ORIGINAL ARTICLE

Comparison of the Efficacy of Azithromycin Versus Doxycycline in Acne Vulgaris: A Meta-Analysis of Randomized Controlled Trials

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Background: Acne vulgaris is one of the most common disorders of the pilosebaceous unit. Although doxycycline is considered to be a first-line anti-acne antibiotic, various other antibiotics have been tried due to its adverse effects and contraindications. We performed a meta-analysis of randomized controlled trials (RCTs) that compared the efficacy of oral azithromycin pulse therapy with that of oral daily doxycycline in the management of moderate to severe acne vulgaris. **Methods:** Five scientific databases (MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science) were searched to identify relevant studies. A review of 1,341 publications produced six RCTs that met our predefined inclusion criteria. The clinical outcome measures were remaining acne lesion counts, patients' self-assessment of treatment, and the investigators' assessment of treatment after 12 weeks. **Results:** We included six studies assessing 906 patients with moderate to severe acne vulgaris. Meta-analyses of clinical outcome measures revealed no significant difference between the two groups regarding remaining acne lesion counts ($p = 0.27$), patients' self-assessment of treatment ($p = 0.67$), and the investigators' assessment of treatment ($p = 0.32$). The incidence of severe adverse events leading to the discontinuation of therapy was higher in the doxycycline daily therapy group when compared with the azithromycin pulse therapy group. **Conclusion:** This study indicates that azithromycin pulse therapy is equivalent to doxycycline at 12 weeks in the efficacy of the treatment for moderate to severe acne vulgaris Therefore, oral azithromycin pulse therapy may be a good alternative to doxycycline in the management of acne for those unable to tolerate doxycycline. **(Ann Dermatol 30(4) 417～426, 2018)**

-Keywords-
Acne vulgaris, Azithromycin, Doxycycline, Meta-analysis

INTRODUCTION

Acne, a follicular disorder involving the specialized pilosebaceous units in the skin, is one of the most common skin disorders treated by dermatologists. The major factors involved in the pathophysiology of acne are obstruction of follicles due to abnormal keratinization of infundibular epithelium, stimulation of sebum secretion by androgen-sensitive sebaceous glands, and inflammation induced by microbial colonization with *Propionibacterium acnes*[1].

Systemic antibiotics have been the mainstay of treatment for moderate to severe acne vulgaris to date, and the effectiveness of several antibiotics, including oxytetracycline, minocycline, doxycycline and erythromycin, in treating

acne has been established[2]. Although doxycycline is considered to be a first-line anti-acne antibiotic, it is known to have side effects, such as gastrointestinal symptoms, tooth discoloration, photosensitive reactions, pigmentation changes, and central nervous system effects[3]. Moreover, doxycycline has many contraindications and drug interactions. For example, it cannot be used during pregnancy or in children under 12 years of age. In addition, the use of doxycycline with isotretinoin, another effective agent in acne treatment, should be avoided because of the increased risk of benign intracranial hypertension[4]. Some authors have emphasized the efficacy of oral azithromycin pulse therapy in acne treatment[5,6].

Azithromycin is an orally administered macrolide antimicrobial drug, structurally related to erythromycin, with an expanded spectrum of activity and improved pharmacokinetic features. Azithromycin is characterized by rapid uptake from the circulation, followed by slow release. The long elimination half-life from tissue permits less-frequent administration[7]. As acne runs a variable course with fluctuations, long-term therapy is often needed. Therefore, drugs with relatively long half-lives such as azithromycin can be useful in increasing patient compliance. In addition, azithromycin can be employed in combination with isotretinoin and can be used during pregnancy and childhood. The adverse effects of azithromycin are limited mainly to mild gastrointestinal discomfort and occur less frequently than with other antibiotics. However, few clinical studies have directly compared oral azithromycin pulse therapy with oral daily doxycycline in the management of acne. Therefore, we conducted a meta-analysis with the aim of comparing the efficacy of oral azithromycin pulse therapy with that of oral daily doxycycline in acne treatment using multiple randomized controlled trials (RCTs).

MATERIALS AND METHODS

This study followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al.[8], 2009) (Supplement 1).

Search strategy

A search was conducted of five scientific databases (MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science) to identify studies in the literature that compared oral azithromycin pulse therapy with oral daily doxycycline in the management of acne. We searched MEDLINE (January 1, 1964 to December 4, 2016), EMBASE (January 1, 1947 to December 4, 2016), and Cochrane

Library (January 1, 1966 to December 4, 2016) with no restriction on language or publication year. The following keywords and medical subject headings were used for the MEDLINE search: "acne vulgaris," "azithromycin," and "doxycycline." The search strategies were developed using indices of the various databases based on the MEDLINE strategy (Supplement 2). In addition to the initial electronic search, manual searching for additional relevant publications was performed.
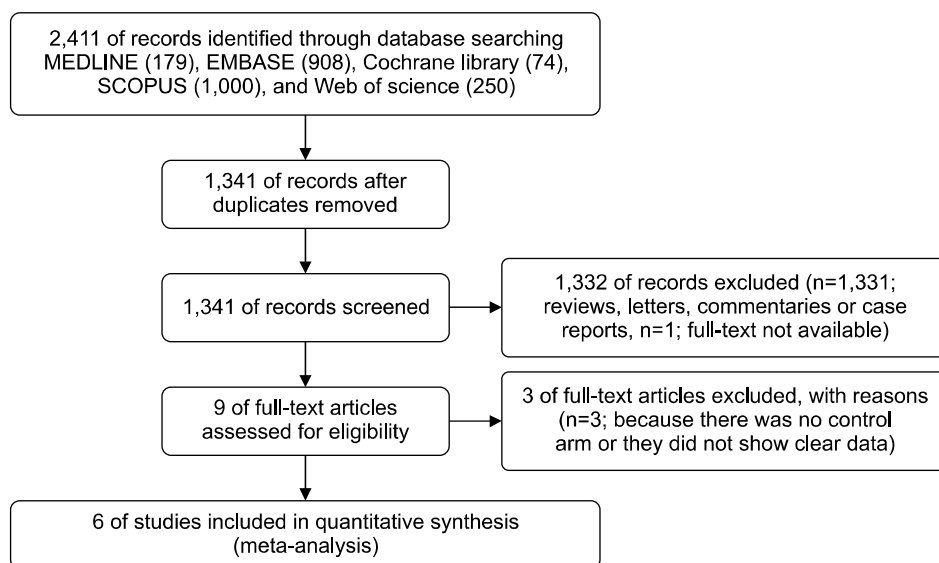
Study selection

Two reviewers independently selected studies based on the following predefined inclusion criteria: 1) moderate or severe acne vulgaris diagnosed clinically or using validated diagnostic criteria; 2) comparison of the clinical outcomes of oral azithromycin pulse therapy and oral doxycycline daily therapy in moderate or severe acne vulgaris; 3) use of clinical outcomes, including the remaining acne lesion count and/or patients' self-assessment of treatment and/or investigators' assessment of lesions at the end of treatment, to evaluate efficacy; 4) maintenance of treatment for at least 3 months; 5) RCT design; and 6) availability of a full-text article. The two reviewers screened titles and abstracts to exclude reviews, letters, commentaries, and case reports. When a study was described in more than one publication, only the most recent or complete article was used. A full list of the exclusion criteria can be found in Fig. 1. Six studies were finally selected.

Data extraction

Two reviewers independently extracted data from the six studies using a predefined data extraction form. All disagreements were resolved by discussion. We extracted the following variables from the studies: 1) authors; 2) year of publication; 3) demographic characteristics of the study population (number, age); 4) inclusion criteria for moderate or severe acne vulgaris; 5) treatment protocol; 6) length of treatment; and 7) method of efficacy evaluation. The relevant clinical data were summarized separately according to the following outcomes: 1) remaining acne lesion count; 2) patients' self-assessment of treatment; and 3) investigators' assessment of treatment. We also evaluated safety outcomes by recording severe side effects that occurred during treatment in all included studies. We defined severe side effects as intolerable side effects that necessitated discontinuation of treatment.

Statistical analysis

We planned to perform a meta-analysis to compare the efficacy of oral azithromycin pulse therapy with that of oral daily doxycycline in the management of moderate to se-

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│  2,411 of records identified through database searching │
│  MEDLINE (179), EMBASE (908), Cochrane library (74),   │
│       SCOPUS (1,000), and Web of science (250)         │
└─────────────────────────────────────────────────┘
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                        ▼
          ┌──────────────────────────┐
          │  1,341 of records after  │
          │     duplicates removed   │
          └──────────────────────────┘
                        │
                        ▼
          ┌──────────────────────────┐      ┌──────────────────────────────────┐
          │                          │      │  1,332 of records excluded (n=1,331; │
          │  1,341 of records screened│─────▶│  reviews, letters, commentaries or case │
          │                          │      │   reports, n=1; full-text not available) │
          └──────────────────────────┘      └──────────────────────────────────┘
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          ┌──────────────────────────┐      ┌──────────────────────────────────┐
          │  9 of full-text articles │      │  3 of full-text articles excluded, with reasons │
          │  assessed for eligibility │─────▶│  (n=3; because there was no control │
          │                          │      │   arm or they did not show clear data) │
          └──────────────────────────┘      └──────────────────────────────────┘
                        │
                        ▼
          ┌──────────────────────────────────────┐
          │  6 of studies included in quantitative synthesis │
          │            (meta-analysis)           │
          └──────────────────────────────────────┘
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Fig. 1. Flow diagram of study identification, inclusion, and exclusion.

vere acne vulgaris. To do so, the clinical treatment outcome was measured according to the following data: remaining acne lesion count, patients' self-assessment of treatment, and investigators' assessment of treatment. Three studies involved inflammatory acne lesion counts, two included non-inflammatory acne lesion counts, two involved patient self-assessment, and all six included the investigators' assessment of treatment. These outcomes were pooled in this analysis. For remaining acne lesion counts, smaller numbers meant a better response to treatment. In evaluating the patient's self-assessment of treatment, favorable responses were defined as "excellent" and "good" ratings. In evaluating the investigators' assessment of treatment, treatment responses were expressed as percentages or by quantitative lesion scores on a 4-point scale (-1, worsened; 0, unchanged; 1, improved; and 2, clear). We defined an excellent response as "a reduction of 75% or more" or "improved or clear state." Next, we defined a moderate response as "a reduction of 50% or more" or an "improved or clear state." We conducted pooled analyses using random-effects weighting for meta-analyses of the outcomes reported by multiple studies that were sufficiently similar to justify combining results. However, if the clinical heterogeneity was too great, studies were not pooled. For dichotomous outcomes, we calculated risk ratios using the Mantel-Haenszel method. For continuous outcomes, we used weighted mean differences (WMDs) and 95% confidence intervals (CIs) with the inverse variance method. Heterogeneity in all meta-analyses was measured using I^2, which indicates the proportion of variation in effect estimates across trials that is due to heterogeneity, rather than sampling error. I^2 values $>50\%$ and p-values from the χ^2 test <0.10 were taken to in-

dicate a statistically large degree of heterogeneity among the included studies. If substantial statistical heterogeneity was noted ($I2>50\%$), we planned to explore individual study characteristics and those of subgroups of the main body of evidence. We performed a sensitivity analysis according to the quality of individual studies and blinding of outcome assessment. All calculations were performed using Review Manager ver. 5.2 (The Cochrane Collaboration, Oxford, UK). This study is based on Cochrane Review Methods.

Assessment of risk of bias

The Cochrane Collaboration's risk of bias tool was used to assess the risk of bias in all included studies. The following items were assessed and recorded: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Each of the included studies was rated as having low, unclear, or high bias based on these items (Supplement 3).

RESULTS

Identification of studies

The database search yielded 1,341 articles, of which 1,331 were excluded because the titles and abstracts indicated that they did not fulfill the selection criteria; an additional article was excluded because the full text was not available. We obtained the full text of the remaining nine articles. We subsequently identified six relevant studies after excluding three (two had no control group, and one

did not provide enough data; Fig. 1). Ultimately, six studies were included in the meta-analysis.
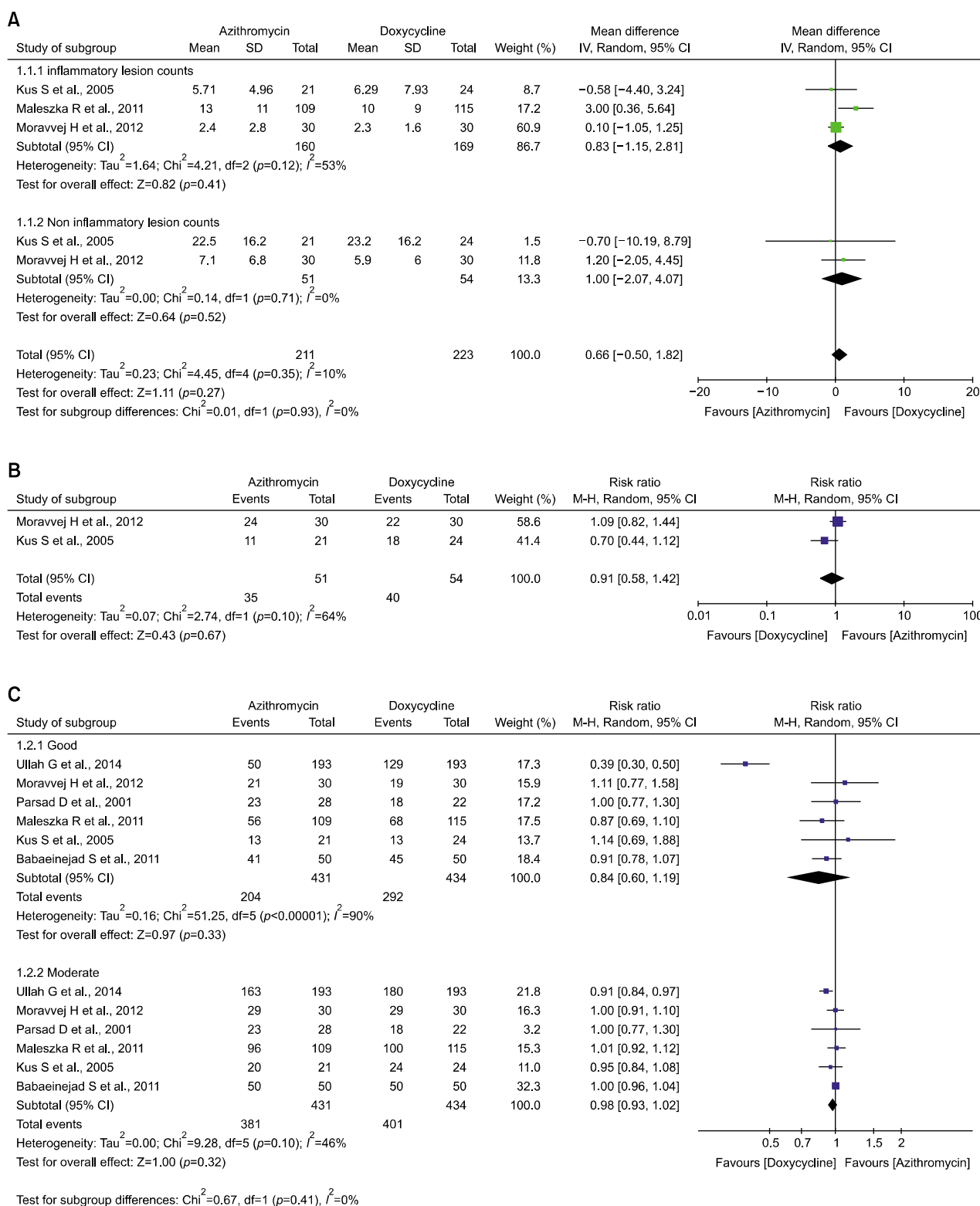
Study characteristics and patients

Of the six studies, two were performed in Iran and one each was performed in India, Turkey, Poland, and Pakistan. The main characteristics of the studies are shown in Table 1. The six studies enrolled a total of 906 patients with moderate or severe acne vulgaris. Overall, 452 patients were assigned randomly to the azithromycin pulse therapy group, and the remaining 454 patients were assigned to the daily doxycycline therapy group. Patients assigned to the azithromycin pulse therapy group took 500 mg of azithromycin 1~3 times weekly or 4 times monthly. Patients in the daily doxycycline group took 100 mg of doxycycline once or twice daily.

Studies defined "moderate acne vulgaris" by using specific tools or by measuring clinical findings. In one study, "moderate acne vulgaris" was defined according to Burke and Cunliffe's Leeds technique[9,10]; in another, recommendations from the Consensus Conference on Acne Classification were used[11,12]. In two studies, "moderate acne vulgaris" was diagnosed by counting inflammatory acne lesions and patients with at least 10 lesions were included[13,14]. In two other studies, "moderate acne vulgaris" was defined based on clinical findings[15,16].
Inflammatory acne lesions were counted in three of the six studies. Of these[13-15], non-inflammatory lesions (comedones) were also counted in two studies[13,14]. Two studies included patients' assessments of their treatment[13,14], with improvement measured on a scale of 0~5 (0, worsening; 1, no change; 2, mild improvement; 3, moderate improve-

Table 1. Characteristics of the six randomized controlled trials included in the final analysis

Study (year)	No. of patient		Age (yr)	Treatments protocol		Methods of evaluating efficacies
	Azithromycin group (n=452)	Doxycycline group (n=454)		Azithromycin group	Doxycycline group	
Parsad et al. (2001)[10]	30 (6.6)	30 (6.6)	≥16	Azithromycin 500 mg 4 d/mo+topical 0.05% tretinoin	100 mg doxycycline once daily+topical 0.05% tretinoin cream	1. Investigator's assessment of treatment using a 4 point scale
Kus et al. (2005)[13]	25 (5.5)	26 (5.7)	18~30	Azithromycin 500 mg 3 d/wk (1st mo), 2 d/wk (2nd mo), once a week (3rd mo)	Doxycycline 100 mg twice a day (1st mo), once daily (2nd mo, 3rd mo)	1. Facial inflammatory, non-inflammatory acne lesion counts 2. Patient's own assessment of treatment using a 5 point scale 3. Investigator's assessment of treatment (treatment responses were expressed as percentages)
Babaeinejad et al. (2011)[12]	50 (11.1)	50 (11.0)	≥13	Azithromycin 500 mg 4 d/mo	100 mg doxycycline once daily	1. Investigator's assessment of treatment (treatment responses were expressed as percentages)
Maleszka et al. (2011)[15]	120 (26.5)	120 (26.4)	≥14	Azithromycin 500 mg 3 d/wk (1st wk), followed by 500 mg weekly	100 mg doxycycline twice a day (1st d), followed by 100 mg doxycycline once daily	1. Facial inflammatory acne lesion counts 2. Investigator's assessment of treatment (treatment responses were expressed as percentages)
Moravvej et al. (2012)[14]	34 (7.5)	35 (7.7)	18~30	Azithromycin 500 mg 3 d/wk	100 mg doxycycline daily	1. Facial inflammatory, non-inflammatory acne lesion counts 2. Patient's own assessment of treatment using a 5 point scale 3. Investigator's assessment of treatment (treatment responses were expressed as percentages)
Ullah et al. (2014)[16]	193 (42.7)	193 (42.5)	14~30	Azithromycin 500 mg 4 d/mo	100 mg doxycycline daily	1. Investigator's assessment of treatment (treatment responses were expressed as percentages)

A

Study of subgroup	Azithromycin Mean	SD	Total	Doxycycline Mean	SD	Total	Weight (%)	Mean difference IV, Random, 95% CI
1.1.1 inflammatory lesion counts								
Kus S et al., 2005	5.71	4.96	21	6.29	7.93	24	8.7	−0.58 [−4.40, 3.24]
Maleszka R et al., 2011	13	11	109	10	9	115	17.2	3.00 [0.36, 5.64]
Moravvej H et al., 2012	2.4	2.8	30	2.3	1.6	30	60.9	0.10 [−1.05, 1.25]
Subtotal (95% CI)			160			169	86.7	0.83 [−1.15, 2.81]

Heterogeneity: Tau^2=1.64; Chi^2=4.21, df=2 (p=0.12); I^2=53%
Test for overall effect: Z=0.82 (p=0.41)

1.1.2 Non inflammatory lesion counts								
Kus S et al., 2005	22.5	16.2	21	23.2	16.2	24	1.5	−0.70 [−10.19, 8.79]
Moravvej H et al., 2012	7.1	6.8	30	5.9	6	30	11.8	1.20 [−2.05, 4.45]
Subtotal (95% CI)			51			54	13.3	1.00 [−2.07, 4.07]

Heterogeneity: Tau^2=0.00; Chi^2=0.14, df=1 (p=0.71); I^2=0%
Test for overall effect: Z=0.64 (p=0.52)

Total (95% CI)			211			223	100.0	0.66 [−0.50, 1.82]

Heterogeneity: Tau^2=0.23; Chi^2=4.45, df=4 (p=0.35); I^2=10%
Test for overall effect: Z=1.11 (p=0.27)
Test for subgroup differences: Chi^2=0.01, df=1 (p=0.93), I^2=0%

Mean difference IV, Random, 95% CI
−20 −10 0 10 20
Favours [Azithromycin] Favours [Doxycycline]

B

Study of subgroup	Azithromycin Events	Total	Doxycycline Events	Total	Weight (%)	Risk ratio M-H, Random, 95% CI
Moravvej H et al., 2012	24	30	22	30	58.6	1.09 [0.82, 1.44]
Kus S et al., 2005	11	21	18	24	41.4	0.70 [0.44, 1.12]
Total (95% CI)		51		54	100.0	0.91 [0.58, 1.42]
Total events	35		40			

Heterogeneity: Tau^2=0.07; Chi^2=2.74, df=1 (p=0.10); I^2=64%
Test for overall effect: Z=0.43 (p=0.67)

Risk ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours [Doxycycline] Favours [Azithromycin]

C

Study of subgroup	Azithromycin Events	Total	Doxycycline Events	Total	Weight (%)	Risk ratio M-H, Random, 95% CI
1.2.1 Good						
Ullah G et al., 2014	50	193	129	193	17.3	0.39 [0.30, 0.50]
Moravvej H et al., 2012	21	30	19	30	15.9	1.11 [0.77, 1.58]
Parsad D et al., 2001	23	28	18	22	17.2	1.00 [0.77, 1.30]
Maleszka R et al., 2011	56	109	68	115	17.5	0.87 [0.69, 1.10]
Kus S et al., 2005	13	21	13	24	13.7	1.14 [0.69, 1.88]
Babaeinejad S et al., 2011	41	50	45	50	18.4	0.91 [0.78, 1.07]
Subtotal (95% CI)		431		434	100.0	0.84 [0.60, 1.19]
Total events	204		292			

Heterogeneity: Tau^2=0.16; Chi^2=51.25, df=5 (p<0.00001); I^2=90%
Test for overall effect: Z=0.97 (p=0.33)

1.2.2 Moderate						
Ullah G et al., 2014	163	193	180	193	21.8	0.91 [0.84, 0.97]
Moravvej H et al., 2012	29	30	29	30	16.3	1.00 [0.91, 1.10]
Parsad D et al., 2001	23	28	18	22	3.2	1.00 [0.77, 1.30]
Maleszka R et al., 2011	96	109	100	115	15.3	1.01 [0.92, 1.12]
Kus S et al., 2005	20	21	24	24	11.0	0.95 [0.84, 1.08]
Babaeinejad S et al., 2011	50	50	50	50	32.3	1.00 [0.96, 1.04]
Subtotal (95% CI)		431		434	100.0	0.98 [0.93, 1.02]
Total events	381		401			

Heterogeneity: Tau^2=0.00; Chi^2=9.28, df=5 (p=0.10); I^2=46%
Test for overall effect: Z=1.00 (p=0.32)

Test for subgroup differences: Chi^2=0.67, df=1 (p=0.41), I^2=0%

Risk ratio M-H, Random, 95% CI
0.5 0.7 1 1.5 2
Favours [Doxycycline] Favours [Azithromycin]

Fig. 2. Forest plot of the meta-analysis for clinical outcome measures. (A) Remaining acne lesion counts. (B) Patient's self-assessment of treatment. (C) Investigator's assessment of treatment. SD: standard deviation, IV: inverse variance, CI: confidence interval, df: degree of freedom, M-H: Mantel-Haenszel.

ment; 4, good improvement; and 5, excellent improvement). Favorable patient responses were defined as "excellent" and "good" ratings. Investigators evaluated the response to treatment in all studies. Treatment responses were expressed as percentages in five studies[12-16] and by quantitative lesion scores on a 4-point scale (-1, worsened; 0, unchanged; 1, improved; and 2, clear) in one study[10]. We defined a meaningful response as a score of 2. Initially, we defined an excellent response as "a reduction of 80% or more" in four studies[12-14,16], "a reduction of 75% or more" in one study[15], and an "improved or clear state" in one study[10]. Next, we defined a moderate response as "a reduction of 50% or more" in five studies[12-16]

and an "improved or clear state" in one study[10]. Each response was then analyzed individually.

Clinical treatment outcome measures

At 12 weeks, remaining inflammatory and non-inflammatory acne lesion profiles were similar in the azithromycin pulse therapy and doxycycline daily therapy groups, with no significant difference between groups and no heterogeneity (WMD, 0.66; 95% CI, $-0.50 \sim 1.82$; $I^2 = 10\%$; Fig. 2A). The meta-analysis of patients' self-assessment data from two studies revealed no significant difference between groups and moderate heterogeneity (relative risk [RR], 0.91; 95% CI, $0.58 \sim 1.42$; $I^2 = 64\%$; Fig. 2B). Also,
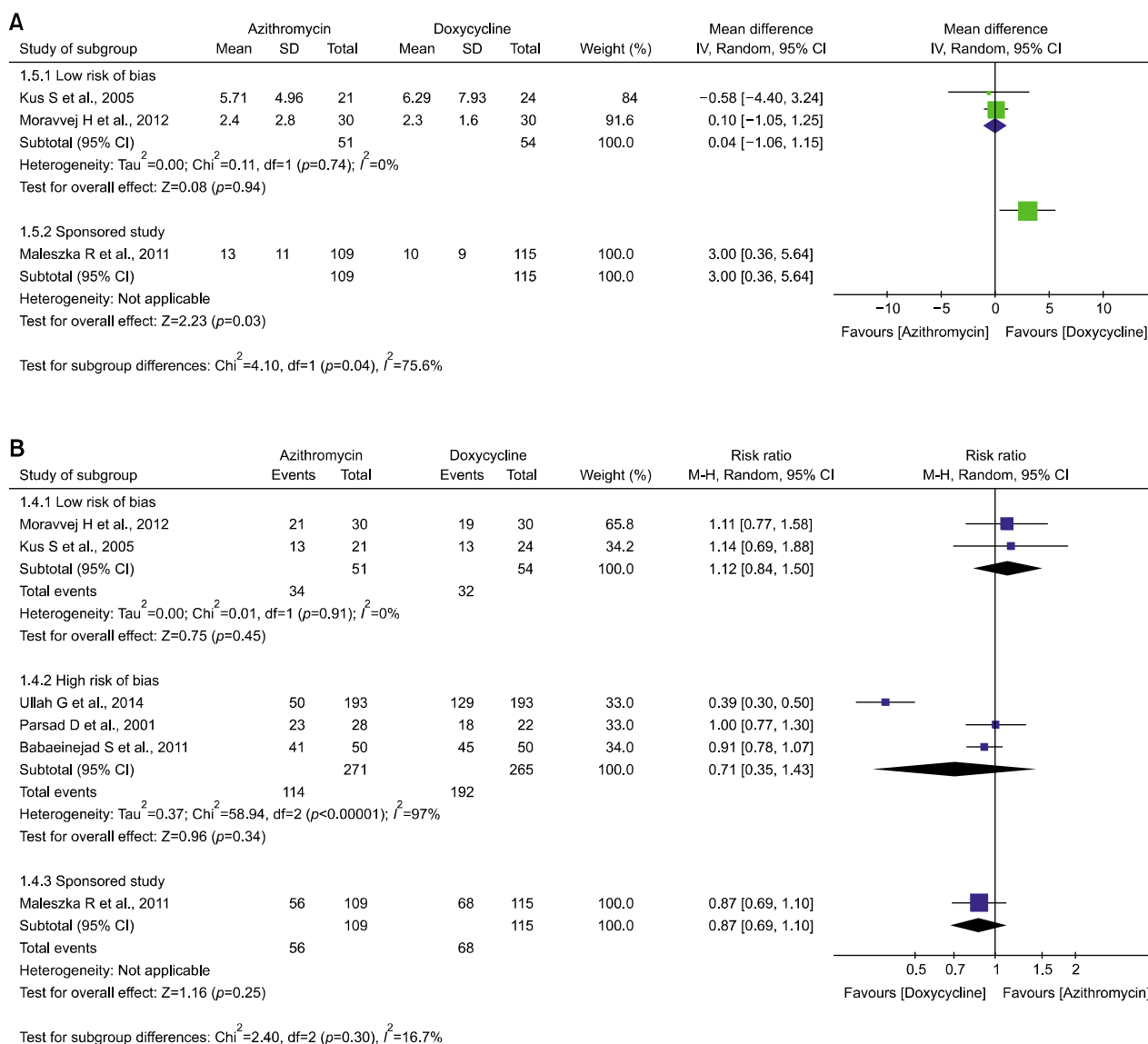
Fig. 3. Forest plot of the meta-analysis for sensitivity analysis. (A) Remaining inflammatory acne lesion counts. (B) Investigator's assessment of treatment. SD: standard deviation, IV: inverse variance, CI: confidence interval, df: degree of freedom, M-H: Mantel-Haenszel.

we conducted a meta-analysis of investigators' assessment of treatment in all six studies. Again, the analysis showed no significant difference between groups in both excellent and moderate response (excellent response: RR, 0.84; 95% CI, 0.60~1.19; $I^2=90\%$; moderate response: RR, 0.98; 95% CI, 0.93~1.02; $I^2=46\%$; Fig. 2C). The assessment outcomes are shown in Fig. 2.

Sensitivity analysis outcomes

We conducted a sensitivity analysis of remaining inflammatory acne lesion counts and investigators' assessment of treatment according to the quality of individual studies and blinding of outcome assessment. The sensitivity analysis outcomes are shown in Fig. 3. The sensitivity analysis changed the direction of clinical outcomes, although it was not statistically significant. At 12 weeks, the remaining inflammatory acne lesion counts were similar in the azithromycin pulse therapy and doxycycline daily therapy groups, with no significant difference between groups (WMD, 0.83; 95% CI, −1.15~2.81; Fig 2A). Among them, two studies were assumed to have a low risk of bias and the other was a sponsored study. The individual sensitivity analysis outcomes showed the direction change (low risk of bias: WMD, 0.04; 95% CI, −1.06~1.15; sponsored study: WMD, 3.00; 95% CI, 0.36~5.64; Fig. 3A). Similarly, we performed a sensitivity analysis about the investigators' assessment of treatment. The meta-analysis of the six included studies showed no significant difference between groups (excellent response: RR, 0.84; 95% CI, 0.60~1.19; Fig. 2C). Among them, two studies were assumed to have a low risk of bias, three studies had a high risk of bias, and the other one was a sponsored study. The individual sensitivity analysis outcomes showed the direction change (low risk of bias: RR, 1.12; 95% CI, 0.84~1.50; high risk of bias: RR, 0.71; 95% CI, 0.35~1.43; sponsored study: RR, 0.87; 95% CI, 0.69~1.10; Fig. 3B).

Table 2. Serious adverse events leading to the discontinuation of therapy

Severe side effect	Doxycycline	Azithromycin
Severe diarrhea	0	4
Severe nausea	2	0
Severe epigastric pain	3	0
Photosensitivity	3	0
Vaginitis	2	0
Abnormal blood cell count	1	0
Severe vertigo	1	0

Safety outcomes

We reviewed all side effects reported in the six studies. In general, the side effects were mild and transient, and did not require the discontinuation of therapy. For example, side effects included mild epigastric pain, diarrhea, vomiting, abdominal pain, constipation, malaise, and mild headache. However, some patients experienced intolerable side effects and subsequently discontinued therapy. Severe side effects are shown in Table 2. Severe side effects were defined as intolerable side effects that necessitated the discontinuation of treatment and included severe gastrointestinal discomfort, photosensitivity, vaginitis, and severe vertigo. Although a statistical analysis of these side effects was not performed, the incidence of severe adverse events was higher in the doxycycline daily therapy group than in the azithromycin pulse therapy group.

DISCUSSION

The results of our meta-analysis show that doxycycline daily therapy and azithromycin pulse therapy had similar efficacy in the treatment of moderate to severe acne vulgaris at 12 weeks, with no significant difference between groups. The clinical outcome measures included the remaining acne lesion count, patients' self-assessment of their treatment, and investigators' assessment of the treatment. In regards to safety outcomes, the doxycycline daily therapy group reported more severe adverse events than the azithromycin pulse therapy group. Even though it was not statistically significant, the meta-analysis of clinical outcome measures was weighed toward the doxycycline daily therapy group. Therefore, we conducted a sensitivity analysis of the remaining inflammatory acne lesion counts and investigators' assessment of treatment according to the quality of individual studies and blinding of outcome assessment. We chose these outcome measures for the sensitivity analysis because the blinding of outcome assessment can have a major influence on them. The sensitivity analysis changed the direction of the two clinical outcomes. Of the three studies[13-15] evaluated for remaining inflammatory acne lesion counts, one study[15] was a company-sponsored study and reported greater efficacy in the doxycycline daily therapy group. In contrast, two studies[13,14] that showed their blinding of outcome assessment clearly reported more favorable efficacy in the azithromycin pulse therapy group. Similarly, of the six studies[10,12-16] that evaluated the investigator's assessment of treatment, three studies[10,12,16] that did not show their blinding of outcome assessment clearly reported more favorable efficacy in the doxycycline daily therapy group. In

contrast, two studies[13,14] that showed their blinding of outcome assessment clearly reported more favorable efficacy in the azithromycin pulse therapy group. The one company-sponsored study[15] showed more favorable efficacy in the doxycycline daily therapy group. Sometimes, company-sponsored studies are significantly more likely to paint a rosy picture of the drug being evaluated than independent trials. Two studies[12,16] did not report any side effects. Both of them reported more favorable efficacy in the doxycycline daily therapy group and were among the previous three studies that showed high detection bias. In light of this, there could also be reporting bias. Taken together, the high risk of blinding of outcome assessment of studies could have led to an overestimation of doxycycline efficacy in their assessment. Of all six studies, one study[16] was distinctively heterogeneous compared with the other five. It reported the most favorable efficacy of doxycycline daily therapy among all six studies. However, the study did not report any adverse events and also did not describe its blinding of outcome assessment. This could have created reporting bias and thus led to an overestimation of doxycycline efficacy.

Antibiotics are a well-known mainstream treatment for acne because of their anti-inflammatory and antimicrobial properties. Systemic antibiotics have been proven to reduce not only, inflammatory, but also non-inflammatory, lesions of acne. Research has also shown that once *P. acnes* colonization occurs, those organisms liberate free fatty acids that are comedogenic, and thus yield non-inflammatory lesions[17]. Among various antibiotics, tetracycline and its derivatives are used widely in the treatment of acne vulgaris. Doxycycline is often preferred to other tetracyclines due to its safer side effect profiles, and it is among the most commonly prescribed antibiotics in the management of acne. Despite its overall safety record, doxycycline has fatal disadvantages. Sometimes, its use must be limited because it is contraindicated in females of childbearing age and children under 12 years of age. Also, doxycycline has been reported to have several side effects. The most common adverse events associated with doxycycline are gastrointestinal, including heartburn, nausea, vomiting, diarrhea, gastritis, and esophagitis. The second most commonly reported side effect is photosensitivity. In addition, several serious doxycycline-induced adverse reactions, such as pseudotumor cerebri and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, have emerged over the last few years. Although discontinuation of the medication yielded improvement in most reported cases, a few patients suffered from a permanent loss of visual acuity or loss of visual field[18-21].

In the context of the fairly large number of adverse events related to tetracycline and its derivatives, some comparative clinical trials have shown that the tolerability profile of azithromycin is superior to that of tetracyclines[13,16,22]. Clinical isolates of *P. acnes* are highly susceptible to macrolide antibiotics. Although such antibiotics can effectively treat acne, they are not considered to be first-line drugs because of the risk of bacterial resistance[23]. Antibiotic resistance among *P. acnes* is increasing globally and may contribute significantly to treatment failure. Among the various macrolide antibiotics, *P. acnes* is more commonly resistant to erythromycin and clindamycin, and less so to azithromycin[24-39]. Moon et al.[33] examined the antibiotic resistance profile of microbial strains isolated from Korean acne patients and reported that higher proportions of *P. acnes* isolates were resistant to clindamycin (30%) and erythromycin (26.7%) than to azithromycin (6.7%) and doxycycline (6.7%).

Also, azithromycin affords many advantages compared with other antibiotics. In terms of pharmacokinetics, azithromycin is known to be more stable in gastric acid than are older generation macrolides, including erythromycin, and it achieves rapid uptake from the circulation with a high tissue concentration following oral administration. Moreover, azithromycin has a long half-life, enabling less-frequent administration and making it suitable for use as pulse therapy, which can improve patient compliance and the development of *P. acnes* resistance; the dose is low. Several studies[1-3] reported that pulse dosing was successful; however, no standard regimen is yet available[6,10,40]. Some studies[4,5] have compared the efficacies of different pulse-dosing protocols and found no significant among-protocol difference in efficacy[41,42]. Accordingly, although the treatment protocols differed slightly among included studies, we could not consider that this a major problem.

Furthermore, azithromycin is well tolerated and has a good safety record. Previously, Bakar et al.[43] reported that the side effects of azithromycin were minimal and well tolerated in most patients treated for papulopustular rosacea. Kashkouli et al.[44] also reported mild and temporary side effects, which did not require treatment, during treatment for meibomian gland dysfunction, whereas the doxycycline group had significantly more side effects. In the six studies included in the present meta-analysis, severe adverse events were detected more frequently in the doxycycline therapy group. Moreover, azithromycin has no major drug interaction. Of the anti-acne antibiotics used frequently, azithromycin is the most eligible for use in combination with isotretinoin. Previous studies showed that a combination of low-dose isotretinoin and oral azi-

thromycin pulse therapy was effective in the treatment of severe acne. Combination therapy might yield synergistic effects and overcome the dose-dependent adverse effects of isotretinoin, as well as lower the incidence of relapse compared with monotherapy[45,46]. Azithromycin is not contraindicated in pregnancy, unlike tetracyclines; thus, it can be safely administered to women of childbearing age and to pregnant women with severe aggravated lesions, with no increased risk of congenital malformation or miscarriage[47]. Due to these advantages, azithromycin is expected to be a good alternative to conventional acne antibiotics. Many previous studies have demonstrated that azithromycin was effective in treating acne, with similar efficacy to that of doxycycline; our results are in line with these reports.

Our study has several limitations. First, only a small number of eligible studies were included. Second, detection and reporting biases may have been present. The inclusion of a greater number of high-quality RCTs is needed in future analyses.

In conclusion, the present work revealed significant evidence that azithromycin pulse therapy is a likely equivalent to daily doxycycline therapy in the management of moderate or severe acne vulgaris and may be a good alternative drug for patients who cannot tolerate tetracycline. In addition, reevaluation of the efficacy of azithromycin in treating acne would be helpful; azithromycin may be used widely with a better safety profile than other drugs, including doxycycline. To our knowledge, this is the first meta-analysis to compare the efficacy of oral azithromycin pulse therapy with that of oral daily doxycycline therapy in the treatment of acne vulgaris.

ACKNOWLEDGMENT

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-30-417-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Supplementary Table 1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#5, #6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#6, #7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#6, #7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#7, #8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#8, #9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	#8, #9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	#9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#9, #10, #11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#10, #11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#11, #12, #13

Supplementary Table 1. Continued

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	#12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#13, #14, #16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#17, #18

Supplement 2. Search strategy on MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science

MEDLINE

1. Acne[TIAB] 13205
2. "Acne Vulgaris"[MeSH] 10280
3. 1 OR 2 15466
4. "Azithromycin"[MeSH] OR "Doxycycline"[MeSH] 12141
5. Azithromycin[TIAB] OR Azythromycin[TIAB] OR Zithromax[TIAB] OR Zitromax[TIAB] OR Doxycycline[TIAB] OR Vibramycin[TIAB] 16706
6. 4 OR 5 20363
7. 3 AND 6 242
8. 7 NOT "review"[Publication Type] OR "review literature as topic"[MeSH Terms] 179

EMBASE

1. Acne:ab,ti 18394
2. 'acne'/exp 29032
3. 1 OR 2 32012
4. Azithromycin:ab,ti OR Azythromycin:ab,ti OR Zithromax:ab,ti OR Zitromax:ab,ti OR Doxycycline:ab,ti OR Vibramycin:ab,ti 23078
5. 'azithromycin'/exp OR 'doxycycline'/exp 64008
6. 4 OR 5 66297
7. 3 AND 6 1457
8. 7 NOT ('conference review'/it OR 'review'/it) 997
9. 8 NOT 'nonhuman'/de 908

Cochrane Library

1. Acne:ti,ab,kw 2642
2. MeSH descriptor: [Acne Vulgaris] explode all trees 907
3. 1 OR 2 2642
4. MeSH descriptor: [Azithromycin] explode all trees 781
5. MeSH descriptor: [Doxycycline] explode all trees 777
6. Azithromycin OR Azythromycin OR Zithromax OR Zitromax OR Doxycycline OR Vibramycin:ti,ab,kw 2839
7. 4 OR 5 OR 6 2839
8. 3 AND 7 77
9. 8/TRIALS 74

SCOPUS

1. TITLE-ABS(Acne) 19947
2. INDEXTERMS ("Acne Vulgaris" OR acne) 30914
3. 1 OR 2 36123
4. INDEXTERMS(Azithromycin OR Doxycycline) 58379
5. TITLE-ABS(Azithromycin OR Azythromycin OR Zithromax OR Zitromax OR Doxycycline OR Vibramycin) 19788
6. 4 OR 5 62281
7. 3 AND 6 1472
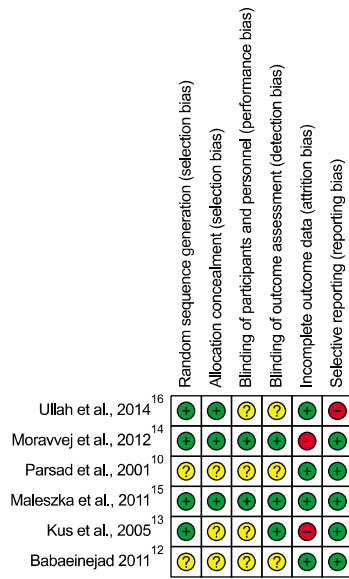8. 7 AND (EXCLUDE (DOCTYPE , "re")) 1000

Web of Science

1. TOPIC: (Acne) OR TITLE: (Acne) 15582
2. TOPIC: (Azithromycin OR Azythromycin OR Zithromax OR Zitromax OR Doxycycline OR Vibramycin) OR TITLE: (Azithromycin OR Azythromycin OR Zithromax OR Zitromax OR Doxycycline OR Vibramycin) 18238

3. 1 AND 2 283
4. 3 Refined by: [excluding] DOCUMENT TYPES: (REVIEW) 250

Supplementary Fig. 1. Risk of bias assessment of the included studies.