Effectiveness of Valganciclovir 900mg Versus 450mg for Cytomegalovirus Prophylaxis in Renal Transplantation: A Systematic Review and Meta-Analysis

Xin Wang, Hui Yang, Xiaodong Zhang, Xiangli Cui, Shihui Wang, Lihong Liu

Department of Pharmacy, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China.

Received, February 27, 2017; Revised, May 26, 2017; Accepted, May 26, 2017; Published May 26, 2017.

ABSTRACT - Objectives: Valganciclovir 900 mg/day is approved for cytomegalovirus (CMV) prophylaxis, but 450 mg/day is seems also effective. We systematically reviewed the efficacy and safety of low-dose versus high-dose valganciclovir prophylaxis in renal transplantation recipients. **Methods**: An electronic search was conducted up to November 29, 2016. The primary outcomes were incidences of CMV, CMV disease, mortality and opportunistic infection. The second outcomes were acute rejection, allograft loss, adverse drug reaction (ADR). **Results**: 7 cohort studies, all with high quality involving (1431 patients) were included. There was no significant difference of the incidence of following CMV disease (1271 patients, odds ratio [OR] 0.74, 95% confidence interval [CI], 0.38-1.43, *p*=0.36), acute rejection (1343 patients, OR 0.77, 95%CI 0.53-1.14, *p*=0.19), allograft loss (1271 patients, OR 0.64, 95%CI 0.31-1.35, *p*=0.24), mortality (1271 patients, OR 0.55, 95%CI 0.20-1.47, *p*=0.23) and opportunistic infections (OI) (985 patients, OR 0.76, 95%CI 0.52-1.10, *p*=0.14) between the low-dose and the high-dose valganciclovir prophylaxis. And no significant difference was observed for premature valganciclovir discontinuation (1010 patients, OR 0.81, 95%CI 0.52-1.25, *p*=0.33) and the incidence of leukopenia (1082 patients, OR 0.65, 95%CI 0.34-1.22, *p*=0.18) between the two regimens. **Conclusion**: 450 mg and 900 mg doses of valganciclovir are equipotent for CMV universal prophylaxis. CMV 450 mg prophylaxis should be used for renal transplant recipients.

INTRODUCTION

In organ transplant recipients, the risk of opportunistic infection is significantly higher than in the general population as a result of exposure to chronic immunosuppression. Cytomegalovirus (CMV) remains a leading cause of such opportunistic infection within the first year of kidney transplantation (1), and is a major contributor to morbidity and mortality (2). Without routine preventative therapy with anti-viral agents, CMV diseases (CMV infection accompanied by clinical signs and symptoms) occurs in about 20%–60% of cases, mostly within the first three months after transplantation (3,4). Currently, two standard approaches have been considered acceptable for preventing CMV infection (the presence of CMV replication regardless of symptoms) after kidney transplantation: universal prophylaxis approach and pre-emptive therapy. According to the recent meta-analysis by Rawal et al (5), prophylactic approach might be superior to pre-emptive approach in preventing CMV infection within the first year of kidney transplantation, and that the risk of developing acute rejection might be lower with prophylactic approach but there was no significant difference in graft loss or mortality with either approach. Antiviral drugs for CMV prophylaxis are valganciclovir (VGC) (oral), ganciclovir (oral or intravenous), or valaciclovir (oral or intravenous) in renal transplant recipients (RTR) (6).

The efficacy of ganciclovir, VGC and valacyclovir prophylaxis has been demonstrated in randomized clinical trials (RCTs) (7-10).

Corresponding Author: Lihong Liu; Pharmacy Department of Beijing Chao-Yang Hospital, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing, China, Email: liulihong@bjcyh.com.

Abbreviations: ACCP, American College of Clinical Pharmacy; ADR, adverse drug reactions; AR, acute rejection; ATG, antithymocyte globulin; BSX, basiliximab; CI, confidence interval; CMV, cytomegalovirus; HD, high-dose; IL-2ra, an interleukin-2 receptor antagonist; IL-10, interleukin 10; LD, low-dose; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NA, not available; NOS, Newcastle-Ottawa Scales; NR: not reported; OI, opportunistic infections; OR, odds ratio; P, prednisone; RCT, randomized controlled trials; RTR, renal transplantation recipients; SRL, sirolimus; TAC, tacrolimus; VGC, valganciclovir.

Among them, VGC is the most commonly used for prophylaxis for its improved bioavailability and its lower pill burden (7,10). When used for prophylaxis, the usual dose of VGC is 900 mg a day, versus treatment dose which is 900 mg twice daily (both should be adjusted for renal function). Recently, several new studies directly comparing VGC 900 mg with VGC 450 mg daily in RTR have been published (11-17), and a meta-analysis compared two regimens only be carried in sold organ transplantation (18). Therefore, it is important and necessary to directly assess the benefits and the risks between VGC 450 mg and VGC 900 mg in RTR in order to produce an evidence-based recommendation for clinical practice.

METHODS

PubMed, Web of Science, Cochrane, Embase were systematically searched from their inception through November 29, 2016. References of the retrieved articles were also searched for additional studies. In addition, available abstracts from the American Transplantation Congress and the American College of Clinical Pharmacy (ACCP) conferences were searched. The following search terms were utilized: ((VGC) OR (ganciclovir L-valyl ester) OR (VGC hydrochloride) OR (Valcyte) OR (Valcyt)) AND ((Cytomegalovirus) OR (CMV)).

Study selection

Inclusion criteria: Articles reported the comparative outcomes of patients treated with the two different dosage regimens (450 mg and 900 mg daily) of VGC; prospective study, retrospective study and RCT. All risk patients for CMV disease were included in our research, including low-risk (donor-seronegative, recipient-seronegative (D–/R–)), moderate-risk (D–/R+ or D+/R+) and high-risk CMV (donor-seropositive, recipient-seronegative (D+/R–)) constellations.

Exclusion criteria: Studies on efficacy of VGC without control group, studies comparing different length of prophylaxis, results of studies with >1 publication were considered once.

Data extraction

The following data were extracted from each study: the characteristics of each study (author, study design, publication year, country), patient population (numbers of patients, CMV sero-status), prophylaxis duration, length of follow up, induction therapy, maintenance immunosuppressive therapy, clinical outcomes (CMV infection, CMV disease, opportunistic infections [OI], acute rejection [AR], allograft loss, and mortality, premature VGC discontinuation, leukopenia) of the two groups in each study.

Primary outcomes

1. CMV infection: the presence of CMV replication regardless of symptoms (this should be distinguished from latent CMV). Depending on the method used, CMV infection can be termed as CMV DNAemia or RNAemia, CMV antigenemia (viral antigen testing) and CMV viremia (culture) (6).
2. CMV disease: CMV infection accompanied by clinical signs and symptoms. CMV disease is categorized into i) CMV syndrome, which manifests as fever and/or malaise, leukopenia or thrombocytopenia, and ii)tissue-invasive CMV disease. CMV infection without any clinical manifestations should be labeled “asymptomatic CMV infection (6).
3. Mortality
4. Opportunistic infections

Secondary outcomes

1. Acute rejection: Acute allograft rejection reported on graft biopsy within 12 months after transplant (5).
2. Allograft loss: Allograft failure requiring

dialysis or repeat transplant within 12 months (5).

3. Adverse drug reactions (ADR): Premature VGC discontinuation and leukopenia.

Quality assessment

Two reviewers (X.W and H.Y) independently evaluated methodological quality. A third review author (X.L.C) resolved any disagreements, and a final consensus was reached by all the authors. RCTs were appraised for methodological quality using the criteria developed by the Cochrane risk of bias tool. Observational studies assessed the quality using the Newcastle-Ottawa Scales (NOS) (19).

STATISTICAL ANALYSIS

Taking the 900 mg dose as the reference, we used the Mantel-Haenszel method to estimate the pooled Odds Ratio (OR) and 95% Confidence Interval (CI) for each outcome (20) for both doses. The Q statistic method and the I-squared method were used to assess heterogeneity. All data were pooled by the use of random-effects model for subgroup analyses in every outcome. In order to evaluate the stability of results without estimation bias from individual study, sensitivity analysis was performed by exclusion of each study one by one. Egger regression was used to evaluate publication bias (21). All statistical analyses were performed using Review Manager for Windows (version 5.3).

RESULTS

Literature search

Our search resulted in 3734 titles and abstracts. A total of 3621 articles were excluded after the review of abstracts, and 113 articles remained for full-text analysis. 106 articles were excluded after full-text review. Overall, 7 studies with 1431 patients were identified that were eligible for inclusion in the meta-analysis (11-17). The whole literature search process was summarized in Figure 1.

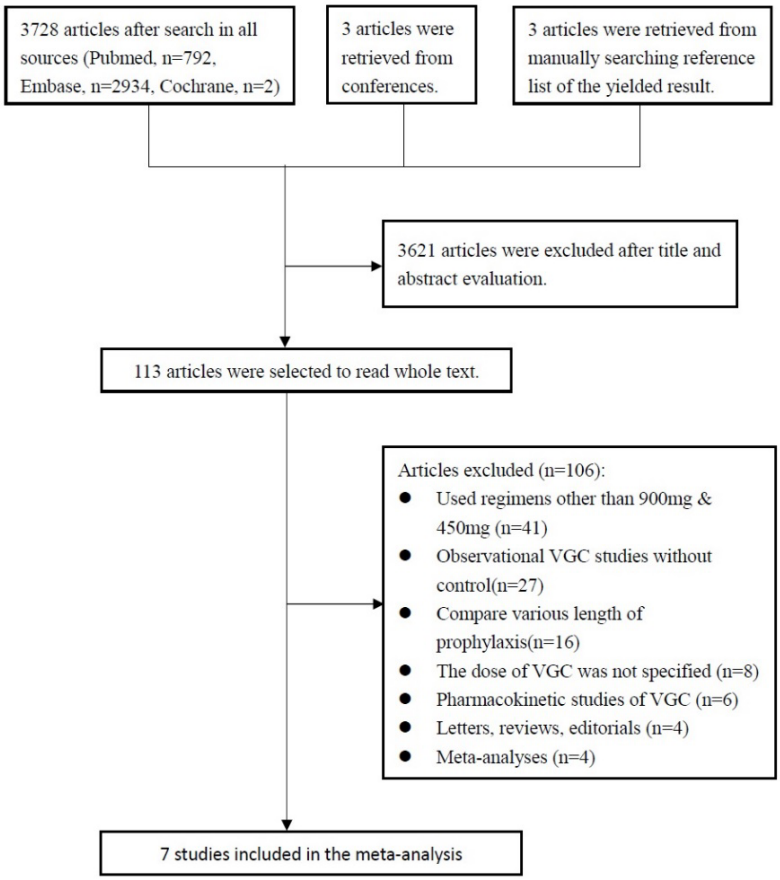

Figure 1. Flow chart depicting the selection process of studies included in the meta-analysis.

Study description

There was no RCT reporting on a direct comparison of VGC 450mg versus VGC 900 mg, therefore, this meta-analysis was based on the comparison of observational cohort studies. Three of these studies reported on high-risk RTR (13,14,17). Three studies (12,15,16) reported on moderate-risk RTR, and one study (11) reported on all risk RTR. The characteristics of the eligible studies were presented in Table 1. The clinical outcomes of included studies were presented in Table 2a and Table 2b.

Quality of included studies

Since there was no RCT comparing the two regimens, risk of bias was assessed using the NOS in all studies. Eight factors were used to assess study quality according to NOS. Included observational studies were of high quality, 2 studies (11,12) missed two indicators, and the other 5 studies (13-17) were missed one indicator. The results presented in Supporting Table 1 showed that all observational studies were high quality.

CMV infection

Two articles reported the incidence of CMV infection, and therefore, statistical analysis was not applied due to limited available data. Gruber et al (11) reported that the incidence of CMV infection was 5.0% with VGC 450 versus 25.0% with VGC 900 mg (p=0.02) no matter what kind of risk for CMV. But Huang et al (17) got the opposite conclusion that the incidence of CMV infection was 21.0% with VGC 450 mg versus 19.0% in VGC 900 mg (p=0.21). And other included studies didn't report the relevant result.

CMV disease

A total of 5 studies evaluated the incidence of CMV disease (12-16). Incidence of CMV disease showed that there was no significant difference between VGC 450 mg and 900 mg (1271 patients, OR 0.74, 95%CI 0.38-1.43, p=0.36; Figure 2). In D+/R− high risk studies (2 studies, n=327), the corresponding value was 0.95 (95%CI: 0.28-3.19, p=0.94). In moderate risk studies (3 studies, n=944), the corresponding value was 0.56 (95% CI: 0.24-1.32, p=0.19). Subgroup analyses indicated no statistical difference in incidence of CMV disease between the two regimens. No significant heterogeneity was found among the studies (I^2=44%, p=0.13). No significant publication bias was detected by an Egger regression (p=0.127). The results of sensitivity analysis showed that the result was reliable after exclusion of individual study one by one.

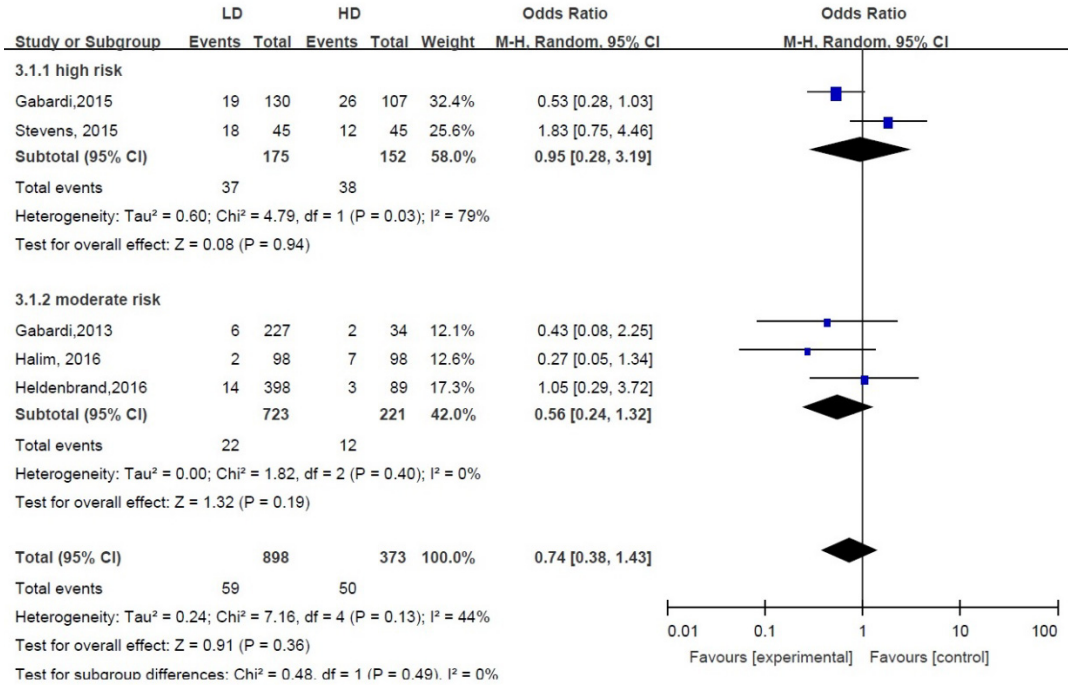

Figure 2. Forest plot depicting the odds ratios of CMV disease with LD versus HD.

Acute rejection

A total of 6 studies evaluated the AR rate (11-16). Incidence of AR showed that there was no significant difference between VGC 450 mg and VGC 900 mg (1343 patients, OR 0.77, 95%CI 0.53-1.14, p=0.19; Figure 3). In high risk studies (2 studies, n=327), the corresponding value was 0.73 (95%CI: 0.20-2.67, p=0.63). In moderate risk studies (3 studies, n=944), the corresponding value was 0.73 (95%CI: 0.46-1.16, p=0.18). Gruber et al (11) reported that the incidence of AR was 5.0% with VGC 450 mg versus 8.3 % with VGC 900 mg (p=0.65) in all risk study (n=72). Subgroup analyses also indicated no statistical difference in incidence of acute rejection between the two regimens. No significant heterogeneity was found among the studies (I^2=0%, p=0.72). No significant publication bias was detected by an Egger regression (p=0.150). The results of sensitivity analysis showed that the result was reliable after exclusion of individual study one by one.

Allograft loss

A total of 5 studies evaluated the allograft loss rate (12-16). Incidence of allograft loss showed no significant difference between VGC 450 mg and VGC 900 mg (1271 patients, OR 0.64, 95%CI 0.31-1.35, p=0.24; Figure 4). In high risk studies (2 studies, n=327) the corresponding value was 0.54 (95%CI: 0.09-3.30, p=0.51). In moderate risk studies (3 studies, n=944) the corresponding value was 0.67 (95%CI: 0.29-1.50, p=0.33). Subgroup analyses also indicated no statistical difference in incidence of allograft loss between the two regimens. No significant heterogeneity was found among the studies (I^2=0%, p=0.96). Egger's test showed no publication bias, and the p value was 0.096, which indicated no statistically significant difference. The results of sensitivity analysis showed that the result was reliable.

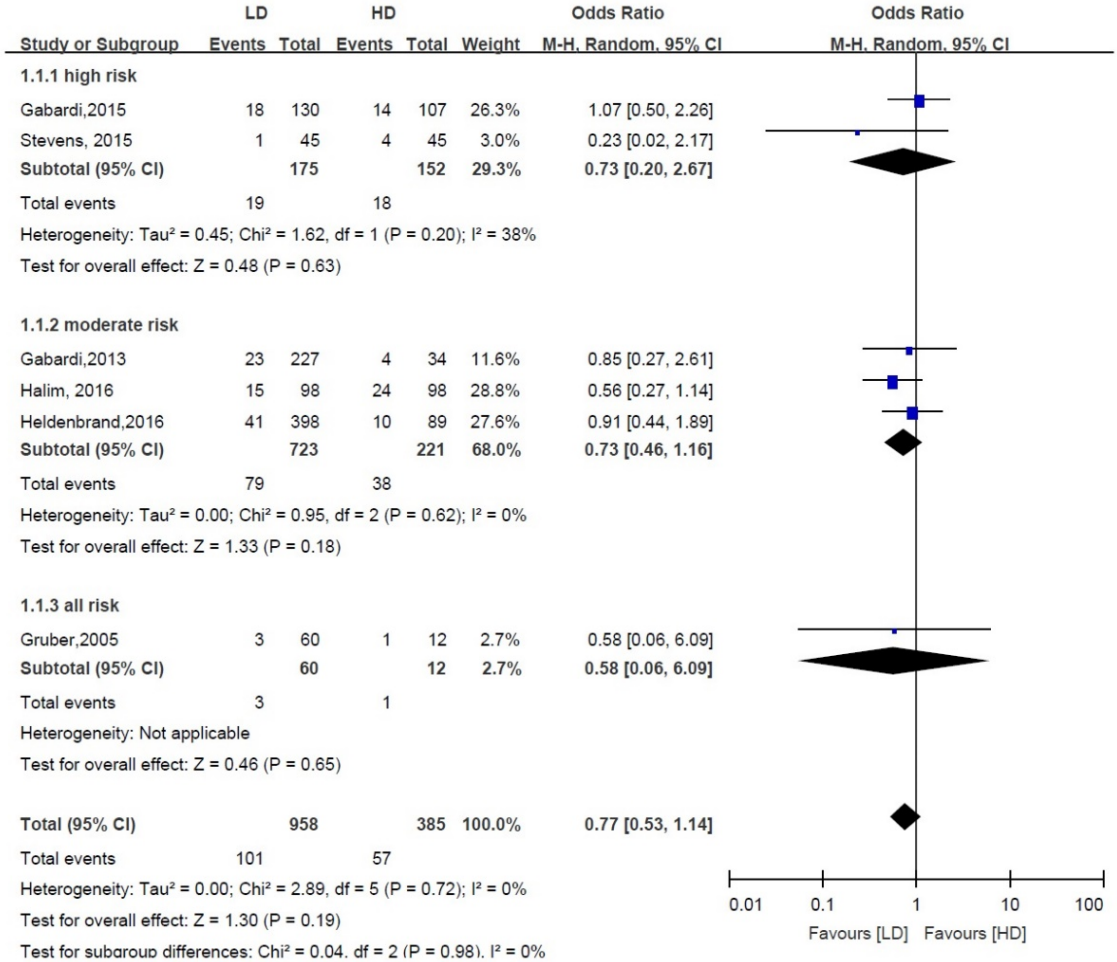

Figure 3. Forest plot depicting the odds ratios of AR with LD versus HD.

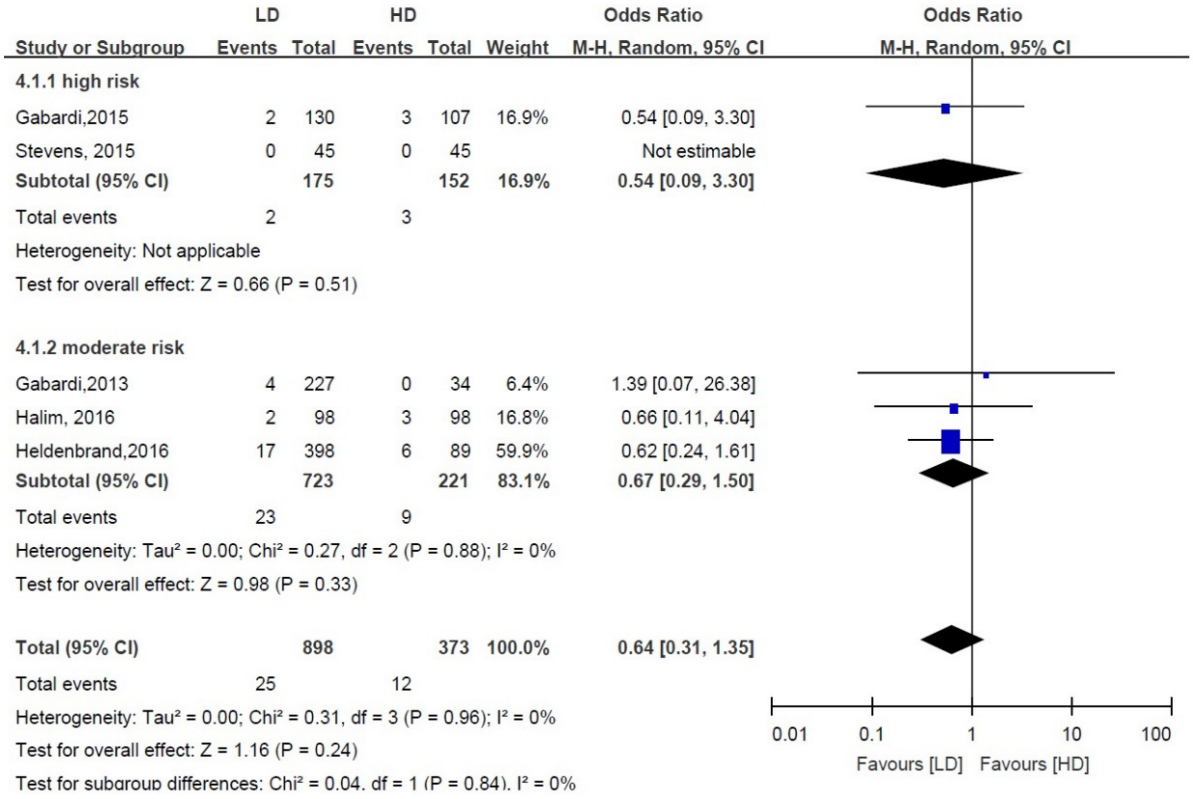

Figure 4. Forest plot depicting the odds ratios of allograft loss with LD versus HD.

Mortality

Pooled outcomes of 5 studies (12-16) that showed the OR of mortality in all renal transplant recipients who received VGC 450 mg or 900 mg was 0.55 [n=1271, 95%CI 0.20-1.47, *p*=0.23; Figure 5]. The corresponding value was 0.19 (95%CI: 0.02-1.65, *p*=0.13) in high risk (2 studies, n=327) studies, and the corresponding value was 0.72 (95%CI: 0.24-2.20, *p*=0.57) in moderate risk (3 studies, n=944) studies. Subgroup analyses also indicated that there was no statistical difference in incidence of mortality between the two regimens. No significant heterogeneity was found among the studies (I^2=0%, *p*=0.67). No significant publication bias was detected by an Egger regression (*p*=0.423). The results of sensitivity analysis showed that the result was reliable after exclusion of individual study one by one.

Opportunistic infections

A total of 3 studies evaluated the allograft loss rate (12,13,16). Incidence of OI showed no significant difference between VGC 450 mg and VGC 900 mg (985 patients, OR 0.76, 95%CI 0.52-1.10, *p*=0.14; Figure 6). Gabardi et al (12) reported that the incidence of OI was 13.7% with VGC 450 mg versus 17.6 % with VGC 900 mg (*p*=0.597) in all risk study (n=72). In moderate risk (2 studies, n=748) studies the corresponding value was 0.68 (95%CI: 0.43-1.08, *p*=0.10). Subgroup analyses also indicated no statistical difference in incidence of OI between the two regimens. No significant heterogeneity was found among the studies (I^2=0%, *p*=0.75). Significant publication bias was detected by an Egger regression (*p*=0.002).

Premature VGC discontinuation

Pooled outcomes of 4 studies (13-16) showed that there was no statistically significant premature VGC discontinuation to VGC 450 mg or 900 mg [n=1010, OR 0.81, 95%CI 0.52-1.25, *p*=0.33; Figure 7]. In high risk studies (2 studies, n=327) the corresponding value was 0.99 (95%CI: 0.51-1.95, *p*=0.98). In moderate risk studies (2 studies, n=683) the corresponding value was 0.82 (95%CI: 0.30-2.22, *p*=0.70). Subgroup analyses also indicated that there was no statistical difference in incidence of premature VGC discontinuation between the two regimens. No

significant heterogeneity was found among the studies (I^2=3%, p=0.38). Egger's test showed no publication bias, and the p value was 0.223, which indicated no statistically significant difference. The results of sensitivity analysis showed that the result was reliable after exclusion of individual study one by one.

Leukopenia

A total of 5 studies evaluated the incidence of leukopenia (11),(13-16). The incidence of leukopenia with VGC 450 mg or 900 mg regimen was no statistically significant (n=1082, OR 0.65, 95%CI 0.34-1.22, p=0.18; Figure 8). In high risk studies (2 studies, n=327), the corresponding value was 0.60 (95%CI: 0.16-2.26, p=0.45). In moderate risk studies (2 studies, n=683) the corresponding value was 0.82 (95%CI: 0.37-1.85, p=0.64). Gruber et al (11) reported that the incidence of leukopenia was 0.0% with VGC 450 mg versus 16.7 % with VGC 900 mg (p=0.03) in all risk study (n=72). In high and moderate risk groups, the incidence of leukopenia indicated no statistical difference between the two regimens. Significant heterogeneity was found among all the studies (I^2=74%, p=0.004). No significant publication bias was detected by an Egger regression (p=0.485).

DISCUSSION

To date, this is the most comprehensive systematic review and meta-analysis to compare high-dose and low-dose VGC prophylaxis on CMV disease outcomes in all at-risk renal transplant recipients. The comparison of VGC 450 mg and 900 mg daily showed similar efficacy for preventing CMV disease independent of CMV sero-status at least within the first year of renal transplantation. And we found that there were no statistical differences between the 450 mg and 900 mg daily dosing with respect to AR, allograft loss, mortality, OI, premature VGC discontinuation and leukopenia.

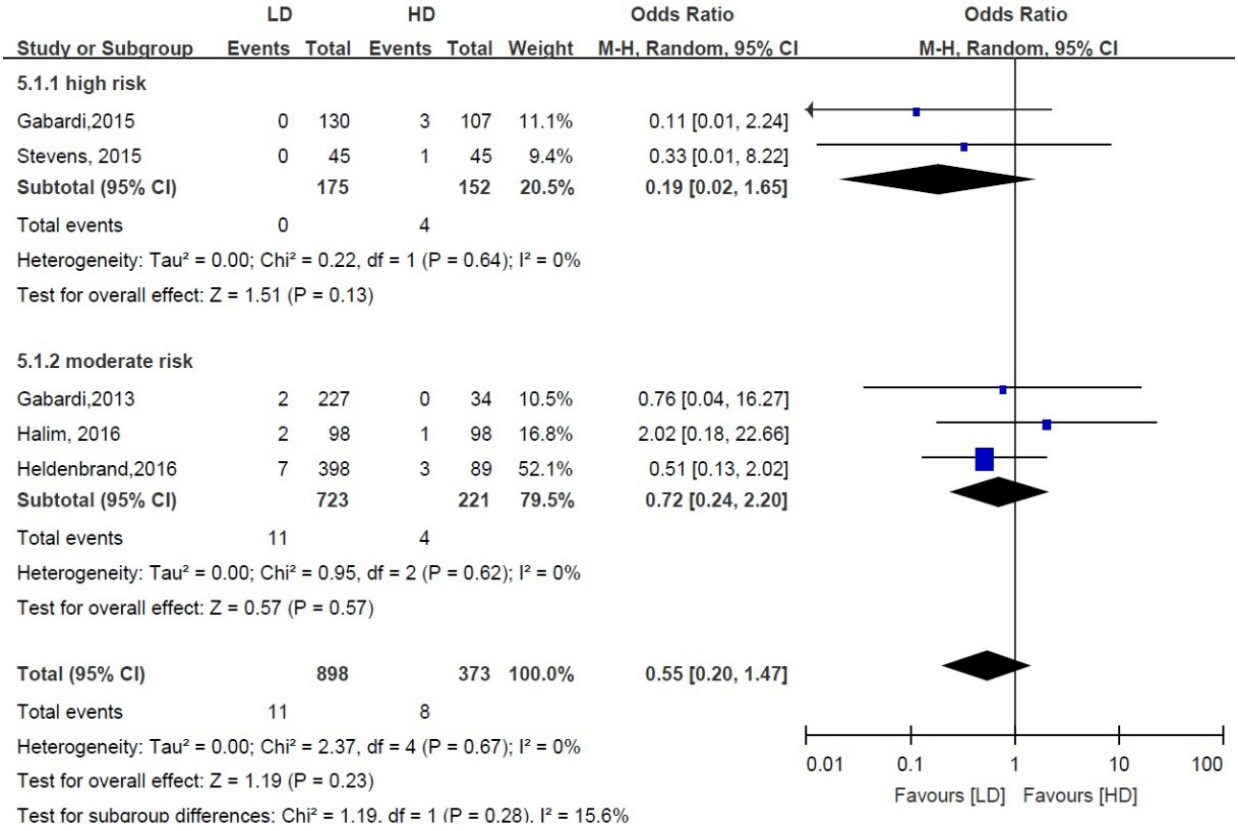

Figure 5. Forest plot depicting the odds ratios of mortality with LD versus HD

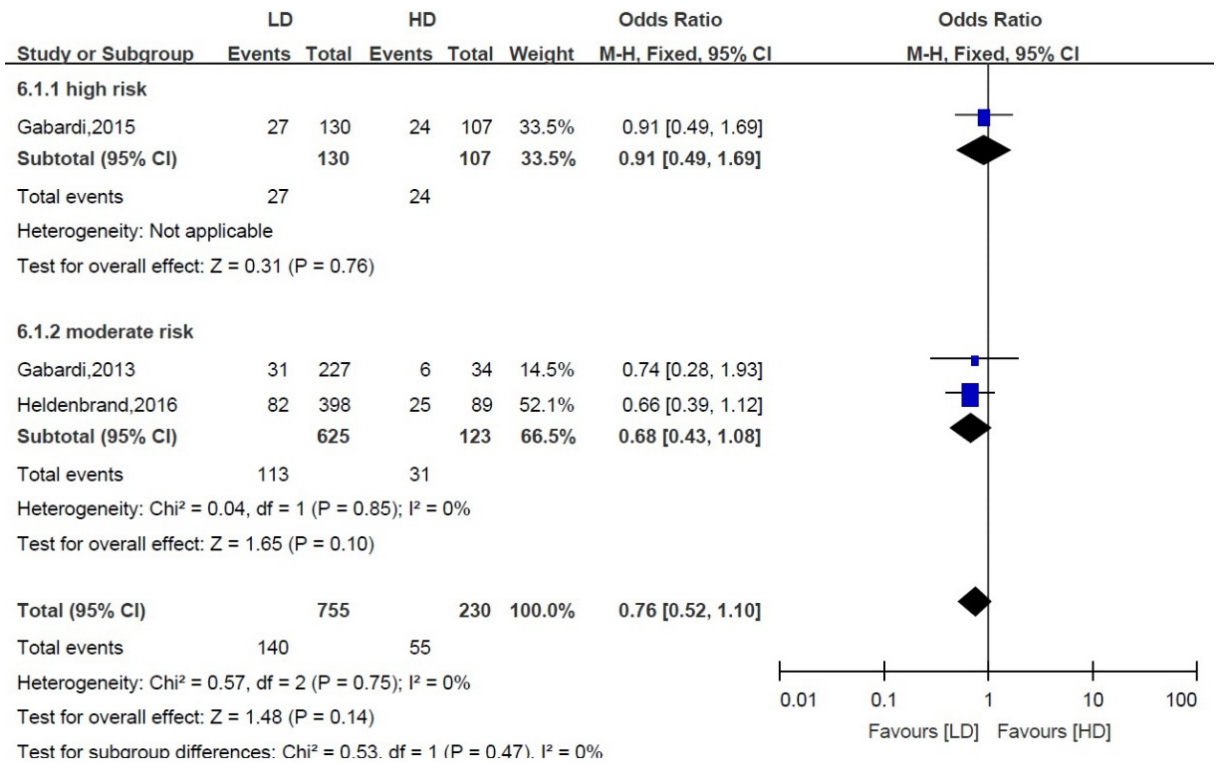

Figure 6. Forest plot depicting the odds ratios of opportunistic infections with LD versus HD

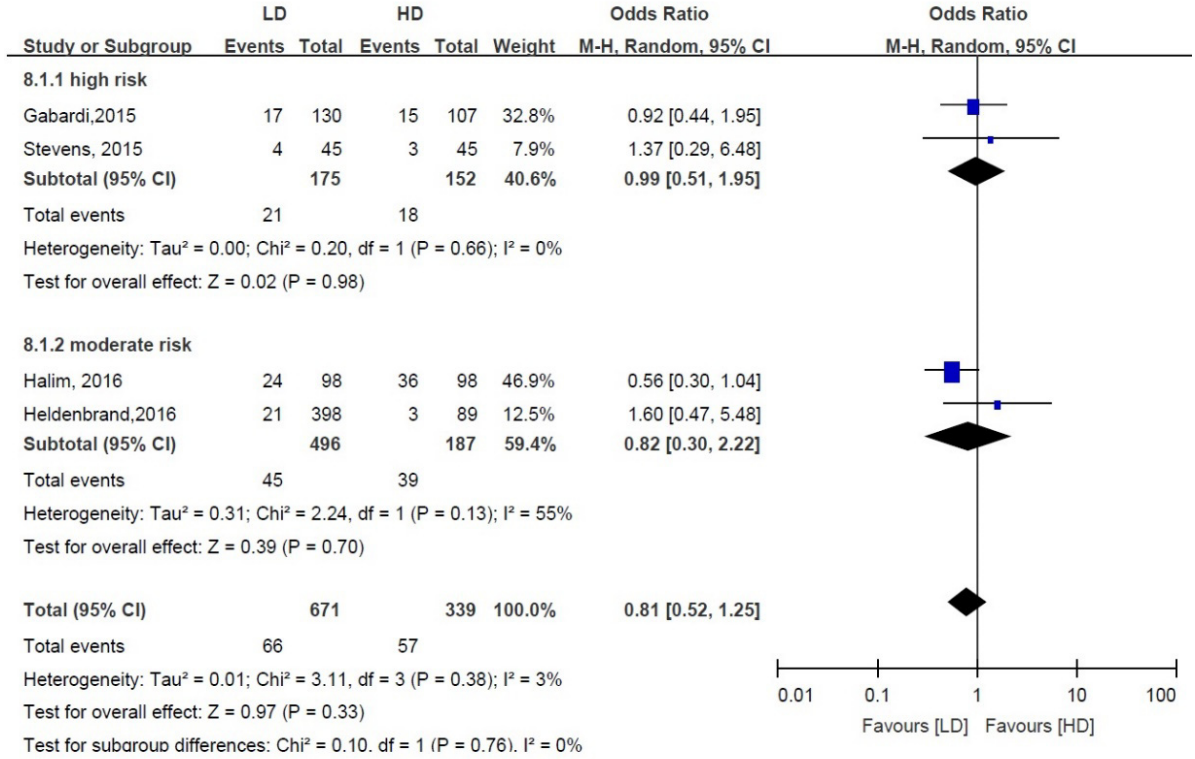

Figure 7. Forest plot depicting the odds ratios of premature valganciclovir discontinuation with LD versus HD

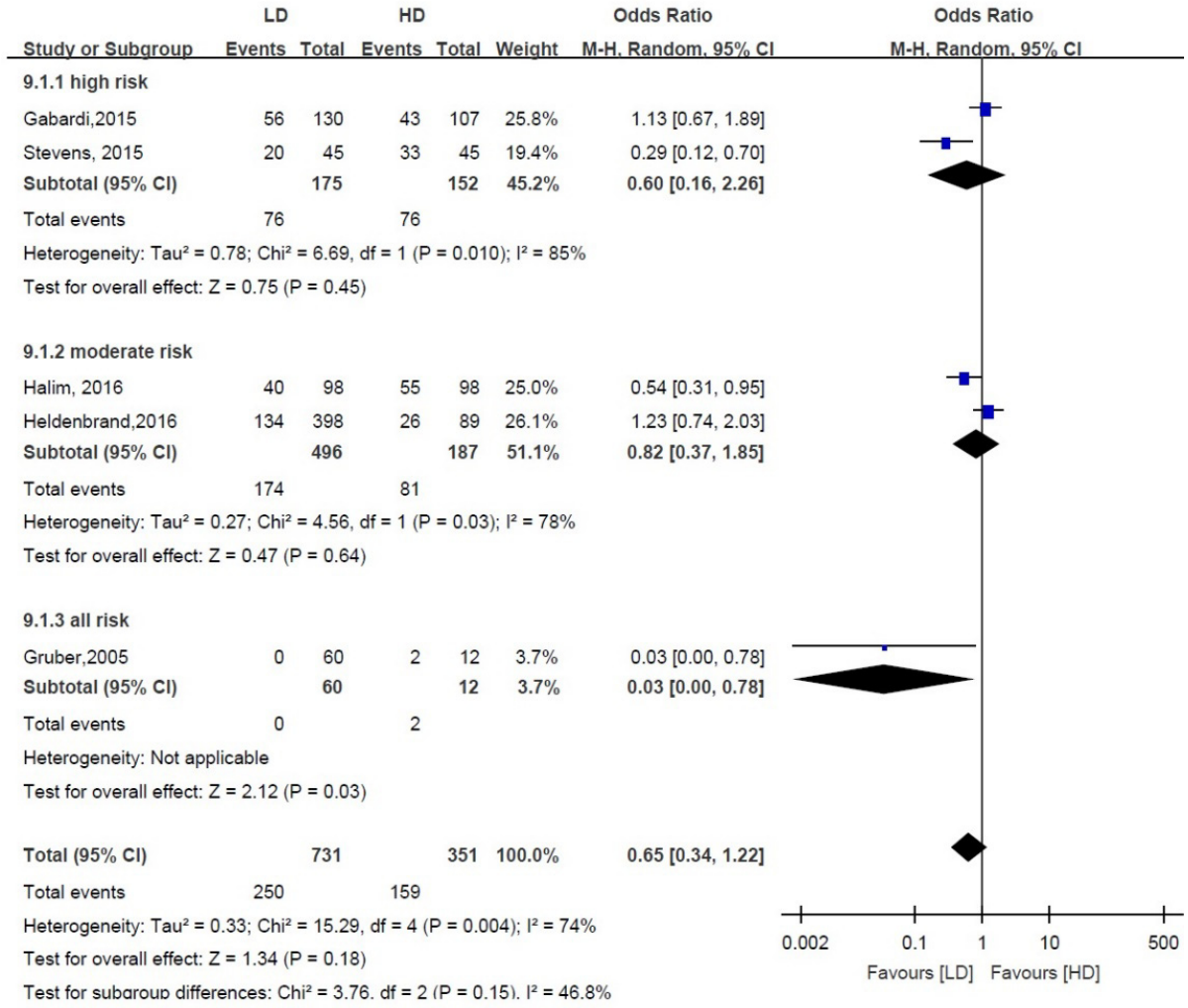

Figure 8. Forest plot depicting the odds ratios of leukopenia with LD versus HD

Gruber et al (11) reported that the incidence of CMV infection was higher in VGC 900 mg than VGC 450 mg in all "at risk" patients. This suggested that the low dose could be associated with better CMV infections prevention. Paradoxical as it seems, a biological explanation could be that patients receiving 900 mg would be more prone to CMV infections than the ones receiving 450 mg. One theory proposed by Singh et al might help to explain this (22), he hypothesized that high-dose VGC provide such a significant antiviral response that it might not allow the host immune system to be exposed to low-level CMV antigenemia. Therefore, once the prophylaxis was completed, these immunologically patients might be more vulnerable to CMV infections because they were unable to mount specific T-cell responses against CMV. This is an interesting and important finding, however, it is inconsistent for the current studies involved. Further data should be generated for a better understanding of this issue.

A detailed previous pharmacokinetic study of low-dose VGC suggests that it provided ample drug exposure for effective CMV prophylaxis in kidney transplant recipients (23). In a meta-analysis, Kalil et al (18) demonstrated that the high-dose and low-dose regimens provided equivalent efficacy for CMV universal prophylaxis after organ transplantation (97% statistical power). The result showed that the VGC 450 mg and 900 mg daily were similar efficacy for preventing CMV disease in patients who received antiviral prophylaxis in all risk

patients. The equivalent efficacy for preventing CMV disease between two regimens may be attributed to reliable assay for monitoring CMV and effective treatment for CMV infection.

Another important finding of our meta-analysis was that the AR, allograft loss and CMV-related mortality were not significantly different using either prevention regimen. The meta-analysis showed that there was no significantly different in the rate of AR between VGC 450 mg daily and 900 mg daily; thus, the similar rejection rate would be a consequence of the similar rate of CMV disease, which was well known to be associated with rejection (24). No significant difference was found in the mortality according to the prevention regimen, this could be due to inclusion of patients with different CMV sero-status, or due to the low rate of events (25).

CMV has immunomodulatory effects through an encoded homologue of interleukin 10 (IL-10) with high affinity for the human IL-10 receptor that leads to decreased T-cell mitogen-stimulated proliferative activity, proinflammatory cytokine production, and human leukocyte antigen surface expression (26). This may result in increased predisposition to opportunistic infections (27, 28). Three studies described opportunistic infections (12,13,16). They found that there was a numerically higher prevalence of opportunistic infections seen in the high-dose group but no significant differences was found between the in two groups.

VGC can result in adverse effects. The prevalence of significant leukopenia was reported as occurring in up to 58% of kidney transplant recipients (29, 30). This side effect is clearly unwelcome in a transplant host who is already severely immunosuppressed and may have splenic dysfunction, which can lead to more serious infections in the first few months after transplantation. Multiple immunosuppressive drugs and other medications were encountered in causing significant leukopenia in these patients (29-32). Our meta-analysis found that there was no statistically significant difference in the leukopenia between the two doses. We would like to evaluate the actual risk of other infections with drug-induced leukopenia, but unfortunately, most studies did not report other bacterial or fungal infections during or other drugs known for causing leucopenia (mycophenolate and induction). The high risk of leukopenia in the two groups demonstrated the severity of these attacks in kidney transplant recipients. Moreover, these attacks were treated by reduction or stopping of VGC, which interrupted the prophylactic effect of the drug against CMV disease. Less leukopenia attacked led to a prolonged and steadier prophylactic drug effect and consequently less CMV disease. This underscores the importance of an uninterrupted course of therapy.

We noted the following limitations: First, there were only 7 studies included in this meta-analysis, and all included studies were cohort studies not RCTs which might bring some of the bias of estimation. Second, the time of follow up was not long enough, and the shortest time was only 6 months. Third, systematic reports of bacterial or fungal infections were not seen in most studies, this did not allow us to evaluate the direct consequences of leukopenia. Fourth, adverse events induced by VGC were not captured at all centers and could not be evaluated, which might have influenced breakthrough CMV and/or CMV resistance rates.

This study aimed to compare the clinical impact of low-dose and high-dose VGC prophylaxis regimen in renal transplantation recipients. In conclusion, the prevention of CMV disease was equivalent with both doses. And significant difference was not found in the risk of leukopenia and premature between VGC 450 mg daily and VGC 900 mg daily. Further data should be generated for a better understanding of the two regimens in the renal transplant population. All in all, VGC 450 mg appeared to be as beneficial and safe as VGC 900 mg for CMV prophylaxis in renal transplantation.

ACKNOWLEDGMENTS

We thank all the original authors of the included studies for their wonderful work. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Each author's specific contributions to the work

The experiments were designed by X.W, H.Y, L.H.L and performed by X.W, H.Y. The data were analyzed by X.D.Z, X.L.C, S.H.W. The

manuscript was written by X.W, H.Y and revised by X.L.C and S.H.W.

& These two authors contributed equally to this work and should be considered co-first authors.

REFERENCES

1. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med, 2007; 357 (25): 2601–14.
2. Ho M. Cytomegalovirus infection and indirect sequelae in the immunocompromised transplant patient. Transplant Proc, 1991; 23: 2–7.
3. Hibberd PL, Tolkoff-Rubin NE, Cosimi AB, et al. Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. Transplantation, 1992; 53 (1): 68–72.
4. Fishman JA, Rubin RH. Infection in organ-transplant recipients. New Engl J Med, 1998; 338 (24): 1741–1751.
5. Rawal BB, Shadrou S, Abubacker F, et al. A systematic review and meta-analysis of prophylactic versus pre-emptive strategies for preventing cytomegalovirus infection in renal transplant recipients. Int J Organ Transplant Med, 2012; 3 (1): 10-7.
6. Razonable RR, Humar A; AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplantation. Am J Transplant, 2013; 13 Suppl 4: 93-106.
7. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of VGC vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant, 2004; 4 (4): 611–620.
8. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. The Oral Ganciclovir International Transplantation Study Group [corrected]. Lancet, 1997; 350: 1729–1733.
9. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group, N Engl J Med 1999; 340 (19): 1462–1470.
10. Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. Am J Transplant, 2010; 10 (5): 1228–1237.
11. Gruber SA, Garnick J, Morawski K, et al. Cytomegalovirus prophylaxis with valganciclovir in African-American renal allograft recipients based on donor/recipient serostatus. Clin Transplant, 2005, 19 (2): 273-278.
12. Gabardi S, Cross R, DePiero K, et al. Prevention of cytomegalovirus with valganciclovir 450 mg daily vs. 900 mg daily in intermediate risk renal transplant recipients (D-/R+); a multicenter safety and efficacy evaluation. Am J Transplant, 2013, 13: 210.
13. Gabardi S, Asipenko N, Fleming J, et al. Evaluation of low- versus high-dose valganciclovir for prevention of cytomegalovirus disease in high-risk renal transplant recipients. Transplantation, 2015; 99 (7): 1499-1505.
14. Stevens DR, Sawinski D, Blumberg E, et al. Increased risk of breakthrough infection among cytomegalovirus donor-positive/recipient-negative kidney transplant recipients receiving lower-dose valganciclovir prophylaxis. Transpl Infect Dis, 2015; 17 (2): 163-173.
15. Halim MA, Al-Otaibi T, Gheith O, et al. Efficacy and safety of low-dose versus standard-dose valganciclovir for prevention of cytomegalovirus disease in intermediate-risk kidney transplant recipients, Exp Clin Transplant; 2016, 14(5): 526-534.
16. Heldenbrand S, Li C, Cross RP, et al. Multicenter evaluation of efficacy and safety of low-dose versus high-dose valganciclovir for prevention of CMV disease in donor and recipient positive (D+/R+) renal transplant recipients. Transpl Infect Dis, 2016; 18 (6): 904-912.
17. Huang Y, Park J, Naik A, Kaul D. Standard dose valganciclovir prophylaxis for high-risk kidney transplant recipients reduces incidences of breakthrough and resistant cytomegalovirus infection. Am J Transplant, 2016; 16 (suppl 3): 777.
18. Kalil AC, Mindru C, Florescu DF. Effectiveness of valganciclovir 900 mg versus 450 mg for cytomegalovirus prophylaxis in transplantation: direct and indirect treatment comparison meta-analysis. Clin Infect Dis, 2011; 52 (3): 313–321.
19. GA Wells, B Shea, D O'Connell, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 20 September 2015.
20. JP Higgins, S Green. Cochrane handbook for systematic reviews of interventions: Cochrane book series [M]. A John Wiley & Sons, Ltd.:Wiley-Blackwell, 2008.
21. Egger M, Davey Smith G, Schneider M, et al.

Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997; 315 (7109): 629–634.
22. Singh N. Late-onset cytomegalovirus disease as a significant complication in solid organ transplant recipients receiving antiviral prophylaxis: a call to heed the mounting evidence. Clin Infect Dis, 2005; 40 (5): 704-708.
23. Chamberlain CE, Penzak SR, Alfaro RM, et al. Pharmacokinetics of low and maintenance dose valganciclovir in kidney transplant recipients. Am J Transplant, 2008; 8 (6): 1297-1302.
24. Kalil AC, Levitsky J, Lyden E, Stoner J, Freifeld AG. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med, 2005; 143 (12): 870–80.
25. Florescu DF, Qiu F, Schmidt CM, Kalil AC. A direct and indirect comparison meta-analysis on the efficacy of cytomegalovirus preventive strategies in solid organ transplant. Clin Infect Dis, 2014; 58 (6): 785-803.
26. Spencer JV, Lockridge KM, Barry PA, et al. Potent immunosuppressive activities of cytomegalovirus-encoded interleukin-10. J Virol, 2002; 76 (3): 1285–1292.
27. Gorensek MJ, Stewart RW, Keys TF, McHenry MC, Babiak T, Goormastic M. Symptomatic cytomegalovirus infection as a significant risk factor for major infections after cardiac transplantation. J Infect Dis, 1988; 158 (4): 884–887.
28. Kalil AC, Freifeld AG, Lyden ER, Stoner JA. Valganciclovir for cytomegalovirus prevention in solid organ transplant patients: an evidence-based reassessment of safety and efficacy. PLoS One, 2009; 4 (5): e5512.
29. Hartmann EL, Gatesman M, Roskopf-Somerville J, Stratta R, Farney A, Sundberg A. Management of leukopenia in kidney and pancreas transplant recipients. Clin Transplant, 2008; 22 (6): 822-828.
30. Brum S, Nolasco F, Sousa J, et al. Leukopenia in kidney transplant patients with the association of valganciclovir and mycophenolate mofetil. Transplant Proc, 2008; 40 (3): 752-754.
31. Grinyó JM, Ekberg H, Mamelok RD, et al. The pharmacokinetics of mycophenolate mofetil in renal transplant recipients receiving standard-dose or low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony pharmacokinetic substudy. NephrolDial Transplant, 2009; 24 (7): 2269-2276.
32. Viglietti D, Peraldi MN. Cytopenias following kidney transplantation. Nephrol Ther, 2011; 7 (6): 474-478.

Table 1. The characteristics of included studies

Reference	Study design, years, country	Prophylaxis duration (months)	Follow up (months)	Sample size	LD	HD	CMV sero-status	Induction therapy,	Maintenance immunosuppressive therapy
11	Cohort, 2001.9-2003.5, African–American	3	22±8	72	60	12	All risk	ATG or BSX	MMF, P and either TAC or SRL
12	Cohort, 2008.1-2011.10, USA	3	12	261	227	34	Moderate risk	ATG or BSX	TAC, MPA with or without corticosteroids
13	Cohort, 2001.8-2009,12. USA	6	12	237	130	107	High risk	ATG or IL-2ra	TAC, MPA, P
14	Cohort, 2009.12-2012.9, USA.	6	6[A]	90	45	45	High risk	ATG	TAC, MPA, steroids
15	Cohort, 2010-2013, Kuwait	6	12	196	98	98	Moderate risk	ATG or BSX	calcineurin inhibitor, MMF, P
16	Cohort, 2008.1-2011.10	3	12	487	398	89	Moderate risk	IL-2ra or rATG	TAC, MPA±steroid
17	Cohort, 2013.1-2014.11, USA	6	12	88	62	26	High risk	Thymoglobulin	TAC, MPA±P

LD: low-dose group = valganciclovir 450 mg/day, HD: high-dose group = valganciclovir 900 mg/day, CMV: cytomegalovirus, ATG: anti-thymocyte globulin, BSX: basiliximab, MMF: mycophenolate mofetil, P: prednisone, TAC: tacrolimus, SRL: sirolimus, NA: not available, MPA: mycophenolic acid, IL-2ra: an interleukin-2 receptor antagonist, rATG: rabbit anti-thymocyte globulin. A: at least 6 months or until death, graft loss, or the time of hospital protocol change back to SD prophylaxis.

Table 2a. The clinical outcomes of included studies

Reference	CMV infection			CMV disease			AR			Allograft loss		
	LD, n/N (%)	HD, n/N (%)	*p*	LD, n/N (%)	HD, n/N (%)	*p*	LD, n/N (%)	HD, n/N (%)	*p*	LD, n/N (%)	HD, n/N (%)	*p*
11	3/60 (5.0)	3/12(25.0)	0.02	NR	NR	NR	3/60 (5.0)	1/12 (8.3)	0.6	NR	NR	NR
12	NR	NR	NR	6/227 (2.6)	2/34 (5.9)	0.280	23/227 (10.1)	4/34 (11.8)	0.763	4/227 (1.8)	0/34 (0.0)	1.00
13	NR	NR	NR	19/130 (14.6)	26/ 107 (24.3)	0.068	18/130 (13.9)	14/107 (13.1)	1.000	2/130 (1.5)	3/107 (2.8)	0.660
14	NR	NR	NR	18/45 (40)[A]	12/45 (26.7)[A]	0.18	1/45 (2.2)	4/45 (8.9)	0.2	0/45 (0.0)	0/45 (0.0)	1
15	NR	NR	NR	2/98 (2.0)	7/98 (7.1)	0.17	15/98 (15.3)	24/98 (24.5)	0.057	2/98 (2.0)	3/98 (3.1)	0.64
16	NR	NR	NR	14/398 (3.5)	3/89 (3.4)	1.000	41/398 (10.3)	10/89 (11.2)	0.848	17/398 (5.0)	6/89 (6.7)	0.403
17	13/62 (21)	5/26 (19)	0.75	NR	NR	NR	NR	NR	NR	NR	NR	NR

AR: acute refection; n: the number of patients with the outcomes; N: the total number of patients; NR: not reported; A: overall CMV infection or disease.

Table 2b. The clinical outcomes of included studies

Reference	Mortality			OI			Premature valganciclovir discontinuation			leukopenia		
	LD, n/N (%)	HD, n/N (%)	*p*	LD, n/N (%)	HD, n/N (%)	*p*	LD, n/N (%)	HD, n/N (%)	*p*	LD, n/N (%)	HD, n/N (%)	*P*
11	NR	NR	NR	NR	NR	NR	NR	NR	NR	0/60 (0.0)	2/12 (16.7)	0.03
12	2/227 (0.9)	0/34 (0.0)	1.00	31/227(13.7)	6/34 (17.6)	0.597	NR	NR	NR	NR	NR	NR
13	0/130 (0.0)	3/107 (2.8)	0.091	27/130(20.8)	24/107 (22.4)	0.754	17/130 (13.1)	15/107 (14.0)	0.85	56/130 (43.1)	43/107 (40.2)	0.693
14	0/45 (0.0)	1/45 (2.2)	1	NR	NR	NR	4/45 (8.9)	3/45 (7.7)	1	20/45 (44.4)	33/45 (73.3)	< 0.01
15	2/98 (2.0)	1/98 (1.0)	0.60	NR	NR	NR	24/98 (24.4)	36/98 (36,7)	0.045	40/98 (40.8)	55/98 (56.1)	0.045
16	7/398 (1.8)	3/89 (3.4)	0.400	82/398(20.6)	25/89 (28.1)	0.156	21/398 (5.28)	3/89 (3.4)	0.594	134/398 (33.7)[A]	26/89 (29.2)[A]	NR

OI: opportunistic infections; n: the number of patients with the outcomes; N: the total number of patients; NR: not reported; A: laboratory values were evaluated at the end of post-transplant months 1, 2, 3, 4, 5, 6, 9, and 12(±10days). All data are summed.

Supporting Table 1. Quality of observational studies (indicators from New-Castle-Ottawa scale)										
Reference	**1[a]**	**2[b]**	**3[c]**	**4[d]**	**5A[e]**	**5B[f]**	**6[g]**	**7[h]**	**8[i]**	**Total quality scores**
11	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
12	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7
13	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
14	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
15	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
16	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8
17	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8

[a] Indicates exposed cohort truly representative

[b] Non-exposed cohort drawn from the same community

[c] Ascertainment of exposure from the same community

[d] Outcome of interest not present at start of study

[e] Cohorts comparable on basis of site and etiology of infection

[f] Cohorts comparable on others factors

[g] Assessment of outcome of record linkage or independent blind assessment

[h] Follow-up long enough for outcomes to occur

[I] Complete accounting for cohor