ORIGINAL ARTICLE

Efficacy and Safety of Azithromycin in Moderate Acne Vulgaris

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ABSTRACT

Introduction: Acne vulgaris is a chronic inflammatory dermatosis caused by *Propionibacterium acnes*. Clinicians are constantly attempting to discover the best antibiotic regimes in treating acne vulgaris. This study compares two regimens in terms of efficacy, tolerability, compliance and recurrence rate to make recommendation on which is the best regime. **Methods:** An open-labelled prospective randomized investigator-blinded interventional study was carried on moderate acne vulgaris patients. Patients were assigned to treatment arm at enrolment followed by follow-up and maintenance visits. Demographic data were collected at enrolment and questionnaire enquiring acne condition, general health and quality of life impairment were filled at every visit followed by blinded dermatologist assessment. Antibiotic tablets were provided based on assigned arm until follow-up 3. **Results:** 26 mild acne vulgaris patients aged 17 to 29 years were recruited. Physician assessment based on GAGS and photo assessment analysis showed an overall significant change ($p<0.05$) with decreasing trend indicating that the treatment is statistically effective. However, no significant differences ($p>0.05$) were found between regimens. Similarly, patient self-perceived assessment and CADI assessment also showed overall significant changes ($p<0.05$) with increasing trend indicating improvement in acne condition but no significant differences ($p<0.05$) between regimens. **Conclusion:** Neither regimen were significantly more efficacious than another. In view of cost, oral azithromycin 500mg daily for consecutive 4 days monthly is suggested as a better option.

Keywords: Acne vulgaris, Azithromycin, Global Acne Grading System (GAGS), Cardiff Acne Disability Index (CADI)

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INTRODUCTION

Acne vulgaris is a common chronic skin inflammatory disease. It is caused by a gram-positive bacteria, *Propionibacterium acnes* which infects the skin leading to presentation of papules, pustules and nodules (inflammatory lesions) or even black heads and white heads (non- inflammatory lesions) (1-3). Acne vulgaris being a multifactorial dermatosis occurring in the pilosebaceous follicles are most commonly caused by increased sebum and inflammatory mediators, genetic predispositions, hormonal abnormalities, psychological and even environmental factors (4). Food and dietary habits has also been reported to be an underlying cause of acne-like skin eruption to an extent but only rarely (5, 6).

An estimate of over 85% of individuals are affected by this inflammatory dermatosis during their adolescence phase or at some point of their life (6). It is a prevalent disease not only found in Asia but also all across Europe. Studies had found the prevalence rate of acne vulgaris among children aged 6 to 7 years at Taiwan to be 17.3% whereas only 9.8% was reported at Hong Kong. In Malaysia, studies conducted at secondary schools within two district among adolescence aged 13 to 18 years had reported the prevalence rate to be 67.5% (1, 7). More recently, a rising trend in the prevalence of acne among children due to accelerated onset of puberty has been reported (8).

Oral antibiotic therapy is commonly the first line treatment of choice among clinicians in managing patients with skin conditions ranging from moderate to severe forms. There is also a growing practice of conservative management among the patients which includes dietary modification and skin hygiene practice (8). Annually, management and treatment of acne vulgaris consumes a large amount of money. The reported amount had been estimated to be RM250 (US 80) for a single patient in one year in Malaysia (2). The treatment strategies suggested for the management of acne vulgaris includes topical antibiotics, salicylic acid,

azelaic acid,benzoyl peroxide, adapalene, isotretinoin, tazarotine, sulphur and dapsone. However, most of the topical therapy carry adverse cutaneous reactions towards the skin such as erythema, burning, dryness and its usage are limited towards the treatment of mild acne(3). It is also important to note that prolonged usage of topical corticosteroids could potentially cause iatrogenic acne vulgaris (9).

Malaysia clinical practice guidelines for acne vulgaris management had suggested a combination therapy of both oral antibiotics and topicals as a mode of treatment for moderate acne vulgaris1. Clinicians are always trying to find the best regimes of antibiotic in terms of efficacy, tolerability, compliance and lower recurrence rate. Among the many antibiotics had been studied so far, Azithromycin had been proven to be effective with a low side effect profile (7, 10, 11). Azithromycin carried the least percentage of total side effects (19%) as when compared to Doxycycline (28%), Erythromycin (28.1%), minocycline (30.7%) and tetracycline (23.8%) (3). So far, there is no documented resistance rate of this drug towards the Propionibacterium acnes (7, 10). Furthermore, minimal data is available on the recurrence rate of acne vulgaris after successful treatment with pulse azithromycin.

Azithromycin dosage on a monthly routine was reported to be comparably effective and statistically significantly (by intention to treat analysis) in comparison to daily doxycycline routine (12). The study showed a reduction of 75.65 % of lesions in the group treated with 500mg Azithromycin 4 days per month against a percentage of 60.2% of lesions in the group treated with 100 mg of daily Doxycycline (12). Various other studies have also documented its safety and efficacy at a dose of 500mg daily for three consecutive days weekly or every 10 days for a duration of 3 months (7, 10, 13-15). Hence, Azithromycin is well established and proven to beeffective in all the regimensas an attribute of its distinctive pharmacokinetics and efficacy.

However, no previous studies had compared these treatment regimens in terms of efficacy, tolerability, compliance and recurrence rate. Thus, it is important that a clear comparison is made in order to put forward recommendations of the best regime in acne vulgaris treatment with regards to efficacy, tolerability, compliance and recurrence rate. This finding will successfully lead clinicians to a better understanding and more efficacious treatment in managing acne.

MATERIALS AND METHODS

This is an open-labelled prospective randomized investigator-blinded interventional study carried out in Skin Clinic of University Malaya Medical Centre and Laurent Bleu Skin Science and Wellness Centre, UCSI University. Patients with moderate acne as defined by Global Acne Grading System (GAGS)(16) were enrolled into this study. Patients with history of allergy to azithromycin, on topical anti-acne treatment within 4 weeks, on systemic corticosteroids or hormonal therapy within 6 months prior to recruitment into the study are excluded from participation.

Enrolment Visit

Patients' demographics data were collected by the attending nurse during the enrolment visit. Patients were then required to fill a questionnaire pertaining to their acne vulgaris, general health condition as well as quality of life (QOL) impairment based on Cardiff Acne Disability Index (CADI) (17).

A blinded dermatologist confirmed the diagnosis of acne vulgaris and assessed the clinical severity using GAGS. Three view photographs of patients' face were taken using Janus facial analysis system (front, 45° left and 45° right). This was followed by five view photographs that were taken using Digital SLR camera, at 2.5 metres distance away from the patient (front, 45° left, 45° right, 90° left and 90° right).

Patients were then assigned to treatment arm based in random numbers generated by the attending nurse. Written instructions on tablet consumption were provided for clear understanding. Number of tablets and topical given were also recorded. All patients were advised to use the supplied sulphur soap twice a day to cleanse their face and to apply Adapelene gel 0.01% as a thin firm over the whole face before sleeping. They were also advised on the following:

1. Not to take other concurrent anti-acne medication (parenteral, oral or topical).
2. Not to go for any facial massage or treatment
3. To continue with current skin care (apart from cleanser) throughout the study period
4. In the event of adverse reaction or doubts, to call the clinic for further instruction instead of stopping the medication
5. To be committed to come for all the follow-up and maintenance visits
6. To bring back the tablets if not finished at the next follow-up visit
7. When any symptoms arise after the treatment that may be attributed to the medication used in the study, participants should stop all study medication and inform the investigator for further instruction.

Follow-up visits

A total of 3 follow-up visits are done at the first, second and third month of treatment using the same protocol. During each follow-up visit, remaining tablets were counted and new supplies of medications were given. Tablets and topical dispensed were recorded.

Assessments on acne presentation on day of visit were

carried out by patient self-administered questionnaires and by a blinded dermatologist in the same manner as the enrolment visit. Side effects from treatment were assessed and recorded. At the third follow-up visit, doxycycline tablets were stopped. Patients were instructed to continue using sulphur soap as well as adapalene gel 0.01% at night.

Maintenance visits

A total of 3 maintenance visits at 2 monthly intervals from the 3rd follow-up visit were made. At each maintenance visit, patient were supplied with a sulphur soap and 15 g of adapalene gel 0.01%. Assessments were carried out by patient self-administered questionnaires and by a blinded dermatologist in the same manner as the enrolment and follow-up visits.

RESULTS

Patients

A total of 26 patients (10male, 16 female) with mild acne vulgaris were recruited in our study. The patients were aged between 17 to 29 years. They were randomized into arm 1 and arm 2 each consisting 14 and 12 patients respectively. The demographic characteristics of patients are shown in Table I. The schematic flow of the clinical investigation involved is summarized in Fig.1.

Table I: Patient's demographic profile

Arm	Arm 1	Arm 2	Both arms
Number of patients	14	12	26
Age, median years (range)	21(18-29)	22 (17-28)	22 (17-29)
Gender			
Male	6	4	10
Female	8	8	16
Ethnicity			
Malay	8	5	13
Chinese	6	5	11
Others	0	2	2
Previous treatment			
No	4	8	12
Yes	10	4	14
Duration of acne, median months (range)	96 (7-156)	60 (15-108)	84(7-156)
First Degree Relative with Acne			
No	4	6	10
Yes	10	6	16

Safety and tolerability

No severe adverse effects were reported by any patient throughout the study duration. Table II summarizes the general adverse reactions that were enquired from each patient at every progressive visit during the study period.

Assessment by Physician - GAGS

With multivariate analysis, an overall significant reduction ($p<0.05$) in GAGS score was observed over the study duration from enrolment visit until maintenance visit 3. The progressive decrease in the GAGS score as illustrated in Fig.2 (A) indicates that treatment is statistically effective. However, no significant differences between two regimens were observed. Fig.2 (B) shows

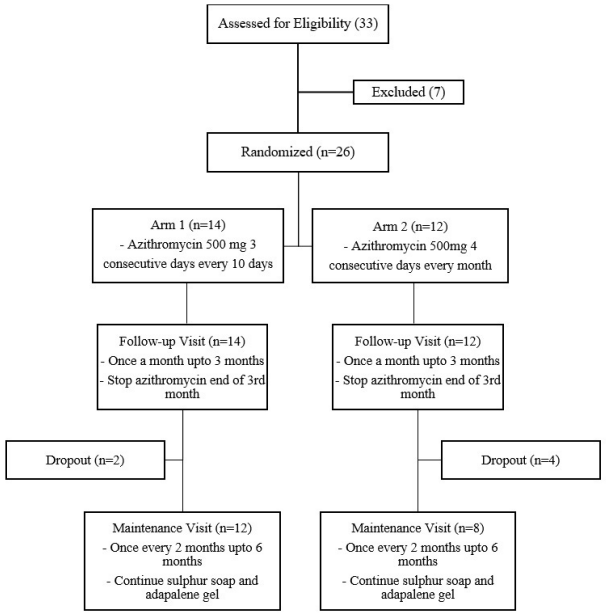

Figure 1: Schematic flow of clinical investigation

Table II: Adverse reactions reported throughout study period

Reactions	Diarrhoea	Nausea	Stomach upset	Vomiting	Menstrual disturbance	Other complications
FV1	3	1	3	0	1	nil
FV2	2	0	3	0	0	Hyperpigmentation
FV3	3	0	2	0	0	nil
MV1	0	0	1	0	0	nil
MV2	0	0	0	0	0	nil
MV3	0	0	0	0	0	nil

the difference between the regimens for the GAGS score.

Assessment by Physician – Photo Analysis

Photography assessment conducted also yield same results where the severity of acne reflected significant reduction ($p<0.05$) in treatment outcome as shown in Fig.2 (C). Between the groups, a more effective treatment in terms of improvement in outcome was observed as shown in Fig.2 (D) with the intake of azithromycin every 10 days instead of monthly regimen. However, these differences were not statistically significant.

Assessment by Patient - Self-perceived

On the whole, the self-perceived assessment of patients on the improvement of their acne is found to show significant changes ($p<0.05$) with an increasing trend for the initial visits and a decrease towards the end of the study duration (Fig.3 (A)). However, when compared between the groups, no significant difference was established. The every 10 day regimen shows a better improvement in general as compared to the monthly regimen which showed greater fluctuations as illustrated in Fig.3 (B) though the findings were statistically inconclusive.

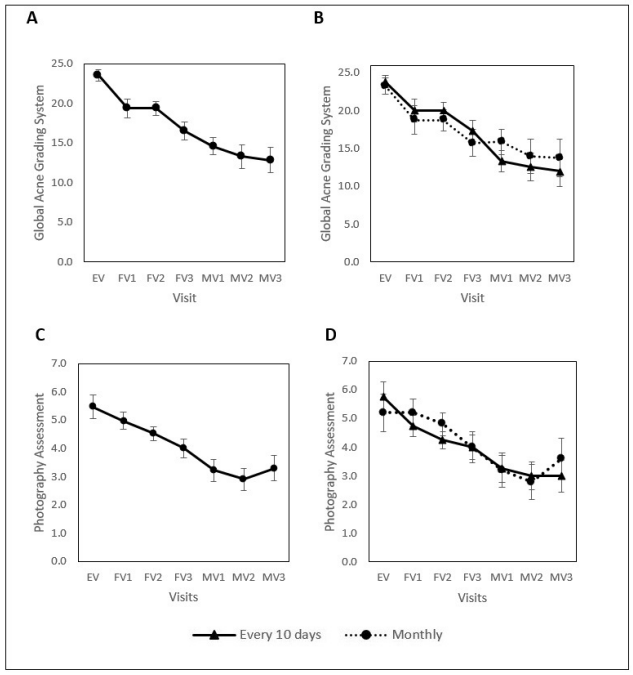

Figure 2: Physician assessment on acne presentation. A) Overall change in Global Acne Grading System (GAGS) score. B) Change in Global Acne Grading System (GAGS) score between regimens. C) Overall change in photography assessment. D) Change in photography assessment between regimens. Values are expressed as means ± standard error (n=26).

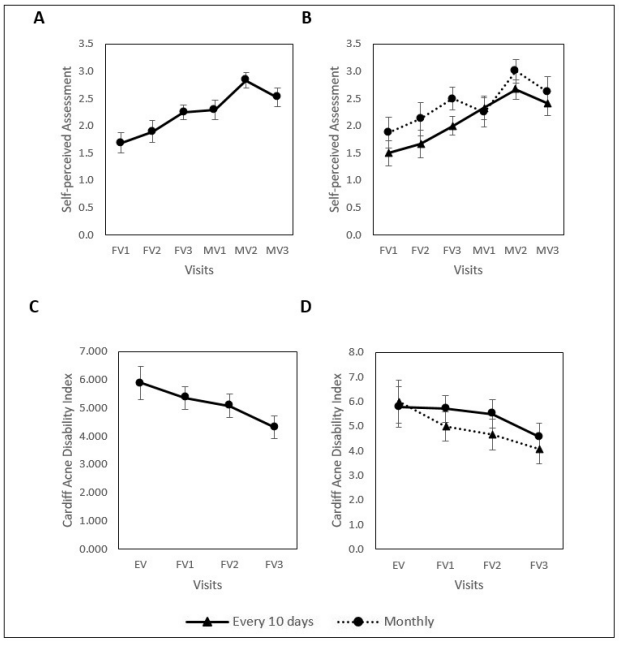

Figure 3: Patient assessment on acne presentation A) Overall change in self-perceived assessment. B) Change in self-perceived assessment between regimens. Values are expressed as means ± standard error (n=26). C) Overall change in Cardiff Acne Disability Index (CADI). D) Change in Cardiff Acne Disability Index (CADI) between regimens. Values are expressed as means ± standard error (n=20).

Assessment by Patient - CADI

The improvement in CADI shows significant reduction ($p<0.05$) as illustrated in Fig.3 (C); thus indicating that treatment was effective. This however includes 4 time points from enrolment visit until follow-up visit 3 only. No significant changes were observed when the maintenance period was included in the test. When compared between regimen groups, no significant difference was established. Fig.3 (D) shows the improvement in CADI between both regimens.

DISCUSSION

The changes in acne presentation among the mild acne patients were assessed by the physician based on GAGS and photography assessment. Collectively, the GAGS scoring was found to show a continuous decrement from the baseline enrolment visit throughout till third maintenance visit. This suggests that azithromycin was effective in improving the acne conditions regardless of which antibiotic regimen the patient is adhered to. Azithromycin, chemically being a 9-methyl derivative of erythromycin acts to inhibit major Gram-negative and Gram-positive (anaerobic and aerobic bacteria) as well as intracellular pathogens effectively (18, 19). When looked into the effects by regimen, a similar trend in improvement of acne was observed suggesting that both regimens were equally effective. Azithromycin on oral uptake rapidly absorbs and is widely distributed throughout the body right up to tissues and cells due to its pharmacokinetics thus producing a significant effect on the bacteria (20).

The photographic assessment on acne presentation among patients was also in line with the finding of GAGS assessment where a continuous improvement in the notable number of acne was observed. However, an unexpected increase was observed after second maintenance visit where rise of new acne were generally found in the photographic assessment at third maintenance visit. This indicates the recurrence of acne after 4 months of being "off-medication" upon completing the antibiotic course; thus suggesting that a low recurrence rate in general. Azithromycin could be administered as a single dose option of treatment as a result of its 68 hour- long terminal phase elimination half-life (20, 21). The low recurrence is most probably to be due to the half-life duration and the extended activity due to high concentrations that are available in the tissue and inflammatory cells where it is slowly released corresponding to its long half-life nature (22). Besides, the high concentrations could also be superior to the minimum inhibitory concentration (MIC) of most common pathogens being present (19). Its penetration capacity into prokaryotic and eukaryotic cells could

also be a factor contributing to the prolonged spectrum of activity (23).

The finding via patient self-perceived and CADI assessment were also parallel with the findings of the physician assessment where a continuous improvement was observed followed by recurrence of acne after the second maintenance visit. No life threatening or severe adverse effects have been reported by participants so it is generally safe. The common side effects of azithromycin that were observed in this study are diarrhoea, nausea and stomach upset; having a relatively low incidence throughout the study duration. This is due to its high stability causing it to produce minimal gastrointestinal adverse effect (14, 21). Two unusual symptoms of menstrual irregularity and generalised hyperpigmentation were also reported by two individual patients respectively. These symptoms could not be directly related to azithromycin and may have been due to other possible factors such as individual life style and general health conditions as it was only observed in single individual patients.

We observe generally good patient compliance, probably due to easy dosing schedule and minimal side effects. In view of cost, azithromycin is a comparatively expensive treatment option; however, in this study, it was provided to the participants at free of cost. In general, a direct comment could not be established with regards to the drug's absolute and relative cost as it highly varies from one country to another.

CONCLUSION

As a conclusion, considering all the beneficial effects, it is believed that azithromycin is an effective and safe alternative option to treat moderate acne vulgaris. As neither regimen is found to be significantly more efficacious than another, therefore, cost-effective treatment option which is using oral azithromycin 500mg daily for consecutive 4 days every 30 days can be recommended. Larger studies with bigger sample size and higher power may need to be conducted in the future to confirm there is no difference in these two regimens. Extended duration of study may potentially capture the expected length of time to observe for recurrence.

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