Oral acyclovir in treatment of pityriasis rosea: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the efficacy of oral acyclovir in treatment of pityriasis rosea (PR).

METHODS

Four independent reviewers systematically searched through electronic databases without language restriction, included Pubmed, Cochrane library, Scopus, and Trip Database. We also performed hand searching to find all relevant studies outside the databases. We assessed quality and risk of bias of the included studies using Jadad score and The Cochrane Collaboration's Tool for Assessing Risk of Bias. We extracted data from the included studies. The meta-analysis was performed where appropriate.

RESULTS

There were four randomized controlled trials identified, involving 251 patients with PR. Using oral acyclovir comparing with placebo or no treatment was associated with 2.76 times higher response rate to treatment (95% confidence interval (CI), 1.86 to 4.09; $P<0.001$; $I^2=11\%$), 2.19 times higher response rate to treatment (95% CI, 1.73 to 2.78; $P<0.001$; $I^2=18\%$) at the first week and the second week, respectively, and 44% relative risk reduction (RR 0.56, 95% CI, 0.41 to 0.77; $P=0.004$; $I^2=21\%$) in occurrence rate of new skin lesion after following in the first week.

CONCLUSION

Oral acyclovir was superior to placebo or no treatment for treating patients with PR regarding response rate to treatment at the first and the second week as well as occurrence rate reduction of the new skin lesion in the first week after starting the treatment.

INTRODUCTION

Pityriasis rosea (PR) is an acute papulosquamous skin disease characterized by pink macules or papules usually appear on trunk with christmas-tree distribution pattern.[1,2] An estimated incidence of PR is 170 per 100,000 with 75% of cases are reported in patients age 10 to 35 years.[3-6] Etiology of PR is remaining incomplete understood, several existing evidences show association between PR and viral infection or endogenous reactivation of human herpesvirus (HHV)-6 and HHV-7.[7-11] Thus, antiviral agents may have a role for treating PR. Although acyclovir is effective against viral infection by its mechanism of deoxyribonucleic acid (DNA) polymerase inhibition,[12] there are studies reporting that it has little or no action against HHV-7 in laboratory condition because its action depends on thymidine kinase and HHV-7 does not possess the gene coding for this enzyme.[13,14] According to the controversy between its mechanism of action and the results from previous studies, we conducted a systematic review to evaluate efficacy of oral acyclovir in treating patients with PR.

METHODS

SEARCH METHODS FOR IDENTIFYING OF STUDIES

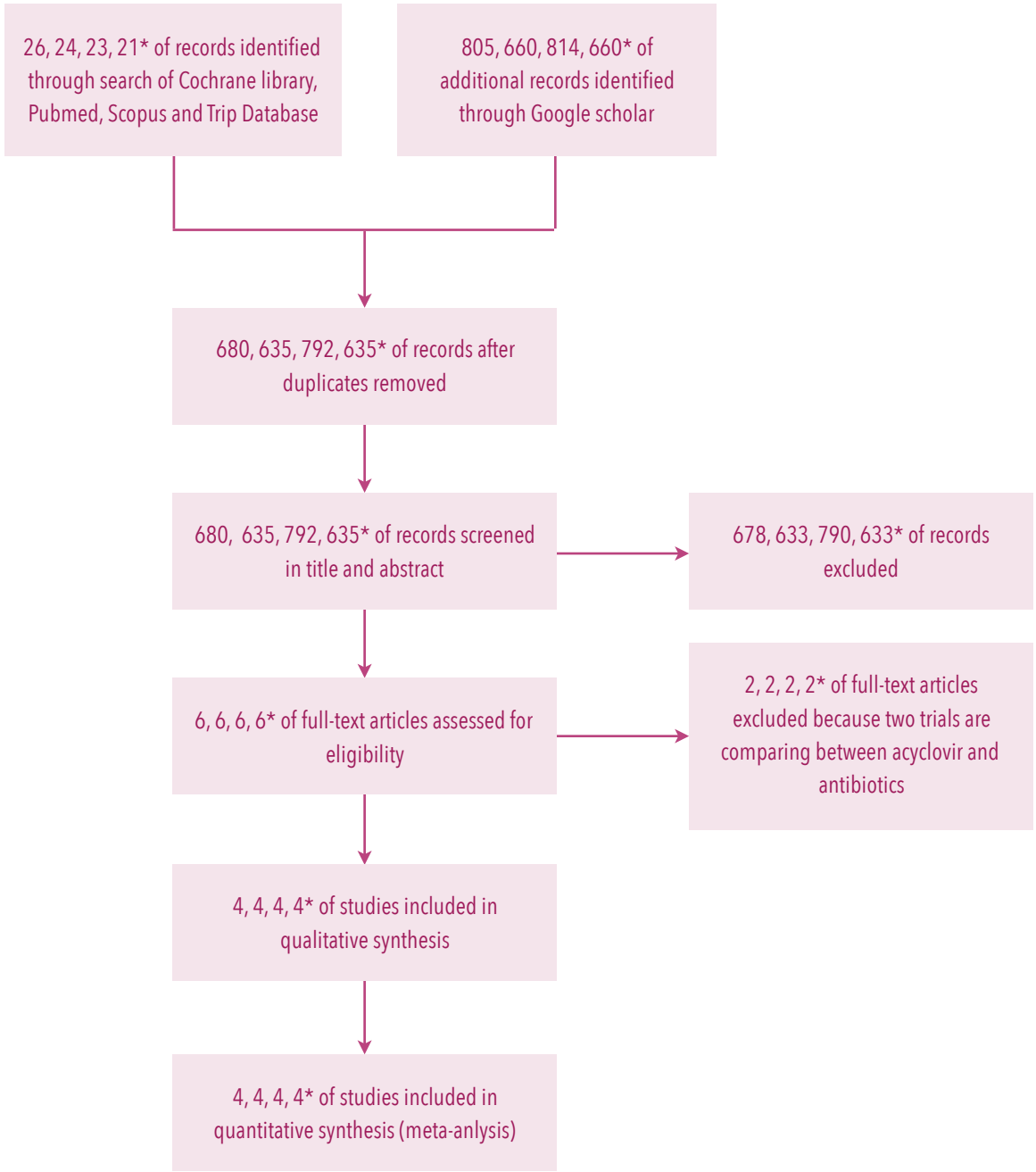
Four independent reviewers systematically searched through electronic databases, included Pubmed, Cochrane library, Scopus and Trip Database using the combination search terms of "pityriasis rosea" and "acyclovir". We also applied Medical Subject Headings (MeSH) searching strategy in term of "Pityriasis Rosea"[Mesh] AND "Acyclovir"[Mesh] to identify studies in Pubmed and Cochrane library. We used PICO searching strategy to identify studies in Trip Database using P: "pityriasis rosea" and I: acyclovir. No restriction of language was assigned and translation was sought when necessary. We also tracked for articles in references of each included study. Moreover, we performed hand searching to find other relevant studies outside the databases.

INCLUSION AND EXCLUSION CRITERIA

Our inclusion criteria were randomized controlled trials (RCTs) that patients with PR were diagnosed by dermatologists, were treated with oral acyclovir and reported outcomes at least on response to treatment at the first and the second week and occurrence rate of new skin lesion after initiating the treatment for one week. To focus on the efficacy of oral acyclovir in treating patients with PR, studies were excluded if they met these following criteria; studies which compared combination therapy of oral acyclovir and other antiviral agents or antibiotics; and studies which compared oral acyclovir with other antiviral agents or antibiotics.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess quality of included trials consist of the evaluations of randomization, blinding methods and adequate description of withdrawals or dropouts.[15] In addition, we used The Cochrane Collaboration's tool for Assessing Risk of Bias to present the risk of bias as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias by categorizing them as high risk, low risk, or unclear risk.[16]



*The 4 numbers refer to the quantity of results searched by Nut Laorueangwatthana, Santhita Pimonbut, Sirinat Suriyachai and Papichaya Songtuntarax, respectively

Figure 1. Flow of Studies by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1. Description of Included Studies.

Trial	No. of patients in intervention/ controlled group	Interventions	Controlled	Outcomes
Daliri, 2008	65/64	Oral acyclovir 800 mg five times daily for 1 week	Vitamin E 100 mg twice daily	Response rate to treatment was higher in acyclovir group than that of placebo group at 1st week (63.2% vs. 28.5%; P=0.014). Response rate to treatment was higher in acyclovir group comparing to that of placebo group at 2nd week (88.1% vs. 47.4%; P=0.014). Formation of new lesion at 1st week was less common in acyclovir group than that of placebo group (47.4% vs. 73.2%; P=0.014).
Rassai et al, 2011	28/26	Oral acyclovir 400 mg five times daily for 1 week	No treatment	Erythema reduction at the 1st week was higher in a acyclovir group than that of placebo group (46.4% vs. 15.4%; P=0.014). Erythema reduction at the 2nd week was higher in acyclovir group comparing to that of placebo group (78.5% vs. 27% P<0.001).
Ganguly, 2014	38/35	Oral acyclovir 800 mg five times daily in adult and 20 mg/kg/ day four times daily in children for 1 week	Vitamin C 100 mg five times daily for adults, 50 mg four times daily for children for 1 week	Response rate to treatment was higher in acyclovir group than that of placebo group (16 vs. 3 out of 30; P=o.oo3 in 1st week and 26 vs. 10 out of 30; P= 0.001 in 2nd week). New skin lesion at the first week was less common in acyclovir group than that of placebo group (o vs. 3 out of 30).
Das et al, 2015	12/12	Oral acyclovir 400 mg thrice daily for 1 week with cetirizine 10 mg once a day at bedtime plus calamine lotion	Cetirizine 10 mg once daily at bedtime plus calamine lotion	New skin lesion at 1st week was less common in acyclovir group than that of placebo group; (2 vs. 7 out of 12; P=0.046).

DATA EXTRACTION

We extracted the data from the included studies regarding the first author, year of publication, number of participants of intervention and controlled groups, dose and duration of study drugs, and outcomes in terms of response rate to treatment at the first and the second week and occurrence rate of new skin lesion after following in the first week.

STATISTICAL ANALYSIS

The meta-analysis was done and reported as relative risk (RR) and 95% confidence interval (CI). We presented the meta-analysis as forest plot. We

calculated I^2 to assess the heterogeneity of the included studies. We used the fixed-effect model if $I^2<50\%$ and the random-effect model if $I^2\geq50\%$. We used funnel plot for assessing publication bias. All statistical analyses were done using Review Manager 5.3 statistical software.

SENSITIVITY AND SUBGROUP ANALYSES

We carried out sensitivity analysis by removing each trial one by one from overall analysis to evaluate the influence of single trial on the pooled analysis. We also restricted the meta-analysis to subgroup of trials that have low risk of bias (Jaded score≥3 and The Cochrane Collaboration's Tool for Assessing Risk of Bias categorized to low risk≥50%).

RESULTS

Initially, there were 831, 684, 837 and 681 studies identified by each of four reviewers as potentially relevant studies from the electronic databases and other sources. Of these, 680, 635, 792 and 635 studies remained after duplicate removed and were screened in title and abstract. Of these, six studies fulfilled the predefined inclusion criteria and were screened in details. We excluded two studies because the studies compared oral acyclovir to oral erythromycin for treating patients with PR.[17,18] Four reviewers finally assent to have four related studies to be included in the quantitative analysis. (Figure 1)

CHARACTERISTICS OF THE INCLUDED STUDIES

We found four trials with 251 patients, met our inclusion criteria. All of them were RCT comparing the use of oral acyclovir with placebo or no treatment for treating patients with PR. A total of 127 patients received oral acyclovir and 124 patients received placebo or no treatment. In two of these trials, patients in the intervention group were prescribed oral acyclovir 800 mg five times daily; in another two studies, patients in intervention group were prescribed oral acyclovir 400 mg five times daily and 400 mg three times daily, respectively. For the two placebo-controlled studies, patients in the controlled group were prescribed one of these following agents as placebo; vitamin E or vitamin C (Table 1).

RISK OF BIAS OF THE INCLUDED STUDIES

Four reviewers assess the quality of the four studies using Jadad score and The Cochrane Collaboration's Tool for Assessing Risk of Bias. Their Jadad scores and the risk of bias summary with graph following The Cochrane Collaboration's tool for Assessing Risk of Bias are summarized in Table 2, Figure 2, respectively.

SUMMARY OF OUTCOMES

RESPONSE RATE TO TREATMENT AT THE FIRST WEEK

For this outcome, there were three trials included with 227 patients. The response rate was significantly higher in the acyclovir group than that of placebo group (RR 2.76; 95% CI, 1.86 to 4.09; $P<0.001$; $I^2=11\%$) (Figure 3).

RESPONSE RATE TO TREATMENT AT THE SECOND WEEK

For this outcome, there were three trials included with 232 patients. The response rate was significantly higher in the acyclovir group than

Table 2. Review Authors' Judgement About Each Risk of Bias for Each Included Study Using Jadad score.

	Daliri, 2008	Rassai et al, 2011	Ganguly, 2014	Das et al, 2015
Was the study described as randomized ?	1	1	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	0	1	1	1
Was the study described as double blind ?	1	0	1	0
Was the method of double blind described and was it	0	0	1	0
Was there a description of withdrawals and dropouts ?	0	0	0	1
Total score	2	2	4	3

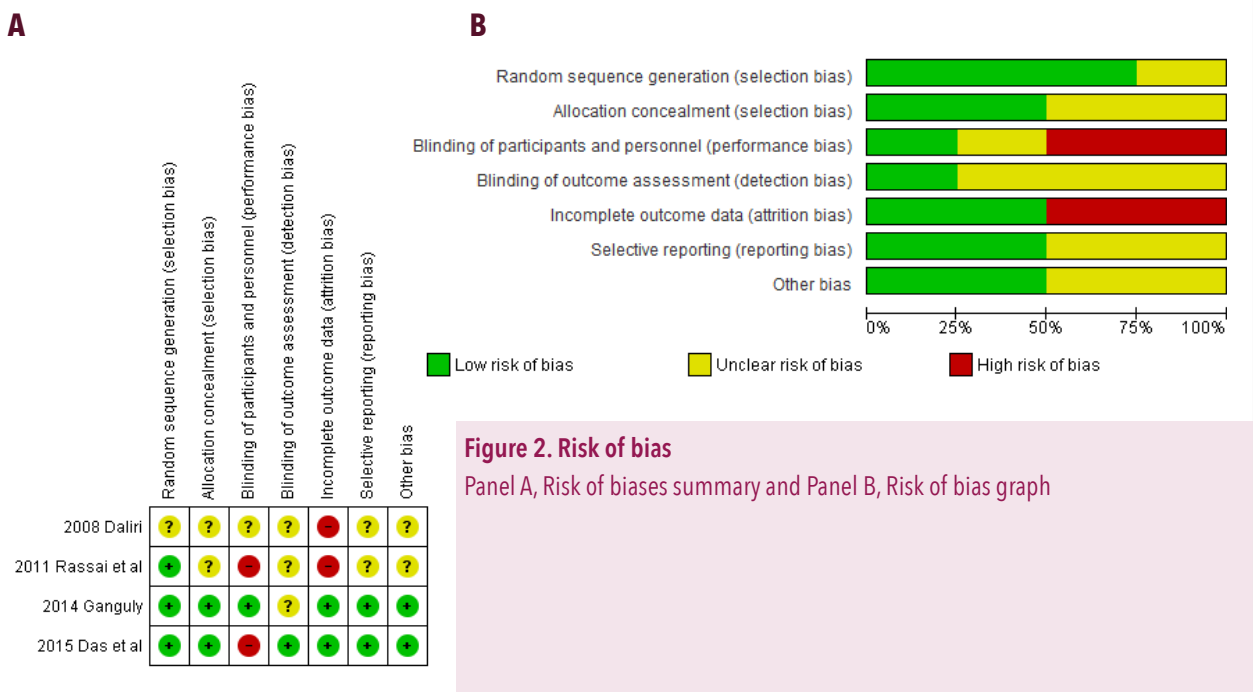


Figure 2. Risk of bias
Panel A, Risk of biases summary and Panel B, Risk of bias graph

that of placebo group (RR 2.19; 95% CI, 1.73 to 2.78; P<0.001; I^2=18%) (Figure 4).

OCCURRENCE RATE OF NEW SKIN LESION AFTER INITIATING THE TREATMENT FOR ONE WEEK

For this outcome, there were three trials included with 197 patients. The occurrence rate of new skin lesion was significantly lower in the acyclovir group than that of placebo group (RR 0.56; 95% CI, 0.41 to 0.77; P=0.004; I^2=21%) (Figure 5).

ADVERSE EFFECTS

Das et al, 2015 reported adverse effects that occurred in both acyclovir and placebo group. Of 12 patients received oral acyclovir, two patients

experienced increased sleep, three patients had headache, two patients had nausea and vomiting and one patient had metallic taste sensation. Of 12 patients in placebo group, only one patient experienced increased sleep.

NUMBER OF DAYS TAKEN TO CURE

Ganguly, 2014 reported time taken for clearance of skin lesion in acyclovir group. The study reported that if treatment started less than 7 days after the onset of the lesions, it took 5.3 days to clear. But if treatment started more than 7 days after the onset of lesions, it took 6.7 days to clear. However, the difference of results between the two groups were not significant (P=0.287).

SENSITIVITY AND SUBGROUP ANALYSIS

None of the studies individually affected the overall results either response rate to treatment at the first or the second week or occurrence rate of new skin lesion after initiating the treatment for one week. The subgroup analysis of low risk of bias trials comprising two RCTs. With 84 patients, occurrence rate of new skin lesion after initiating the treatment for one week was significantly lower in the acyclovir group than that of placebo group (RR 0.24; 95% CI, 0.07 to 0.83; P=0.02; I^2=0%) (Figure 6).

PUBLICATION BIAS

We generated the funnel plots of the treatment outcomes at the first and the second week as well as occurrence rate of new skin lesion after initiating the treatment for one week comparing oral acyclovir and placebo. However, the number of the studies using in the funnel plot were too few to assess for publication bias (Figure 7).

DISCUSSION

SUMMARY OF THE RESULTS

In this meta-analysis, of four trials involving 251 patients, oral acyclovir was superior to placebo or no treatment regarding response rate to treatment as well as reducing the occurrence rate of new skin lesion in treating patients with PR. Adverse events were reported from one trials including increased sleep, headache, nausea and vomiting and metallic taste sensation.

STRENGTH AND LIMITATIONS OF THE REVIEW

From our results, this is the first systematic review comparing oral acyclovir to placebo or no treatment in treating patients with PR. Our review complied to the Cochrane handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (PRISMA). We comprehensively searched through four electronic databases and also performed hand searching, no study seemed to be missed. In addition, the heterogeneity between the included trials was low.

Our study had several limitations. Firstly, our systematic review consisted of a small number of participants, since only four trials met our predefined inclusion and exclusion criteria. Secondly, the quality and risk of bias of each included trial were varied, there were two trials that have high risk of bias; Daliri and Rassai et al, because of their unclear description about methods of randomization and blinding.[19,20] Finally, each trial prescribed different dosage of acyclovir which may affect the results and cause heterogeneity among studies. Due to the mentioned limitations, implementation of our findings should be done with cautions.

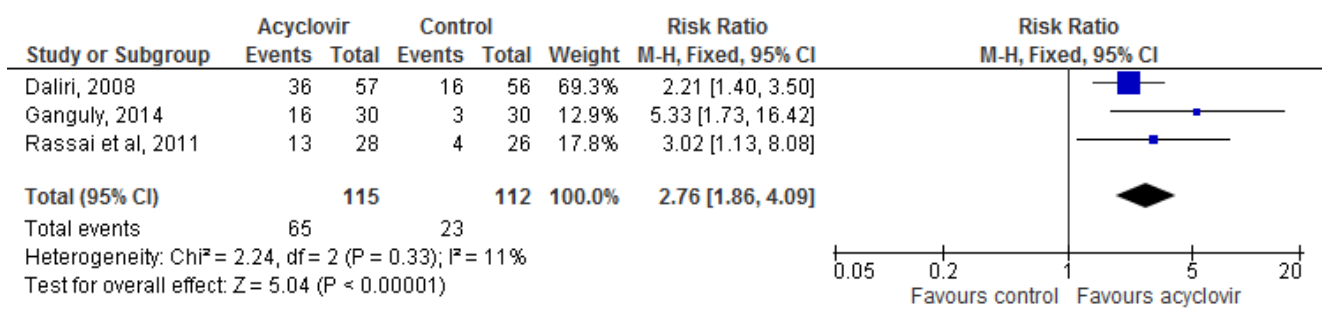


Figure 3. Response Rate to Treatment at the First Week

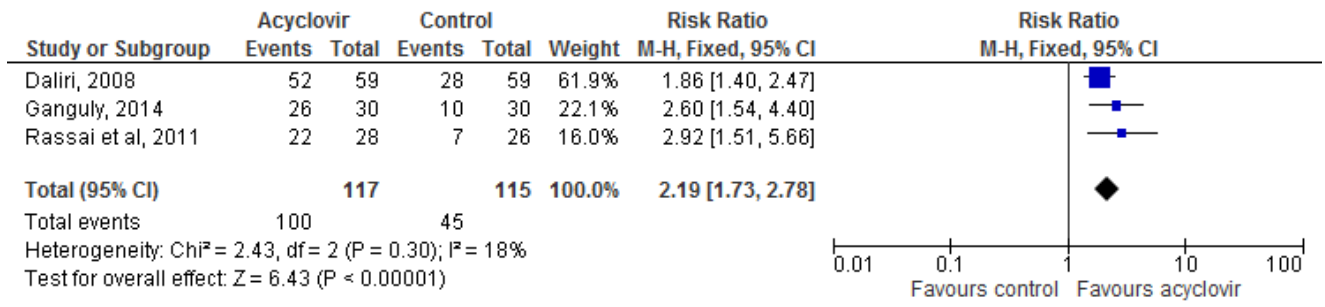


Figure 4. Response Rate to Treatment at the Second Week

COMPARISON TO OTHER STUDIES

We found that using oral acyclovir had superior effect to that of placebo or no treatment for response rate to treatment at the first and the second week as well as reducing occurrence rate of new skin lesion after initiating the treatment for one week. In addition, there were other two relevant studies; a cohort study and an RCT. A former study by Drago et al stated that oral acyclovir might be effective in patients with PR, which consorted with our results.[23] However, the latter study by Singh et al, concluded that oral acyclovir was not effective for PR.[24] The reason of this controversy might be due to a smaller number of patients (N=27) in the study by Singh et al which was also mentioned as its limitations in the study.

Aside from PR, there are several studies reported that oral acyclovir is effective in treatment of various diseases that are caused by virus, such as mucocutaneous herpes simplex, herpes zoster and varicella zoster. However, those studies also reported adverse effects of oral acyclovir comprising of the following systems; (i) central nervous system including headache, dizziness, delirium, ataxia and meningoencephalitis, (ii) respiratory and otolaryngeal system including pneumonia, otitis media, bronchitis, coryza and pharyngitis, (iii) digestive system including dyspepsia, diarrhea and nausea and vomiting and

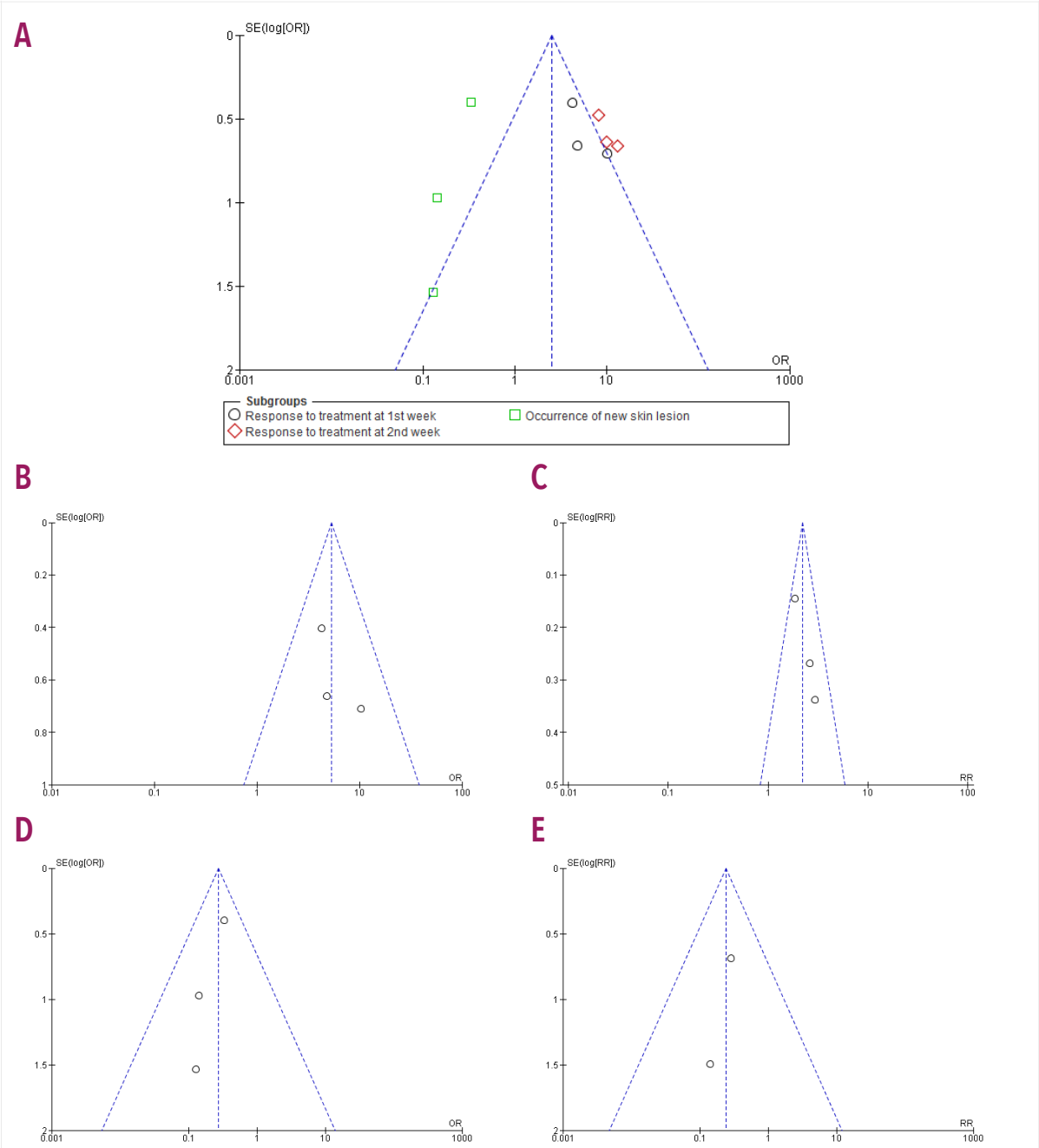


Figure 7. Publication bias

Panel A, Funnel plot comparison: main results

Panel B, Funnel Plot Comparison: Response Rate at the First Week

Panel C, Funnel Plot Comparison: Response Rate at the Second Week

Panel D, Funnel Plot Comparison: Occurrence rate of New Skin Lesion After Following in the First Week

Panel E, Funnel Plot Comparison for Subgroup Analysis: Occurrence rate of New Skin Lesion After Following in the First Week

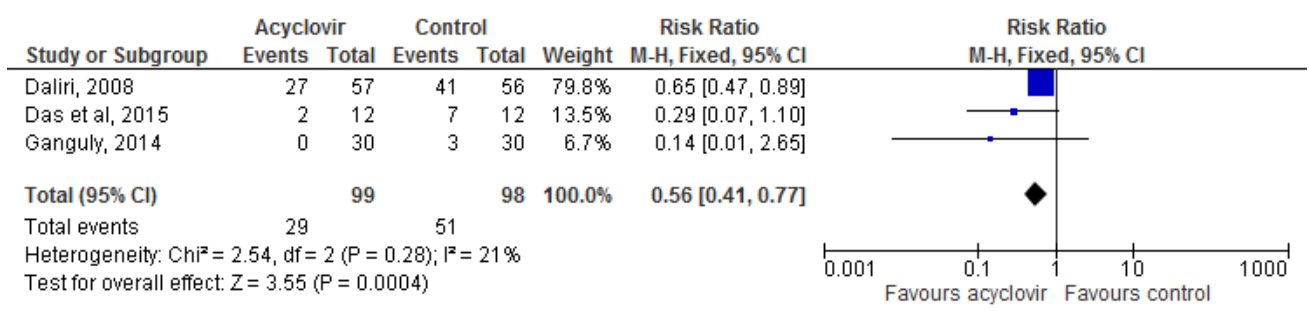


Figure 5. Occurrence Rate of New Skin Lesion After Following in the First Week

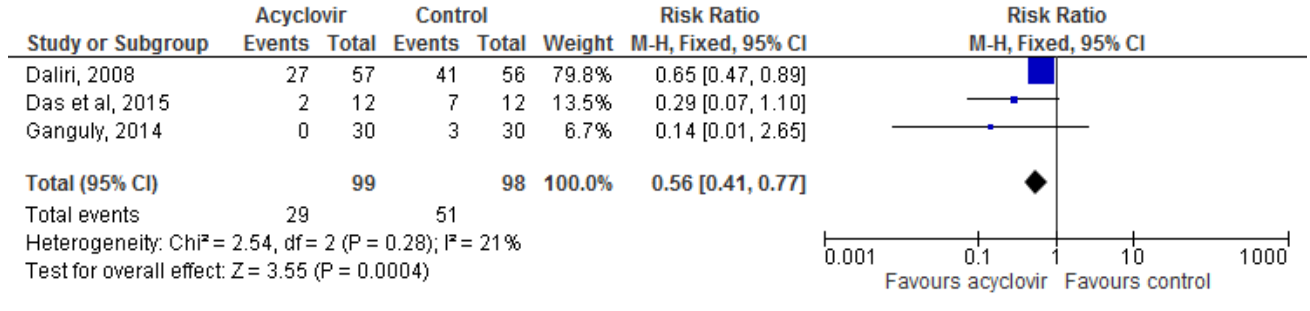


Figure 6. Subgroup Analysis of Trials That Have Low Risk of Bias: Occurrence Rate of New Skin Lesion After Following In the First Week

(iv) urinary system including renal colic, renal polyp, acute kidney injury and acute glomerulonephritis.[25-29] In our review, adverse effects were relatively less common than that of previous studies.

CONCLUSION AND IMPLICATION OF THE RESULTS

Oral acyclovir was superior to placebo in treating patients with PR in terms of response rate to treatment in the first and the second week and reducing occurrence rate of new skin lesion in the first week after the treatment started. PR can cure itself with no sequelae, acyclovir is still not a first-line therapy for treatment of PR.[30] Patient's education and reassurance that the lesion will resolve were all needed in general practice.[30,31] Thus, the use of acyclovir might depend on individual opinion of each physician and each patient's status at that moment.

Efficacy of acyclovir in the treatment of PR is likely to be related to its mechanism of DNA polymerase inhibition.[12] Early administration of high-dose acyclovir before 7 days after onset of lesions could shorten duration of the disease.[24] Nevertheless, there are complexities of using acyclovir, for instance, there are multiple kinetics of acyclovir including high protein binding ratio and poor oral bioavailability that interfere its effect in human body.[12] Multiple doses daily is

recommended due to its short half-life.[12] Moreover, one trial included in our meta-analysis showed that patients who received oral acyclovir had more adverse events than that of placebo group.[22] We also suggested that further RCT should perform subgroup analyses in different patient's status, such as immunosuppression. As well as a network meta-analysis that compared efficacy and safety of various interventions, including acyclovir, in treating patients with PR.

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COMPETING INTERESTS: This study has no competing on interest.
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