

COMPARISON OF MONTHLY PULSE OF ORAL AZITHROMYCIN WITH DAILY DOXYCYCLINE IN THE TREATMENT OF MODERATE ACNE VULGARIS

Muhammad Mudassir, Ali Amar, Naeem Raza, Ayesha Khokhar, Adeel Siddiqui*, Najia Ahmed**

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Pakistan Air Forces Hospital, Sargodha/National University of Medical Sciences (NUMS) Pakistan, **Pakistan Naval Ship Shifa Hospital, Islamabad/National University of Medical Sciences (NUMS) Pakistan

ABSTRACT

Objective: To compare oral azithromycin with doxycycline in treatment of moderate acne vulgaris.

Study Design: Randomized control trial.

Place and Duration of Study: Department of Dermatology, Pak Emirates Military Hospital (PEMH), Rawalpindi, Aug 2017 to Jan 2018.

Methodology: A total of 92 patients with moderate Acne were selected from Dermatology outpatient department (OPD) PEMH, after written informed consent. Patients were arbitrarily allocated by lottery method to one of the two treatment groups: group A/B. Group A was given Azithromycin 500 mg daily for four consecutive days each month for 03 months & group B was given Doxycycline 100 mg daily for 03 months. Patients were reviewed monthly for 03 months & acne severity index (ASI) was recorded at baseline, at 01 month and 03 months. Primary outcome measured was more than 50% decrease from baseline in acne severity index within 03 months of treatment, using global acne grading system (GAGS).

Results: Total 92 patients equally divided in Azithromycin (A) and Doxycycline (B) groups were enrolled. Mean age of group A & B were 21.80 ± 4.64 and 21.61 ± 4.48 years respectively. In group A mean pre-treatment acne severity index was 24.83 ± 3.15 & mean post-treatment ASI was 10.15 ± 1.7 . In group B mean pre-treatment acne severity index was 25.30 ± 2.96 & mean post-treatment acne severity index was 9.86 ± 1.58 .

Conclusion: Azithromycin was found comparable to Doxycycline in terms of mean change in acne severity index, in treatment of moderate acne vulgaris.

Keywords: Acne severity index, Azithromycin, Doxycycline, Moderate acne Vulgaris.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Acne vulgaris is one of the common cutaneous disorder affecting adolescents and young adults¹. It is estimated to affect 9.4% of global population, making it the eighth most prevalent disease worldwide¹. Cumulative incidence of acne is 91% in males and 79% in females during adolescence, that drops to 3% in males and 12% in females during adulthood². These patients can have significant scarring and pigmentation on face leading to psychological morbidity in the form of anxiety, depression disorders or suicidal ideas which can impact the employment and social lives of affected individuals¹. Acne presents early in females than in males and affects appro-

ximately 85% of the adolescent population³. Although Acne is mostly considered as a teenager's disease but can also occur in early ages³.

The development of Acne is a multifactorial process involving both endogenous and exogenous factors including genetic, hormonal, dietary and environmental⁴. It involves a complex interplay of these factors, stimulating innate and cellular immune responses. The exact pathology is incompletely understood but the main underlying mechanisms are hyper-proliferation of keratinocytes, increased production of sebum, inflammation and altered colonization with *Propionibacterium acnes*⁵.

Acne is characterized by non-inflammatory, open and close comedones and inflammatory papules, pustules, nodules and pseudocysts, (in extreme cases) canalizing and deep, inflamed,

Correspondence: Dr Muhammad Mudassir, Consultant Dermatologist, Pak Emirates Military Hospital, Rawalpindi Pakistan
Received: 23 May 2019; revised received: 06 Feb 2020; accepted: 09 Feb 2020

sometimes purulent sacs⁶. The papulopustular lesions of Acne resolve as the age advances and can lead to stigmatizing disfigurement of face¹. More commonly affected sites are face (99%), back (60%) and chest (15%)⁶.

Severity of Acne is graded by various scoring systems like Global Acne Grading System (GAGS), lesion counting, subjective self-assessment, multimodal digital imaging⁷. However, measuring Acne objectively has inherent difficulties and there is no consensus on any single method to be used. GAGS/ Acne Severity Index (ASI) is one of the methods commonly suitable to practice clinically in which Acne is graded according to ASI. Mild Acne have ASI <19, Moderate 19-30 and Severe >30 ASI⁷.

Treatment of Acne is challenging and paucity exists in literature regarding its optimal treatment⁸. Oral Doxycycline is a commonly used antibiotic in moderate to severe Acne Vulgaris. It has antibacterial and anti-inflammatory activity⁸. It reversibly binds to the 30S subunit of ribosomes and prevents the attachment of aminoacyl tRNA with the bacterial ribosome resulting in termination of the translation process and thus inhibits protein synthesis by bacteria⁸. However, it cannot be used in all patients due to its various side effects including gastrointestinal irritation, photo sensitivity, dental discoloration, skin hyperpigmentation, fixed drug eruption and vaginal candidiasis⁹. Rare adverse effect is benign intracranial hypertension especially when combined with systemic retinoids⁹. Daily doxycycline/other tetracyclines makes the basis for these side effects hence a regimen which is more cost effective and with less side effects is required.

Oral Azithromycin is a nitrogen-containing macrolide which has anti-inflammatory and antibacterial effect by inhibiting protein synthesis via reversible binding to the 50S ribosomal subunit within the bacterial cell¹⁰. Due to high lipid solubility and ion trapping, the tissues concentration of Azithromycin can be >50 times higher as compared to plasma. This extensive distribution allows pulse-dose regimen recommendation for

amplified compliance⁹. Its main side effects are allergic reactions, gastrointestinal upset, transient deafness, hepatotoxicity and toxic pustuloderma⁹.

The objective of this study was to compare these two drugs in the treatment of moderate Acne Vulgaris in tertiary care setting as there is a need for a more compliant regimen that should also be cost effective and less side effects.

METHODOLOGY

This study was carried out at dermatology department of Pak Emirates Military Hospital (PEMH) Rawalpindi, from August 2017 to January 2018 after approval from ethics committee of the institute. The sample size was calculated on WHO calculator by using results of the reference study. A total of 92 patients were enrolled after written informed consent by non-probability consecutive sampling technique and data was analyzed.

Individuals of age between 14-30 year, of both genders, having moderate Acne (ASI 19-30) were included in the study. Detailed history was taken and complete physical examination was performed to rule out associated diseases. Baseline investigations included CBC, LFTs, UPT, Hep B & C serology was done to rule out any underlying diseases. Patients having mild or severe Acne, history of hypersensitivity to any of the drugs being used in the study, history of PCOs, pregnancy/lactation, use of hormonal contraceptives, those on any other concomitant treatment or who have had their Acne treated in the preceding six weeks and patients with unreliable follow up were excluded of this study.

Patients were arbitrarily allocated to one of the two treatment groups: group A (Azithromycin, n=46) and group B (Doxycycline, n=46) by lottery method. Group A was given 500 mg oral Azithromycin daily for four consecutive days once a month for 03 months whereas group B was given 100 mg oral Doxycycline once daily for 03 months¹¹. All patients were reviewed monthly for 03 months and ASI was recorded at baseline, at one month and three months. The efficacy measured was in terms of decrease (>50% dec-

rease from baseline) in ASI within 3 months of treatment, using GAGS. A specially designed proforma was used to record all data.

SPSS version 21 was used to analyze data. The quantitative variables like age (in years) and severity score were calculated as means and standard deviations. The qualitative variables like gender and efficacy of treatment (yes/no) were calculated as frequency and percentages. Confounders were controlled by stratification of data with regard to age and gender. Post stratification Pearson chi square was applied to compare the efficacy between two groups. The p -value ≤ 0.05 was considered significant.

RESULTS

A total of 92 patients, fulfilling the inclusion criteria were recruited. Primary outcome measure was proportion of participants whose ASI decreased more than 50% from baseline after 3 months

Efficacy in terms of decrease in ASI (>50% from baseline) at 3 months following therapy was seen in 34 patients (73.90%) of group-A and 36 patients (78.26%) of group-B (p -value 0.625) using chi square test (table-I).

Table-I: Comparison of efficacy at 3 months.

Efficacy	Group-A (n=46), n (%)	Group-B (n=46), n (%)	p -value (n=92)
Yes	34 (73.9)	36 (78.26)	0.625
No	12 (26.1)	10 (21.74)	

Stratification was done to control confounding factors like gender, age, duration and ASI. Gender stratification in terms of efficacy among study groups showed p -value of 0.947 and 0.666 for male and female genders respectively. Age group stratification in terms of efficacy among study groups is shown in table-II. There was no significant difference between Azithromycin and Doxycycline groups in terms of efficacy.

Table-II: Age group stratification.

Age Groups		Efficacy, n (%)		p -value
		Yes	No	
14-19 years	Group A (Azithromycin)	10 (58.82%)	7 (41.17%)	0.724
	Group B (Doxycycline)	11 (64.7%)	6 (35.3%)	
20-24 years	Group A (Azithromycin)	18 (90%)	2 (10%)	0.544
	Group B (Doxycycline)	15 (83.33%)	3 (16.66%)	
25-30 years	Group A (Azithromycin)	6 (66.66%)	3 (33.33%)	0.178
	Group B (Doxycycline)	10 (90.9%)	1 (9.09%)	

following start of treatment.

Out of 92 patients, 46 were in each group. Overall mean pre-treatment ASI was 25.07 ± 3.052 and mean post-treatment ASI was 11.01 ± 2.527 with $p < 0.05$ using chi square test showing significant difference in terms of improvement of ASI in both treatment groups.

In group A, patients mean age was 21.80 ± 4.64 years. Male and females were 25 (54.3%) and 21 (45.7%) respectively. Mean pre-treatment ASI was 24.83 ± 3.15 and mean post-treatment ASI was 10.15 ± 1.7 ($p=0.625$).

In group B, patients mean age was 21.61 ± 4.48 years. Male and females were 30 (65.2%) and 16 (34.8%) respectively.

DISCUSSION

Acne vulgaris is a multifactorial disease⁴. Facial scars and psychological distress are to be prevented by effective treatment¹². Anti-inflammatory and antibacterial drugs are mainstays of treatment in moderate to severe disease⁸. Its well-known effective oral antibiotics are Oxytetracycline, Doxycycline, Minocycline, Macrolides and Trimethoprim⁹. Out of which, tetracyclines are mainly used. Patients with decreased response to the current treatment may be due to emerging Propionibacterium resistance to antibiotic¹³. Azithromycin is highly effective against Propionibacterium acnes¹². Tetracyclines are known for their photosensitivity, gastro-intestinal and vestibular side effects⁹.

Gruber *et al*¹⁴ compared Azithromycin and Minocycline in 72 patients. In that study, 500mg oral Azithromycin daily was used for 4 days in each cycle of 10 days. Minocycline was found to be as effective as Azithromycin. Among the patients treated with azithromycin, 75.8% showed good, moderate or slight improvement, while 70.5% of the patients treated with minocycline showed such improvement. These results of Azithromycin were comparable with our study. The difference from our study was small sample size (72 patients), short duration of study (6 weeks) and different dosage regimen of Azithromycin.

Prasad *et al*¹² compared 100 mg oral Doxycycline daily with 500 mg oral Azithromycin daily for four days per month. After 12 weeks percentage reduction in severity grade in the treatment groups A & B was 75.5 ± 12.2 and 77.6 ± 14.1 respectively. In their study, Azithromycin was as effective as Doxycycline which was similar to our study. The difference between the referred study and our study was their concomitant application of 0.05% tretinoin cream in both groups, small sample size (total 60 patients), and inclusion of moderate to severe Acne Vulgaris patients.

Singhi *et al*¹⁵ compared 100 mg oral Doxycycline daily with 500 mg oral Azithromycin daily for three consecutive days in a 10 days cycle. There was 63.74% improvement in the Doxycycline group in comparison to 77.26% in the Azithromycin group and this difference was statistically significant. They concluded that Doxycycline was not as effective as Azithromycin in the treatment of Acne which was contrary to this study. The difference between the referred study and our study was inclusion of patients of moderate to severe Acne Vulgaris, concomitant application of topical erythromycin to both groups, their small sample size (total 70 patients) and three days dosage cycle per ten days of Azithromycin.

Fernandez *et al*¹⁶ prescribed 250 mg oral Azithromycin daily for three days per week, for the treatment of his enrolled patients. There was 85% reduction in Acne lesions after 4 weeks as

compared to 77.1% for other antibiotics (Tetracycline, Doxycycline and Minocycline) and differences observed were not statistically significant. His study showed that Azithromycin was effective alternative and a safe to Doxycycline which were comparable with our study. The difference from our study was small sample size (79 patients), short duration of study (4 weeks) and different dosage regimen of Azithromycin.

Babaeinejad *et al*¹⁷ enrolled 100 patients with moderate Acne Vulgaris and compared 500 mg oral Azithromycin daily for four consecutive days per month with 100 mg oral Doxycycline daily. After three months he showed that in patients older than 18 years, Doxycycline had better therapeutic results and in patients under 18 years Azithromycin was mostly effective. This difference from our study may be due to large sample size (100 patients), difference of ethnicity and consideration of age.

Kus *et al*¹⁸ compared the efficacy of Doxycycline with Azithromycin after enrolling fifty-one patients. One group was given 100mg oral Doxycycline twice daily for the first month and once daily for the second and third months. The other group received 500mg oral Azithromycin daily on three consecutive days per week in the first month, on two consecutive days per week in the second month, and one day per week in the third month. Comparing the above two treatment groups, significant differences were not noted in terms of global response rates, percentage reduction of lesions and own assessment of patients. These results of Azithromycin were comparable with our study. The difference was smaller sample size (51 patients) in the referred study.

Ullah *et al*¹¹ from Lady Reading Hospital, Peshawar Pakistan compared Azithromycin with Doxycycline in treatment of Acne. It was suggested that Azithromycin was significantly inferior than Doxycycline in the treatment of moderate Acne Vulgaris. The reason of disparity between our results and theirs might have been their large sample size (total 386 patients) and longer study duration (1 year).

LIMITATION OF STUDY

The main limitation of our study was that it was conducted in a single center with small sample size, short duration of study, so the findings might not be generalized to larger populations. Also, this study was conducted only on moderate Acne patients so it cannot be applied on all Acne patients.

RECOMMENDATIONS

It is recommended that further studies comparing Azithromycin with Doxycycline be done to strengthen the scientific evidence.

To determine duration, optimal dose and issues of compliance, further randomized controlled trials are required.

CONCLUSION

Efficacy of Azithromycin was found comparable to Doxycycline in terms of mean change in ASI in the treating moderate Acne Vulgaris.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to be declared in this study.

REFERENCES

- Lukaviciute L, Navickas P, Navickas A, Grigaitiene J, Ganceviciene R, Zouboulis C. Quality of life, anxiety prevalence, depression symptomatology and suicidal ideation among acne patients in Lithuania. *J Eur Acad Dermatol Venereol* 2017; 31(11): 1900-6.
- Semyonov L. Acne as a public health problem. *Ital J Public Health* 2010; 7(2): 112-4.
- Alshamrani HM, Alsolami MA, Alshehri AM, Salman AK, Alharbi MW, Alzuhayri AJ, et al. Pattern of skin diseases in a university hospital in Jeddah, Saudi Arabia: age and sex distribution. *Ann Saudi Med* 2019; 39(1): 22-8.
- O'Neill AM, Gallo RL. Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris. *Microbiome* 2018; 6(1): 177-93.
- Das S, Reynolds RV. Recent advances in acne pathogenesis: implications for therapy. *Am J Clin Dermatol* 2014; 15(6): 479-88.
- Asai Y, Baibergenova A, Dutil M, Humphrey S, Hull P, Lynde C, et al. Management of acne: Canadian clinical practice guideline. *Can Med Assoc J* 2015; 188(2): 118-26.
- Hacivelioglu S, Gungor A, Gencer M, Uysal A, Hizli D, Koc E et al. Acne severity and the global acne grading system in polycystic ovary syndrome. *Int J Gynaecol Obstet* 2013; 123(1): 33-6.
- Nast A, Dréno B, Bettoli V, BukvicMokos Z, Degitz K, Dressler C, Finlay AY, Haedersdal M, Lambert J, Layton A, Lomholt HB. European evidence based (S3) guideline for treatment of acne-update 2016-short version. *J Eur Acad Dermatol Venereol* 2016; 30(8): 1261-8.
- Farrar G, Tan E. The use of oral antibiotics in treating acne vulgaris: a new approach. *Dermatol Ther* 2016; 29(5): 377-84.
- Kim JE, Park AY, Lee SY, Park YL, Whang KU, Kim HJ. Comparison of the efficacy of aithromycin versus doxycycline in acne vulgaris: a meta-analysis of randomized controlled trials. *Ann Dermatol* 2018; 30(4): 417-26.
- Ullah G, Noor SM, Bhatti Z, Ahmad M, Bangash AR. Comparison of oral Azithromycin with oral Doxycycline in treatment of acne vulgaris. *J Ayub Med Coll Abbottabad* 2014; 26(1): 64-7.
- Parsad D, Pandhi R, Nagpal R, Negi KS. Azithromycin monthly pulse vs. daily Doxycycline in the treatment of acne vulgaris. *J Dermatol* 2001; 28(1): 1-4.
- Dessinioti C, Katsambas A. Propionibacterium acnes and antimicrobial resistance in acne. *Clin Dermatol* 2016; 35(2): 163-7.
- Gruber F, Grubisic-Greblo H, Kastelan M, Brajac I, Lenković M, Zamolo G. Azithromycin compared with minocycline in the treatment of acne comedonica and papulopustulosa. *J Chemother* 1998; 10(6): 469-73.
- Singhi MK, Ghiya BC, Dhabhai RK. Comparison of oral Azithromycin pulse with daily Doxycycline in the treatment of acne vulgaris. *Indian J Dermatol Venereol Leprol* 2003; 69(4): 274-6.
- Fernandez-obregon AC. Azithromycin for the treatment of acne. *Int J Dermatol* 2000; 39(1): 45-50.
- Babaeinejad S, Khodaeiani E, Fouladi RF. Comparison of therapeutic effects of oral Doxycycline and Azithromycin in patients with moderate acne vulgaris: What is the role of age? *J Dermatolog Treat* 2010; 22(4): 206-10.
- Kus S, Yucelten D, Aytug A. Comparison of efficacy of Azithromycin vs. Doxycycline in the treatment of acne vulgaris. *Clin Exp Dermatol* 2005; 30(3): 215-20.