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ORIGINAL ARTICLE

Effectiveness, Safety, and Quality of Life among Patients with Moderate to Severe Acne on Oral Doxycycline versus Oral Azithromycin with Add-on Topical Retinoids: A Prospective Observational Study in a Tertiary Care Centre

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Abstract

Background: Acne vulgaris is a common chronic inflammatory disorder with significant psychosocial impact, for which systemic antibiotics combined with a topical retinoid are standard therapy. This study compared oral doxycycline and oral azithromycin, each with topical adapalene, for effectiveness, safety, and quality of life in moderate to severe acne. **Methods:** In this prospective comparative study at a tertiary care centre, 114 patients received oral doxycycline 100 mg twice daily (n = 57) or oral azithromycin 500 mg once daily for three consecutive days per week (n = 57), each with daily topical adapalene 0.1% for 8 weeks. Acne severity was assessed by the Global Acne Grading System (GAGS), quality of life by the Cardiff Acne Disability Index (CADI), and adverse drug reactions assessed. **Results:** Significant reductions in GAGS scores (doxycycline 28.00 to 9.93; azithromycin 27.61 to 10.07; $p < 0.001$) and CADI scores (doxycycline 8.95 to 4.47; azithromycin 9.19 to 4.65; $p < 0.001$) were seen in both groups, with no significant between-group difference in GAGS ($p = 0.438$) or CADI ($p = 0.855$) reduction. Adverse drug reactions were mild, self-limiting, and related to gastrointestinal tract, with no significant difference between groups (doxycycline 12.3%, azithromycin 7.0%; $p = 0.53$). **Conclusion:** Oral doxycycline and oral azithromycin, each with topical adapalene, produced comparable effectiveness and quality-of-life improvement in moderate to severe acne with no significant between-group difference, and both were well tolerated. The choice between them can be individualised.

Keywords: Acne vulgaris, Doxycycline, Azithromycin, Adapalene, Quality of life, Global Acne Grading System

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Graphical Abstract

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Methods

In this prospective comparative study at a tertiary care centre, 114 patients received oral doxycycline 100 mg twice daily (n = 57) or oral azithromycin 500 mg once daily for three consecutive days per week (n = 57), each with daily topical adapalene 0.1% for 8 weeks. Acne severity was assessed by the Global Acne Grading System (GAGS), quality of life by the Cardiff Acne Disability Index (CADI), and adverse drug reactions assessed.

Baseline characteristics of the two treatment groups

Characteristic	Doxycycline (n = 57)	Azithromycin (n = 57)	p-value
Age, years (mean $\pm$ SD)	28.26 $\pm$ 4.80	28.74 $\pm$ 5.23	0.615
Sex, male/female, n (%)	29 (50.9) / 28 (49.1)	30 (52.6) / 27 (47.4)	1.000
Baseline GAGS (mean $\pm$ SD)	28.00 $\pm$ 4.75	27.61 $\pm$ 4.43	0.654
Baseline CADI (mean $\pm$ SD)	8.95 $\pm$ 2.92	9.19 $\pm$ 2.84	0.650

Change in CADI score from baseline to 8 weeks (secondary outcome)

Group	Baseline	8 weeks	Mean reduction	Within-group p value
Doxycycline (n = 57)	8.95 $\pm$ 2.92	4.47 $\pm$ 2.09	4.48 $\pm$ 1.99	< 0.001
Azithromycin (n = 57)	9.19 $\pm$ 2.84	4.65 $\pm$ 1.94	4.54 $\pm$ 2.11	< 0.001
Between-group p value	0.650	0.643	0.855	



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Conclusions Oral doxycycline and oral azithromycin, each with topical adapalene, produced comparable effectiveness and quality-of-life improvement in moderate to severe acne with no significant between-group difference, and both were well tolerated.

Introduction

Acne vulgaris is a chronic inflammatory disorder which involves the pilosebaceous unit. It is clinically characterised by comedones, papules, pustules, nodules, and scarring in more severe cases [1,2]. It is among the most common conditions in dermatological practice, ranking among the three problems most frequently encountered in primary and secondary care. It typically begins around 12 to 14 years of age and affects the majority of adolescents and young adults of both sexes [1]. Although the condition is not life-threatening, it can impose a substantial physical and psychosocial burden which includes poor self-image, depression, anxiety, and sometimes, permanent disfiguring or scarring [1,2]. Its aetiology is multifactorial and the pathogenic factors involved are follicular hyperkeratinization, colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), increased sebum

production, and a complex inflammatory response [2,3].

A reliable grading of acne severity is needed for guiding treatment decisions, monitoring response to therapy, and also to enable comparison across studies. The Global Acne Grading System (GAGS) is a reliable, easy-to-use tool that is widely applied for this purpose [4]. The GAGS classifies acne by scores as mild (1–18), moderate (19–30), severe (31–38), or very severe (>39). It is simple, accurate, and reproducible, with low inter- and intra-rater variability [5].

Topical adapalene 0.1% has a positive influence on quality of life and is effective when used alone or in combination [6]. Systemic antibiotics are combined with topical retinoids to limit bacterial resistance in treatment of moderate to severe acne [7]. Efficacy, adverse-effect profile, and resistance considerations guide the choice of antibiotics. The most commonly used

systemic antibiotics are doxycycline and azithromycin.

Doxycycline acts by inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit and also has anti-inflammatory effects, including inhibition of chemotaxis and metalloproteinase activity. However, it is associated with gastrointestinal disturbance, phototoxicity and is contraindicated in pregnancy [2]. Azithromycin binds to the 50S ribosomal subunit and, due to its extensive tissue distribution with a long elimination half-life of approximately three days, it can be administered in intermittent “pulse” regimens. This shortens treatment and improves patient compliance, with a favourable tolerability profile [8,9].

The disease-specific quality-of-life scales are used to capture the patient’s experience because the impact of acne extends beyond visible lesions. The Cardiff Acne Disability Index (CADI) is a short questionnaire that has been developed for teenagers and adults. It has an established validity, internal consistency, reliability, and responsiveness to modification [10]. The CADI’s measure of quality-of-life impairment corresponds with clinical severity and has a correlation with the GAGS score, thereby highlighting the importance of evaluating both severity and quality of life simultaneously [11].

The results from previous studies directly comparing the two antibiotics remain inconsistent. A meta-analysis found azithromycin pulse therapy equivalent in efficacy to daily doxycycline in moderate to severe acne, with fewer adverse-event discontinuations [12]. Some studies favour doxycycline for overall lesion clearance [13], whereas several reports found azithromycin to be comparable or modestly superior with a favourable safety profile

[9,14,15]. Majority of the studies have assessed the antibiotics alone, without the topical retinoid. Few studies have simultaneously assessed safety and patient-reported quality of life in the same cohort, which is crucial for a disorder whose burden is as much psychological as physical [1,9,15].

Additional real-world evidence directly comparing these regimens is needed to support individualised treatment selection [1]. The choice between the two antibiotics may therefore be guided by dosing convenience, tolerability, contraindications, and antibiotic stewardship [2,8]. This study was therefore conducted to compare oral doxycycline and oral azithromycin, each with an add-on topical retinoid to evaluate effectiveness, safety, and quality of life simultaneously in a tertiary care setting.

Aims and Objectives

The primary objective of this study was to compare the clinical effectiveness of oral doxycycline and oral azithromycin with an add-on topical retinoid for each, in patients with moderate to severe acne vulgaris.

The secondary objectives were to compare the safety between the two regimens and to evaluate patient’s quality of life.

Materials and Methods

This was a prospective, observational, comparative study conducted in the Departments of Pharmacology and Dermatology at Mandya Institute of Medical Sciences (MIMS), Mandya, India. The study was conducted from February 2026 to June 2026, after approval from the Institutional Ethics Committee. Adults aged 18 years or older

of either sex with a clinical diagnosis of moderate to severe acne vulgaris, graded using the GAGS, who provided informed consent were eligible for inclusion. Patients were divided into two groups, group A received oral doxycycline 100 mg twice daily and group B received oral azithromycin 500 mg once daily for three consecutive days per week with an add-on daily topical adapalene 0.1% gel for each. Patients with mild acne not requiring systemic antibiotics, pregnant or lactating women, and patients who were on hormonal therapy or contraceptives were excluded. The sample size of 114 (57 per group) was calculated using the formula for the comparison of two means, taking a 5% level of significance, 80% power, and an expected between-group difference of 1.63 in mean GAGS reduction derived from a previous comparative study [14].

At enrolment, sociodemographic details, clinical history, and treatment history were recorded on a semi-structured proforma, and baseline acne severity and quality of life were assessed using the GAGS and the CADI. Both scales were used at the end of eight weeks, and any adverse drug reactions spontaneously reported by patients during the treatment period were documented. The severity of each reaction was graded using the Modified Hartwig and Siegel scale [16], and its causal association with the study drug was assessed using the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) causality assessment scale [17]. The change in GAGS score from baseline to eight weeks served as the primary outcome, while the change in CADI score and the nature and frequency of adverse drug reactions were the secondary outcomes.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS version 31. Categorical variables such as sex were assessed as frequencies and percentages, and continuous variables such as age, GAGS score, and CADI score as mean $\pm$ standard deviation. The changes within each group were assessed using the paired t-test and the changes between the two groups using the unpaired t-test. The frequency of adverse drug reactions between the two groups was assessed using Fisher's exact test. A p-value of < 0.05 was considered statistically significant. Analysis of covariance (ANCOVA), with the baseline score as a covariate, was used to compare eight-week GAGS and CADI scores between groups, yielding adjusted mean differences with 95% confidence intervals.

Results

Baseline characteristics of the study population

A total of 121 patients were enrolled with 114 patients completing the study and 7 were lost to follow-up. The overall mean age was 28.5 ± 5.0 years (range 18–42 years), and the two groups were comparable in age (doxycycline group 28.2 ± 4.8 years vs azithromycin group 28.7 ± 5.2 years; $p = 0.615$). The sex distribution was also similar, with males comprising 29 (50.9%) of the doxycycline group and 30 (52.6%) of the azithromycin group ($p = 1.000$). At baseline, acne severity and quality-of-life scores did not differ significantly between the groups, confirming that the two groups were comparable (baseline GAGS $p = 0.654$; baseline CADI $p = 0.650$) (Table 1).

Table 1. Baseline characteristics of the two treatment groups

Characteristic	Doxycycline (n = 57)	Azithromycin (n = 57)	p-value
Age, years (mean $\pm$ SD)	28.26 $\pm$ 4.80	28.74 $\pm$ 5.23	0.615
Sex, male/female, n (%)	29 (50.9) / 28 (49.1)	30 (52.6) / 27 (47.4)	1.000
Baseline GAGS (mean $\pm$ SD)	28.00 $\pm$ 4.75	27.61 $\pm$ 4.43	0.654
Baseline CADI (mean $\pm$ SD)	8.95 $\pm$ 2.92	9.19 $\pm$ 2.84	0.650

Effect on acne severity

The mean GAGS score significantly decreased in both groups between baseline and eight weeks. The score decreased from 28.00 $\pm$ 4.75 to 9.93 $\pm$ 2.88 in the doxycycline group and from 27.61 $\pm$ 4.43 to 10.07 $\pm$ 2.16 in the azithromycin group. The reductions of scores within each group were statistically significant ($p < 0.001$). The mean reduction in GAGS score was 18.07 $\pm$ 3.80 with doxycycline and 17.54 $\pm$ 3.41 with azithromycin. The between-

group difference in GAGS reduction was not statistically significant (mean difference 0.53; 95% CI -0.81 to 1.87; $p = 0.438$). Eight-week GAGS scores were also comparable between the two groups ($p = 0.769$). After adjustment for baseline severity using ANCOVA, the between-group difference at eight weeks remained non-significant (adjusted mean difference -0.27; 95% CI -1.02 to 0.47; $p = 0.468$) (Table 2).

Table 2. Change in GAGS score from baseline to 8 weeks

Group	Baseline	8 weeks	Mean reduction	Within-group p value
Doxycycline (n = 57)	28.00 $\pm$ 4.75	9.93 $\pm$ 2.88	18.07 $\pm$ 3.80	< 0.001
Azithromycin (n = 57)	27.61 $\pm$ 4.43	10.07 $\pm$ 2.16	17.54 $\pm$ 3.41	< 0.001
Between-group p value	0.654	0.769	0.438	

GAGS, Global Acne Grading System

Effect on quality of life

The patients' quality of life, measured by the CADI, improved significantly in both groups. The mean CADI score decreased from 8.95 $\pm$ 2.92 to 4.47 $\pm$ 2.09 in the doxycycline group and from 9.19 $\pm$ 2.84 to 4.65 $\pm$ 1.94 in the azithromycin group. The reduction of scores within the group was statistically significant ($p < 0.001$). The mean reduction in CADI scores was 4.48 $\pm$ 1.99 with

doxycycline and 4.54 $\pm$ 2.11 with azithromycin, a difference that was not statistically significant between the groups (mean difference -0.07; 95% CI -0.83 to 0.69; $p = 0.855$). After adjustment for the baseline CADI score using ANCOVA, the between-group difference at eight weeks remained non-significant (adjusted mean difference -0.05; 95% CI -0.59 to 0.48; $p = 0.840$) (Table 3).

Table 3. Change in CADI score from baseline to 8 weeks (secondary outcome)

Group	Baseline	8 weeks	Mean reduction	Within-group p value
Doxycycline (n = 57)	8.95 ± 2.92	4.47 ± 2.09	4.48 ± 1.99	< 0.001
Azithromycin (n = 57)	9.19 ± 2.84	4.65 ± 1.94	4.54 ± 2.11	< 0.001
Between-group p value	0.650	0.643	0.855	

CADI, Cardiff Acne Disability Index

Adverse drug reactions

Adverse drug reactions were infrequent, self-limiting, and related to gastrointestinal tract in both groups, and none required discontinuation of treatment. As shown in Table 4, reactions were reported in 7 of 57 patients (12.3%) receiving doxycycline and in 4 of 57 patients (7.0%) receiving azithromycin. In the doxycycline group these comprised epigastric pain in 4 patients and nausea in 3 patients, whereas in the azithromycin group

they comprised diarrhoea in 2 patients and nausea in 2 patients. All reactions resolved spontaneously without specific treatment. All reactions were graded as mild on the Modified Hartwig and Siegel severity scale, and their causal relationship to the study drug was categorised as “possible” on the WHO–UMC causality assessment scale. The difference in the overall frequency of adverse drug reactions between the two groups was not statistically significant ($p = 0.53$).

Table 4. Adverse drug reactions by group

Adverse reaction	Doxycycline (n = 57)	Azithromycin (n = 57)
Epigastric pain	4	0
Nausea	3	2
Diarrhoea	0	2
Total, n (%)	7 (12.3)	4 (7.0)

Discussion

This is a prospective, observational, comparative study which was conducted in a tertiary care setting to compare oral doxycycline and oral azithromycin, each combined with an add-on topical adapalene, in patients with moderate to severe acne vulgaris. Both groups showed significant and comparable reductions in acne severity. There was no statistically significant difference between the groups. This is in agreement with the meta-analysis

by Kim et al., which concluded that azithromycin pulse therapy is equivalent to daily doxycycline in moderate to severe acne [12], and also with Ahsan et al. and Gurung et al., who reported the two drugs to be similarly efficacious [9,18]. Conversely, some studies have found that azithromycin has a better efficacy than doxycycline, an earlier onset of action, or fewer adverse effects with pulse therapy [14,19,20]. These discrepancies are most likely due to differences in study design,

dosing schedules, concomitant topical therapy, outcome measures, and follow-up duration. In our study, both groups received topical adapalene, in keeping with the principle that retinoids form the core of acne therapy and should be used in combination with systemic antibiotics [2,6,7]. Therefore, the present results should thus be interpreted as a comparison of two systemic antibiotics with add-on daily topical adapalene rather than of the antibiotics in isolation.

Adverse drug reactions were related to gastrointestinal tract and were less frequent with azithromycin than with doxycycline, but this difference was not statistically significant. A tolerability advantage for azithromycin has been reported in several comparative studies [8,9,12,19]. The higher frequency of adverse drug reactions in the doxycycline group, comprising nausea and epigastric pain, is consistent with the recognised potential of doxycycline to cause gastrointestinal disturbance [2].

The patient's quality of life which was assessed with the CADI scale showed significant improvement in both groups. This corresponded with the clinical response and reflects the close relationship between acne severity and quality-of-life impairment reported previously [11]. A similar concurrent improvement in quality of life was reported by Mekala et al., who evaluated it alongside efficacy and safety in a comparison of the two antibiotics [15]. The baseline quality-of-life impairment observed in the patients is consistent with the findings of Pradhan et al., who reported that acne impairs self-image and quality of life among patients attending a dermatology outpatient department [21]. As the burden of acne is as much psychological as physical [1], the finding

that both regimens relieve this burden equally is clinically meaningful. This supports the inclusion of patient-reported outcomes, rather than lesion-based measures alone, in the assessment of acne therapy. In summary, these findings suggest that, when systemic antibiotics were combined with topical adapalene, the choice of systemic antibiotic has limited influence on the overall clinical and quality-of-life response in moderate to severe acne vulgaris.

Limitations

The study was conducted at a single centre using convenience sampling, which may limit generalisability. The eight-week duration with a single end-of-treatment assessment precludes conclusions about relapse and the durability of the quality-of-life benefit.

Conclusions

In moderate to severe acne vulgaris, oral doxycycline and oral azithromycin, each combined with topical adapalene, produced comparable improvements in acne severity and quality of life, with no statistically significant difference between them, and both were well tolerated. Therefore, the choice between the two regimens can be individualised on the basis of tolerability, dosing convenience, contraindications, and antibiotic stewardship. Larger randomised trials with longer follow-up are needed to confirm these findings and to assess relapse and the durability of the quality-of-life benefit.

Statements and Declarations

Conflicts of Interest

The authors declare that they do not have conflict of interest.

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