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Article type : Original Report

Comparison of universal prophylaxis and preemptive approach for CMV associated outcome measures in renal transplant patients; a meta-analysis of available data

Running title: CMV in renal transplant patients

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Acknowledgement:

The authors declare no conflicts of interest. This study did not obtain any financial support.

Abstract

Cytomegalovirus (CMV) is a ubiquitous latent human virus that often causes complications in renal transplantation recipients. Universal prophylaxis and preemptive therapy are alternative strategies to prevent CMV associated complications. This meta-analysis aimed to assess available data comparing the effectiveness of prophylaxis and preemptive therapy for preventing adverse outcomes. We searched the PubMed, Ovid, Web of Science, Cochrane Library, and Open Grey databases using a combination of keywords. Random effects models along with the Paule-Mandel estimator were used to synthesize pooled effect estimates. Eleven studies were eligible for the final analysis. Universal prophylaxis was better at preventing CMV disease than the preemptive approach (Risk Difference (RD) = -0.0459; CIs = -0.0791, -0.0127; *p*-value = 0.0067; number needed to treat [NNT] = 22 (1/0.0459) (high, 79(1/0.0127) patients; low, 13 (1/0.0791) patients). Subgroup analysis revealed a more consistent effect among studies published after 2010, with negligible between-study heterogeneity. The NNT for universal prophylaxis to prevent one excess CMV disease concerning preemptive therapy was 16 (1/0.0630) patients (high, 25 (1/0.0394); low, 12 (1/0.0867) patients) in the subgroup of studies performed after 2010. We detected no significant difference between the two strategies regarding acute rejection and graft loss, with negligible variability due to heterogeneity between studies. Although universal prophylaxis performed better than the preemptive strategy for the prevention of CMV disease, the high NNT value may discourage the use of CMV prophylaxis. Since there were no differences between the strategies concerning acute rejection and graft loss, this study supports the use of the preemptive approach as an alternative to universal prophylaxis.

Keywords: Cytomegalovirus; Viremia; Antiviral Agents; Kidney Transplantation; Ganciclovir

Introduction

CMV is a latent virus, infecting 40–100% of the population worldwide [1]. It has the largest genome among human viruses and carries genes dedicated to adaptation and coevolution of CMV with human immune system progenitor cells [2]. Recent studies documented the existence of genes with high homology between CMV and components of the human immune system [3]. Data indicate that CMV may have some affirmative interactions with the human immune system [4,5].

CMV latently resides in immune progenitor cells. Disorders inducing progenitor cells such as infections naturally promote the replication of CMV [6,7]. The reactivation of CMV in critically ill patients is associated with adverse outcomes [8]. However, it is unclear if CMV viremia is merely a marker of an unfavorable outcome or the cause of adverse outcomes [8].

CMV viremia is a significant complication of kidney transplantation; without antiviral intervention, it develops among two-thirds of recipients [9]. Studies among renal transplant patients demonstrated an association between CMV disease and allograft outcomes [10]. Therefore, prophylaxis with an appropriate antiviral drug, such as ganciclovir, is the suggested standard care for renal transplant

recipients [11]. However, due to the high toxicity of ganciclovir and concerns about antiviral resistance, recent studies focused on either low-dose ganciclovir prophylaxis or a preemptive approach [12,13].

This study aimed to assess available data comparing universal prophylaxis and preemptive strategies regarding the outcome measures CMV disease, acute rejection, and graft loss.

Methods

Literature search and study selection

We searched the PubMed, Web of Science, Ovid and Cochrane Library databases for published literature without language or time limitation. We limited our search strategy to the following combination of keywords: "kidney AND transplant* AND outcome AND (cytomegalo* OR cmv) AND preempt* AND prophylaxis*". For unpublished literature, we searched Open Grey (www.opengrey.eu) using various combinations of above-mentioned keywords to enable a broad coverage of any preliminary work.

After removing duplicates, four investigators screened all abstracts individually and voted on including/excluding the study for full-text evaluation. The same investigators evaluated the full-text articles for eligibility. Studies were eliminated mostly due to the study design not fitting to the aims of this study, selective reporting of data, or reporting incomplete outcome data.

Randomized controlled trials (RCTs) and observational studies were included. Studies including pediatric populations were excluded.

Risk of bias assessment

Four investigators individually assessed the risk of bias in full-text studies according to the following criteria. The Cochrane Collaboration's Risk of Bias Tool was used to evaluate RCTs, and the Newcastle-Ottawa scale was used to assess the quality of observational studies [14,15]. We evaluated the overall quality of data from an RCT at low risk of bias if all domains were at low risk of bias otherwise as high risk of bias. We considered observational studies according to total points obtained from each domain. Accordingly, we considered more than 7 points as low risk of bias, 5 to 7 points as moderate risk of bias and less than 5 points high risk of bias.

Definitions and outcomes

CMV viremia was defined as the detection of virus DNA above the threshold level of 400 copies/mL in a blood sample. In studies published after 2010, CMV disease was defined according to the definitions of "The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation" [16]. Accordingly, CMV syndrome, which is CMV viremia with compatible symptoms or CMV tissue-invasive disease documented by molecular or histopathologic studies at the tissue level, was categorized as CMV disease. Acute graft rejection was defined as biopsy-proven acute rejection (BPAR), and graft loss was defined as a return of the patient to conditions before the transplantation regarding renal function.

The outcomes of this study were CMV disease, BPAR, and graft loss among kidney transplant patients who received universal prophylaxis or the preemptive approach to protect against CMV reactivation.

Data extraction

The frequency of CMV disease, BPAR, and graft loss in both arms was extracted from tables or the text of eligible studies either directly or by calculating from the given percentages. No data were obtained from plots. We included only the recent outcome rates from studies with more than one follow-up period. Two investigators individually checked all outcome rates twice.

The CMV serostatus of the transplant recipients and the study type (RCT versus observational study) were extracted as potential moderators of homogeneity between the studies.

Statistical methods

All statistical analyses were performed using the packages meta, metafor, and metagear in the open source platform R [17,18].

We analyzed the data used in this study as rare events data. One study had zero events; others had one or only few events. In rare events data, small changes have the potential to distort variances and the direction of effect sizes. Rare and zero events data therefore need to be analyzed and pooled with special measures to minimize bias on weights. Therefore, we constructed a random effects model using the Paule-Mandel estimator to assess between-study variances and the associated uncertainties [19,20]. We used the Mantel-Haenszel method without continuity correction to estimate effect sizes [21]. Finally, we used an absolute measure, RD, to pool the effect estimates. The RD has some advantages for rare events data as it does not require zero-cell corrections and can be simply converted to the number needed to treat (NNT). One divided by the RD provides the NNT, which is a straightforward scale that can be used by physicians to interpret rare events [22].

Between-study heterogeneity was assessed with the I^2 statistics and is presented as forest plots. We conducted sensitivity analysis using a leave-one-out test. Publication bias was assessed by funnel plots. The Egger test was used to determine plot asymmetry. Where required, meta-regression models with potential moderators were used to assess the source of heterogeneity. Meta-regression test was performed via metareg function of the meta package.

Results

We retrieved 378 titles from the databases; no unpublished data were identified. After excluding duplicates, 250 studies were further evaluated. Studies that received ≥2 adverse decisions from the investigators were excluded, leaving 34 full-text articles. Among the full text articles, 23 were excluded due to following reasons. One study had been conducted twice; thus, the earlier version was excluded [23]. One study was excluded as it was in a pediatric population and another one as it was a meta-analysis. Two studies were excluded because we could not extract data. The other

excluded studies either had a quasi-experimental or sequential design where the baseline characteristics of study arms could not be compared or the design did not include two arms. Finally, 11 studies were found to be eligible (Figure 1).

Overall, the quality of data was low to moderate (Figure S1). All RCTs were open-label and except one neither had adequately randomized. Therefore, we assessed risk of bias among RCTs as high. Observational studies obtained scores between 5 to 7, and thus we considered risk of bias as moderate. However, we admit that our assessments do not necessarily represent the exact level of quality of these studies [24].

Table 1 presents the features of the 11 studies that were included in the final analysis. Five studies were open-label RCTs [25-29]. Of the observational studies, five had a retrospective cohort design [10,30-33] and one a prospective cohort design [34]. Four RCTs and one observational study included both CMV-seropositive and -seronegative recipients, while the others restricted the study populations to only seropositive recipients. Of note, studies published in 2010 or later included only seropositive recipients. The follow-up duration varied across studies (from 1 to 7 years).

We presented details of studies in Table S1. Briefly, only three studies presented data for CMV syndrome while others gave combined data for CMV disease. All studies used PCR to detect CMV viremia. Three studies used ≥ 400 copies /mL as threshold while others accepted ≥ 1000 or ≥ 2000 copies/mL. Three studies administered prophylactic antiviral drugs for 100 days while others for three months. Except for one study all others used ganciclovir or valganciclovir either at high or low daily doses.

The data of 10 studies (5 RCTs and 5 observational studies) were analyzed for CMV disease. Because only three studies reported event rates of CMV syndrome, we could not synthesize effects for CMV syndrome alone (Table S1) [26-28]. The random effects model for CMV disease revealed a significant effect favoring universal prophylaxis (RD = -0.0459; confidence interval [CI] = -0.0791, -0.0127; *p*-value = 0.0067). The NNT for universal prophylaxis to prevent one excess CMV disease was as high as 79 (1/0.0127) patients and as low as 13 (1/0.0791) patients. The model displayed a moderate level of heterogeneity (I^2 = 38.9%). To address variability due to heterogeneity between studies, we constructed meta-regression models by study type and recipient serostatus as moderators (Table S2). The meta-regression models indicated that the serostatus had a significant moderator effect (estimate = -0.11; CI = -0.02, -0.19). A forest plot of CMV disease using subgroups according to the serostatus of patients revealed the existence of considerable heterogeneity between studies including both seropositive and seronegative recipients (Figure 2). Interestingly, these studies were all conducted before 2010. Studies conducting in or after 2010 included only seropositive patients. In this subgroup prophylaxis was better than preemptive approach with a negligible heterogeneity. The NNT for universal prophylaxis in the subgroup of studies published in 2010 or later was 16 (1/0.0630) with CIs of 25 (1/0.0394) and 12 (1/0.0867)) patients. Visual inspection of the forest plot (Figure 2) raised doubts about two studies (Kliem – 2008 & Witzke -2018) as being outliers. However, Influential analysis revealed that excluding these studies one by one or both did not change the direction of the overall effect (without "Kliem – 2008" RD = -0.0413 [-0.0751; -0.0076], *p* = 0.0165; without "Witzke – 2018", RD = -0.0389 [-0.0722; -0.0056], *p* = 0.0219; without both, RD = -0.0345 [-0.0672; -0.0018], *p* = 0.0385).

We also pooled effect estimates in subgroups of study types (RCTs and observational studies) (Figure 3). In the subgroup of observational studies the prophylaxis approach performed better on CMV disease (RD = -0.0570; CIs = 0.0823, -0.0317) with a negligible heterogeneity. A subgroup of studies according to quality scores would obtain virtually the same subgroup of study types. Therefore, we consider that subgroup analysis according to study types represent subgroup analysis according to study qualities.

We were able to pool data from all 11 studies for BPAR. The random effects model showed a non-significant pooled estimate (RD = -0.0309; CIs= -0.0697, 0.0080; p-value = 0.1191); the between-study heterogeneity was low (I^2 = 21.8%). Sensitivity analysis indicated one study as an outlier with a negligible effect on the pooled effect direction. After removing this study from the analysis [28], the model performed better with minimal variability due to heterogeneity (Figure 4).

The data of nine studies were analyzed for graft loss. The pooled effect of these studies showed a non-significant association between the CMV preventive approaches and graft loss (Figure 5). The variability due to heterogeneity was low (I^2 = 0%).

Figure S2 presents the funnel plot. The linear regression test (Egger test) did not detect a significant asymmetry in the funnel plot which indicates that publication bias might not be significant.

Discussion

This meta-analysis revealed a moderate quality of evidence on the effectiveness of prophylaxis versus preemptive therapy for preventing adverse outcomes associated with CMV viremia among kidney transplant patients.

In this study, the RD for CMV disease in the subgroup of studies published after 2010 favored universal prophylaxis over the preemptive approach, with negligible between-study heterogeneity. In the subgroup of studies published before 2010, there was no excess risk between the two CMV preventive approaches. However, the between-study variability was considerably high, making this finding highly speculative. Similarly, a meta-analysis published in 2011 that included earlier studies did not find a significant association between CMV preventive strategies and CMV disease [35]. In this meta-analysis, the heterogeneity was also considerably high. The heterogeneity between studies published before 2010 might be due to the broad definition of CMV syndrome. These early studies used various definitions and may have misclassified some patients with CMV syndrome.

In 2010, an expert panel published definitions for CMV disease among transplant patients [16]. This panel also recommended not to use the preemptive approach in seronegative recipients. Accordingly, studies published after 2010 included only seropositive recipients and utilized the panel's definitions. It is likely that the panel recommendations minimized the variability between studies after 2010. The random model analysis of the subgroup of studies published after 2010 indicated that universal prophylaxis performed better than the preemptive approach for the prevention of CMV disease. However, the NNT was 16 patients (high, 25; low, 12) , implying that 16 patients have to receive universal prophylaxis to prevent one excess CMV disease. The high NNT value is a negative tradeoff for the prophylaxis strategy.

We found no significant advantage for either of the CMV preventive strategies regarding BPAR and graft loss. Similarly, a previous meta-analysis found non-significant effects of CMV preventive strategies on BPAR or graft loss among solid organ transplant recipients [36].

Our study showed that universal prophylaxis outperformed the preemptive approach in CMV disease. However, CMV viremia is frequently detected in patients with severe infections [8], and so one must be skeptical about making a diagnosis of CMV disease in a patient with non-specific symptoms and CMV viremia. Rigorous screening for other infectious etiologies must gain more attention to avoid the misdiagnosis of CMV disease and unnecessary exposure of recipients to highly toxic substances such as ganciclovir.

Most significant limitations of this analysis were that the studies have moderate to high risk of bias and have rare events. Especially the latter limitation is prone to biased effect estimates and restricts the generalizability of our results.

Since, prophylaxis and the preemptive approach showed a comparable performance regarding serious outcomes such as BPAR and graft-loss and universal prophylaxis had a high NNT value for preventing CMV disease, this study encourages the use of the preemptive approach among kidney transplant recipients. However, the quality of the included studies was not high enough to derive firm recommendations. Future blinded and appropriately randomized studies are needed to confirm this study's findings.

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Table 1. Features of studies included in the final analysis

	Study	Study type [1]	n		CMV		Follow-up (years)	
			Prophylaxis	Preemptive	Serostatus [2]	disease	BPAR [3]	Graft Lost
1	Junge - 2001	RCT	34	36	Both	overall	1	1
2	Khoury - 2006	RCT	49	49	Both	overall	1	1
3	Reischig - 2007	RCT	34	36	Both	overall	1	1
4	Kliem - 2008	RCT	73	65	Both	overall	1	4
5	Spinner - 2010	Retr. cohort	48	47	Both		1	4
6	Weclawiak - 2010	Retr. cohort	150	132	Positive	overall	2	2
7	Couzi - 2012	Retr. cohort	24	72	Positive	overall	1	1
8	Fernandez-Ruiz - 2015	Pros. cohort	185	190	Positive	early	1	1
9	Werzowa - 2015	Retr. cohort	109	78	Positive	overall	1	1
10	Luna - 2016	Retr. cohort	167	66	Positive	overall	1	1
11	Witzke - 2018	RCT	148	151	Positive	overall	7	7

[1] RCT, randomized controlled study; Retr. Cohort, retrospective cohort; Pros. cohort, prospective cohort

[2] Both, CMV seropositive and seronegative recipients

[3] BPAR, biopsy proven acute rejection

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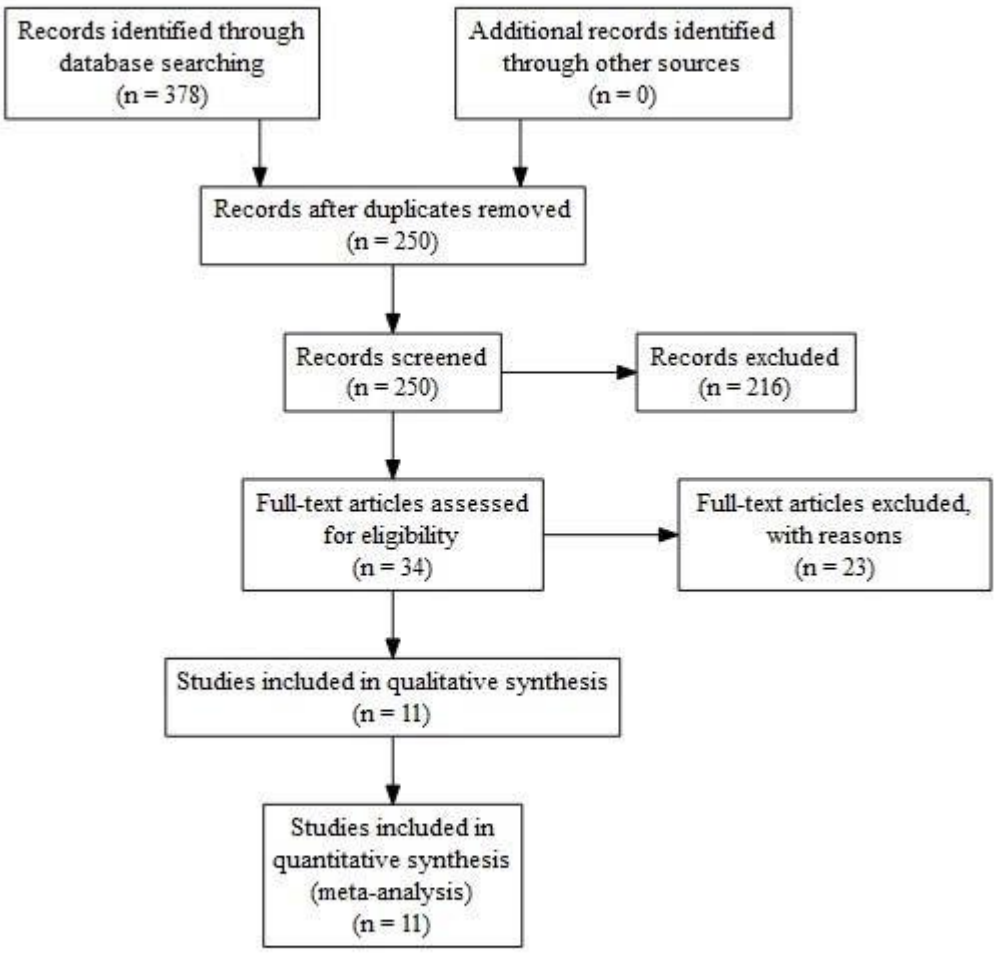

Figure 1.

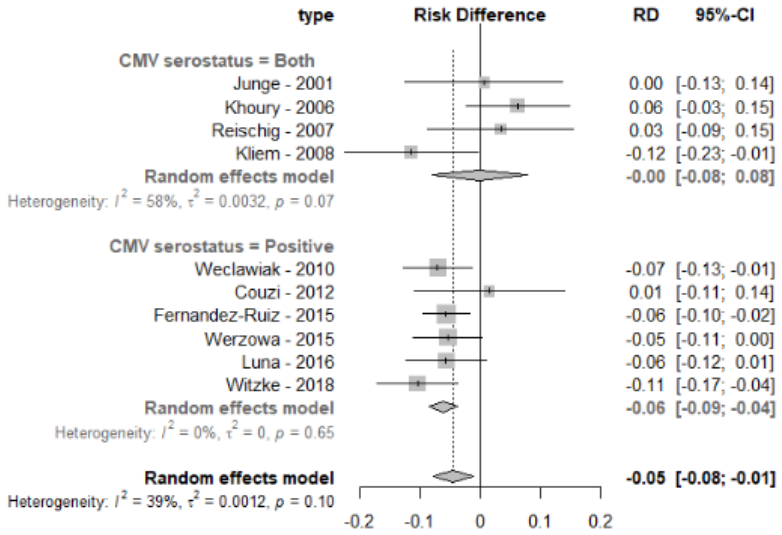

Figure 2

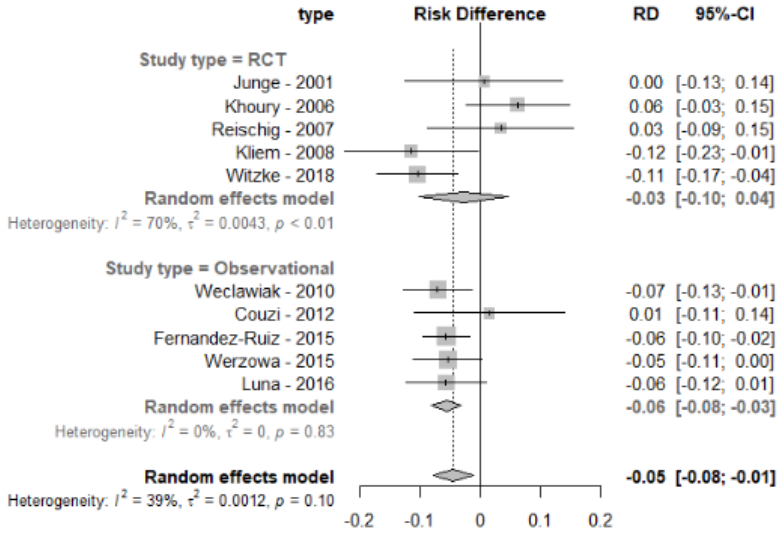

Figure 3

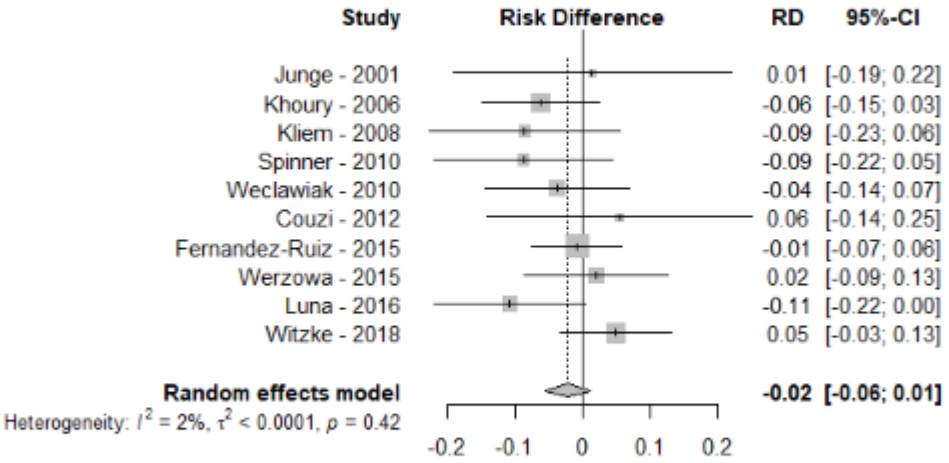

Figure 4

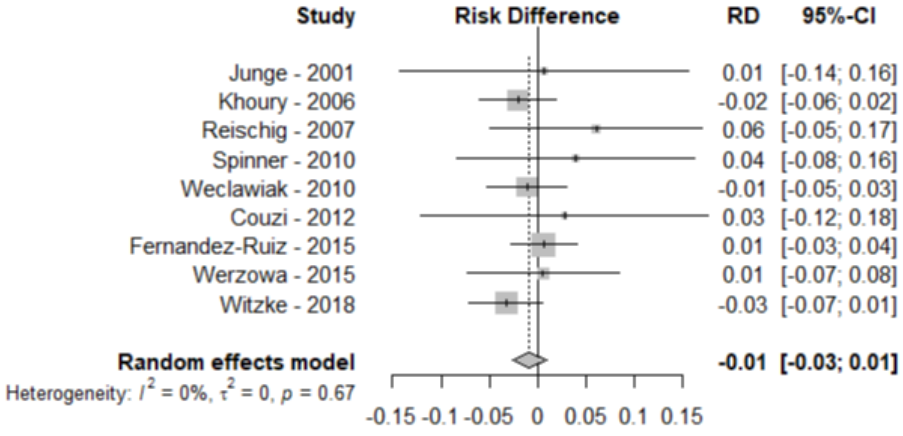

Figure 5