Efficacy of Oral Low-Dose Isotretinoin in the Treatment of Acne Vulgaris in Vietnam

Thanh Le Thai Van1,2, Phuong Nguyen Minh3, Phuong Tran Thi Thuy1, Marco Gandolfi4, Francesca Satolli5, Claudio Feliciani6, Michael Tirant7, Aleksandra Vojvodic1, Torello Lotti8

1Department of Dermatology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam; 2Department of Plastic and Cosmetic Surgery, University Medical Center, Ho Chi Minh City, Vietnam; 3Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam; 4Unit of Dermatology, University of Parma, Parma, Italy; 5University of Rome G. Marconi, Rome, Italy; 6Psoriasis Eczema Clinic, Melbourne, Australia; 7Department of Dermatology and Venereology, Military Medical Academy of Belgrade, Belgrade, Serbia

Abstract

BACKGROUND: Oral isotretinoin is an effective therapy for acne. However, isotretinoin can induce hyperhomocysteinemia and decreased serum folic acid level, which may be a risk for cardiovascular disease and thrombosis, as well as psychoses. Besides, many recent types of research emphasise the safety and effects of the low dose isotretinoin therapy.

AIM: The aim of our study was to evaluate the effect of the low-dose isotretinoin on the plasma homocysteine and serum folic acid level in the Vietnamese population.

METHODS: We conducted a longitudinal study to evaluate the effectiveness of the low-dose therapy on the plasma homocysteine and serum folic acid level of 52 acne patients after 6-8-week treatment at University Medical Center Ho Chi Minh City, Viet Nam. Patients had moderate-severe acne with the prolonged course, and most of them had a scar.

RESULTS: With a low dose of oral isotretinoin (0.37 ± 0.11 mg/kg/day), after 6-8-week treatment, patients dropped the severity of disease, increased the plasma homocysteine level and decreased the serum folic acid level with significant differences in comparison to those before treatment. However, these changes do not exceed the normal range.

CONCLUSION: In overall, low dose isotretinoin treatment had effectiveness in decrease the severity of disease and no increasing the plasma homocysteine level as well as the serum folic acid level.

Introduction

Acne is a popular skin disease with the incidence in adolescence of up to 85-100%, including 30% moderate and 10% severe acne [1], [2], [3], [4]. Isotretinoin has been used to treat moderate-severe acne where standard treatment was not effective. Compared to other treatments, isotretinoin has been shown to be more responsive in decreasing the size and secretion of sebaceous gland [5]. However, isotretinoin may result in elevated plasma homocysteine and decreased serum folic acid which in turn contribute to cardiovascular diseases, thrombosis, cognitive function disorders and dementia [6], [7], [8].

Many researchers have evaluated which isotretinoin dose would have the most efficacy and less adverse events. Recent studies indicated the safety of the oral isotretinoin therapy where the low dose of isotretinoin (< 0.5 mg/kg/day) had no significant effects in metabolic disorders [9], [10]. Effective treatment and less severe side effects were found in a study among 638 patients, both male and female, with moderate acne that were treated with isotretinoin at 20 mg/d (approximately 0.3-0.4 mg/kg per day) for 6 months [9]. Another study among 150 Malaysian patients treated with isotretinoin at 10mg on the daily basis until a cumulative dose of 90-110 mg/kg showed that after 24 weeks of treatment, all patients cleared of acne lesions with a low rate of elevated liver enzymes and serum lipid at 3.3% and 2.7% respectively. There was no case of discontinuation in treatment [11]. The hyperhomocysteinemia with low serum folic acid level...
cause many severe side effects, but there was no study in the literature about this disorder in low-dose isotretinoin therapy.

Therefore, in this study, we evaluated the changes of the homocysteine and folic acid level during oral isotretinoin treatment in Vietnamese acne patients. Findings from this study might contribute to the literature whether we should monitor the plasma homocysteine and serum folic acid in patients treated with oral low-dose isotretinoin to prevent hyperhomocysteinemia, decrease folic acid level and possibly related disorders.

Methods

Setting and Participants

In September 2014, a longitudinal study was conducted at the Skin Care Department, University medical centre HCMC. We recruited 52 acne patients above 18 years old. All patients received the explanation of objects and procedures and signed the consent form. Patients were then treated with oral Isotretinoin once a day for 6 – 8 weeks. Those who had hepatic/kidney failure or under treatment with drugs such as phenytoin, L-dopa, methotrexate, theophylline, penicillamine, vitamin B12, vitamin B6, acid folic were excluded. All procedures in this study were approved by the Ethics Committee at HCMC University of Medicine and Pharmacy, Vietnam.

Procedures

All patients were asked about their medical history and examined to assess the skin type and acne status by a dermatologist from the Department of Dermatology, HCMC University of Medicine and Pharmacy. They have then measured the concentration of plasma homocysteine and serum folic acid level. After 6 – 8 weeks of treatment, patients were re-measured the concentration of the plasma homocysteine and serum folic acid level as well as re-assessed the clinical characteristics and the severity of acne.

Measurements

The plasma homocysteine level was measured by a quantitative method, direct chemiluminescent immunoassay with the ADVIA Centaur machine of Siemens. The serum folic acid level was quantified by the Architect C16000 machine of Abbott using chemiluminescent microparticle immunoassay technology. Patient’s history was assessed by onset age (< 25 years old and ≥ 25 years old) and disease duration (≥ 24 months and < 24 months). Clinical symptoms of acne are assessed by skin types (oily, normal, combined variants), acne lesions (papule, pustule, nodule, cyst, opened and closed comedones), affected areas (face, chest, back, arm) and scar (atrophic + keloid scar, no scar).

The severity of acne is evaluated using GAGS (Global Acne Grading System) of Doshi, Zaheer and Stiller. The GAGS considers six locations on the face (forehead, cheeks, nose, chin, chest and back). Each is derived by multiplying the factors-2 for forehead, 2 for each cheek, 1 for nose, 1 for chin, 3 for both chests and back by the most heavily weighted lesion within each region (1 for ≥ one comedone, 2 for ≥ one papule, 3 for ≥ one pustule, and 4 for ≥ one nodule).

The score for each area (local score) is calculated using the formula: Local score = Factor × Grade (0-4). The global score is the sum of local scores, and acne severity is graded using the global score. A score of 1-18 is considered mild; 19-30 as moderate; 31-38 as severe; and ≥ 39 as very severe.

The 25th percentile of the mean cumulative isotretinoin dose in our research was 18.5 mg/kg. We use this cut-off value to compare pre- and posttreatment plasma homocysteine levels and serum folate levels based on the accumulative dose of isotretinoin.

Data analysis

We described data using frequency and percentage for qualitative variables, the mean and standard deviation for quantitative variables. Association between patients’ characteristics and plasma homocysteine and serum folate levels was evaluated using t-test. Comparison of mean plasma concentrations of plasma homocysteine and folic acid before and after treatment was conducted using a paired t-test. Type I error was set at 5%. All data analysis was done using SPSS 20.0.

Results

In 52 acne patients treated with oral isotretinoin therapy at University Medical Center, the majority was female (80.8%) with the mean age of 22 years old and the mean weight of 52.77 kg (SD = 8.97 kg). Almost all patients had oily skin (90.4%), onset age under 5 years old (94.2%) and had acne on the face (98.1%). Most patients suffered from moderate and severe acne and had scars.

The mean severity of disease evaluated by GAGs score was 25.98 ± 6.5 score as shown in Table 1.
Table 1: Characteristics of acne patients treated with oral isotretinoin

| N (%) | Homocysteine (µg/l) | Folate (ng/ml) |
|-------|---------------------|---------------|
|       | M (SD)              | p              | M (SD)              | p              |
| Sex    | Male                | Female         | Male                | Female         |
|        | 10 (19.2)           | 42 (80.8)      | 11.55               | 1              |
|        | 10.97 ± 2.58        | 7.69 ± 6.83    | 9.24 ± 2.84         | 8.27 ± 2.88    |
| Onset age | ≥ 25 years old    | < 25 years old |                          |                |
|        | 3 (5.6)             | 49 (94.2)      |                          |                |
|        |                    |                |                       |                |
| Duration | ≥ 24 months        | < 24 months    |                          |                |
|        | 40 (76.9)           | 12 (23.1)      | 8.79 ± 2.37          | 0.30           |
|        | 8.40 ± 2.37         | 8.01 ± 1.97    | 7.94 ± 2.84          | 0.860          |
| Disease | < 24 months        | < 24 months    |                          |                |
|        | 12 (23.1)           | 8.01 ± 1.97    | 8.10 ± 2.59          | 0.790          |
| Skin type | Oily               | Other          | 8.56 ± 2.37          | 0.98           |
|        | 47 (90.4)           | 5 (9.6)        | 8.01 ± 2.74          | 0.790          |
|        | 8.64 ± 1.41         | 7.65 ± 3.32    |                          |                |
| Acne lesion | Close comedone     | Open comedones |                          |                |
|        | 51 (98.1)           | 47 (90.4)      |                          |                |
|        | 8.79 ± 2.37         | 8.40 ± 2.37    |                          |                |
|        | 8.01 ± 1.97         | 8.10 ± 2.59    |                          |                |
|        | 8.56 ± 2.37         | 8.01 ± 2.74    |                          |                |
|        | 8.64 ± 1.41         | 7.65 ± 3.32    |                          |                |
| Scar   | Atrophic scar       | Keloid         |                          |                |
|        | 38 (73.1)           | 0 (0)          |                          |                |
|        | 8.40 ± 2.37         | 8.01 ± 2.74    |                          |                |
|        | 8.79 ± 2.37         | 8.01 ± 2.74    |                          |                |
|        | 8.79 ± 2.37         | 8.01 ± 2.74    |                          |                |
| Severity of acne | Mild               | Moderate       |                          |                |
|        | 12 (23.1)           | 32 (61.5)      | 9.68 ± 2.57          | 0.860          |
|        | 8.40 ± 2.37         | 8.17 ± 2.09    | 8.61 ± 2.19          | 0.018          |
|        | 8.79 ± 2.37         | 8.01 ± 2.74    | 8.61 ± 2.55          | 0.005          |

The oral isotretinoin dose during 6-8-week treatment was 0.37 ± 0.11 mg/kg/day; the accumulative dose was 14.67 (18.5-21.95) mg/kg. After 6-8-week treatment with oral isotretinoin, the severity of acne followed GAGs and serum folate level was statistically significantly decreased; plasma Homocysteine levels were significantly statistically elevated (P < 0.05) as shown in Table 2.

Table 2: The severity of acne, the plasma homocysteine and serum folate levels in patients before and after 6-8 weeks isotretinoin treatment

| The severity followed GAGs | Before treatment | After treatment | P     |
|----------------------------|-----------------|----------------|-------|
| Homocysteine (µg/l)        | 25.98 ± 6.50    | 15.56 ± 6.87   | < 0.001|
| Male                       | 8.61 ± 2.29     | 9.23 ± 2.37    | 0.016 |
| Female                     | 10.58 ± 1.12    | 11.42 ± 1.96   | 0.252 |
| Female                     | 7.69 ± (6.63 - 9.20) | 8.27 ± (7.20 - 10.05) | 0.018 |
| Folate (ng/ml)             | 7.90 ± 2.76     | 7.16 ± 2.42    | 0.005 |

Post-treatment plasma homocysteine and serum folic acid were significantly changed compared with the initial values in a group of patients with the higher mean accumulative dose of isotretinoin (> 18.5 mg/kg), as shown in Table 3. There were no statistical differences in others.

Table 3: Comparison of pre- and post-treatment plasma homocysteine levels and serum folate levels based on accumulative dose of isotretinoin

| Accumulative dose | Homocysteine (µg/l) | Folate (ng/ml) |
|------------------|---------------------|---------------|
| ≤ 18.5 mg/kg     | 8.43 ± 2.94         | 8.74 ± 2.04   |
| > 18.5 mg/kg     | 8.79 ± 2.38         | 9.67 ± 2.31   |

Discussion

This was the first Vietnamese study that evaluates the effects of low dose isotretinoin on the plasma homocysteine and serum folic acid level in acne patients. The results showed that the severity of disease of patients treated with a mean dose of isotretinoin 0.37 ± 0.11 mg/kg/day after 6-8 weeks decreased statistically. This demonstrated that the low dose oral isotretinoin therapy is an effective treatment in acne. Besides, the plasma homocysteine level increased and the serum folic acid level decreased with significant differences in comparison to those before treatment. However, these changes do not exceed the normal range. Our findings were consistent with previous studies where low dose isotretinoin has been shown to be beneficial in the treatment and a decrease in relapse [9], [10], [11]. Hence, to minimise the side effects of drugs, the low dose isotretinoin should be considered in the treatment of acne disease.

The hyperhomocysteinaemia is a risk factor for cardiovascular diseases and venous thrombosis and also affects negatively on endothelial cells, smooth muscle cells in recent reports [6], [7], [8], [12]. The hyperhomocysteinaemia was also reported in some researches in acne patients treated with isotretinoin. In these studies, the plasma Homocysteine level significantly increased after treated with oral isotretinoin (≥ 0.5 mg/kg/day) during 45 days or more [13], [14], [15], possibly because the inhibitions of cystathionine β synthase, leading to disrupt the metabolism of homocysteine [16]. Another possible reason could be that the drug decreased the level of folic acid and vitamin B12, resulting in rising homocysteine level [14]. Our results also indicated that the plasma homocysteine level after 6-8 week treatment increased significantly in comparison with the initial level (8.61 ± 2.29 µg/l with 9.23 ± 2.37 µg/l). However, this plasma homocysteine level after treatment did not exceed the normal biologically range of the plasma homocysteine level (15 µg/l).

Regarding the level of folic acid, our results confirmed the conclusions of previous national studies, in which the serum folic acid dropped markedly after oral isotretinoin therapy [17], [18], [14]. Karadag et al. observed a decrease of serum acid folic level during treatment isotretinoin 0.5 mg/kg/day for 4 months [14]. In our study, the serum folic acid level after 6-8-week treatment was significantly lower in comparison with the initial level (7.98 ± 2.76 mg/ml with 7.16 ± 2.42 mg/ml). Nevertheless, similarly to the changes in homocysteine level, although this difference was statistically significant but not clinically meaningful because this decreased level was in normal range. The deficiency of folic acid may induce some disorders such as neuropathy, psychoses and dementia. This deficiency also contributes to advance homocysteine level, leading to adverse events of hyperhomocysteinaemia. According to the results, there is no risk for folic acid deficiency-induced disorders when the low dose isotretinoin is used.

Generally, the adverse effects of isotretinoin depend on dose. In our study, patients treated with...
the higher mean accumulative dose of isotretinoin had more markedly changes of the serum homocysteine and folic acid. Consequently, when using of high dose or long term of isotretinoin therapy which may increase the cumulative dose, it is essential to prevent the risk of rising homocysteine or falling folic acid. Vitamin intake such as vitamin B12 or folic acid might be proved an effective preventive measure against some complication due to hyperhomocysteinemia [13], [14], [16].

This study was subject to several limitations. First, the effects of the long-term low dose isotretinoin could not be assessed due to the limited followed-up period. Second, we could not clarify the changes in homocysteine and folic acid due to the hepatic dysfunction or effect on a certain enzyme involved by the drug in the synthetic process of 2 substances. Third, because there was no control group, the different effects of high dose and low dose isotretinoin on homocysteine and folic acid level were not able to describe. Finally, we were only able to sample clients from one hospital in HCMC. Thus, it is possible that climatic, socio-economic and/or other differences existed among clients across different areas and settings. In this regard, further studies were needed.

In conclusion, we found that moderate and severe acne patients treated with low dose isotretinoin (< 0.5 mg/kg/day) had no change in the homocysteine and folic acid level of the blood, which can induce adverse events biologically. Therefore, during treatment with the low dose isotretinoin, it is unessential to monitor the level of homocysteine and folic acid. However, when treated with the higher dose or for a long-term period, the risk of increasing of the plasma homocysteine and decreasing serum folic acid level should be considered.

Acknowledgements

The authors would like to thank Dr Nguyen Hoang Bac, Dr Van The Trung and Dr Nguyen Anh Tuan for their continuous support during the study. We appreciate all patients for their participation in this study.

References

1. Zaenglein AL, Graber EM, Thiboutot DM. (2012). Acne vulgaris and acneiform eruption. Fitzpatrick’s Dermatology in general medicine: Mc Graw Hill, 2012:897-917.

2. Bhate K, Williams HC. Epidemiology of acne vulgaris. British Journal of Dermatology. 2013; 168(3):474-85. https://doi.org/10.1111/bjd.12149 PMid:23210645

3. Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook’s textbook of dermatology. John Wiley & Sons, 2016. https://doi.org/10.1002/9781118441213

4. Tan JK, Bhate K. A global perspective on the epidemiology of acne. British Journal of Dermatology. 2015; 172:3-12. https://doi.org/10.1111/bjd.14626 PMid:25593739

5. Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. Expert opinion on drug safety. 2004; 3(2):119-29. https://doi.org/10.1517/14740338.3.2.119 PMid:15006718

6. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA. 2002; 288(16):2015-22. https://doi.org/10.1001/jama.288.16.2015

7. Den Heijer M, Rosendaal FR, Blom HJ, Gerrits WB, Bos GM. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. Thrombosis and Haemostasis-Vienna. 1998; 80(8):874-7. https://doi.org/10.1159/00001615380

8. Zylberstein DE, Lissner L, Börkelund C, Mehlig K, Thelle DS, Gustafsson D, Östling S, Waern M. Hyperhomocysteinemia and late-life homocysteine and late-life dementia in women. A prospective population study. Neurobiology of ageing. 2011; 32(3):380-6. https://doi.org/10.1016/j.neurobiolaging.2009.02.024 PMid:19342123

9. Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. Journal of the American Academy of Dermatology. 2006; 54(4):644-6. https://doi.org/10.1016/j.jaad.2005.11.1061 PMid:16548686

10. Sardana K, Karg VK, Sehgal VN, Mahajan S, Bhushan P. Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. Journal of the European Academy of Dermatology and Venereology. 2009; 23(5):556-60. https://doi.org/10.1111/j.1468-3083.2008.03022.x PMid:19143903

11. Yap FB. Safety and efficacy of fixed-dose 10 mg daily isotretinoin treatment for acne vulgaris in Malaysia. Journal of cosmetic dermatology. 2017; 16(3):348-52. https://doi.org/10.1111/jocd.12268 PMid:27539948

12. Hoţoleanu C, Porojan‐Luga M, Rusu ML, Andercou A. Hyperhomocysteinemia: clinical and therapeutic involvement in venous thrombosis. Romanian journal of internal medicine= Revue roumaine de medecine interne. 2007; 45(2):159-64.

13. Kamal M, Polat M. Effect of different doses of isotretinoin treatment on the levels of serum homocysteine, vitamin B 12 and folic acid in patients with acne vulgaris: A prospective controlled study. JPMA. The Journal of the Pakistan Medical Association. 2015; 65(9):950-953. PMid:26338739

14. Karadag AS, Tutar E, Ertugrul DT, Akin KO. Effect of isotretinoin treatment on plasma holotranscobalamin, vitamin B12, folic acid, and homocysteine levels: non‐controlled study. International journal of dermatology. 2011; 50(12):1564-9. https://doi.org/10.1111/j.1365-4632.2011.05027.x PMid:22098008

15. Roodarsi MR, Akbari MR, Sarraf‐Rad N, Saeedi M, Gheisari M, Kavand S. The effect of isotretinoin treatment on plasma homocysteine levels in acne vulgaris. Clinical and Experimental Dermatology: Clinical dermatology. 2010; 35(6):624-6. https://doi.org/10.1111/j.1365-2230.2010.03778.x PMid:20236286

16. Schulpis KH, Karikas GA, Georgala S, Michas T, Tsakiris S. Elevated plasma homocysteine levels in patients on isotretinoin therapy for cystic acne. International journal of dermatology. 2001; 40(1):33-6. https://doi.org/10.1046/j.1365-4362.2001.00146.x PMid:11277950

17. Gökalk H, Bulur I, Gürrer MA. Decreased vitamin B12 and folic Acid concentrations in acne patients after isotretinoin therapy: a controlled study. Indian journal of dermatology. 2014; 59(6):630. https://doi.org/10.4103/0019-5154.143533 PMid:25484410 PMCID:PMC4248518

18. Javanbakht AM, Pour HM, Tarrah MJ. Effects of oral isotretinoin on serum folic acid levels. Journal of drugs in dermatology: JDD. 2012; 11(8):e23-4. PMid:23155667