Regarding the socio-demographic characteristics of studied acne patients, as shown in table 1. The age ranged between 13 and 33 years. The mean age of the studied cases was 20.84 ± 3.40 years. More than two thirds of them (68.4%) were females, and 82.5% were single. Those with university education constituted 71.9%. Less than two thirds (63.1%) of acne cases were students and 61.8% were urban residents.

The pattern of use of isotretinoin among the studied cases is shown in table 2. More than one third (36.8%) of cases were taking the maximum dose of oral isotretinoin (80 mg/day) while 8.4% of cases were taking the least dosage (20 mg/day). Concerning the frequency of drug intake, 78.9% of cases were taking the drug twice daily. As for the duration of taking the drug, 12.9% of cases were taking the drug for one month, 20.4% of cases were taking it for two months, 30.2% of cases were taking it for 3 months and 36.5% were taking it for 4-6 months.

Table 3 shows a comparison between laboratory investigations results before and after treatment. It is evident from the table that the mean ALT level increased from 24.95 ± 5.18 before to 40.06±12.95 IU/L after treatment, AST level increased from 24.46 ± 4.84 before to 40.06±12.95 IU/L while cholesterol level increased from 148.72 ± 23.05 before to 193.68±26.25mg/dl after treatment and the difference between both levels in all the
laboratory tests were statistically significant ($p < 0.05$). The percent change in the mean levels of enzymes and cholesterol was 60.56% for ALT, 53.23% for AST and 30.23% for cholesterol.

Table 1: Distribution of the studied acne cases treated with isotretinoin by their socio-demographic characteristics

| Socio-demographic characteristics | Acne cases treated with isotretinoin (n=285) | No. | % |
|-----------------------------------|---------------------------------------------|-----|----|
| Age (years)                       |                                             |     |    |
| <15                               | 6                                           | 2.1 |    |
| 15-                               | 95                                          | 33.3|    |
| 20-                               | 139                                         | 48.8|    |
| 25+                               | 45                                          | 15.8|    |
| Mean ±SD.                         | 20.84 ± 3.40                                |     |    |
| Sex                               |                                             |     |    |
| Male                              | 90                                          | 31.6|    |
| Female                            | 195                                         | 68.4|    |
| Marital status                    |                                             |     |    |
| Single                            | 235                                         | 82.5|    |
| Married                           | 50                                          | 17.5|    |
| Education                         |                                             |     |    |
| Illiterate                        | 3                                           | 1.1 |    |
| Primary                           | 3                                           | 1.1 |    |
| Preparatory                       | 8                                           | 2.8 |    |
| Secondary                         | 66                                          | 23.1|    |
| University                        | 205                                         | 71.9|    |
| Occupation                        |                                             |     |    |
| Students                          | 180                                         | 63.1|    |
| Professionals                     | 60                                          | 21.1|    |
| Not working                       | 34                                          | 11.9|    |
| Workers                           | 11                                          | 3.9 |    |
| Residence                         |                                             |     |    |
| Urban                             | 176                                         | 61.8|    |
| Rural                             | 109                                         | 38.2|    |

Applying the classification of the United States National Cancer Institute for patients treated with isotretinoin, more than one quarter (29.1%) of the cases had grade one (41–100 IU/L) serum ALT level and 23.2% of the cases had grade one serum AST level. More than one fifth of the cases (21.2%) had also grade one (201–300 mg/dl) serum level of cholesterol as shown in figure 1.

Table 4 shows the relation between the pattern of using the drug and the elevation in serum level of liver enzymes. Regarding ALT serum level (U/L), more than one fifth (23.3%) of patients who took the reference therapeutic doses (20-60 mg/day) had elevation in ALT level while nearly two fifths (39%) of those taking 80 mg/day had elevation in ALT level. Those taking 80 mg/day were nearly 2 times more prone to have elevation in ALT level [(OR (CI)= 2.105 (1.248–3.549)]. A weak positive correlation was found between the mean dose of isotretinoin and the elevation in ALT level and it was statistically significant (Spearman coefficient=0.310, $p < 0.001$). Concerning the frequency of taking the drug, 28.3% of acne patients who took the drug once daily and 29.3% of those who took the drug twice daily had elevation in ALT level, however, this difference was not statistically significant ($p= 0.880$). There is a significant association between the duration of taking the drug and the elevation of ALT. Patients taking the drug for 4-6 months are about 22 times more prone to have ALT elevation [OR (CI)= 22.065 (5.040–96.598)] Also, a weak positive correlation was found between the duration of taking the drug and the elevation in ALT level and it was statistically significant (Spearman coefficient=0.474, $p < 0.001$).

Concerning the elevation in AST serum level, table 4 also revealed that 15% of patients taking 20-60 mg/day of drug had elevation in AST level while more than one third (37.1%) of cases taking 80 mg/day had elevation in AST level occurring in grade I. Those taking 80 mg/day were nearly 3 times more prone to have elevation in AST level [OR (CI)= 3.348 (1.895–5.917)]. A weak positive correlation was found between the mean dose of isotretinoin and the elevation in AST level and it was statistically significant (Spearman coefficient=0.346, $p < 0.001$). More than a quarter (30%) of those taking the drug once daily and more than one fifth (21.3%) of patients taking it twice daily were having elevation in the AST level, however, this difference was not statistically significant ($p= 0.157$). Concerning the duration of taking the drug, acne patients who were taking the drug for 4-6 months were 16.2 times more prone to have grade I of AST level than those taking the drug for less duration [OR (CI) = 16.204 (3.704–64.598)]. Also, a weak positive correlation was found between the duration of taking the drug and the elevation in AST level and it was statistically significant (Spearman coefficient=0.408, $p < 0.001$).

Table 4 also shows the relation between pattern of using the drug and the elevation in the cholesterol serum level. Regarding dose, 13.9% of patients taking 20-40 mg/day had elevation in cholesterol level while one third
(33.3%) of those taking 80 mg/day of the drug had elevation in cholesterol level. Those taking 80 mg/day were nearly 3 times more prone to have elevation in cholesterol level [OR (CI)= 3.17 (1.726–5.569)]. A weak positive correlation was found between the mean dose of isotretinoin and the elevation in cholesterol level and it was statistically significant (Spearman coefficient=0.317, p <0.001). It appears from the table that nearly one quarter (23.3%) of those taking the drug once daily, and one fifth (20.4%) of those taking it twice daily were found to have an elevation in cholesterol level, however, this difference was not statistically significant (p= 0.626). There is a statistically significant association between the duration of taking the drug and the elevation in serum level of cholesterol. Patients taking the drug for 4-6 months are about 15 times more prone to have elevated serum level of cholesterol [OR(CI)= 15.00 (3.428–65.643)]. Also, a weak positive correlation was found between the duration of taking the drug and the elevation in cholesterol level and it was statistically significant (Spearm coefficient= 0.396, p <0.001).

Table 3: Comparison between laboratory investigations for acne patients receiving isotretinoin before and after treatment

| Laboratory investigation | Before treatment | After treatment | p       | % change |
|--------------------------|------------------|----------------|---------|----------|
| ALT (U/L)                |                  |                |         |          |
| Min. – Max.              | 17.0 – 38.0      | 25.0 – 87.0    | 'p <0.001' | 60.56    |
| Mean ± SD.               | 24.95 ± 5.18     | 40.06 ± 12.95  |         |          |
| Median                   | 25.0             | 37.0           |         |          |
| AST (U/L)                |                  |                |         |          |
| Min. – Max.              | 15.0 – 36.0      | 21.0 – 82.0    | 'p <0.001' | 53.23    |
| Mean ± SD.               | 24.46 ± 4.84     | 37.48 ± 11.21  |         |          |
| Median                   | 24.0             | 36.0           |         |          |
| Cholesterol (mg/dl)      |                  |                |         |          |
| Min. – Max.              | 110.0 – 200.0    | 150.0 – 300.0  | 'p <0.001' | 30.23    |
| Mean ± SD.               | 148.72 ± 23.05   | 193.68 ± 26.25 |         |          |
| Median                   | 150.0            | 190.0          |         |          |

* Statistically significant at p ≤ 0.05

Figure 1: Classification of the acne patients after treatment with isotretinoin by ALT, AST, cholesterol levels based on the classification of the United States National Cancer Institute
Table 4: Relation between the pattern of using isotretinoin and the elevation in serum liver enzymes and serum cholesterol level of acne patients

| Laboratory investigations | Grade 1 | Normal | Test of Sig. | p   | OR | Sig. | 95% CI     |
|---------------------------|---------|--------|--------------|-----|----|------|------------|
| ALT (U/L)                 |         |        |              |     |    |      |            |
| Dose (mg)                 |         |        |              |     |    |      |            |
| 20 -60 (n=180)³           | 42      | 23.3   | 138          | 76.7|     |      |            |
| 80 (n = 105)              | 41      | 39.0   | 64           | 61.0|     |      |            |
| r, (p)                    | 0.310*  | (<0.001) |            |     |    |      |            |
| Frequency                 |         |        |              |     |    |      |            |
| Once daily (n=60)         | 17      | 28.3   | 43           | 71.6|     |      |            |
| Twice daily (n=225)       | 66      | 29.3   | 159          | 70.6|     |      |            |
| Duration of treatment (months) |       |        |              |     |    |      |            |
| 1(n=37)                   | 1       | 2.7    | 36           | 97.3|     |      |            |
| 2 (n=58)                  | 2       | 3.4    | 56           | 96.6|     |      |            |
| 3 (n=86)                  | 22      | 25.6   | 64           | 74.4|     |      |            |
| 4-6 (n=104)               | 58      | 55.8   | 46           | 44.2|     |      |            |
| r, (p)                    | 0.474*  | (<0.001) |            |     |    |      |            |
| AST (U/L)                 |         |        |              |     |    |      |            |
| Dose (mg)                 |         |        |              |     |    |      |            |
| 20 – 60 (n = 180)³        | 27      | 15.0   | 153          | 85.0|     |      |            |
| 80 (n = 105)              | 39      | 37.1   | 66           | 62.9|     |      |            |
| r, (p)                    | 0.346*  | (<0.001) |            |     |    |      |            |
| Frequency                 |         |        |              |     |    |      |            |
| Once daily (n=60)         | 18      | 30.0   | 42           | 70.0|     |      |            |
| Twice daily (n=225)       | 48      | 21.3   | 177          | 78.6|     |      |            |
| Duration of treatment (months) |       |        |              |     |    |      |            |
| 1 (n=37)                  | 2       | 5.4    | 35           | 94.6|     |      |            |
| 2 (n=58)                  | 5       | 8.6    | 53           | 91.4|     |      |            |
| 3 (n=86)                  | 9       | 10.5   | 77           | 89.5|     |      |            |
| 4 - 6 (n=104)             | 54      | 52.0   | 50           | 48.0|     |      |            |
| r, (p)                    | 0.408*  | (<0.001) |            |     |    |      |            |
| Cholesterol (mg)          |         |        |              |     |    |      |            |
| Dose (mg)                 |         |        |              |     |    |      |            |
| 20 – 40 (n = 180)³        | 25      | 13.9   | 155          | 86.1|     |      |            |
| 80 (n = 105)              | 35      | 33.3   | 70           | 66.7|     |      |            |
| r, (p)                    | 0.317*  | (<0.001) |            |     |    |      |            |
| Frequency                 |         |        |              |     |    |      |            |
| Once daily (n=60)         | 14      | 23.3   | 46           | 76.7|     |      |            |
| Twice daily (n=225)       | 46      | 20.4   | 179          | 79.6|     |      |            |
| Duration of treatment (months) |       |        |              |     |    |      |            |
| 1 (n=37)                  | 2       | 5.4    | 35           | 94.6|     |      |            |
| 2 (n=58)                  | 6       | 10.3   | 52           | 89.7|     |      |            |
| 3 (n=86)                  | 38      | 44.2   | 48           | 55.8|     |      |            |
| 4 - 6 (n=104)             | 48      | 46.2   | 56           | 53.8|     |      |            |
| r, (p)                    | 0.396*  | (<0.001) |            |     |    |      |            |

(³) Fisher Exact test was used as (20.0%) of the cells or more have expected count less than 5
(*) Statistically significant at p <0.05
**DISCUSSION**

In the current study, the proportion of females with acne was 68.4% and 82.5% of patients were in the adolescence age. A study in Rome (2018) by Skroza et al.\(^{(12)}\) revealed that 85% of acne patients were females and 58.7% of patients were adolescents while many studies showed that acne was affecting approximately 57.8-95% of the adolescents.\(^{(2,13,14)}\) Elevation in serum ALT, AST and cholesterol is one of the most important side effects associated with the use of isotretinoin.\(^{(15)}\) In the present study, the difference in serum levels of liver enzymes and the cholesterol before and after starting the treatment was found to be statistically significant. In the present study, the ALT, AST, and cholesterol serum levels increased to grade 1 after treatment in 29.1% and 23.2% and 21.2% of the cases respectively. A study in Egypt (2015) showed that serum cholesterol increased in the majority of patients during treatment and the ALT and AST levels were normal in all patients before treatment and significantly increased in the majority of patients during treatment.\(^{(16)}\) In Brazil (2012), a retrospective study conducted through record review of data of 70 patients showed that after 3 months of treatment with isotretinoin, AST and ALT levels increased in 8.6% and in 7.3% of the acne patients respectively\(^{(17)}\), while an Iranian study (2012) showed that AST and ALT levels increased in 7% and 7.9% of the patients respectively after 3 month of treatment.\(^{(15)}\) In Turkey (2014), a retrospective study conducted among 322 medical records of patients found that after 3-months treatment, the levels of AST and ALT increased in 0.9% and 3.4% of the patients respectively.\(^{(18)}\)

In the current study, the ALT level was elevated (from 14.95 ± 5.18 to 40.06 ± 12.95 U/L) after an average duration 3.64 ± 0.64 months while the AST level was elevated (from 24.46 ± 4.84 to 37.48 ± 11.21 U/L) after 2.68 ± 1.02 months and the cholesterol level was elevated (from 148.72 ± 23.05 to 193.68 ± 26.25 mg/dl) after 2.71 ± 1.01 months. Therefore, the duration of treatment had a great effect on the elevation in the ALT, AST and cholesterol serum level which was statistically significant. (OR 13.938, 9.172, and 8.689 respectively). A systematic review and meta-analysis revealed that the difference in mean values of AST level between baseline and after 6 weeks was 4.52 U/L (99% CI, 2.91-6.13 U/L). The difference in cholesterol level mean values between baseline and the mean after 11 weeks follow-up was 19.73 mg/dL (99% CI, 16.00-23.47 mg/dL). After 16 weeks, the difference from baseline was 23.51 mg/dL (99% CI, 16.84-30.18 mg/dL).\(^{(10)}\) In a study done in USA in 2016, the mean duration of treatment before elevations in levels of liver enzymes and cholesterol were detected after 61.9 days for ALT, and 50.1 days for cholesterol.\(^{(20)}\)

The limitations of the study included the difficulty in finding patients with baseline investigations and hence taking more time than expected to reach the required sample size of severe acne patients with the predetermined inclusion criteria. Also, the nature of the used study design (cross sectional) made the researchers unable to generalize their results. It is better for future research to use a cohort design.

**CONCLUSION AND RECOMMENDATIONS**

From the results of the study, it could be concluded that there was a statistically significant difference in the level of serum cholesterol and liver enzymes before and after the use of isotretinoin. There was a weak positive correlation between the dose and/or the duration of taking the drug and the elevation in the liver enzymes and cholesterol. The study revealed that the increased dose (80 mg/day) and duration of taking the drug for 4-6 months had a significant impact on the elevation of liver enzymes and cholesterol levels.

It is recommended to conduct baseline laboratory investigations (liver enzymes and cholesterol) for all patients before starting treatment. The dose and duration of treatment should be well monitored. Follow up laboratory
investigations should be done every month during the period of treatment.

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CONFLICT OF INTEREST
All authors declare no conflict of interest.

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