Comparison of Oral Isotretinoin vs Azithromycin in the Treatment of Acne Vulgaris

Alaa Sh. Abdulbari[1], Noor M. Ali [2], Ahmed R. Abu Raghif [3], Nadheer A. Matloob [4]

[1]Lecturer, Pharmary Department, Al-Israa University College, Baghdad, Iraq, [2]Prof., Department of Chemistry and Biochemistry, College of Medicine of AL-Nahrain University, Baghdad, Iraq, [3]Prof., Department of Pharmacology, College of Medicine of AL-Nahrain University, Baghdad, Iraq, [4]Prof., Section of Dermatology & Venereology, College of Medicine of AL-Nahrain University, Baghdad, Iraq

Abstract

Background: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles, common in adolescents, characterized by comedones, papules, pustules, cysts, nodules, and occasionally scars. This study was designed to compare multi B vitamins, folic acid and homocysteine levels in patients with moderate to severe acne vulgaris with those of the apparently healthy control group and to investigate the effect of isotretinoin and azithromycin treatments on these biochemical parameters and comparison between two drugs.

Methods: This study was conducted on sixty women patients with acne and thirty as a control group. The patients were allocated into two groups, A and B, group A was given 500 mg of azithromycin taken on alternative days for 3 months and group B was given 40mg/day isotretinoin for 3 months.

Results: The study showed significant differences ($p<0.05$) in serum levels of vitamins B_6, B_7, B_{12} and folic acid, while no significant difference in serum homocysteine in patient group when compared to control group. The results showed significant positive correlation between serum vitamins and clinical score and significant difference were detected in both group when compared between pre and post treatment.

Conclusions: The results indicate higher pre-treatment vitamin B_{12} levels, versus the control group and positive correlation between clinical score and vitamin B_{12}, support the assertion that vitamin B_{12} plays a role in the etiopathogenesis of acne vulgaris. Both azithromycin and isotretinoin were effective in acne treatment but azithromycin has less side effects.

Key-words: *Acne; azithromycin; isotretinoin; vitamin B_7; vitamin B_{12}*

Introduction

Acne is one of the chronic inflammatory diseases for pilosebaceous units. It can be characterized by seborrhea, erythematous pustules and papules and in more cases of severe nodules, the closed and open comedones formation, pseudocysts and deep pustules. Inflammatory lesions are followed by scarring [1]. In latest years, therapy of combination has become a vital part of acne treatment. There are different treatment modalities to acne vulgaris including systemic and topical drugs, depending on severity [2].

Isotretinoin (13cis-retinoic acid) Fig. 1-7 is a vitamin A derivative frequently given over a 20-week course (16–24 weeks), with a dosage of 0.5–1 mg/kg/day, depending on clinical response and side effects [3]. It has significant results in sebum production reduction, decreasing in surface and ductal *P. acnes,* influences comedogenesis and shows properties of anti-inflammatory [4]. Azithromycin is one of the antibiotics that have been prescribed, for treatment of acne which is as effective as doxycycline and minocycline [5]. Azithromycin belongs to the azalide group of antibiotics and is closely related structurally to macrolides like erythromycin [6]. This study was undertaken with the main objective of moderate to severe AV treatment,

and to investigate the efficiency and side effects of azithromycin and isotretinoin and compared between them.

Material and Methods

This is a randomized, case-control study that was carried out in the dermatology unit at the Al Imamain Alkadhimain Teaching Medical City/ Baghdad to compare the side effects between 500 mg of azithromycin taken in alternative days and 40mg/ day isotretinoin for 12 weeks of treatment. All patients having moderate to severe acne as categorized by the Global Acne Grading Score (GAGS) were clinically diagnosed and included in the study. The samples were collected within eight months starting from September 2016 until the end of May 2017. Serum samples were collected from 60 Iraqi women patients aged between (15 -35 years old) and were investigated with moderate to severe acne. Control group was consisted of 30 apparently healthy individuals. Cases were excluded if they had any of the following criteria: azithromycin hypersensitivity, renal disease, liver disease, diabetes mellitus, metabolic impairment pregnant women or under multi-vitamin supplementation. The patients were allocated into two groups, A and B, group A was given 500 mg of azithromycin taken on alternate days for 3 months and group B was given 40mg/day isotretinoin for 3 months. Together with the systemic drug, patients were given 5% topical benzoyl peroxide gel to apply to the affected areas of the face and trunk once daily after the skin had been cleansed and dried. Patients were examined at baseline, 6 weeks and 12 weeks, in order to evaluate their clinical improvement and to measure several biochemical parameters. Patients were educated concerning compliance, side effects and constant follow up. The study was accomplished with the institutional review board agreement and written consent was taken from all patients.

Venous blood about 5 ml was drawn from the patients each time before starting treatment, at 6 weeks and at the end of 12 weeks of treatment. The blood was allowed to clot for at least 10-15 min at room temperature, centrifuged for 10 min at 4000xg. Serum was removed and divided into two parts, the first to measure homocysteine by ELISA kit and the other part was deproteinized and stored at - 18 ^{0}C until the time of HPLC assay to measure several vitamin concentrations.

Serum levels of vitaminB_6, vitamin B_7, vitaminB_{12} and folic acid were measured by HPLC method [7]. While serum homocysteine was measured by sandwich enzyme-linked immunosorbent assay (ELISA) kit (Kono Biotech. Co. China).

Results

The results showed that were significant differences ($p<0.05$) in serum levels of vitamins B_6, B_7, B_{12} and folic acid, while no significant difference in serum homocysteine in patient group when compared to control group as listed in table 1. Application of Person correlation test revealed significant positive correlated of vitamin B6 with clinical score in AV patient (r=0.38, P=0.002). There was a significant positive correlation between serum vitamin B12 and clinical score in AV patient (r=0.43, P=<0.001) and also positive correlation between folic acid and clinical score in AV patients (r=0.37, P=0.004) as listed in Table 2.

The results showed there were significant difference- in the two groups- ($p<0.05$) when compared with baseline readings (pre-treatment) of serum folic acid, vitamin B_{12}, vitamin B_7, vitamin B_6, homocysteine and clinical score and those after 12 weeks of treatment (post-treatment) as listed in the table 3 and table 4. Comparison between azithromycin and isotretinoin after 12 weeks of treatment in the two groups (A and B) was listed in table 5.

Discussion

The current results showed a significant decrease in serum folic acid and vitamin B_6 in the patient group compared with the group of control, while there was a considerable elevation in serum vitamin B_7 and vitamin B_{12}. Even a marginal deficiency of vitamins B, B_2, B_{12}, niacin, biotin, pantothenic acid, folic acid, vitamin C, vitamin E, or essential fatty acid that could result in reduced development of skin cells, which manifests itself in the skin which is less elastic, less smooth, more prone, to accelerated aging and prone, to lesions [8]. Elevation in serum vitamin B_{12} in acne patients due to the correlation between the severity of acne and vitamin B_{12} that proved in this study. Also result showed a slight increase in serum homocysteine in patients, but there was no significant difference observed as compared with

control group and these results disagree with Jiang *et al.* that showed significantly elevated serum homocysteine levels in patients with severe and moderate acne compared with the control group [9]. However, it can be reported that different vitamin supplements (the most prominently are vitamin B_{12}), could exacerbate existing acne and/or lead to the development of acneiform eruptions [10]. After administration with isotretinoin, the results showed a reduction in the serum level of folic acid and vitamin B_{12}, while anincrease in the serum homocysteine level after 3 months of treatment. With isotretinoin, this results in agreement with several studies [11, 12, 13], while disagreeing with [14]. Folic acid and vitamin B_{12} (and their interrelated metabolism) are essential vitamins in different metabolic pathways (including the homocysteine pathway). Folic acid and vitamin B_{12} are methyltransferase enzyme cofactors and with their deficiency, hyperhomocysteinemia is noted [12]. In addition, isotretinoin may also affect cystathionine- β-synthase, the enzyme responsible for homocysteine metabolism in the liver and may lead to hyperhomocysteinemia. This hyperhomocysteinemia, as an isotretinoin side effect, might contribute to the missing link between isotretinoin and neuropsychiatric disorders [15]. The previous study concluded that homocysteine level elevation in spite of the normal responsible vitamins values for the amino acid metabolism powerfully suggested that the drug might affect cystathionine-β-synthase, acting as enzyme inhibitor or liver dysfunction which is caused by isotretinoin [13], Karadag *et al.,* are of the opinion that when the treatment with isotretinoin greater cumulative doses lasts longer, it might cause subclinical folic acid and vitamin B_{12} deficiencies that have more effects on the homocysteine level [11]. The exact isotretinoin mechanism action on folic acid reduction is still unknown. Javanbakht *et al.,* suggest that it is probable that isotretinoin interacts with some essential groups in the active site of important proteins or enzymes at folic acid metabolism. This interference might be initiated by the changes in the intestinal absorption of folic acid, different steps of formation tetrahydrofolate from folic acid, induction of enzymes in the liver and finally depletion of folic acid [16], Hilal et al., also propose that using isotretinoin for a long-term may decrease the absorption of vitamin B_{12} and intestinal folic acid [12].

Long-term use of isotretinoin in higher doses affects hair growth and is associated with increased hair loss [17]. The current study showed a decreased level of vitamin B_7 when compared with pre-treatment values, and supports the assertion that isotretinoin leads to hair loss as its side effects.

Increase concentration of vitamin B_6 post-treatment versus the pre-treatment may be due to increasing homocysteine level that leads to increase the conversion of homocysteine to cystathionine in the presence of vitamin B_6 dependent enzyme cystathionine-β-synthase and then cystathionine convert to cysteine and α-ketobutyrate via cystathionine-γ-lyase (vitamin B_6 dependent enzyme) [18].

For our information, the current study is the first one achieving changes in serum vitamin B_7 and vitamin B_6 levels in patients receiving isotretinoin treatment.

After administration with azithromycin, the result showed a significant decrease in serum folic acid and vitamin B_7 may be due to the effects of azithromycin on the absorption of these vitamins, while there was a significant increase in serum vitamin B_{12}. The increase in the serum vitamin B_{12} in the current study may be due to azithromycin effects on one of the mechanisms that lead to increase vitamin B_{12} concentration. This study shows a significant elevation in serum vitamin B_6 which may be due to the relation between vitamin B_6 deficiency and increased facial seborrhea [19] so, the drug may increase the absorption of this vitamin to decrease the facial seborrhea in order to minimize sebum production.

To our knowledge, this is the first study investigating changes in serum vitamin levels in patients with AV that were treated with azithromycin and therefore we could not compare our results with any such studies.

The current study showed a significant increase in serum homocysteine and vitamin B_7 in patients under isotretinoin treatments when compared to those under azithromycin treatment after the same duration (12 weeks), while there was a significant decrease in serum folic acid, vitamin B_{12} and vitamin B_6, this result can indicate wide side effects range of isotretinoin when compared to azithromycin, however the effect of isotretinoin on acne lesion is greater than the effect of azithromycin. In spite of the clinical score of

azithromycin being less than that of isotretinoin because the clinical score in isotretinoin group at the baseline was greater than that of the azithromycin group and also the duration of treatment with isotretinoin will continue 5-6 months so, at the end of treatment the lesion was almost clear.

Conclusions

Higher pre-treatment vitamin B_{12} levels, versus the control group and positive correlation between clinical score and vitamin B_{12}, support the assertion that vitamin B_{12} plays a role in the etiopathogenesis of acne vulgaris. Isotretinoin in dose 40mg/day or azithromycin in dose 500mg on an alternative day was effective in the treatment of patients with moderate to severe acne, but the results indicated that a wide range of side effects -of isotretinoin when compared to azithromycin although, the isotretinoin was more effective and can decrease vitamin B_{12} levels.

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