ORIGINAL ARTICLE

A Randomised Study Comparing the Efficacy of Low-Dose Oral Azithromycin versus Doxycycline in Combination with Topical Benzoyl Peroxide in the Treatment of Moderate to Severe Acne Vulgaris

Darshni Chandrasakaranpillay, *MRCP*, Ting Guan Ng, *AdvMDerm*

Department of Dermatology, Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia

Abstract

Background

Acne vulgaris is a common chronic inflammatory skin disease. Long term therapy involving antibiotics warrants for drug with a long half-life to increase compliance of patients.

Methods

A twelve-week prospective randomized study was performed on 40 subjects with moderate to severe facial acne to compare the efficacy of oral azithromycin with oral doxycycline. Thirty-six subjects completed the study. Subjects in azithromycin group received azithromycin 250mg three times a week plus topical benzoyl peroxide 5% (BPO), whereas subjects in doxycycline group received doxycycline 100mg daily plus topical BPO 5%. Efficacy evaluation included treatment success rate (Comprehensive Acne Severity Score /CASS of 0 or 1 or improvement of two grades from baseline) and lesion counts.

Results

Treatment was successful in 94.4% of subjects in azithromycin group, compared to 88.9% in doxycycline group (*p=1.000*) at week 12.However, percentage of clear or almost clear by CASS was higher in the doxycycline group (83.3% vs 66.7%; *p= 0.443*).Percentage reduction of inflammatory lesion counts in azithromycin and doxycycline group following treatment for 12 weeks were 78.3% and 85.3% (*p=0.133*) respectively, whereas for non-inflammatory lesion counts were 77.7% and 78.8% (*p=0.852*) respectively. Nausea was reported in 77.8% at week 6 and 66.7% at week 12 in doxycycline group, but none in azithromycin group. There were no significant differences in incidence of diarrhoea and abdominal pain.

Conclusion

Azithromycin 250mg three times a week plus topical BPO 5% is as effective as doxycycline 100mg daily plus topical BPO 5%.

Key words: *Acne vulgaris; Azithromycin; Doxycycline; Efficacy; Adverse effects*

Corresponding Author
Dr Darshni Chandrasakaranpillay
Department of Dermatology,
Hospital Tengku Ampuan Rahimah,
Jalan Langat, Klang, Selangor, Malaysia
Email: shni84@hotmail.com

Introduction

Acne is an important disease worldwide and is the eighth most prevalent disease defined by the global burden of disease.[1] Approximately 9.4% of the world's population are affected, with over 90% of males and 80% of females in all ethnic group.[1,2] The prevalence of acne varies among various countries.[3] In Malaysia, the prevalence of acne is around 67.5% -68.1% among adolescents

(13 - 18 years old), and among medical students from year 1 to 5, with males and females almost equally affected (1:1.1).[4,5] Acne vulgaris affects both genders, but the severity may be greater in male patients. In the pathogenesis of acne, there is interplay between follicular epithelial hyperproliferation with resultant follicular plugging, excessive production of sebum, inflammation, and *Propionibacterium acnes (P. acnes*) activity.[6] Face is the primary site of acne. It can also affect the back, chest and shoulders. At the trunk, lesions are usually concentrated near the midline.[6]

Mild acne can be managed with topical treatments such as benzoyl peroxide, topical retinoids or topical combination therapy (e.g.: benzoyl peroxide + antibiotic or retinoid + benzoyl peroxide or retinoid + benzoyl peroxide + antibiotic).[7] Systemic antibiotics have been widely used in the treatment of moderate to severe acne vulgaris. The anti-*Propionibacterium acnes* properties in antibiotics inhibit colonization of pilosebaceous glands by bacteria and prevent further inflammation.[7] Doxycycline (tetracycline group) and erythromycin (macrolide group) are among the drugs commonly prescribed in these group of patients.[8,9] Doxycycline use is contraindicated in certain populations, such as pregnant and lactating mothers, and children under 8 years of age.[10] Oral erythromycin has been shown to be as effective as tetracycline with good tolerability.[11] However, increasing evidence of the development of erythromycin resistant strains of *P. acnes* have prompted researchers to look for an alternative macrolide with a long half-life.[11]

Thus, studies on azithromycin as an alternative treatment for acne vulgaris emerged. Successful usage of azithromycin in treating acne was first reported by Fernandez-Obregon AC in 1997.[12]

Azithromycin is a 9-methyl derivative of erythromycin. It has a long half-life of 2.3-3.2 days. Azithromycin is better absorbed and is more vastly distributed into tissues compared to erythromycin. It has the ability to achieve high concentrations within cells (including phagocytes) compared to serum. These properties improve the safety and efficacy of azithromycin, whereas the long half-life reduces the frequency of drug use. Besides that, metabolization of azithromycin via the hepatic pathways other than cytochrome P450 reduces the risk of drug interactions as well.[13,14] There is also increasing evidence that azithromycin exert immunomodulatory effects by diminishing production of Interleukin-1alpha and Interleukin 8 cytokines (which are observed to be upregulated in acne patients).[15] Many studies have reported the efficacy and safety of azithromycin in comparison to other drugs with mixed results -either better than the other drug[16,17] or no significant difference to the other drug.[12,18] Additionally, studies also reported monthly pulse dosage of azithromycin, on 4 consecutive days a month to be as effective as daily dosage of doxycycline, which is an alternative option for subjects with poor compliance.[11,24] In terms of safety, mild to moderate gastrointestinal discomforts were the most commonly reported side effects.[11,12,16-18,20]

In the Malaysian setting, according to the Clinical Practice Guideline on Management of Acne, the recommended dose of azithromycin is 500mg three times per week.[21] This is the most commonly used regime according to current available evidences. Two studies have shown that azithromycin 250mg three times per week can effectively treat acne.[16,18] However, to the authors best knowledge at the time of this study, there has been no randomised study published to compare the efficacy of azithromycin 250mg three times per week with doxycycline 100mg daily for the treatment of moderate to severe acne vulgaris. Furthermore, there is no resistance of azithromycin towards *P. acnes* reported in Malaysia. On the other hand, erythromycin, which is a cheaper and commonly preferred macrolide in the current clinical setting till date, was already found to have a resistance rate of 7.5% towards *P. acnes* in 2010 and could be predicted to be higher at present time.[8,21]

Therefore, the purpose of this study is to

determine whether azithromycin 250mg thrice weekly is as effective and tolerable in terms of its adverse effects as doxycycline 100mg daily in the treatment of moderate to severe acne vulgaris.

Materials and Methods

Study Drugs
In this study, oral antibiotics-doxycycline or azithromycin were combined with topical benzoyl peroxide 5% as recommended by acne guidelines to reduce antibiotic resistance.[22]

Disease Severity Assessment
Comprehensive Acne Severity Scale (CASS)
Evaluation included assessment of subjects using Comprehensive Acne Severity Scale (CASS),[23] a validated tool for acne severity grading. It has reproducibility, inter-rater reliability and intra-rater reliability. All the inspection was done at a distance of 2.5 meters away for acne on face.

Acne lesion count
Other than CASS assessment, subjects' acne lesions were also manually counted. The lesions were divided into non-inflammatory (open and closed comedones) and inflammatory (papule, pustule, nodule, cyst). Only lesions on the face were counted. The lesions were counted before the therapy (baseline), at 6-week and at 12-week of treatment by a single assessor. Photographs of the affected area were also taken from those who consented.

Finally, all subjects were evaluated for possible side effects by conducting an interview and then a complete physical examination. Subjects were also informed to contact the dermatology clinic / the principal investigator in the event they experienced undesirable side effects any time before their follow up assessment scheduled dates, once the treatment started.

All subjects were thoroughly briefed on the technique of benzoyl peroxide 5% (BPO 5%) gel application, i.e. to wash their face, pat dry and allow to dry thoroughly before application and to apply enough to cover the affected face area (avoiding the eye area) once a day at night.

Study Population
The study population were patients seen and diagnosed with moderate to severe acne vulgaris at the Dermatology Clinic of Hospital Tengku Ampuan Rahimah who fulfil the inclusion and exclusion criteria during the study period 1st October 2019 – 31st July 2020. Convenience sampling method was used and all subjects who met the eligibility criteria within the study period were randomized to receive either doxycycline or azithromycin.

The inclusion criteria were subjects aged 18 to 40, diagnosed with moderate to severe facial acne vulgaris as defined by Comprehensive Acne Severity Score (CASS: score of 3-4 on a scale from 0 -5), willing and able to comply with the requirements of study protocol. All subjects should be able to give written informed consent as well.

The exclusion criteria were subjects younger than 18 years and aged more than 40 years, subjects with acne conglobata, acne fulminans, drug induced acne, and nodulocystic acne that would require oral isotretinoin; subjects who were pregnant or breastfeeding mothers, subjects that received systemic antiacne antibiotics within 1 month, history of oral isotretinoin in the last 6 months, use of topical antiacne preparations, medicated shampoos or cleansers within 2 weeks, subjects with symptoms of hyperandrogenism, females with irregular menstruation, subjects who had chemical peels or physical therapies (e.g. laser) within 1 month, liver disease, history of arrhythmias, heart failure, history of hypersensitivity to doxycycline or azithromycin, subjects with concurrent use of oral contraceptive pills, concurrent dermatological problems that would interfere with the course of treatment or evaluation and finally patients who were treated with doxycycline for acne previously.

Subjects were also given the liberty to withdraw from the study at any time if the protocol was not followed or the investigator deems that it is detrimental or risky for the subject to continue.

However, all withdrawn/dropout subjects were not replaced.

Randomization and Blinding

Block randomization was carried out by an independent unit- the Hospital Tengku Ampuan Rahimah (HTAR) Clinical Research Centre to ensure the number of recipients of azithromycin therapy and doxycycline therapy were similar during all phases of the study. The sizes of the blocks were also randomized to reduce possibility of guessing the choice of treatment for the next patient. Randomization was done using the "RANDBETWEEN (0,1)" function in Microsoft Excel 2007, whereby "0" was assigned to azithromycin group; and "1" was assigned to doxycycline group. Concealment of allocation was done by placing the printed, folded allocation into sealed opaque envelopes. The sequence of the envelopes was then printed on a separate piece of paper and pasted on the front of the envelopes.

Study Design

This was an interventional, prospective, randomized, open label comparative study of azithromycin 250mg three times a week with BPO 5% and doxycycline 100mg daily with BPO 5% in moderate to severe acne vulgaris. The study was conducted at the Dermatology Clinic of Hospital Tengku Ampuan Rahimah over a 12 weeks period. After obtaining consent, subjects were screened and those who met the inclusion/exclusion criteria were randomized to either azithromycin group or doxycycline group during the baseline visit.

In azithromycin group, subjects received oral azithromycin 250mg three times per week for 12 weeks along with topical benzoyl peroxide gel 5%. In doxycycline group, subjects received oral doxycycline 100mg daily with topical benzoyl peroxide gel 5 % for 12 weeks. Each group consisted of 20 subjects. The subject and the investigator were aware of the type of medication allotted after baseline assessment was done by the investigator. Subjects were clinically assessed and evaluated at baseline, 6 weeks and 12 weeks by the principal investigator, who was the only assessor. Subjects were provided with a diary to record the medication taken, any missed pills, and adverse events. At each visit, pills were counted and topical BPO tubes were inspected.

Efficacy Measures

Primary efficacy outcome of the study was an improvement in CASS from baseline to week 12. This outcome was dichotomized to success or failure using one of the following two criteria to be selected:

a) Clear or almost clear (Grades 0 or 1) as success: Success is defined as "Clear" (Grade 0) or "Almost clear" (Grade 1) at week 12.
b) Two grades improvement as success: Success is defined as improvement of two grades from the baseline score.

Success rate was defined as the percentage of subjects with a CASS of 0 (clear) or 1 (almost clear) at each post baseline visit or improvement of 2 grades from baseline score to week 6 and 12.

Secondary efficacy outcome was the change in acne lesion count. Percentage change from baseline to week 6 and week 12 in acne lesion counts (inflammatory, non-inflammatory and total lesion counts) were determined.

Safety Assessment

Safety outcome was assessed by incidence of adverse effects self-reported by subjects, and by using a checklist for side effects attributable to either drug. Adverse events were managed accordingly depending on the type and severity.

Ethical Approval

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Ethical approval was obtained from the Medical Research and Ethics Committee with the research code of NMRR-19-2433-49831.

Statistical analysis

Normality of continuous data was assessed using Shapiro Wilk test. Natural log transformation was performed on acne counts (inflammatory lesion, non-inflammatory lesion and total lesion), and percentage of change in acne counts at 12 weeks prior to comparison analysis, as the data were found to have skewed distribution. Mean and standard deviation were used to describe normally distributed data, while median and interquartile range were used to describe skewed distributions. Frequencies and percentages were used to describe the categorical data. Independent t-test or Mann Whitney U Rank test was used to compare continuous data between the treatment groups. Paired t-test was used to compare continuous data within groups. Fisher's Exact test or Chi Square test was used to assess the association between categorical variables and study groups.

Statistical analyses were performed with IBM SPSS Statistics 25.0. All statistical significance was set at $p<0.05$.

Results

A total of 40 subjects were randomized to doxycycline and azithromycin group. Each group consisted of 20 subjects. Two subjects from each group were lost to follow up. Thirty-six subjects completed the study.

Demographic and Clinical Characteristics of the Study Population

Majority of the subjects were females (82.5%), and distribution of subjects according to gender and ethnicity were similar in both treatment groups ($p=1.000$ for age; $p=0.737$ for ethnicity). Median age of subjects were 21 years (IQR=4.0). Median duration of acne among subjects was 2.5 years (IQR=4.0). Median CASS score of the study population was 3.0 (IQR=0.0). Mean lesion counts for inflammatory lesions, non-inflammatory lesions and total lesions were 25.5 (SD=13.0) ,41.0 (SD=22.1) and 66.5 (SD=40) respectively. There were no significant differences in demographics and baseline characteristics between the 2 treatment groups ($p>0.05$). (Table 1)

Efficacy

Comparison of treatment success at 6 and 12 weeks between azithromycin and doxycycline treatment groups are displayed in Table 2. Treatment was a success in 11.1% of subjects in azithromycin group, as opposed to 22.2% in doxycycline group at 6 weeks ($p=0.658$). However, at 12 weeks, 94.4% of subjects in azithromycin group achieved treatment success, as opposed to 88.9% in doxycycline group. The treatment success rates at week 12 were not statistically significant between the treatment groups ($p=1.000$).

Table 1. Demographic data and clinical characteristics

			Total	Treatment groups		*P value*
				Azithromycin plus topical BPO	Doxycycline plus topical BPO	
			(n=40)	(n=20)	(n=20)	
Gender	Male	n (%)	7 (17.5)	4 (20.0)	3 (15.0)	*1.000*[a]
	Female	n (%)	33 (82.5)	16 (80.0)	17 (85.0)	
Ethnicity	Malay	n (%)	36 (90.0)	19 (95.0)	17 (85.0)	*0.737*[a]
	Chinese	n (%)	2 (5.0)	1 (5.0)	1 (5.0)	
	Others	n (%)	2 (5.0)	0 (0.0)	2 (10.0)	
Age (years)		Median (IQR)	21.0 (4.0)	20.5 (4.0)	22.0 (5.0)	*0.121*[b]
Acne duration (years)		Median (IQR)	2.5 (4.0)	3.0 (4.0)	2.0 (4.0)	*0.883*[b]
CASS score		Median (IQR)	3.0 (0.0)	3.0 (1.0)	3.0 (0.0)	*0.183*[b]
Inflammatory lesion count		Mean (SD)	25.5 (13.0)	21.7 (13.6)	22.9 (12.2)	*0.154*[c]
Non-inflammatory lesion count		Mean (SD)	41.0 (22.1)	43.5 (25.2)	38.6 (17.5)	*0.495*[c]
Total lesion count		Mean (SD)	66.5 (40.0)	71.5 (32.2)	61.5 (22.0)	*0.256*[c]

Data was analysed with [a]Fisher's Exact test; [b]Mann Whitney U Rank Test; [c]Independent t-test.

Table 2. Comparison of treatment success at 6 and 12 weeks between treatment groups (n=36)

		Treatment groups		*P value*
		Azithromycin plus topical BPO (n=18)	**Doxycycline plus topical BPO** (n=18)	
CASS at 6 weeks	Success n (%)	2 (11.1)	4 (22.2)	*0.658*
CASS at 12 weeks	Success n (%)	17 (94.4)	16 (88.9)	*1.000*

Data was analysed with Fisher's Exact test. Only patients with complete follow-up data were included in the analysis.
Success defined as achieving ' clear '(grade 0) or 'almost clear' (grade 1), or improvement in 2 grades from baseline to week 6 and 12

In terms of CASS, percentage of clear or almost clear was higher in the doxycycline group at week 12 (83.3% vs 66.7%) with no significant difference between the two groups (*p=0.443*). (Table 3)

Table 3. Percentage of 'clear' or ''almost clear' according to CASS at 12 weeks between treatment groups (n=36)

		Treatment groups		*P value*
		Azithromycin plus topical BPO (n=18)	**Doxycycline plus topical BPO** (n=18)	
CASS 0 or 1 at 12 weeks	n (%)	12 (66.7)	15(83.3)	*0.443*

Data was analysed with Fisher's Exact test. Only patients with complete follow-up data were included in the analysis.
CASS=Comprehensive Acne Severity Score; CASS '0'= clear, CASS '1'=almost clear

Our study also found a significant reduction in the mean number of inflammatory lesions from baseline to week 6 within the azithromycin group (27.4+13.9 vs 12.2+8.5, *p<0.001*) and doxycycline group (23.9+12.4 vs 10.1+5.4, *p<0.001*), and significant reduction in the mean number of non-inflammatory lesions from baseline to week 6 in azithromycin group (40.5+23.8 vs 19.1+12.4, *p<0.001*) and in doxycycline group (40.4+17.5 vs 19.9+11.3, *p<0.001*). Finally, total lesion counts also showed significant reduction from baseline to week 6 in azithromycin group (67.9+29.1 vs 31.3+18.8, *p<0.001*) and in doxycycline group (64.3+21.2 vs 29.9+14.7, *p<0.001*). (Table 4).

An overall reduction of 53.8% (SD=20.0) of inflammatory lesions at week 6 was observed compared to baseline. Specifically, there were mean reductions of 54.0% (SD=16.6) and 53.6% (SD=23.3) of inflammatory lesions in azithromycin group and doxycycline group, respectively. However, there was no statistical difference in mean changes of inflammatory lesions at week 6 between the treatment groups (*p=0.948*). Similarly, an overall reduction of 49.8% (SD=19.9) was observed for non-inflammatory lesions at week 6 compared to baseline. Specifically, there were mean reduction of 50.1% (SD=19.4) and 49.5% (SD=20.9) of non-inflammatory lesions in azithromycin and doxycycline group respectively. Again, there was no statistical difference in mean changes of non-inflammatory lesions at week 6 between the treatment groups (*p=0.930*). Mean reduction of total lesions was 53.2% (SD=17.5), with a decrease of 53.8% (SD=15.6) in azithromycin group and 52.6% (SD=19.6%) in doxycycline group. The reduction in total lesions percentage was not significant between the treatment groups (*p=0.844*) (Table 5).

Table 4. Comparison of acne lesion count from baseline to week 6 within treatment groups (n=36)

Acne lesion count		**Treatment groups**					
		Azithromycin plus topical BPO (n=18)			**Doxycycline plus topical BPO** (n=18)		
		Baseline	**Week 6**	**P value**	**Baseline**	**Week 6**	***P value***
Inflammatory lesions	Mean (SD)	27.4 (13.9)	12.2 (8.5)	<0.001**	23.9 (12.4)	10.1 (5.4)	*<0.001***
Non-inflammatory lesions	Mean (SD)	40.5 (23.8)	19.1 (12.4)	<0.001**	40.4 (17.5)	19.9 (11.3)	*<0.001***
Total lesions	Mean (SD)	67.9 (29.1)	31.3 (18.8)	<0.001**	64.3 (21.2)	29.9 (14.7)	*<0.001***

Data was analysed with paired t-test. Only patients with complete follow-up data were included in the analysis.
***significant at p<0.001Data was analysed with paired t-test. Only patients with complete follow-up data were included in the analysis.*
***significant at p<0.001*

Table 5. Comparison of percentage change of acne lesion count from baseline to Week 6 between treatment groups (n=36)

Change of acne lesions		Total	Treatment groups		*P value*
			Azithromycin plus topical BPO	Doxycycline plus topical BPO	
		(n=36)	(n=18)	(n=18)	
Inflammatory lesions (%)	Mean (SD)	-53.8 (20.0)	-54.0 (16.6)	-53.6 (23.3)	*0.948*
Non-inflammatory lesions (%)	Mean (SD)	-49.8 (19.9)	-50.1 (19.4)	-49.5 (20.9)	*0.930*
Total lesions (%)	Mean (SD)	-53.2 (17.5)	-53.8 (15.6)	-52.6 (19.6)	*0.844*

Data was analysed with independent test. Only patients with complete follow-up data were included in the analysis.
Percentage of change = [(lesion count at week 6 - lesion count at baseline/lesion count at baseline)

Significant reduction in the mean number of inflammatory lesions from baseline to week 12 was observed within the azithromycin group (27.4+13.9 vs 5.7+4.4, *p<0.001*) and doxycycline group (23.9+12.4 vs 3.4+3.1, *p<0.001*). There was also significant reduction in the mean number of non-inflammatory lesions from baseline to week 12 in azithromycin group (40.5+23.8 vs 8.3+6.2, *p<0.001*) and doxycycline group (40.4+17.5 vs 8.3+6.2, *p<0.001*). Finally, total lesions count also showed significant reduction from baseline to week 12 in azithromycin group (67.9+29.1 vs 13.9+9.4, *p<0.001*) and doxycycline group (64.3+21.2 vs 11.7+8.0, *p<0.001*) (Table 6).

There was an overall reduction of 81.8% (SD=13.2) of inflammatory lesions at week 12 compared to baseline. Specifically, there were mean reductions of 78.3% (SD=13.0) and 85.3% (SD=12.7) of inflammatory lesions in azithromycin and doxycycline group, respectively. However, there was no statistical differences in mean changes of inflammatory lesions, non-inflammatory lesions and total lesions at week 12 between the treatment groups (*p=0.133* vs *p=0.852* vs *p=0.654*) (Table 7).

Table 6. Comparison of acne lesion count from baseline to week 12 within treatment groups (n=36)

Acne lesion count		Treatment groups					
		Azithromycin plus topical BPO (n=18)			Doxycycline plus topical BPO (n=18)		
		Baseline	Week 12	P value	Baseline	Week 12	*P value*
Inflammatory lesions	Mean (SD)	27.4 (13.9)	5.7 (4.4)	<0.001**	23.9 (12.4)	3.4 (3.1)	*<0.001***
Non- inflammatory lesions	Mean (SD)	40.5 (23.8)	8.3 (6.2)	<0.001**	40.4 (17.5)	8.3 (6.2)	*<0.001***
Total lesions	Mean (SD)	67.9 (29.1)	13.9 (9.4)	<0.001**	64.3 (21.2)	11.7 (8.0)	*<0.001***

Data was analysed with paired t-test. Only patients with complete follow-up data were included in the analysis.
***significant at p<0.001*

Table 7. Comparison of percentage change of acne lesion count from baseline to week 12 between treatment groups (n=36)

Change of acne lesions		Total	Treatment groups		*P value*
			Azithromycin plus topical BPO	Doxycycline plus topical BPO	
		(n=36)	(n=18)	(n=18)	
Inflammatory lesions (%)	Mean (SD)	-81.8 (13.2)	-78.3 (13.0)	-85.3 (12.7)	*0.133*
Non- inflammatory lesions (%)	Mean (SD)	-78.2 (12.7)	-77.7 (12.5)	-78.7 (13.3)	*0.852*
Total lesions (%)	Mean (SD)	-80.2 (11.3)	-79.1 (10.3)	-81.3 (12.4)	*0.654*

Data was analysed with independent test. Only patients with complete follow-up data were included in the analysis.
*Percentage of change = ((lesion count at week 12 – lesion count at baseline) / lesion count at baseline) *100%*

Table 8. Comparison of adverse effects at 6 and 12 weeks between treatment groups (n=36)

Adverse Effects	6 Weeks			12 Weeks		
	Treatment groups		*P value*	Treatment groups		*P value*
	Azithromycin plus topical BPO (n=18)	Doxycycline plus topical BPO (n=18)		Azithromycin plus topical BPO (n=18)	Doxycycline plus topical BPO (n=18)	
Nausea	0 (0.0)	14 (77.8)	*<0.001***[a]	0 (0.0)	12 (66.7)	*<0.001***[a]
Vomiting	0 (0.0)	3 (16.7)	*0.229*	0 (0.0)	0 (0.0)	*n/a*
Diarrhoea	3 (16.7)	6 (33.3)	*0.443*	1 (5.6)	4 (22.2)	*0.338*
Abdominal pain	3 (16.7)	4 (22.2)	*1.000*	1 (5.6)	1 (5.6)	*1.000*
Giddiness	1 (5.6)	0 (0.0)	*1.000*	0 (0.0)	0 (0.0)	*n/a*

Data was analysed with Fisher's Exact test or [a]Chi square test. Only patients with complete adverse events follow-up data at 6 and 12 weeks were included in the analysis.

Safety and tolerability

At 6 weeks, none of the subjects receiving azithromycin reported nausea while 14 (77.8%) from doxycycline group developed nausea, and the difference between treatment groups was statistically significant (*p<0.001*). After 12 weeks of treatment, 12 (66.7%) subjects from doxycycline group reported nausea (*p<0.001*), which is lesser than the percentage at 6 weeks (Table 8).

Discussion

Thirty-six subjects managed to complete the study and it was comparable to Kus et al (2005) which included 45 patients aged 18 to 40 suffering from moderate acne vulgaris.[20] The age group of subjects in this study is comparable to Moravvej et al. (2012).[12] Most of the previous similar studies included subjects aged 13-48 years with a sample size of 50 to 80.[12,16,18]

According to the current findings, treatment was a success only in 11.1% of subjects in azithromycin group, as opposed to 22.2% of subjects in doxycycline group at 6 weeks. At 12 weeks, treatment was a success in 94.4% of subjects in azithromycin group, as opposed to 88.9% of subjects in doxycycline group. The difference was however not statistically significant (*p>0.05*). Additionally, both treatment groups showed more reductions in terms of total lesions, inflammatory lesions and non-inflammatory lesions at 12 weeks compared to 6 weeks of treatment with no significant difference between the treatment groups (*p>0.05*). There was no significant difference found in terms of percentage of lesions reductions following treatment between doxycycline or azithromycin groups at both 6 and 12 weeks as well.

Our current findings were similar to few other reported studies.[11,12,20,24] In a randomized study with 50 patients (more than 16 years old) for 12 weeks done by Parsad et al. (2001), monthly pulse dosing of azithromycin 500mg 4 times each month was tested against doxycycline 100mg daily plus topical tretinoin 0.05%.[11] Based on their results, pulse azithromycin plus topical tretinoin 0.05% was as effective as doxycycline 100mg daily plus topical tretinoin 0.05%. This was similar to Kus et al. (2005) where azithromycin with dosage of 500mg/day on 3 consecutive days per week in the first month, followed by 2 consecutive days per week in the second month and consecutively one day per week in the third month; were found to give significant and similar improvement to doxycycline twice a day for the first month and once a day for the second and third months.[20] In another randomized, double-blind clinical trial, Babaeinejad et al. (2011) compared the efficacy and safety of oral azithromycin 500mg daily, 4 consecutive days per month for 3 consecutive months and doxycycline, 100mg daily for 3 consecutive months.[24] However, they did set the age as the influencing parameter. It

was concluded that although azithromycin is as effective as doxycycline in the treatment of moderate acne vulgaris, doxycycline is a better treatment option for patients above 18 years old. Another report by Moravvej et al. (2012) indicated similar efficacy between the two drugs in reducing the acne lesions too.[12] Their 12 weeks study included 60 subjects with moderate facial acne and comparison was done between azithromycin 500mg/day, three times a week plus topical tretinoin versus doxycycline 100mg/day plus topical tretinoin.

Few studies reported azithromycin to be more effective than the other drug too.[16,17] In a retrospective study by Fernandez-Obregon et al. (2000) involving 79 patients (13- 48 years old),[16] individuals who were intolerant to tetracycline, doxycycline, minocycline and erythromycin were treated with azithromycin 250mg three times a week. By 4 weeks, azithromycin was found to be significantly better. There were more than 80% reduction in inflammatory acne lesions (85.7%) versus an average of 77.1% for all other agents.[16] In a different non-randomized study done by Singhi et al. (2003), 62 patients were treated with either daily dose of azithromycin 500mg for 3 consecutive days in a 10 days cycle plus topical erythromycin, with seven drug free days each cycle; or doxycycline 100mg/day with topical erythromycin over 12 weeks period.[17] Azithromycin with topical erythromycin combination was found to be significantly better compared to doxycycline with topical erythromycin.

Kapadia and Talib (2004) treated acne patients with azithromycin 500mg 3 times weekly and found that 83% showed at least a 60% improvement in only 4 weeks and that the majority achieved 80% clearance in 12 weeks.[25] In a study by Naieni et al. (2006), all 3 different azithromycin regimens- 5 consecutive days of treatment each month with 500mg on the first day and 250mg/day for another 4 days per month; 500mg/day for 4 consecutive days per month; and 250mg/day thrice weekly were effective in the treatment of acne vulgaris with no significant difference in their efficacies.[18] This was a 12 weeks investigator blind, randomized study involving 58 moderate to severe acne patients.

On the other hand, Ullah et al. (2014) found that doxycycline worked better for acne with a significant difference at 12 weeks.[19] It was a randomized study design with 386 patients of moderate acne (14- 30 years old) comparing azithromycin 500mg/day, for 4 consecutive days monthly, and doxycycline 100mg/day. In this study however, no topical treatment was given to study subjects.[19]

A large scale worldwide observational study of adherence with acne therapy by Dreno et al. (2010) reported that approximately 48% of Asian patients from Hong Kong, India, Philippines, and Singapore are likely to adhere poorly to their acne treatment regimen. 53% of Asian patients adhered poorly to systemic treatment.[26] Thus, azithromycin could be a rational treatment because there is a possibility of better compliance with lower frequency dosing regimen. Based on our findings, azithromycin 250mg thrice weekly is as effective as doxycycline 100mg daily, hence suggesting this regimen could be used as an alternative for patients who are intolerant or contraindicated to doxycycline. This would also be more cost effective than the current Clinical Practice Guidelines on Management of Acne recommendation of 500mg three times per week, with potential lesser gastrointestinal side effect. [11,12,17,20]

In terms of adverse effects, nausea was reported by the majority in the doxycycline group but none in the azithromycin group. However, both the study drugs were found tolerable, safe with no subjects withdrawing due to the adverse effects of the drugs by 6 and 12 weeks. Other reported adverse effects from this study include; diarrhoea, abdominal pain, vomiting, and giddiness. Most commonly reported adverse effects in patients receiving azithromycin 500mg of various dosing were, slight gastrointestinal upset and diarrhoea.[11,12,17,20]

Limitations and recommendations

The main limitation of our study is small

sample size and single assessor, which may cause bias of assessment. Hence, a multi-centre study involving larger sample size would be needed. Further longer study up to 24 weeks is also helpful to determine the relapse rate of both group of patients.

Conclusion

This study demonstrated that in moderate to severe facial acne vulgaris, both low-dose oral azithromycin and doxycycline in combination with topical BPO are equally effective. Azithromycin can be considered as an alternative oral antibiotic for patients who are intolerant/ allergic or contraindicated to doxycycline such as pregnant and lactating mothers.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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