MAJOR ARTICLE

Preventing Post–Organ Transplantation Cytomegalovirus Disease with Ganciclovir: A Meta-Analysis Comparing Prophylactic and Preemptive Therapies

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(See the editorial commentary by Meylan and Pascual on pages 881–3)

Background. Cytomegalovirus (CMV) causes significant morbidity and mortality in transplant recipients, but there is no consensus regarding the most appropriate prevention method. The goal of this meta-analysis was to compare the efficacy of universal prophylaxis and preemption using ganciclovir.

Methods. Literature searches for randomized and nonrandomized controlled trials of ganciclovir prophylaxis and preemption were conducted. Because of the lack of head-to-head trials, indirect comparisons of meta-analyses of the prevention strategies were performed. Meta-analyses were conducted using a random effects model to estimate the overall risk ratios for various clinical outcomes. We assessed the event rates for control groups across the trials for comparability.

Results. Literature searches identified 17 universal prophylaxis trials and 9 preemption trials with 1560 and 457 subjects, respectively. Overall event rates for CMV disease in control groups across the studies were similar (~26%). The relative risk of CMV disease in prophylaxis trials was 0.34 (95% confidence interval, 0.24–0.48) when trials of patients with prophylaxis of short duration and trials that only evaluated patients with high-risk serostatus were excluded. The relative risk of CMV disease for study subjects in all preemption trials was 0.30 (95% confidence interval, 0.15–0.60), compared with that for control subjects. There was no statistically significant difference in CMV disease between prevention strategies. Similarly, no differences between strategies were found for all-cause mortality or rejection. There were insufficient data to adequately evaluate graft loss and opportunistic infection.

Conclusions. On the basis of indirect comparisons of meta-analyses of prevention strategies, universal prophylaxis and preemption are equally effective in reducing the incidence of CMV disease.

Cytomegalovirus (CMV) infection is a serious condition among immunosuppressed individuals that causes morbidity and mortality [1, 2] and necessitates prevention strategies [3]. The most common methods are universal prophylaxis or preemption protocols.

Universal prophylaxis involves administration of anti-CMV medication soon after transplant and is continued to a predetermined temporal end point [4]. The goal is to prevent CMV replication or infection and avert symptomatic CMV disease. Preemption strategies include administration of anti-CMV medication when evidence of asymptomatic CMV infection is detected by CMV assay [5]. The strategy is to detect CMV replication or infection and prevent symptomatic CMV disease. Other CMV prevention protocols also exist, including targeted prophylaxis, in which anti-CMV medication is administered only in individuals at high risk, such as patients receiving antilymphocyte therapy [6, 7].

Numerous antiviral medications have been used for CMV prevention. These include acyclovir and valacyclovir [8, 9], but ganciclovir and, more recently, val-

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ganciclovir have more in vitro activity and clinical efficacy and are more appropriate for CMV prevention and treatment [10].

No consensus regarding CMV prevention strategies exists, and debate is fueled by issues of efficacy and economics [5, 11, 12]. Although cost and logistics of the strategies are considerations, the purpose of this analysis was a quantitative comparison of efficacy.

Few trials directly compared the 2 prevention strategies [13]. Systematic reviews evaluating some aspects of CMV prevention have been published [14–16]. These previous analyses have included acyclovir and valacyclovir protocols among the CMV prevention strategies, although these regimens would in fact not be considered optimal. Furthermore, some of these analyses have classified targeted prophylaxis as preemption [17]. The goal of the present study was to compare the efficacies of universal prophylaxis and preemption strategies that are based on ganciclovir or valganciclovir.

METHODS

Search strategy and study selection. Entries in the Medline (1966 to the first week of July 2005), Embase (1974 to the 27th week of July 2005), and the Cochrane Central Registry of Controlled Trials [18] databases were searched using the terms "transplantation or transplants or transplant" and "valganciclovir or ganciclovir." Titles and abstracts were reviewed for studies that addressed universal prophylactic or preemptive CMV prevention in solid organ transplant recipients (figure 1). Randomization and blinding were evaluated for quality assessment but were not used as exclusion criteria.

Appropriate interventions and controls for evaluation were based on therapeutic guidelines [10]. Universal prophylaxis was defined as administration of a course ganciclovir or valganciclovir at the time of transplant or soon thereafter. Preemption was defined as administration of ganciclovir or valganciclovir in response to detection of CMV by pp65 antigen or PCR assays. Despite acyclovir and valacyclovir having some efficacy in preventing CMV disease, this analysis considered acyclovir and its derivatives to be inferior to the ganciclovir-based strategies and classified them as controls. Similarly, immunoglobulin was considered to be a control. Acceptable controls were the absence of prevention therapy, use of placebo, immunoglobulin level, use of acyclovir, or any combination thereof.

Data abstraction. Data that were collected included transplanted organ, donor and/or recipient CMV serostatus, antirejection methods, and CMV detection assay. Antiviral therapy data included drug, route of administration, dosage, and duration of therapy. Therapy initiation criteria were noted for preemption trials. Primary outcomes collected were CMV infection, active CMV disease, mortality, organ rejection, graft loss, and opportunistic infection. Outcome definitions were accepted as they were described in each trial.

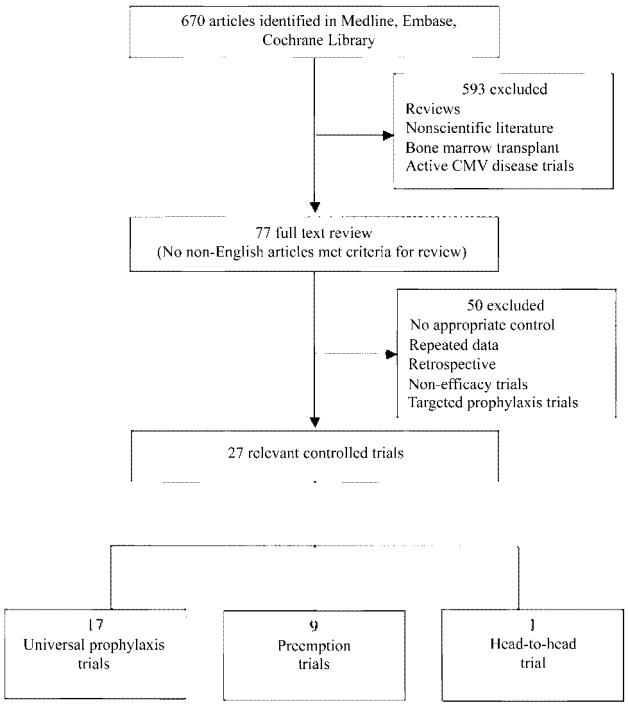

Figure 1. Study selection for meta-analysis of cytomegalovirus (CMV) infection prevention strategy.

Statistical methods. CMV disease, mortality, organ rejection, graft loss, and opportunistic infection rates were evaluated using an indirect comparison method that compared strategies in relation to common controls [19–21]. Asymptomatic infection data were collected but not compared, because, by definition, preemption will be associated with higher rates of infection than prophylaxis. Relative risks of clinical events were combined and used to compare ganciclovir prophylaxis with controls, and a similar meta-analysis was performed that evaluated ganciclovir preemption. Control group event rates were combined across the trials for each meta-analysis to derive an overall rate. The overall control rate of each strategy was used as a measure to assess the comparability of the populations between the 2 strategies. Control rates and relative risks were calculated using random effects models (Meta-Analyst software, version 0.99 [Joseph Lau]). Differences in the relative risks between the 2 strategies were then assessed using Student's *t* test.

Where data were available, a subgroup analysis was performed to evaluate the outcomes relative to CMV serostatus by excluding studies that only included subjects with high risk, donor-positive/recipient-negative serostatus. Furthermore, a subgroup analysis of prevention therapy duration was performed by only including studies with prophylaxis durations of 6 $\geqslant$weeks.

Additional stratification was performed to evaluate the effect of using acyclovir-based protocols as controls by excluding the acyclovir-controlled studies in a subgroup analysis.

Table 1. Characteristics of a studies of post–organ transplantation cytomegalovirus disease.

Study type, study	Organ	Donor/recipient serostatus, no. of subjects			Gan intervention				Therapy duration, weeks
		D+/R−	D+/R+ or D−/R+	D−/R−	No. of subjects	Drug(s)	Total daily dose of Gan[a]	Route of administration	
Prophylaxis trials									
[22]	H	…	31	…	16	Gan	10 mg/kg	IV	2
[23]	K	16	35	…	35	Gan	1000 or 1500 mg	Oral	12
[24]	K	8	23	12	21	Gan	1500 mg	Oral	12
[25]	L	25	130	12	83	Gan and Acy[b]	10 mg/kg	IV	2[b]
[26]	K	5	37	…	19	Gan	3000 mg	Oral	12
[27]	L	10[c]	50[c]	…	33	Gan	10 mg/kg	IV	2
[28]	K	27	52	…	40	Gan and Ig[d]	3000 mg	Oral	12
[29]	L	46	256	2	150	Gan	3000 mg	Oral	14
[30]	L	56	…	…	29	Gan and Ig	5 mg/kg	IV	4
[31]	K	23	…	…	13	Gan	10 mg/kg	IV	2
[32]	H	16	40	…	28	Gan	5 /kg MWF	IV	6–8
[33]	H	35	112	2	76	Gan	6–10 mg/kg[e]	IV	6
[34]	K	10	32	8	24	Gan and Acy[f]	5 mg/kg	IV/oral[f]	2[f]
[35]	K	2	36	…	14	Gan	3000 mg	Oral	12
[36]	K	32	…	…	17	Gan	10 mg/kg	IV	2
[37]	H, K, or L	155	…	…	77	Gan[g]	3000 mg	Oral[g]	12
[38]	L	…	219	…	110	Gan[h]	3000 mg	Oral[h]	14
Preemption trials									
[39]	K	5	31	…	15	Gan	NS	IV	NS
[40]	K or L	3	9	…	5	Gan	10 mg/kg	IV	2
[41]	L	20	49	…	35	Gan	3000 mg	Oral	8
[42]	L	10	21[i]	21[i]	16	Gan and Ig	15 mg/kg	IV	2
[43]	L	13[j]	38[j]	1[j]	30	Gan	3000 mg	Oral	2
[44]	L	17	40	…	29	Gan	3000 mg	Oral	8
[45]	K	8	72	…	42	Gan	3000 mg	Oral	7 (mean)
[46]	L	4	42	1	23	Gan	5 mg/kg	IV	1
[47]	L	3[l]	61[l]	…	40	Gan	3000 mg	Oral	7 (median)

NOTE. Acy, acyclovir; D+, donor positive; D−, donor negative; Gan, ganciclovir; H, heart; K, kidney; L, liver; MWF, Monday, Wednesday, and Friday; NPT, no prevention therapy; NS, not specified; R+, recipient positive; R−, recipient negative; Val, valacyclovir;

[a] Standard doses are reported; however, renal dosing was used in all studies when necessary.
[b] Gan was given for 2 weeks, followed by Acy for 15 weeks. The comparator arm received Acy for 17 weeks.
[c] The serostatuses of 5 donors/recipients were unknown.
[d] All D+/R− subjects received intravenous Ig in addition to the study drug.
[e] Ten mg/kg daily for 2 weeks, followed by 6 mg/kg on weekdays.
[f] The experimental group received 2 weeks of Gan followed by 10 weeks of oral Acy.
[g] All subjects received 5–10 days of intravenous Gan followed by 12 weeks of either oral Gan or oral Acy.
[h] All subjects received 14 days of intravenous Gan followed by 14 weeks of either oral Gan or oral Acy.
[i] There were 10 D+/R− subjects and 21 non-D+/R− subjects; no further details of serostatus are known.
[j] The serostatuses of 8 donors/recipients were unknown.
[k] This group received Acy prophylaxis for 24 weeks.
[l] The serostatus of 1 donor/recipient was unknown.

The preemption trials used 2 methods of subject enrollment; some trials enrolled subjects immediately after transplantation, whereas other trials enrolled patients only on detection of CMV replication and initiation of preemptive therapy. Subgroup analyses were performed on studies using each of these methods, and the analyses were compared to determine whether either method would significantly affect outcome data.

RESULTS

Study characteristics. Detailed characteristics of the individual studies are summarized in table 1. Seventeen universal prophylaxis controlled trials [22–38] and 9 preemption controlled

Control intervention				Duration of follow-up, months	Randomized	Blinded
No. of subjects	Drug(s)	Acy or Val dosage, mg/day[a]	Route of administration			
15	Ig	…	IV	6	Yes	NS
16	NPT	…	…	6	Yes	No
22	NPT	…	…	9	Yes	No
84	Acy	3200	Oral	12	Yes	NS
23	Acy	400	Oral	6	Yes	No
32	NPT	…	…	18	Yes	No
39	Acy and Ig[d]	3200	Oral	6	Yes	NS
154	Placebo	…	Oral	12	Yes	Yes
27	Placebo and Ig	…	IV	6	Yes	Yes
10	NPT	…	…	6	Yes	NS
28	NPT	…	IV	21	Yes	Yes
73	Placebo	…	IV	5	Yes	Yes
26	Placebo	…	IV	6	Yes	NS
24	Val	8000	Oral	3	Yes	NS
15	NPT	…	…	6	Yes	No
78	Acy[g]	1200	Oral	6	Yes	NS
109	Acy[h]	3200	Oral	12	Yes	NS
21	NPT	…	…	16 (mean)	Yes	No
7	Placebo	…	IV	3	Yes	Yes
34	Placebo	…	Oral	4	Yes	No
15	NPT	…	…	21–41	No	No
30	NPT	…	…	12–36	Yes	No
28	Placebo	…	Oral	4	Yes	Yes
38	NPT	…	…	12	Yes	No
24	Acy[k]	3200	Oral	6	Yes	No
25	NPT	…	…	6	No	No

trials [39–47] met the inclusion criteria for analysis (figure 1). One prospective head-to-head trial was identified that is not included in the meta-analysis, but it will be discussed later [13].

Universal prophylaxis studies included 785 subjects in the treatment groups and 775 subjects in control groups. Preemption studies included 235 subjects in treatment groups and 222 subjects in control groups. All trials used pp65 antigen or PCR assays for CMV detection [48, 49].

Trials had various immunosuppression protocols, which differed between and within studies. In many cases, antilymphocyte treatment was used in accordance with institution transplant protocols. Specific data on immunosuppression were not included in this analysis, because the studies did not include detailed data to perform pertinent subgroup analyses.

Individual trial outcome data are shown in table 2, and meta-analyses results are summarized in tables 3–6.

CMV disease. Sixteen of 17 prophylaxis trials reported the outcome of developing CMV disease. Event rates of this outcome in the control groups ranged from 5% to 90% (weighted mean, 27%). All 9 preemption trials reported the outcome of CMV disease and had control group event rates ranging from 13% to 71% (weighted mean, 26%). The meta-analysis of ganciclovir prophylaxis revealed a relative risk of 0.49 (95% CI, 0.39%–0.60%) for developing CMV disease, compared with that for controls. The relative risk for ganciclovir preemption was 0.30 (95% CI, 0.15%–0.60), compared with that for controls (figure 2). Indirect comparison of the 2 strategies demonstrated a nonsignificant trend of greater risk reduction for preemption ($P = .07$).

Subgroup analyses of duration and serostatus. In a subgroup analysis that excluded studies that evaluated only high-risk donor-positive/recipient-negative transplants and excluded studies that used prophylaxis durations of <6 weeks, the rate of occurrence of CMV disease in the control groups of the 8 qualifying studies ranged from 5% to 61% (weighted mean, 24%). The relative risk for CMV disease was 0.34 (95% CI,

Table 2. Outcome data in studies of post–organ transplantation cytomegalovirus (CMV) disease.

	No. of subjects													
	Ganciclovir intervention							Control intervention						
Study	Total	CMV Infection	CMV disease	Death	Rejection	GL	OI	Total	CMV infection	CMV disease	Death	Rejection	GL	OI
Prophylaxis trials														
[22]	16	13	1	2	NR	0	2	15	14	6	1	NR	0	2
[23]	35	1	NR	0	1	0	0	16	6	NR	1	1	1	1
[24]	21	1	0	0	1	NR	NR	22	6	1	1	4	NR	NR
[25]	83	31	9	6	45	NR	NR	84	48	19	7	48	NR	NR
[26]	19	13	4	NR	6	NR	NR	23	23	14	NR	3	NR	NR
[27]	33	16	9	1	NR	4	NR	32	24	10	6	NR	7	NR
[28]	40	1	1	NR	13	NR	NR	39	14	9	NR	7	NR	NR
[29]	150	7	6	10	77	8	NR	154	29	19	16	93	10	NR
[30]	29	16	5	6	18	2	NR	27	11	7	4	20	5	NR
[31]	13	7	6	NR	6	NR	NR	10	9	9	NR	5	NR	NR
[32]	28	NR	6	NR	NR	NR	NR	28	NR	10	NR	NR	NR	NR
[33]	76	NR	12	3	NR	NR	NR	73	NR	31	1	NR	NR	NR
[34]	24	13	6	0	3	NR	NR	26	18	14	0	7	NR	NR
[35]	14	4	2	NR	5	NR	7	24	17	9	NR	10	NR	17
[36]	17	12	8	0	10	1	NR	15	12	11	0	9	2	NR
[37]	77	25	15	3	27	NR	17	78	39	21	1	36	NR	16
[38]	110	NR	1	21	38	NR	NR	109	NR	8	16	37	NR	NR
Preemption trials														
[39]	15	14	6	0	3	0	NR	21	19	9	0	4	2	NR
[40]	5	5	0	NR	NR	NR	NR	7	7	5	NR	NR	NR	NR
[41]	35	35	1	NR	0	NR	1	34	34	7	NR	1	NR	2
[42]	16	16	0	NR	4	NR	NR	15	15	2	NR	9	NR	NR
[43]	30	30	3	4	NR	NR	NR	30	30	6	3	NR	NR	NR
[44]	29	29	2	NR	NR	NR	NR	28	28	7	NR	NR	NR	NR
[45]	42	42	0	NR	4	NR	NR	38	38	9	NR	7	NR	NR
[46]	23	6	1	3	NR	4	NR	24	10	7	3	NR	0	NR
[47]	40	11	1	4	NR	NR	NR	25	6	5	4	NR	NR	NR

NOTE. GL, graft loss; NR, not reported; OI, opportunistic infection.

0.24–0.48), compared with controls for those who received ganciclovir prophylaxis (figure 3). No significant difference was found in the indirect comparison of the prophylaxis and preemption relative risks.

Subgroup analyses evaluating the exclusion of high-risk serostatus alone and duration alone are summarized in table 3. Similar subgroup analyses of preemption studies were not possible, because there were no preemption donor-positive/ recipient-negative–only studies and because of the smaller number of preemption trials making statistically significant stratification difficult. A subgroup analysis, which excluded all acyclovir controlled trials was also performed. The outcome of the analysis was similar to the outcome of the analysis that included all trials.

Late CMV disease. Six universal prophylaxis and 3 preemption trials discriminated CMV disease occurring >90 days after transplant. There were 678 and 192 subjects in the available prophylaxis and preemption trials, in which there were 22 and 5 events, respectively. Prophylaxis yielded a relative risk of 1.02 (95% CI, 0.43–2.44), and the relative risk of preemption was 0.69 (95% CI, 0.15–3.11). A comparison of these relative risks yielded a P value of .20.

Mortality. In the 12 prophylaxis studies that reported all-cause mortality, control groups reported mortality rates of 0%–19% (weighted mean, 8%). The relative risk of all-cause mortality in the ganciclovir groups was 0.99 (95% CI, 0.68–1.43). The control groups of the 4 trials reporting preemption all-cause mortality found rates between 0% and 16% (weighted mean, 10%). The relative risk of all-cause mortality for treatment groups was 0.94 (95% CI, 0.43–2.07). Results of indirect comparison of prophylaxis and preemption strategies were not significant. Subgroup analyses for therapy duration and donor and recipient serostatus are summarized in table 4. A subgroup analysis excluding acyclovir-controlled trials showed a trend in mortality reduction, compared with the mortality for all trials. When acyclovir controlled trials were excluded from the analysis, the risk ratios of prophylaxis and preemption were 0.77 (95% CI, 0.45–1.31) and 0.91 (95% CI, 0.36–2.29), respectively. There was no difference between strategies. Additionally, an analysis of mortality in studies with follow-up periods ≤6

Table 3. Analysis summary of cytomegalovirus (CMV) disease.

Variable	No. of studies	Ganciclovir intervention		Control intervention		RR (95% CI)	*P*
		No. of subjects	Event rate (range)	No. of subjects	Event rate (range)		
CMV disease							
Prophylaxis	16	750	0.12 (0.00–0.47)	759	0.27 (0.05–0.90)	0.49 (0.39–0.60)	.07
Preemption	9	235	0.06 (0.00–0.40)	222	0.26 (0.13–0.71)	0.30 (0.15–0.60)	
Excluding studies that included only D+/R− subjects							
Prophylaxis	12	614	0.09 (0.00–0.27)	629	0.25 (0.05–0.61)	0.41 (0.31–0.54)	.19
Preemption[a]	9	235	0.06 (0.00–0.40)	222	0.26 (0.13–0.71)	0.30 (0.15–0.60)	
Prophylaxis duration ⩾6 weeks							
Prophylaxis	9	535	0.09 (0.00–0.21)	550	0.24 (0.05–0.61)	0.40 (0.28–0.57)	.24
Preemption[a]	9	235	0.06 (0.00–0.40)	222	0.26 (0.13–0.71)	0.30 (0.15–0.60)	
Prophylaxis duration ⩾6 weeks and excluding studies that included only D+/R− subjects							
Prophylaxis	8	458	0.07 (0.00–0.21)	472	0.24 (0.05–0.61)	0.34 (0.24–0.48)	.37
Preemption[a]	9	235	0.06 (0.00–0.40)	222	0.26 (0.13–0.71)	0.30 (0.15–0.60)	
Excluding studies that used acyclovir as a control							
Prophylaxis	11[b]	421	0.15 (0.00–0.47)	413	0.33 (0.05–0.73)	0.47 (0.36–0.62)	.08
Preemption	8	198	0.06 (0.00–0.40)	198	0.25 (0.13–0.71)	0.32 (0.15–0.66)	

NOTE. D+/R−, donor positive/recipient negative.

[a] Subgroup analysis was not possible with available data.

[b] One study [35] had separate "no prophylaxis" and valacyclovir control groups. The valacyclovir group was excluded in this subgroup analysis.

months and another analysis of studies with follow-up periods >6 months did not reveal any significant differences from the previous findings.

Rejection. The overall control group rejection rate for 13 prophylaxis trials and 4 preemption trials was 45% (range, 6%–74%) and 19% (range, 3%–60%), respectively. The corresponding relative risks for rejection were 0.90 (95% CI, 0.79–1.01) and 0.54 (95% CI, 0.29–1.01), respectively, with no significant difference between strategies. Rejection subgroup analyses for therapy duration and donor and recipient serostatus are summarized in table 5.

Graft loss and opportunistic infection. Prophylaxis trials reporting graft loss and opportunistic infections had a mean control rate of 13% (range, 0%–29%) and 27% (range, 6%–71%), respectively. Compared with those of controls, relative risks were 0.90 (95% CI, 0.61–1.33) and 0.84 (95% CI, 0.56–1.27) respectively. Subgroup analyses and corresponding analyses of preemption studies could not be performed, as there were insufficient reported data for these outcomes.

DISCUSSION

This meta-analysis compares CMV prevention strategies and emphasizes the use of ganciclovir. Because there was only 1 head-to-head trial, trials that compared individual strategies against controls were evaluated. The meta-analysis revealed reduction of CMV disease using preemption or universal prophylaxis. Overall, there was a trend for an increased benefit using preemption; however, in subgroup analyses, excluding short duration prophylaxis and high-risk CMV serostatus-only trials, this trend in favor of preemption did not remain. With optimized therapy, CMV disease risk reduction approached 70% for either strategy. The only randomized head-to-head trial available agreed with these findings [13] and found that oral ganciclovir prophylaxis of 90 days and oral ganciclovir preemption of 14 days, when they were necessary, were comparable in preventing CMV disease.

In the subgroup analyses that excluded short duration prophylaxis and donor-positive/recipient-negative–only trials, 3 of the 4 studies that only evaluated donor-positive/recipient-negative transplantations were also short-duration prophylaxis trials. Therefore, there was some confounding in performing a univariate subgroup analysis. Similar subgroup analyses of preemption trials were not performed, because there were no preemption trials that included only donor-positive/recipient-negative transplants, and duration was often not reported or was determined by a clinical end point, such as progression to CMV disease or eradication of CMV infection.

The range of CMV disease event rates for controls in prophylaxis trials was wide (5%–90%) and was attributed to heterogeneity of a number of variables. Lower control group CMV

Table 4. Analysis summary of all-cause mortality.

Variable	No. of studies	Ganciclovir intervention		Control intervention		RR (95% CI)	*P*
		No. of subjects	Event rate (range)	No. of subjects	Event rate (range)		
All-cause mortality							
Prophylaxis	12	671	0.08 (0.00–0.21)	651	0.08 (0.00–0.19)	0.99 (0.68–1.43)	.55
Preemption	4	108	0.10 (0.00–0.13)	100	0.10 (0.00–0.16)	0.94 (0.43–2.07)	
Excluding studies that included only D+/R− subjects							
Prophylaxis	9	548	0.08 (0.00–0.19)	531	0.09 (0.00–0.19)	0.92 (0.62–1.36)	.31
Preemption[a]	4	108	0.10 (0.00–0.13)	100	0.10 (0.00–0.16)	0.94 (0.43–2.07)	
Prophylaxis duration ⩾6 weeks							
Prophylaxis	6	469	0.08 (0.00–0.19)	452	0.08 (0.01–0.15)	1.01 (0.60–1.70)	.72
Preemption[a]	4	108	0.10 (0.00–0.13)	100	0.10 (0.00–0.16)	0.94 (0.43–2.07)	
Prophylaxis duration ⩾6 weeks and excluding studies that included only D+/R− subjects							
Prophylaxis	5	392	0.09 (0.00–0.19)	374	0.09 (0.01–0.15)	0.94 (0.54–1.64)	.44
Preemption[a]	4	108	0.10 (0.00–0.13)	100	0.10 (0.00–0.16)	0.94 (0.43–2.07)	
Excluding studies that used acyclovir as a control							
Prophylaxis	9	401	0.06 (0.00–0.21)	380	0.08 (0.00–0.19)	0.77 (0.45–1.31)	.37
Preemption	3	85	0.09 (0.00–0.13)	76	0.09 (0.00–0.16)	0.91 (0.36–2.29)	

NOTE. D+/R−, donor positive/recipient negative.

[a] Subgroup analysis was not possible with available data.

disease rates were noted in trials where acyclovir was the control, which is expected. CMV disease control rates were low for liver transplants, whereas heart and kidney transplants had high control rates. Outliers with the highest control rates of 73% and 90% were small studies that only included donor-positive/recipient-negative subjects [31, 36]. The lowest control rate (5%) was found in a small trial that included a significant donor-negative/recipient-negative population [24]. Preemption trials had less variation in transplant type, control intervention, and serostatus, which is reflected in the narrower control rate range.

As CMV disease prevention has become more effective, late CMV disease has become an issue. An analysis of disease occurring >90 days after transplant yielded limited data with no significant differences. Nevertheless, a trend for reduction in the incidence of late CMV disease was noted when preemption therapy was compared with controls, as well as when it was compared with universal prophylaxis.

There was no significant mortality benefit using either prevention strategy or in any subgroup analyses. Reported mortality rates were for all-cause mortality, rather than for attributable mortality. It is likely that a detailed analysis of CMV attributable mortality would detect a benefit, but these data were not specifically reported. This is in contrast to recent meta-analyses that showed mortality benefit [15, 16]. This is likely because of the fact that acyclovir has some benefit in reducing CMV disease incidence, as well as the incidence of other opportunistic infections. Because this study considers acyclovir to be a control, some of the mortality benefit of ganciclovir was negated. Indeed, in a subgroup analysis that excluded acyclovir-controlled trials, trends of decreased mortality were noted.

Trends of decreased organ rejection were noted in both prevention strategies. The overall risk reduction trend was higher for preemption trials, compared with that for prophylaxis trials, with or without subgroup analyses. The difference between strategies was not statistically significant. Notably, mean control rates were more than twice as high in prophylaxis trials, compared with rates in the preemption trial group. This may be attributed to the heterogeneity of CMV serostatus matching, which was present in the prophylaxis trials, but not in preemption trials. Trials with the highest rejection rates were those that had higher proportions of donor-positive/recipient-negative subjects.

Although the goals of this study also included evaluations of opportunistic infection and graft loss, it was not possible to make a meaningful analysis because of insufficient data reporting. Trends of decreased opportunistic infection and graft loss were noted among the few universal prophylaxis trials reporting these outcomes. Preemption trials reporting these outcomes were too few for analysis.

This study also aimed to provide data on the use of oral valganciclovir, because it is becoming an attractive alternative

Table 5. Analysis summary of rejection.

Variable	No. of studies	Ganciclovir intervention		Control intervention		RR (95% CI)	*P*
		No. of subjects	Event rate (range)	No. of subjects	Event rate (range)		
Rejection							
Prophylaxis	13	632	0.40 (0.03–0.62)	627	0.45 (0.06–0.74)	0.90 (0.79–1.01)	.17
Preemption	4	108	0.10 (0.00–0.25)	108	0.19 (0.03–0.60)	0.54 (0.29–1.01)	
Excluding studies that included only D+/R− subjects							
Prophylaxis	9	496	0.38 (0.03–0.54)	497	0.42 (0.06–0.60)	0.93 (0.79–1.10)	.22
Preemption[a]	4	108	0.10 (0.00–0.25)	108	0.19 (0.03–0.60)	0.54 (0.29–1.01)	
Prophylaxis duration ⩾6 weeks							
Prophylaxis	8	466	0.36 (0.03–0.51)	465	0.41 (0.06–0.60)	0.91 (0.75–1.12)	.20
Preemption[a]	4	108	0.10 (0.00–0.25)	108	0.19 (0.03–0.60)	0.54 (0.29–1.01)	
Prophylaxis duration ⩾6 weeks and excluding studies that included only D+/R− subjects							
Prophylaxis	7	389	0.36 (0.00–0.25)	387	0.40 (0.06–0.60)	0.97 (0.76–1.25)	.21
Preemption[a]	4	108	0.10 (0.00–0.25)	108	0.19 (0.03–0.60)	0.54 (0.29–1.01)	

NOTE. D+/R−, donor positive/recipient negative.

[a] Subgroup analysis was not possible with available data.

to oral and intravenous ganciclovir. No valganciclovir trials met the inclusion criteria for this analysis. Valganciclovir trials mostly use ganciclovir as a comparator and were consequently not acceptable for this analysis. In the interest of completing a thorough commentary on the subject, a literature review and informal analysis of available trials was performed. Any CMV prevention trial evaluating valganciclovir versus any ganciclovir protocol was included. Three prophylaxis trials and 1 preemption trial were identified, with a total 343 valganciclovir and 254 ganciclovir recipients [50–53]. Using a random effects model, a CMV disease rate of 16% was present among ganciclovir recipients, and the relative risk for valganciclovir was 1.01 (95% CI, 0.70–1.46). Additionally, another study of 90 subjects receiving prophylactic valganciclovir found significant CMV disease risk reduction, compared with that for 140 historic acyclovir prophylaxis controls [54]. These data suggest that valganciclovir and ganciclovir have similar efficacy in preventing CMV disease and that some extrapolation from the present study may be made regarding valganciclovir use in prophylaxis or preemption.

This study does have some limitations. The study was designed to evaluate the efficacy of ganciclovir-based therapy against all others, including acyclovir. Acyclovir has better efficacy than no preventive therapy; however, a preanalysis decision was made to evaluate currently accepted therapies. Subgroup analyses excluding studies with acyclovir controls found results for CMV disease risk reduction that were similar to results of the analysis that included the acyclovir studies (table 3). Therefore, it seems likely that considering acyclovir as a control did not confound the control data in CMV disease analysis. However, a similar subgroup analysis found that the analysis of mortality might have been affected by considering acyclovir to be a control.

Notably, there were trial design differences between the pre-

Table 6. Analysis summary of graft loss and opportunistic infection.

Variable	No. of studies	Ganciclovir intervention		Control intervention		RR (95% CI)	*P*
		No. of subjects	Event rate (range)	No. of subjects	Event rate (range)		
Graft loss							
Prophylaxis	6	280	0.05 (0.00–0.12)	259	0.10 (0.00–0.21)	0.59 (0.33–1.08)	…[a]
Preemption	2	38	0.11 (0.00–0.17)	45	0.04 (0.00–0.10)	1.64 (0.05–52.10)[a]	
Opportunistic infection							
Prophylaxis	4	142	0.18 (0.00–0.50)	133	0.27 (0.06–0.71)	0.84 (0.56–1.27)	…[a]
Preemption	1	35	0.03 (0.03–0.03)	34	0.06 (0.06–0.06)	…[a]	

[a] Insufficient data for adequate analysis.

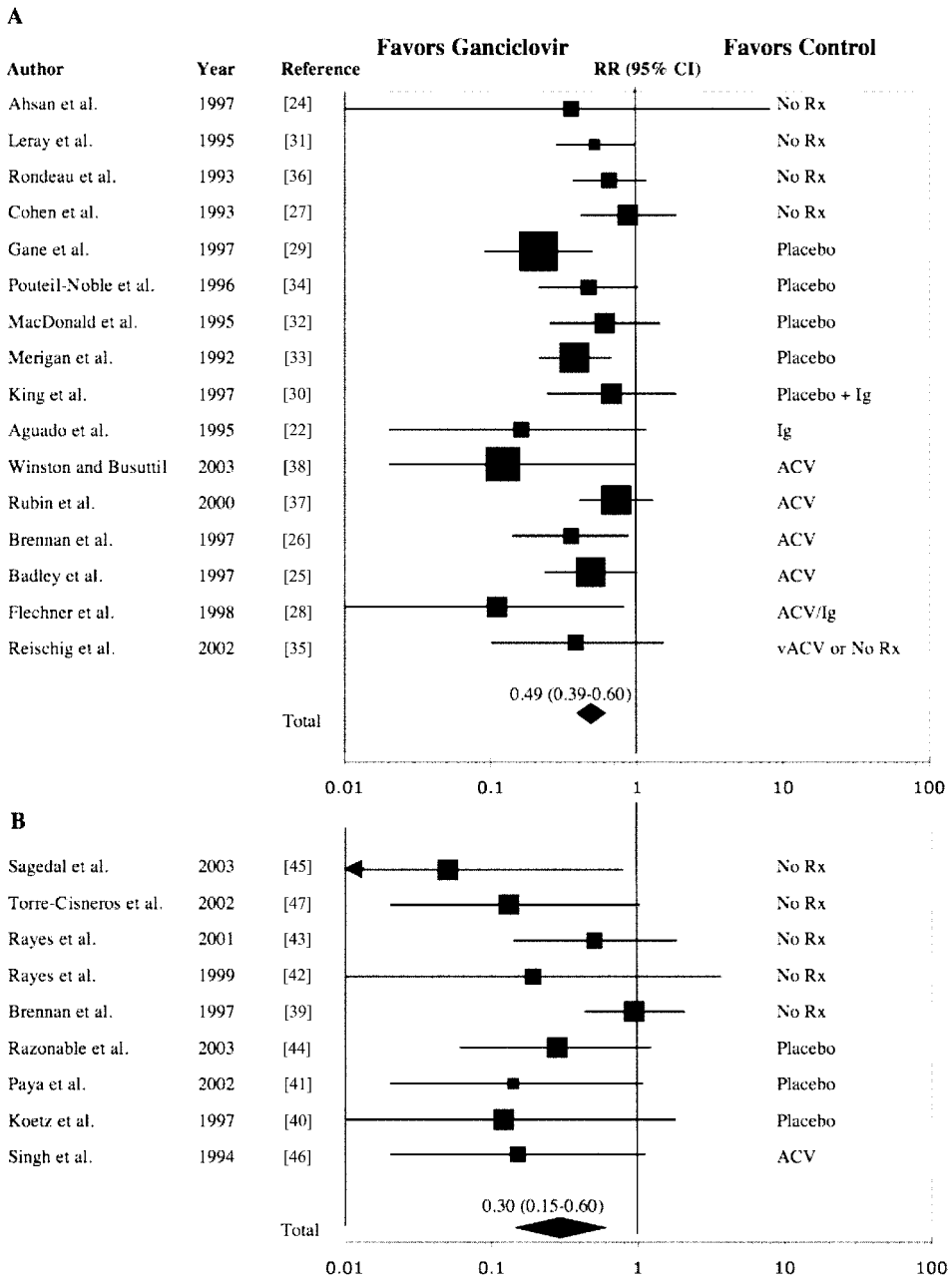

Figure 2. Cytomegalovirus (CMV) disease analysis. *A,* All prophylaxis trials reporting CMV disease. Donor subjects and recipient subjects constituted 30% of the population (mean control rate, 0.27). *B,* All preemption trials reporting CMV disease. Donor positive and recipient negative subjects consistuted 19% of population (mean control rate, 0.26). RR, relative risk.

emption trials. Some trials enrolled subjects at the onset of CMV detection [40–45], whereas others enrolled subjects at the time of transplant [39, 46, 47]. Because trials using both methods were included in this study, a subgroup analysis of trials using each method was performed. The relative risk of CMV disease among all preemption trials was 0.30 (95% CI, 0.15–0.60), as previously noted. In an analysis including the 3 trials that enrolled subjects at time of transplant, the relative risk was 0.34 (95% CI, 0.08–1.48). Conversely, when the 6 trials that enrolled subjects at onset of CMV detection were evaluated, the relative risk of CMV disease was 0.25 (95% CI, 0.11–0.53). Although the difference in these relative risks was not significant ($P = .57$), the improved efficacy when enrollment was at onset of CMV detection may be explained by failure to detect subjects who developed CMV disease in the absence of early CMV detection. Because enrollment at time of transplant would include all patients with CMV disease, the benefit of prevention would not be as pronounced. There were insufficient data to

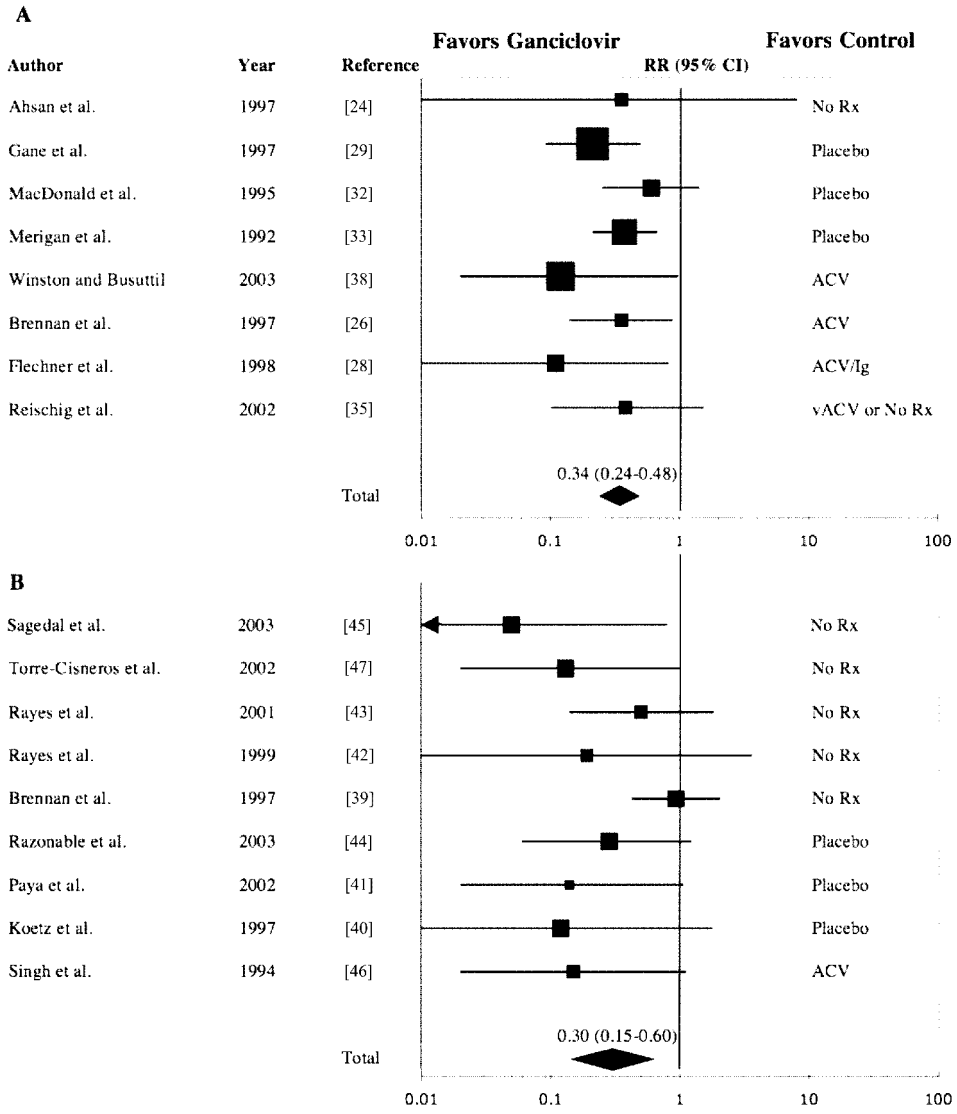

Figure 3. Cytomegalovirus (CMV) disease subgroup analysis. *A,* Prophylaxis trials reporting CMV disease, excluding trials of only donor-positive/recipient-negative (D+/R−) subjects and those with a treatment duration <6 weeks. D+/R− subjects constituted 16% of the population (mean control event rate, 0.24). *B,* All preemption trials reporting CMV disease. D+/R− subjects constituted 19% of the population (mean control event rate, 0.26). RR, relative risk.

perform similar analyses for other outcomes. Immunosuppression may increase the risk of CMV infection and disease. As stated, many of the trials provided little detail of immunosuppression used; therefore, it was not possible to incorporate this risk factor into the analysis.

A common problem in meta-analyses is the issue of publication bias. A technique that has been advocated for bias detection is the funnel plot analysis, in which outcomes are plotted against a measure of precision. An unbiased study should have symmetric distribution on a plot that resembles an inverted funnel. Asymmetry and deviation from the predicted distribution may indicate significant bias within the analysis. Studies specifically evaluating this technique have not shown accurate prediction of bias [55, 56]. Although bias may be a significant factor in this study, no quantitative measurement of bias has been employed, because there are no sufficiently proven measurement techniques.

Although this meta-analysis found no difference between the 2 prevention strategies, the analysis was based on indirect comparisons and subject to the effects of confounders. Additional trials that directly compare the 2 prevention strategies are warranted and needed before the CMV prevention debate can be resolved. Because both strategies are widely used, a large multicenter trial should be feasible and would be useful for further evaluation of the significant issue that CMV represents in the transplant population.

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