REVIEW ARTICLE

Efficacy of valganciclovir and ganciclovir for cytomegalovirus disease in solid organ transplants: A meta-analysis

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Background: Cytomegalovirus (CMV), a problematic virus in solid organ transplant recipients (SOTR) such as liver, can worsen overall mortality and transplant outcome, so its prevention and treatment is a key of success in such patients. This study is aimed to compare the efficacy of ganciclovir (GCV) and valganciclovir (VGC) for prevention and treatment of infection with CMV. **Materials and Methods:** After sensitive and systematic search in PubMed, EMBASE, Cochrane and other available databases, both prospective and retrospective studies on effect of VGC and GCV in prevention and treatment of CMV disease among SOTR, which had our study criteria, were included. The pooled risk estimates were calculated using random-effects models. **Results:** Among 1324 title, 19 studies were included. In 11 prophylactic studies (2368 patients), the pooled risk of CMV disease (VGC relative to GCV) was 1.16, 95% confidence interval (CI): 0.91-1.49 and in studies of liver transplant recipients, 1.53, 95% CI: 0.86-2.70. Rate of viremia eradication in VGC to GCV was 1.05, 95% CI: 0.97-1.13. In 3 treatment studies (422 patients), rate of successful treatment in VGC to GCV was 0.98, 95% CI: 0.91-1.06 and viremia eradication 0.95, CI 95% 0.77-1.16. All these values did not show statistically significantly differences between GCV and VGC. **Conclusion:** It can be concluded that VGC as an alternative to GCV can be used with equal efficacy in prevention and treatment of CMV disease in SOTR.

Key words: Cytomegalovirus, meta-analysis, solid organs, valganciclovir

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INTRODUCTION

Cytomegalovirus (CMV) a viral pathogen of herpesviridae, can cause serious disease in immunecompromise patients such as solid organ transplant recipients (SOTR). Despite our comprehensive knowledge about its management, CMV has been identified as the most frequently occurring complication, which affects mortality and morbidity of SOTR. Five-fold rise in overall mortality and 11-fold in CMV infection associated death are caused by CMV disease in SOTR.[1] CMV induces its effects through direct and indirect mechanism, which contain CMV syndrome, tissue invasive disease, acute and chronic graft rejection, opportunistic infection, posttransplant lymphoproliferative disorder and postliver transplant aggravation of C hepatitis.[1-6] Hence, prevention and treatment of CMV infection and disease is the key in ensuring the success of transplant outcome.[7]

Monitoring in posttransplant period is performed with PP65 antigenemia and polymerase chain reaction (PCR) assays.[8] In prophylactic method all patients immediately or shortly after transplant receive anti CMV drugs: Ganciclovir (GCV), 5 mg/kg/day, po., GCV, 1 g. Tid or valganciclovir (VGC), 900 mg po./day. In most studies, late onset CMV disease (disease occurrence after discontinue of prophylaxis), is the most frequent complication. In preemptive method regular weekly monitoring by PCR or antigenemia tests is accomplished 3 months after transplantion and once detectable viremia achieved before symptomatic disease, anti CMV drug (intravenous [IV] GCV or po. VGC) with therapeutic dose (5 mg/kg Bid and 900 mg Bid) is initiated till two negative tests are achieved. Treatment of symptomatic CMV disease is done with therapeutic doses of above named drugs and duration of treatment determined like preemptive therapy, but should not be <2 weeks.[7] Oral VGC, IV and oral GCV are the two most popular drugs, which used for these purposes.[9-11] Many studies has proved efficacy of IV route compared with po. GCV in decreasing CMV disease and mortality, so IV GCV is approved for both prevention and treatment and its po form for prophylaxis of CMV disease in SOTR.[3,4,12,13]

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The main problems of IV GCV administration are the need to long term access of an IV line, thrombosis and infection in site of injection.[14-16] Oral GCV despite its great influence on diminishing CMV infection and disease compared to placebo in SOTR, low systemic level[14,17] besides the need to prolong administration, can induce mutant serotypes that are followed by GCV resistance,[18,19] mortality and morbidity rising specially in high risk D+/R− CMV serology recipients.[19,20] VGC, L-valyl ester of GCV, with 10-fold bioavailability compare to po. GCV and equal to IV. GCV and therefore negligible risk to cause resistance, is a suitable po. alternative to GCV.[18,21,22] It has comparable efficacy to GCV in viremia eradication and less complication and now is the most common drug that is used in transplant centers for prophylaxis and treatment of CMV infection and disease.[23-25] In some trials VGC efficacy in liver transplant recipients (LTR) had not been significant as other solid organs,[10,26] while in others had similar effect as GCV in all solid organs.[18,23,24] Various efficacy of VGC in LTR is seen and it is necessary to adopt an optimal method for prevention and treatment of CMV disease in LTR to improve transplant outcome.

This present systematic review and meta-analysis aimed to compare the effect of VGC and GCV in prevention and treatment of CMV in LTR and other solid organs.

MATERIALS AND METHODS

Literature search of English published studies through PubMed, Ovid, Elsevier, Cochrane Central register of control trials, Cochrane Central register of systematic Reviews and some motor searches like Google scholar, was performed up to December 2010. The keywords used were: VGC, CMV, transplant (transplantation or transplants or transplant) and solid organs. After title and abstract review of 1324 captured papers, 82 articles were selected to read whole text. Furthermore, we search references list of these full texts to find more articles. Two separate groups read these articles and clinical trials were evaluated with JADAD scores. Due to the sparse number of randomized clinical trials, other prospective and retrospective observational studies were searched and if suitable after evaluation were included [Figure 1].

Study selection

Inclusion criteria

all cohorts, randomized and nonrandomized clinical trials plus case-control studies that compared VGC with GCV in prevention (prophylaxis and preemptive) and treatment of CMV infection among SORTS were included. The outcomes of interests were: CMV infection, CMV disease, GCV resistance and overall mortality rates.

Exclusion criteria

The following studies were excluded: Studies on efficacy of VGC without control group,[23-42] use of VGC and GCV with two different strategies in one study,[43-45] evaluation of long-term outcome of GCV resistance and late onset CMV disease without pure results of any drug,[46-51] compare different length of prophylaxis or treatment,[52-55] compare the combination regimens of GCV and VGC without result of one drug,[56,57] results of studies with >1 publication was considered once.[10,18,24,58-60]

Data extraction

Two separate groups of authors extracted data by using information sheets that included: Type of study and authors, prophylactic regimen, number and CMV serology of patients, duration of regimens, method of diagnosis and monitoring, duration of posttransplant follow-up, rate of CMV disease, viremia or infection eradication, GCV resistance and overall mortality. Discrepancy between two groups was resolved with discussion.

Endpoints definitions

For the purpose of this study CMV infection defined as presence of the virus that can be detected by growing it *in vitro*, PCR or antigenemia assays. CMV disease defined as presence of infection along with symptoms attributable to CMV syndrome or tissue invasive disease.

In addition, GCV resistance was regarded as occurrence of known UL97 or UL54 mutations that are usually followed by resistance to GCV and clinical failure of response to anti CMV drugs and finally all-cause mortality as well as death associated with CMV in posttransplant period after receiving therapeutic or preventive regimens were regarded as mortality.[3]

Statistical analysis

In order to produce summary estimate we used inverse variance as the weight for each study. Fix effect was used when there was no heterogeneity among the result of studies. In order to check the heterogeneity, we used Chi-square test. In addition we assessed heterogeneity by checking t^2 as well as I^2. We pooled the results of prophylaxis, preemptive and treatment studies separately and where there were available data we run subgroup analysis for each endpoints. Furthermore, studies were classified by the transplanted organ. The data were analyzed using Stata 10 (StataCorp. 2007).

RESULTS

Our sensitive search resulted in capturing 1335 title (including 11 from search in references list) and during the process of study selection 19 articles were included. From total 13 articles compared VGC and GCV in

prophylaxis, three during preemptive and three in treatment period.

Prophylaxis studies

Of 13 studies (2368 patients), all except two,[61,62] used oral GCV 1 g. Tid and VGC 900[10,18,46,61-64] or 450 mg/day.[65-70] Study population in 7 articles was all patients unrelated to donor/recipient CMV serology and in 6 articles was only D+/R− high risk group. In 4 studies patient population were only LTR [Table 1].[46,63-65]

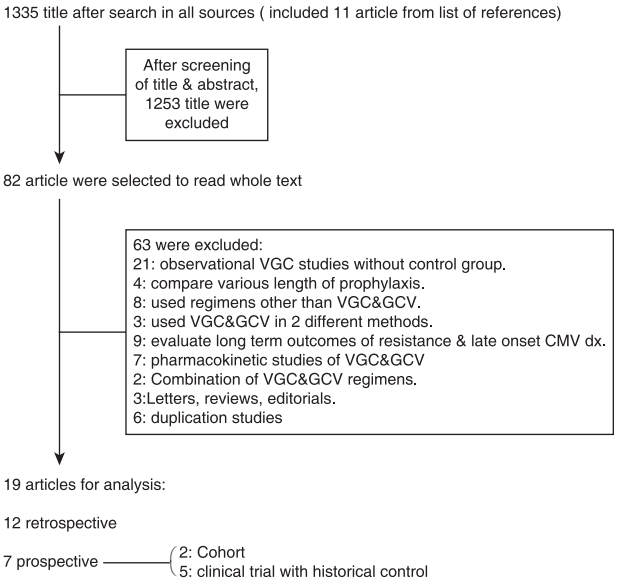

Figure 1: Flowchart of study selection

After prophylaxis, CMV disease was reported in 11 articles (study by Boivin *et al.*, 2004 was excluded as they used patients participated in PV16000[18]) and using a random model it was 16% more in VGC group compared to GCV (relative risk [RR] = 1.16, 95% confidence interval [CI]: 0.91-1.49) [Figure 2]. In D+/R− high risk studies the corresponding value was 1.23 (95% CI: 0.70-2.13) [Figure 3]. The subgroup analysis for those using low dose VGC the RR was 1.20 (95% CI: 0.88-1.63). When we limited the analysis

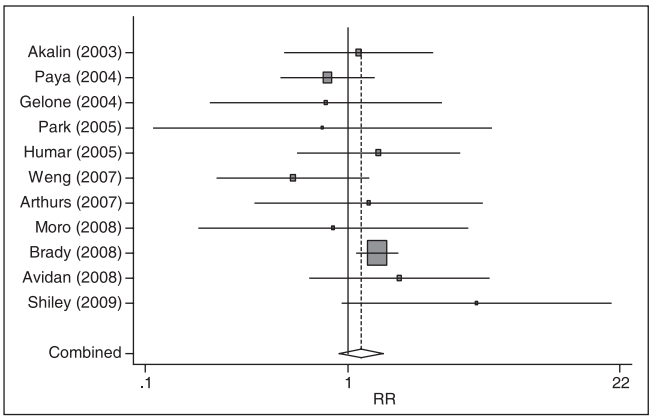

Figure 2: Meta-analysis of 12 prophylaxis studies comparing cytomegalovirus disease in valganciclovir and ganciclovir

Table 1: Characteristic of prophylaxis studies comparing VGC and GCV

Author	Study type	D+/R− or all	Number	Transplanted organ	Prophylaxis regimen	Duration of prophylaxis	Method of monitoring	Follow-up
Humar *et al.*[62]	Prospective with historical control	All	V: 40 G: 40	Lung	Giv + Vpo Giv + Gpo	100 days	PCR	6-12 months
Paya *et al.*[10]	Clinical trial	D+/R−	V: 239 G: 125	SOTR	V 900 mg/day G 1 g tid	100 days	PCR	6-12 months
Moro *et al.*[61]	Case-control	D+/R−	V: 17 G: 36	Heart	V 900 mg/day G 5 mg/kg/day	–	–	6-12 months
Keven *et al.*[68]	Case-control	All	V: 136 G: 75	Kidney, pancreas	V 450 mg/day G 1 g tid	3-8 months	PCR or PP65	6-12 months
Arthurs *et al.*[46]	Case-control	D+/R−	V: 58 G: 9	Liver	V 900 mg/day G 1 g tid	92 days	–	12 months
Park *et al.*[65]	Case-control	All	V: 60 G: 4	Liver	V 450 mg/day G 1 g tid	90 days	PCR	12 months
Brady *et al.*[63]	Case-control	All	V: 43 G: 21	Liver	V 450 mg/day G 1 g tid	V 6 months G 3 months	PCR or PP65	12 months
Weng *et al.*[66]	Case-control	All	V: 205 G: 292	Kidney, pancreas	V 450 mg/day G 1 g tid	90 days	PCR and culture	12 months
Akalin *et al.*[67]	Case-control	All	V: 47 G: 68	Kidney, pancreas	V 450 mg/day G 1 g tid	90 days	CMV DNA Murex capture	12 months
Avidan *et al.*[69]	Case-control	D+/R−	V: 94 G: 127	Kidney	V 450 mg/day G 2 g/day	90 days	CMV DNA Murex capture	12-46 months
Gelone *et al.*[70]	Case-control	All	V: 76 G: 141	Kidney	V 450 mg/day G 1 g/tid	90 days	PP65	6-12 months
Shiley *et al.*[64]	Case-control	D+/R−	V: 27 G: 39	Liver	Po VGC 900 mg/day Po/IV GCV	100 days	Pp65 or Bx.	Not mentioned

SOTR = Solid organ transplant recipients; PCR = Polymerase chain reaction; CMV = Cytomegalovirus; VGC = Valganciclovir; GCV = Ganciclovir

to the studies of liver transplant the RR was 1.53 (95% CI: 0.86-2.70) showing that in VGC group rate of CMV disease was greater compare to GCV group albeit, nonstatisticaly significant.

Of four article that reported the viremia eradication,[10,61,62,68] the overall result showed that 5% more in VGC group, with no statistical significance, (1.05, 95% CI. 0.97-1.13).

Two studies reported that there was an absence of GCV resistance 6 months posttransplant[18,62] and a pooled analysis showed a 12% more in VGC group with no statistical significance (1.12, 95% CI: 0.89-1.35). Overall mortality was reported only in study by Paya *et al.*;[10] 2% and 1.6% in VGC and GCV.

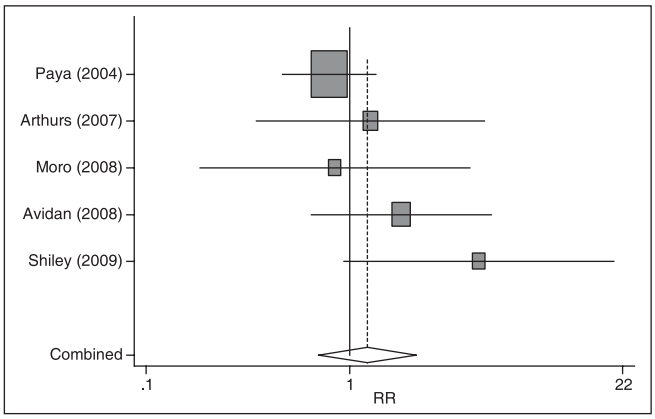

Figure 3: Meta-analysis of high risk group prophylaxis studies comparing cytomegalovirus disease in valganciclovir and ganciclovir

Preemptive studies

For the purpose of this part three studies were included [Table 2].[71-73] From these three, two studies reported that no case of CMV disease was seen in follow-up period.[71,72] Regarding to viremia eradication, while study by Singh *et al*.[71] reported 94% and 76% in VGC and GCV, two other studies reported mean reduction of viral load that was similar for VGC and GCV in both studies [Table 2].[72,73] None of preemptive studies reported any data about GCV resistance.

Treatment studies

Three studies were included.[27,74,75] Efficacy of treatment was evaluated with two different endpoints of viremia eradication at day 21 and treatment success. Definition of Treatment success in all studies was improvement of CMV disease associated symptoms plus eradication of viremia at day 21 [Table 3]. Meta-analysis of results of two studies reported viremia eradication showed no statistical differences between two treatments (RR of VGC compared to GCV = 0.95, 95% CI: 0.77-1.16).[24,74] In addition, after meta-analysis of three studies, there was no clinically and statistically differences between two groups in terms of treatment success (RR = 0.98, 95% CI: 0.91-1.06).

Table 2: Characteristics of preemptive studies comparing VGC and GCV

Author	SOT or special organ	D+/R− or all	Number of patients	Received preemptive therapy	Method of monithoring	Length of follow-up	Type of study	CMV dx. (%)	Viremia eradication %	Survival %
Singh *et al*.[71]	Liver	All	139 V: 59 G: 80	39 V: 17 G: 21	PP65	V: 20.4 person/year G: 106.6 person/year	Prospective, cohort	0	V: 94 G: 76	V: 91.5 G: 90
Kalpoe *et al*.[72]	Kidney, kidney-pancreas	All	57	27 V: 18 G: 9	PCR	6 months	Prospective, cohort	0	V: 0.12log10copy/ml (IQR: 0.0, −0.39) G: 0.09log10 (−0.04, −0.25)	–
Mattes *et al*.[73]	Liver, kidney	All	NA	45 V: 22 G: 23	PCR	–	Retrospective	–	V: −0.98log10 (−2.12, 0.29) G: −1.17 (−3.07, 1.07)	–

CMV = Cytomegalovirus; SOT = Solid organ transplant; NA = Not available; PCR = Polymerase chain reaction; IQR = Interquartile range; VGC = Valganciclovir; GCV = Ganciclovir

Table 3: Characteristics of therapeutic studies comparing VGC and GCV

Author	SOT/special organ	All or D+/R−	Patients	Method of monitoring	Type of study
Asberg *et al*.[24]	SOT	All	321 V: 164 G: 157	PP65 or NAT	Prospective
Humar *et al*.[74]	SOT	All	64 V: 32 G: 32	PP65 or PCR	Prospective with historical control
Luan *et al*.[75]	Kidney, kidney-pancreas	D+/R−	37 V: 22 G: 15	PCR	Case-control

SOT = Solid organ transplant; PCR = Polymerase chain reaction; NAT = Nucleic acid test; VGC = Valganciclovir; GCV=Ganciclovir

DISCUSSION

In all studies of prophylaxis regardless of type of transplanted organ, D/R serology of CMV and dose of VGC and also in high risk D+/R− group studies, we found that VGC has no statistical difference with GCV in regard to CMV disease existence, eradication of infection and GCV resistance. However in only liver transplant studies rate of CMV disease was higher after VGC prophylaxis compare to GCV. Therefore with due attention to higher bioavailability of VGC compare to oral GCV,[76] so higher systemic exposure to GCV following VGC administration and delay in viremia occurrence after discontinuation of prophylaxis,[77] we can use oral VGC with ease of administration and more patient acceptance as an alternative of GCV with similar efficacy in all SOTR except LTR.

In comparison to meta-analysis of 9 studies in 2009 by Kalil *et al*.,[78] we could take the pooled risk of GCV resistance in prophylaxis studies that had no statistical difference between VGC and GCV. In addition, risk of CMV disease in Kalil *et al*. for VGC to GCV was 0.98 with 95% CI: 0.67-1.43 which was similar to our results in terms of no statistically significance differences between two treatment. However, they found significant neutropenia in VGC compare to GCV and therefore they did not recommended substitution of GCV by VGC in prophylaxis of CMV disease in SOTR. In a systematic review of 10 studies in 2008 by Sun *et al*.[79] prevention and decreasing CMV disease by prophylactic and preemptive oral VGC was successfully performed. In meta-analysis by Hodson *et al*.,[16] neutrophill counts below 1_109/L occurred in 13% of patients received VGC compared with 8% of those received GCV, but the difference was not significant and also VGC and intravenous GCV were as effective as oral GCV.

In the present study, we compared VGC and GCV in the treatment of CMV disease in SOTR and we did not find significant differences in treatment success and viremia eradication between two drugs. Therefore GCV can be substituted by VGC.[14,80] Similarly in a study by Asberg *et al*.[24] the efficacy and clinical complication of VGC and GCV was similar in treatment of CMV disease in SOTR. In study by Humar *et al*., in spite of similar efficacy of VGC and GCV in treatment, they recommended that patients with signs of malabsorption and life-threatening CMV disease should be candidate for IV GCV.[74]

Although for preemptive studies analysis was not possible, all of them proclaimed that VGC and GCV are similar in decreasing CMV disease and infection, other opportunistic infection and treatment outcome.

One of the limitations of our study is that we could not compare the mortality of recipients, because most original studies did not report such outcomes. In order to include higher number of studies, we also included retrospective case-control studies as well as randomized clinical trials.

Because our primary objective was to compare these two drugs efficacy, so we did not focus on complications such as cytopenia.

CONCLUSION

Consider to similar efficacy of VGC and GCV in decreasing CMV infection and disease, we can use VGC as an alternative to GCV in prophylaxis and treatment of CMV disease in SOTR except LTR, with ease of administration and less complication. It is believed that VGC has better patient acceptance. Further studies need to be done with more focus on safety profile of two drugs.

AUTHOR'S CONTRIBUTION

SV: contributed in the conception of the work,conducting the study, revising the draft,approval of the final version of the manuscript, and agreed for all aspects of the work. ZP: contributed in the conception of the work, did the data collection, contribution in doing analysis, preparing the first draft,approval of the final version of the manuscript, and agreed for all aspects of the work. BS: contributed in the conception of the work, contribution in data collection, contribution in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. FM: contributed in the conception of the work, contribution in data collection, revising the draft,approval of the final version of the manuscript, and agreed for all aspects of the work. AJ: contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MA: contributed in the conception of the work, revising the draft,approval of the final version of the manuscript, and agreed for all aspects of the work. FN: contributed in the design of the work, doing the analysis, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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