Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial

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*The investigators and institutions that participated in the Maribavir 1263–300 study are listed in p 1 of the webappendix

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Summary

Background Available drugs against cytomegalovirus have adverse effects that compromise their prophylactic use in recipients of allogeneic stem-cell transplants. We assessed the safety, tolerability, and antiviral activity of oral maribavir in such patients.

Methods In this placebo-controlled, randomised, double-blind, multicentre phase 3 study, we enrolled adult patients recipient-seropositive or donor-seropositive for cytomegalovirus who had undergone allogeneic stem-cell transplantation. Patients were recruited from 90 centres in Canada, Europe, and the USA. After engraftment, patients were stratified by recipient cytomegalovirus serostatus and conditioning regimen (myeloablative or reduced-intensity) and assigned (2:1) by masked computer-generated randomisation sequence to receive maribavir 100 mg twice daily or placebo for up to 12 weeks, with weekly blood cytomegalovirus surveillance. If the virus was detected, administration of study drug was stopped and pre-emptive anticytomegalovirus treatment started. The primary endpoint was cytomegalovirus disease within 6 months of transplantation. Analysis was by intention-to-treat. This study is registered with ClinicalTrials.gov, NCT00411645.

Findings Between December, 2006, and May, 2008, 681 patients were enrolled and assigned to receive maribavir (454) or placebo (227). The incidence of cytomegalovirus disease within 6 months was 20 of 454 (4%) for the maribavir group and 11 of 227 (5%) for the placebo group (OR 0·90; 95% CI 0·42–1·92). During the 100 days following transplantation, cytomegalovirus infection rates as measured by pp65 antigenaemia were lower in the maribavir group (26·4%) than in the placebo group (34·8%; OR 0·67; 0·47–0·95), but not when measured by plasma cytomegalovirus DNA PCR (27·8% *vs* 30·4%; OR 0·88; 0·62–1·25), nor by initiation of treatment against cytomegalovirus (30·6% *vs* 37·4%; OR 0·73, 0·52–1·03). Maribavir was well tolerated: most adverse events, including incident acute graft-versus-host disease and neutropenia, affected both groups equally, except for taste disturbance (15% maribavir, 6% placebo).

Interpretation Compared with placebo, maribavir prophylaxis did not prevent cytomegalovirus disease when started after engraftment. Cytomegalovirus disease as a primary endpoint might not be sufficient to show improvements in cytomegalovirus prevention in recipients of allogeneic stem-cell transplants in the setting of pre-emptive antiviral treatment. Clinical and virological composite endpoints should be used in future trials.

Funding ViroPharma Incorporated.

Introduction

Before the availability of effective antiviral strategies, cytomegalovirus disease was a common cause of morbidity and mortality after allogeneic stem-cell transplantation.[1] Currently, this disease can be prevented in most recipients of allogeneic stem-cell transplant either by pre-emptive treatment based on cytomegalovirus detection in blood by antigenaemia[2] or PCR,[3] or by universal prophylaxis initiated in at-risk patients at engraftment and continued until 100 days after transplantation.[4,5] Although these strategies reduce cytomegalovirus disease, they are limited by neutropenia caused by ganciclovir or valganciclovir. Second-line antiviral drugs foscarnet[6] and cidofovir[7] cause renal toxic effects and other adverse events. Finally, even in the pre-emptive therapy era,[8] recipient patients seropositive for cytomegalovirus continue to have a higher mortality than do seronegative recipients.[9] Thus, more effective and safer antiviral drugs that can be given prophylactically to recipients of allogeneic stem-cell transplant are clearly needed.

Maribavir (ViroPharma Incorporated) is an orally available antiviral drug that binds to the human cytomegalovirus protein kinase UL97 and causes inhibition of viral encapsidation and nuclear egress of viral particles from infected cells.[10,11] In vitro, maribavir is more potent than is ganciclovir against cytomegalovirus, and is active against ganciclovir-resistant cytomegalovirus strains.[12] In a phase 2 study of recipients of allogeneic stem-cell transplant,[13] maribavir prevented cytomegalovirus infection significantly better than did

placebo; no cases of cytomegalovirus disease were recorded in patients given maribavir. We did a phase 3 study to assess the safety, tolerability, and anti-cytomegalovirus activity of oral maribavir in recipients of allogeneic stem-cell transplant.

Methods

Patients

Patients were recruited from 90 centres in the USA, Europe, and Canada. Recipients of allogeneic stem-cell transplant older than 18 years, who were recipient or donor seropositive for cytomegalovirus, were eligible for the study. Dosing with maribavir had to start 14–30 days after transplantation, at which time patients had to have evidence of engraftment, no detectable cytomegalovirus infection, and the ability to swallow tablets. Exclusions to study entry included history of cytomegalovirus disease 6 months before randomisation, treatment for cytomegalovirus after transplantation, and severe hepatic or renal dysfunction (for detailed criteria see webappendix p 2). The institutional review boards at every centre approved the study. Patients gave written informed consent before enrolment.

Randomisation and masking

Eligible patients were randomly assigned (2:1) to receive either oral maribavir 100 mg twice daily or matching placebo with concealed allocation. Randomisation was done by use of a 24-h centralised computerised automated voice response system. Randomisation was stratified study-wide by cytomegalovirus serostatus of recipients and by type of transplant conditioning (myeloablative or reduced intensity). Study personnel, site pharmacists, and patients were masked to drug assignment throughout the study.

Treatment and follow-up

Because all doses tested in the phase 2 study[13] (100 mg twice daily, 400 mg once daily, and 400 mg twice daily) were associated with similar cumulative incidences of cytomegalovirus infection without evidence of a dose-response effect, we selected a dose of 100 mg twice daily for this trial. Treatment-emergent dysgeusia and nausea were reported by 35% of patients randomised to the highest maribavir dose, whereas these events were reported in 18–25% of patients at the lower doses (placebo rates were 0% and 7%, respectively).[13] A regimen of 100 mg twice daily of maribavir seemed to provide good tolerability and activity for cytomegalovirus prophylaxis.

Treatment was continued for up to 12 weeks. During this time, use of other treatment for cytomegalovirus was prohibited. The use of aciclovir, valaciclovir, or famciclovir at prophylactic doses for herpes simplex or varicella zoster viruses was allowed. While receiving study drug, patients had weekly surveillance testing for cytomegalovirus infection. If infection was detected or cytomegalovirus disease was diagnosed, treatment was discontinued and patients were given either ganciclovir or another antiviral drug against cytomegalovirus at the discretion of the investigators. Patients who completed 12 weeks of treatment had follow-up assessments up to week 24 to continue surveillance testing and to monitor for cytomegalovirus disease, bacterial or fungal infections, graft-versus-host disease, and survival. Patients were followed up from week 24 up to week 48 to monitor for cytomegalovirus disease and survival.

Study monitoring and study outcomes

Laboratory procedures are described in p 4 of the webappendix. Safety was assessed weekly by recording adverse events, changes in physical examination, and results of standard haematological and chemistry tests; electrocardiograms and urinalyses were done monthly during study drug administration. Investigators used standard criteria to diagnose and grade acute graft-versus-host disease.[14] An unblinded independent data monitoring

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See **Online** for webappendix

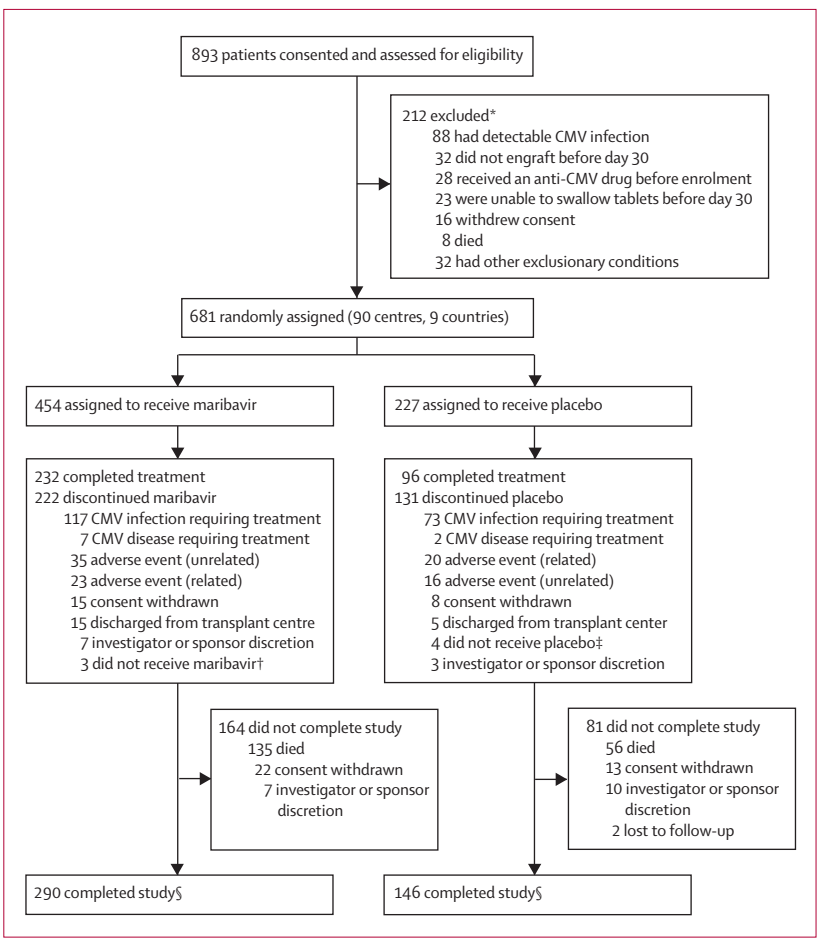

Figure 1: **Trial profile**
CMV=cytomegalovirus. *Some participants had more than one reason that led to exclusion. †Two patients withdrew consent and one was admitted to hospital for loss of consciousness after randomisation but before administration of first dose of study drug. ‡One patient started foscarnet prophylaxis the night before administration of study drug, one had CMV viraemia, and two withdrew consent. §Study completion includes all randomised patients.

committee reviewed all available safety data roughly every 6 months during the study. A separate endpoint committee remained blinded and adjudicated all investigator-reported cases of cytomegalovirus disease according to published definitions.[15]

The primary endpoint of the study was the incidence of cytomegalovirus disease confirmed by the endpoint committee within 6 months of transplantation. Prespecified secondary efficacy endpoints included the time of onset of cytomegalovirus disease, the incidence and time of onset of cytomegalovirus infection, and start of treatment against cytomegalovirus (as pre-emptive therapy or as treatment of cytomegalovirus disease). For analysis purposes, cytomegalovirus infection was defined as a positive pp65 antigenaemia assay (≥1 positive cell per 100 000 leucocytes) or positive plasma cytomegalovirus DNA PCR (≥1000 DNA copies per mL). Safety endpoints included all adverse events, mortality, and changes in laboratory assessments. Adverse events were defined as events that started or worsened during administration of study drug or within 7 days of the last dose of study drug. Additional specific predefined safety endpoints included the occurrence of acute or chronic graft-versus-host disease, neutropenia, invasive fungal or bacterial infections, and non-cytomegalovirus herpes-virus infections.

	Placebo n=227	Maribavir n=454
Median age in years (range)	52 (18–77)	52 (18–74)
Sex		
Men	129 (57%)	265 (58%)
Women	98 (43%)	189 (42%)
Underlying disease		
Acute leukaemia	107 (47%)	257 (57%)
Lymphoma	33 (14%)	62 (14%)
Myelodysplastic syndrome	36 (16%)	46 (10%)
Chronic lymphocytic leukaemia	13 (6%)	26 (6%)
Multiple myeloma	14 (6%)	20 (4%)
Chronic myeloid leukaemia	9 (4%)	20 (4%)
Aplastic anaemia	4 (2%)	7 (2%)
Other	11 (5%)	16 (3%)
Donor type		
Matched related	112 (49%)	212 (47%)
Mismatched related	5 (2%)	6 (1%)
Unrelated	110 (48%)	236 (52%)
Stem-cell source		
Peripheral blood	192 (85%)	381 (84%)
Bone marrow	19 (8%)	48 (11%)
Cord blood	16 (7%)	25 (5%)
Conditioning regimen		
Myeloablative	120 (53%)	253 (56%)
Reduced intensity	107 (47%)	201 (44%)
Cytomegalovirus serostatus		
Donor seronegative, recipient seropositive	96 (42%)	185 (41%)
Donor seropositive, recipient seropositive	92 (41%)	192 (42%)
Donor seropositive, recipient seronegative	39 (17%)	76 (17%)
Donor seronegative, recipient seronegative	0	1 (<1%)
Baseline acute graft-versus-host disease (any grade)	48 (21%)	105 (23%)
Baseline acute graft-versus-host disease (≥grade 2)	21 (9%)	52 (11%)
Antiviral prophylaxis		
Aciclovir	157 (69%)	306 (67%)
Valaciclovir	61 (27%)	127 (28%)
Famciclovir	0	8 (2%)
Median days from transplantation to randomisation (range)	24 (14–41)	24 (13–32)

Table 1: **Patient characteristics of intention-to-treat population**

Sample size and statistical analysis

On the basis of published data[16] and the phase 2 study,[13] we assumed the incidence of cytomegalovirus disease within 6 months after transplantation to be 3% for maribavir and 9% for placebo. Allowing for a loss to follow-up because of death or other reasons of 16%[13] and the stratified randomisation (ratio 2:1), we planned a target of at least 613 patients to ensure 80% power for detection of a treatment difference with type 1 error of 0·05 for two-sided tests. The primary efficacy analysis was done on the intention-to-treat population, which included all patients who were randomly assigned in the study. Safety data were analysed for patients who received at least one dose of study drug. All analyses for binary endpoints of cytomegalovirus infection or disease and initiation of treatment against cytomegalovirus were done with a Cochran-Mantel-Haenszel test for comparison between study treatment groups, adjusting for randomisation strata. Any patient who died within 6 months of transplantation without previous cytomegalovirus disease confirmed by endpoint committee, or who was lost to follow-up within 6 months of transplantation without previous confirmed cytomegalovirus disease, was ground-ruled as no event. Kaplan-Meier estimates, log-rank testing, and Cox proportional hazard model analyses adjusting for cytomegalovirus serostatus of recipients and type of transplant conditioning were used to analyse all time-to-event endpoints for assessment of treatment effects. This trial is registered with ClinicalTrials.gov, NCT00411645.

Role of the funding source

The sponsor of the study contributed to study design and coordination, data collection, and prespecified data analysis according to the protocol. The authors had full access to all the data and wrote the report with input from the sponsor. All authors had final responsibility for the decision to submit for publication.

Results

From Dec 6, 2006, to May 23, 2008, 893 patients consented to participate in the study. 212 patients were not eligible (figure 1). The most common reasons for exclusion were detectable cytomegalovirus infection at the time of screening (42%), lack of engraftment (15%), treatment

	100 days					6 months				
	Placebo (n=227)	Maribavir (n=454)	OR	95% CI	p value	Placebo (n=227)	Maribavir (n=454)	OR	95% CI	p value
EC-confirmed CMV disease	6 (2·6%)	11 (2·4%)	0·91	(0·33–2·51)	0·86	11 (4·8%)	20 (4·4%)	0·90	(0·42–1·92)	0·79
CMV infection or EC-confirmed disease										
pp65 antigen*	79 (34·8%)	120 (26·4%)	0·67	(0·47–0·95)	0·02	88 (38·8%)	143 (31·5%)	0·72	(0·52–1·01)	0·06
DNA PCR*	69 (30·4%)	126 (27·8%)	0·88	(0·62–1·25)	0·47	77 (33·9%)	152 (33·5%)	0·98	(0·70–1·38)	0·90
Either pp65 antigen or PCR*	92 (40·5%)	157 (34·6%)	0·77	(0·56–1·08)	0·13	101 (44·5%)	183 (40·3%)	0·84	(0·61–1·16)	0·29
Initiation of treatment against CMV	85 (37·4%)	139 (30·6%)	0·73	(0·52–1·03)	0·07	92 (40·5%)	172 (37·9%)	0·89	(0·64–1·24)	0·49

OR=odds ratio. CMV=cytomegalovirus. EC=endpoint committee. *Combined results of tests done at either local laboratories or the central laboratory.

***Table 2*: Cochran-Mantel-Haenszel analysis of maribavir versus placebo of the intention-to-treat population**

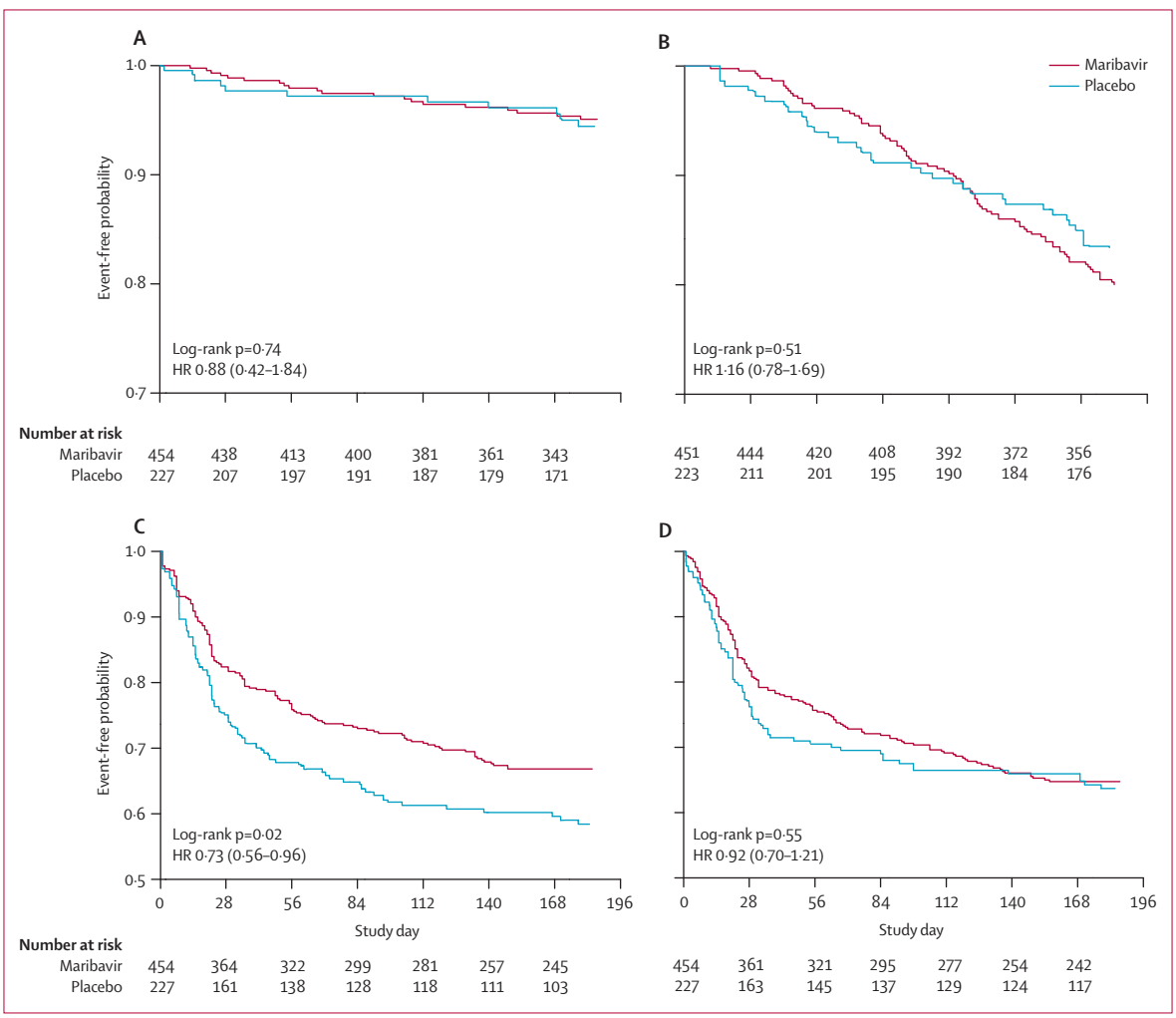

***Figure 2*: Cytomegalovirus events and mortality within 6 months of transplantation**

Kaplan-Meier curves are shown for patients receiving maribavir and placebo over time relative to the start of drug treatment. Results are shown for cytomegalovirus disease confirmed by the endpoint committee (A, primary endpoint), all-cause mortality (B, intention-to-treat, safety population), cytomegalovirus infection (determined by pp65 antigen testing) or disease (C), and cytomegalovirus infection (determined by DNA PCR testing) or disease (D). Panels C and D include results from tests done at either local laboratories or the central laboratory. Hazard ratios (HR) and 95% CIs were obtained by Cox modelling adjusting for recipient cytomegalovirus serostatus and conditioning regimen.

with a drug with anticytomegalovirus activity before enrolment (13%), and inability to take oral medications before day 30 after transplantation (11%). Of the 681 patients assigned study drug, 43 (6%) patients (21 placebo, 22 maribavir) were erroneously stratified at randomisation; this information was corrected for all

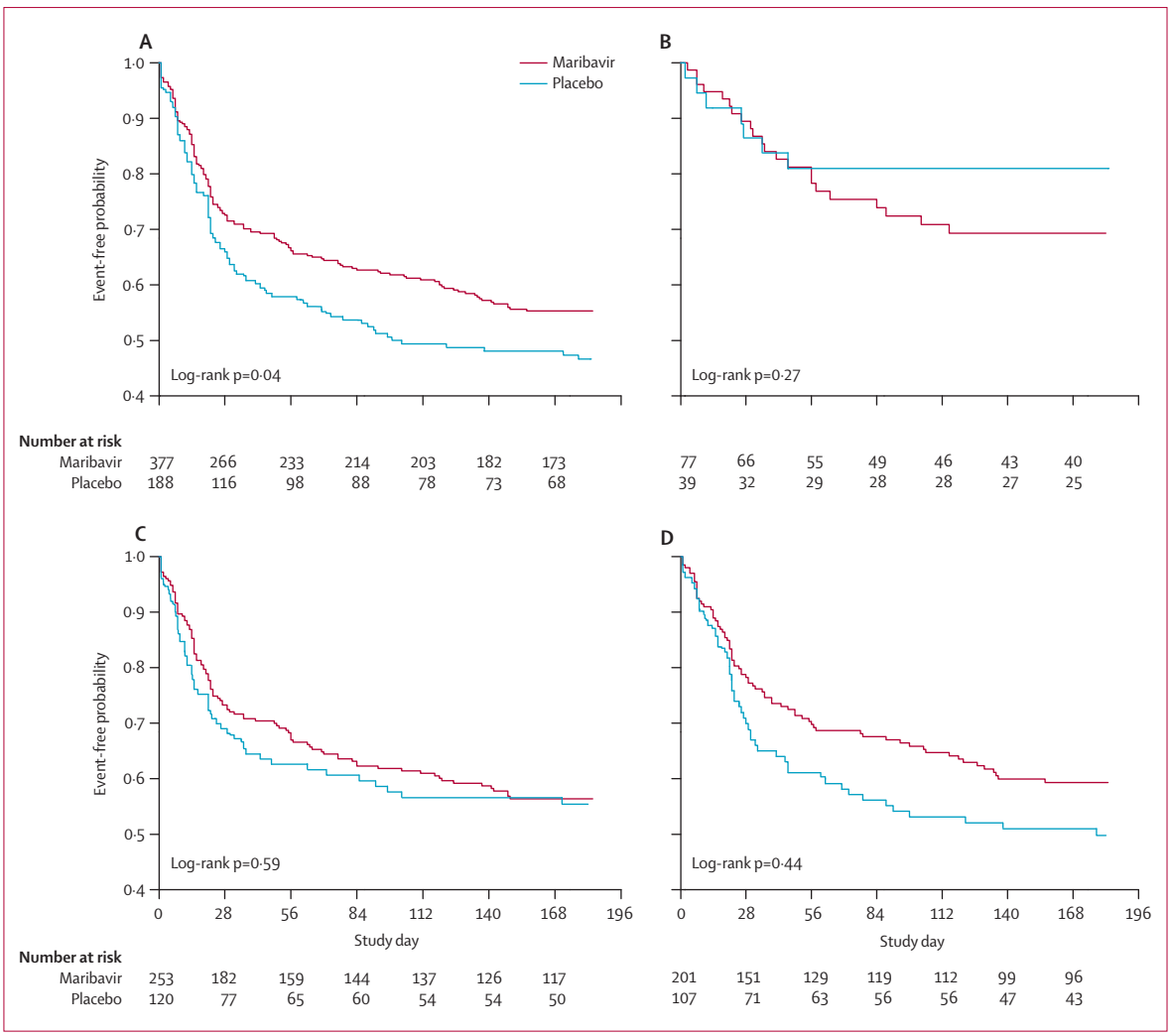

Figure 3: **Cytomegalovirus infection or disease within 6 months by stratification subsets**
Kaplan-Meier curves are shown for patients receiving maribavir and placebo over time relative to the start of treatment. All panels present results for cytomegalovirus infection (as determined by either pp65 antigen or DNA PCR, at either local laboratories or the central laboratory) or cytomegalovirus disease. Results are shown for patients who were seropositive (A) and seronegative (B) for cytomegalovirus, patients who received myeloablative transplant conditioning regimens (C), and patients who received reduced-intensity transplant conditioning regimens (D).

analyses. Deviations in eligibility criteria were documented for 76 (11%) patients (31 placebo, 45 maribavir) including 34 (5%) who had detectable cytomegalovirus infection or a test for the virus that did not occur within 5 days of randomisation (15 placebo, 19 maribavir), 22 (3%) started taking study drug outside the 14–30 day window after transplantation (eight placebo, 14 maribavir), ten (1%) received an antiviral drug against cytomegalovirus after transplantation (three placebo, seven maribavir), nine (1%) did not have absolute neutrophil counts above 500 per μL for three consecutive measurements (five placebo, four maribavir), four (1%) had liver test abnormalities higher than allowed by study entry criteria (two placebo, two maribavir), and one patient each did not have positive cytomegalovirus serostatus, had a pregnancy test done more than 5 days before study enrolment, or was receiving phenytoin at the time of enrolment (all maribavir; some patients had more than one deviation in eligibility criteria). All patients were included in the analyses. The study groups were similar in terms of age, sex, underlying disease, donor type, stem-cell source, conditioning regimen, and cytomegalovirus serostatus (table 1).

Patients started treatment at a median of 24 days (range 13–41) after transplantation and received maribavir for a median of 75 days (1–92) and placebo for 47 days (1–89). Maribavir plasma concentrations were consistent with data from patients receiving maribavir 100 mg twice daily in the phase 2 study[13] (webappendix p 5). For both treatment groups, the most common reason for not completing the planned 12 weeks of treatment was cytomegalovirus infection or disease needing antiviral treatment (maribavir 27%, placebo 33%),

followed by adverse events (maribavir 13%, placebo 16%), withdrawal of consent (3% for each group), and exclusion at the discretion of the local investigator (1% for each group, figure 1).

The two treatment groups did not differ significantly in the number of patients who developed confirmed cytomegalovirus disease within 6 months of transplantation (OR 0·90, 95% CI 0·42–1·92; table 2, figure 2). All but one of the cases of cytomegalovirus disease occurred in recipients who were seropositive for cytomegalovirus at a median of 83 days after transplantation (range 27–202 days). The most common presentations of cytomegalovirus disease in both groups were gastrointestinal (71%) and pulmonary (26%).

The cumulative incidences of the combination of confirmed cytomegalovirus disease or infection were assessed with pp65 antigenaemia, cytomegalovirus DNA PCR, either test positivity in the central or site laboratories or by start of anticytomegalovirus treatment, at 100 days and 6 months after transplantation (table 2, figure 2). In these analyses, fewer patients in the maribavir group had confirmed cytomegalovirus disease or infection than in the placebo group for both timepoints. Times to cytomegalovirus infection were delayed in the maribavir group compared with the placebo group. These differences were not significant with the exception of when cytomegalovirus infection was defined as pp65 antigenaemia (p=0·02). Time to initiation of treatment for cytomegalovirus was significantly longer in patients receiving maribavir by 100 days after transplantation than in those receiving placebo (hazard ratio [HR] 0·72, 95% CI 0·55–0·95), but the difference decreased by 6 months after transplantion (HR 0·82, 95% CI 0·64–1·05).

When events were analysed combining cytomegalovirus infection and confirmed disease, patients who were recipient-seronegative and had a seropositive donor had fewer cytomegalovirus events than seropositive-recipient patients. Although time-to-cytomegalovirus events occurred later during study course in patients receiving reduced intensity conditioning, the probability of an event for these patients did not differ from that of those receiving myeloablative conditioning (figure 3). When patients were stratified by occurrence of acute graft-versus-host disease, those with no or grade I acute disease had fewer cytomegalovirus events than those with grade II–IV acute graft-versus-host disease. When death and loss to follow-up were included as events in addition to cytomegalovirus disease, 57 of 454 (13%) patients given maribavir reached this composite endpoint by 100 days after transplantation compared with 36 of 227 (16%) patients given placebo (OR 0·76, 95% CI 0·49–1·20); at 6 months after transplantation the rates were 122 of 454 (27%) in the maribavir group and 63 of 227 (28%) in the placebo group (0·96, 0·67–1·37).

98% of patients given maribavir and 96% given placebo had at least one treatment-emergent adverse event during the study (table 3). The proportion of patients who had treatment-emergent serious adverse events was similar in both groups (44%; table 4). A similar proportion of patients discontinued treatment because of adverse events (maribavir 17%, placebo 19%). Treatment-emergent dysgeusia occurred in 66 of 451 (15%) patients given maribavir and in 13 of 223 (6%) patients given placebo. The incidence of neutropenia, the use of haemopoietic growth factors, or transfusional support requirements did not differ between groups; neither did the incidence of other laboratory or clinical adverse events. No genotypic evidence of maribavir resistance was detected (webappendix p 6).

The overall proportion of patients with acute graft-versus-host disease did not differ between patients treated with maribavir and those treated with placebo: 180 of 451 (40%) versus 87 of 223 (39%), respectively, 100 days after transplant and 198 of 451 (44%) versus 96 of 223 (43%) 6 months after transplant. 87 of 451 (19%) patients given maribavir and 55 of 223 (25%) patients given placebo developed chronic graft-versus-host disease 6 months after transplant.

	Placebo (n=223)	Maribavir (n=451)
Patients with ≥1 adverse event	213 (96%)	440 (98%)
Adverse events		
Acute graft-versus-host disease	74 (33%)	164 (36%)
Diarrhoea	42 (19%)	93 (21%)
Fatigue	22 (10%)	73 (16%)
Pyrexia	39 (17%)	72 (16%)
Nausea	35 (16%)	71 (16%)
Dysgeusia	13 (6%)	66 (15%)
Anaemia	17 (8%)	63 (14%)
Rash	30 (13%)	60 (13%)
Peripheral oedema	28 (13%)	58 (13%)
Vomiting	31 (14%)	52 (12%)
Renal failure	20 (9%)	46 (10%)
Headache	21 (9%)	44 (10%)
Hypertension	13 (6%)	43 (10%)
Weight decrease	29 (13%)	41 (9%)

Table 3: **Adverse events reported in 10% or more of patients, intention-to-treat, safety population**

	Placebo (n=223)	Maribavir (n=451)
Patients with ≥1 serious adverse event	98 (44%)	197 (44%)
Serious adverse events		
Acute graft-versus-host disease	25 (11%)	56 (12%)
Pyrexia	14 (6%)	28 (6%)
Relapse of underlying disease	13 (6%)	21 (5%)
Bacteraemia	6 (3%)	18 (4%)
Renal failure	4 (2%)	14 (3%)
Cytomegalovirus infection	4 (2%)	10 (2%)
Diarrhoea	1 (<1%)	7 (2%)

Table 4: **Serious treatment-emergent adverse events reported in 2% or more of patients, intention-to-treat, safety population**

Panel: **Research in context**

Systematic review

We searched PubMed via its Clinical Queries Tool[22] with the terms "cytomegalovirus", "allogeneic", and "prophylaxis" for studies addressing antiviral chemoprophylaxis against cytomegalovirus in patients having allogeneic haemopoietic stem-cell transplantation. We identified eight randomised clinical trials[2,4,5,13,23–26] and a systematic review and meta-analysis.[27]

Interpretation

Aciclovir or valaciclovir prophylaxis at high dose could reduce cytomegalovirus infection, but not cytomegalovirus disease after allogeneic stem-cell transplantation, and had no effect on overall survival.[8,27,28] Ganciclovir prophylaxis reduced cytomegalovirus infection and disease, but had no effect on overall survival likely because of drug-induced neutropenia leading to secondary bacterial and fungal infections.[8,27,28] Although maribavir prophylaxis at different doses showed a reduction in cytomegalovirus infection in the phase 2 trial,[13] the dose of 100 mg twice daily beginning after engraftment used in this trial did not prevent cytomegalovirus disease when compared with systematic blood surveillance and pre-emptive treatment against cytomegalovirus in a background of low-dose aciclovir prophylaxis.

Standardisation of cytomegalovirus disease definitions,[15] progress in cytomegalovirus surveillance technologies linked to pre-emptive treatment,[8,28] and positive secular trends[29,30] in overall transplantation care in the past 20 years have reduced the incidence of cytomegalovirus disease in recipients of allogeneic stem-cell transplant to less than 3% by day 100 and to less than 5% by 6 months. Despite this progress, cytomegalovirus seropositivity remains associated with worse survival in patients undergoing allogeneic stem-cell transplantation.[9] Non-myelosuppressive antivirals deployed before engraftment or in the setting of acute graft-versus-host disease might benefit patients at higher risk of cytomegalovirus disease and have an effect on overall survival, but such strategies remain to be studied in properly done trials with clinical and virological endpoints that portray the progress in the field.

The incidence of invasive bacterial and fungal infections was lower in the maribavir group than in the placebo group but the magnitude of the differences was small (55 of 451 [12%] for maribavir and 39 of 223 [17%] for placebo at 100 days, and 88 of 451 [20%] for maribavir and 50 of 223 [22%] for placebo by 6 months). The cumulative treatment-emergent adverse events related to Epstein-Barr virus infections, including post-transplant lymphoproliferative disorder, were similar in both study groups (incidence of 12 of 451 [3%] for maribavir and nine of 223 [4%] for placebo by 100 days; 18 of 451 [4%] for maribavir and 11 of 223 [5%] for placebo by 6 months).

By 100 days after transplantation, 19 of 223 (9%) patients died in the placebo group compared with 30 of 451 (7%) in the maribavir group (figure 2). At the completion of study follow-up (48 weeks), 198 deaths were reported: 139 (31%) in the maribavir group and 59 (26%) in the placebo group.

Discussion

Despite promising early results from the phase 2 study,[13] the results from this phase 3 study did not show superiority of maribavir prophylaxis to placebo in prevention of cytomegalovirus disease when started after engraftment. Maribavir prophylaxis showed only a modest antiviral effect in prevention of cytomegalovirus reactivation.

One possible explanation for why these results differed from those of the phase 2 trial[13] is the selected maribavir dose. Phase 1 and phase 2 data suggest that, although maribavir could be given in doses up to 2400 mg daily,[17] taste disturbance was an important problem. Moreover, no clear efficacy dose effect was shown in studies in HIV-infected patients with cytomegalovirus shedding in semen[17] and in cytomegalovirus seropositive recipients of allogeneic stem-cell transplant receiving maribavir prophylaxis.[13] Therefore, the lowest dose with the least toxicity profile was chosen. Moreover, the present trial revealed that toxic effects were fewer than previously reported. Only five patients reported taste disturbance that led to drug discontinuation. In six patients with refractory or resistant cytomegalovirus infections given maribavir at doses of 400 mg twice daily or higher,[18] two reported dysgeusia—it was transient, mild-to-moderate in intensity, and did not lead to treatment discontinuation. Importantly, no haematological, renal, or hepatic toxic effects were noted. The apparent absence of a dose-response effect in suppression of cytomegalovirus reactivation[13] might have been due to the small number of patients treated in each dose group in the phase 2 study, and shorter duration of follow-up.

A second possible reason for this difference in results is the chosen strategy for cytomegalovirus surveillance with both cytomegalovirus antigenaemia and PCR. There was a very modest antiviral effect of maribavir in the present study with an overall reduction of cytomegalovirus antigenaemia and PCR positivity of 15% and a reduction in use of pre-emptive treatment by 18% at 6 months. The effect was more pronounced and statistically significant when analysis was done with cytomegalovirus antigenaemia than with PCR (table 2, figure 2). In fact, there was almost no difference in PCR positivity between the groups at 6 months. Reactivation of cytomegalovirus at the DNA level could therefore be particularly difficult to prevent because of the increased sensitivity of the assay and the biology of cytomegalovirus replication.[19] An earlier study showed that even with daily intravenous ganciclovir prophylaxis cytomegalovirus DNA could be detected by PCR in up to 40% in plasma and 80% in peripheral blood leucocytes.[20]

A third possible reason for the failure to show a beneficial effect of maribavir in reduction of cytomegalovirus disease is that the trial excluded the highest-risk patients. The study excluded patients who had any sign of low-level cytomegalovirus reactivation after engraftment due to the concern that such patients might progress to disease early when randomised to placebo. Indeed, 42% of all screen failures were excluded for this reason. These patients would have had a higher risk of early failure of pre-emptive treatment and breakthrough disease and therefore potentially would have had the greatest benefit of maribavir prophylaxis.

Indeed, pre-emptive treatment worked exceptionally well in the placebo group as shown by cytomegalovirus disease rates that were about half of that projected from natural history studies,[1,8,21] much lower than those used in the statistical projections for this trial. Since maribavir was very safe (eg, having no bone marrow suppressive effect) an earlier start of prophylaxis could be contemplated and might have given a different result.

This trial was one of the largest done for licensure of a new compound against cytomegalovirus in recipients of allogeneic stem-cell transplant (panel). Before the study, the feasibility of doing a trial with a clinical endpoint of cytomegalovirus disease in a setting in which pre-emptive treatment based on optimised PCR assays is now standard of care was a contentious issue.[28,31] Ultimately, the cytomegalovirus disease endpoint was chosen because of regulatory requirements for licensure. The results of this trial raise major concerns about the design of future clinical trials of drugs for cytomegalovirus in transplant recipients. One has to question whether a superiority trial with cytomegalovirus disease as the primary endpoint in prophylaxis trials is still feasible in transplant recipients with the present standard of care. This trial showed that, with optimised pre-emptive treatment, cytomegalovirus disease rates of 2·5% at day 100 and 5% at day 180 after allogeneic stem-cell transplantation are a reality these days. To reduce these numbers by 50% with any new therapeutic drug, a sample size of about 1900 patients would be needed. Thus, we believe that the use of surrogate virological endpoints,[32] composite clinical and virological endpoints, or the need for or extent of pre-emptive antiviral drug treatment should be considered. Since all drugs currently used for pre-emptive treatment have a poor toxicity profile, a reduced use of these drugs is a substantial clinical benefit.

Although dose selection might have contributed to the failure in this particular trial, the results also show that the standard used in the control group is highly effective in prevention of cytomegalovirus disease. The results also have important implications for the design of future pivotal studies of novel therapeutic drugs against cytomegalovirus since they raise doubts as to whether cytomegalovirus disease can be used as a clinical endpoint in this setting.

Contributors

All authors and investigators listed in the webappendix p 1, except SAV and HC, recruited patients, did study procedures and collected data. SAV, PL, DJW, and MB contributed to the study concept and design. FMM, PL, MB, and SAV analysed and interpreted the data. HC did the statistical analyses. FMM wrote the first draft of the report with contributions from PL and MB. All authors revised the report for important intellectual content and approved the final version.

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Conflicts of interest

SAV and HC are employees of ViroPharma Incorporated. All other authors received research funding from ViroPharma Incorporated in association with this clinical trial. FMM, PJ, GAP, DJW, RFC, JM, MS, HE, and MB have served as paid consultants for ViroPharma Incorporated. FMM has received research funding from Chimerix and Vical, and has served as a paid consultant for AiCuris and Cubist. PL has received research funding from Pfizer, Merck, and Genzyme, has served in the data safety monitoring board for studies sponsored by AiCuris and Opal, and has served as a paid consultant for Vical and GlaxoSmithKline. GAP has received research funding from Pfizer and Enzon, and has served as a paid consultant for Astellas, Schering-Plough, and Pfizer. DJW has received research funding from Chimerix. RFC has received research funding from AiCuris. JHY has received research funding from AiCuris and Chimerix. MB has received research funding from Roche, Chimerix, and Vical, and has served as a paid consultant for Chimerix, Vical, Genentech, Boehringer Ingelheim, Astellas Pharma Inc, Theraclone Sciences, and Novartis.

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