

# A POTENTIAL FOR THE SHORTEST TREATMENT OF MODERATELY SEVERE ACNE VULGARIS WITH THE USE OF MINIMUM- AND LOW-DOSE OF ISOTRETINOIN



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## ABSTRACT

### *Background*

Acne vulgaris is a common human skin disease. Isotretinoin is one of many pharmaceutical agents used in the treatment of patients with moderate and severe forms of acne.

### *Objectives*

To use minimum- and low-dose of isotretinoin for the shortest period in the treatment of patients with moderate acne vulgaris.

### *Patients and methods*

We have carried out this study on 210 patients with moderate papulopustular acne. From the beginning to compare between the patients they were divided into two age groups: the first group between 12 and 20 years; the second group between 21 and 35 years. Both groups of patients were followed up for four years. All patients were treated for 4 months with isotroin capsules with a dosage of 40 mg/day in two divided doses for two months and then decreased to 20 mg/day for another two months. Before and after the two and four months treatment laboratory tests were carried out for complete blood cell counts, liver and lipid profiles (cholesterol and triglycerides). Pregnancy tests were also carried out before treatment in female patients of child-bearing potential and interested in this regimen.

### *Results*

The first group included 110 patients, with a female/male ratio of 2:1, mean age 17.2 years, and a mean body weight of 56.3 kg. 99.1% of the patients achieved complete remission, whilst 0.9% of the patients failed to respond to the treatment. The relapse rate was 3.6% and the mean total dosage of isotroin was 63.9 mg/kg, whereas and the daily dose of the drug was 0.5 mg/kg/day. The second group included 100 patients, with a female/male ratio of 2.6:1, mean age 25.3 years, and a mean body weight of 66.8 kg. 99% of the patients achieved complete remission, whilst 1% of the patients failed to respond to the treatment.

The relapse rate was 4%, the mean total dosage of isotroin was 53.9 mg/kg and the daily dose of the drug was 0.45 mg/kg/day. In both groups, the most common side effects in all the patients were mild to severe cheilitis and dryness of the skin. Only one patient suffered of epistaxis. After the 4-month treatment only one of the patients had high serum triglycerides. None of the patient had elevation of liver enzymes.

### *Conclusion*

In moderately severe acne vulgaris, excellent results can be obtained with minimum- and low-dose oral isotretinoin for only four months of treatment.

**Keywords:** *Isotretinoin, Moderate acne vulgaris.*

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## INTRODUCTION

Acne vulgaris is a common human skin disease, characterized by areas of skin with seborrhea (scaly red skin), comedones (blackheads and whiteheads), papules (pinheads), pustules (pimples), nodules (large papules) and possibly scarring<sup>(1)</sup>. Acne is classified into mild, moderate, severe and very severe<sup>(2)</sup>.

There has been a significant increase in the prevalence of adult acne<sup>(3)</sup>. However, the frequency of acne in Sulaimani city (Iraq) was found to be around 9%<sup>(4)</sup>.

Isotretinoin belongs to a group of medicines known as retinoids and is a substance related to vitamin A that was approved by the Food and Drug Administration for the indication of severe nodulocystic acne in 1982. Subsequent to its approval, isotretinoin has become a widely prescribed medication despite its well-known teratogenic effects<sup>(5)</sup>.

Isotretinoin's main indication is for the treatment of severe cystic acne vulgaris<sup>(6)</sup>. Many dermatologists also support its use for treatment of lesser degrees of acne that prove resistant to other treatments, or that produce physical or psychological scarring<sup>(7)</sup>. The introduction of isotretinoin in the early 1980s revolutionized the treatment of acne in reducing its residual cosmetic and psychological damage. Initially, the use of isotretinoin tended to be limited only to the more severe cases of nodulocystic acne, but in recent years the drug is being increasingly prescribed in moderate cases of acne that are unresponsive to conventional therapy. In both cases, isotretinoin is known to effectively reduce scarring and psychological distress<sup>(8)</sup>.

Until now, the classical recommended dose has usually been 0.5 to 1.0 mg/kg per day for 4 to 8 months but it causes many side effects that are usually dose dependent. Nowadays, it is common practice in some areas to administer a low-dose regimen for the not so severe cases of acne, but this practice has not yet been truly well established<sup>(9)</sup>. Kligman in 1996 suggested that a lower dosage would be of benefit in acne treatment<sup>(10)</sup>.

Although there are many studies, but very large evidence-based study is lacking to confirm the dosing schedule. The approved dose is 0.5-2 mg/kg/day, which is usually given for 20 weeks

<sup>(11)</sup>. Alternatively, lower dose can be used for longer period, with a total cumulative dose of 120 mg/kg<sup>(9)</sup>. Lower-dosage treatments, such as 10–20 mg/day (approximately half the high dosage treatments above), are also highly effective, with greatly diminished side effects<sup>(9)</sup>.

New developments and future trends are low-dose long-term isotretinoin regimens and new isotretinoin formulations (micronized isotretinoin)<sup>(12)</sup>. However, such lower dosage courses may be associated with higher relapse rates, requiring additional courses, especially if not taken for sufficient time<sup>(13)</sup>. Oral retinoid is indicated in severe, moderate-to-severe acne or lesser degree of acne producing physical or psychological scarring, unresponsive to adequate conventional therapy. It is the only drug that affects all four pathogenic factors implicated in the etiology of acne<sup>(14)</sup>.

Isotretinoin's exact mechanism of action is unknown but several studies have shown that isotretinoin induces apoptosis (cell death) in various cells in the body such as cells in meibomian glands<sup>(15)</sup>, hypothalamic cells<sup>(16)</sup>, hippocampus cells<sup>(17)</sup> and in sebaceous gland cells<sup>(18)</sup>.

Side effects of isotretinoin include those of musculoskeletal, mucocutaneous, and ophthalmic systems, as well as headache, and central nervous system effects. Most of the side effects are temporary and resolves after the drug is discontinued<sup>(19)</sup>. The most common side effects are mucocutaneous and ocular in nature (i.e., cheilitis, ocular sicca, and decreased dark adaptation). It can also cause xerosis. Patients should be made aware of these side effects before taking isotretinoin and also that use of moisturizers and eye drops can help to mitigate them. Sometimes, however, the dose needs to be decreased to reduce the induction of side effects<sup>(20)</sup>. Oral isotretinoin is a potent teratogen. Therefore, women of child-bearing age require negative pregnancy test before treatment, strict contraceptive measures essential before, during and even 6 weeks posttherapy<sup>(21)</sup>.

The objective of this study was to use the minimum-dose, low-dose and shortest-duration of isotretinoin in the treatment of moderate acne vulgaris.

## **PATIENTS AND METHODS**

Our study has been conducted in the consultant dermatologist private clinic in Sulaimani city – Iraqi Kurdistan – and consisting of 210 patients with moderate papulopustular acne. The patients were treated for 4 months and to evaluate the drug effectiveness they have been followed up over a period of 4 years by monthly and annual examinations.

The following patients have been excluded: mild and severe nodular acne, pregnant women with acne, and patients with result of high laboratory tests.

The following patients have been included: non-pregnant patients with acne and those who promised not to conceive for next one year and patients with normal laboratory tests.

Based on the researcher's experience the assessment of the acne was done using a simple and rapid means of assessing acne patients based on color photographs using (I phone camera version 4) ranking the acne according to severity, the criteria for which are extent of inflammation, range and size of inflamed lesions, and associated erythema.

This study included only acne patients with moderate severity, who presented with papular and pustular lesions surrounded by slight erythema without nodules, cysts, or deep scars.

The patients were treated with a dosage of 40 mg/day in two divided doses for two months and then decreased to 20 mg/day for next other two months of isotroin (Cipla).

The evaluation was done by the same study researcher, before and after second and fourth month of the treatment and then annually.

Before and after two months and four months of the treatment certain laboratory tests were carried out including complete blood cell counts, liver and lipid profiles (cholesterol and triglycerides). Pregnancy tests were also carried out before treatment in female patients of child-bearing potential and interested in this regimen and instructed not to conceive in next one year.

To compare between the two groups, from the beginning the patients were divided into two age groups. The first group was between 12 and 20 years; the second group between 21 and 35 years. An (excellent) result was defined as complete remission of acne lesions. A (failure) was defined

in those who showed no improvement, requiring subsequent increases in isotretinoin dosage or even additional treatment. A relapse was defined as the reappearing of pretreatment severity of acne in the treated patient during the four years of the follow up.

The data were analyzed by means of the chi square test. Data obtained in (table 1) revealed that there were insignificant differences between the two groups in improvement rate ( $\chi^2 = 0.005$ ;  $P = 0.94$ ) or relapse rate ( $\chi^2 = 0.020$ ;  $P = 0.85$ ).

## **RESULTS**

In this prospective study, among the patients with moderate acne vulgaris treated successfully in the researcher's private clinic 210 patients (145 females and 65 males) have been followed up for four years and entered the study, Table 1.

The first group included 110 patients, with a female/male ratio of 2:1, mean age 17.2 years, and a mean body weight of 56.3 kg.

99.1% of the patients achieved complete remission (Figure 1, 2 and 3), but 0.9% of the patients failed to respond to the treatment, and the relapse rate was 3.6%.

The mean total dosage of isotroin was 63.9 mg/kg and the daily dose of the drug was 0.5 mg/kg/day.

The second group included 100 patients, with a female/male ratio of 2.6:1, mean age 25.3 years, and a mean body weight of 66.8 kg. 99% of the patients achieved complete remission, but 1% of the patients failed to respond to the treatment, and the relapse rate was 4%. The mean total dosage of isotroin was 53.9 mg/kg and the daily dose of the drug was 0.45 mg/kg/day.

In both groups, the most common side effects in all the patients were mild to severe cheilitis and dryness of the skin, Table 2. Only one patient suffered of epistaxis. After the four months treatment only one of the patients had high serum triglycerides 460 mg/dL (normal = 69-195 mg/dL). None of the patients had elevation of liver enzymes. In spite of strict instruction to use regular oral contraceptive pills, after stoppage of the treatment in few months three patients became pregnant; babies of two of them born with multiple organ cardiac and brain congenital anomalies and the other one became pregnant after six months whose baby born with normal organs but none of the patients developed depression or other psychological side effects.

Table 1. Statistical and clinical data results of patients with acne.

|                                | Group 1      | Group 2      |
|--------------------------------|--------------|--------------|
| <b>Age (y)</b>                 | <b>12-20</b> | <b>21-35</b> |
| <b>Number of patients</b>      | 110          | 100          |
| <b>Female/male ratio</b>       | 2:1          | 2.6:1        |
| <b>Mean age (y)</b>            | 17.2         | 25.3         |
| <b>Mean weight (kg)</b>        | 56.3         | 66.8         |
| <b>Improvement (%)</b>         | 99.1%        | 99%          |
| <b>Failure (%)</b>             | 0.9%         | 1%           |
| <b>Relapse (%)</b>             | 3.6%         | 4%           |
| <b>Mean total dose (mg/kg)</b> | 63.9         | 53.9         |
| <b>Daily dose (mg/kg/day)</b>  | 0.5          | 0.45         |

Table 2. Encountered side effects of isotretinoin treatment

|   | Group 1<br>n = 110 | Group 2<br>n = 100                 | % of side<br>effects in both<br>groups |
|---|--------------------|------------------------------------|--|
| <b>Cheilitis and dryness of the skin</b>              | All                | All                                | 100%                                   |
| <b>Epistaxis</b>                                      | 1                  | None                               | 0.5%                                   |
| <b>Hyperlipidemia</b>                                 | None               | 1 patient<br>Triglycerides:<br>460 | 0.5%                                   |
| <b>Elevation of liver enzymes</b>                     | None               | None                               | 0%                                     |
| <b>Pregnancies and teratogenicity</b>                 | None               | 3 patients                         | 1.4%                                   |
| <b>Depression or other psychological side effects</b> | None               | None                               | 0%                                     |

**Before treatment with isotretinoin**



**After treatment with isotretinoin**



**Figure 1.**

**Before treatment with isotretinoin**



**After treatment with isotretinoin**



**Figure 2.**

**Before treatment with isotretinoin**



**After treatment with isotretinoin**



**Figure 3.**

**DISCUSSION**

In conventional dosage, the use of oral isotretinoin has been limited not only by the occurrence of mucocutaneous adverse effects, teratogenicity and depression with suicidal ideation, but also by biochemical abnormalities such as impaired liver function and hyperlipidaemia<sup>(22)</sup>.

Regimens with fixed low-dose isotretinoin 20 mg per day and 20 mg on alternate days for a total duration of six months have been found to be effective in moderate acne<sup>(23)</sup>.

Mandekou-Lefaki *et al.* achieved excellent results in 68% and fair to good results in 31.2% in a group of 32 patients who received low-dose isotretinoin, 0.15 to 0.4 mg/kg per day for a mean duration of 8 months; the mean total dosage was 78.9 mg/kg<sup>(24)</sup>.

In our study with the minimum dose of (0.5 mg/kg per day), low-dose of (0.45 mg/kg per day) regimen of isotroin and shorter duration (only four months) in two age groups patients, excellent results were obtained (99.1% and 99%) with very mild side effects.

Regarding the improvement and side effects our results were found to be similar to or rather better than those reported in the literature in patients with moderate acne using the low-dose isotretinoin of 0.4 mg/kg per day and classical dosage of 0.5 to 1.0 mg/kg per day<sup>(24)</sup>.

Hyperlipidemia is one of the more common laboratory finding of isotretinoin and appears in up to 35% of the patients receiving conventional therapy<sup>(21)</sup>.

In our study, however, abnormal serum lipids values were found in only one patient (0.45%) of the patients. Elevation of liver enzymes was 10% in patients treated with the classical regimen<sup>(21)</sup>. While in our study, elevation of liver enzymes was not recorded.

Despite excellent results and strict instructions there were three pregnancies in our study; babies of two of them born with cardiac and brain congenital anomalies and one born with normal organs but no patients developed depression or other psychological side effects.

These excellent results in this study, however, may be explained by the fact that the patients participating in our study were only suffering from moderate acne. The classical higher dosage is, in fact, used in patients with more severe acne.

The minimum-dose regimen, low-dose and shortest duration of isotretinoin make the treatment more acceptable for patients with moderate acne at a lower cost and shorter duration than the classical higher doses; the classical higher doses should be used in more severe cases of acne.

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