Comparison of Efficacy and Safety of Low-dose Versus High-dose Oral Azithromycin in the Treatment of Moderate Acne Vulgaris

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ABSTRACTS:

RATTANAKAEMAKORN P*, NOKDHES Y, SRISUWANWATTANA P*, TECHAPICHETVANICH T**, COMPARISON OF EFFICACY AND SAFETY OF LOW-DOSE VERSUS HIGH-DOSE ORAL AZITHROMYCIN IN THE TREATMENT OF MODERATE ACNE VULGARIS.**

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Background: The efficacy of oral azithromycin in the treatment of inflammatory acne vulgaris has been established in some open-label clinical studies. However, the optimal dose and duration of azithromycin has not been clearly defined.

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Objectives: To compare the efficacy and tolerability of low-dose versus high-dose oral azithromycin in the treatment of moderate acne vulgaris.

Materials and Methods: In this investigator-blind, randomized, comparative study, 20 patients with more than 10 inflammatory acne papules were randomized into two groups. The low-dose group received 6 g of oral azithromycin in 10 weeks while the high-dose group received 12 g in 8 weeks. All patients were allowed to apply only topical 0.1% adapalene gel once a day. Inflammatory lesion counts and side effects were recorded at baseline, 4 weeks and the last week of azithromycin use in each group. The overall satisfaction, compliance and adverse drug reactions were evaluated in all subjects.

Results: At the end of treatment, the mean percentage reduction of inflammatory lesions was 87.7±19.6 and 65.7±26.8 in the low-dose and high-dose group, respectively. However, no statistically significant difference was found between both groups. In terms of side effects, four patients in the high-dose group had diarrhea but it did not occur in the low-dose group. Patients satisfaction were comparable in both groups as most of the patients rated as "moderate improvement".

Conclusion: In this randomized control trial, there was no statistical difference in terms of treatment outcome for moderate acne vulgaris between low-dose and high dose azithromycin. However, our results suggest that low-dose azithromycin had less side effects, less cost and more simple to administer when compared to high-dose azithromycin.

Key words: Acne, Azithromycin

บทคัดย่อ:

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การศึกษาเปรียบเทียบประสิทธิภาพและผลข้างเคียงของยาปฏิชีวนะอะซิโทรมัยซิน ขนาดต่ำและขนาดสูงในการรักษาสิวอักเสบระดับรุนแรงปานกลาง วารสารโรคผิวหนัง 2561; 34: 130-142.

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มีหลายการศึกษารายงานว่ายาอะซิโทรมัยซินมีประสิทธิภาพในการลดจำนวนสิวอักเสบอย่างมีนัยสำคัญ อย่างไรก็ตามการศึกษาที่เปรียบเทียบประสิทธิภาพของยาในการรักษาสิวโดยใช้ขนาดยาที่แตกต่างกันยังมีน้อย ดังนั้นขนาดของยาที่เหมาะสมจึงไม่ทราบแน่ชัด

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิภาพและผลข้างเคียงของยาปฏิชีวนะอะซิโทรมัยซินขนาดต่ำและขนาดสูงในการรักษาสิวอักเสบระดับรุนแรงปานกลาง

วิธีการศึกษา: ผู้ป่วยจำนวน 20 คนที่มีสิวอักเสบบนใบหน้ามากกว่าหรือเท่ากับ 10 รอยโรคจะถูกแบ่งออกเป็นสองกลุ่มโดยการสุ่ม ได้แก่กลุ่มที่ได้รับการรักษาโดยการกินยาอะซิโทรมัยซินขนาดรวม 6 กรัมใน 10 สัปดาห์และกลุ่มที่ได้รับการรักษาโดยการกินยากินยาอะซิโทรมัยซิน ขนาดรวม 12 กรัมใน 8 สัปดาห์ ผู้เข้าร่วมวิจัยทั้งสองกลุ่มจะได้รับยาทามาตรฐาน 0.1% adapalene gel ทาทั่วหน้าก่อนนอนด้วยเพียงอย่างเดียว แพทย์จะประเมินผลการรักษาโดยนับจำนวนสิวอักเสบและบันทึกอาการข้างเคียงที่สัปดาห์ที่ 0 (ก่อนทำการรักษา), สัปดาห์ที่ 4 และสัปดาห์สุดท้ายของแต่ละกลุ่ม (สิ้นสุดการรักษา) ผู้ป่วยจะประเมินความพึงพอใจโดยรวม ความสม่ำเสมอในการกินยา และความถี่ที่เหมาะสมในการบริหารยา โดยการตอบแบบสอบถามเมื่อสิ้นสุดการวิจัย

ผลการศึกษา: หลังสิ้นสุดการรักษา จำนวนเปอร์เซ็นต์สิวอักเสบเฉลี่ยลดลง 87.7±19.6 และ 65.7±26.8 ในกลุ่มที่ได้รับการรักษาโดยการกินยาอะซิโทรมัยซินขนาดต่ำ (6 กรัมใน 10 สัปดาห์) และขนาดสูง (12 กรัมใน 8 สัปดาห์) ตามลำดับ สำหรับผลข้างเคียงผู้ป่วย 4 คนในกลุ่มที่ได้รับยาขนาดสูงมีอาการท้องเสียแต่ไม่พบอาการนี้ในกลุ่มที่ได้รับยาขนาดต่ำ ผลการประเมินโดยผู้ป่วยเมื่อสิ้นสุดการรักษาพบว่าไม่มีความแตกต่างกันในด้านความพึงพอใจโดยรวมในผู้ป่วยทั้งสองกลุ่ม โดยผู้ป่วยป่วยส่วนใหญ่มีความพึงพอใจต่อการรักษาด้วยวิธีนี้ปานกลาง

สรุปผล: จากรายงานการศึกษานี้ พบว่าประสิทธิภาพของยาปฏิชีวนะอะซิโทรมัยซินขนาด 6 กรัมใน 10 สัปดาห์และขนาด12 กรัมใน 8 สัปดาห์ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญในการรักษาสิวอักเสบระดับรุนแรงปานกลาง อย่างไรก็ตามขนาดยา 6 กรัมใน 10 สัปดาห์พบผลค้างเคียงที่น้อยกว่า การบริการยาของผู้ป่วยสะดวกกว่า และราคายารวมน้อยกว่า

คำสำคัญ : สิว, อะซิโทรมัยซิน

Introduction

Acne vulgaris is a common skin disease affecting 9.4% of the world population, especially teenagers, and remains a major cause of visits to the dermatologist's office.[1-2] It is a multifactorial inflammatory disease of the sebaceous follicles.[3] Systemic antimicrobial therapies in combination with topical treatment are indicated in moderate to severe inflammatory acne.[4-6] The tetracycline class such as doxycycline, tetracycline and minocycline is recommended as the first line systematic antibiotics for acne treatment.[7] However, uncomfortable side-effects, including nausea, vomiting, headaches, photosensitive dermatoses and vulvovaginal candidiasis are notable, in addition, twice daily dose regimen may lead to suboptimal adherence to doxycycline and treatment outcome. *Cutibacterium acnes* resistant to erythromycin is the most common followed by tetracycline, doxycycline and minocycline.[8] Macrolides, particularly azithromycin, has been introduced. Azithromycin is a macrolide antibiotic structurally related to erythromycin. The pharmacokinetic profile of azithromycin is characterized by rapid and extensive uptake form the circulation into intracellular compartment followed by slow

release.[9-13] Azithromycin binds with the 50s subunit of the bacterial ribosome and *in vitro* study has demonstrated activity against *Cutibacterium acnes*.[7,14] Unlike the short half-life of tetracyclines, azithromycin has a longer half-life therefore permits less frequent dosage so it can be administered weekly and improves compliance. Comparing with doxycycline, weekly oral azithromycin was found to be as effective or even superior to daily doxycycline in comparative studies.[15]

However, the optimum azithromycin dose and duration has not been clearly defined. A study administering 500 mg of azithromycin thrice weekly for 8 weeks (total 12.0 g) has shown to be a safe and effective treatment for acne vulgaris in adolescents while another study administering 4.5 g in 7 weeks, 6.0 g in 10 weeks and 7.5 g in 13 weeks appeared to have positive results as well.[16,17] Therefore, this study was conducted to compare the efficacy and safety of low-dose and high-dose oral azithromycin in the treatment of moderate acne vulgaris.

Materials and Methods

This is a prospective randomized investigator-blinded comparative study. Patients with moderate acne vulgaris defined by Plewig and Kligman's grading system demonstrating more than ten inflammatory papules on the face who have no systemic diseases were included.[18] Patients with history of systemic antibiotics therapy, topical acne therapies and oral isotretinoin prior to the study within a two-month period or any history of macrolides allergy or current drug use that has drug interactions with azithromycin were excluded from the study. Moreover, pregnant and lactating women were also excluded.

Twenty patients with eligible criteria were randomized into 2 groups; low-dose and high-dose group. The low-dose group received 6 g of oral azithromycin in 10 weeks starting at 500mg/day for three days then 500 mg per week until the end of treatment. While the high-dose group received 12 g of azithromycin in 8 weeks also starting at 500mg/day for three days then 1,500 mg per week until the end of treatment.(Figure 1) All patients were allowed to apply only 0.1% topical adapalene gel once a day. The primary outcome of this study is percentage reduction of inflammatory lesions count done by the researcher at baseline, week 4 and at the end of the study (last week of azithromycin treatment in each groups). The secondary outcomes include global response to treatment evaluated by two-blinded dermatologists from clinical photography and subjective efficacy assessment graded by patients at the end of the study. Global response to treatment divides patients' response into 4 categories including cure, good, moderate and failure depending on percentage of

inflammatory lesions reduction of more then 75, 50, 25 and less than 25. Patients's efficacy self-assessment was conducted using 5-point scales as follows: worsening; no improvement; mild improvement; moderate improvement and good improvement. In the evaluation form, patients were also asked the question whether they preferred to take oral medications every days or once a week. All side effects were also recorded in every visit. Data was analyzed by SPSS version 18.

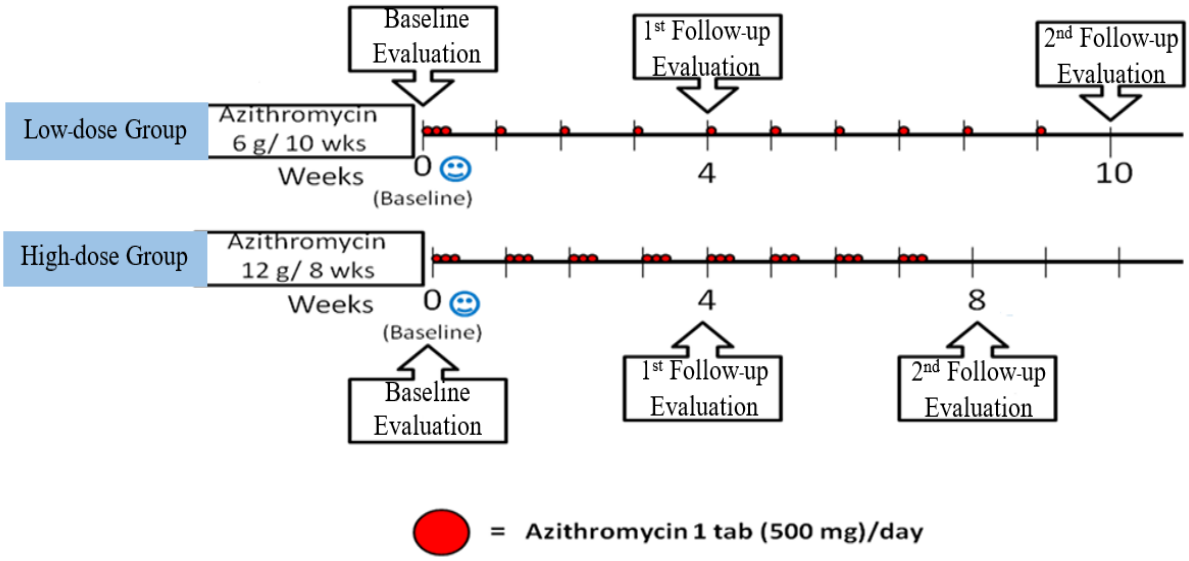

Figure 1 Treatment regimen and follow up schedule

Table 1 Demographic Data and Characteristics of the low-dose and high-dose group

Character	Low-dose group Mean (min-max)	High-dose group Mean (min-max)
Age (years)	23 (20-46)	25 (17-39)
Duration of acne (months)	12 (6-60)	60 (2-96)
Inflammatory lesions count at baseline	27(13-37)	19(11-30)

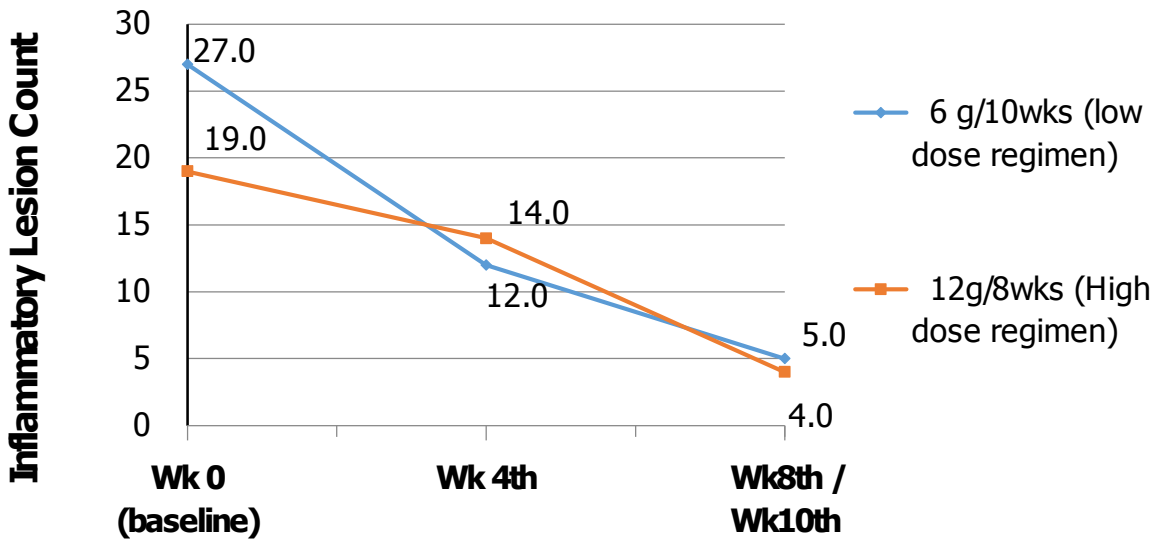

Figure 2 Inflammatory Lesions Count comparing between the Low-dose and High-dose group

Results

Twenty patients were included; 19 of which are women. Demographic data and baseline characteristics of the patients in both treatment groups did not appear statistically significantly different. (Table 1)

After 4 weeks, the mean inflammatory lesion counts significantly decreased from 27 to 12 and 19 to 14 in the low-dose and high-dose group, respectively. The mean percentage of acne reduction had decreased as well with 24.0% and 12.4% in the low-dose and high-dose group, respectively.

At the end of the study, the mean percentage reduction of inflammatory lesions of low-dose azithromycin treatment group was 87.7%±19.6 while it was reduced to 65.7%±26.8 in the high-dose azithromycin treatment group. However, there was no statistical significant difference found between both groups. In terms of median inflammatory lesions count, both groups reduced significantly when compared to before receiving treatment. Inflammatory lesions

count reduced from 27 to 5 and 19 to 4 lesions in the low-dose and the high-dose group, respectively. Though no statistical significant difference was demonstrated comparing both groups, lesions in the low-dose group showed more rapid decrease in inflammatory lesions than the high-dose group. (Figure 2)

Both groups were also compared according to the global response to treatment. Six patients in the low-dose azithromycin treatment group were graded as "cure" while only two patients in the high-dose azithromycin treatment group was defined as "cure". Moreover, one patient in the high-dose group who omitted two doses of azithromycin was graded as "failure" to treatment. Nevertheless, there were no statistical significant difference in global response rate between two groups (Figure 3)

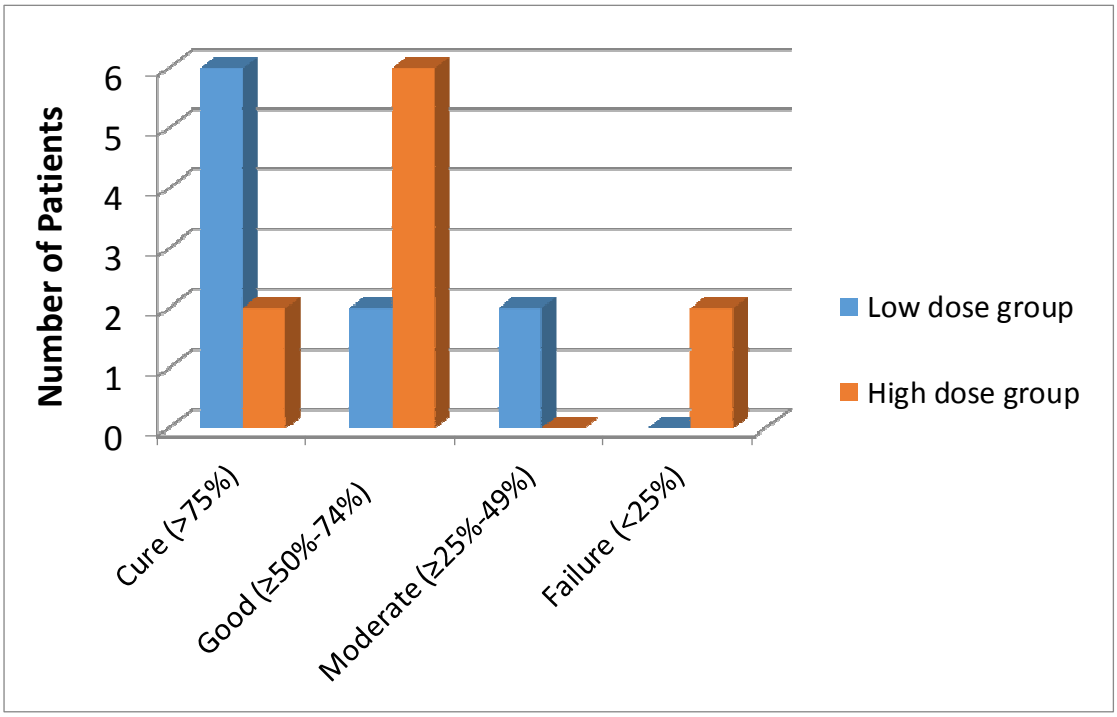

Figure 3 Global response to treatment (Reduction percentage) comparing between the Low-dose and High-dose group

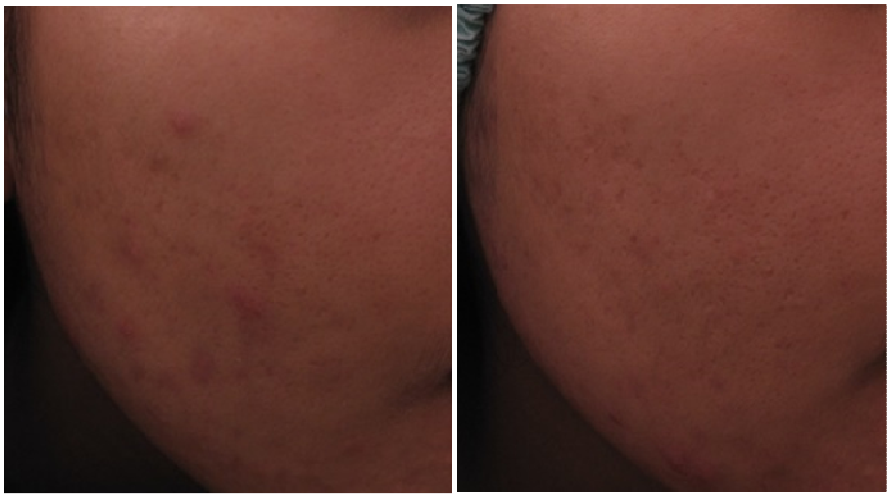

Figure 4 This figure demonstrates a patient being treated with azithromycin 6 g in 10 weeks (Low-dose group)

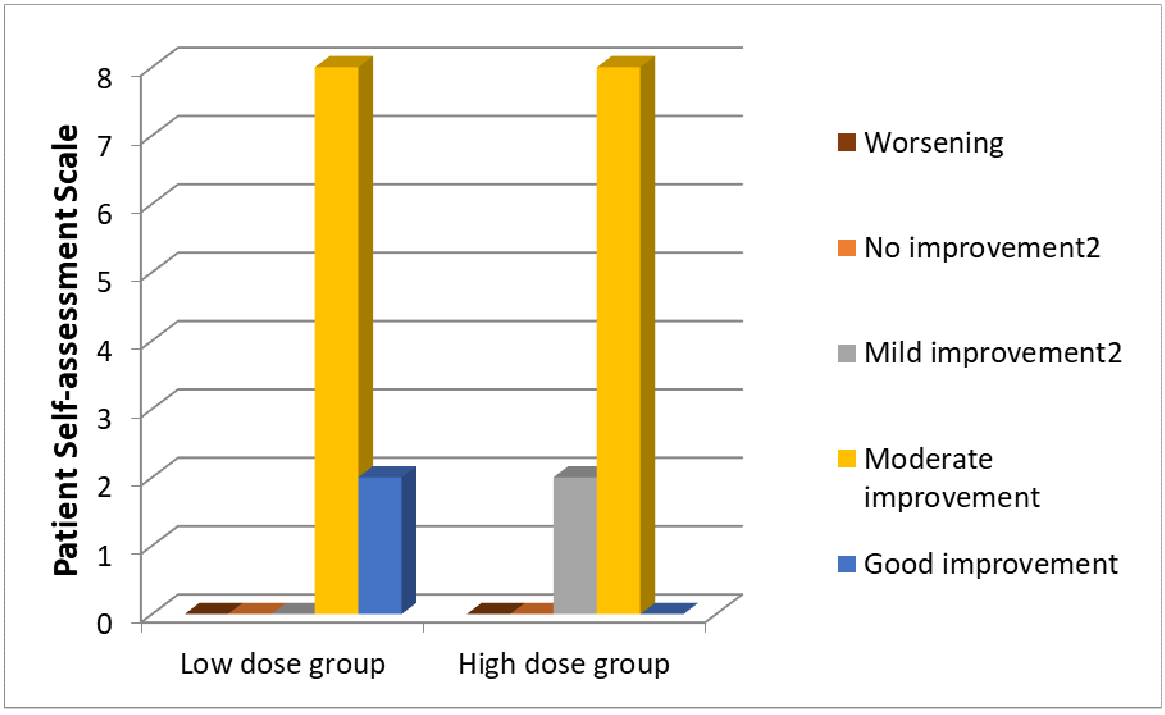

Figure 5 Patient Self-assessment Improvement Scale

This is a picture of patients in low dose azithromycin treatment group. At baseline, the patient has multiple inflammatory lesions on face. After the end of treatment, the lesions had

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almost clear. (Figure 4) For patients self-assessment, most of patients (8 out of 10) in each treatment groups grade their improvement as moderate improvement of acne severity while 2 participants in low-dose group rated their response as good improvement. (Figure 5) In terms of compliance questionnaire, 8 (80%) of patients in each group preferred weekly administered drugs rather than daily drug administration.

Regarding side effects, four patients in the high-dose treated group had diarrhea whereas none of the low-dose group had diarrhea. One patient in the low-dose group had mild facial dryness. No serious side effect occurred in both groups of treatment. All patients can continue oral azithromycin until the end of study.

Discussion

Systemic antibiotics have played an important role in inflammatory acne.[7] Because of the proliferation of *Cutibacterium acnes* inducing inflammation, systemic antibiotics help to inhibit activity of this specific bacteria and decrease chemotaxis of polymorphonuclear leukocytes.

In the latest guideline of care for the management of acne vulgaris by the American Academy of Dermatology, published in 2016, stated that the first-line systemic antibiotic to be considered in the treatment of moderate to severe acne vulgaris is tetracyclines.[7] The effective dose of doxycycline varies from 1.7 to 2.4 mg/kg.[19-20] The second-line drugs include macrolides such as erythromycin and azithromycin.[7] However, recently in 2017, a study has revealed increased bacterial resistant to erythromycin.[21] Therefore, azithromycin has become more and more frequently used these days. Inhibiting the activity of *Cutibacterium acnes* in combination with its anti-inflammatory properties, studies have exhibited positive results for azithromycin in the treatment of acne for both efficacy and safety.[8,15,22-27] However, the optimal dose and duration of azithromycin has not been clearly defined.

Open-label, non-comparative studies have been conducted to evaluate the efficacy of azithromycin in the treatment of acne.[23-24] One study used pulses of azithromycin by administering 500 mg for 3 consecutive days followed by a 7-day interval for a three months' period. Results showed statistically significant reduction of lesions count in different regions of the face between the baseline and final visits.[23] While another study giving 500 mg of azithromycin thrice weekly for 12 weeks exhibited significant lower average global acne grading system score beginning at week 4 of therapy and continued to be evident at 8 and 12 weeks of treatment.[24]

Furthermore, an open-label multicenter comparative randomized controlled trial of 120 patients has been initiated to compare the

dosage regimens of azithromycin in pulse therapy. In this study patients were divided into three groups consisting of a cumulative dose of 4.5, 6.0 and 7.5 g in 7, 10 and 13 weeks, respectively. The group receiving a cumulative dose of 4.5 g was less effective compared to the groups receiving a cumulative dose of 6.0 and 7.5 g. Although no significant difference was found in this study.[17]

In our study, even though in term of statistical analysis, there was no difference in terms of treatment outcome for moderate acne vulgaris between low-dose and high dose azithromycin at the end of the study, we found that patients in low-dose group receiving total of 6 g azithromycin had more reduction in mean percentage of inflammatory lesions than the high-dose group receiving 12 g. Moreover, at 4-weeks of treatment high-dose group did not show more rapid response compared to low-dose group.

In terms of the cost, low-dose oral azithromycin costs less than half when compared to high-dose oral azithromycin and oral doxycycline due to the less amount required. Furthermore, the high-dose oral azithromycin has demonstrated more side effects including diarrhea as high as 40% (4 out of 10 patients).

Our study has some limitations. The sample size is quite small and we only compared 2 doses of azithromycin. In addition, there was no control group with doxycycline; the first-line drug of acne vulgaris treatment. However, when ask about compliance 80% of patients preferred weekly drug administration to daily drug administration. Further studies should be conducted to evaluate the proper dose of azithromycin in comparison to doxycycline as well.

Conclusion

In conclusion, this randomized-control trial study shows that oral azithromycin is a safe, effective, and tolerable agent with good compliance in Asian population. There was no statistical difference in terms of treatment outcome for moderate acne vulgaris between low-dose and high dose azithromycin. However, from our question low-dose azithromycin may seem to have less side effects, less cost and more simple to administer when compared to high-dose azithromycin.

References

1. Tan JK, Bhate K. A global perspective on the epidemiology of acne. Br J Dermatol. 2015; 172: 3-12.
2. Bhate K, Williams HC. Epidemiology of acne vulgaris. Br J Dermatol. 2013; 168: 474-85.
3. Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: Some new aetiological, clinical and therapeutic strategies. Br J Dermatol. 2000; 142: 1084–91.

4. Tan J, Humphrey S, Vender R, et al. A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin. Br J Dermatol. 2014; 171: 1508-16.
5. Zaenglein AL, Shamban A, Webster G, et al. A phase IV, open-label study evaluating the use of triple-combination therapy with minocycline HCl extended-release tablets, a topical antibiotic/retinoid preparation and benzoyl peroxide in patients with moderate to severe acne vulgaris. J Drugs Dermatol. 2013; 12: 619-25.
6. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. Cutis. 2010; 85: 94-104.
7. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016; 74: 945-73.e33.
8. Tan HH, Goh CL, Yeo MG, Tan ML. Antibiotic sensitivity of Propionibacterium acnes isolates from patients with acne vulgaris in a tertiary dermatological referral centre in Singapore. Ann Acad Med Singapore. 2000; 30: 22-5.
9. Labro MT. Anti-inflammatory activity of macrolides: a new therapeutical potential. J Antimicrob Chemother. 1998; 41: 37-46.
10. McDonald PJ, Pruul H. Phagocyte uptake and transport of azithromycin. Eur J Clin Microbiol Infect Dis. 1991; 10: 828-33.
11. Scaglione F, Rossoni G. Comparative anti-inflammatory effects of roxithromycine, azithromycin and clarithromycin. J Antimicrob Chemother. 1998; 41: 47-50.
12. Allvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin, azithromycin. Mayo Clin Proc. 1999; 74: 613-34.
13. Braun-Falco O, Plewig G, Wolff HH, et al. Dermatology. 4th ed. Berlin: Springer-Verlag. 1996; 1053-70.
14. Peters DH, Friedel HA, McTavish D. Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficiency. Drugs. 1992; 44: 750-99.
15. Ullah G, Noor SM, Bhatti Z, Ahmad M, Bangash AR. Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris. J Ayub Med Coll Abbottabad. 2014; 26: 64-7.
16. Bardazzi F, Savoia F, Parente G, et al. Azithromycin: a new therapeutical strategy for acne in adolescents. Dermatol Online J. 2007;13:4.
17. Basta-Juzbasić A, Lipozencić J, Oremović L, et al. A dose-finding study of azithromycin in the treatment of acne vulgaris. Acta Dermatovenerol Croat. 2007;15:141-7.
18. Plewig G, Kligman A. Acne: morphogenesis and treatment. New York: Springer-Verlag, 1975:162-3.
19. Toossi P, Farshchian M, Malekzad F, Mohtasham N, Kimyai-Asadi A. Subantimicrobial-dose

doxycycline in the treatment of moderate facial acne. J Drugs Dermatol. 2008; 7: 1149-52.

20. Moore A, Ling M, Bucko A, Manna V, Rueda MJ. Efficacy and Safety of Subantimicrobial Dose, Modified-Release Doxycycline 40 mg Versus Doxycycline 100 mg Versus Placebo for the treatment of Inflammatory Lesions in Moderate and Severe Acne: A Randomized, Double-Blinded, Controlled Study. J Drugs Dermatol. 2015; 14: 581-6.
21. Aubin GG, Kambarev S, Guillouzouic A, Khammari A, Dréno B, Corvec S. Draft Genome Sequence of an Erythromycin-Resistant Propionibacterium acnes Isolate Recovered from Folliculitis of the Scalp. Genome Announc. 2017; 5: e01490-16.
22. Maleszka R, Turek-Urasinska K, Oremus M, Vukovic J, Barsic B. Pulsed azithromycin treatment is as effective and safe as 2-week-longer daily doxycycline treatment of acne vulgaris: a randomized, double-blind, noninferiority study. Skinmed. 2011; 9: 86-94.
23. Antonio JR, Pegas JR, Cestari TF, Do Nascimento LV. Azithromycin pulses in the treatment of inflammatory and pustular acne: efficacy, tolerability and safety. J Dermatolog Treat. 2008; 19: 210-5.
24. Innocenzi D, Skroza N, Ruggiero A, Concetta Potenza M, Proietti I. Moderate acne vulgaris: efficacy, tolerance and compliance of oral azithromycin thrice weekly for. Acta Dermatovenerol Croat. 2008; 16: 13-8.
25. Kus S, Yucelten D, Aytug A. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. Clin Exp Dermatol. 2005; 30: 215-20.
26. Parsad D, Pandhi R, Nagpal R, Negi KS. Azithromycin monthly pulse vs daily doxycycline in the treatment of acne vulgaris. J Dermatol. 2001; 28: 1-4.
27. Gruber F, Grubisić-Greblo H, Kastelan M, Brajac I, Lenković M, Zamolo G. Azithromycin compared with minocycline in the treatment of acne comedonica and papulo-pustulosa. J Chemother. 1998; 10: 469-73.