

A Review of Azithromycin for the Treatment of Acne Vulgaris

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Acne vulgaris is a common condition that can be socially isolating and physically scarring. It affects almost everyone at some point in life. As an inflammatory condition worsened by colonization with *Propionibacterium acnes*, it often requires systemic antibiotics for adequate treatment. Many different antimicrobials have been used over the past 5 decades to treat acne. First-line antibiotic therapy has included the tetracyclines as well as the macrolides, most commonly erythromycin. Because of increasing bacterial resistance to erythromycin, many dermatologists are now using azithromycin, a different macrolide, to combat acne. This article reviews the literature describing the use of azithromycin against acne.

Acne vulgaris is a common disorder, affecting 79% to 95% of the adolescent population and virtually everyone at some point in their lives.¹ It can lead to significant psychological distress and long-lasting scarring. Acne comprises lesions of varying morphologies, ranging from comedones, papules, and pustules to nodules and cysts. The pathogenesis of acne is multifactorial. It involves excessive sebum production, abnormal epithelial hyperkeratinization in sebaceous follicles, the presence of microbial organisms, notably the anaerobic diphtheroid *Propionibacterium acnes*, and inflammation.² The acne armamentarium contains many different therapeutic options, including topical benzoyl peroxide, topical and oral antibiotics, topical and oral retinoids, and hormonal agents.

TREATING ACNE VULGARIS WITH ANTIBIOTICS

Since the late 1950s, oral antibiotics have been a mainstay in the treatment of acne. Systemic antibiotics are frequently used in patients with moderate to severe

inflammatory acne, acne resistant to topical medications, acne causing pigment changes or permanent scarring, and truncal acne.³ Oral antibiotics exert an antibacterial effect by reducing the follicular colonization of *P acnes*. Systemic antibiotics also possess various anti-inflammatory and immunomodulatory properties. For years, the first-line antibiotics have consisted of tetracycline and its derivatives along with erythromycin, a macrolide. Macrolides have a wide spectrum of activity, are well absorbed orally, and are lipid soluble, thus penetrating well into skin structures and body fluids. They inhibit protein synthesis by binding to the 23S rRNA molecule in the 50S subunit of bacterial ribosomes. Erythromycin, commonly used for years in the treatment of acne, has been shown to be as efficacious as the tetracyclines in several studies.^{4,5} In addition, erythromycin has been a popular choice, especially in the summer months, when tetracycline and doxycycline may be too photosensitizing.⁶ Another advantage of macrolides over tetracyclines is their safety in case of accidental pregnancy. However, because of increased reports of *P acnes* resistance to erythromycin,^{7,8} it is now appropriate to consider additional antimicrobials for the treatment of acne. One such agent for consideration is a different antibiotic in the macrolide class, azithromycin. This review focuses on the use of azithromycin for the treatment of acne.

Azithromycin is a 9-methyl derivative of erythromycin that inhibits atypical intracellular pathogens, such as

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the *Chlamydia* and *Mycobacterium* species, in addition to gram-positive and gram-negative aerobic and anaerobic bacteria, including *P. acnes*.⁹ It is indicated for mild to moderate infections involving the upper and lower respiratory tracts, infections of the skin and skin structures, sexually transmitted diseases, and some mycobacterial infections.¹⁰ Unlike other oral antibiotics, the pharmacokinetic profile of azithromycin is characterized by rapid uptake from blood to tissues at concentrations more than 10 times that of erythromycin.¹¹ With a terminal half-life of approximately 68 hours, the medication remains in intracellular compartments for a prolonged period at levels higher than the minimum inhibitory concentration for many pathogens.^{10,12} Compared with erythromycin, azithromycin has also been shown to cause fewer gastrointestinal symptoms.⁹ With the potential for improved compliance because of a higher tolerability profile and longer half-life, azithromycin is a logical option to consider for the treatment of acne.

STUDIES OF AZITHROMYCIN

The first case series of 3 patients using azithromycin to treat acne was published in 1997. Fernandez-Obregon¹³ reported that azithromycin 250 mg 3 times per week improved acne significantly at 4 weeks and maintained the improvement at 12 weeks. One female patient who had failed other antibiotics or discontinued prior therapies because of unfavorable adverse effects such as vaginal candidiasis tolerated azithromycin well and reported excellent compliance. Fernandez-Obregon⁹ later followed up his small case series with a retrospective analysis of 79 patients, 21 of whom were treated with azithromycin 250 mg every Monday, Wednesday, and Friday for an average of 11 to 12 weeks. He compared these patients with those he had treated in the past with tetracycline, doxycycline, minocycline, and erythromycin. Although not statistically significantly different from patients treated with the other antibiotics, the azithromycin group had the greatest percentage of patients (85.7%) with a significant amount of lesion reduction (>80%). They also had the lowest incidence of adverse effects. It should be noted that many of these patients were concurrently using various topical medications.

In 1998, Gruber et al¹⁴ studied oral azithromycin therapy (dosed 500 mg daily for 4 consecutive days and repeated every 10 days for 4 cycles) in 32 patients compared with daily minocycline therapy in an additional 40 patients. They concluded that azithromycin was as effective and as well tolerated as minocycline. A "satisfactory response" occurred in 75.8% of patients taking the azithromycin regimen versus 70.5% of patients in the minocycline arm. These results were not statistically different. In another study, Elewski¹⁵ treated 20 patients

with both oral azithromycin and topical tretinoin 0.01% gel. A 75% improvement in acne was reported when azithromycin was dosed 500 mg on day 1, followed by 250 mg for 4 days (equivalent to a Z-PAK[®]) on the first and fifteenth days of each month for 3 months. This regimen was well tolerated. In 2004, Kapadia and Talib¹¹ treated acne patients with azithromycin 500 mg 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. The authors noted excellent compliance in their patients, with only 11% reporting mild gastrointestinal distress.

Three randomized comparative trials studying azithromycin for the treatment of acne have been conducted. Kus et al⁶ dosed azithromycin 500 mg 3 consecutive days per week for 4 weeks, then 2 consecutive days per week for 4 weeks, and then once weekly for 4 weeks. They compared this regimen with a regimen of doxycycline 100 mg taken twice daily for 4 weeks, then once daily for 8 weeks. They measured efficacy with multiple parameters and discovered no significant difference in efficacy or tolerability with either antibiotic. Parsad et al¹⁶ showed that 500 mg of azithromycin given on 4 consecutive days each month as a monthly "pulse" dose was as effective as daily doxycycline. The "pulse" azithromycin minimized the need for frequent administration. Rafiei and Yaghoobi¹⁷ conducted the largest randomized, investigator-blinded trial with azithromycin to date, comparing it with tetracycline. The 100 cases evaluated in the azithromycin arm took 500 mg daily for 3 consecutive days per week in the first month, then 250 mg every other day for 2 months. The 94 cases evaluated in the tetracycline group took 1 g daily for 1 month and then 500 mg daily for the following 2 months. The patients receiving azithromycin fared slightly, but not significantly, better than those in the tetracycline arm: 84.7% improvement versus 79.7% improvement, respectively. The investigators concluded that azithromycin was a safe and effective therapy in the treatment of inflammatory acne.

SUMMARY

Based on these trials (summarized in the Table), azithromycin appears to be at least as efficacious and well tolerated as doxycycline and minocycline; azithromycin also appears to have a better side effect profile, especially regarding photosensitivity, gastrointestinal symptoms, headaches, and vulvovaginal candidiasis.⁹ In particular, it may be a very good option in summer months, when the photosensitizing tetracyclines are ill advised. Because azithromycin is effective at doses given 1 to 3 times weekly, compliance may also be superior. Azithromycin may be a better option for less compliant patients, such as adolescents and those intolerant of or unable to take tetracyclines. Given the

Summary of Studies: Azithromycin for the Treatment of Acne Vulgaris*

Study, Year	Design	Dosage	Main Findings
Fernandez-Obregon, 1997 ¹³	3-patient case series	Azithromycin 250 mg po TIW	"Significant improvement" at 4 wk and 12 wk Minimal side effects
Gruber et al, 1998 ¹⁴	72 patients Nonblinded comparative study of azithromycin vs minocycline	Azithromycin 500 mg po daily for 4 d every 10 d in 4 cycles vs minocycline 100 mg po daily for 6 wk	"Satisfactory clinical response" seen in azithromycin (75.8%) vs minocycline (70.5%) Not statistically different Both well tolerated
Elewski, 2000 ¹⁵	20 patients Nonblinded comparative study Concomitant tretinoin 0.01% gel	Azithromycin 500 mg po on day 1, then 250 mg/d for 4 d on days 1 and 15 of each month for 3 mo	75% average improvement Well tolerated
Fernandez-Obregon, 2000 ⁹	79 patients Retrospective case series Compared with tetracycline, erythromycin, minocycline, doxycycline Concurrent topical therapy	Azithromycin 250 mg po M,W,F; other antibiotics taken as usually prescribed	85.7% of patients had improvement at 4 wk for azithromycin vs 77.1% average improvement for other antibiotics Not statistically different
Parsad et al, 2001 ¹⁶	60 patients Randomized comparative study Azithromycin vs doxycycline Concomitant tretinoin 0.05% cream	Azithromycin 500 mg po daily for 4 consecutive days per month for 12 wk vs doxycycline 100 mg/d	Azithromycin at least as effective as doxycycline
Kapadia and Talib, 2004 ¹¹	35 patients Open, noncomparative study Concomitant tretinoin 0.05% cream	Azithromycin 500 mg po TIW for 12 wk	60% improvement in 4 wk 80% clear at 12 wk 17.1% of patients without benefit Minimal side effects
Kus et al, 2005 ⁶	51 patients Randomized comparative study Investigator blinded Azithromycin vs doxycycline	Azithromycin 500 mg/d for 3 consecutive days per week in month 1, 2 d/wk in month 2, and 1 d/wk in month 3 vs doxycycline 100 mg po BID for 1 mo, then daily for 2 mo	Azithromycin equally effective as doxycycline Minimal side effects
Rafiei and Yaghoobi, 2006 ¹⁷	290 patients Randomized comparative study Investigator blinded Azithromycin vs tetracycline	Azithromycin 500 mg for 3 consecutive days per week in month 1, then 250 mg QOD for 2 mo vs tetracycline 1 g/d for 1 mo, then 500 mg/d for 2 mo	Azithromycin 84.7% improvement vs tetracycline 79.7% improvement Not significantly different

*po indicates by mouth; TIW, 3 times per week; M, Monday; W, Wednesday; F, Friday; BID, twice daily; QOD, every other day.

array of protocols and imprecise grading of improvement, further studies need to be conducted to better establish a standardized dosing regimen. However, it does appear that all of the various dosing regimens published in the aforementioned studies have been efficacious.

In conclusion, azithromycin appears to be a viable option for the treatment of acne within the macrolide class, with multiple studies indicating similar efficacy to the tetracyclines. It also has the benefits of dosing regimens that may be more convenient and increased tolerability.

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