Efficacy of Azithromycin in Treatment of Acne Vulgaris: A Mini Review

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ABSTRACT

BACKGROUND
Antibiotics are commonly used in the treatment of acne vulgaris. Considering the rise of antibiotic resistance, alternative medications may be used in the main anti-acne armamentarium. The aim of this study was to investigate the efficacy of oral azithromycin in the treatment of acne vulgaris.

METHODS
Database searches were performed in PubMed and Scopus using the keywords “azithromycin” and “acne”.

RESULTS
Azithromycin 500 mg once daily for 3 days per week or in cycles of 10 days for 12 weeks are the most commonly used regimens.

CONCLUSION
Available experimental data suggest that oral azithromycin is an effective and well-tolerated option for treatment of acne vulgaris.

KEYWORDS
Azithromycin; Tetracycline; Doxycycline; Acne vulgaris; Treatment

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INTRODUCTION
As a chronic inflammatory disorder of the skin, acne vulgaris affects almost 90% of adolescents, while an increasing number of adults are suffering from this disease.1,2 Furthermore, with an accelerated onset of puberty, the prevalence is also showing a rising trend among children.1 Besides the widespread use of conservative management protocols such as controlling dietary factors3 and face-washing,4 oral antibiotic therapy remains the first line of treatment for acne patients who are afflicted with physical and psychosocial side effects of moderate to severe forms of this skin condition.5

Tetracyclines, including tetracycline, doxycycline, minocycline and lymecycline, as well as drugs like erythromycin, clindamycin, co-trimoxazole and trimethoprim have been shown to be effective oral agents.6,7 Macrolide antibiotics have a substantial cumulative effect in many tissues especially epithelial lining fluid and host defense cells, such as macrophages and polymorphonuclear

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leukocytes. Macrolides share mild to moderate side effects such as nausea, vomiting, diarrhea, and abdominal pain, which are usually observed in erythromycin administration. Azalides like azithromycin, as a class of macrolides, possess advantageous pharmacokinetic and pharmacodynamic properties compared to other macrolides.

Delivery to the infection site by phagocytes and fibroblasts results in higher concentration levels of the drug in tissues compared to serum level. This improves the safety and efficacy of azithromycin, which in turn not only reduces the dosage, but also decreases the frequency of drug use. Another pharmacological advantage of azithromycin is metabolism via hepatic pathways other than cytochrome P450, which lowers the risk of drug interactions. A bioavailability of 37% after a single 500 mg oral dose and a half-life of 2.3 to 3.2 days depending on the tissues have been reported for azithromycin.

Due to the remarkable pharmacokinetics and efficacy, azithromycin is well established as a potent treatment for skin infections in adult and pediatric patients. In dermatology, clinical uses of azithromycin are not solely limited to infectious diseases. In addition to the antibacterial effects, due to the immunomodulatory and anti-inflammatory potentials of this agent, it appears that azithromycin can be administered to patients with dermatological disorders including intractable rosacea, psoriasis and synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. Upregulated expression of proinflammatory factors such as IL-1α, TNF-α, PGE2, and IL-8 has been observed in acne patients. Thus, the therapeutic effects of azithromycin in acne vulgaris patients might be mediated by antimicrobial aspects of this agent as well as anti-inflammatory and immunomodulatory potentials. Many studies focused on the comparison of azithromycin and doxycycline, suggesting significant improvement by using each of these medications with no remarkable differences in treatment results.

In addition, Babaeinejad et al. concluded that doxycycline is more effective in patients above 18 years old. It should also be noted that in both these studies, patients were treated with 4 consecutive days of 500 mg azithromycin per month; while it seems that intermittent higher doses, mainly three times in 10-days or thrice-weekly, may be more advantageous. Further, administration of azithromycin in combination with topical erythromycin results in significantly better improvement than doxycycline combined with topical erythromycin. Also, no beneficial effects of minocycline were observed when compared to azithromycin.

RESULTS

Articles were summarized in Table 1 for easier comparison. The studies were conducted in various countries and differed in methodology. Study design, grouping, treatment dosage, duration and main results were described for each article.

DISCUSSION

For a long time, it has been believed that administration of macrolides such as azithromycin has anti-inflammatory effects. In 2000, Ianaro et al. demonstrated that macrolides can suppress inflammation by inhibiting production of proinflammatory molecules such as PGE2, TNF-α, and NO. In addition, it has been observed that macrolides down-regulate neutrophil migration, ROS production and apoptosis. There is also growing evidence that macrolides, particularly azithromycin, exert immunomodulatory effects by diminishing production of IL-1α and IL-8 cytokines.

Moreover, upregulated expression of proinflammatory factors such as IL-1α, TNF-α, PGE2, and IL-8 has been observed in acne patients. Thus, the therapeutic effects of azithromycin in acne vulgaris patients might be mediated by antimicrobial aspects of this agent as well as anti-inflammatory and immunomodulatory potentials. Many studies focused on the comparison of azithromycin and doxycycline, suggesting significant improvement by using each of these medications with no remarkable differences in treatment results. However, the study by Ullah et al. on 386 patients showed that doxycycline was more effective.

In addition, Babaeinejad et al. concluded that doxycycline is more effective in patients above 18 years old. It should also be noted that in both these studies, patients were treated with 4 consecutive days of 500 mg azithromycin per month; while it seems that intermittent higher doses, mainly three times in 10-days or thrice-weekly, may be more advantageous. Further, administration of azithromycin in combination with topical erythromycin results in significantly better improvement than doxycycline combined with topical erythromycin. Also, no beneficial effects of minocycline were observed when compared to azithromycin.
### Table 1: Comparison of different studies conducted in various countries regarding study design, grouping, treatment dosage, duration and main results.

<table>
<thead>
<tr>
<th>Author et al. (Year)</th>
<th>Study Design</th>
<th>Grouping and Dosage</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ullah et al., 2014 (21)</td>
<td>Randomized, 386 patients, 12 weeks</td>
<td>Group 1: Azithromycin 500 mg/day, 4 consecutive days monthly; Group 2: Doxycycline 100 mg/day</td>
<td>25.9% response in azithromycin group, 66.8% response in doxycycline group, Doxycycline was a better option for acne treatment with a significant difference.</td>
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<td>Rassai et al., 2013 (22)</td>
<td>Investigator-blind, randomized, 148 patients, 8 weeks</td>
<td>Group 1: Azithromycin 500 mg/day, 3 days a week plus oral Levamisole 150 mg/day, 2 days a week; Group 2: Azithromycin 500 mg/day, 3 days a week</td>
<td>Azithromycin plus levamisole was significantly more effective than azithromycin alone in reducing inflammatory acne lesions.</td>
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<td>Hasibur et al., 2013 (23)</td>
<td>Open-label, non-comparative, 82 patients, 24 weeks</td>
<td>Pulsed oral Azithromycin: 500 mg/day on 3 consecutive days in each week for 1 month with low-dose Isotretinoin: 0.3 mg/kg/day for 6 months</td>
<td>Complete cure in 80 (97.56%) patients, Low-dose isotretinoin plus oral azithromycin pulse can be effective in moderate to severe acne.</td>
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<tr>
<td>Moravvej et al., 2012 (24)</td>
<td>Investigator-blind, randomized, 60 patients, 12 weeks</td>
<td>Group 1: Azithromycin 500 mg/day three times a week; Group 2: Doxycycline 100 mg/day. All patients used topical tretinoin cream every other night.</td>
<td>Both groups showed significant and similar improvements in inflammatory lesion count with mild and transient side effects.</td>
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<td>Kayhan et al., 2012 (25)</td>
<td>Randomized, 60 patients, 12 weeks</td>
<td>Group 1: oral Azithromycin 500 mg/day on 3 consecutive days followed by 7 days rest (a 10-day cycle); Group 2: Doxycycline 100 mg/day. Topical adapalene gel was added to the systemic treatment in both groups.</td>
<td>Both treatments were safe and effective with significant and similar improvement in the quality of life scale scores and minimal side effects.</td>
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<td>Babaeinejad et al., 2011 (26)</td>
<td>Double-blind, randomized, 100 patients, 12 weeks</td>
<td>Group 1: Azithromycin: 500 mg/day, on 4 consecutive days per month; Group 2: Doxycycline: 100 mg/day</td>
<td>Both antibiotics were effective with minor complications the in treatment of moderate acne. Doxycycline was significantly more effective in patients above 18 years. 93.9% complete clearance and 11.3% disease relapse. The combination of low-dose isotretinoin and oral azithromycin was an effective treatment for severe acne with acceptable adverse-effects.</td>
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<td>De et al., 2011 (27)</td>
<td>Open-label, non-comparative, 66 patients, 16 weeks</td>
<td>Combination of low-dose Isotretinoin 0.3 mg/kg/day and pulsed oral azithromycin 500 mg/day on 3 consecutive days every 2 weeks</td>
<td>Similar reduction in number of lesions with both azithromycin and doxycycline, No difference was observed in the incidence of side effects between the two treatment groups.</td>
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<td>Maleszka et al., 2011 (28)</td>
<td>Double-blind, randomized, 240 patients, 12 weeks</td>
<td>Group 1: Azithromycin 500 mg/day for 3 days in the first week, followed by 500 mg tablets weekly to complete 10 weeks of treatment; Group 2: 2 Doxycycline 100 mg capsules on the first day, then once a day during 12 weeks of treatment</td>
<td>Azithromycin was well tolerated with a significant reduction in the number of lesions. The majority of adverse effects were related to the gastrointestinal and central nervous systems.</td>
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<td>Antonio et al., 2008 (29)</td>
<td>Open-label, non-comparative, randomized, 57 patients, 12 weeks</td>
<td>Azithromycin: 500 mg on 3 consecutive days with intervals of 7 days without medication</td>
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<tr>
<td>Author(s)</td>
<td>Study Design</td>
<td>Number of Patients</td>
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<td>Innocenzi et al., 2008</td>
<td>Open-label, non-comparative,</td>
<td>46 patients, 12</td>
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<td>Wahab et al., 2008</td>
<td>Randomized, 60 patients, 12 and 20 weeks</td>
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<td>Bardazzi et al., 2007</td>
<td>Open-label, non-comparative,</td>
<td>52 patients, 8</td>
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<td>Basta-Juzbašić et al., 2007</td>
<td>Open-label, randomized, 93 patients, 24 weeks</td>
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<td>Ghoshal et al., 2007</td>
<td>Randomized, 61 patients, 12 weeks</td>
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<td>Naieni et al., 2006</td>
<td>Investigator-blind, randomized, 58 patients, 12 weeks</td>
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<tr>
<td>Rafiei et al., 2006</td>
<td>Investigator-blind, randomized, 290 patients, 12 weeks</td>
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</table>
A study by Rafiei et al. found azithromycin to have a slightly higher efficacy in the treatment of inflammatory acne lesions in comparison to tetracycline.\textsuperscript{36} On the other hand, retrospective study of patients who could not tolerate tetracycline, erythromycin, minocycline, and doxycycline proved that azithromycin is a significantly better antibiotic regimen for acne.\textsuperscript{41} Despite the usefulness of both isotretinoin and azithromycin in the treatment of moderate to severe acne, superior efficacy of isotretinoin is evident.\textsuperscript{31}

To enhance treatment outcome, various studies have utilized adjuvant drugs in combination therapies including topical tretinoin, adapalene, benzoyl peroxide and erythromycin. The combination of oral isotretinoin with either topical adapalene\textsuperscript{44} or oral levamisole\textsuperscript{22} provided more efficacious treatment than azithromycin alone. In combination with isotretinoin, two studies have reported cure rates above 90\%\textsuperscript{23,27} Also, combined with adapalene plus benzoyl peroxidase, azithromycin was indicated as a safe option.\textsuperscript{30} Considering azithromycin dosing for acne treatment, the most commonly used strategies are 3 consecutive days of 500 mg azithromycin in 10 days for 12 weeks,\textsuperscript{25,29,39} azithromycin 500 mg three times per week for 8\textsuperscript{22,32} or 12 weeks\textsuperscript{24,30,31,34,38} and also 4 consecutive days per month continued for 12 weeks.\textsuperscript{21,26,35}
In general, azithromycin was considered to be tolerable with low adverse effects including GI (namely nausea, diarrhea and abdominal pain)\textsuperscript{29-32,35,36} and CNS symptoms.\textsuperscript{29} With regard to tetracycline induced photosensitivity, use of azithromycin may also be beneficial in summer months.\textsuperscript{37} Low side effects and clinical tolerance along with convenient consumption have resulted in good patient compliance with azithromycin.\textsuperscript{25,28,32,35,37-39,41,42} Various advantages have been suggested for azithromycin compared with other macrolides. There has always been a debate regarding the administration of antibiotics to pregnant and lactating patients due to possible side effects on fetus and infant.\textsuperscript{51}

In spite of the potential risks of azithromycin crossing placental barrier, no adverse effects have been observed in fetal development in animal models. Furthermore, FDA has classified azithromycin as a B category drug for treatment of acne vulgaris, confirming the compatibility of this drug with pregnancy.\textsuperscript{51,52} Although azithromycin has the longest half-life among macrolides and can be transferred to breast milk, it has not shown toxicity to fetus or infant.\textsuperscript{53} Moreover, studies have indicated that administration of azithromycin to pregnant patients is as efficient as doxycycline in non-pregnant acne vulgaris patients.\textsuperscript{53} Overall, these studies approved the use of azithromycin for the treatment of lactating or pregnant acne vulgaris patients.

Given the differences in azithromycin dosing and timing of administration, the conclusion on a specific effective therapeutic regimen for acne vulgaris remains indefinite. Nonetheless, most studies applied azithromycin thrice weekly or in 10 days with successful results. With regards to low incidence and mild side effects and also potential anti-inflammatory and immunomodulatory effects of azithromycin, this agent is a good choice for those who cannot tolerate other commonly used oral antibiotics. It is also important to consider that azithromycin is a safe drug for lactating and pregnant women suffering from acne vulgaris, making this drug a promising treatment. Furthermore, no resistance has been yet reported regarding treatment of acne vulgaris with azithromycin.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

REFERENCES


Azithromycin in acne vulgaris


