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Efficacy and Safety of Maribavir Dosed at 100 mg Orally Twice Daily for the Prevention of Cytomegalovirus Disease in Liver Transplant Recipients: A Randomized, Double-Blind, Multicenter Controlled Trial

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Maribavir is an oral benzimidazole riboside with potent *in vitro* activity against cytomegalovirus (CMV), including some CMV strains resistant to ganciclovir. In a randomized, double-blind, multicenter trial, the efficacy and safety of prophylactic oral maribavir (100 mg twice daily) for prevention of CMV disease were compared with oral ganciclovir (1000 mg three times daily) in 303 CMV-seronegative liver transplant recipients with CMV-seropositive donors (147 maribavir; 156 ganciclovir). Patients received study drug for up to 14 weeks and were monitored for CMV infection by blood surveillance tests and also for the development of CMV disease. The primary endpoint was Endpoint Committee (EC)-confirmed CMV disease within 6 months of transplantation. In a modified intent-to-treat analysis, the noninferiority of maribavir compared to oral ganciclovir for prevention of CMV disease was not established (12% with maribavir vs. 8% with ganciclovir: event rate difference of 0.041; 95% CI: −0.038, 0.119). Furthermore, significantly fewer ganciclovir patients had EC-confirmed CMV disease or CMV infection by pp65 antigenemia or CMV DNA PCR compared to maribavir patients at both 100 days (20% vs. 60%; $p < 0.0001$) and at 6 months (53% vs. 72%; $p = 0.0053$) after transplantation. Graft rejection, patient survival, and non-CMV infections were similar for maribavir and ganciclovir patients. Maribavir was well-tolerated and associated with fewer hematological adverse events than oral ganciclovir. At a dose of 100 mg twice daily, maribavir is safe but not adequate for prevention of CMV disease in liver transplant recipients at high risk for CMV disease.

Key words: Cytomegalovirus, liver transplantation, Maribavir, prevention

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Introduction

Cytomegalovirus (CMV) can be a common cause of infection and symptomatic disease in liver transplant recipients and has been indirectly associated with an increased risk for rejection, decreased allograft survival, and in some cases, higher overall post-transplant mortality (1,2). Common manifestations of CMV disease include CMV syndrome (fever, fatigue, leukopenia), gastrointestinal infection with abdominal pain and diarrhea, hepatitis, and pneumonia. Depending upon the CMV serostatus of the liver transplant recipient and donor prior to transplantation, the incidence of CMV disease after transplantation varies. Despite the use of either oral ganciclovir or valganciclovir prophylaxis after transplantation, CMV-seronegative patients receiving a liver allograft from a CMV-seropositive donor continue to have the highest incidence of CMV disease (3,4).

In a randomized controlled trial, oral ganciclovir was found to provide effective prophylaxis against CMV disease in liver transplant recipients (5). Recent meta-analyses have

also shown that antiviral prophylaxis reduces the indirect effects of CMV infection and is generally more effective than pre-emptive therapy for prevention of CMV disease in high-risk CMV seronegative patients with CMV seropositive donors (6–8). Similarly, oral valganciclovir, which has much higher oral bioavailability than ganciclovir (9), is approved for CMV prophylaxis in kidney and heart transplant recipients, although it failed to gain Food and Drug Administration (FDA) approval for use in liver transplant patients (10). Nevertheless, despite their effectiveness, the use of both ganciclovir and valganciclovir has been limited by frequent myelotoxicity (5,10) as well as the emergence of ganciclovir-resistant CMV strains (11,12). Thus, there is a growing need for newer antiviral agents, which are active against both wild-type and ganciclovir-resistant CMV strains and do not cause myelosuppression.

Maribavir is an orally bioavailable benzimidazole riboside with a novel mechanism of action against CMV. Maribavir inhibits both CMV DNA assembly and egress of viral capsids from the nucleus of infected cells (13,14). *In vitro*, maribavir is more potent than ganciclovir against CMV, including some CMV strains resistant to ganciclovir (15). In phase 1 studies among human immunodeficiency virus (HIV)-infected patients, oral maribavir, at doses up to 1200 mg twice daily, decreased CMV levels in semen, caused no myelosuppression, and except for a reversible taste disturbance and skin rash, was well-tolerated (16,17). More recently, a dose-ranging study of oral maribavir (200–800 mg daily) in CMV-seropositive allogeneic stem-cell transplant recipients showed that maribavir reduces CMV infection and does not cause myelosuppression when compared to placebo (18). No cases of CMV disease occurred among these stem-cell transplant patients receiving prophylactic maribavir. Based on these results, we performed a multinational, multi-center phase 3 study to evaluate the efficacy and safety of prophylactic oral maribavir for prevention of CMV disease in high-risk CMV-seronegative liver transplant patients with CMV-seropositive donors.

Methods

Patients

Patients from 70 centers in the United States and Europe were enrolled in the study. Recipients of orthotopic liver transplants who were ≥18 years-old and CMV-seronegative with a CMV-seropositive donor (D+/R-) were eligible for the study. Dosing with maribavir had to start within 10 days post-transplantation. Patients had to have no detectable CMV infection post-transplantation and be able to swallow pills at time of enrollment. Exclusions to study entry included a history of CMV organ disease within 6 months prior to enrollment, treatment for CMV at time of enrollment, estimated creatinine clearance of <10 mL/min, need for dialysis, infection with HIV, mechanical ventilation, or other serious illness precluding study compliance. Patients undergoing repeat liver transplantation or multi-organ transplantation were also excluded. The institutional review board at each center approved the study. Patients gave informed consent prior to enrollment.

Dose Selection

The dosing regimen of maribavir selected for this study was 100 mg twice daily. This dose was chosen based on the results of a previous phase 2 study evaluating prophylactic maribavir for up to 12 weeks in CMV-seropositive recipients of allogeneic stem-cell transplants (18). Three dosing regimens of maribavir were evaluated in this study (100 mg twice daily, 400 mg once daily, and 400 mg twice daily). Compared to placebo, all three dosing regimens reduced the incidence of CMV infection. The incidences of CMV infection appeared to be similar for the three dosing regimens, but drug-related dysgeusia and nausea were more common with the highest maribavir dose. Thus, a regimen of 100 mg twice daily of maribavir was chosen to provide optimal tolerability, as well as activity for CMV prophylaxis. Furthermore, based upon the results of a pharmacokinetic study of maribavir in patients with moderate hepatic impairment (19), a regimen of 100 mg twice daily of maribavir in liver transplant recipients was likely to provide drug exposure similar to levels well-tolerated in other patients. Because maribavir lacks *in vitro* activity against herpes simplex virus and varicella-zoster virus (14), oral acyclovir at a dose of 400 mg twice daily was given concomitantly with maribavir. Such a low dose of oral acyclovir is generally not considered effective for CMV prophylaxis.

Randomization

Eligible patients were randomly assigned (1:1) to receive either oral maribavir (100 mg twice daily) with oral acyclovir (400 mg twice daily) or oral ganciclovir alone (1000 mg three times daily). Oral ganciclovir was used as the comparative study drug since oral ganciclovir is the only agent currently approved by the FDA for prevention of CMV disease in liver transplant recipients (20). Allocation was concealed by matching placebo pills for either maribavir and acyclovir or ganciclovir. Treatment with study drugs was planned for 14 weeks. Subjects were stratified within each center by the use of anti-lymphocyte antibody (ALA) induction therapy. Study personnel, pharmacists, and patients were masked to drug assignment throughout the study. Dosing adjustments of ganciclovir for renal insufficiency were based on published recommendations (20). Similar dosing adjustments of maribavir for renal failure are not required (21).

Study monitoring and follow-up

Through the planned period of study drug administration, surveillance tests for CMV infection were performed biweekly. Additional testing for CMV was done at weeks 15, 18, 22, and 26 during the follow-up period and whenever there was a case of suspected CMV disease. Tests for CMV pp65 antigenemia (CMV Brite Turbo Kit, Biotest Diagnostics), plasma CMV DNA (COBAS Amplicor CMV Monitor Assay, Roche Diagnostics), and serum CMV antibody were performed by a central laboratory. These tests for CMV infection by the central laboratory were not done in real-time, so the results were not available to the investigators during the study. However, the results of CMV testing done by local laboratories using any preferred assays were used by investigators at each study site to make decisions about treatment for CMV disease. If a patient developed CMV infection or disease requiring treatment, study drugs were discontinued, and nonstudy antiviral therapy for CMV was initiated according to the standard practice and investigator's discretion at each transplant center.

Because the likelihood of observing a given event (e.g., CMV disease or infection, an adverse event or AE, death) is dependent on the duration of the evaluation period, knowing how these periods compare between the two therapy groups is important. All study patients had planned follow-up assessments at weeks 15, 18, 22, and 26 after enrollment. These assessments included CMV surveillance testing and the evaluation for CMV disease, use of antiviral therapy for CMV prevention or treatment, graft rejection, repeat transplantation, survival, and the occurrence of infections caused by other herpes viruses, bacteria, and fungi. Seventy-two percent and 67% of patients in the ganciclovir 1000 mg TID and maribavir 100 mg

BID groups, respectively, remained under evaluation into study week 26. In addition, patients were to be monitored through study week 52 for CMV disease, repeat transplantation and survival. However, when the study was terminated early, follow-up was restricted to 6 months after transplantation.

The median evaluation period for CMV infection assessment, based on last documented CMV assay, was 180 days in the ganciclovir group (range, 1–205 days) and 179 days in the maribavir group (range, 1–204 days), while the median time for evaluation of CMV disease was 204 days in both the ganciclovir group (range, 2–207 days) and maribavir group (range, 4–207 days).

Safety was evaluated by recording adverse events (AEs), changes in physical examinations, and results of standard laboratory tests, electrocardiograms, and urinalyses. Investigators used standard criteria to diagnose allograft rejection. An unblinded data monitoring committee (DMC) reviewed all available safety data approximately every 6 months. Whenever possible, clinical isolates of CMV recovered from cultures were evaluated for resistance to maribavir (22).

Study endpoints

The primary endpoint of the study was the incidence of CMV disease within 6 months of transplantation (either symptomatic CMV infection or CMV organ disease), as adjudicated by an independent Endpoint Committee (EC) using published criteria (23). Pre-specified secondary efficacy endpoints included the time to onset of CMV disease, the incidence and time to onset of CMV infection, and the start of either preemptive therapy or the treatment of established CMV disease. For purposes of analysis, CMV infection was defined as a positive pp65 antigenemia assay (≥1 positive cells per 100,000 leukocytes), a positive plasma CMV DNA polymerase chain reaction (PCR) or CMV hybrid capture assay (≥1000 DNA copies/mL), or any positive CMV culture. Results from both the central laboratory and any local laboratory were used for these analyses. Whenever results from the central and local laboratories were discordant, the test result positive for CMV infection was used for analysis. Discordant results between the central and local laboratories were reported for 9% of patients in each study group.

Sample size and statistical methods

A sample size of 174 patients per study group (a total of 348 patients) was planned to give 80% power to demonstrate the non-inferiority (with margin of 0.05) of maribavir compared to oral ganciclovir for prevention of CMV disease. This sample size was based on a 1:1 allocation of patients to the ganciclovir and maribavir groups and assumed incidences of CMV disease in the ganciclovir and maribavir groups of 12% and 8%, respectively (5,10,18).

In February 2009, the unblinded DMC determined that there was an imbalance between the maribavir and ganciclovir groups in the incidence of CMV infection. Concurrently, the results of a phase 3 trial in allogeneic stem cell transplant recipients showed that maribavir at a dose of 100 mg twice daily did not prevent CMV disease when compared to placebo (24). Thus, although there were no concerns about the safety of maribavir, the committee recommended discontinuing enrollment into the trial and stopping study drug in all subjects. All study patients were then changed to each transplant center's standard regimen for prevention of CMV infection. For those who had already had the opportunity to complete the planned 14-week period of study drug administration, follow-up was continued through 6 months after transplantation and these patients comprised the modified intent-to-treat cohort. For patients who could not receive the planned 14 weeks of study drug due to early termination of the study, there was no follow-up through 6 months after transplantation. Efficacy analyses were performed using all available data in the smaller modified intent-to-treat (ITT-M) population, while safety analyses included all patients who received at least one dose of study drug (ITT-S).

The primary analysis was to determine the non-inferiority of maribavir to oral ganciclovir for the incidence of EC-confirmed CMV disease within 6 months post-transplantation in the ITT-M population. The 95% confidence interval (CI) for the difference in the incidence of CMV disease between maribavir and ganciclovir was determined. Non-inferiority was considered established if the upper limit of the CI was less than the prespecified margin of 0.05. Additionally, the Cochran-Mantel–Haenszel test was used for comparisons of the primary endpoint (CMV disease) and the secondary endpoints (CMV infection, initiation of CMV therapy) between study groups, adjusting for receipt of induction ALA therapy and geographic region (United States or Europe). Kaplan–Meier estimates, log-rank tests, and the Cox proportional hazards model were used to analyze all time-to-event endpoints. All secondary efficacy analyses were performed for both the 100-day post-transplantation period as well as the 6-month post-transplantation period on the ITT-M population.

Results

Disposition of patients

From July 2007 to February 2009, 348 patients were screened for participation in the study. Forty-one patients were screen failures and excluded from the study (Figure 1). Of the 41 patients excluded, 32 patients were excluded for violation of inclusion and/or exclusion criteria, eight withdrew consent, and 1 patient died prior to randomization. The most common violations of inclusion/exclusion criteria were detectable CMV infection at time of screening or a liver donor sero-negative for CMV antibody (8 patients) and inability to begin dosing with study drug within 10 days post-transplantation (8 patients). Three hundred seven patients entered the study and were randomized to receive either oral ganciclovir or oral maribavir for CMV prophylaxis. Four patients never received study drug after randomization. Of the remaining 303 patients (156 ganciclovir, 147 maribavir) who received at least one dose of study drug (ITT-S population), 233 patients (120 ganciclovir, 113 maribavir) either completed 14 weeks of study drug or had the potential to receive 14 weeks of study drug, and were included in the ITT-M population for the efficacy analyses. Seventy patients (36 ganciclovir, 34 maribavir) did not meet the criteria for inclusion in the ITT-M population. Ninety-five percent of ganciclovir patients and 94% of maribavir patients received at least 90% of scheduled doses of study drug.

Table 1 shows the characteristics of the 303 patients who were randomized and received study drug. Generally the two study groups were similar in terms of age, sex, underlying liver disease, donor source, type of biliary anastomosis, MELD score, and maintenance immunosuppressive drugs used for prevention of rejection. A greater proportion of patients in each study group were male. Hepatitis C virus infection and alcoholic cirrhosis were the most common underlying liver diseases leading to the need for liver transplantation. More than 90% of the patients received

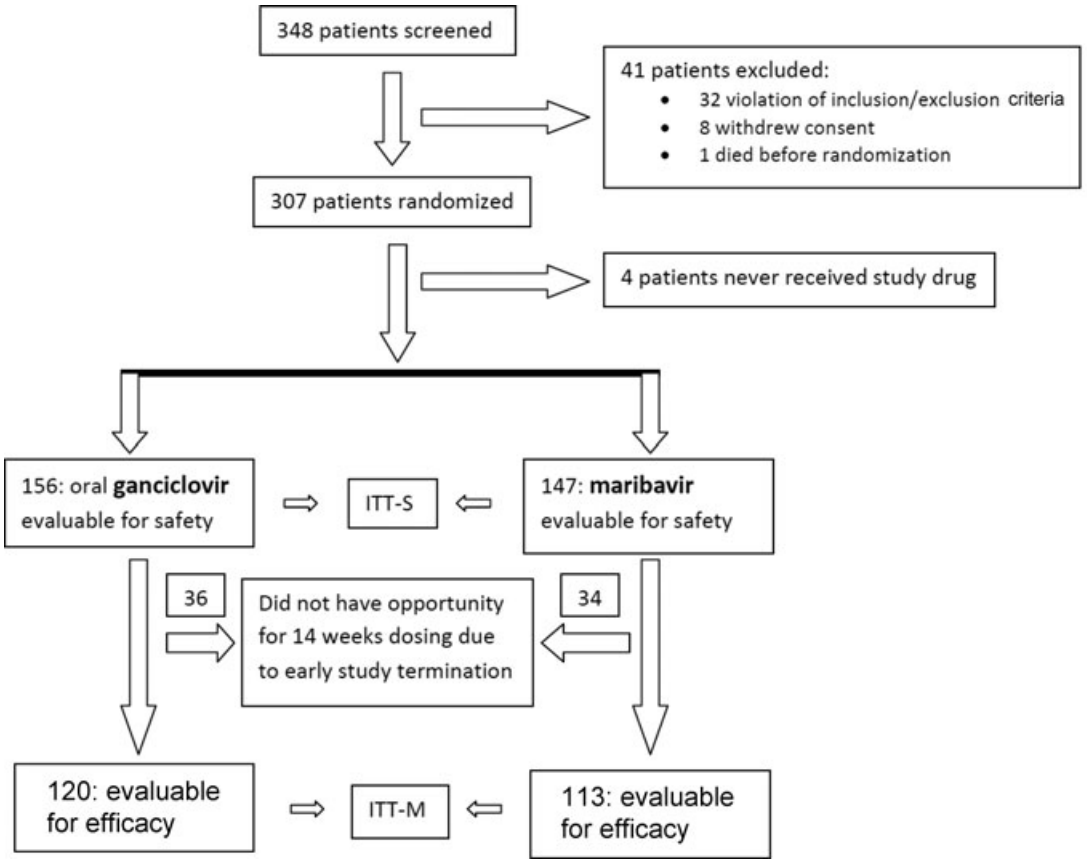

Figure 1: Study Profile.

a whole liver graft from a deceased donor. Similarly, most of the transplants were performed with a duct-to-duct biliary reconstruction. Ten percent of the cohort receiving ganciclovir and 7% of the cohort receiving maribavir had a MELD score ≥30. Ten percent of the ganciclovir cohort and 10% of the maribavir cohort received induction ALA therapy. Mean organ ischemia time and the amount of intra-operative blood products used were similar for the two study groups.

Efficacy

Table 2 summarizes the incidences of CMV infection or disease in the ITT-M population. For the primary endpoint of EC-confirmed CMV disease within 6 months after transplantation, 8% of the ganciclovir patients and 12% of the maribavir patients developed CMV disease. The noninferiority of maribavir compared to oral ganciclovir for prevention of CMV disease was not established (event rate difference: 0.041; 95% CI: −0.038, 0.119). The corresponding treatment difference assessed by odds ratio (OR) was 1.586 with 95% CI: (0.682, 3.690), which is not statistically significant. When the treatment difference in incidence of CMV disease within 6 months after transplantation was further compared by the Cochran-Mantel-Haenszel test adjusting for the use of induction ALA therapy and geographic region, there was no significant difference between the ganciclovir and maribavir groups ($p = 0.2754$). There was no treatment difference in time to onset of EC-confirmed CMV disease within 6 months after transplantation (hazard ratio: 1.63, 95% CI: (0.72, 3.69); $p = 0.2371$). However, within 100 days after transplantation, when most patients were still to have been receiving study drug per protocol, the incidence of EC-confirmed CMV disease was significantly lower in the ganciclovir group (0 patients) compared to the maribavir group (9%, $p = 0.0007$). The most common types of CMV disease were CMV syndrome with viremia (13 patients), gastrointestinal disease (5 patients), hepatitis (3 patients), and pneumonia (3 patients). Death from CMV disease was adjudicated by the EC in one patient with CMV pneumonia.

For the secondary endpoints of the combination of CMV infection (pp65, PCR, or either) or EC-confirmed CMV disease, the ganciclovir group had a significantly lower incidence of either compared with the maribavir group at both 100 days after transplantation (all $p < 0.0001$) and at 6 months after transplantation ($p = 0.0283$, 0.0024 and 0.0053; Table 2). For initiation of anti-CMV therapy, significantly fewer ganciclovir patients than maribavir patients had EC-confirmed disease or received additional anti-CMV

Table 1: Characteristics of patients receiving study drug (ITT-S population)

Parameter[1]	Ganciclovir 1000 mg TID (N = 156)	Maribavir 100 mg BID (N = 147)
Age (mean, range), years	53 (19–72)	55 (19–71)
Sex, no. (%)		
Male	119 (76%)	120 (82%)
Female	37 (24%)	27 (18%)
Principle liver disease		
Hepatitis C virus	43 (28%)	53 (36%)
Alcoholic cirrhosis	36 (23%)	26 (18%)
Hepatocellular carcinoma	14 (9%)	17 (12%)
Hepatic steatosis	11 (7%)	14 (10%)
Cryptogenic cirrhosis	12 (8%)	8 (5%)
Sclerosing cholangitis	8 (5%)	9 (6%)
Autoimmune hepatitis	5 (3%)	4 (3%)
Hepatitis B	2 (1%)	6 (4%)
Primary biliary cirrhosis	5 (3%)	2 (1%)
Other	20 (13%)	8 (5%)
Concomitant carcinoma		
Hepatocellular	51 (33%)	61 (41%)
Biliary tract	4 (3%)	2 (1%)
Donor source		
Deceased-donor whole liver	150 (96%)	135 (92%)
Deceased-donor split-liver graft	3 (2%)	5 (3%)
Live-donor graft	3 (2%)	7 (5%)
Type of biliary reconstruction		
Duct-to-duct	139 (89%)	134 (91%)
Roux-en-Y	17 (11%)	13 (9%)
MELD score at time of liver transplant[2]		
<15	24 (15%)	22 (15%)
15–19	23 (15%)	26 (18%)
20–24	55 (35%)	64 (44%)
25–29	38 (24%)	24 (16%)
30–34	7 (4%)	8 (5%)
≥35	9 (6%)	3 (2%)
Maintenance immunosuppression		
Tacrolimus	142 (91%)	137 (93%)
Mycophenolate mofetil	116 (74%)	121 (82%)
Prednisone	104 (67%)	103 (70%)
Use of ALA as induction immunosuppression	15 (10%)	14 (10%)
Rejection within 6 months of transplantation	23 (15%)	20 (14%)

[1]None of the differences between study groups have statistical significance ($p > 0.05$).
[2]MELD, model for end-stage liver disease.

Table 2: Incidence of CMV infection or disease in the modified intent-to-treat population

	100 days posttransplantation			6 months posttransplantation		
Parameter	Ganciclovir 1000 mg TID (N = 120)	Maribavir 100 mg BID (N = 113)	p-Value[1]	Ganciclovir 1000 mg TID (N = 120)	Maribavir 100 mg BID (N = 113)	p-Value[1]
EC-confirmed CMV disease	0	10 (9%)	0.0007	10 (8%)	14 (12%)	0.2754
Investigator-determined CMV disease	3 (3%)	17 (15%)	0.0008	18 (15%)	22 (19%)	0.3742
CMV infection or EC-confirmed disease						
pp65 antigenemia[2]	19 (16%)	49 (43%)	< 0.0001	49 (41%)	63 (56%)	0.0283
CMV DNA PCR[2]	18 (15%)	59 (52%)	< 0.0001	52 (43%)	72 (64%)	0.0024
pp65 antigenemia or CMV DNA PCR[2]	24 (20%)	68 (60%)	< 0.0001	64 (53%)	81 (72%)	0.0053
Initiation of anti-CMV therapy	5 (4%)	37 (33%)	< 0.0001	39 (33%)	46 (41%)	0.2339

EC = endpoint committee.
[1]P value from Cochran-Mantel-Haenszel test, adjusting for receipt of induction ALAs and geographic region (US or Europe).
[2]Combined results from either local laboratories or central laboratory.

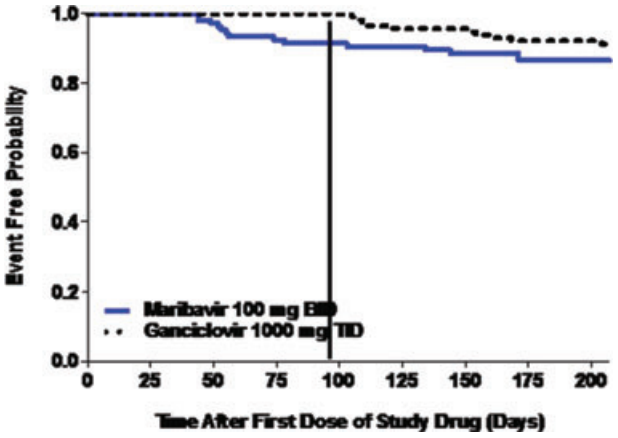

Figure 2: Kaplan–Meier curves for time to onset of EC-confirmed CMV disease within 6 months after transplantation in the modified intent-to-treat population. Antiviral prophylaxis planned until day 98 (vertical line).

therapy at 100 days post-transplantation (4% vs. 33%, $p < 0.0001$), but not at 6 months post-transplantation (33% vs. 41%, $p = 0.2339$). The treatment difference was statistically significant in time to onset of CMV infection (by pp65 or PCR) or EC-confirmed CMV disease, in favor of ganciclovir group with longer time to onset compared to the maribavir group, at both 100 days and at 6 months post-transplantation ($p < 0.0001$; Figures 2 and 3).

Only 3 CMV isolates were available for antiviral susceptibility testing. Two CMV isolates were obtained after maribavir dosing, and one CMV isolate was obtained after ganciclovir dosing. All 3 CMV isolates were sensitive to maribavir (range of mean IC_{50} μM, 0.19–0.77 μM).

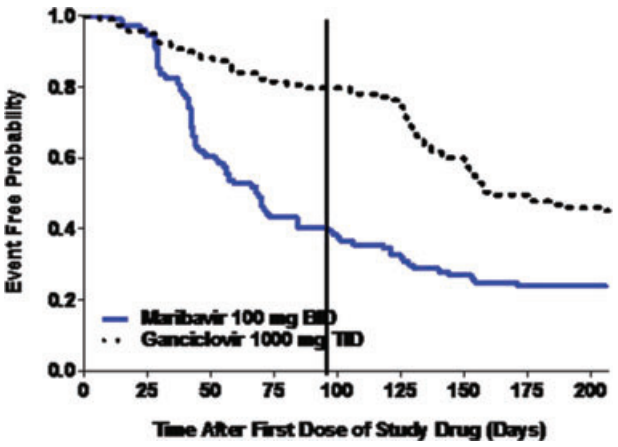

Figure 3: Kaplan–Meier curves for time to onset of CMV infection (determined by pp65 antigen test or CMV DNA PCR at local or central laboratory) or EC-confirmed CMV disease within 6 months after transplantation in the modified intent-to-treat population. Antiviral prophylaxis planned until day 98 (vertical line).

Table 3: Treatment-emergent AEs reported in 10% or more of patients who received study drug (ITT-S population)

	Ganciclovir 1000 mg TID (N = 156)	Maribavir 100 mg BID (N = 147)
Patients with ≥1 treatment-emergent adverse event	152 (97%)	139 (95%)
Adverse events[1]		
Diarrhea	38 (24%)	42 (29%)
Tremor	20 (13%)	25 (17%)
Increased hepatic enzyme	17 (11%)	24 (16%)
Urinary tract infection	12 (8%)	23 (16%)
Dysgeusia	20 (13%)	22 (15%)
Peripheral edema	15 (10%)	21 (14%)
Headache	29 (19%)	20 (14%)
Hyperkalemia	23 (15%)	20 (14%)
Pyrexia	20 (13%)	19 (13%)
Hypertension	21 (13%)	18 (12%)
Recurrent hepatitis C	10 (6%)	16 (11%)
Liver transplant rejection	19 (12%)	15 (10%)
Nausea	29 (19%)	15 (10%)
Renal failure	13 (8%)	15 (10%)
Decreased appetite	6 (4%)	14 (10%)
Hypomagnesaemia	12 (8%)	14 (10%)
Vomiting	17 (11%)	14 (10%)
Leukopenia	20 (13%)	12 (8%)
Fatigue	18 (12%)	10 (7%)
Abdominal pain	17 (11%)	13 (9%)
Insomnia	17 (11%)	13 (9%)
Anemia	17 (11%)	10 (7%)

[1]None of the differences between study groups have statistical significance ($p > 0.05$).

Other infections

Nine subjects in the ITT-S analysis had one or more non-CMV herpesvirus infections documented within 6 months after transplantation (4 ganciclovir, 5 maribavir). Four of the subjects had documented Epstein-Barr virus infection (3 ganciclovir, 1 maribavir), three subjects had documented herpes zoster infection (1 ganciclovir, 2 maribavir) and two subjects had oral herpes simplex infection (both maribavir). The incidences of invasive bacterial and fungal infections at both 100 days after transplantation (11% of ganciclovir patients, 10% of maribavir patients) and at 6 months after transplantation (15% of ganciclovir patients, 12% of maribavir patients) were similar in both study groups.

Adverse events

As expected in this study population, AEs were common. Ninety-seven percent of ganciclovir patients and 95 percent of maribavir patients had one or more treatment-emergent AEs during the study (first day of study drug through 7 days after last dose of study drug). Table 3 summarizes treatment-emergent AEs reported by investigators in 10 percent or more of patients in either therapy group. Generally, the incidences and types of most AEs were similar for the two study groups. Diarrhea was the most frequently reported AE in both study groups. The incidence

Table 4: Serious treatment-emergent adverse events reported in 3% or more of patients who received study drug (ITT-S population)

	Ganciclovir 1000 mg TID (N = 156)	Maribavir 100 mg BID (N = 147)
Patients with ≥1 treatment-emergent serious adverse event	76 (49%)	71 (48%)
Serious adverse events[1]		
CMV infection	2 (1%)	12 (8%)
Increased hepatic enzyme	4 (3%)	8 (5%)
Bile duct stenosis	2 (1%)	4 (3%)
Liver transplant rejection	12 (8%)	4 (3%)
Post-procedural bile leak	2 (1%)	4 (3%)
Pyrexia	7 (4%)	4 (3%)
Renal failure	3 (2%)	4 (3%)
Ascites	4 (3%)	3 (2%)
Diarrhea	4 (3%)	2 (1%)
Anemia	4 (3%)	1 (1%)
Death within 6 months after transplantation	6 (4%)	9 (6%)

[1]Only the difference in CMV infection (1% vs. 8%) between study groups has statistical significance ($p < 0.05$).

of dysgeusia or taste disturbance, an AE commonly associated with maribavir in previous clinical studies, was similar for ganciclovir and maribavir patients. On the other hand, nausea, leukopenia, and anemia were more frequent in the ganciclovir patients. Hematological AEs (the combined AEs of leukopenia, neutropenia, thrombocytopenia, or pancytopenia) were reported by investigators more frequently in the cohort receiving ganciclovir than in the cohort receiving maribavir (21% vs. 14%). The use of hematopoietic growth factors was also somewhat greater in the ganciclovir cohort as compared with the maribavir cohort in the 6-month assessment period (20% vs. 15%). Neutropenia (absolute neutrophil count <1000 cells/uL) based on analysis of laboratory data occurred in 14% of ganciclovir patients (22 of 154) while on ganciclovir or valganciclovir and in 6% of maribavir patients (8 of 143) while on maribavir ($p < 0.05$).

The proportion of patients who had serious treatment-emergent AEs was similar in the two study groups (Table 4). Except for the higher incidence of CMV infection among patients receiving maribavir prophylaxis ($p < 0.05$), the types of serious AEs were similar for both ganciclovir and maribavir cohorts. Since the study design required discontinuation of study drug for any CMV infection or CMV disease requiring treatment, more maribavir (18%) than ganciclovir patients (9%) discontinued study drug due to an AE ($p < 0.05$).

Graft function and patient survival

Twenty-three (15%) ganciclovir patients and 20 (14%) maribavir patients had acute liver graft rejection within 6 months after transplantation. Twelve of these cases of liver graft rejection among ganciclovir patients (8%) and 4 of the cases of rejection among maribavir patients (3%) were reported as serious AEs by investigators (Table 4). The incidence of graft failure within 6 months after transplantation was also similar in both study groups (3% in ganciclovir cohort; 2% in maribavir cohort). Two patients in each study group required repeat liver transplantation.

Six ganciclovir patients (4%) and 9 maribavir patients (6%) expired within 6 months after transplantation. There was no statistically significant difference between the treatment groups for the time to all cause death within 100 days and 6 months (all *p*-values > 0.1). The number of deaths and time to death within 100 days after transplantation were also similar in both treatment groups. Mortality related to sepsis was responsible for 4 of the 6 deaths in the ganciclovir cohort and 1 of 9 deaths in the maribavir cohort. The other 2 deaths in the ganciclovir cohort were the result of lung cancer and CMV pneumonia. The remaining 8 deaths in the maribavir cohort were the result of the following (n = 1 each): myocardial infarction, cardiac failure, cardiac arrest, portal vein thrombosis, hepatocellular carcinoma, intra-abdominal hemorrhage, subarachnoid hemorrhage and respiratory failure (and eventual wound evisceration in the same patient).

Discussion

Liver transplant recipients who are CMV-seronegative and receive an organ from a CMV-seropositive donor have the highest risk for developing CMV disease (1,25). The net state of immunosuppression also influences the risk for CMV disease. In particular, the use of ALAs as either induction immunosuppression or therapy for rejection is associated with a higher incidence of CMV disease (25). Consequently, we conducted this study in CMV-seronegative recipients with CMV-seropositive donors and stratified randomization by receipt of ALAs for induction immunosuppression.

Oral ganciclovir is currently the only oral drug approved by the FDA in the United States for prevention of CMV disease in liver transplant recipients (20). In a randomized controlled trial involving high-risk CMV-seronegative solid-organ transplant patients receiving a kidney, heart, liver, kidney-pancreas, kidney-heart or kidney-liver graft from a CMV-seropositive donor, oral valganciclovir to day 100 was found to be as effective as oral ganciclovir for prevention of CMV disease in the kidney and heart transplant patients, but less effective than oral ganciclovir in the liver transplant patients (10). Nonetheless, valganciclovir, due to its better oral bioavailability and lower pill burden, has replaced oral ganciclovir at many liver transplant centers. In this phase 3 study designed to demonstrate the non-inferiority of maribavir to the approved agent for CMV prophylaxis in liver transplant recipients, oral ganciclovir had to be used as the comparative drug for licensure of maribavir as an agent for CMV prophylaxis.

Despite maribavir's potent *in vitro* activity for CMV and the favorable results from a previous phase 2 study of maribavir prophylaxis in stem-cell transplant patients (13,14,18), this study failed to demonstrate the non-inferiority of maribavir at a dose of 100 mg twice daily to oral ganciclovir 1000 mg three times daily for prevention of CMV disease. There was no significant difference between the ganciclovir and maribavir groups for the incidence of EC-confirmed CMV disease at 6 months post transplantation, but the incidence of CMV disease within the period of 100 days after transplantation (when most patients were still to have been on study drug per protocol) was significantly lower in the ganciclovir group compared to the maribavir group (Table 2). Furthermore, for the secondary endpoints of the combination of CMV infection or EC-confirmed CMV disease, fewer patients in the ganciclovir cohort had CMV infection or CMV disease at both 100 days after transplantation and at 6 months after transplantation (Table 2).

Although this study failed to demonstrate the non-inferiority of maribavir to oral ganciclovir for prevention of CMV disease, it is still possible that the low dose of 100 mg twice daily may have had some antiviral effect. Among CMV-seronegative liver transplant patients with CMV-seropositive donors, the incidences of CMV infection and disease approach 100% and 50%, respectively, without antiviral prophylaxis (1). These incidences are considerably higher than the 72% incidence of infection or disease and the 12% incidence of disease at 6 months after transplantation among the maribavir patients in this study.

The dosing regimen of 100 mg twice daily of maribavir used in this study was chosen to minimize AEs while maintaining anti-CMV activity. Phase 1 and 2 study data suggested that, although maribavir could be given in doses up to 2400 mg daily, taste disturbance at higher doses could be a limiting toxicity (16–18). Furthermore, no dose-response effect for maribavir had been shown in smaller previous studies of HIV-infected patients with CMV shedding in semen or in CMV-seropositive stem-cell transplant recipients receiving maribavir prophylaxis (16–18). Of note, maribavir at doses up to 800 mg twice daily for several months has been used to eradicate ganciclovir-resistant or refractory CMV viremia in a small case series of transplant patients who had failed multiple previous therapies (26). The higher maribavir doses (up to 800 mg twice daily) were well-tolerated in those patients. The results of this study and the effect seen in CMV-viremic patients successfully treated with higher doses of maribavir suggest that higher doses may be effective for CMV prophylaxis and should be studied further.

The DMC identified no safety signals with maribavir in this study, although the study was stopped prior to completion based on the failure of maribavir to show superiority over placebo in another phase 3 prophylaxis study in stem cell transplant recipients (24) as well as the considerably higher incidence of CMV viremia seen by the unblinded committee in the maribavir cohort in this study. The occurrence of taste disturbance, an AE associated with maribavir in previous clinical studies, was similar among maribavir and ganciclovir patients. On the other hand, hematological AEs, which have limited the effectiveness of ganciclovir prophylaxis, were less frequent with maribavir.

In summary, maribavir at the low dose of 100 mg twice daily is not adequate for CMV prophylaxis in liver transplant recipients. Due to the continuing demand for novel anti-viral agents that are safer than ganciclovir and also effective against ganciclovir-resistant infections, additional studies of newer and potentially safer drugs like maribavir for both treatment and prevention of CMV disease are clearly needed. Future studies must first define a dosing regimen of maribavir that is effective in reducing viral replication and improving symptomatic CMV disease. Once an adequate dosing regimen is determined, additional prophylactic trials of maribavir could then be considered.

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Contributors: All authors except SAV, HC, and MEU recruited patients, performed study procedures and collected data. SAV and MEU contributed to study concept and design. SAV and MEU were responsible for medical monitoring and pharmacovigilance. SAV, HC and MEU were responsible for analysis of data for the clinical study report. All authors reviewed the study data, participated in manuscript draft preparation and/or reviewed for intellectual content and approved the final version.

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Dedication: This manuscript is dedicated to Mark Pescovitz who passed away after the completion of this study. He devoted his professional life to helping transplant patients live a better quality of life and to finding newer and better treatments for patients suffering from CMV disease. He will be missed.

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